WASHINGTON STATE HEALTH CARE AUTHORITY

Glucose Monitoring:

Self-monitoring in individuals with insulin dependent diabetes, 18 years of age or under

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Executive Summary

Introduction

Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) are two techniques that persons with diabetes use at home help them maintain blood glucose within a safe range. Intensive treatment with tight control of blood glucose has become the standard of care for diabetes. Such intensive treatment requires monitoring as part of that regimen: by knowing the blood sugar level the patient or caregiver can adjust diet, exercise, and insulin appropriately. SMBG has become a standard practice recommendation for patients with type 1 diabetes. Children and teenagers under the age of 18 with diabetes are most likely to have type 1 diabetes and have the most to gain from maintaining good glucose control yet present some of the greatest challenges in achieving and maintaining good control. As they will probably have many years at risk, children and adolescents with diabetes are at high risk for microvascular complications related to poor glucose control.

This technical review will assess the value of SMBG and CGM for persons under the age of 18 who have diabetes and use insulin. Most persons in this age group with diabetes and that require insulin have type 1 diabetes. The primary focus is on evaluation of self-monitoring methods used to assess glucose levels at home (versus data used exclusively by providers in a clinical setting) for daily decision making regarding self-care, based on the context and key questions provided below by the Washington State Health Technology Assessment Program.

Self-monitoring of blood glucose (SMBG), sometimes called intermittent monitoring, using meters which analyze small amounts of capillary blood on reagent-coated test stripes, provides immediate documentation of glycemic status. This allows one to implement strategies to address and avoid out of range glucose values. It provides only a snapshot of the blood glucose level and thus, cannot provide information on whether there is a trend toward higher or lower levels.

Minimally-invasive devices which measure interstitial fluid glucose concentration via sensors which have been inserted subcutaneously have become more widely available. These devices take samples very 1-20 minutes over the time that the device is worn. Such continuous glucose monitors (CGM) may download data to an insulin pump and/or are stored in a receiver device. CGMs may guide real-time adjustment of food and insulin. Frequent readings may assist patients in seeing if there is a trend toward increasing or decreasing glucose levels so that they can act accordingly. They may aid in identifying times of consistent hyperglycemia or increased risk of hypoglycemia. Some may sound an alarm based on specific targets values and rate of change of interstitial glucose which may facilitate initiation of the appropriate action(s) to avoid hyper- or hypoglycemic events. In those with hypoglycemia unawareness, CGM and appropriate setting of alarm thresholds may be of particular benefit. CGM may not be used alone for treatment decisions and confirmatory SMBG be done.

The effectiveness and optimal frequency of self-monitoring of blood glucose in patients is controversial. Several lines of evidence have suggested an association between glucose monitoring and increased discomfort, inconvenience and worsening of depression scores with regular self-monitoring, along with a lack of clinically relevant improvement in diabetes-related outcomes in patients who self-test. On the other hand, children and adolescents can be especially at risk for some diabetes related complications (e.g. hypoglycemia, ketoacidosis) recommended. Information about the best options for glucose monitoring in diabetic persons persons 18 and under, including evidence of efficacy and safety and cost; and correlation of frequency (including strip frequency and continuous monitoring) to improved outcomes is needed.

Key questions

For patients 18 years of age or under with insulin requiring diabetes mellitus:

1. What is the evidence of efficacy and effectiveness of self-glucose monitoring? Including consideration of:
    a. Achieving target A1C levels
    b. Maintaining target A1C levels
    c. In conjunction with provider specific report cards for target (e.g. under 7/over 9)
    d. Reduce hospitalizations or acute episodes of diabetic ketoacidosis, hyperglycemia and hypoglycemia
    e. Reduce microvascular complications (retinopathy, nephropathy, neuropathy)
    f. Reduce Mortality
    g. Effect on medication or nutritional management
    h. Quality of life

2. What is the evidence on optimal or improved efficacy or effectiveness of glucose monitoring based on frequency or mode (continuous versus self-monitoring) of testing?
3. What is the evidence of the safety of glucose monitoring? Including consideration of:
    a. Adverse events type and frequency (mortality, major morbidity, other)
4. What is the evidence that glucose monitoring has differential efficacy or safety issues in sub populations? Including consideration of:
    a. Gender
    b. Age (differential within the 18 and under population)
    c. Psychological or psychosocial co-morbidities
    d. Other patient characteristics or evidence based patient selection criteria
    e. Provider type, setting or other provider characteristics
    f. Health care payer type, including worker's compensation, Medicaid, state employees
5. What is the evidence of cost implications and cost-effectiveness of self-glucose monitoring? Including consideration of:
    a. Costs (direct and indirect) in short term and over expected duration of use
    b. Estimates of costs saved by preventing morbid events

Methods for evaluating comparative effectiveness

Studies for inclusion were based on the following Patients-Intervention-Comparators-Outcomes, (PICO) summary. A detailed list of inclusion/exclusion criteria are found in the evidence section of this report.

> ***Patients:*** Persons ≤ 18 years old with insulin-requiring diabetes mellitus. (Included studies must have ≥ 80% of the population in this age group or stratify results by age).
>
> ***Intervention:*** Self-monitoring of blood glucose (SMBG) or currently available FDA-approved continuous glucose monitor (CGM) that allows for patient real-time use of data. Studies of periodic CGM use where glucose data were only retrospectively evaluated were excluded from sections evaluating efficacy and effectiveness.
>
> ***Comparators:*** Comparisons of different frequency of SMBG; standard care; SMBG versus CGM; Self-monitoring as a stand-alone intervention versus self-monitoring as part of a package including education, feedback, and support.
>
> ***Outcomes:*** Achieving A1C targets, maintaining A1C targets, hospitalization, hypoglycemia, hyperglycemia, diabetic ketoacidosis, microvascular and macrovascular complications, effect on medication or nutritional management, quality of life, mortality, device-related safety, direct and indirect costs and long term benefits.

A formal, structured systematic search of the peer-reviewed literature across a number of databases in addition to searches of pertinent databases related to clinical guidelines and previously performed assessments was done. This report focuses on the highest quality of evidence available (high quality comparative studies and full economic evaluations) that are published in English in peer-reviewed journals or publically available FDA reports.

Pertinent studies were critically appraised using the Spectrum Research, Inc. Level of Evidence (LoE) system, which evaluates the methodological quality based on study design as well as factors that may bias studies. An overall Strength of Evidence (SoE) combines the LoE and related assessment of potential for bias, with consideration of the number of studies across different populations and the magnitude and consistency of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Results

Summary by key question

Information on determination of overall strength of evidence is found in the appendices.

Key question 1: Efficacy and effectiveness of self-monitoring.

Efficacy

No randomized controlled trials or observational studies which directly evaluated current methods of SMBG testing, as an independent component of management were found. The Diabetes Complications and Control Trial (DCCT) provides indirect evidence regarding the

efficacy of SMBG as part of a package of comprehensive, intensive diabetes care, which included SMBG four or more times per day and education on how to use the information to adjust insulin, diet and exercise compared with the then standard of care (urine or SMBG once/day, only periodic insulin adjustment). The long-term intervention (mean 7.4 years) allowed for evaluation of diabetes-related complications.

Overall, participants 13-17 years old (N=195) at baseline (N = 195, mean age 15 years) in the intensive treatment group (across both cohorts over the entire study period) experienced:

- Significantly lower mean A1C levels by 6-12 months that remained lower for the remainder of the 7.4 year trial, (8.06% intensive treatment versus 9.76% conventional treatment; (P value for test of medians was < 0.0001, loss to follow-up unclear).
- Lower average daily blood glucose concentrations ($P< 0.0001$)
- A higher rate of hypoglycemia resulting in coma or seizures (RR 2.93; 95% CI, 1.75, 4.90; P < 0.001).
- A 61% risk reduction in sustained ≥ three-step retinopathy (95% CI 30% to 78%; p=0.02) after adjusting for baseline retinopathy
- No statistical difference in rate of ketoacidosis (18% for intensively treated, 20% for conventionally treated).
- No significant differences in nephropathy in the primary prevention cohort or the combined cohorts. (Participants in the secondary prevention cohort who were intensively treated experienced a statistically significant reduction in risk (55%) of having microalbuminuria (95% CI 3, 79%, P = 0.042) compared with those in this cohort who were conservatively treated.)
- Significantly higher peripheral motor and sensory nerve conduction velocities compared with the conventionally treated group at 5 years. No statistically significant difference in neuropathy between treatment groups were seen in the combined cohort.

Effectiveness

Indirect evidence on the effectiveness of SMBG is based on (the Epidemiology of Diabetes Interventions and Complications (EDIC) the observational follow-up to the DCCT at four and ten years. All participants in the conventional treatment arm were offered instruction in the use of intensive therapy and intensive treatment group patients were encouraged to continue such treatment.

Overall, in those who were <18 years old at the start of the DCCT and followed in the EDIC:

- Mean A1C values were similar between the former intensive and former conventional groups at the end of years 4 and 10.
- Among the former intensive treatment group, the prevalence a ≥ 3 step progression of retinopathy and of progression to proliferative or severe nonproliferative retinopathy were significantly reduced by compared with the former conventional groups at year four. At year 10, however, there were no significant differences among former intensive and conventional treatment groups in the progression of retinopathy (≥ 3 step progression of retinopathy, severe nonproliferative retinopathy, proliferative retinopathy clinically significant macular edema or photocoagulation therapy.
- No differences in nephropathy were seen at the end of either follow-up period.

At 10 years of observation following the completion of the DCCT, the progression of retinopathy ≥3 levels and proliferative retinopathy was less in the prior intensive group of adolescents compared with the conventional group, but the difference was not statistically significant. However, the entire EDIC cohort (including all ages) who had been in the DCCT intensive treatment group experienced a statistically significant reduction at 10 year follow-up. The authors suggest that the waning effect in the adolescent cohort may have been because the adolescents did not achieve as low an A1C during the DCCT as the older study subjects, and thus the "memory effect" was less. It should also be noted that the adolescent EDIC sample size was much smaller. The long term impact of intensive treatment on the cardiovascular complications for those who were adolescents at entry to DCCT is not yet fully known as even after 10 years of follow-up, this group would be young adults. A delay in observed benefit would be consistent with current understanding of the cumulative damage and thus may take more years to become clinically evident. This is also true for retinopathy, neuropathy and nephropathy outcomes.

Key question 2: Efficacy and effectiveness by frequency or mode of testing.

Efficacy

There were no randomized controlled trials (RCT) that directly evaluated the efficacy of SMBG frequency. Indirect evidence from the DCCT (described above) provides information with respect to frequency in that the intensive group was instructed to test at least four times per day compared with the conventional care group's once per day.

The bulk of the evidence on efficacy of mode of self-monitoring comes from RCT's of continuous glucose monitors (CGM) where patients had real-time access to data comes. Data from one primary JDRF 2008 report that provided result stratified by age (n = 114, 8-14 year olds) and one smaller RCT (n = 40, 12-18 year olds) that also stratified by age, form the primary basis for the overall evidence summary. The other, JDRF (2009) study has few outcomes stratified by age. In all studies, CMG was used in conjunction with SMBG (for calibration and verification per FDA recommendations) and was compared with SMBG alone. In the JDRF studies, 84% of both CGM and SMBG groups used insulin pumps (which did not communicate with the CMG) and 100% of patients in the Hirsch study used pumps integrated with the CMG device in the CGM arm only. This heterogeneity in study design precluded pooling of data. There are currently no long-term comparative studies on these devices for evaluation of benefits, complications or diabetes-related comorbidities on those ≤ 18 years old.

The overall strength of evidence for efficacy is low. Results for follow-up to 26 weeks in these studies on the efficacy of CGM (in conjunction with SMBG) over SMBG include the following:

- Two RCTs reported A1c results stratified by age. Differences in the change in mean A1C between treatment arms were not statistically significant in the larger JDRF 2008 study or the smaller (Hirsch) RCT (P = 0.29, P = 0.10, respectively). Differences in the change in mean A1C between groups were of questionable clinical significance (based on 0.5% as a threshold) across two RCTs. In the JDRF 2008 RCT, changes in A1C levels were -0.37 in the CGM arm and -0.22% in the SMBG arm. In the smaller RCT, change in A1C levels were -0.80% in the SMBG arm and -0.38% in the CGM arm].
- Two of the three RCTs reported on proportions of patients achieving A1C targets: In the JDRF 2008 participants in the CGM group were roughly twice as likely to achieve A1C targets of <7% (RD = 15%), relative A1C decreases of ≥ 10% (RD = 17%) and absolute decreases of ≥ 0.5% (RD = 23%).. These changes were achieved without significant differences in hypoglycemic events. In the other RCT [Hirsch 2008], the difference in

reaching A1C targets did not reach significance (p=0.052) perhaps as a function of sample size.

- Neither of two JDRF RCTs found significant differences in the effects of CGM versus SMBG alone on episodes of hypoglycemia (measured as the proportion of participants with one or more severe hypoglycemia episode, rate of severe hypoglycemic episodes (CGM: 17.9/100,000 person-years versus SMBG: 24.4/100,000 person-years), amount of time blood glucose levels were lower than either 70 mg/dl (CGM: 47 min/day versus SMBG: 59 min/day) or 50 mg/dl (CGM: 10 min/day versus SMBG: 13 min/day)).
- Hyperglycemia rates were reported in one RCT: No significant differences in episodes of hyperglycemia (measured as the amount of time spent with blood glucose levels greater than either 180 mg/dl (CGM: 643 min/day versus SMBG: 635 min/day) or 250 mg/dl(CGM: 242 min/day versus SMBG: 268 min/ day)).
- There were no differences in any QOL measures between participants in either treatment arm or parents of participants at 26 weeks or in change from baseline to 26 weeks in the one RCT reporting on this.
- No RCTs of the effect of monitoring mode on any of the following outcomes were found for the following: a) maintaining A1C levels, b) achieving target A1C levels in conjunction with provider specific report cards, c) acute episodes of diabetic ketoacidosis, d) microvascular complications, or e) medication or nutritional management.
- No studies relating specifically to pregnant patients ≤ 18 years old or patients ≤ 18 years old with type 2 diabetes who require insulin were found.
- Specific information regarding how data were used for management decisions was not provided in any trial, thus conclusions regarding the direct, independent impact of monitoring on decision making are not possible.

Effectiveness

Frequency of CGM use: Subanalyis and extended follow-up studies of the JDRF 2008 RCT population provide the primary evidence. In the absence of additional studies evaluating frequency and consistency of CGM use in different patient populations, the overall strength of evidence is low.

- Based on a subanalysis of the JDRF 2008 trial, consistent use of CGM ≥ 6 days per week for 6 months was associated with lower mean A1c values compared with baseline. In an extension study of the group who had been randomized to CGM, a greater number of participants meeting targets of < 8.0% for 8−12 year olds and <7.5% for 13−17 year olds compared with those who used it < 6 days per week. Those who continued use of CGM ≥ 6 days per week for 6 months after the end of the trial (i.e. a total of12 months). maintained lower mean A1C values and an additional number achieved targets. These improvements in A1c were achieved while the incidence of hypoglycemia remained low for all users.
- In another JDRF extension study of those initially randomized to SMBG who switched to CGM after the trial, no consistent pattern for improvement in A1C of ≥ 0.5% or achieving A1C <7% was seen at 6 months in those 8-12 years old. Prior to CGM use, severe hypoglycemia occurred in 26.4 per 100 person-years compared with 13.0 per 100 person-years after 6 months of CGM use (p-value not stated).
- In these reports, specific information on how data from CGM or SMBG were used to influence management was not provided, thus the independent impact of monitoring itself cannot be determined.

Frequency of SMBG. The overall strength of evidence is low.

- Performing SMBG 4 to 5 times per day was associated with lower mean A1C, based on data from one large registry study and six prognostic studies (all LoE III). In these cross-sectional studies, however, it is not possible to sort out the extent to which lower A1c is causally related to the frequency of SMBG. It is not known, if those who test more frequently tend to have lower A1c and may be more compliant with their treatment regimen in general.
- In 11 cross-sectional studies and one registry study (all LoE III), more frequent SMBG was associated with lower A1C, however specific data on frequency and A1C values were not provided. In nine of these studies, the correlation was significant.
- There is conflicting evidence regarding whether more frequent SMBG is associated with lower rates of hypoglycemia. One large registry reported hypoglycemia rates are higher with greater frequency of testing while one cohort study reported hypoglycemia rates are lower with greater frequency of testing. It is unclear whether the increase in events in the larger study may be due to increased frequency of testing in those more likely to have hypoglycemic events.
- The presence of an association in cross-sectional studies does not infer that the relationship is causal as temporal sequence and other relevant factors are unknown.

Key question 3: Safety

Safety issues related to CGM or SMBG device design and implementation are described as safe use is a function of both design and implementation. The overall strength of evidence is moderate based on the number and quality of studies. No major adverse events were reported. Hypoglycemia and hyperglycemia are described under Key Questions 1 and 2.

CGM: Data from RCTs, observational studies and FDA SSED reports were used. There were no major adverse events reported.

- The most frequent insertion site problems included redness and/or itching (16%-45%), dry skin (21%), mild and moderate acute skin changes (14% each) and irritation, bruising or pain (0-53%) based on information across RCTs and observational studies, some of which had small sample sizes.
- The most frequent sensor/device related concerns were alarms interfering with daily routine (38%), irritation by alarms (38%-50%), sensor too bulky (22%-75%) and sensor pulled out accidentally (10-13%) based on information across RCTs and observational studies, some of which had small sample sizes.
- Thresholds can be set for alerting patients when glucose values have reached a specified low or high level, allowing patients to take appropriate action. The primary safety concerns for CGM relate to false alerts and missed alerts (occasions when the alarm should have sounded but did not). The rates for these varied across blood glucose thresholds and across devices, based on FDA Summaries of Safety and Efficacy Data used for FDA approval. False positive alerts may be annoying and lead the patient to ignore subsequent alarms. False negative alerts, i.e., times when the device did NOT alarm may be more problematic as the person is not prompted to consider action and may give him/her a false sense of security. While these are human/behavioral factors, they have the potential to lead to adverse events and therefore are considered in the context of safe device implementation.
- No deaths among participants ≤ 18 years old were reported in any study.

SMBG: Reports of problems at the finger stick site come from old studies, published 1983−1988, and devices used for drawing blood have improved. The primary concerns reported

were sore fingers and difficulty obtaining blood in these studies. These are related to the device used for drawing blood, rather than the glucose monitor itself.

Key question 4: Differential efficacy or safety in sub-populations

One RCT and one large registry study directly assessed differential outcomes for either CGM or SMBG by subpopulations. The overall strength of evidence is low.

CMG compared with SMBG: One RCT

- Patients 8-14 years old and those 15-24 years old had similar results with regard to A1C and achieving targets for CGM and SMBG with no evidence of differential efficacy by age was demonstrated, based on one RCT.

SMBG frequency: Evidence is from one large registry study.

- There is limited evidence for differential effectiveness for frequency of SMBG by age. For 13-18 year olds an average improvement in A1C of 0.3% ± 0.011 for each additional SMBG was reported. This appears to apply up to tests five per day. In contrast, for ages 0-5 and 6-12, beyond one test per day, improvement in A1C was much less and averaged 0.04% ± 0.018 and 0.12% ± 0.010 respectively beyond one SMBG per day.
- There may be some evidence differential of effectiveness for frequency of SMBG by insulin regimen. Patients using continuous subcutaneous insulin infusion (CSII) experienced a mean reduction of 0.27% in A1C (%) for one additional SMBG per day. This group came closest to approaching A1C targets of between 7.0% and 7.5%. Those using multiple daily injections (MDI) experienced a 0.24% decrease in A1C.

Key question 5: Economic studies

There is no evidence available to assess the cost effectiveness of SMBG or CMG in persons with diabetes ≤18 years old who require insulin. No full economic studies which focused on the cost-effectiveness of CGM or the frequency of SMBG were found.

Summaries of overall strength of evidence by key question

Table 1. Summary of evidence for Key Question 1: Efficacy and effectiveness of monitoring

Key Question 1: What is the evidence of efficacy and effectiveness of self-monitoring of blood glucose?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
• Intensive diabetes care package (SMBG ≥ 4/day, education on how adjust insulin, diet and exercise)	• Standard care (urine or SMBG up to 1/day, no daily changes in insulin, diet)	**Low**	**Efficacy** No RCTs or observational studies directly evaluating current SMBG methods. Indirect evidence from DCCT (n = 195) on SMBG as part of intensive program for tight control: • <u>In the short-term</u> (6-12 months) Intensive program participants had lower A1C and average daily blood glucose levels • <u>In the longer-term</u> (to mean 7.4 years. Intensive program participants sustained lower A1C and average daily blood glucose levels (177 ± 31 mg/dL vs. 260 ± 52 mg/dL; *P*< .0001), had risk reduction of 61% for retinopathy but no differences in ketoacidosis or nephropathy in the primary or combined cohorts. A55% reduction in microalbuminuria was seen in intensively treated participants in the secondary prevention cohort (P = 0.042). Nerve conduction velocities were significantly higher in the intensively treated group.	+	-	-

Key Question 1: What is the evidence of efficacy and effectiveness of self-monitoring of blood glucose?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
• Prior participation in DCCT Intensive treatment arm; Participants encouraged to continue intensive treatment	• Prior participation in DCCT conventional treatment arm; Participants provided education on intensive treatment	Low	**Effectiveness** No observational studies directly evaluating current SMBG methods. Indirect evidence from EDIC observational follow-up of DCCT: • 4 years after the end of DCCT (n=175): Adolescents who were in the intensive treatment arm had significantly lower rates of retinopathy progression and no difference in mean A1c%. Prevalence of microalbuminuria and albuminuria were lower in those in the former intensive treatment group statistical significance was not achieved. • 10 years after the end of DCCT (n=156): Adolescents who were in the Intensive treatment arm no difference in mean A1c% or retinopathy progression. There were no differences in microalbuminuria or albuminuria	+	-	-

Table 2. Summary of Evidence for Key Question 2: Efficacy and effectiveness by mode or frequency

Key Question 2: What is the evidence of efficacy and effectiveness by mode or frequency?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
• CGM (in conjunction with SMBG)	• SMBG alone	Low	**Efficacy** JDRF 2008 RCT (n = 114; 8-14 year olds) and one small RCT (n = 40, 12-18 year olds) form basis for the overall evidence summary. A third RCT provided limited data. • In the short-term (to 26 weeks) No clinically meaningful differences in mean A1C or mean change, hypoglycemia or hyperglycemia. Limited evidence (1 report) that CGM participants were twice as likely to achieve ADA age-specific A1C targets. • In the longer-term : There are no long-term studies or follow-up studies to RCTs in the long term	+	-	-
• Consistent CGM use (in conjunction with SMBG)	• Less frequent use	Low	**Effectiveness** Sub-analysis of JDRF RCT: More frequent CGM use was associated with a greater reduction in A1c from baseline to 6 months ($p < 0.001$ among 8-14 year olds) Extension studies of JDRF RCT: • Among those randomized to CGM, those who continued use of CGM ≥ 6 days per week for an additional 6 months (12 months total) maintained lower mean A1C values and an additional number achieved ADA age-specific targets compared with those who didn't continue past the 6 month trial end or those who used it < 6 days/week. Improvements in A1c were achieved while the incidence of hypoglycemia remained low for all users. • Among those randomized to SMBG, who switched to CGM after the trial, no consistent	+	-	-

Key Question 2: What is the evidence of efficacy and effectiveness by mode or frequency?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
			pattern in improvement in A1C of ≥ 0.5% or achieving A1C <7% was seen at 6 months in those 8-12 years old . Prior to CGM use, incidence of severe hypoglycemia was higher than the incidence after 6 months of CGM use			
• Higher SMBG frequency	• Lower SMBG frequency	Low	One large registry and six prognostic studies (all cross-sectional) suggest an association between greater SMBG frequency and lower A1C. Causality cannot be inferred from cross-sectional studies. • SMBG 4 to 5 times per day was associated with lower mean A1C across reports. Causality cannot be inferred. • Eleven cross-sectional studies and one registry study found an inverse correlation between frequency of SMBG and A1C. • Conflicting evidence regarding whether more frequent SMBG is associated with lower rates of hypoglycemia: the large registry's rates of hypoglycemia are higher with greater frequency of testing while one cohort study reported lower rates. Causality cannot be inferred.	-	+	+

Table 3. Summary of Evidence for Key Question 3: Safety

Key Question 3: What is the evidence of Safety?					
Mode/Method	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
• CGM	Moderate	Information from RCTs, observational studies and FDA SSED reported no major adverse events. Denominators in some studies were very small. • Insertion site problems (e.g. redness, irritation, mild to moderate skin changes ranged from 0%-53% • Sensor/device related concerns related to interference of daily routine (38%), irritation by alarms • False alerts may be annoying and missed alerts may not prompt the individual to take action and give a false sense of security. Rates varied across devices and blood glucose thresholds in FDA SSED reports.	+	+	-
• SMBG	Moderate	There were no data from modern devices. Data from old RCTs and one observational study. No device-related major adverse events reported. Sore fingers and difficulty obtaining blood samples were the primary events reported	-	-	+

Table 4. Summary of Evidence for Key Question 4: Differential efficacy and safety in subpopulations

Key Question 4: What is the evidence of efficacy and effectiveness with respect to sub-populations?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
Age						
• CGM (in conjunction with SMBG)	• SMBG alone	Low	Data from 1 RCT (LoE II) –there is no difference by age • <u>In the short-term</u> (to 26 weeks) Participants 8-14 years old and 15-24 years old had similar results with regard to A1C and achieving targets for CGM and SMBG with no evidence of differential efficacy by age, based on one RCT • <u>In the long-term</u>: no data are available	+	-	-

Key Question 4: What is the evidence of efficacy and effectiveness with respect to sub-populations?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
• Higher SMBG frequency	• Lower SMBG frequency	Low	Data from cross-sectional analysis of large registry:N = 26,723) suggests the association may be influenced by age: • For 13-18 year olds an average improvement in A1C of 0.3% ± 0.011 ($p < 0.001$) for each additional SMBG was reported. This appears to apply up to tests five per day. For ages 0-5 year olds an average improvement in A1C of 0.04% ± 0.018 for each additional SMBG was reported. For 6-12 year olds an average improvement in A1C of 0.12% ± 0.010 for each additional SMBG was reported.	-	-	-
Insulin Regimen						
• Higher SMBG frequency	• Lower SMBG frequency	Low	Data from large registry: cross-sectional analysis) suggests the association between SMBG and A1C may be modified by regimen: patients using CSII who also test up to 10 times per day may come closest to meeting targets. • For participants using CSII, a mean reduction of 0.27% in A1C for one additional SMBG per day. This group came closest to approaching A1C targets of between 7.0% and 7.5%. Participants using multiple daily injections (MDI) experienced a 0.24% decrease in A1C per additional test/day.	-	-	-

Table 5. Summary of Evidence for Key Question 5: Economic

Key Question 3: What is the evidence of Cost-effectiveness?					
Mode/Method	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**

Key Question 3: What is the evidence of Cost-effectiveness?					
Mode/Method	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
• CGM	No evidence	• No studies found	-	-	-
• SMBG Frequency	No evidence	• No studies found	-	-	-

Appraisal

Rationale

Intensive treatment with tight control of blood glucose has become the standard of care for diabetes. Such intensive treatment requires SMBG (or CGM) as part of that regimen: knowing the blood sugar level provides information on which the patient or caregiver can adjust diet, exercise, and insulin appropriately to achieve and maintain glycemic control. SMBG has become a standard practice recommendation across clinical guidelines. The scope of this HTA is to evaluate the evidence for glucose monitoring based on the context and key questions provided by the Health Technology Assessment Program.

Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) are two techniques that persons with diabetes use at home to help them maintain blood glucose within a safe range. Children and teenagers 18 years old and under with diabetes have the most to gain from maintaining good glucose control yet present some of the greatest challenges in achieving and maintaining good control. This technical review will assess the value of SMBG and CGM for persons 18 years old and under who have diabetes and require insulin. The primary focus is on evaluation of self-monitoring methods used to assess glucose levels at home (versus data used exclusively by providers in a clinical setting) for daily decision making regarding self-care

Children with diabetes who require insulin (most of whom have type 1 diabetes) represent a special population. Monitoring and medication regimens can be quite complex. Adherence to these regimens may differ between children and adults and may differ based on a child's age as well as other factors. Care of children involves and impacts her/his family and other caregivers.

Self-monitoring of blood glucose (SMBG), sometimes called intermittent monitoring, using meters which analyze small amounts of capillary blood on reagent-coated test strips, provides immediate documentation of glycemic status. This allows one to implement strategies to address and avoid out of range glucose values. It provides only a snapshot of the blood glucose level and thus, cannot provide information on whether there is a trend toward higher or lower levels.

Minimally-invasive devices that measure interstitial fluid glucose concentration via sensors that have been inserted subcutaneously have become more widely available. These devices take samples every 1-20 minutes over the time that the device is worn. Such "continuous" glucose monitors (CGM) may download data to an insulin pump and/or are stored in a receiver device.

CGMs may guide real-time adjustment of food and insulin. Frequent readings assist patients determining whether there is a trend toward increasing or decreasing glucose levels, allowing them to intervene accordingly. They may aid in identifying times of consistent hyperglycemia or increased risk of hypoglycemia. Some may sound an alarm based on specific target values and rate of change of interstitial glucose, which may facilitate initiation of the appropriate action(s) to avoid hyper- or hypoglycemic events. Those with hypoglycemic unawareness may benefit as the devices will alarm when glucose is below a specified range or with rapid rate of fall of glucose. High rates of false alarms led the FDA to specify that CGM should not be used alone for treatment decisions and that confirmatory SMBG be done.

Although organizations have made recommendations regarding frequency of use of blood glucose monitoring, the effectiveness and optimal frequency of self-monitoring of blood glucose in patients is controversial. Several lines of evidence suggest an association between glucose monitoring and increased discomfort, inconvenience and worsening of depression scores with regular self-monitoring, along with a lack of clinically relevant improvement in diabetes-related outcomes in patients who self-test. On the other hand, children and adolescents can be especially at risk for some diabetes related complications (e.g. hypoglycemia, ketoacidosis). It is unclear in the literature how CGM may be best used in those ≤ 18 years of age. Information about the best management strategies for diabetics ≤18, including evidence of efficacy and safety and cost; and correlation of frequency (including strip frequency and continuous monitoring) to improved outcomes is needed. There are concerns about efficacy, safety, cost, and health impact of glucose monitoring on clinical outcomes among patients with diabetes (and/or subgroups). Important questions remain about its effect on patient outcomes, education regimens, titration schemes, and determining adequacy of an overall treatment plan. Specific to this topic, the core of the glucose monitoring concerns described by the Health Technology Assessment Program are reflected in key question #2 below around evidence about when, what type, and how much.

Objective

The primary aim of this assessment is to systematically review, critically appraise and analyze available research evidence comparing the efficacy, effectiveness and safety of self-glucose monitoring in persons 18 years of age or younger who require insulin for the control of diabetes mellitus. Available information on the economic impact of this will also be summarized and critically appraised.

Key questions

For patients 18 years of age or under with insulin requiring diabetes mellitus:

1. What is the evidence of efficacy and effectiveness of self-glucose monitoring?
   Including consideration of:
   a. Achieving target A1C levels
   b. Maintaining target A1C levels
   c. In conjunction with provider specific report cards for target (e.g. under 7/over 9)
   d. Reduce hospitalizations or acute episodes of diabetic ketoacidosis, hyperglycemia and hypoglycemia
   e. Reduce microvascular complications (retinopathy, nephropathy, neuropathy)

f. Reduce Mortality
g. Effect on medication or nutritional management
h. Quality of life

2. What is the evidence on optimal or improved efficacy or effectiveness of glucose monitoring based on frequency or mode (continuous versus self-monitoring) of testing?
3. What is the evidence of the safety of glucose monitoring? Including consideration of:
    a. Adverse events type and frequency (mortality, major morbidity, other)
4. What is the evidence that glucose monitoring has differential efficacy or safety issues in sub populations? Including consideration of:
    a. Gender
    b. Age (differential within the 18 and under population)
    c. Psychological or psychosocial co-morbidities
    d. Other patient characteristics or evidence based patient selection criteria
    e. Provider type, setting or other provider characteristics
    f. Health care payer type, including worker's compensation, Medicaid, state employees
5. What is the evidence of cost implications and cost-effectiveness of self-glucose monitoring? Including consideration of:
    a. Costs (direct and indirect) in short term and over expected duration of use
    b. Estimates of costs saved by preventing morbid events

Primary outcomes

Ideally, direct evidence over a long term of follow-up from randomized controlled trials that evaluate the impact of SMBG and CGM on diabetes-related morbidity and mortality would be available. Hemoglobin A1C is considered an intermediate (surrogate) outcome and, in the absence of such trials, provides the best available evidence as it is considered a predictor of diabetes complications

Data on the following outcomes related to efficacy and effectiveness of SMBG and CMG (that allowed for patient real-time use of data) were sought:

- Achieving target A1C levels
- Maintaining target A1C levels
- Acute episodes of diabetic ketoacidosis, hyperglycemia and hypoglycemia
- Reduction of microvascular complications (retinopathy, nephropathy, neuropathy)
- Mortality
- Effect on medication or nutritional management
- Quality of life

The primary safety outcomes considered include device-specific factors and mortality. For full economic evaluations, incremental cost-effectiveness ratios are desirable.

Key considerations highlighted by clinical experts

Interventions

Results from the Diabetes Control and Complications Trial [1] ushered in a new era of diabetes management in establishing the value of intensive treatment with tight control. Follow-up of the DCCT participants indicates reduced risk for some diabetes- related complications in those who received intensive treatment. Such intensive treatment requires SMBG as one part of that regimen. Therefore, SMBG has become a standard practice recommendation particularly for patients with type 1 diabetes despite lack of high quality evidence of its efficacy outside of a package of self-care behaviors. [2] Internationally, SMBG is considered an integral part of type 1 diabetes management.

SMBG provides a "snapshot" of blood glucose levels. What real-time CGM adds is the ability to have information about the direction and rate of blood glucose change. It allows for evaluation of multiple data points to obtain a more accurate picture of glycemic variability versus SMBG (or A1C), which may be valuable for management decisions. A primary goal in type 1 diabetes management is to achieve good control without increasing risk of hypoglycemic events. Frequent blood glucose monitoring is considered critical to identify and prevent hypoglycemia. CGM devices are evolving. The accuracy and tolerability of newer, second-generation devices have shown a marked improvement from the early, retrospective devices. Tolerability is still an area where improvement is needed as is accuracy. The role of real-time continuous glucose monitors (rt-CGM) for pediatric use is evolving, as is identification of which individuals may most benefit from its use. The evidence base on rt-CGM for pediatric is still relatively sparse and is evolving as well.

RCTs are generally conducted by those with extensive, special expertise in diabetes management and the follow-up and attention that study subjects receive may not be typical outside the research setting. That is true of any RCT: the extent that results can be extrapolated to routine practice may not be clear.

Adherence to SMBG with or without CGM is still required for optimal glycemic control. Consistency of use, education and patient skill regarding what to do with the information are important. Many children and teens with type 1 diabetes are technologically savvy and might welcome the CGM as a gadget, but many may not like the annoyance of responding to alerts, the bulk of the device or still having to do SMBG. Alerts for hypoglycemia may be of particular importance in children and those with hypoglycemic unawareness and are an important part of accepting the technology. Although only the pediatric versions of the Medtronic Minimed Guardian® and Paradigm ®REAL-time CGM have been approved for use in those ≤18 years old, off label use of the other systems is common in the clinical setting.[3]

Individual vs. Population-based impact

The primary goals for treatment of youth with type 1 diabetes are to maintain plasma glucose and A1C levels as close to normal as possible while minimizing episodes of severe hypoglycemia. In the long-term, this assists with reducing complications. This is not an easy task in some patients. With regard to children and adolescents, physiological as well as psycho-social changes influence metabolism and adherence to self-care behaviors. The ADA and others suggest that A1C goals be individualized. The targets are intended as guidance.

Although many organizations have published guidelines on A1c levels, the choice of the optimum A1C should be individualized, based on persons medical status, degree of difficulty to control glucose levels, psychosocial issues include cognitive ability, motivation, family and social support, and finances for medications, supplies, and technology. Very small children have limited language and cognitive abilities to detect hypoglycemia. National guidelines at this time suggest higher A1C goals for children and even less stringent A1C goals for pre-school age children, but we know that these higher levels of A1c increase the child's risk of health problems and shorter life expectancy. Improved methods to monitor blood glucose, especially for hypoglycemia, could make it safer to achieve lower glucose levels.

Effective use of CGM requires that the pediatric patient (and/or parent depending on the child's age) understand important aspects of intensive insulin therapy and understanding that the trend of glucose rise or fall is more important than the value displayed by the meter. Given the FDA requirements for SMBG testing for decision making, they need to be willing to continue to do multiple SMBG and change behaviors that influence daily glycemic control based on the information obtained. [4]

A child's activities and quality of life are affected by diabetes care regimens. Care of diabetic children involves parents, family members and other caregivers thus impacting their activities and quality of life as well. Monitoring of blood sugar levels provides parents/caregivers with data to assist with that care as well as some measure of confidence and peace of mind in caring for the child, knowing what the blood sugar is at any given time. The DCCT results suggest that near-normal levels of A1C would be ideal to minimize the risk of chronic complications, but the lower the A1C, the more likely the person is to experience severe hypoglycemia and it is important to parents/caregivers

Costs

Diabetes care is costly. The costs of SMBG (strips) contribute significantly to the overall cost of care. Two studies specific to pediatric patients indicate that SMBG strips may comprise 37% - 53% of the mean total costs per year.[5,6] Although these studies are in populations outside of the US, they may provide some initial idea of the SMBG expenses.

CGM devices are expensive. Information in a 2009 article by Hirsch suggests that the initial costs of devices are around $1250 with monthly costs for sensors ranging from $175 - $450. [4]

At this point it is not clear what the cost for incremental benefit of CGM in either A1C reduction or longer term health outcomes may be. How much improvement, and in what measures, make it worth the extra cost and effort?

Professional considerations

There is a need for education and follow-up of patients who use CGM and thus an appropriate clinical environment and infrastructure are required.[4] Clinician questions in this regard include those about staffing requirements (number, training), increased call volume, and reimbursement for extra training and management duties.

Washington State utilization and cost data

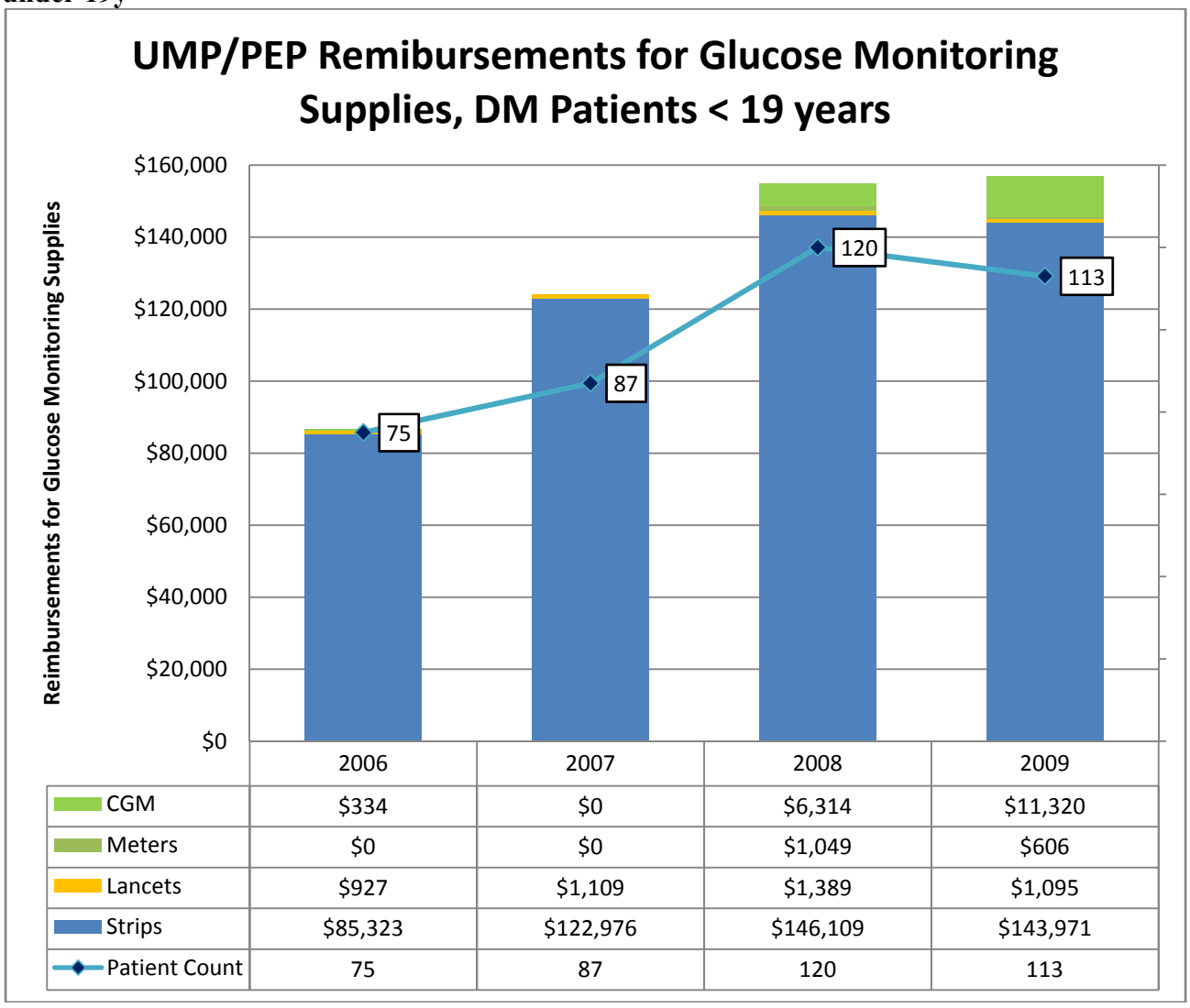
Information in this section was provided by the Washington State Health Technology Assessment Program.

Figure 1 State Agency Reimbursements for Glucose Monitoring Supplies for Patients <19

Glucose Monitoring Supplies for Patients Under 19	2006	2007	2008	2009	4 year Total
UMP/PEP GM Supply reimbursements					
Total Annual Reimbursements	$86,584	$124,085	$154,861	$156,992	$522,522
Test Strip Reimbursements Cost	$85,323	$122,976	$146,109	$143,971	$498,379
Test Strip % Total Reimbursement	98.5%	99.1%	94.3%	91.7%	95.4%
Under 19 Patient Count	75	87	120	113	358*
Avg Test Strip Cost Per Patient	$1,138	$1,414	$1,218	$1,274	$1,392
DSHS GM Supply reimbursements					
Total Annual Reimbursements	$233,037	$354,126	$457,470	$459,607	$1,504,240
Test Strip Reimbursements Cost	$187,544	$281,533	$373,214	$390,454	$1,232,745
Test Strip % Total Reimbursement	80.5%	79.5%	81.6%	85.0%	82.0%
Under 19 Patient Count	667	679	800	829	1884*
Avg Test Strip Cost Per Patient	$281	$415	$467	$471	$654
Overall GM Supply reimbursements					
Total Annual Reimbursements	$319,621	$478,211	$612,331	$616,599	$2,026,762
Test Strip Reimbursements Cost	$272,867	$404,509	$519,323	$534,425	$1,731,124
Test Strip % Total Reimbursement	85.4%	84.6%	84.8%	86.7%	85.4%
Under 19 Patient Count	742	766	920	942	2242
Avg Test Strip Cost Per Patient	$368	$528	$564	$567	$772

**4 year total patient counts are a separate count of unique patients over 4 year, not the total of annual patient counts.*
Note: supplies evaluated are limited to Continuous Glucose Monitoring supplies, Blood Glucose Test Strips and Lancets, and Glucose Meters

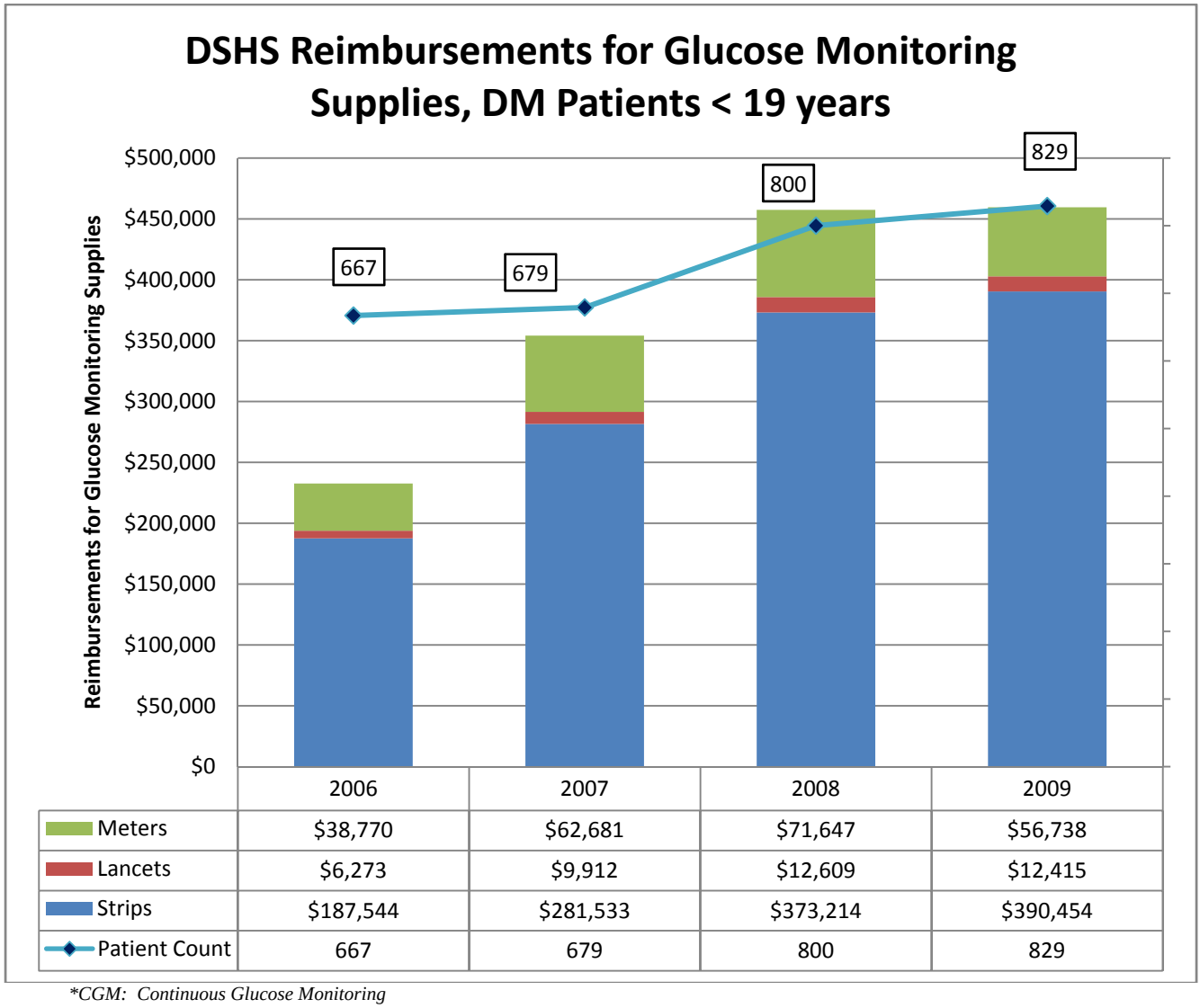
Figure 2a. UMP/PEP Total Reimbursements for Glucose Monitoring in DM Members under 19y



	2006	2007	2008	2009
CGM	$334	$0	$6,314	$11,320
Meters	$0	$0	$1,049	$606
Lancets	$927	$1,109	$1,389	$1,095
Strips	$85,323	$122,976	$146,109	$143,971
Patient Count	75	87	120	113

**CGM: Continuous Glucose Monitoring*

Figure 2b. DSHS Total Reimbursements for Glucose Monitoring in DM Members under 19y



	2006	2007	2008	2009
Meters	$38,770	$62,681	$71,647	$56,738
Lancets	$6,273	$9,912	$12,609	$12,415
Strips	$187,544	$281,533	$373,214	$390,454
Patient Count	667	679	800	829

**CGM: Continuous Glucose Monitoring*

Figure 3a: UMP/PEP U19 DM Patient Characteristics and Adverse Events

Population	2006		2007		2008		2009	
	Count	% mbrs	Count	% mbrs	Count	% mbrs	Count	% mbrs
All DM member count	**11037**		**12274**		**14927**		**15418**	
U19 member count	**85**	**0.8%**	**103**	**0.8%**	**132**	**0.9%**	**121**	**0.8%**
DM Type 1 mbr count	**71**	**83.5%**	**84**	**81.6%**	**118**	**89.4%**	**110**	**90.9%**
DM Type 2 mbr count	**14**	**16.5%**	**19**	**18.4%**	**14**	**10.6%**	**11**	**9.1%**
CGM mbr count	**2**	**2.4%**	**0**	**0.0%**	**9**	**6.8%**	**16**	**13.2%**
Insulin Delivery/Monitoring								
Hemo A1C Tests	**476**	**5.6%**	**250**	**2.4%**	**345**	**2.6%**	**330**	**2.7%**
Infusion Pumps (Insulin)	**26**	**30.6%**	**36**	**35.0%**	**49**	**37.1%**	**51**	**42.1%**
Adverse Events								
Mbrs w/ER visits	**17**	**20.0%**	**14**	**13.6%**	**22**	**16.7%**	**15**	**12.4%**
Mbrs w/Critical Care, 1sth	**4**	**4.7%**	**2**	**1.9%**	**6**	**4.5%**	**3**	**2.5%**
Ketoacidosis member ct	**13**	**15.3%**	**7**	**6.8%**	**5**	**3.8%**	**6**	**5.0%**
Ketoacidosis events	**16**		**10**		**5**		**6**	
Hyperglycemia mbr ct	**1**	**1.2%**	**2**	**1.9%**	**2**	**1.5%**	**4**	**3.3%**
Hyperglycemia events	**1**		**2**		**2**		**4**	
Diabetic coma member ct	**0**	**0.0%**	**0**	**0.0%**	**3**	**2.3%**	**2**	**1.7%**
Diabetic coma events	**0**		**0**		**3**		**2**	

Figure 3b: DSHS U19 DM Patient Characteristics and Adverse Events

Population	2006		2007		2008		2009	
	Count	% mbrs	Count	% mbrs	Count	% mbrs	Count	% mbrs
All DM member count	13,031		13,645		14263		16058	
U19 member count	667	5.12%	679	4.98%	800	5.61%	829	5.16%
DM Type 1 mbr count	416	62.07%	452	66.57%	530	66.25%	547	65.86%
DM Type 2 mbr count	241	36.13%	222	32.70%	255	31.88%	273	32.93%
Unknown DM Type ct	10	4.98%	5	2.25%	15	5.88%	9	3.66%
Insulin Delivery/Monitoring								
Hemo A1C Tests	402	60.27%	454	66.86%	545	68.13%	628	75.75%
Infusion Pumps (Insulin)	4	0.60%	59	8.69%	59	7.38%	92	11.10%
Adverse Events								
Mbrs w/ER visits	229	34.33%	311	45.80%	352	44.00%	471	56.82%
Mbrs w/Critical Care,1sth	42	6.30%	67	9.87%	59	7.38%	95	11.46%
Ketoacidosis member ct	75	11.24%	104	15.32%	106	13.25%	135	16.28%
Ketoacidosis events	190		281		301		294	
Hyperglycemia mbr ct	19	2.85%	33	4.86%	37	4.63%	34	4.10%
Hyperglycemia events	24		41		59		46	
Diabetic coma mbr ct	3	0.45%	2	0.29%	7	0.88%	4	0.48%
Diabetic coma events	4		2		7		4	

Figure 4a: UMP/PEP Average Test Strip Cost per Patient by Patient Age

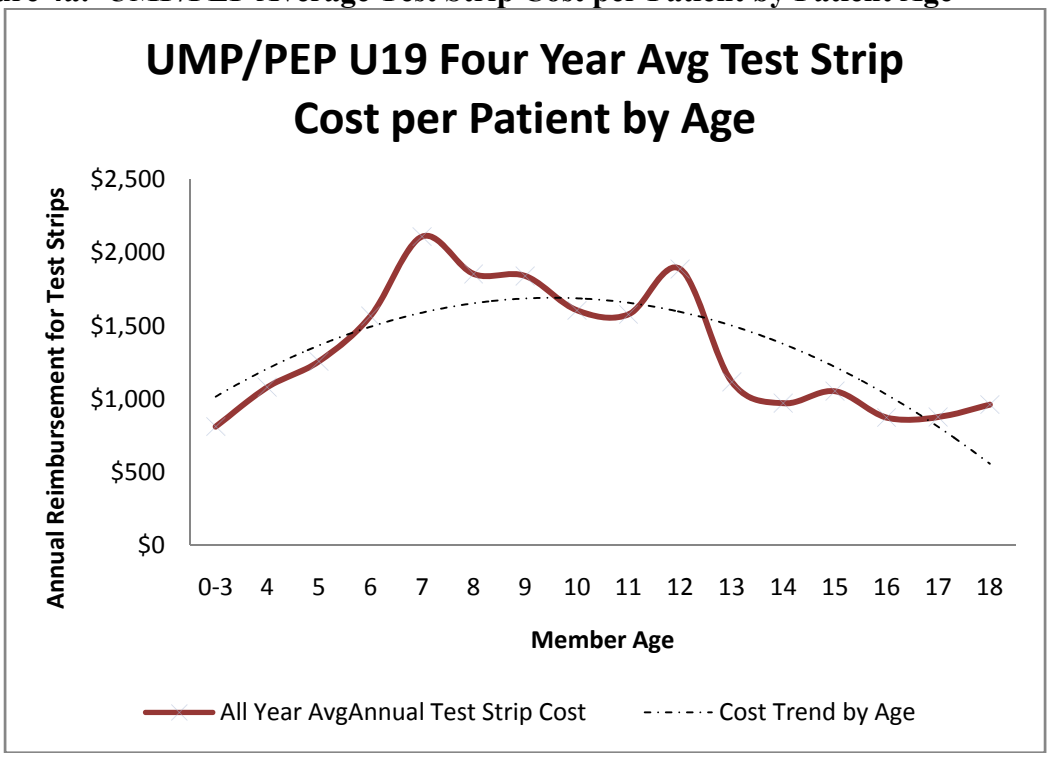
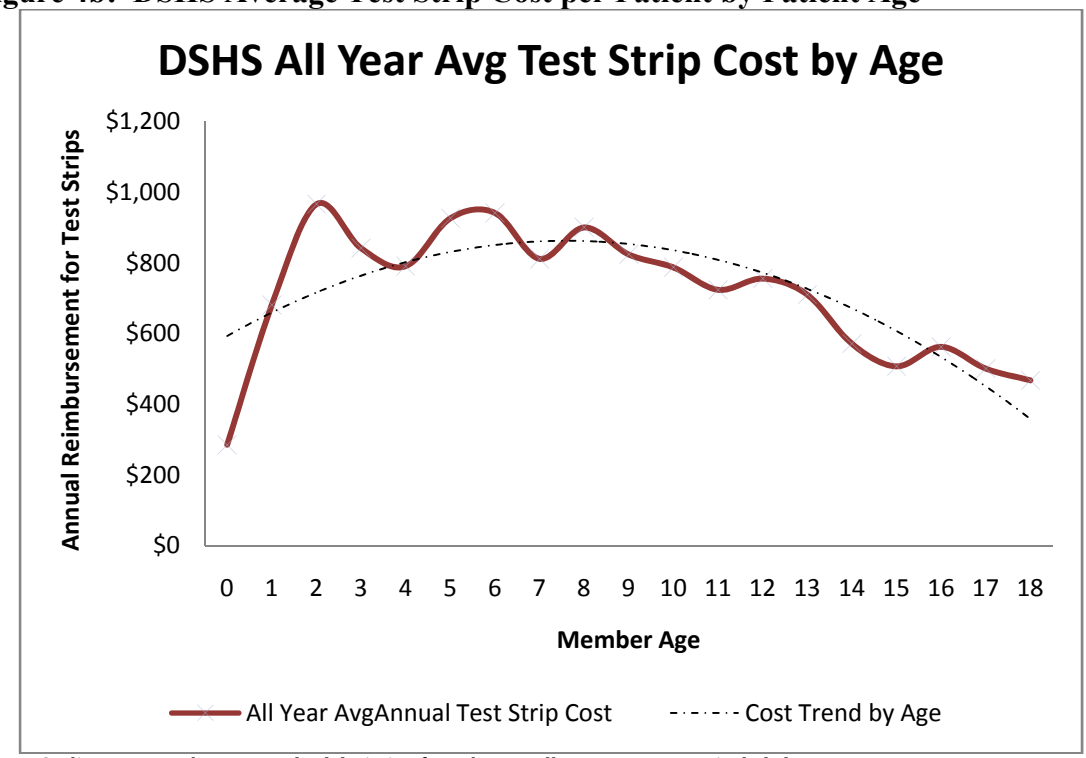


Figure 4b: DSHS Average Test Strip Cost per Patient by Patient Age



Note: Outliers at more than 6x standard deviation from the overall average were not included.

Figure 5a: UMP/PEP Counts and Average age by DM Type and Gender

DM Type / Gender	2006		2007		2008		2009		4 Yr	
	Mbr Ct	Avg Age	Mbr Ct	Avg Age	Mbr Ct	Avg Age	Mbr Ct	Avg Age	Mbr Ct	Avg Age
DM Type 1										
Female	35	12.6	41	12.6	55	13.0	52	13.1	183	12.8
Male	36	14.5	43	13.0	63	13.0	58	13.3	200	13.4
Total DM1	**71**	**13.6**	**84**	**12.8**	**118**	**13.0**	**110**	**13.2**	**383**	**13.1**
DM Type 2										
Female	8	13.3	12	14.9	6	14.5	7	15.0	33	14.5
Male	6	14.5	7	12.9	8	15.0	4	12.8	25	13.9
Total DM2	**14**	**13.8**	**19**	**14.2**	**14**	**14.8**	**11**	**14.2**	**58**	**14.2**
Grand Total	**85**	**13.6**	**103**	**13.0**	**132**	**13.2**	**121**	**13.3**	**441**	**13.3**

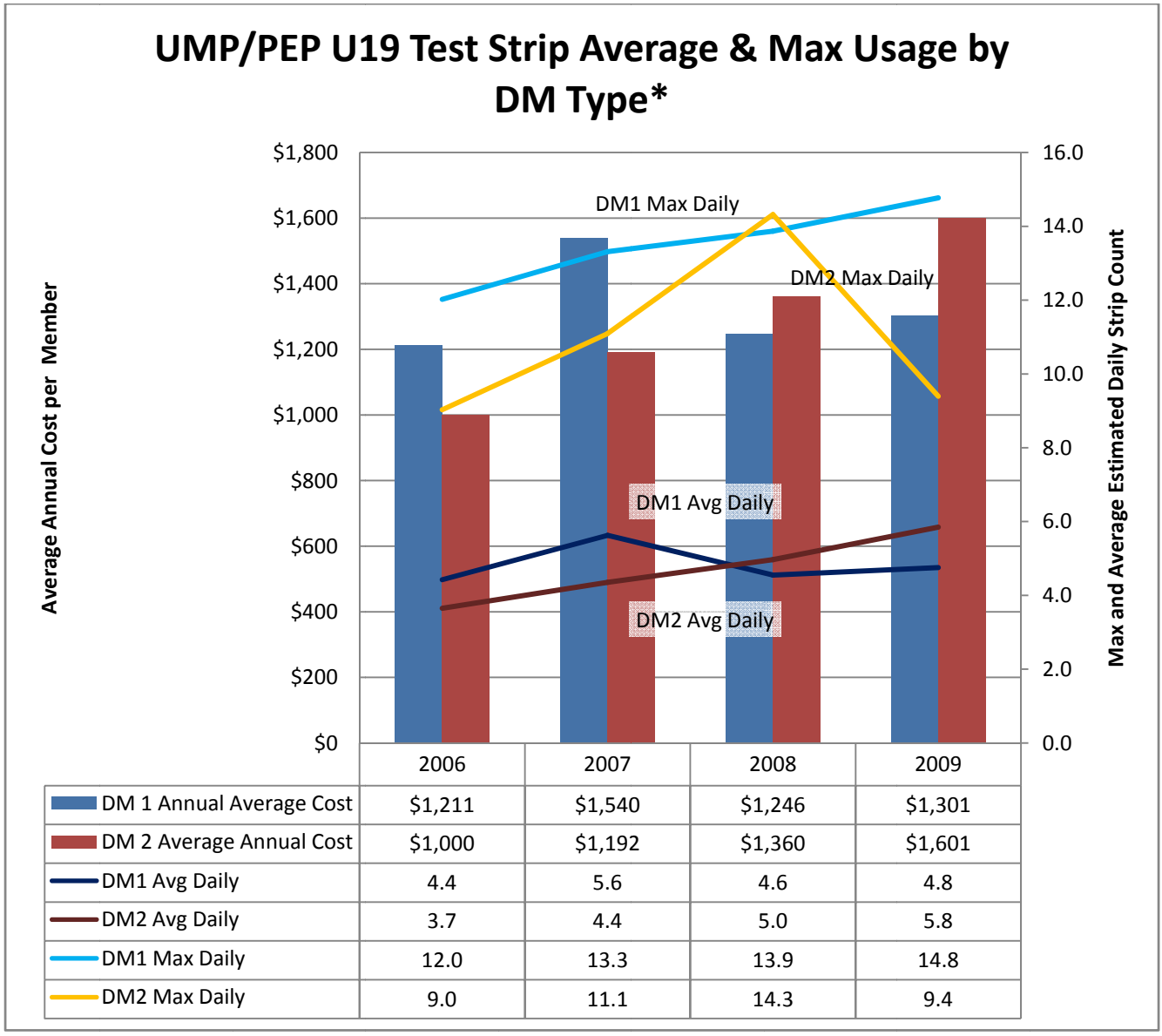
**4 year total patient counts are a separate count of unique patients over 4 year, not the total of annual patient counts.*

Figure 5b: DSHS Counts and Average age by DM Type and Gender

DM Type / Gender	2006		2007		2008		2009		4 Yr	
	Mbr Ct	Avg Age	Mbr Ct	Avg Age	Mbr Ct	Avg Age	Mbr Ct	Avg Age	Mbr Ct	Avg Age
DM Type 1										
Female	256	12.6	278	12.7	313	12.9	310	12.9	642	12.8
Male	217	12.8	232	12.7	278	12.7	291	13.1	574	12.8
Total DM1	**473**	**12.6**	**510**	**12.7**	**591**	**12.8**	**601**	**13.0**	**1216**	**12.8**
DM Type 2										
Female	91	14.5	82	15.3	103	15.0	116	13.8	312	14.6
Male	93	12.5	82	11.8	91	13.6	102	13.8	320	13.0
Total DM2	**184**	**13.5**	**164**	**13.6**	**194**	**14.3**	**218**	**13.8**	**632**	**13.8**
Grand Total	**657**	**12.9**	**674**	**12.9**	**785**	**13.2**	**819**	**13.2**	**1848**	**13.1**

**4 year total patient counts are a separate count of unique patients over 4 year, not the total of annual patient counts.*
Note: Patients for whom no clear diagnosis of type 1 or type 2 could be determined were excluded from analysis.

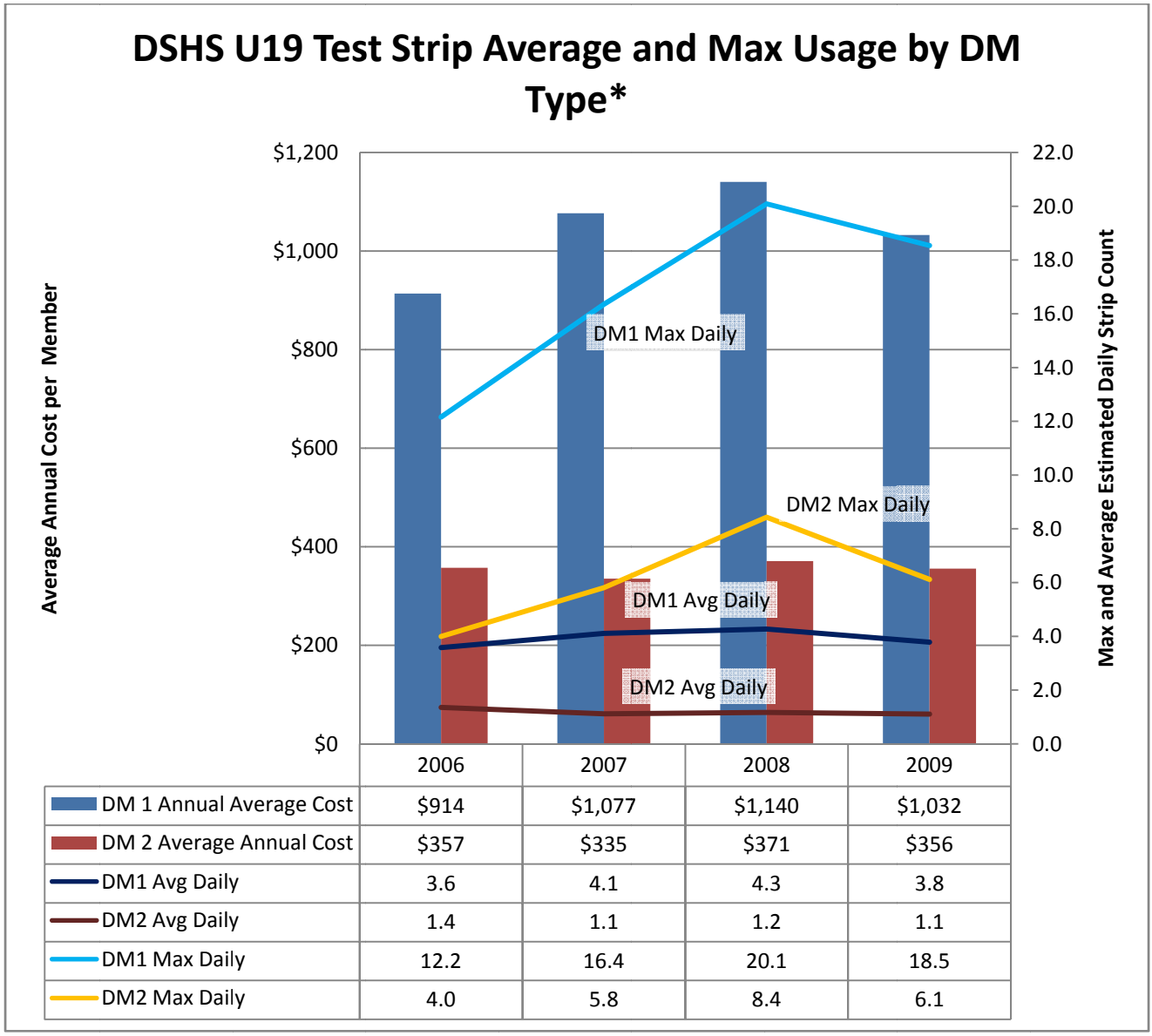
Figure 6a: UMP/PEP Test Strip Average Usage by DM Type*



	2006	2007	2008	2009
DM 1 Annual Average Cost	$1,211	$1,540	$1,246	$1,301
DM 2 Average Annual Cost	$1,000	$1,192	$1,360	$1,601
DM1 Avg Daily	4.4	5.6	4.6	4.8
DM2 Avg Daily	3.7	4.4	5.0	5.8
DM1 Max Daily	12.0	13.3	13.9	14.8
DM2 Max Daily	9.0	11.1	14.3	9.4

**Excludes members using Continuous Glucose Monitoring*
Note that test strip usage was estimated from payment data using $.75/strip. This high estimate of strip cost may artificially lower our estimate of strip usage among this population.

Figure 6b: DSHS Test Strip Average Usage by DM Type*



	2006	2007	2008	2009
DM 1 Annual Average Cost	$914	$1,077	$1,140	$1,032
DM 2 Average Annual Cost	$357	$335	$371	$356
DM1 Avg Daily	3.6	4.1	4.3	3.8
DM2 Avg Daily	1.4	1.1	1.2	1.1
DM1 Max Daily	12.2	16.4	20.1	18.5
DM2 Max Daily	4.0	5.8	8.4	6.1

**Patients for whom no clear diagnosis of type 1 or type 2 could be determined were excluded from analysis*
Test strip daily usage was calculated using the number of strips purchased per year, with a per strip average reimbursement ranging from $.71 to .75 each.

HEDIS MEASURES: Codes to Use to Identify Diabetes

Description	ICD-9-CM Diagnosis
Diabetes	250, 357.2, 362.0, 366.41, 648.0

Related Medical Codes			
Code Type	**Code**	**Description**	**Category**
Diagnosis	**250.****	250.x1, 250.x3 = DMI 250.x0,250.x2 = DMII	Selection Diagnosis
	250.1*	Diabetes with ketoacidosis	Adverse event
	250.3*	Diabetes with coma	Adverse event
	250.8	Diabetic hypoglycemia/ Hypoglycemic shock	Adverse event
CPT Codes	**95250**	GLUCOSE MONITORING, CONT	CGM
	95251	GLUC MONITOR, CONT, PHYS I&R	CGM
	92962	Glucose blood by glucose monitoring device(s) cleared by the FDA specifically for home use	DME
	83036	Glycated Hemoglobin Tests	Stability monitoring
	99282-5	Emergency Room Visits	Adverse event
	99291	Critical Care – First hour	Adverse event
HCPCS Codes	**A4230/1**	Insulin Infusion Pumps	Stability monitoring
	A4233	Batteries for home blood glucose monitors	Supplies
	A4234	Batteries for home blood glucose monitors	Supplies
	A4235	Batteries for home blood glucose monitors	Supplies
	A4236	Batteries for home blood glucose monitors	Supplies
	A4253	Blood glucose test or reagent strips for home blood glucose monitor, per 50 strips	Supplies
	A4255	Platforms for home blood glucose monitor, 50 per box	Supplies
	A4256	CALIBRATOR SOLUTION/CHIPS	Supplies
	A4258	LANCET spring loaded device, EACH	Supplies
	A4259	LANCETS PER BOX	Supplies
	A9275	Home glucose disposable monitor, includes test strips	Supplies
	A9276	DISPOSABLE SENSOR, CGM SYS	CGM
	A9277	EXTERNAL TRANSMITTER, CGM	CGM
	A9278	EXTERNAL RECEIVER, CGM	CGM
	E0607	BLOOD GLUCOSE MONITOR HOME	DME
	S1030	Continuous non-invasive glucose monitoring device, purchase	CGM

	S1031	Continuous non-invasive glucose monitoring device, rental, including sensor, sensor replacement, download to monitor	CGM

1. Background

Introduction
Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) are two techniques that persons with diabetes use at home to help them maintain blood glucose within a safe range. Children and teenagers 18 years old and under with diabetes have the most to gain from maintaining good glucose control yet present some of the greatest challenges in achieving and maintaining good control. As they will probably have many years at risk, children and adolescents with diabetes are at high risk for microvascular complications related to poor glucose control. Intensive treatment with tight control of blood glucose has become the standard of care for diabetes. Such intensive treatment requires monitoring as part of that regimen: by knowing the blood sugar levels the patient or caregiver can adjust diet, exercise, and insulin appropriately. SMBG has become a standard practice recommendation for patients with type 1 diabetes. This technical review will assesses the value of SMBG and CGM for persons 18 years old and under who have diabetes and use insulin, based on the highest quality evidence available. The primary focus is on evaluation of self-monitoring methods used by patients ≤18 years old (who require insulin) to assess glucose levels at home (versus data used exclusively by providers in a clinical setting) for daily decision making regarding self-care. The majority of these patients will have type1 diabetes.

1.1 The condition

Classification of Diabetes Mellitus
Diabetes mellitus, or diabetes, is a serious chronic disease of various etiologies characterized by elevation of blood glucose. No definitive cure is known at this time. Diabetes is categorized into three major types based on etiology. [7]

a. Type 1 diabetes (T1DM) (formerly called juvenile diabetes or insulin-dependent diabetes mellitus (IDDM)), is an autoimmune disorder that destroys the pancreatic beta islet cells where insulin is made. The damage progresses quickly and completely, leading to death within a few weeks without insulin. Type 1 diabetes is the predominant form of diabetes in children but can occur in adulthood. The risk of T1DM has been linked with certain genes, viral infections, and family history of T1DM or other autoimmune disorders.

b. Type 2 diabetes (T2DM) (formerly called adult onset diabetes mellitus (AODM) or non-insulin dependent diabetes (NIDDM)) is caused by insulin resistance, disordered and inadequate insulin release, and excessive glucose production (gluconeogenesis) in the liver. T2DM is a progressive disease that ultimately requires insulin therapy, although diet, exercise and medications may be effective for the first few years. T2DM occurs more often in adults, but the prevalence in teens and children is increasing. The risk of T2DM is associated with a family history of T2DM, non-white race, obesity, lifestyle and metabolic syndrome.

c. Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy.[8] (Women with type 1 or type 2 diabetes who become pregnant

are described as having "pregestational" diabetes.) The glucose elevation occurs in the last half of pregnancy and usually resolves after delivery. GDM is associated with family history of T2DM diabetes and is associated with increased risk of developing T2DM.
d. Type "other" is a miscellaneous collection of etiologies that damage the beta cell, including infection, cystic fibrosis, trauma, toxins (e.g. alcohol), tumors, and rare genetic disorders. These are uncommon and generally treated like T1DM.

Incidence and Prevalence of diabetes in children
T1DM accounts for 5%-10% of diagnosed diabetes. Approximately 0.2% of the population under 20 years of age has diagnosed diabetes (estimated in 2007), impacting a total of 186,300 young people. [http://diabetes.niddk.nih.gov/dm/pubs/statistics/#d_allages, accessed 10/17/2010]. The SEARCH for Diabetes Survey conducted in 2002 and 2003 estimated that 15,000 youth in the United States were newly diagnosed with T1DM each year and 3,700 youth were newly diagnosed with T2DM each year. The incidence of T1DM was 19 per 100,000 youth and the incidence for T2DM was 5.3 per 100,000 youth per year.[9]

Because the most common form of diabetes in persons ≤ 18 years old *who require insulin* is type T1DM, and no studies were found specific to the use of monitoring in populations ≤ 18 years old with other forms of diabetes, this report focuses on persons ≤ 18 years old with T1DM.

Morbidity, mortality and costs of diabetes in children
Diabetic ketoacidosis (DKA) is the leading cause of hospitalization, morbidity and death in children with T1DM. DKA is characterized by very high glucose levels, severe dehydration, and acidosis and can quickly lead to coma and death. Over 100,000 cases of DKA occur each year in the US.[10] DKA is the presenting illness for 10-70% of children with T1DM, and 5-52% of children with T2DM [11]DKA after initial diagnosis of T1DM is estimated at eight episodes per 100 patient years, with 20% of patients accounting for 80% of the episodes. Mortality for each episode of DKA internationally varies from 0.15-0.31%, with idiopathic cerebral edema accounting for two-thirds or more of this mortality. Risk of DKA is higher in females during menses, children who lack medical resources and miss insulin injections, and those who suffer child neglect [12]Other causes of acute morbidity in children with T1DM include other acute metabolic derangements, infections, pancreatitis, and acute renal and pulmonary complications.

Chronic complications are similar in T1DM and T2DM and are strongly related to the duration of diabetes and glycemic control. [13] Macrovascular complications consisting of heart disease and stroke are approximately 4 times higher in persons with diabetes than those without. Microvascular complications include retinopathy, nephropathy and neuropathy. Diabetic retinopathy is the leading cause of new cases of blindness among adults ages 20 to 74 years, causing 12,000 to 24,000 new cases of blindness each year. Diabetes is also a major cause of cataracts and glaucoma. In 2007, diabetes was the second leading cause of end-stage renal disease (ESRD), accounting for 44% of new cases of ESRD in the USA.[14] In 2007, 48,172 persons with diabetes started dialysis. .A total of 178,689 people with end-stage kidney disease due to diabetes were living on chronic dialysis or with a kidney transplant in the United States and Puerto Rico in 1997.[13] Over 60 percent of persons with diabetes develop mild to severe neuropathy, including distal symmetric polyneuropathy (impaired sensation in feet and hands),

mononeuropathy (e.g. carpal tunnel syndrome), erectile dysfunction, and autonomic neuropathy (e.g. gastric paresis). Neuropathy is a major contributing cause of lower-extremity amputations.More than 60 percent of nontraumatic lower-limb amputations occur in people with diabetes. About 71,000 nontraumatic lower-limb amputations were performed in people with diabetes in 2004.

Pregnancy relation complications in poorly controlled diabetes before during the first trimester of pregnancy include a 5-10% risk of major birth defects and 15 to 20% risk of spontaneous abortions. [13]Poorly controlled diabetes during the second and third trimesters of pregnancy can result in macrosomia, increased failure to progress, shoulder dystocia and Cesarean sections. [8]

Other diabetes related complications include increased risk of infections, cancer and other autoimmune disorders including celiac sprue, thyroid disease, rheumatoid arthritis, and vitiligo.

Mortality – Diabetes was the seventh leading cause of death in 2007, accounting for 71,382 deaths.[15]. This is an underestimate of the impact of diabetes because all cardiovascular death takes precedence per mortality coding regulations. Death rates are twice as high among middle-aged persons (i.e., persons aged 45 to 60 years) with diabetes than among persons without diabetes. Mortality rates between 1971 and 2000 decreased for persons without diabetes and to a lesser extent for men with diabetes, but showed no change for women with diabetes. [16]

Costs of diabetes for all persons with diabetes in 2007 exceeded $174 billion. The medical expenditures for persons with diabetes are approximately 2.3 times higher than the expenditures for persons who do not have diabetes. Approximately 1 in 10 health care dollars is attributed to diabetes. Indirect costs include factors such as increased absenteeism, reduced productivity, and lost productive capacity due to early mortality. About two-thirds of the excess cost of diabetes is due to direct medical expenditures and one-third is attributed to loss of productivity. [17]

Insulin Therapy

Insulin therapy is the only effective therapy for persons with T1DM and is used for T2DM who cannot produce sufficient insulin [18] and pregnant women of any type with elevated glucose.[8] The insulin dose depends on body weight, age, food intake, and activity. Insulin requirements increase with stress, infection, and certain medications (e.g. steroids). Insulin therapy is more effective if it mimics the insulin release pattern in persons without diabetes. About half of the insulin is released continuously, and the other half is released after meals in a quick, large burst. Persons with T1DM also need extra insulin during the night called the dawn effect, but the timing of this increased need varies by pubertal status.[19] Children going through growth spurts have sporadic releases of growth hormone that has some insulin-like effects, further complicating the dosing decisions.

Multiple daily injections (MDI) attempts to mimic the normal insulin release pattern using a long acting insulin for basal insulin coverage once or twice a day and rapid onset insulin injected at each meal [18] This system attempts to carefully match carbohydrate intake, exercise, and insulin dose and timing. The glucose value obtained from pre-meal testing is used to calculate the correction dose of insulin to return the glucose to desired goal. The patient then estimates how

much insulin will be needed for the upcoming meal and adds that to the correction dose. The final dose is then adjusted for planned activity. Patients benefit from knowing how to do carbohydrate counting, which typically requires an approximation of planned carbohydrate intake, to calculate the needed insulin. The older insulins Regular and NPH didn't mimic the normal insulin release profile very well and were absorbed unreliably. Analog insulins now provide more reliable options for insulin therapy with shorter or longer action to better mimic a natural insulin curve. Routine dietary intake and exercise make it easier to match insulin, but routine is difficult for children.

Continuous subcutaneous insulin infusion (CSII) is a technology that releases insulin from a small pump through a small catheter inserted under the skin that permits greater flexibility in dosing. The first portable insulin pump was approved by the FDA in 1983; since then pumps have become smaller, more comfortable and more reliable. The electronic controls on the meters allow for changes in the baseline or mealtime dosages. Total daily insulin dose is about 20% less than with MDI. A Cochrane Review of CSII versus MDI published in 2010 found that CSII improved glycemic control (A1C change of -0.3% (95% CI −0.1 to −0.4) reduced severe hypoglycemia, and improved quality of life measures. Both parents and children indicated a preference for CSII. There was insufficient evidence regarding adverse events, mortality, morbidity and costs.[20] Now, with the ability to change the insulin dose on a moment to moment basis, patients needed a better method to obtain frequent glucose measurements.

Hypoglycemia

Hypoglycemia, or low blood glucose, is defined as glucose below 70 mg/dl.[18] Hypoglycemia can occur from too much insulin or exercise or too little food intake. Severe hypoglycemia is defined as the need for assistance, but children and toddlers will also require assistance for recognition and treatment. The body's counter-regulatory mechanisms attempt to stabilize the blood glucose and cause the symptoms that signal impending hypoglycemia. Initial symptoms include hunger, confusion and unsteadiness, followed by diaphoresis, tachycardia, and finally seizures and coma. Persons who have had repeated episodes of hypoglycemia and children under the age of 7 do not experience these warning symptoms and are said to have hypoglycemia unawareness. Severe hypoglycemia is three times more common in children compared to adults with T1DM [21,22]and persons with T1DM are three times more likely to experience hypoglycemia compared to those with T2DM. [21,23]Hypoglycemia during the night may not be detected until the child has a seizure, but milder hypoglycemia is suggested by night sweats or vivid nightmares. A study using CGM in adults and children with T1DM found hypoglycemic events during 8.5% of the nights and one-fourth of the episodes lasted for at least 2 hours.[24] Severe hypoglycemia can damage the developing brain permanently. Two recent meta-analyses found that children with diabetes have mildly lower cognitive scores across most cognitive domains, and these differences are most pronounced and pervasive for those with early onset diabetes (diagnosis before age 4-7 years). [25,26]Hypoglycemic comas and convulsions have been estimated to occur at a rate of 20 events per 100 patient years in children using conventional therapy.[27] Frequent blood glucose monitoring is critical to identify and prevent hypoglycemia.

Children's smaller size, erratic dietary intake, and unpredictable exercise pattern make it difficult to predict insulin doses to achieve glycemic control without incurring hypoglycemia. [28]The

normal developmental issues for children and adolescents of increasing autonomy, peer pressure and desire of "not being different" increase the difficulty of adhering to a rigorous diet, exercise and insulin regimen. Very young children also have limited language and cognitive abilities that impair their ability to detect and report the early signs of hypoglycemia.

Assessment of long-term glucose control
The hemoglobin A1C, or A1C, is a blood test to assess long-term blood glucose control in clinical practice and research settings.[29] The hemoglobin in red blood cells forms a stable bond with glucose, called glycated hemoglobin or A1C. The test reflects the glucose control over the past 90−120 days (the lifespan of a red blood cell) and is reported as the percentage of red blood cells that have been glycated. The upper range of normal is 6%. By 1990 over 20 different assays were available with various names including glycosylated hemoglobin, glycohemoglobin, HbA1C, HbA1, or A1C. Each assay used a slightly different analytic method resulting in a different range of normal, hampering efforts to compare results among research studies or set national guidelines. The National Glycation Hemoglobin Standardization Project (NGSP) was established in 1993 to develop a standard test for glycated hemoglobin and improve accuracy of participating laboratories. [30]By the end of 2002, 98% of the 2000 labs that were surveyed reported they were using the standard HbA1C test as compared to 50% in 1993 and 97% were using the NGSP-certified method. The ADA suggested that the standardized test be called "A1C test". [29]The A1C test does not provide accurate results for persons with rapid or delayed red cell turnover, such as anemia, hemoglobinopathies, or renal failure. Glycation can occur with other blood proteins[31] The glycation of albumin is called fructosamine, and provides summary information about glucose control over the prior 30 days. It is often used for persons who have hemoglobinopathy, renal failure, or unexpected A1C levels. A1C and fructosamine provide an assessment of the average glucose over a time interval, but provide no information on the variability of the glucose levels over that same time interval. Some research suggests that increased variability is associated with increased cardiovascular adverse events and additional research on the impact of variability on health outcomes is needed.

The American Diabetes Association suggests that A1C should be obtained every 3 months on anyone who is on insulin therapy and suggests that the A1C goal for adolescents should be under 7.5%, school age children (age 6-12 years) below 8%, and toddlers and preschool (under 6 years) 7.5% to 8.5%. [18]The A1C goals for children are higher than those recommended for adults due to the difficulty of achieving good control without incurring undue hypoglycemia. The A1C goal should be individualized for each patient. By contrast, the recommended glycemic thresholds for pregnant women are considerably more stringent than the guidelines for the non-pregnant person. [32]

1.2 The technologies and comparators

A. Urine testing
Urine testing for glucose using chemicals embedded on paper strips was introduced around 1910 and replaced the reliance on clinical symptoms of polyuria and polydipsia .[33] Glucose begins to appear in the urine when the blood glucose approaches 180 mg/dl, but this renal threshold is often lower for children and pregnant women and during illness. Urine test results are

retrospective, semiquantitative, readily influenced by hydration status and cannot provide any information on hypoglycemia. Urine testing was abandoned when home blood glucose monitors became widely available after 1975, and is no longer recommended.

B. Self-monitoring blood glucose (SMBG)

Self-monitoring blood glucose (SMBG), sometimes called intermittent monitoring, is a technique for testing blood glucose using a portable glucose meter designed for home use.[31] Glucose meters incorporate paper strips impregnated with glucose oxidase, glucose dehydrogenase, or hexokinase. When a drop of blood is added, these chemicals convert blood glucose into gluconic acid and hydrogen peroxide that can be quantified by colorimetric methods, reflectance photometry, absorbance photometry, or electrochemistry. Whole blood has about 15% less glucose than plasma, so meters translate the result into a plasma equivalent to make the results comparable to results obtained in a clinical lab. The first SMBG meter was approved for home use in 1975 and became the preferred method for home monitoring within a decade.[34]

Over time, glucose meters have become smaller, easier to use and more accurate, but still are not as accurate as testing in a hospital laboratory. The International Organization for Standardization (http://www.iso.org) recommends that more than 95% of readings be within 15 mg/dl) for glucose readings that are less than 75 mg/dl (4.2 mmol/L), and within 20% for higher blood glucose values when compared with the standard YSI 2700 reference method (Yellow Springs Instruments, Yellow Springs, Ohio). The College of American Pathologists (CAP) publishes the results of a voluntary proficiency testing program. Considerable imprecision between different meters from the same manufacturer and between different types of meters have been documented.[33]

A more common source of inaccuracy comes from operator-related errors, including calibration failures, poor hand washing, dirty meters, high environmental temperature, improper handling or storage of glucose strips, insufficient sample volume and ingestion of certain drugs (e.g. ascorbic acid, acetaminophen). Improvements in meter design to reduce human error include alerts if the sample of blood is too small, and calibration is sometimes embedded into the strip. In the 1980's, studies documented that patients failed to record the glucose values accurately in their paper log, so meters now have memory capability and many can perform simple summary statistics. The meters can download the data into a computer for further analysis or to export to a provider over the internet. Patient education on proper technique and review of limitations of the accuracy of the meter should be taught initially and reviewed periodically with the patient to improve accuracy.

A major barrier to testing is the discomfort associated with puncture of the fingertip. Improved lancet blade design and devices to control the depth of the prick have made the sample collection process less painful. Recent meters have been approved to test alternate sites on the forearm or thigh, where there are fewer pain receptors. The results from these alternate testing sites is similar to testing from the fingertip before meals (when blood glucose is fairly stable), but the results can differ significantly when the blood glucose is rapidly changing. Fingertip testing is preferred in circumstances of rapidly changing blood glucose levels including after a meal, injection of a rapid acting insulin or exercise.

Other barriers to testing include inconvenience, lack of a private place to test, and lack of safe sharp disposal systems, lack of education on the importance of testing, and costs of the strips. Psychological barriers include the denial and frustration over extreme values. SMBG provides an instantaneous reading of current blood glucose level, but cannot indicate whether the glucose level is on its way up or down.

C. Continuous glucose monitoring (CGM) is a technology that measures glucose every few minutes (thus isn't really continuous). The methodology was developed to provide frequent blood glucose data for persons who had difficulty achieving control or were using CSII.

The Minimed Continuous Glucose Meter System (CGMS) Gold (Medtronic Minimed, Northridge, CA), approved in 1999, was the first CGM approval by the FDA.[35]The meter incorporated glucose oxidase coating on a wire that was placed subcutaneously. Readings were obtained every 5 minutes for 3 days. The meter was directly wired to the sensor, making it difficult to bathe or engage in sports. The accuracy, especially for hypoglycemia, was substandard.[36] Because of the poor accuracy; the FDA specified that CGM should not be used for treatment decisions. [37] Thus, the meter readings were blinded and only available retrospectively. This meter is described in the literature as "Holter meter-like," "retrospective analysis" or "professional analysis data." Most of the early studies of CGM used this meter. A meta-analysis of these early studies failed to show improved A1C ,[38] but other analyses noted that clinicians made more appropriate dose changes and patients improved their diabetes-related behavior [37,39]In 2005, the FDA approved a new model with alarms for hypo- and hyperglycemia, called the Minimed Guardian. In 2005 the FDA approved the Guardian for real time data display.

The GlucoWatch_Biographer (Cygnus, Redwood City, CA) was the first FDA real-time approved CGM. The initial approval for adults was granted in 2001 and expanded to children age 7 to 17 years in 2002.[40] The meter was fashioned to look like a wrist watch. The Glucowatch incorporated transdermal technology by drawing glucose through the skin using a process called reverse iontophoresis. A 20 minute lag occurred between the plasma glucose and the GlucoWatch readings. The device required a 2 hr warm-up period and calibration every 13 hrs. Up to 36 readings could be obtained in a 12 hour period. Alarms could be set to detect hypo- and hyper-glycemia. The meter had a high false positive rate for the detection of hypoglycemia, yet often skipped readings with perspiration (a common sign of hypoglycemia).[36]The GlucoWatch also caused skin irritation. The product was taken off the market in 2007 after the patent was purchased by Animas, a large CSII company and subsidiary of Johnson & Johnson. No non-invasive glucose meter is currently available in the US, but a noninvasive meter called the Pendra (Pendragon Medical, Zurich, Switzerland) is available in Europe.

Currently, four CGM systems are approved and available.[4] Only the Paradigm REAL-Time System and Guardian REAL-Time System (Pediatric Versions) are currently approved for use in persons ≤18 years old. All of these meters incorporate minimally invasive sensors placed subcutaneously with signals sent wirelessly to the monitor. The Dexcom (San Diego, CA; Dexcom SEVEN) and Medtronic (ParadigmReal-Time and Paradigm Guardian) use a glucose oxidase methodology. The enzyme is embedded onto the sensor so that glucose and water will form gluconic acid and

hydrogen peroxide. Under a basal electric current, the hydrogen peroxide dissociates, and a modified charge is produced directly proportional to the concentration of the glucose. The Freestyle Navigator (Abbott Diabetes Care, Alameda, CA) uses oxidase coupled with osmium-based mediator molecules anchored on a polymeric backbone film termed "wired enzyme" technology. Glucose levels are sent to a remote monitor located up to 10 feet away from the sensor. The data can coordinate with an insulin pump or download later to a computer for review by the user and/or provider. Alarms can be set to signal low or high glucose levels; some meters also alarm for rapid decrease or increase in the glucose levels.

The CGM value may lag the plasma glucose level.[4] This occurs because diffusion of glucose from the capillaries into the interstitial space where it is measured by CGM can take 10 to 20 minutes, then measurement of the glucose by the CGM sensor takes about 7 to 15 minutes before it is displayed. This lag time can make the meter appear inaccurate, especially when blood glucose levels are changing quickly. The FDA has not approved any CGM device for insulin dosing decisions, so persons using CGM must still conduct SMBG several times a day. In addition, SMBG tests are needed to calibrate the CGM. The accuracy of CGM standards are the same for SMBG technology. CGM data is assessed in several ways. The mean absolute difference (MAD) and median absolute difference (MedAD) are computed as the mean/median of the absolute values of the differences between sensor readings and reference blood glucose values. The mean absolute relative difference (MARD) and the median absolute relative difference (MedARD) are the absolute differences expressed as a percentage of the reference blood glucose values.

The abundance of data provided by CGM created a new difficulty in communicating the results, especially when a single summary value is desired. [41] A *glucose curve* can be constructed by plotting the glucose levels vs. time on a graph and connecting each of the glucose measurements. The *area under the curve (AUC)* provides a single number summary of the total glucose exposure. The AUC calculated by using the trapezoidal method (the polygon defined by the two adjacent data points and the zero points at the corresponding times) yields similar results to more complex mathematical modeling of the glucose curve. To control for the differences in the initial glucose level, some researchers subtract the baseline glucose value from all points before integration, yielding an *"incremental area"* This method can yield negative results, so others avoid this problem by reporting only the positive values above baseline, termed "positive incremental area." Truncating the data in either fashion discards valuable data about the glucose variability and yields biased estimates. Complex modeling of the curves can be used in regressions to determine differences between treatment and control groups, much like an ANOVA, but takes great mathematical sophistication. Other researchers just subtract the AUC for the control group from the AUC of the treatment group. One of the simplest solutions to compare the results of two groups is to calculate the sum or mean of all of the data points collected at a specified interval over a defined period of time for each group. Another method compares minutes in a particular glycemic band and is particularly relevant for assessment of hypoglycemia.

Presenting a graphical display of an "average" glucose curve for a group of persons is problematic. Plotting the average of the glucose values for the group at each time point (curve of

averages) creates a curve that is flatter and wider than any one of the constituent curves and thus does not accurately reflect the "average glucose curve". The preferred method is to fit a curve for each subject, then average the parameters of the curve for the entire group. This curve then can be used by clinicians to compare with the glucose curve in their patients and by researchers to assess the characteristics of the average glucose curve.

Summary

Improved methods to monitor blood glucose, especially for hypoglycemia, could make it safer to achieve lower glucose levels. Glucose monitoring should be less intrusive, be easy to use and incorporate into insulin dose changes, and minimize discomfort. Meters intended for use with children need to be smaller and indestructible. The current goal for CGM technology is to integrate with CSII into a "closed loop system" that would eliminate the need for complex management of insulin, diet and exercise.

1.3 Clinical guidelines

The National Guideline Clearinghouse (NGC), along with major bibliographic databases (e.g. PubMed), was searched for guidelines related to the use of self-monitoring blood glucose (SMBG) and continuous glucose monitoring (CGM) in children. Key word searches (and combinations of key word searches) performed included: "*self-monitoring blood glucose*", "*continuous glucose monitoring*", "*type 1 diabetes*", "*children*" and "*adolescents*". A total of 16 potentially relevant documents were recovered of that five addressed the population of interest and are summarized below. Some guidelines that do not address children but do provide recommendations on patients with type 1 diabetes are briefly included at the end of this section. Guidelines from the following organizations addressed the population of interest:

1. American Diabetes Association (ADA)
2. Diabetes Coalition of California, California Diabetes Program
3. International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2009 Compendium
4. National Institute for Health and Clinical Excellence (NICE)
5. American Association of Clinical Endocrinologists (AACE)
6. British Society of Pediatric Endocrinology

Evidence grading systems for clinical practice recommendations vary across organizations, as do methods of guideline creation. The ADA and ISPAD use A-C to denote level of evidence support from high quality evidence (Grade A based on well-conducted trials, meta-analyses) to low quality evidence (Grade B poorly controlled or uncontrolled trials, case reports/series) and give a rating of E to denote expert consensus or clinical experience. NICE recommendations graded A-D based on study quality level of evidence ratings from I –IV. A grade is based directly on level I evidence and D based on Level IV evidence directly or extrapolated from levels I, II or III. They also note if the grade is based on a NICE technology appraisal. Additional information may be found on the NGC website.

<u>American Diabetes Association (ADA)</u>

The following guidelines are from the ADA publication "Standards of medical care in diabetes--2010." *Diabetes Care*33 Suppl 1: S11-61.[18] The information provided is based on evidence from published studies whenever possible and, when not, is supported by expert opinion or consensus. The level of evidence (A-E) supporting each guideline is provided when available.

Frequency of self-monitored blood glucose (SMBG)
SMBG in general has been extensively reviewed by the ADA and is recommended for patients of all ages with type 1 diabetes. The 2010 report did not specifically address frequency for children, however, in a statement published in 2005 by the ADA entitled Care of Children and Adolescents with Type 1 Diabetes[28] it is recommended that SMBG be performed at least four times daily.

Continuous glucose monitoring (CGM)
"Continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a useful tool to lower A1C in selected adults (age ≥ 25 years) with type 1 diabetes. (A) Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. (C) CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. (E)"

Glycemic goals (E)
"Consider age when setting glycemic goals in children and adolescents with type 1 diabetes, with less stringent goals for younger children." In this statement, age specific A1C values are listed with the caveat that goals should be individualized and lower goals may be reasonable based on benefit-risk assessment:

- Toddler and preschoolers, 0–6 years: 7.5%–8.5%
  - Rationale: high risk and vulnerability to hypoglycemia
- School age, 6–12 years: < 8%
  - Rationale: risks of hypoglycemia and relatively low risk of complications prior to puberty
- Adolescents and young adults, 13–19 years: < 7.5%
  - Rationale: risk of severe hypoglycemia; developmental and psychosocial issues; a lower goal (< 7.0%) is reasonable if it can be achieved without excessive hypoglycemia

<u>Diabetes Coalition of California, California Diabetes Program</u>
"Basic guidelines for diabetes care." Sacramento (CA): Diabetes Coalition of California, California Diabetes Program; 2008.[42] Published evidence demonstrating efficacy or effectiveness and expert opinion were used in compiling this report and are consistent with the ADA's Clinical Practice Recommendations. This guideline addresses adults, children, and adolescents with type 1 and type 2 diabetes mellitus. Only information specifically related to children/adolescents with type 1 diabetes is reported below:

SMBG testing
"Typically test at least 4x/daily."

Lab exams

"A1C should be checked 1–2/year if stable, quarterly if treatment changes or if not meeting goals. Target goal < 7.0% or < 1% above lab norms. For children, modify as necessary to prevent significant hypoglycemia."

"Microalbuminuria should be checked beginning with puberty once the duration of diabetes is > 5 years unless proteinuria has been documented."

Self-care behaviors
"…as appropriate for child's developmental stage."

International Society for Pediatric and Adolescent Diabetes (ISPAD)
ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. "Assessment and monitoring of glycemic control in children and adolescents with diabetes." *Pediatr Diabetes*10 Suppl 12: 71-81.[43] The level of evidence (A-D) supporting each guideline is provided when available.
In summary:

> "SMBG is an essential tool in the optimal management of childhood and adolescent diabetes and, when financially possible, should be made available for all children with diabetes. The cost of BG monitoring is very expensive and in many countries the cost relative to the cost of living may make this technology unavailable. However, all centers caring for young peoplewith diabetes should urge nations, states, and health care providers to ensure that children and adolescents with diabetes have adequate glucose monitoring supplies. It should be recognized that without accurate monitoring, the risks of acute crises and long-term vascular and other damaging complications are greatly increased leading to high levels of health care costs and personal disability."

The specific recommendations are as follows:
Frequency of self-monitored blood glucose (SMBG)
"SMBG should be prescribed at a frequency to optimize each child's diabetes control, usually 4–6 times a day, because frequency of SMBG correlates with glycemic control." (A, B)

Continuous glucose monitoring (CGM)
"Continuous monitoring devices are becoming available that may particularly benefit those with hypoglycemic unawareness, as the devices will alarm when glucose is below a specified range or with rapid rate of fall of glucose." (A, B)

Glycemic goals (A, B)
"The target HbA1C for all child age-groups is recommended to be < 7.5%."

"Every child should have a minimum of one measurement of HbA1C per year. Ideally, there should be four to six measurements per year in younger children and three to four measurements per year in older children."

"Targets for all age-groups include the requirement for minimal levels of severe hypoglycemia and absence of hypoglycemia unawareness."

"When hypoglycemia unawareness is present, glycemic targets must be increased until hypoglycemia awareness is restored."

National Institute for Health and Clinical Excellence (NICE)

Below is a summary of the findings from the following report commissioned by NICE: National Collaborating Centre for Women's and Children's Health (NCC-WCH). "Type 1 diabetes: diagnosis and management of type 1 diabetes in children and young people." London (UK), Royal College of Obstetricians and Gynecologists. Sept 2004.[44] The guideline was developed by a multi-professional and lay working group (the Guideline Development Group, GDG) convened by the NCC-WCH that provided methodological support, undertook systematic searches, retrieval and appraisal of the evidence, and wrote successive drafts of the guideline. The level of evidence supporting each guideline is provided.

Frequency of self-monitored blood glucose (SMBG)

"…who are trying to optimise their glycaemic control and/or have intercurrent illness should be encouraged to measure their blood glucose levels more than four times per day." (GPP, Good practice point based on the view of the GDG)

"…should be encouraged to perform frequent blood glucose monitoring as part of a continuing package of care that includes dietary management, continued education and regular contact with their diabetes care team." (C)

Continuous glucose monitoring (CGM)

"…who have persistent problems with hypoglycaemia unawareness or repeated hypoglycaemia or hyperglycaemia should be offered continuous glucose monitoring systems." (B)

Glycemic goals

"…should be encouraged to use blood glucose measurements for short-term monitoring of glycemic control because this is associated with reduced levels of glycated haemoglobin." (A)

"…the target for long-term glycaemic control is an HbA1C level of less than 7.5% without frequent disabling hypoglycaemia and [the child's] care package should be designed to attempt to achieve this." (A)

"…the optimal targets for short-term glycaemic control are a preprandial blood glucose level of 4–8 mmol/l and a postprandial blood glucose level of less than 10 mmol/l." (D)

"… using multiple daily injection regimens should be encouraged to adjust their insulin dose if appropriate after each preprandial, bedtimeand occasional night-time blood glucose measurement." (D)

"… using twice-daily injection regimens should be encouraged to adjust their insulin dose according to the general trend in preprandial, bedtime and occasional night-time blood glucose measurements." (D)

"…should be offered testing of their HbA1C levels two to four times per year (more frequent testing may be appropriate if there is concern about poor glycemic control)." (D)

"Current HbA1C measurements should be made available in outpatient clinics because their availability can lead to immediate changes in insulin therapy and/or diet and so reduce the need for follow-up appointments." (D)

American Association of Clinical Endocrinologists (AACE)
In 2010, the AACE published a Consensus Statement regarding CGM using evidence compiled by its Continuous Glucose Monitoring Task Force. Blevins TC, Bode BW, Garg SK, et al. "Statement by the American Association of Clinical Endocrinologists Consensus Panel on Continuous Glucose Monitoring" *Endocr Pract.* 2010; 16(No. 5): 730-745.

Personal CGM is recommended for patients with type 1 DM and following characterisctics: "hypoglycemic unawareness or frequent hypoglycemia; HbA_{1c} over target, or with excess glycemic variability (eg, hypoglycemia judged to be excessive, potentially disabling, or life-threatening); requiring HbA_{1c} lowering without increased hypoglycemia; during preconception or pregnancy."

"Personal CGM use is recommended for children and adolescents with type 1 DM who have achieved HbA_{1c} levels less than 7.0% (these patients and their families are typically highly motivated); youth with type 1 DM who have HbA_{1c} levels of 7.0% or higher and are able to use the device on a near-daily basis."

"The following patients might be good candidates for personal CGM, and a trial of 2 to 4 weeks is recommended: youth who frequently monitor their blood glucose levels; committed families of young children (< 8 years old), especially if the patient is having problems with hypoglycemia."

"Intermittent use of profession CGM may be useful for youth with type 1 DM who are experiencing changes to their diabetes regimen or have problems with: nocturnal hypoglycemia/dawn phenomenon; hypoglycemia unawareness; postprandial hyperglycemis."

British Society of Pediatric Endocrinology
Below is a summary of the findings from the following report: "Continuous glucose monitoring: consensus statement on the use of glucose sensing in outpatient clinical diabetes care-2009."[45]

Proven clinical indication:
"To lower HbA1C, when this remains above the individual's target despite optimized use of intensive insulin regimens (MDI or insulin pump therapy)".

Potential clinical indications:
Diagnostic: suspected nocturnal hypoglycemia and/or early morning hyperglycemia; suspected unrecognized hypoglycemia (e.g. exceptionally low HbA1C without reported hypoglycemia); HbA1C above individualized target despite intensified insulin therapy apparently optimized with self-monitoring; persistent disabling hypoglycemia despite conversion from MDI to CSII
Therapeutic: Further optimization of pump therapy regimens when HbA1C cannot be consistently lowered below 7.5%; protection against recurrent disabling hypoglycemia, and for those with hypoglycemia unawareness or debilitating fear of hypoglycemia.

"When continuous use does not result in any clinical improvement, either in terms of glycemic control or patient-related benefit, CGM should be discontinued."

Other Guidelines
The following guidelines do not provide specific recommendations for children and adolescents or do not specifically address the questions posed in this report but warrant mention.

American Association of Clinical Endocrinologists (AACE)
The 2007 Clinical Practice Guidelines for the Management of Diabetes Mellitus does not address the care of children and adolescents with type 1 diabetes separately.[46] The report states that advances in blood glucose monitoring and continuous glucose monitoring of interstitial glucose, along with the introduction of "smart" insulin pumps, provide clinicians and patients with powerful tools to monitor and adjust treatment regimens. The guidelines recommend arranging for continuous glucose monitoring for patients with type 1 diabetes with unstable glucose control and for patients unable to achieve an acceptable HbA1C level; continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and postprandial hyperglycemia.

American Diabetes Association (ADA)
American Diabetes Association. "Diabetes care in the school and day care setting." *Diabetes Care* 2010 Jan; 33(Suppl 1):S70-4.[47]The ADA published a guideline in 2010 addressing diabetes care in the school and the day care setting:

"It is best for a student with diabetes to monitor blood glucose levels and to respond to the results as quickly and conveniently as possible. This is important to avoid medical problems being worsened by a delay in monitoring and treatment and to minimize educational problems caused by missing instruction in the classroom. Accordingly, a student should be permitted to monitor his or her blood glucose level and take appropriate action to treat hypoglycemia and hyperglycemia in the classroom or anywhere the student is in conjunction with a school activity, if preferred by the student and indicated in the student's DMMP. However, some students desire privacy for blood glucose monitoring and other diabetes care tasks, and this preference should also be accommodated."

"Ultimately, each person with diabetes becomes responsible for all aspects of routine care, and it is important for school personnel to facilitate a student in reaching this goal. However, regardless of a student's ability to provide self-care, help will always be needed in the event of a diabetes emergency."

International Diabetes Federation (IDF)
International Diabetes Federation (IDF). "Guideline for management of postmeal glucose." Brussels, Belgium: International Diabetes Federation (IDF); 2007 Oct. 29.[43] This guideline addresses patients with both type 1 and type 2 diabetes and does not differentiate between age groups. Levels of evidence ratings are given. Major recommendations include:

"Self-monitoring of blood glucose (SMBG) should be considered because it is currently the most practical method for monitoring postmeal glycaemia (Level 1++)."

"It is generally recommended that people treated with insulin perform SMBG at least three times per day (Level 4)".

"Postmeal hyperglycemia is harmful and should be addressed. Postmeal and postchallenge hyperglycemia are independent risk factors for macrovascular disease (Level 1+)".

"Implement treatment strategies to lower postmeal plasma glucose in people with postmeal hyperglycaemia. Treatment with agents that target postmeal plasma glucose reduces vascular events (Level 1-)".

"A variety of both non-pharmacologic (diets, Level 1+) and pharmacologic therapies (Level 1++) should be considered to target postmeal plasma glucose."

"Two-hour postmeal plasma glucose should not exceed 7.8 mmol/l (140 mg/dl) as long as hypoglycaemia is avoided (Level 2++)"

International Diabetes Center (IDC)
Bergenstal RM and Gavin JR. (2005) "The Role of Self-Monitoring of Blood Glucose in the Care of People with Diabetes: Report of a Global Consensus Conference." *Am Journal of Med.* 118(9A): 1S-6S. This report was published by the IDC, a World Health Organization Collaborating Center for Diabetes Education and Translation, and it addresses both type 1 and type 2 diabetes and does not report recommendations for children separately.

"Both HbA_{1c} and SMBG are essential for assessing glycemic control: HbA_{1c} assesses long-term glycemic control, has been shown to be a predictor of diabetes complications, and reflects the combination of pre- and postprandial glucose; SMBG is required to determine recent patterns of pre- and postprandial glucose."

"SMBG should be recommended to all patients with diabetes as an integral part of an overall diabetes management program because it provides: real-time, reliable blood glucose

concentrations; ability to assess pre- and postprandial hyperglycemia; improved safety through detection of hypoglycemia; possibility of timely therapeutic adjustments."

"SMBG is an essential component for insulin-treated patients with diabetes, both for safety reasons (detection of hypoglycemia) and enhancement of effectiveness of insulin through dose adjustment."

"Recommended frequency of SMBG testing will depend on: type of therapy; degree of glycemic control; risk of hypoglycemia; need for short-term adjustment of treatment; special situations (before and during pregnancy, concurrent illness, etc.)"

"For patients at or above target receiving multiple daily insulin injections or using and insulin pump, [the recommended frequency of SMBG testing is] ≥ 3 to 4 times daily. Many patients will require more frequent monitoring which includes both pre- and postprandial (and occasional 2:00 and 3:00 a.m.) values."

"SMBG should be performed at various times of the day, including preprandially and 1 to 2 hours postprandially, to obtain glucose profiles."

"SMBG should be used by patients and healthcare professionals in conjunction with a diabetes management action plan."

National Academy of Clinical Biochemistry
This guideline was written to systematically review and synthesize the available evidence on the effectiveness of point-of-care-testing (POCT) in the diagnosis and management of diabetes.[48] Information is only given regarding type 1 diabetes.

"The evidence to support the guideline developers' view is from systematic reviews, randomized controlled trials (RCTs), as well as controlled trials without randomization, and cohort/case control studies. The evidence is, however, conflicting, and our recommendation is therefore of type I, i.e., there is insufficient evidence to recommend for or against routinely using SMBG."

"…there is good evidence to support the use of point-of-care-testing (POCT) for HbA1C in both the primary and secondary care setting (A)."

"There are no studies that have formally investigated the frequency of measurement of A1C in any setting. The guideline developers therefore recommend that A1C testing be performed between 2 and 4 times per year, in line with the patient's individual requirements. It is recommended that more frequent testing be required in those patients with extremely increased HbA1C levels and less frequently in those with levels approaching the reference range (I)."

Summary of Clinical Guidelines: Clinical guidelines specific to children or adolescents who require insulin recommend SMBG at least four times a day. They recommend CGM may be helpful to some patients and should be offered.

1.4 Previous systematic reviews/technology assessments

The current literature regarding the efficacy, safety, and economics of patient self-monitoring of blood glucose levels or continuous glucose monitoring in pediatric patients requiring insulin is limited. Previously conducted systematic reviews and technology assessments that address this question were identified. The following tables summarize only those portions of the reviews that pertain to pediatric patients who require insulin (most of which have type 1) and the conclusions of the review with respect to those pediatric populations, if found. Studies with relevance to the key questions of this HTA that were identified from these reviews are included in this HTA and described elsewhere in this report.

Table 6. Overview of previous technology assessments of glucose monitoring in pediatric patients with type 1 diabetes

Assessment (year)	Lit search dates	Monitoring method	Evidence base available	Critical appraisal	Comments	Primary conclusions
California Technology Assessment Forum report (CTAF) (2009)[49]	2004-2009 (since last report)	SMBG with blood glucose meter and lancet CGM: DexCom STS-7; Guardian RT-CGMS; Mini-med Paradigm REAL-Time Insulin Pump and CGM System; Abbott Free-Style Navigator CGMS	3 RCTs; N = 27-36; and 2 RCTs with mixed ped/adult population, N = 30 and N = 322 with 98 less than 25 years old 4 observational studies; N = 10-60	Yes - Studies graded for level of evidence (system not described) Level of evidence: 1, 2, 5	Update to the 2003 report using newer literature of current devices	**Efficacy and Safety:** TA Criterion 1 (technology must have final approval from government regulatory bodies) is met; children not specified TA Criterion 2 (scientific evidence must permit conclusions of effectiveness regarding health outcomes) is met; children not specified TA Criterion 3 (technology must improve net health outcomes) is not met for children TA Criterion 4 (technology must be as beneficial as any established alternatives) is not met for children TA Criterion 4 (improvement must be attainable outside the investigational setting) is not met for children **Economic**: not addressed in this report
National Institute for Health Research (NIHR) RCT and HTA (2009) [50]	RCT: 1966-2008 - Meta: 1966-2008	CGM: Gluco-watch, Guardian, DexCom STS, FreeStyle Navigator	7 studies in pediatric populations and 3 with mixed ped/adult population	No – not described	This report is an RCT of CGM in adults with type 1 diabetes; with a systematic review that includes the analysis of available literature Glucowatch has been withdrawn from the market	**Efficacy:** finds little clinical value in children for CGM. A pattern was seen for declining GlucoWatch use in children followed 3 months or longer; in one study the watch was used an average of 3.5 (requirement for 4 times) times per week during the first 12 weeks and usage was greater during the initial weeks than during the final weeks. In another study, while unclear how often children were to be wearing the watch, only 28% of successfully calibrated watches were worn for the entire night and only 15 (33%) worn on all of the nights that it was available for them to wear. **Safety:** One study found CGM did not interfere with the care of the child and was well accepted by the children and their families. One study found minor pruritis in GlucoWatch use; 43% of the children in this study did not rate skin irritation as a problem, 43% rated it as a minor problem and 14% rated it as a major problem; 74% found it helpful overnight but 32% said that their sleep had been disrupted by alarms at night. **Economic:** does not address
Canadian Optimal Medication Prescribing and Utilization Service (COMPUS)[51] report (2009)	not reported	SMBG	1 RCT; N = 60 with 8 over 18 years of age	Yes - very low; rating by GRADE working group process		**Efficacy:** Evidence was not sufficient to recommend SMBG frequency; but recommends that optimal daily frequency be individualized **Safety:** Not addressed in this report **Economic:** No data available for this report

Australia and New Zealand Horizon Scanning Network (ANZHSN) HTA (2006)[52]	Up to March 2006	CGM systems	5 studies in 7 reports in pediatric populations; N = 483;	Yes - Level of evidence II-III-1; National Health and Medical Research Council (1999) guidelines		**Efficacy:** Age (3-18 years) was found to have no effect on the function of either the original CGMS® , the CGMS® System Gold™ or the GlucoWatch® G2. Two studies found therapy adjustments on the basis of CGMS® resulted in improvements in HbA1C levels **Safety:** quality of the evidence was very limited and no conclusions were made **Economic:** does not address in pediatric population
National Collaborating Centre for Women's and Children's Health; National Institute for Clinical Excellence (NICE) guidelines and evidence tables[53] (2004; updated 2009)	Up to 2004	SMBG CGM (Minimed and HemoCue, Glucosensor Unitec Ulm, Glucoday, and others)	Coster (NICE 2000) systematic review summarized; also individual studies including 8 RCTs and 16 test evaluation comparison studies of type 1 diabetic pediatric and adult patients	Yes - Evidence ratings: Ib - IIb	The Minimed device is the only one approved for use in children.	**Efficacy: Recommendations of this report include that Children and young people with type 1 diabetes and their families should be:** encouraged to perform frequent blood glucose monitoring as part of a continuing package of care; offered achoice of equipment for undertaking monitoring of capillary blood glucoseto optimise their glycaemic control in response to adjustment of insulin, diet andexercise; in the context of optimizing glycaemic control and/or intercurrent illness, encouraged to measuretheir blood glucose levels more than four times per day; if persistent problems with hypoglycaemia unawareness or repeated hypo- or hyperglycaemia, should be offered continuous glucose monitoring systems; and offered blood glucose monitors with memories (as opposed to without) because these are associated with improved patient satisfaction. **Safety:** does not summarize for children **Economic:** does not summarize for children
Australia and New Zealand Horison Scanning Network (ANZHSN) HTA (2004)[54]	Up to 2004	Minimed CGM: Guardian continuous monitoring system	No specfics provided for studies pertaining to pediatric populations	No – not described	A short report of the Minimed CGMS, not yet approved at the time of the report for use in Australia	**Efficacy:** does not address **Safety:** does not address **Economic:** does not address
BCBS Technology Evaluation Center (2003)[55]		GlucoWatch Biographer Minimed CGMS	Two RCTs conducted in children out of 5 reported	Not described Critical appraisal in text	Included non-published abstracts and reports	**Efficacy:** insufficient evidence to permit conclusions on the effect of interstitial fluide glucose monitors on health outcomes; does not meet TEC criteria. **Safety**: False alarm rates for GlucoWatch described;
CADTH, Canadian Coordinating Office for Health Technology Assessment (CCOHTA) (2002)[56]	Studies inclusive of dates 1999-2000	Minimed CGMS GlucoWatch Biographer	No specifics provided for studies pertaining to pediatric populations	No - not described	A short report of the two devices, one of which (the GlucoWatch) has been withdrawn from the market.	**Efficacy:** does not address **Safety:** does not address **Economic:** does not address

NICE 2000; Coster UK (2000) [57]	1990-1999	SMBG	4 RCTs in pediatric populations; N = 160	Yes - Quality ratings, were low; 13-14 (out of 28, with higher ratings reflecting better quality) for the 4 RCTs concerning children	This is a 2000 analysis; and included children as well as adults in analysis	**Efficacy:** results were inconclusive for children **Safety:** does not address **Economic:** does not address
The reports below are policy statements or otherwise consensus statements from various national agencies.						
NHS National Institute for Health and Clinical Excellence [58](NICE 151) (2008)	This consensus statement regarding subcutaneous insulin infusion or insulin pump therapy explains the etiology of diabetes type 1 and the rationale of the insulin pump for regulation of blood sugar levels. Information regarding self-monitoring of blood glucose in pediatric populations is not addressed in this document.					
Institute of Health Economics (IHE) (2006)[59]	This consensus statement provides an overview of the state of diabetes in Canada, the disease process, the treatments available and the pros and cons of continuous self-monitoring of glucose, with recommendation for insurance coverage of this technology and partnering with patients for optimization of care resulting from self-monitoring. It does not address children specifically in recommendations.					
NHS Scotland Evidence note [60](2005)	This evidence note outlines the use, benefits and effectiveness, drawbacks, and general cost factors for the use of continuous blood glucose monitoring devices. The NICE guidance is cited that recommends that "continuous glucose monitoring systems be offered to children and young people with Type 1 diabetes who have persistent problems with impaired awareness of hypoglycaemia or repeated hypo- and hyperglycaemia." Other specifics recommendations regarding the use of these devices in pediatric diabetic populations are not made.					

Table 7. Overview of previous systematic reviews of glucose monitoring.

Assessment (year)	Lit search dates	Monitoring method	Evidence base available	Critical appraisal	Comments	Primary conclusions
St John (2010)[61]	1996 to June 2008	Glucose strips or glucose meters for SMBG; otherwise unspecified	34 original papers including 38 studies; 7 RCTs comparing SMBG with usual care 2 nonexperimental studies in peds	Method or details not described	Studies with both type 1 and type 2 diabetic patients were reviewed in this report, and review did not focus on pediatric outcomes.	**Efficacy:** no statements specific to pediatric patients **Safety:** no statements specific to pediatric patients **Economic:** not considered in this report
Schwartz (2010)[62]	1994-2009	BGM, devices not specified	30 studies with 5353 children and adolescent with type 1 diabetes including 3 studies that were chart reviews, 2 with longitudinal data, and the rest were case-series (cross-sectional); age range of included studies were 2-60 years; with two studies of patients up to 60 years of age and two studies of patients up to 25 years of age; two studies did not report age range; the remainder included age ranges of no more than a maximum of 19 years of age	No – none described	Risk factors and nonadherence behaviors are the focus of this report, based on sociodemographics of the patients; the frequency of intermittent GSM or duration of CGM was considered as an OUTCOME, associated with various patient characteristics. In addressing most key questions, frequency of intermittent GSM is a PREDICTOR of an outcome (such as HgA1C).	**Efficacy:** not addressed in this report **Safety:** not addressed in this report **Economic:** not addressed in this report

Hood (2009)[63]	1950-2008	Glucose monitoring, specific methods/devices not specified in report	21 studies of youth < 19 years with type 1 diabetes, including N = 2492 patients	Method or details not described	The focus of the report is on economic status and self-care adherence in general; the frequency of intermittent GSM or duration of CGM was examined as an OUTCOME, associated with various patient characteristics. In addressing most key questions, frequency of intermittent GSM is a PREDICTOR of an outcome (such as HgA1C).	**Efficacy:** adherence to an intensive insulin regiment (of which glucose monitoring is a part) results in improved glycemic control and reduced risk of long-term disease complications; one study found children-young adults (age 8-24 years) who used real time CGM did not experience significant glycemic control improvements, but these cohorts already have better glycemic outcomes than found by larger-scale epidemiological studies, so relatively adherent to begin with. **Safety:** not addressed in this report **Economic:** not addressed in this report
Chetty (2008)[64]	1996-March 2007	Medtronic continuous glucose monitoring with control groups of self-blood glucose monitoring	5 studies of pediatric type 1 diabetic patients (age < 18 years); N = 131	Used Jadad scores; described in text; 2 were grade 0, one grade 1, one grade 3, and one grade 4 Higher scores reflect higher quality.	Relevant studies from this SR were considered for the HTA.	**Efficacy:** A significant reduction was seen in HBA1C in favor of the CGMS vs SBGM (0.37%; 95% CI: 0.71% to 0.02%, p = 0.036) for the pediatric patients; which may reflect parental input on therapy adjustments, or a tendency to not use the more aggressive SBGM regime because of the ‘‘pain factor’’, leading to an exaggerated treatment effect in favor of CGMS. **Safety:** not addressed in this review **Economic:** not addressed in this review

Golicki (2008)[38]	Through June 2007	CGM devices; comparing Continuous Glucose Monitoring System (CGMS) with self-monitoring of blood glucose	5 RCTs with N = 131 type 1 diabetic patients; age ranges between 2-19 years for four studies, and ≤ 18 years in the fifth.	Yes - Used Cochrane standards; with details of study appraisal results in text; scores not assigned in text		**Efficacy:** Weighted mean difference was -0.02 (95% CI, -0.74 to 0.74) for HbA1C difference for patients with insulin doses adjusted on the basis of CGMS and SMBG data vs SMBG data only (P = 0.87). **Safety:** No severe hypoglycemic events were seen in either the CGMS or control groups; one study reported no difference was seen in the number of minor hypoglycemic events for the CGMS vs the control group (mean difference 0.53, 95% CI -0.68 to 1.74); mild local side effects reported in one study included redness in 21 cases (23%), redness and itching in 14 cases (16%), and painful redness in one case; another study reported one patient withdrew from insulin infusion due to skin irritation at the sensor site, and one ketoacidosis event required hospital admission. **Economic:** not addressed in this review

1.5 Medicare and representative private insurer coverage policies

Overall, most coverage policies found do not vary by age thus no plans were found that addressed coverage in children and adolescents specifically. Some provide descriptions for those < 25 years old. In the policies listed below, home blood glucose monitors (SMBG) are covered for the management of diabetes mellitus and a number of insurance carriers now cover continuous glucose monitoring (CGM) as well. Overview of payer assessments and policies for SMBG and CGM are found in the table below. The listing is not meant to include policies of all private insurers offering coverage in Washington. (Requirements for this report are to provide information on Medicare NCD and information on two bell-weather payers.)

- **Medicare**
  Home blood glucose monitors and related accessories and supplies are considered medically necessary and are covered as long as certain criteria are met by the patient or the patients' care giver.[65,66]No policies relating to CGM were found.

- **Aetna**
  Home blood glucose monitors, short (72 hours) and long-term CGM, and related supplies are all considered medically necessary and are covered for all patients with type 1 diabetes as long as certain criteria are met.[67] Specifically relating to younger persons, long-term CGM is covered for those < 25 years old with type 1 diabetes who have had

recurrent episodes of severe hypoglycemia with unawareness, and alternate site blood glucose monitors are covered for children ≤ 12 years old when recommended by a physician.

- **Cigna**
  Home blood glucose monitoring as well as CGM are considered medically necessary and are covered in all patients with type 1 diabetes as long as certain criteria are met.[68] Specifically relating to younger persons, long-term CGM is medically necessary in type 1 diabetes who are < age 25 years AND have recurrent severe hypoglycemic events despite appropriate modifications in insulin therapy and compliance with frequent self-monitoring of blood glucose (≥ 4 times /day).

- **Blue Cross/Blue Shield**
  CGM is covered in the short term (72 hours) for patients with type 1 diabetes who primarily have poorly controlled diabetes despite best the current use of best practices and, in the case of long-term CGM, for recurrent, unexplained, symptomatic episodes of severe hypoglycemia.[55]

- **Harvard Pilgrim**

Home blood glucose monitors, CGM, and related accessories and supplies are considered medically necessary and are covered in all patients with diabetes of any type as long as certain criteria are met.[69]

- **Nordian Medicare B**

Home blood glucose monitors and related accessories and supplies are considered medically necessary and are covered in all people with diabetes as long as certain criteria are met by the patient or the patients' care giver.[70] No policies relating to CGM were found.

Table 8.Overview of payer technology assessments and policies for home blood glucose monitoring and continuous glucose monitoring in children and adolescents.

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
Centers for Medicare and Medicaid Services (2008)[65,66]	▪ Not reported	No specific policy addressing children To be eligible for coverage of home blood glucose monitors and related accessories and supplies, the patient (or patient's care-giver) must meet all the following criteria: ▪ Diagnosed with diabetes that is being treated by a physician ▪ Glucose monitor and related supplies ordered by the treating physician with documentation of medical necessity for the prescribed frequency of testing ▪ Successfully completed training or is scheduled to begin training in the use of these items ▪ Capable of using the test results to assure appropriate glycemic control ▪ Device is designed for home use Home blood glucose monitoring with special features are covered if the 5 above criteria are met and the treating physician verifies the patient has a visual impairment or other condition requiring this special device Supplies covered: ▪ Up to 100 test strips and lancets every month for beneficiaries who are insulin dependent and every 3 months for those who are non-insulin dependent, and one lancet device every 6 months for both indications	▪ Rationale not reported Covered if selection criteria are met: ▪ CPT/HCPCS codes: E0607, E0620, E2100, E2101, A4233, A4234, A4235, A4236, A4244, A4245, A4246, A 4247, A4250, A4253, A4255, A4256, A4257, A4258, A4259, A9275, A9276, A9277, A9278 ▪ ICD-9 codes: 249.00–249.91, 250.00–250.93

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
Aetna Clinical Policy (2010)[67]	▪ 2 HTAs ▪ 2 SRs (N = 466) ▪ 2 RCTs (N = 722, f/u 6–18 months) ▪ various cohort studies and reviews	No specific policy addressing children <u>The following are considered medically necessary and covered</u>: *DME*: ▪ Blood glucose monitors ▪ Blood glucose monitors with enhanced features for individuals with a visual or severe manual dexterity impairment ▪ Continuous glucose monitors o Short term (up to 72 hours): in diabetic patients who have hypoglycemia unawareness or repeated hypoglyecemia and hyperglycemia at the same time each day (no more than 2 CGM periods within a 12-month period covered) o Long term (greater than 72 hours): as an adjunct to fingerstick testing of blood glucose in adults 25 years and older with type 1 diabetes; for younger persons with type 1 diabetes who have had recurrent episodes of severe hypoglycemia with unawareness ▪ Alternate site blood glucose monitors: when recommended by a physician, for children ≤ 12 years old or persons who have used conventional blood glucose meters and who have been noncompliant because of pain sensitivity or heavily callused fingers ▪ Jet injectors (when the member or caregiver is physically unable to safely use a conventional needle-syringe) *Supplies (coverage varies by medical/pharmacy plan)*: ▪ Blood glucose test strips ▪ Lancets ▪ Alcohol swabs ▪ Control solutions ▪ Insulin pens ▪ Needles and syringes for insulin administration ▪ Urine test tablets/strips <u>Medically necessary quantities of test strips/lancets</u>: ▪ Up to 100 test strips and up to 100 lancets every 3 months are considered medically necessary when *both* of the following criteria are met: o The member has nearly exhausted the supply of test strips and lancets previously dispensed; *and* o The supplier of the test strips and lancets maintains in its records the order from the treating physician. ▪ More than 100 test strips and more than 100 lancets every 3 months are considered medically necessary when *all* of the following criteria below are met: o If refills of quantities of supplies that exceed the utilization guidelines are dispensed, there must be documentation in the physician's records or in the supplier's records that the member is actually testing at a frequency that corroborates the quantity of supplies that have been dispensed. If the member is regularly using quantities of supplies that exceed the utilization guidelines, new documentation must be present at least every 6 months; and o The member has nearly exhausted the supply of test strips and lancets previously dispensed; and o The supplier of the test strips and lancets maintains in its records the order from the treating physician; and o The treating physician has ordered a frequency of testing that exceeds the utilization guidelines and has documented in the member's medical record the specific reason for the additional materials for that particular patient; and o The treating physician has seen the member and has evaluated his/her diabetes control within 6 months prior to ordering quantities of strips and lancets that exceed the utilization guidelines. <u>The following are considered experimental and investigational and are not covered</u>:	▪ Policy is in accordance with FDA, ADA and NICE recommendations Covered if selection criteria are met: ▪ CPT codes: 82947, 82948, 82950, 82962, 83519, 86341, 95250, 95251 ▪ HCPCS codes: A4206–A4209. A4211–A4215, A4221, A4222, A4230–A4236, A4244–A4247, A4250, A4252, A4253, A4255, A4256, A4258, A4259, A9274, A9275, A9276–A9278, E0607, E0784, E2101, G0108, G0109, J1815, J1817, S1030, S1031, S5550–S5553, S5560, S5561, S5565, S5566, S5570, S5571, S8490, S9140, S9141, S9145, S9353, S9455, S9460, S9465 ▪ ICD-9 codes: 250.00–250.93, 333.91, 648.00–648.04, 648.80–648.84

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
		▪ Laser blood glucose monitoring devices ▪ Devices to measure glycated serum proteins ▪ GlucoWatch or other glucose meters designed to be worn on the wrist The following are considered non-covered convenience items: ▪ I-Port	
Cigna Medical Coverage Policy (2010)[68]	▪ NICE, AACE, various SRs, RCTs, and case-series	No specific policy addressing children The following SMBG devices are covered and considered medically necessary when used for the management of diabetes mellitus: ▪ A standard home blood glucose monitor ▪ An enhanced feature glucose monitor for individuals with a visual or severe manual dexterity impairment	▪ Policy is in accordance with FDA and ADA recommendations, and NICE guidelines
	▪ ECRI HTA, various SRs, RCTs, cohorts, and case-series	CGM is medically necessary for ANY of the following: ▪ Long-term use in type 1 diabetics who are < age 25 years AND have recurrent severe hypoglycemic events despite appropriate modifications in insulin therapy and compliance with frequent self-monitoring of blood glucose (≥ 4x/day) ▪ Long-term use in type 1 diabetes ≥ 25 years of age ▪ Up to 3 days (72 hours) for the management of difficult to control insulin-treated diabetes mellitus for up to 6 separate session in a 12 month period	▪ Policy is in accordance with FDA and ADA recommendations
	▪ NICE, AACE, various SRs, RCTs, and case-series	The following diabetic supplies are covered and considered medically necessary: ▪ Alcohol wipes ▪ Blood test strips (glucose/ketones) ▪ Insulin pens ▪ Needles and syringes for insulin administration ▪ Standard lancets ▪ Urine test tablets/strips (glucose/ketones) ▪ Needle-free insulin injection systems or jet injectors when EITHER the individual has a needle phobia or the individual/caregiver is unable to use standard syringes	▪ Policy is in accordance with ADA and NICE recommendations
	▪ 1 RCT (N = 29, age 5–17 years, f/u 6 months, fingertip vs. AST) ▪ 3 RCTs (GlucoWatch)	Not covered – considered experimental, investigational, or unproven ▪ Alternative site blood glucose monitoring (AST) ▪ GlucoWatch G2 Biographer	▪ There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of AST or GlucoWatch ▪ Policy is in accordance NICE guidelines Covered when medically necessary ▪ CPT codes: 95250, 95251 ▪ HCPCS codes: A4206, A4210, A4211, A4215, A4245, A4250, A4252, A4258, A4259,A9276, A9277, A9278, E0607, E2100, E2101, S1030, S1031, S5560, S5561, S5570, S5571, S8490 ▪ ICD-9: 250.00–250.93, 648.00–648.04, 648.80–648.84

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
BlueCross BlueShield Corportate Medical Policy (2010)[55]	▪ Not reported	No specific policy addressing children The following forms of CGM are considered medically necessary and covered when the following terms are met ▪ Short-term (72 hours): o Patients with type 1 diabetes who despite current use of best practices have poorly controlled diabetes, including hemoglobin A1C not in acceptable target range for the patient's clinical situation, unexplained hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia, or recurrent diabetic ketoacidosis. o Patients with type 1 diabetes prior to insulin pump initiation to determine basal insulin levels. ▪ Long-term CGM , including real-time, monitoring o Patients with type 1 diabetes who have recurrent unexplained, severe, symptomatic (generally blood glucose levels less than 50 mg/dl) hypoglycemia for whom hypoglycemia puts the patient or others at risk	▪ Policy is in accordance with FDA and ADA recommendations
Harvard Pilgrim HealthCare TA Policy (2010)[69]	▪ Not reported	No specific policy addressing children Covers equipment, education and management, and supplies necessary for the treatment of diabetes (type 1 or 2, gestational, and/or insulin or non-insulin dependent) including: ▪ Blood glucose monitors ▪ Blood glucose monitors with special features, such as voice synthesizers and automatic timers for the visually impaired and/or members with severely impaired manual dexterity. ▪ Continuous glucose monitoring systems. ▪ Blood glucose test or reagent strips for home blood glucose monitor ▪ Dosage gauges (e.g., Inject Aid, Syringe Support) ▪ Injectors (insulin injection aids like Novolin Pen, Inject-ease). ▪ Insulin pumps and supplies. ▪ Lancet devices (e.g., Autolance, Glucolet). ▪ Needle-less injection systems for members or their caregivers unable to safely administer insulin with a needle or syringe due to a visual or neurological impairment. ▪ Routine lab tests (HbA1C, urinary protein/microalbumin, lipid profiles) Not covered: ▪ Batteries for glucose monitors ▪ Blood glucose analyze ▪ Continuous glucose monitoring systems for persons with Type 2 diabetes ▪ Diabetes training programs/camps ▪ Glucowatch ▪ Laser skin piercing device, not determined to be medically necessary	▪ Rationale not reported Covered when medically necessary ▪ CPT codes: 80000 series, 95250, 95251, 97802–97804, 99200 series, 942 (requires HCPCS code G0108 or G0109) ▪ HCPCS codes: A4206–A4210, A4211–A4215, A4230–A4232, A4253, A4255, A4256, A4258, A4259, A5500–A5508, A5510, A5512, A5513, A9276, A9277, A9278, E0607, E0784, E1399, E2100, E2101, G0108–G0109, G0270, G0271, G8015–G8026, J1610, J1815, J1817, L3000–L3030, L3031, L3040–L3060, L3070–L3090, S1030, S1031
Nordian Medicare B (2010)[70]	▪ Not reported	No specific policy addressing children Coverage of home glucose monitors is limited to patients meeting the following conditions: ▪ The patient has been diagnosed as having diabetes; ▪ The patient's physician states that the patient is capable of being trained to use the particular device prescribed in an appropriate manner.In some cases, the patient may not be able to perform this function, but a responsible individual can be trained to use the equipment and monitor the patient to assure that the intended effect is achieved. This is permissible if the record is properly documented by the patient's physician; and ▪ The device is designed for home use rather than clinical use. ▪ Home blood glucose monitoring with special features are covered if the 3 above criteria are met and the treating physician verifies the patient has a visual	▪ Rationale not reported Covered when medically necessary ▪ HCPCS codes: A4233, A4234, A4235, A4236, A4253, A4256, A4258, A4259, E0607, E2100, E2101

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
		impairment or other condition requiring this special device Supplies covered: ▪ Up to 100 test strips and lancets every month for beneficiaries who are insulin dependent and every 3 months for those who are non-insulin dependent, and one lancet device every 6 months for both indications	

AACE: American Association of Clinical Endocrinologists; ADA: American Diabetes Association; AST: alternate site testing; CGM: continuous glucose monitoring; CPT: Current Procedural Terminology; DME: durable medical equipment; FDA: Federal Drug Administration; HCPCS: Healthcare Common Procedure Coding System; HTA: health technology assessment; ICD-9: International Statistical Classification of Diseases and Related Health Problems; NICE: National Institute for Health and Clinical Excellence; RCT: randomized controlled trial; SMBG: self-monitoring blood glucose; SR: systematic review.

2. The Evidence

2.1 Methods of systematic literature review

2.1.1 Focus and inclusion/exclusion criteria

The primary focus of this HTA is on evaluation of self-monitoring methods used by patients ≤18 years old and younger to assess glucose levels at home (versus data used exclusively by providers in a clinical setting) for daily decision making regarding self-care. The inclusion and exclusion criteria are described in the PICO table below.

Table 9.Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Participants	◆ Studies of patients ≤ 18 years old with insulin-requiring diabetes mellitus. They may include patients with type 1 or type 2 diabetes. ◆ Studies including patients with insulin-requiring diabetes mellitus > 18 years old if at least 80% of the patients are ≤ 18 years old. ◆ Studies including patients with insulin-requiring diabetes mellitus > 18 year old if results for those ≤ 18 years old are reported separately. ◆ Studies of pregnant patients ≤ 18 years old	◆ Studies in which <80% of patients are ≤ 18 years old ◆ Studies of patients with diabetes who do not require insulin ◆ Studies focusing on pregnant patients ≥18 years old
Intervention	◆ Self-monitoring using blood glucose meters that are currently approved by the FDA ◆ Self-monitoring using continuous glucose monitors that are currently approved by the FDA ◆ Self-monitoring in conjunction with provider report cards for target HgA1C ◆ Self-monitoring using glucose monitors that are integrated with an insulin pump ◆ Self-monitoring using glucose meters or monitors that are no longer available in older landmark studies of high quality if their methods for measuring glucose correlate with currently-available methods	◆ Non-FDA−approved glucose meters ◆ Non-FDA−approved glucose monitors ◆ Non-FDA approved combination devices (monitor + pump) ◆ Tests for urine glucose ◆ Tests for urine ketones ◆ Tests for serum beta-hydroxybutyrate ◆ Glucose tests using colorimetric strips ◆ Devices that are no longer being marketed ◆ Continuous glucose monitors collecting only data to be used retrospectively ◆ Monitors whose results are used only in a clinician's office or laboratory. ◆ Initial studies comparing accuracy of devices and feasibility ◆ Studies of alternate anatomic sites for monitoring
Comparators	◆ Comparisons of different frequency of self-monitoring using blood glucose meters ◆ Self-monitoring using blood glucose meters vs. continuous glucose monitors ◆ Attention control ◆ Standard care ◆ No self-monitoring ◆ Self-monitoring as a stand-alone intervention vs. self-monitoring as part of a package including education,	

	feedback, and support	
Outcomes	◆ Achieving target (ie, age-appropriate) HgA1C level ◆ Maintaining target (ie, age-appropriate) HgA1C level ◆ Hospitalization ◆ Acute episodes of hyperglycemia ◆ Acute episodes of hypoglycemia ◆ Acute episodes of diabetic ketoacidosis ◆ Microvascular complications (eg, vision loss, kidney failure, peripheral neuropathy) ◆ Macrovascular complications (eg, stroke, MI) ◆ Mortality ◆ Morbidity from glucose meters or monitors ◆ Direct and indirect costs, both short- and long-term and benefits (may be expressed as cost savings by preventing morbid events) ◆ Effect on medication or nutritional management ◆ Quality of life	◆ Fructosamine levels
Study Design	◆ Only high quality (Spectrum level I or II) comparative studies (eg, randomized controlled trials, cohort studies with concurrent controls, crossover studies) will be primarily considered for questions 1-4. ◆ Observational studies (eg, longitudinal studies whose inception cohort is ≤ 18 years old) correlating intermediate outcomes (eg, HgA1C) with long term clinical outcomes will be considered for questions 1-4. If no LoE I/II studies available, LoE III studies will be considered. ◆ Formal economic studies will be sought for question 5. Studies using modeling may be used to determine costs over the full duration of glucose monitoring, which is a lifetime.	◆ Studies other than comparative studies with concurrent controls for questions 1-4 ◆ Studies of low quality (Spectrum's LoE IV) ◆ Case reports ◆ Case series ◆ Studies assessing the reliability and validity of glucometers or continuous monitors
Publication	◆ Studies published in English in peer reviewed journals or publically available FDA reports ◆ For question 5, full formal economic analyses (eg, cost-utility studies) published in English in a peer reviewed journal	◆ Abstracts, editorials, letters ◆ Duplicate publications of the same study that do not report different outcomes ◆ Single reports from multicenter trials ◆ White papers ◆ Narrative reviews ◆ Articles identified as preliminary reports when full results are published in later versions ◆ Incomplete economic evaluations such as costing studies

2.1.2 Data sources and search strategies

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based

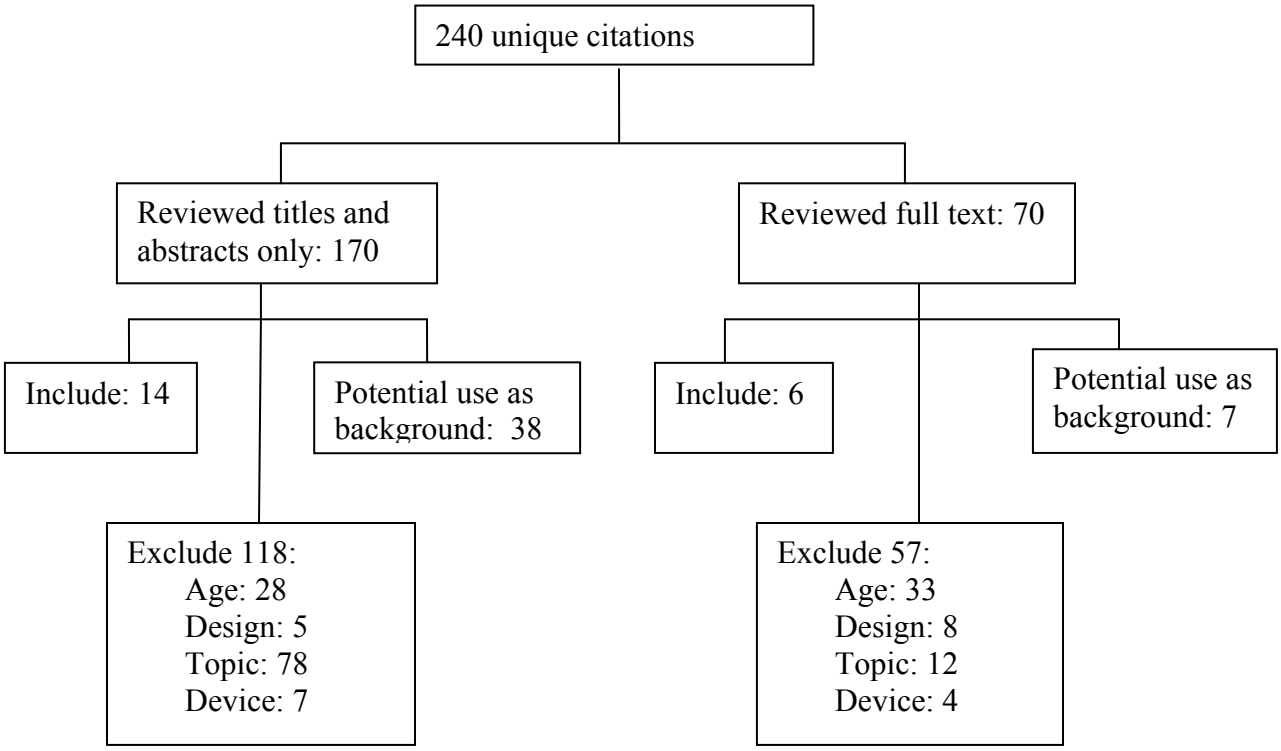
on the criteria above were included. Any unresolved disagreement between screeners resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.
Electronic databases searched included PubMed, EMBASE, CINAHL, ClinicalTrials.gov, NIH Reporter, *The Cochrane Library*, EconLIT, PsychINFO, AHRQ, National Guideline Clearinghouse and INAHTAfor eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and FDA reports. Reference lists of all eligible studies were also searched. The search strategies used for PubMed and EMBASEare shown in Appendix B. The figure below shows a flow chart of the results of all searches for included primary studies. Articles excluded at full-text review are listed in Appendix C.

Additional articles identified by peer reviewers and the public were added if the met the inclusion criteria.

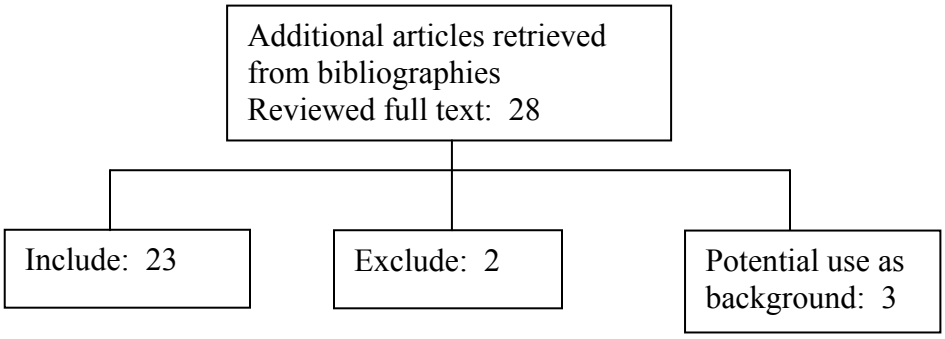
Search Strategy for Citations retrieved through Medline and EMBASE

A single investigator searched PubMed and EMBASE and retrieved 244 citations that seemed relevant based on their titles. (EconLit was also searched but yielded no relevant citations.) There were 4 pairs of duplicates (articles retrieved both by name of study group and by name of first author), leaving 240 unique citations. Then, two investigators (CO and JK) reviewed titles and abstracts independently and categorized them as "Include," "Exclude" or "Unclear." Together, they discussed those on which they disagreed and those they both categorized as unclear. If needed, they reviewed the full text or included review by a third investigator , and re-categorized the citations. Articles were excluded because subjects did not meet age criteria, the study design did not meet criteria, the topic did not meet criteria, or the device was no longer marketed. Some citations did not meet criteria for inclusion in the formal technology assessment, but were used as background. Some citations contained data relevant to multiple key questions. Additional information on article selection, search strategies and excluded articles can be found in Appendices A-C.

Figure 1. Flow chart showing results of literature search



Another 28 potentially relevant articles were identified from bibliographies of other health technology assessments, systematic reviews, and primary evidence articles retrieved. All underwent full text review. Of these, 23 were used as primary evidence, 2 were excluded, and 3 were used as background.



Commentators cited 131 distinct articles. All were reviewed at the title, abstract, or full-text level. Of these, 10 were already included in our HTA and 6 reports were added as primary evidence, two of which described follow-up to previously included studies and captured by in the search. The other 115 did not meet inclusion criteria for this HTA

2.1.3 Data extraction

Reviewers extracted the following data from the included comparative clinical studies that provided primary evidence for this report: study population characteristics, study type, study period, patient demographics and characteristics, study interventions, follow-up time, study outcomes, adverse events, and other complications. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. For full economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted.

2.1.4 Study quality assessment methods: Level of evidence (LoE) evaluation

The method used for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of rating scheme developed by the Oxford Centre for Evidence-based Medicine,[71] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[72]and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[73]Taking into account features of methodological quality and important sources of bias combines epidemiologic principles with characteristics of study design.

Details of the Level of Evidence (LoE) methodology are found in Appendix D. Each clinical/human study chosen for inclusion was given a LoE rating based on the quality criteria listed in Appendix D. Standardized abstraction guidelines were used to determine the LoE for each study included in this assessment.
Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence for the relevant question or topic is determined. The method and descriptions of overall strength are adapted for diagnostic studies from system described by the GRADE Working Group[72] for the development of clinical guidelines. Details are provided in Appendix D.

2.2 Quality of literature available

2.2.1 Overview of retained studies

Some studies had data relevant to more than one key question.

Key questions 1 and 2:

The following table provides an overview of the RCTs and related follow-up studies included in this HTA. Descriptions of these studies and additional observational studies are provided below.

Study	Comparators	Included Reports/citation	Comments
DCCT and EDIC follow-up studies	Intensive care (SMBG ≥ 4/day) vs. conventional care	**DCCT (RCT) 1994** ▪ "Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial." J Pediatr.**125**(2): 177-188 **EDIC (Observational) follow-up studies** ▪ White, N. H., P. A. Cleary, et al. (2001). "Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after	All reports are on the same underlying population.

		the conclusion of the Diabetes Control and Complications Trial (DCCT)." J Pediatr.**139**(6): 804-812 ▪ White N, H., Sun W., et al. (2010). "Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents." Diabetes.**59**(5): 1244-1253.	
JDRF 2008	CGM vs. SMBG	**Main RCT** ▪ Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, W. V. Tamborlane, et al. (2008). "Continuous glucose monitoring and intensive treatment of type 1 diabetes." N Engl J Med**359**(14): 1464-1476 **Subanalysis (observational)** ▪ Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, R. W. Beck, et al. (2009). "Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes." Diabetes Care **32**(11): 1947-1953. **Observational/extension studies** ▪ Chase, H. P., R. W. Beck, et al. (2010). "Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial " Diabetes Technology Therapeutics. 12(7): 507-15. ▪ Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group (2010). "Effectiveness of Continuous Glucose Monitoring in a Clinical Care Environment: Evidence from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring (JDRF-CGM) trial." Diabetes Care. **33**: 17-22.	Analyses in the same underlying population Participants from main RCT included in JRDF 2010 Quality of life analysis Observational extension studies looked at the CGM group who continued to use CGM 6 months after the trial and those in the former SMBG group who opted to use CGM for 6 months after the trial in two separate studies
JDRF 2009	CGM vs. SMBG	▪ Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group (2009). "The effect of continuous glucose monitoring in well-controlled type 1 diabetes." Diabetes Care 32(8): 1378-83.	Participants with A1C <7% included in the JDRF 2010 Quality of life analysis listed below
The JDRF 2010	CGM vs. SMBG	▪ Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, R. W. Beck, et al. (2010). "Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial." Diabetes Care33(10): 2175-2177	Is a combined analysis of the JDRF trials conducted in parallel study populations (participants with A1c <7% at baseline and >7% at baseline)
Hirsch	CGM vs. SMBG (All had pump)	▪ Hirsch, I. B., J. Abelseth, et al. (2008). "Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study." Diabetes Technol Ther 10(5): 377-383.	
Bergenstal	CGM/Pump vs. MDI/SMBG	▪ Bergenstal, R. M., W. V. Tamborlane, et al. (2010). "Effectiveness of sensor-augmented insulin-pump Therapy in Type 1 Diabetes." New Engl J Med363: 311-320	

One RCT, the Diabetes Control and Complications Trial (DCCT) was included as the only trial that provides evidence regarding the efficacy of SMBG as part of a package of comprehensive care.[22] It has LoE II Four older RCTs (1985–1983) compared SMBG with urine testing.[74-77] These four early studies of SMBG in children are viewed more as feasibility and acceptance

studies, rather than studies of efficacy regarding the potential impact of SMBG on A1C or health outcomes and mortality. They reflect standards of care and devices that may have been considered acceptable in their era, but may no longer be used. They are only briefly described for historical context. Two reports on the observational follow-up (LoE II) study of participants (who were adolescents at the start of DCCT) after the completion of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, provide information on the longer-term effectiveness of prior participation in a clinical trial of SMBG as part of a package of comprehensive care.[78,79]Results from individuals who were 18 years old or under at the time of the original DCCT are included in this HTA

Three RCTs (LoE II)[80-82] were found that compared real-time patient use of CGM (in conjunction with SMBG) with SMBG alone and provided information to patients on how to use information for daily management. One additional RCT (LoE II) allowed use of the real-time features of CGM, but compares two different treatment interventions; use of an integrated CGM and insulin pump system versus multiple daily injections with SMBG.[83] Given that this study compares two different monitoring methods as well as two different treatment methods, the effect of CGM cannot be separately assessed. Five RCTs comparing periodic, short-duration use of CGM with SMBG alone did not provide patients with access to CGM data.[84-88] Even though some of these devices may have been capable of providing real-time information to patients (it is not clearly stated), this feature was not used and the data were downloaded retrospectively by the researchers or clinicians to evaluate glucose changes/patterns and make treatment recommendations. In general, these studies do not provide specifics about how the data were used in the decision making process and therefore evaluation regarding the role of these devices for patient management was not available. They are described primarily to provide context and detail is provided in the appendices.

Three reports describing the impact of frequency and consistency of CGM use on A1C. One was a sub-analysis to the JDRF 2008 RCT described above that focused on consistency of patient real-time use of CGM during the trial.[89]Two of these were extension studies published separately from the main RCT report, one that evaluated use of CGM up to an additional 6 months after the trial in those initially randomized to CGM [90] and the other among those initially randomized to SMBG but who used CGM after the end of the trial.[91]Since randomization is not preserved in these analyses, they are considered as prospective cohort studies.

Seven non-randomized studies (LoE III) assessed specific frequencies of SMBG and association with outcomes of interest[92-97] One was a registry study by Ziegler.[92]It was the only study found with the primary purpose of evaluating the relationship between frequency of SMBG with A1C, the frequency of hypoglycemia and ketoacidosis, and whether the associations between SMBG and those outcomes were influenced by the patient's age or treatment regimen. Five additional non-randomized studies and data from on an RCT provided some detail on specific numbers of

SMBG tests in relation to A1C values as part of studies that were not directly focused on detailed evaluation of this relationship.[93-98] Studies that looked only at general correlation between SMBG frequency and A1C and did not provide information on specific numbers of SMBG tests done were briefly summarized but not described in detail.[99-110] Two of the nonrandomized studies [92,108] described associations between SMBG frequency and hypoglycemia and one described rates of diabetic ketoacidosis.[92]

With the exception of the registry study by Ziegler, all were considered prognostic studies.

Key Question 3
Safety and adverse-event data from the three RCTs (LoE II)[80-82] described in Key Question 2 that compared real-time patient use of CGM (in conjunction with SMBG) with SMBG alone are summarized. Studies of periodic, short duration CGM use (LoE II), including five RCTs[84-88] and seven nonrandomized studies[111-117], were included to provide additional safety profile information. Information from the FDA Summary of Safety and Efficacy Data (SSED) reports for the three CGM devices used in these trials are also summarized.[118-120] These are based on studies submitted for device approval. The only information available for SMBG came from older studies (published 1983-1988) that are not relevant to modern devices: Two RCTs[74,75] and one observational study[121] were included.

Key Question 4
The JDRF 2008 trial[80] (LoE II) is the only randomized study that provides a direct comparison of monitoring modes with respect to different age groups in the same study population.

A registry study (LoE III) by Ziegler was the only study found that had the primary purpose of evaluating the relationship between frequency of SMBG with quality of treatment as measured by hemoglobin A1C and the frequency of hypoglycemia and ketoacidosis, as reported in Key Question 2.[92] They also explored the modification of the relationship between SMBG frequency and A1C by patient age and insulin regimen.

No studies were found that directly compared groups based on gender, psychological, psycho-social factors, patient characteristics, provider characteristics or health benefit/payer systems were found. Examples of factors associated with A1C/glycemic control from correlational studies are briefly described.[102-108,122,123] Without explicit, direct comparison of how the outcomes differ between groups of patients with and without the various factors and with respect to specific frequency of SMBG (or comparison with CMG), no conclusions can be drawn from these studies with regard to differential efficacy or effectiveness.

Key Question 5
No formal, full economic evaluations of SMBG and/or CGM that were relevant to the patient population for this HTA were found.

2.2.2 Critical appraisal and level of evidence evaluation

Key Question 1. Randomized controlled trials

Studies of self-monitoring of blood glucose (SMBG) efficacy
One RCT, the Diabetes Control and Complications Trial (DCCT) was included as the only trial that provides *indirect* evidence regarding the efficacy of SMBG as part of a package of comprehensive care[1]. The study included 195 adolescents age 13 to 17 years who were described in a separate report. [22] The subjects were recruited at 29 sites in the United States between 1983 and 1989 and followed for an average of 6.5 years. The primary prevention (PP) cohort included 125 adolescents who had had diabetes from 1 to 5 years and had no evidence of retinopathy or nephropathy defined as urine excretion less than 40 mg per 24 hrs. The secondary intervention cohort included 70 adolescents that had had diabetes from1 to 15 years and had mild-to moderate non-proliferative retinopathy and urinary albumin excretion of less than 200 mg per 24 hrs.

These two cohorts were randomly assigned to intensive treatment or conventional treatment. The conventional treatment group injected insulin once or twice a day, and used daily monitoring of blood glucose or urine. They did not adjust the insulin on a day to day basis. Treatment goals for the usual treatment group were to avoid ketoacidosis, symptoms of hyperglycemia (i.e. polyuria, polydipsia), hypoglycemia, and maintain normal growth and development. The intensive treatment group was placed on three or more insulin injections a day or an insulin pump. They were taught to test the blood glucose several times a day and adjust the insulin dose, diet, and exercise to maintain the preprandial (before meal) blood glucose between 70 mg/dl and 120 mg/dl. An A1C was obtained monthly in the intensive treatment group and every 3 months on the usual treatment group. Eye exams were administered every 6 months to both groups. A significant change was defined as a change of 3 or more stages on the Early Treatment Diabetic Retinopathy Study scale. Microalbuminuria was defined as urine protein excretion over 30 mg/24 hours and albuminuria as excretion over 300 mg/24 hrs. Any women who were planning a treatment during the pregnancy, then were returned to the conventional treatment group.

The DCCT was rated as a LoE II RCT. Intention to treat analysis, statement of concealed allocation, and blinded assessment of outcomes were reported. The authors state that participants were followed for a mean of 7.4 years (4-9), with no voluntary withdrawals for a total of 1448, person-years, and that more than 95% of scheduled examinations were completed but for some outcomes, it is not clear how many persons contributed data to some outcomes. .The duration of time and number of participants contributing data at different time periods is not clear in the figures or data provided for some outcomes. Rates are, however, in person-years and cumulative incidence reported for specific events. Adjustment or stratification for differences in baseline characteristic was done. For some analyses, it isn't clear whether methods for repeated measures analysis were used. The authors reported that nine young women in the conventional therapy group were treated in the intensive therapy group during pregnancy, but do not state whether there was any additional cross-over during the length of the follow-up or the extent to which treatment in the conventional group in particular may have varied with time. None-the- less, it appears that patterns and differences between groups for A1C and capillary glucose remained consistent over time. By design, co-interventions (e.g. insulin doses, advice on diet) were different between groups.

Key Question 1. Non-randomized studies

Observational studies of effectiveness: SMBG frequency

White 2001 and White 2010 report on the results of the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the observational follow-up of the DCCT for years four and ten respectively in the same study population.[78,79] These reports represent the longest follow-up of children with type 1 diabetes and the impact of intensive intervention. At the end of the DCCT (1994), all participants in the conventional treatment arm were offered instruction in the use of intensive therapy and intensive treatment group patients were encouraged to continue such treatment. The EDIC cohort initially included 175 (91%) of the 195 adolescents originally enrolled in the DCCT. White 2001 reports the 4-year follow-up and White 2010 reports the 10-year follow-up (N=156, 80% of original DCCT population) with respect to mean A1c, progression of retinopathy (≥ 3 step of retinopathy, presence of severe non-proliferative diabetic retinopathy or worse, proliferative retinopathy, laser photocoagulation therapy, clinically significant macular edema), and nephropathy (microalbuminuria and clinical grade albuminuria). Not all participants had data for all outcomes at all time periods. The reports compare the frequency of these outcomes between individuals who participated in the intensive intervention versus conventional treatment arms of the DCCT. Both reports describe the use of multivariate statistical methods, but for some outcomes, it is not clear whether the reported estimates are adjusted or if adjusted, what factors were included in the models.

Key Question 2. Randomized studies

Studies of continuous glucose monitoring (CGM) efficacy compared with SMBG

There were five reports from four RCTs identified that allowed patients to make use of the real-time features of CGM[80-83,124] that provide the primary evidence describing the efficacy of CGM. Interventions compares in these trials are summarized below. Some included adults and provided limited information stratified by age. The Bergenstal study compares two different monitoring methods as well as two different treatment methods. [83]Thus, the effect of CGM versus SMBG cannot be separately assessed. Direct comparisons between the Bergenstal and the JDRF and Hirsch studies are not appropriate so evidence summaries will focus on these studies. As noted throughout this report, confirmatory SMBG is done with CGM. Thus, the comparison is of *CGM in conjunction with SMBG* versus SMBG alone for these studies.

Table 10. Description of Randomized Controlled Trials of real-time Continuous Glucose Monitors

Study	Intervention	How were glucose data used for therapeutic changes?
RCTs of real-time use of CGM data		
JDRF 2008* **(N=114 age 8-14)**	**CGM arm:** CGM 7 days/week and ≥ 4 per SMBG/day for 1 year	**CGM arm:** participants instructed to use CGM in conjunction with SMBG data to adjust insulin dose
	SMBG arm: ≥ 4 per day for 1 year; blind CGM worn for 1 week at baseline, 12 and 26 weeks	**SMBG arm:** participants instructed to use SMBG data only to adjust insulin dose
JDRF (Beck) 2009 † **(N=29 age 8-14)**	**CGM arm:** Continuous CGM and ≥ 4 per SMBG/day for 1 year	**CGM arm:** participants instructed to use CGM in conjunction with SMBG data to adjust insulin dose
	SMBG arm: ≥ 4 per day for 1 year; blind CGM worn for 1 week at baseline, 12 and 26 weeks	**SMBG arm:** participants instructed to use SMBG data only to adjust insulin dose
JDRF (Beck) ‡ 2010 **(N=218 age8-18)**	**CGM arm:** CGM 7 days/week and ≥ 4 per SMBG/day for 1 year	**CGM arm:** participants instructed to use CGM in conjunction with SMBG data to adjust insulin dose
	SMBG arm: ≥ 4 per day for 1 year; blind CGM worn for 1 week at baseline, 12 and 26 weeks	**SMBG arm:** participants instructed to use SMBG data only to adjust insulin dose
Hirsch 2008§ **(N=40 age8-18)**	**CGM arm:** Integrated CGM with Insulin pump **SMBG arm:** SMBG with Insulin pump and blind CGM	**CGM arm:** participants received training in the use of CGM and intensive diabetes management **SMBG arm:** participants received training in intensive diabetes management
Bergenstal 2010 ** **(N=156 age7-18)**	**CGM arm:** Integrated CGM with Insulin pump **SMBG arm:** SMBG and insulin pump, . Blind CGM worn for 1 week at baseline, 6 months, and 1 year.	**CGM arm:** participants received training in CGM, insulin-pump and intensive diabetes management **SMBG arm:** participants received training in intensive diabetes management

* N represents study participants age 8 to 14 years old; all participants had baseline A1C ≥ 7%

†N represents study participants age 8 to 14 years old; all participants had baseline A1C < 7%

‡N represents total number of study participants in both JDRF interventions (JDRF 2008 and Beck 2009) age 8 to 18 years old

§Participants not using insulin pump for 6 months or more were excluded

** Participants already using an insulin pump were excluded; This study is not comparable to JDRF and Hirsch given that two different monitoring methods as well as two different treatment methods were compared.

The first two RCTs, one of which is the JDRF 2008 (n=114 age 8 to 14) with data on those ≤ 18 years old, were conducted by the Juvenile Diabetes Research Foundation (JDRF).[80,82] Both trials are LoE II RCTs, which compare the use of rt-CGM (participant choice of either the DexCom Seven, MiniMed Paradigm, or FreeStyle Navigator) continuously for 26 weeks (as a supplement

to standard SMBG) to SMBG ≥ 4 times per day in patients who had use of the data on a daily basis. These multi-center trials used identical intervention designs and were conducted in parallel using different populations; one was restricted to type 1 diabetics in good glycemic control (defined as A1C < 7% at baseline) (JDRF 2009),[82] and the other was conducted in type 1 diabetics with baseline A1C levels from 7% to 10% (JDRF 2008).[80] The same procedures were used in both trials; written instructions were provided to both CGM and SMBG groups on how to use the data provided by CGM and blood glucose meters to make real-time adjustments of insulin doses and on the use of computer software to retrospectively review glucose data to alter future insulin doses (CGM arm only). Participants in the CGM arm received additional instructions for modifying their insulin doses and treatment of hypoglycemia on the basis of glucose trend. At follow-up visits (1, 4, 8, 13, 19 and 26 weeks post-randomization), and phone contacts between visits, glucose data were reviewed and therapy was adjusted for all participants. Both trials were conducted in adults as well as adolescents, and results (for at least one outcome of interest) were stratified into three age groups (8 to 14 years, 15 to 14 years and ≥ 25 years). The primary outcomes for both trials includedA1C (laboratory derived), and several measures of hyper- and hypoglycemia (amount of time per day glucose levels were hypoglycemic (≤70 or ≤50 mg/dl) or hyperglycemic (≥180 or ≥250 mg/dl)), which were calculated using 1-week CGM data (unblinded in the CGM arm and blinded in SMBG alone arm) collected after the 13- and 26-week visits. In both studies sensor use declined over time, and in the JDRF study among participants in poor glucose control (JDRF 2008) 2 participants discontinued sensor use prior to the end of the study, whereas no participants in the JDRF study among participants in good glycemic control discontinued sensor use (JDRF 2009).

The JDRF 2010[124] is not a distinct RCT, but a combined analysis of the JDRF trials conducted in parallel study populations (participants with A1C <7% at baseline and ≥7% at baseline); therefore, the methods and LoE are identical to those described in the prior paragraph. The primary difference is that this manuscript specifically focuses on the effects of CGM versus SMBG on quality of life issues, which were not reported in any of the other RCTs reports. The primary outcomes of interest include diabetes-specific and general assessments of quality of life. Both participants and parents of participants < 18 years of age completed these assessments at baseline and the end of the trial (26 weeks). All data were stratified into adolescents (<18 years) and adults (≥ 18 years)

Hirsch et al[81] is also a LoE II randomized controlled trial comparing intermittent use of an integrated CGM and insulin pump (Medtronic Paradigm 722 System, Medtronic) with SMBG and insulin pump among 40 adolescents 12 to 18 years of age (and 98 adults). In this 26-week study, participants in the integrated CGM arm wore the monitor for a total of 18 days within a 30-day period, and participants in the SMBG arm were asked to complete SMBG at least 4 times daily. Both integrated CGM and SMBG arms were trained in intensive diabetes management and participants in the integrated CGM arm received additional training in the use of CGM data; however, it is unclear whether study investigators reviewed glucose data to make therapeutic changes during the trial. This trial was also conducted in older participants and the primary A1C results were stratified by age (12 to 17 years and 18 to 72 years); however, data for other outcomes (hypoglycemia and hyperglycemia) was not stratified by age and therefore could not be included. Data on CGM compliance and drop-out rate were not stratified by age.[81]

One additional RCT allowed use of the real-time features of CGM, but compared two different treatment interventions; use of an integrated CGM and insulin pump system versus multiple daily injections with SMBG.[83] Bergenstal et al. is a LoE II randomized controlled trial comparing continuous use of an integrated CGM and insulin pump (Medtronic Paradigm System, Medtronic) with SMBG plus multiple daily insulin injections among 156 adolescents age 7 to 18 years (as well as 329 adults). Both CGM and SMBG arms were trained in intensive diabetes management and use of the insulin-pump, and participants in the CGM arm also received sensor training. Patients were first placed on insulin-pump therapy for 2 weeks, and then glucose sensors were introduced. At follow-up visits (3, 6, and 9 months post-randomization), glucose data were reviewed and therapy was adjusted for all participants. This trial was also conducted in older participants and all results were stratified by age (7 to 18 years versus ≥ 19 years). The primary outcomes for this trial include A1C (laboratory derived), and several measures of hyper- and hypoglycemia (area under the curve <70 or <50 mg/dl) or hyperglycemic (area under the curve >180 or >250 mg/dl)), which were calculated using 1-week CGM data (unblinded in the integrated CGM arm and blinded in SMBG arm) collected at baseline and 1 year. There is no mention of either compliance to the meter or drop-out rates stratified by age in this reference.[83]

Treatment assignment

None of the four studies stated whether treatment arm assignment was concealed from study staff prior to allocation.

Sample size

Sample size for the four studies ranged from 40 (CGM n = 23 and SMBG n = 17)[81] to 156 (78 participants per treatment arm).[83] Four[80,82,83,124] provided information on sample sizes required for primary outcomes; however, in one trial power was not specifically calculated for the age group of interest (< 18 years)[82] and one did not report an estimate of sample size required for primary outcomes.[81]

Independent or blind assessment

All of the four studies reported the use of independent or blind assessment[80-83] for most outcomes except for self-reported quality of life. [JDRF 2010 quality] A1C values were objective outcomes derived from laboratories and could not be biased by investigator knowledge of treatment arm.

Statistical analysis

All five studies delineated the descriptive and inferential statistics used, and three stated an *a priori* alpha level of .05 for statistical significance. Four stated that they controlled for possible confounding factors via various statistical methods,[80,81,83,124] and one did not state control for possible confounding factors although the distribution of potential confounders appeared to be equal between treatment arms.[82]

Follow-up time and percent of patients followed

These studies provide limited information on continued, long-term use of CGM as the longest follow-up time in any study was one year.

Follow-up periods ranged from 26 weeks[80] to one year.[83] In two of the studies,[83,124] follow-up rates were provided for the entire study population (> 99% and 98%), but could not be explicitly determined for the age range of interest. Follow-up rates for remaining studies were > 99%, [80]> 93%[124] and > 99%.[81]
Information from the FDA SSED reports of RCTs for the devices used by studies cited in this report is described in the safety section. These reports do not provide sufficient details of methods to allow for detailed critical appraisal and are not rated. The studies are in populations older than those that comprise the focus of this HTA but provide some information on the broader safety profile of the devices used.

Key Question 2. Non-randomized studies

Observational studies of effectiveness: SMBG frequency
All observational studies for SMBG were rated as LoE III.

The primary purpose of the majority of these studies was not to evaluate the effect of SMBG on A1C levels. In these studies, SMBG was one of a number of factors considered as potential confounders or modifiers of associations between other exposures (e.g. insulin regimen or psychological factors) on A1C. It is also important to note that the majority of these studies employ a cross-sectional research design for evaluation of SMBG and the results can give information about associations, and not about causal relationships. . Laffel et al [Laffel 2003] conducted an RCT of family focused team-work vs. conventional therapy for glycemic control in 105 children/adolescents. As part of a multivariate subanalysis to their RCT, the association between frequency of SMBG and A1c was examined at the end of the 1-year study. For the purpose of this HTA, such an analysis is considered a cohort study, not an RCT. Studies by Ziegler, Levine, Moreland, Anderson 1997 and Anderson 2002 did examine the association between SMBG frequency by category and control for potentially confounding factors.[92-94,96-98]The study by Paris which also looked at SMBG categories reported unadjusted estimates.[95]Studies assessing frequency of SMBG as a continuous variable for its association with A1C primarily used the SMBG as a covariate in models. As a result, generally only unadjusted results are available to describe associations between SMBG and A1C in most of these studies. This later group of studies will not be described in detail.

In all of these studies, although SMBG may be a significant predictor of A1C, since they are cross-sectional, the temporal sequence is not known and causality cannot be inferred. It is unknown if those who test more often are more likely to be more adherent to factors such as diet and exercise (as well as monitoring) than those who test less frequently.

Ziegler 2010
Ziegler et al[92] analyzed data from the a German/Austrian database comprised of 26,723 children and adolescents aged 0–18 years with type 1 diabetes recorded from 1995 to 2006. This was the only study found that explicitly sought to evaluate the relationship between SMBG and A1C. Mean age, gender, and mean duration of diabetes were not provided. A1C levels were

mathematically standardized to the DCCT reference by mean of the "multiple of the mean method" to adjust for different laboratory methods. The authors did investigate the relationship between frequency of SMBG and A1C levels and controlled for possible confounding factors of this association. The authors further report a significant positive relationship between the rate of hypoglycemia and the number of blood glucose measurements performed, as well as a significant and inverse relationship between the frequency of DKA and the frequency of SMBG, and state that these associations were also controlled for confounding factors. Person-years at risk (per 100 years) were calculated. The authors explored the modification of the association between SMBG and A1C by categories of age and insulin regimen and adjusted for potentially confounding factors. This study received a LoE III.

Anderson 2002

Anderson et al[94] report on the baseline data from a 2-year prospective, cross-sectional study in 104 children (from 128 eligible), age 8 to 17 years old, with type 1 diabetes. The primary purpose of this study was to investigate possible parental/family behaviors or "conflicts" that related to adherence to SMBG and glycemic control in children with diabetes. Patients from families who opted not to participate in the study were on average 1.5 years older than participants with no differences in duration of glycemic control. The children were divided into younger and older groups. There were 69 patients ages 8 to 12 years (mean age 10.7 years, 51% female, mean duration of diabetes 2.7 years) and 35 patients ages 13 to 17 years (mean age 14.7 years, 40% female, mean duration of diabetes 2.4 years). The only difference between the two groups was that the younger age group received significantly fewer injections per day (65% injecting twice daily) than those in the older group (32% injecting twice daily). The authors did, however, examine the relationship between self-reporting of daily SMBG frequency and A1C levels and controlled for possible confounding factors (age, sex, diabetes duration, child conflict, parent conflict) of this association. Data were gathered via structured interviews and questionnaires. No information was provided as to the completion rate of either the interviews or the questionnaires (i.e. follow-up rate). A significance level of $P< .05$ was prospectively determined. This registry study received a LoE grade of III.

Anderson 1997

Anderson et al[93] conducted a chart review looking for children and adolescents with insulin-dependent diabetes mellitus, aged 10 to 15 years, who met certain eligibility criteria. Of the 140 eligible families who received a letter and a follow-up phone call asking them to participate in the study, 89 (64%) agreed and were enrolled. The authors report that there were no significant differences between study families and those who declined study participation with respect to age, disease duration, frequency of injections per day, or metabolic control. The children were divided into younger and older age groups. There were 51 children ages 10 to 12 years (mean 11.7 years, 55% female, mean duration of diabetes 5.3 years) and 38 children ages 13 to 15 years (mean 14.0, 45% female, mean duration of diabetes 6.0 years). The only significant difference between the two groups was that patients in the younger group checked their blood sugar concentrations more often per day. The main purpose of this study was to identify specific parental behaviors that related to improved compliance with SMBG and glycemic control. Other predictors of glycemic control, to include frequency of SMBG, were also investigated, and the authors did control for potential confounders (sex, diabetes duration, Tanner stage) of this

association. Of note, initially glycemic control was measured using total glycosylated hemoglobin (HbA1). During the study period the laboratory began to measure HbA1C. For comparison between HbA1 and HbA1C values, the authors developed a conversion formula, derived from a regression analysis of 700 samples analyzed by both methods. All glycemic control data were reported as HbA1C values. Data were collected via structured interviews and completion of The Adherence Scale by the patient's parent or caregiver. No information was given as to the follow-up period or the completion rate of either interviews or the questionnaires (i.e. follow-up rate). This study received a LoE grade of III.

Levine 2001

Levine et al[96] assessed the association between frequency of SMBG and A1C by analyzing data from 300 children (from 351 eligible) with type 1 diabetes involved in a prospective, longitudinal study that examined factors related to baseline glycemic control and the influence of glycemic control on short term adverse events such as hypoglycemia. Unfortunately the association between SMBG and A1C reported examined only baseline A1C and report of SMBG in a cross-sectional way and did not take advantage of the prospective design for reporting on this association. The authors did perform a multivariate analysis to control for diabetes duration, pubertal stage and sex when assessing the relationship between frequency of SMBG and A1C. The authors state that baseline characteristics of those patients who declined to participate did not differ significantly from those of study participants with respect to age, HbA1C values, or diabetes duration. Mean patient age was 11.9 years (range, 7–16) and 56% were female. Blood samples were drawn at each visit to measure A1C values, the primary outcome used to assesses glycemic control. In a small number of patients A1C was assayed at a different laboratory and the authors describe a standardization procedure used to adjust for variations among local A1C assays. The occurrence of clinically significant events, such as hospitalizations, emergency room visits, and hypoglycemic events (moderate and severe) was determined by questionnaires administered to families at each visit and confirmed by review of the medical record when possible. Patients were followed for 1 year or until they dropped out of care. However, the relationship between the clinically significant events and frequency of SMBG was not reported. As only the association between SMBG and A1c at baseline is relevant to this HTA, it was assessed as a cross-sectional study and received a LoE grade of III.

Laffel et al[98] randomized children with type 1 diabetes to family-focused teamwork or standard care. Eighty-one percent of those invited to participate agreed to do so. Children were eight to 17 years old and had diabetes for 2 months to 6 years; 53% were male. Factors predictive of A1c at the end of the 1-year trial were analyzed in a multivariate analysis. The model included treatment group, frequency of SMBG, age, duration of diabetes, gender, and dose of daily insulin. It is unclear whether the SMBG frequency used in the model was from baseline or 1 year. If baseline values were used, it would be considered a prospective design for purposes of this analysis. If one year values were used, it would be considered a cross-sectional design. Only frequency of SMBG and the interventions were significant predictors of A1c at one year. Authors note that during the course of the year, frequency of SMBG decreased despite increased intensity of insulin therapy. This study received a LoE grade of III.

Moreland 2004

Moreland et al[97] conducted a cross-sectional study in 153 children (from 174 eligible), ages 8 to 16 years, with type 1 diabetes. Mean age of the patients was 12.9 years, 56% were female, and the mean duration of diabetes was 6.3 years. The majority of children received daily injections (77%) while the remainder (23%) had continuous subcutaneous insulin infusions (pump therapy). The main objective of this study was to assess the impacts of physiological (i.e. pubertal stage), therapeutic (i.e. mode of insulin therapy), and psychosocial (i.e. parental involvement/conflict) variables on glycemic control. The authors did examine the relationship between frequency of SMBG and A1C levels and controlled for possible confounding factors (pubertal status, parental report of family involvement) of this association. Data were collected via questionnaires completed by both the patient and their parents. No information was given as to the follow-up period or the completion rate of the questionnaires (i.e. follow-up rate). A significance level of $P < .05$ was prospectively determined. This study received a LoE grade of III.

Paris 2009
Paris et al[95] used data from the SEARCH for Diabetes in Youth study, a large (N = 2743) population-based, multi-center, cross-sectional study conducted in children and adolescents with type 1 diabetes. Mean age of the patients was 13.2 years, 50% were female, and the mean duration of diabetes was was 5.0 years. The study's primary purpose was to describe and evaluate factors associated with insulin regimen and clinical outcomes, primarily A1C. Authors did do multivariate regression controlling for confounders for the association between insulin regimen and clinical outcomes but only report unadjusted estimates for the association between SMBG and A1C. SMBG was one of the factors considered and used to adjust for confounding. Authors report that regardless of insulin regimen, those who tested infrequently (≤ 2 times/day) had higher A1C levels than those who checked more frequently (≥ 4 times/day), but do not provide tests of statistical significance for the association nor do they directly (statistically) compare A1C with respect to categories of SMBG frequency. These observational data were gathered from a single study visit asking patients or parents to recall incidences occurring in the 6 months prior to the study. Completion rate (i.e. follow-up rate) is unclear or unable to be determined. This study received a LoE grade of III.

Observational studies of effectiveness: Consistency and frequency of CGM use

Chase 2010
Chase et al[90] conducted an extension study in which 80 subjects who completed the JDRF study, a 6-month RCT, and who opted to continue use of CGM in a 6-month extension study. The subjects were 8 to 17 years of age at enrollment in the JDRF. Mean age of the children was 13.0 years and 50% were female. The main purpose of this study was to report the patterns of CGM uses and biochemical and clinical outcomes over the entire 12 months. A secondary purpose was to compare A1C levels, sensor glucose levels, rates of severe hypoglycemia, and the benefit and limitations of current CGM technology as perceived by the patients and parents in those who continued to use CGM regularly for 12 months and those who did not. The patients were categorized into three groups based on CGM use in months 6 and 12: ≥ 6 days/week in month 12; ≥ 6 days/week in month 6

but < 6 days a week in month 12; and < 6 days a week in both months 6 and 12. CGM use was found to be associated with age, thus all subsequent models were adjusted for this factor. Furthermore, the outcomes of change in A1C from baseline to 12 months according to CGM use and the percentage of subjects meeting the ADA A1C target at 12 months by CGM group were also adjusted for baseline A1C values. Analyses included only subjects completing the 12-month (94%) visit and there was no mention of independent or blind assessment of outcomes. There is no mention of a predetermined significance level. Complete follow-up was available in 94% (n = 75/80) of patients. This study received a LoE of II.

JDRF 2010 Effectiveness
Another JDRF extension study [91] describes 61 subjects age 8 to 14 who were randomized to SMBG in the JDRF study, completed the 6-months trial, then were offered use of CGM in a 6-month extension study. The main purpose of this study was to report the patterns of CGM uses and biochemical and clinical outcomes in a typical clinical practice setting. The patients were categorized into three groups based on CGM use in month 12 (6^{th} month of CGM use): (0 days/week; >0 ≤ 4 days/week; 4 to < 6 days; or ≥ 6 days a week. Analyses included subjects completing the 12-month visit (98%) and there was no mention of independent or blind assessment of outcomes. There is no mention of a predetermined significance level. This study received a LoE of III.

JDRF 2009(Beck)
This subanalysis of the primary JDRF 2008 RCT includes the 6-month follow-up data from the 232 subjects randomly assigned to the CGM arm of the JDRF CGM study.[89] Of these participants, 74 (32%) were aged 8 to 14 years old. All other demographic variables were reported for the entire population only. The purpose of this article was to explore associations between demographic, clinical, and psychosocial factors and successful CGM use (defined as average use of ≥ 6 days/weeks during the 6^{th} month of the trial) and reduction in A1C levels from baseline to 6 months. After initial screening, all patients wore blinded CGM to obtain baseline data before randomization. Subjects were instructed to use the CGM device on a daily basis and were given written instructions on how to use the CGM data to make real-time insulin dose adjustments and on using computer software to review past glucose data in order to change future insulin dosing. A1C levels were obtained at baseline, 3 months, and 6 months and measured in a central laboratory. A significance level of $P < .05$ was prospectively determined. Multivariate models were used to control for confounding when looking at factors, such as age, associated with both CGM use and a reduction in A1C. There was no mention of independent or blind assessment of outcomes and complete follow-up percentage could not be determined. This study received a LoE of III.

Key Question 3. Observational studies: Safety

One observational study contributed data on SMBG,[121] and seven to CGM safety.[111-117] [Boland, Cemerglu, Messer, DRCN, Gandrud, Wong, Jeha]. The overall quality of these studies

was poor (LoE III). Of these, two were retrospective.[111,112] Only one controlled for potentially confounding factors.[114] Only one study described independent or blind assessment of outcomes, but may not have had sufficient sample size.[116]

Key Question 4 and 5.
One RCT (LoE II)[80] and one registry study (LoE III)[92] contributed evidence for Key Question 4. Descriptions and appraisal of these studies are found in the previous discussion.

No studies were found that met our inclusion criteria to address key question 5.

2.3 Description of study population

The following table summarizes the patient populations from randomized controlled trials that provided data on participants ≤18 years of age. Studies by Hirsch and the JDRF 2009 did not provide descriptive information stratified by age.[81,89]

Table 11. Summary of participant characteristics for included randomized controlled trials.

	DCCT 1994[22]			
	Primary Prevention* Cohort		Secondary Intervention† Cohort	
Variable	IT‡ (n = 55)	CT§ (n = 70)	IT‡ (n = 37)	CT§ (n = 33)
Patient demographics				
Sex				
No. males (%)	31 (56)	33 (47)	18 (49)	13 (39)
No. females (%)	24 (44)	37 (53)	19 (51)	20 (61)
Age, years; mean (SD)	15 ± 1	15 ± 1	15 ± 1	15 ± 1
Non-Hispanic white race, no. (%)	54 (98)	68 (97)	35 (95)	28 (85)
BMI, mean (SD)				
Male	22 ± 2	21 ± 2	21 ± 2	20 ± 3
Female	22 ± 3	22 ± 3	24 ± 2	22 ± 3
Duration of DM, months; mean (SD)	38 ± 20	37 ± 20	89 ± 43	97 ± 42
Glycated hemoglobin (%), mean (SD)	9.3 ± 1.9	9.2 ± 1.8	9.8 ± 1.8	10.1 ± 1.8
Plasma glucose (mg/dl), mean (SD)	261 ± 106	243 ± 103	254 ± 112	305 ± 114
Hypoglycemia in year before study				
Required medical assistance, no. (%)	0 (0.0)	3 (4.3)	1 (2.7)	0 (0.0)
Loss of consciousness, no. (%)	2 (3.6)	11 (15.7)	3 (8.1)	1 (3.0)
Retinopathy, no. (%)	0 (0.0)	0 (0.0)	37 (100)	33 (100)
Urinary albumin excretion (mg/24 hr), mean (SD)	15 ± 15	15 ± 9	26 ± 32	29 ± 40
Clinical neuropathy	1 (1.9)	3 (4.3)	0 (0.0)	1 (3.0)

BMI: body mass index; CT: conventional treatment; IT: intensive treatment.
*Subjects with insulin-dependent diabetes but no retinopathy at baseline.
†Subjects with insulin-dependent diabetes and mild retinopathy.
‡Administration of insulin three or more times daily by injection or an external pump and short-acting insulin before meals that was adjusted according to planned dietary intake, anticipated exercise, and the results of self-monitoring of blood glucose levels, performed at least four times daily.
§One or two daily insulin injections, including mixed intermediate and rapid-acting insulins, once-daily self-monitoring of urinary or blood glucose values, and diet and exercise education.

	JDRF 2008[80] [8–14 year-olds]		Bergenstal 2010[83] [7–18 year-olds]	
	CGM	Control*	SAPT†	Control‡

Variable	(n = 56)	(n = 58)	(n = 78)	(n = 78)
Patient demographics				
Sex				
No. males (%)	29 (52)	29 (50)	281 (75.6)	284 (76.3)
No. females (%)	27 (48)	29 (50)	91 (24.4)	88 (23.7)
Age, years; mean (SD)	11.4 ± 2.0	11.6 ± 2.1	11.7 ± 3.0	12.7 ± 3.1
Non-Hispanic white race, no. (%)	51 (91)	54 (93)	70 (90)	69 (88)
BMI, mean (SD)	NR	NR	20.2 ± 3.8	20.6 ± 4.5
z-score < -0.5, no. (%)	2 (4)	1 (2)	NR	NR
z-score -0.5 to 0.5, no. (%)	16 (29)	11 (19)	NR	NR
z-score > 0.5, no. (%)	38 (68)	46 (79)	NR	NR
Duration of DM, years; mean (SD)	6.2 ± 3.1	5.3 ± 2.8	4.7 ± 3.1	5.4 ± 3.7
Insulin administration, no. (%)				
Pump	47 (84)	49 (84)	78 (100)	0 (0.0)
Multiple daily injections	9 (16)	9 (16)	0 (0.0)	78 (100)
Glycated hemoglobin (%)				
Mean (SD)	8.0 ± 0.7	7.9 ± 0.6	8.3 ± 0.6	8.3 ± 0.5
7.0–8.0, no. (%)	32 (57)	34 (59)	NR	NR
8.1–8.9, no. (%)	18 (32)	23 (40)	NR	NR
≥ 9.0, no. (%)	6 (11)	1 (2)	NR	NR
≥ 1 episodes of severe hypoglycemia during previous 6 mo., no. (%)	2 (4)	3 (5)	NR	NR
Daily home glucose-meter reading, no./day	6.7 ± 2.1	7.0 ± 2.5	NR	NR

BMI: body mass index; CGM: continuous glucose monitoring; DM: diabetes mellitus; NR: not reported; SAPT: sensor-augmented pump therapy.
*Self-monitoring blood glucose 4x/daily.
†The pump-therapy group used a device that integrates an insulin pump with continuous glucose monitoring (MiniMed Paradigm REAL-Time System, Medtronic).
‡Multiple daily insulin (glargine and aspart) injections and self-monitoring blood glucose.

DCCT 1994[22]: The study included 195 adolescents age 13 to 17 years. Sexual development in the adolescents had to be at least Tanner stage II or beyond. Among the adolescents, 41% were age 13 and 14 years of age, 47% were 15 and 16 years of age, and 12% were 17 years of age. Any women who were planning a pregnancy or became pregnant in the conventional treatment group were put on the intensive treatment group, then after the pregnancy, were returned to the conventional treatment group.

Included studies that did not stratify demographic information by age

Beck (JDRF) 2009[89] included a total of 129 subjects, 29 (22%) of whom were children age 8 to 14 years. The majority of the population used an insulin pump (n = 111, 86%) and the percent of such patients was similar across treatment arms. The CGM group (n = 67) included 18 (27%) children and the control group (SMBG ≥ 4 times per day, n = 62) of 11 (18%) children. In this age group, the duration of diabetes was 4.9 ± 2.6 and 4.4 ± 3.2 years, respectively, and the total daily dose of insulin was 0.8 ± 0.1 and 0.8 ± 0.3 units/kg.

Of the 138 patients who completed the study by Hirsch 2008,[81] 40 (29%) were adolescents age 12 to 18 years, and made 26% (n = 17/66) of the CGM(integrated CGM plus insulin pump) and 32% (n = 23/72) of the SMBG group (SMBG plus insulin pump). No further demographic information was given for this age group.

2.4 Description of study outcomes

2.4.1 Efficacy and effectiveness measures

Ideally, direct evidence over a long term of follow-up from randomized controlled trials that evaluate the impact of SMBG and CGM on diabetes-related morbidity and mortality would be available. Hemoglobin A1C is considered an intermediate (surrogate) outcome as it is a predictor of diabetes complications and, in the absence of such trials provides the best available evidence

The primary outcome measure available in most studies was hemoglobin A1C. The proportion of individuals achieving a specific target would ideally be reported. There is some uncertainty regarding what the appropriate target(s) may be. Information from the DCCT did not establish a single, optimum target that maximizes benefit while minimizing risk. The American Diabetes Association suggests that the A1C goal for adolescents should be under 7.5%, school age children (age 6-12 years) below 8%, and toddlers and preschool (under 6 years) 7.5% to 8.5%.[18] The A1C goals for children are higher than those recommended for adults due to the difficulty of achieving good control without incurring undue hypoglycemia. The grade of this recommendation is "E" indicting that it is based on expert opinion and clinical experience. From the DCCT, adolescents in the intensively treated group achieved a mean A1C of 8.1%. The JDRF study used 7% as well as the higher values to describe the percent of patients achieving targets. Similarly, there is no consensus on what constitutes a clinically meaningful change in A1C; thus, a value of 0.5%, which was suggested as clinically meaningful in other studies, was used in this HTA

Hypoglycemia and hyperglycemia were defined and reported in various ways across studies. Event rates are summarized where reported. The abundance of data provided by CGM allows for construction of a *glucose curve* by plotting the glucose levels versus time on a graph and connecting each of the glucose measurements. The *area under the curve (AUC)* provides a single number summary of the total glucose exposure. The time spent within a certain glucose range (e.g. < 70 mg/dl) can be determined. Aggregate data for these are reported in addition to event rates where data were available.

The DCCT was the only RCT that reported on retinopathy and nephropathy. To evaluate retinopathy, eye exams were administered every 6 months and a significant change was defined as a change of 3 or more stages on the Early Treatment Diabetic Retinopathy Study scale that includes 25 steps to represent the overall extent of retinopathy in both eyes. In the primary prevention cohort, retinopathy was defined as the presence of >1 microaneurysm on two consecutive 6-month fundus photographs. Worsening was defined as a change of at least three steps from baseline sustained for ≥ 6 months. Nephropathy was described as episodes of microalbuminuria (defined as urine protein excretion over 30 mg/24 hours) and albuminuria as excretion over 300 mg/24 hours) and creatinine clearance ≤ 70ml/min per 1.73 m^2.

The JDRF trial used several quality of life measures including diabetes-specific measures (Hypoglycemia Fear Survey (HFS) worry subscale (scale 0–100 with higher score denoting more fear), Pediatric Quality of Life Inventory (PedsQL) Type -1 Diabetes module (scale 0–100 with higher score denoting higher QOL) and Problem Areas In Diabetes (PAID), aparent survey

evaluating parental burden associated with diabetes care; norm-based score with higher score denoting better functioning) and general assessments of quality of life (PedsQL- Generic; scale 0–100 with higher score denoting higher QOL).

2.4.2 Safety measures

The background section provides an overview of primary safety issues related to CGM and further definition of measures is presented in key question 3. Information on mortality is included here as well.

2.4.3 Economic Measures

Incremental cost-effectiveness ratios from full economic studies provide the optimal outcome measure. No relevant full economic studies were found.

3. Results

3.1 Key question 1: What is the evidence of efficacy and effectiveness of glucose monitoring?

Including consideration of:

a. Achieving target A1C levels
b. Maintaining target A1C levels
c. Achieving target A1C levels in conjunction with provider specific report cards (e.g. under 7/over 9)
d. Reduced hospitalizations or acute episodes of diabetic ketoacidosis, hyperglycemia and hypoglycemia
e. Reduced microvascular complications (retinopathy, nephropathy, neuropathy)
f. Reduced mortality
g. Effect on medication or nutritional management
h. Quality of life

3.1.1 Efficacy of SMBG

The method used by most persons with diabetes for self-glucose monitoring and evaluation of daily glycemic control is self-monitoring of blood glucose (SMBG). No recent RCTs on the efficacy of SMBG were found. The evidence base for efficacy is derived primarily from the results of the Diabetes Control and Complications Trial (DCCT) and older, poor quality randomized controlled trials comparing early SMBG methods with urine testing. Urine testing has since been determined inaccurate and is generally considered obsolete by the professional community. The technology used for SMBG in these studies is also outdated.

Overview of findings

No recent randomized controlled trials of the efficacy of SMBG were found.

The Diabetes Control and Complications Trial (DCCT)was a landmark study (n = 195 adolescents age 13 to 17 years) that assessed intensive glucose control in persons with type 1 diabetes mellitus (T1DM) in the United States.[1,22] It provides only indirect evidence regarding the efficacy of SMBG as part of a package of comprehensive, intensive diabetes care package, which included SMBG several times per day and education on how to use the information to adjust insulin, diet and exercise over the long term. (Patients were followed a mean of 7.4 years) This was compared with conventional care that included SMBG *or* urine monitoring once per day and no adjustment of insulin dose on a daily basis. Patients were recruited for either the primary prevention (PP) cohort (if they had no retinopathy or nephropathy) or the secondary intervention (SI) cohort (if they had mild-to moderate retinopathy). Details of the study design and population have been described in the previous section and are highlighted below.

Overall, in participants 13–17 years old at baseline (mean age 15 years) across both cohorts over the entire study period:

- Mean A1c levels between the intensive and conventional arms were significantly different by 6–12 months and that they remained so for the remainder of the 7.4 year

trial: 8.06% for the intensive treatment arm vs. 9.76 for the conventional treatment arm. (P value for test of medians was < 0.0001).

- Average daily blood glucose concentrations were significantly lower in the intensively treated group (9.8 ± 4.7 mmol/L or 177 ± 31 mg/dl) compared with the conventionally treated group (14.4 ± 2.9 mmol/L or 260 ± 52 mg/dl), *P*< .0001.
- A 61% risk reduction in sustained ≥ three-step retinopathy (95% CI 30%,78%) was reported for those in the intensively treated group, p=0.02 after adjusting for based line retinopathy
- No statistically significant difference in nephropathy were reported based on estimate adjusted for baseline urinary albumin level, *P* = .75.
- Similar percentages of patients in each group experienced ketoacidosis (18% for intensively treated, 20% for conventionally treated.
- An approximately threefold higher risk of hypoglycemia resulting in coma/seizure was seen in those receiving intensive treatment (RR 2.93, 95% CI 1.75 4.90, *P*< .001)

Primary and secondary cohort findings:

- In both cohorts, there was a statistically significant risk reduction for sustained ≥ three-step retinopathy, 53% (95% CI 1% to 78%) in the PP Cohort, and 70% (25, 88) in the SI Cohort (*P*< .05) following adjustment for baseline retinopathy.
- For nephropathy, no significant difference between treatment arms was seen in the PP cohort, and a 55% (3, 79%) risk reduction was seen in the SI cohort (following adjustment for baseline urinary albumin).

Four older RCTs (1985–1983) comparing SMBG with urine testing have been described in previous HTAs and were captured in the search for this HTA.[74-77] Devices and testing methods used in these studies are no longer considered state-of-the art. These four early studies of SMBG in children are viewed more as feasibility and acceptance studies, rather than studies of efficacy regarding the potential impact of SMBG on A1C or health outcomes and mortality. They reflect standards of care and levels of A1c considered acceptable in their era. The results from these studies may suggest some trend toward improved glycemic control but no statistically significant improvement in A1C was reported in three of four studies. There were few episodes of severe hypoglycemia and DKA in any of the studies, and the ability to detect and correct hypoglycemia was greater using SMBG, but did not reach significance. In all of the studies, the patients and their parents preferred SMBG over urine testing and most of the subjects chose to continue using SMBG after the study ended. This may suggest that the benefit of detecting hypoglycemia alone may be valuable to these children and their parents and that the discomfort of glucose testing and hassle of working with the meter was not a significant obstacle. These studies are only briefly described for historical context, with details available in the Appendices.

Details of findings

The DCCT study included 195 adolescents age 13 to 17 years who were described in a separate report.[1,22] The primary prevention (PP) cohort included 125 adolescents who had had diabetes from 1 to 5 years and had no evidence of retinopathy or nephropathy. The secondary intervention (SI) cohort included 70 adolescents that had had diabetes from1 to 15 years and had mild-to moderate non-proliferative retinopathy. The conventional treatment group injected insulin once or twice a day, and used daily monitoring of blood glucose or urine. They did not adjust the insulin on a day to day basis. The intensive treatment group was placed on three or more insulin injections a day or an insulin pump. They were taught to test the blood glucose several times a day and adjust the insulin dose, diet, and exercise to maintain the preprandial (before meal) blood glucose between 70 mg/dl and 120 mg/dl.

The intensive treatment group achieved the A1C nadir at 6 months that was significantly lower than the conventional therapy group and maintained that difference for the entire study. Mean A1C values at follow-up were 8.06% ± 0.13 and 9.76% ± 0.12 respectively for the intensively and conservatively treated groups. Authors do not provide results of significance tests and the figure indicates that while 98% of the population had A1C data at 3 years, only 78%, 52% and 42.5% contributed A1C data by years 5, 7 and 9 respectively. (A p-value of <0.001 is reported in this figure showing median values over 10 years.)The mean glucose for the intensive treatment group was 260 ± 52 mg/dl in the conventional treatment group and 177 ± 31 mg/dl in the intensive treatment group.

Other outcomes
Primary findings with respect to rates of hypoglycemia, ketoacidosis, retinopathy and nephropathy for the study period are summarized in the following two figures.

Figure 2. Rate of hypoglycemic and ketoacidosis events among the combined cohorts (N = 195) in the DCCT[22]

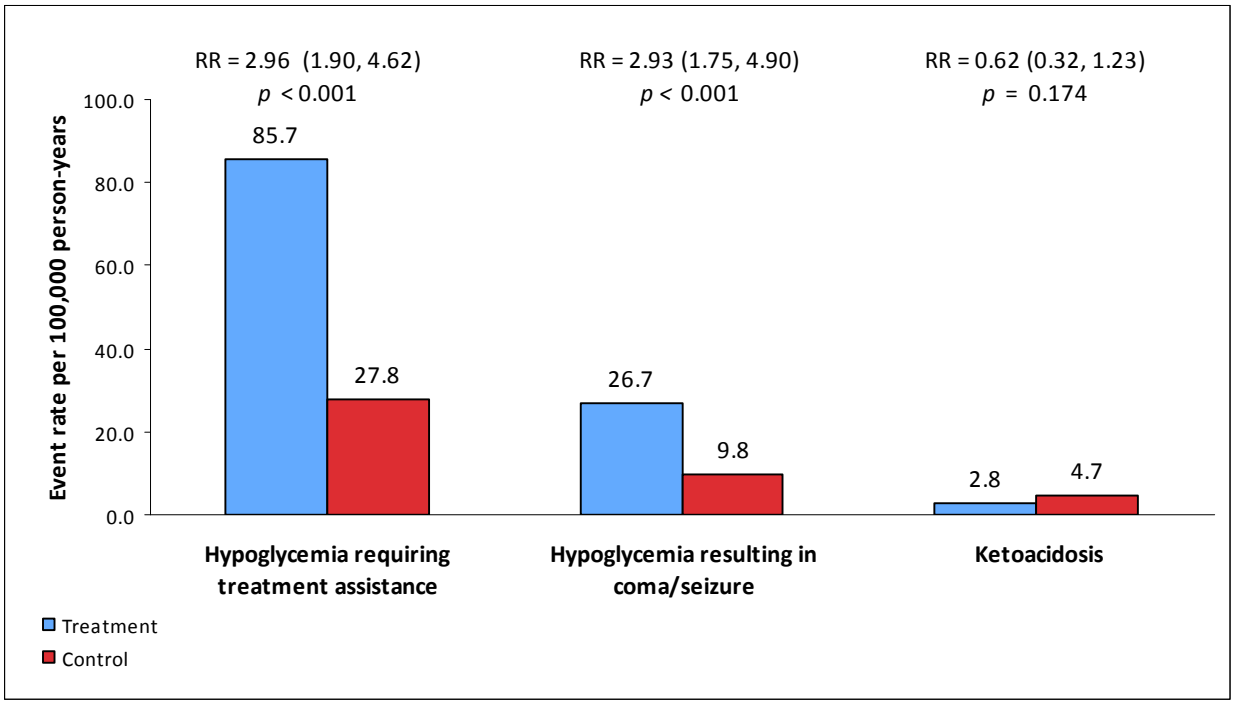
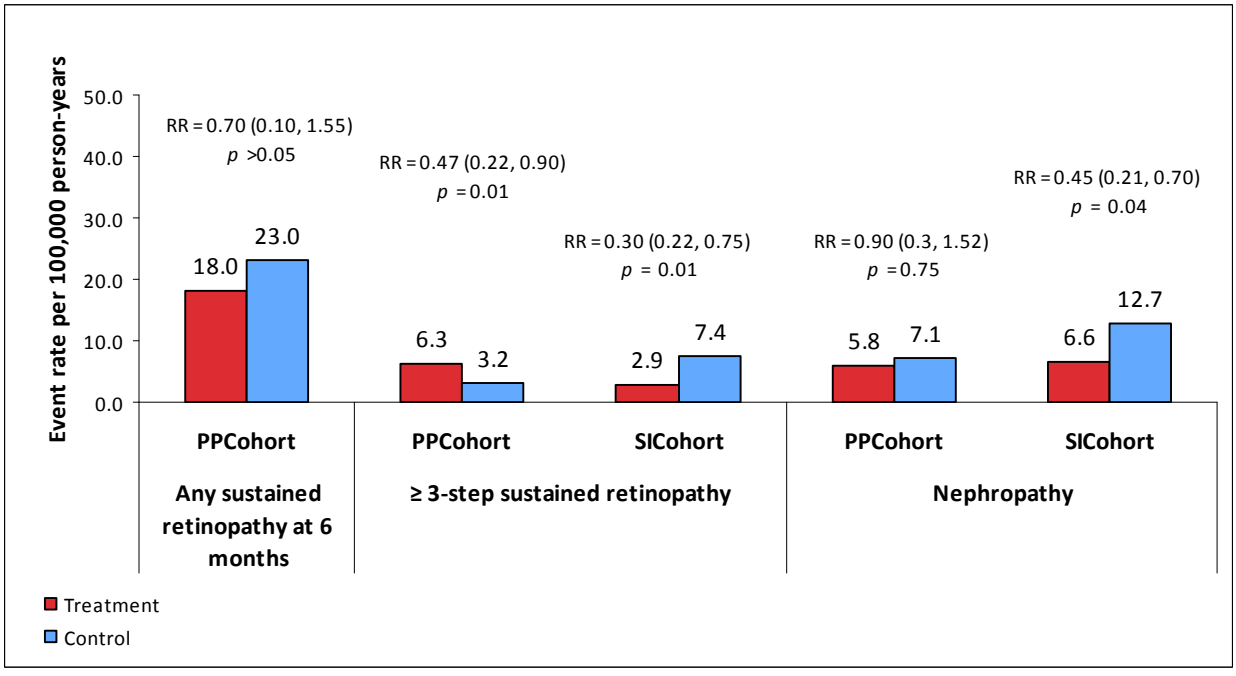


Figure 3.Rate of retinopathy and nephropathy events among the Primary Prevention (n = 125) and Secondary Intervention (n = 70) Cohorts in the DCCT[22]



PP = primary prevention cohort, SI = secondary intervention cohort.

Ketoacidosis occurred in conventional group 4.7 episodes/100 person years versus 2.8/100 person-years in the intensive treatment group. The rate of ketoacidosis in the adult study subjects was much lower: 1.8 episodes/100 person-years in the intensive treatment group and 1.3 episodes/100 person-years in the conventional treatment group.

Severe hypoglycemia, defined as hypoglycemia that required assistance, was three times higher in the intensive treatment group compared to the conventional treatment group for all age groups, and occurred almost three times more often in adolescents. The adolescents in the intensive therapy group experienced 85.7 episodes of severe hypoglycemia/100 person-years compared to 27.8 episodes/100 person-years in the conventional treatment group. The intensive therapy group experienced a coma or seizure 26.7 episodes/100 person-years as compared to 9.7 episodes/100 person-year for the conventional therapy group.

Retinopathy: The intensive treatment group experienced a reduced adjusted mean risk of retinopathy. The PP cohort experienced 53% percent (95% CI 1% to 78%) reduction in the development of retinopathy. The SI cohort experienced a reduced risk of progression of retinopathy by 70 % (95% CI 25%, 88%). Seven adolescents in the conventional treatment group developed proliferative or severe nonproliferative retinopathy as compared to 2 adolescents in the intensive treatment group ($P = 0.087$) by 47 % (95% CI 15%, 67%) and laser treatment was required by 4 adolescents in the intensive treatment group as compared to 2 adolescents in the conventional therapy group ($P = 0.573$). (Similar findings of benefit were noted for the entire study population and because of the larger sample size, were statistically significant.)

Nephropathy –Episodes of microalbuminuria in the primary prevention adolescents were 7.1 in the conventional group to 5.8 in the intensive treatment group (not significant) (The reduction for the overall study group was 55 % (95% CI 3% to 79%).) The risk of microalbuminuria in the secondary prevention group of adolescents was reduced by 55% (95% CI 3% to 79%) (Similar findings in the entire study group.)

Neuropathy – In adolescents, the conventional therapy group experienced a statistically significant reduction in the nerve transmission speed as compared to the intensive treatment group. Mean velocities for median motor, median sensory, peroneal an sural nerves were significantly greater in the intensively treated group, compared with the conventionally treated group (p values were < 0.003, 0.4, <0.001 and < 0.004 respectively). The numbers of participants with clinical neuropathy were seven and three, respectively.

Macrovascular – The young age of the participants made cardiovascular events unlikely. In adolescents, the mean total cholesterol at the end of the study was 260 ± 52 mg/dl in the conventional group and 177 ± 31 mg/dl in the intensive therapy group ($P = 0.02$), but no changes in the LDL cholesterol or blood pressure were noted.

Adverse events – Mortality did not differ between the treatment groups. Two adolescents died: one participant from the intensive treatment group died from a motor vehicle accident that was not related to hypoglycemia and a particpant from the conventional treatment group died of

suicide. Two other study subjects were taken out of the study for a few months due to the stress of the study.

Hospitalization was required to treat severe hypoglycemia for 14 participant in the intensive treatment group and five in the conventional treatment group.

Weight gain was more common in the intensive therapy group. At the end of the study, 9.6% of the intensive therapy group were overweight as compared to 4.7% of the conventional therapy group. There was no difference in growth or progression of sexual maturation.

Older studies of SMBG
The available data from four older RCTs (1985–1983)[74-77] comparing SMBG with urine testing suggested that SMBG may not greatly improve metabolic control in the majority of children with type-1 diabetes based on hemoglobin A1C values. Results are briefly summarized as follows:

- Three of the four RCTs reported no statistically significant improvements in A1C levels after a range of 3 to 18 months SMBG testing as compared with urine testing.
- SMBG may be a useful for resolving or preventing more acute problems, such as severe hypoglycemia, and for avoiding ketoacidosis and hospital admission.
- Most children appeared to prefer SMBG over urine testing, however, because it allowed them to feel more in control of and more informed about their diabetes.

There are a number of methodological shortcomings to these studies, the devices used for SMBG are no longer current and the use of urine testing is no longer recommended as a standard for self- care. These reflect standards of care and A1c levels considered acceptable in their era. These early studies of SMBG in children should be viewed more as feasibility and acceptance studies, rather than definitive proof that SMBG alone could lower the A1C, and more importantly, that SMBG could play a role in changing health outcomes and mortality.

3.1.2 Effectiveness of SMBG

Indirect evidence on the effectiveness of SMBG is based on the observational follow-up to the DCCT at four and ten years.[78,79]

Overview of Results

After completion of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study conducted long-term follow-up of the DCCT participants. At the end of the DCCT, all participants in the conventional treatment arm were offered instruction in the use of intensive therapy, and intensive treatment group participants were encouraged to continue such treatment during the EDIC. A total of 175 (91%) of the 193 surviving DCCT participants enrolled in EDIC.

Overall, in those who were <18 years old at the start of the DCCT followed in the EDIC:

- Mean A1C values were similar between the former intensive and former conventional groups at the end of years 4 and 10.
- Among the former intensive treatment group, the prevalence a ≥ 3 step progression of retinopathy and of progression to proliferative or severe nonproliferative retinopathy were significantly reduced by compared with the former conventional groups at year four. At year 10, however, there were no significant differences among former intensive and conventional treatment groups in the progression of retinopathy (≥ 3 step progression of retinopathy, severe nonproliferative retinopathy, proliferative retinopathy clinically significant macular edema or photocoagulation therapy.
- No differences in nephropathy were seen at the end of either follow-up period.

At 10 years of observation following the completion of the DCCT, the progression of retinopathy >3 levels and proliferative retinopathy was less in the prior intensive group of adolescents compared with the conventional group, but the difference was not statistically significant. However, the entire EDIC cohort (including all ages) who had been in the DCCT intensive treatment group experienced a statistically significant reduction at 10 year follow-up. The authors suggest that the waning effect in the adolescent cohort may have been because the adolescents did not achieve as low an A1c during the DCCT as the older study subjects, and thus the "memory effect" was less. It should also be noted that the adolescent EDIC sample size was much smaller.

The long term impact of intensive treatment on the cardiovascular complications for those who were adolescents is not yet known. During the mean 17 years of follow-up of the full DCCT population (all ages), those from the intensive group experienced a 42% reduction in risk for any cardiovascular disease event and 57% risk reduction in non-fatal myocardial infarction, , stroke or death from cardiovascular disease.[125] Even at the time of the 10 year follow-up, those who began DCCT as adolescents would have only reached young adulthood. The impact of maintaining tight control on these persons may not be evident for some time. A delay in observed benefit among those who were adolescents at the start of the DCCT would be consistent with current understanding of the cumulative damage and thus may take more years to become clinically evident. This is also true for retinopathy, neuropathy and nephropathy outcomes.

Detailed Results

After completion of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a longer-term follow-up of the DCCT participants was initiated. At the end of the DCCT, all participants in the conventional treatment arm were offered instruction in the use of intensive therapy, and intensive treatment group patients were encouraged to continue such treatment during the EDIC. A total of 175 (91%) of the 193 surviving DCCT participants enrolled in EDIC. At the 10 year follow-up, 156 (80%) were reportedly included. The percent of participants using SMBG ≥ 4 times/day was reported as 24% and 29% of the former intensive and conventional groups respectively at the four year follow-up, whereas the 10 year follow-up reports 38.9% and 64.5% of the former intensive and conventional groups respectively performed SMBG ≥ 4 times/day. The reason for this discrepancy is not described by the authors.

Maintaining target A1c levels

At the end of the DCCT (which had a mean 7.4 years follow-up), the intensive intervention group had significantly lower A1C levels than the conventional treatment group. As reported in the DCCT 1994 paper, mean A1C was 9.8 ± 0.12 in the conventional treatment group and 8.06 ± 0.13 in the intensive treatment group (no p-value provided). However, after 4 years of follow-

up, A1C levels were similar between the former intensive and conventional treatment arms (8.38% versus 8.45%, respectively). Among the former intensive treatment group participants, there was a slight but significant increase in A1c levels by year 1 and A1c in the former conventional treatment group decreased significantly by year 1.[79] The authors suggest that it is possible that the withdrawal of the high level of staff support in the group and the initiation of intensive therapy among majority of former conventional treatment participants contributed to this result. There was also no difference in A1c levels between former intensive and conventional treatment groups at year 10.[78]

Hypoglycemia
During the first four years of the EDIC, the rate of severe hypoglycemia that required assistance, including coma or seizure was greater among the former conventional intervention group than the former intensive intervention group (57 per 100 patient-years versus 51 per 100 patient-years), though this difference was not statistically significant (RR = 0.90,(no confidence interval provided) p = 0.75)

Microvascular Complications: Retinopathy and nephropathy
During the first four years of the EDIC, the rate of further progression of at least 3 steps in retinopathy level was 77% lower among former the intensive intervention group compared to the former conventional treatment group (25.4% versus 7.1%, respectively; OR=0.23, 95%CI 0.08, 0.61; p = 0.004).[79] However, by year 10 of the EDIC, the rate of further progression of at least 3 steps in retinopathy level were similar between the former intensive and conventional treatment groups (50.9% versus 53.4%, respectively; p= 0.84).[78]

Similarly, during the first four years of the EDIC, the rates of severe nonproliferative diabetic retinopathy (NPDR) or worse, and proliferative retinopathy were significantly higher among the former conventional treatment group than among the former intensive intervention group (CON: 14.5% versus INT: 1.4%, p=0.005; and CON: 8.7% versus INT: 1.4%, respectively). Rates of clinically significant macular edema, and laser therapy did not significantly differ between the former conventional and intensive treatment groups during the first four years of the EDIC. [79]

By year 10 of the EDIC, the rates of severe nonproliferative diabetic retinopathy (NPDR) or worse and proliferative retinopathy did not significantly differ between the former conventional and intensive treatment groups. There were also no differences in the rates of clinically significant macular edema, and laser therapy between the former conventional and intensive treatment groups at year 10 of the EDIC.[78]

With regard to nephropathy at four years for those who were free of microabluminuia at the close of DCCT, rates of progression to microalbuminuria were lower for the former intensive treatment goup but not statistically different from the former conventionally treated group(n = 128, INT 8.1%, versus CON: 13.6% p = 0.28). Similaryly among those without albuminuria at DCCT close progression to albuminuria was lower in the former intensively treated group but were not statistically different compared with the convential treatment arm(n = 156, INT 1.3% versus CON: 9.9%, p = 0.08). No patients in either group required renal dialysis or transplantation by EDIC year 4.

At the10 year follow up reported percentages of participants with albumin excretion rates (AER) either >40mg/24 hour (microalbuminuria) or >300mg/24 hours (clinical grade albuminuria) were not statistically different at 10 years between groups: An AER > 40 mg/24 hours was reported for 20.8% and 20.7% of former intensively and conventionally treated participants respectively with 5.6% and 4.9% of participants in the respective treatment groups having an AER of >300mg/24 hours.

3.2 Key question 2: What is the evidence on optimal or improved efficacy or effectiveness of glucose monitoring based on frequency or mode (continuous versus self-monitoring) of testing?

Efficacy evidence from randomized controlled trials (RCT) of SMBG with respect to frequency will be addressed first followed by efficacy evidence from RCTs of continuous glucose monitoring (CGM) compared with self–monitoring of blood glucose (SMBG). Evidence related to effectiveness with respect to frequency of use for CGM and SMBG are then described.

3.2.1 Efficacy of self–monitoring of blood glucose (SMBG) with respect to frequency

The DCCT compared "intensive care," which included SMBG at least 4 times per day as part of a comprehensive plan for glycemic control, with usual care, which included SMBG once per day. As it provides the primary evidence for efficacy, it has been summarized in key question 1 and will not be re-described here. No other RCTs directly evaluating frequency of SMBG were found.

3.2.2 Efficacy of continuous glucose monitoring (CGM) compared with self–monitoring of blood glucose (SMBG)

Five reports from four RCTs that allowed patients to make use of the real-time features of CGM were found and provide the primary evidence describing the efficacy of CGM (in conjunction with SMGB) compared with SMBG alone.[80-83,124]Two of the studies provide data on different outcomes of the same trial.[80,124] In these five studies, patients in both treatment groups were educated on the use of glucose data to make adjustments in diabetes management (details are provided in previous section). Those in the CGM groups received education on device use and were instructed to verify CGM readings with SMBG checks before making therapeutic decisions. A fifth trial allowed use of the real-time features of CGM, but compared two different treatment interventions; use of an integrated CGM and insulin pump system versus multiple daily injections with SMBG.[83] Because the effects that are due to CGM versus SMBG cannot be separated from those related to different insulin regimens in this trial, the results of this trial cannot be directly compared with those of JDRF 2008, (JDRF (2009), JDRF (2010), and Hirsch,[80-82,124] and will not be considered in the overall evidence summary, but information will be provided.

Five additional RCTs comparing periodic use of CGM (in conjunction with SMGB) with SMBG alone did not have patients use CGM data in real-time and therefore only provide information on use of CGM data retrospectively by providers to recommend therapeutic changes.[84-88] None provides detail about how CGM data were used in clinical decision-making, nor to what extent the participants were involved in reviewing the data, therefore, conclusions on the efficacy of CGM use involving patient-related decision making are difficult to make. These studies are briefly summarized for context and additional detail on them may be found in the Appendices.

Summary

In three studies in which patients used CGM data directly, the mean baseline A1C levels for participants in two of these studies was > 7.0%,[80,81,83] and in one study was < 7.0%.[82] Differences in study design, insulin regimens and device use should be considered when interpreting these results. In one of these trials, few of the results were stratified by age, and only those results relevant to the population of interest for this HTA are reported here.[82] One study did not directly compare CGM with SMBG and cannot directly address questions of monitoring posed for this HTA.[83]

Overall, these studies provide inconclusive evidence for the efficacy of CGM (in conjunction with SMBG) over SMBG alone with respect to reduction of mean A1C up to 26 weeks, or for reducing acute episodes of hypoglycemia or hyperglycemia. However, there is limited evidence that a greater percentage of participants who used CGM achieved A1C targets compared with those using SMBG alone. These changes were achieved without significant difference in hypoglycemic events. No differences in quality of life measures were found.

- Of the two studies that reported A1C results stratified by age, the larger (N = 114) reported a greater decrease in A1C levels in the CGM (-0.37%) compared with the SMBG arm (-0.22%)[80]; however the smaller RCT (N = 40) reported a larger decrease in A1C levels in the SMBG (-0.80%) compared with the CGM arm (0.38%).[81] Neither of the differences in the change in mean A1C between treatment arms in these studies were statistically significant ($P = 0.29$, $P = 0.10$, respectively) nor clinically significant (based on 0.5% as a threshold).
- Two RCTs reported the proportion of participants achieving A1C targets. In the JDRF 2008,, participants in the CGM group were roughly twice as likely to achieve A1C targets of < 7% (Risk Difference (RD) = 15%), relative A1C decreases of ≥ 10% (RD = 17%) and absolute decreases of ≥ 0.5% (RD = 23%).[80] In the other RCT [Hirsch 2008], the difference in reaching A1c targets was marginally insignificant (p = 0.052), perhaps due to small sample size.
- Neither of the two RCTs reporting on episodes of hypoglycemia that stratified by age[80,82] found significant differences in the effect of CGM versus SMBG on episodes of hypoglycemia (as measured by the proportion of participants with one or more severe hypoglycemic episode (CGM: 7% versus SMBG: 10%), rate of severe hypoglycemic episodes (CGM: 17.9 per 100,000 person-years (py) versus SMBG: 24.4/100,000 py), amount of time blood glucose levels were lower than either 70 mg/dl (CGM: 47 min/day versus SMBG: 59 min/day) or 50 mg/dl (CGM: 10 min/day versus SMBG: 13 min/day)). As noted previously, the goal of intensive treatment is to maintain good glycemic control without increasing the frequency of hypoglycemic events.

- Only one RCT reported on episodes of hyperglycemia stratified by age.[80] No significant differences in the effect of CGM versus SMBG on episodes of hyperglycemia (as measured by the amount of time spent with blood glucose levels greater than either 180 mg/dl (CGM: 643 min/day versus SMBG: 635 min/day) or 250 mg/dl (CGM: 242 min/day versus SMBG: 268 min/day)).
- One RCT reported QOL outcomes. There were no differences in any QOL measures (Hypoglycemia Fear Survey worry subscore, Quality of Life Inventory Generic and Type 1 Diabetes and PAID-Parent) between participants in CGM and SMBG arms or parents of participants in CGM and SMBG arms at 26 weeks or in change from baseline to 26 weeks.[80,83]
- No studies of the effect of glucose monitoring mode on any of the following outcomes were found: a) maintaining A1C levels, b) achieving A1C targets in conjunction with provider specific report cards, c) acute episodes of diabetic ketoacidosis, d) microvascular complications, or e) medication or nutritional management.
- No studies relating specifically to pregnant patients ≤ 18 years old or those with type 2 diabetese who require insulin were found.
- There were no deaths reported in any RCT among participants ≤ 18 years old.

Detailed results of RCTs

A total of three RCTs compared real-time use of CGM data (in conjunction with SMBG) with SMBG alone.[80-82] Two RCTs directly assessed the effect of these modes for blood glucose monitoring.[80,82] Both studies included participants older than 18 years of age with some results stratified into three age groups, 8–14 years, 15–24 years and ≥ 25 years, and one study was conducted among patients with well-controlled diabetes (A1C < 7%) and provides insight into the question of maintaining A1C targets.[82] The third study compared use of an integrated CGM and insulin pump system to SMBG with an insulin pump. This trial provides insight into the combined effect of continuous monitoring and insulin regimen; however, is not directly comparable to the JDRF trials in which the CGM and insulin delivery were not integrated. This study also included participants older than 18 years of age with some results stratified into adolescents (12 to 17 years) and adults (18 years or older).[81]

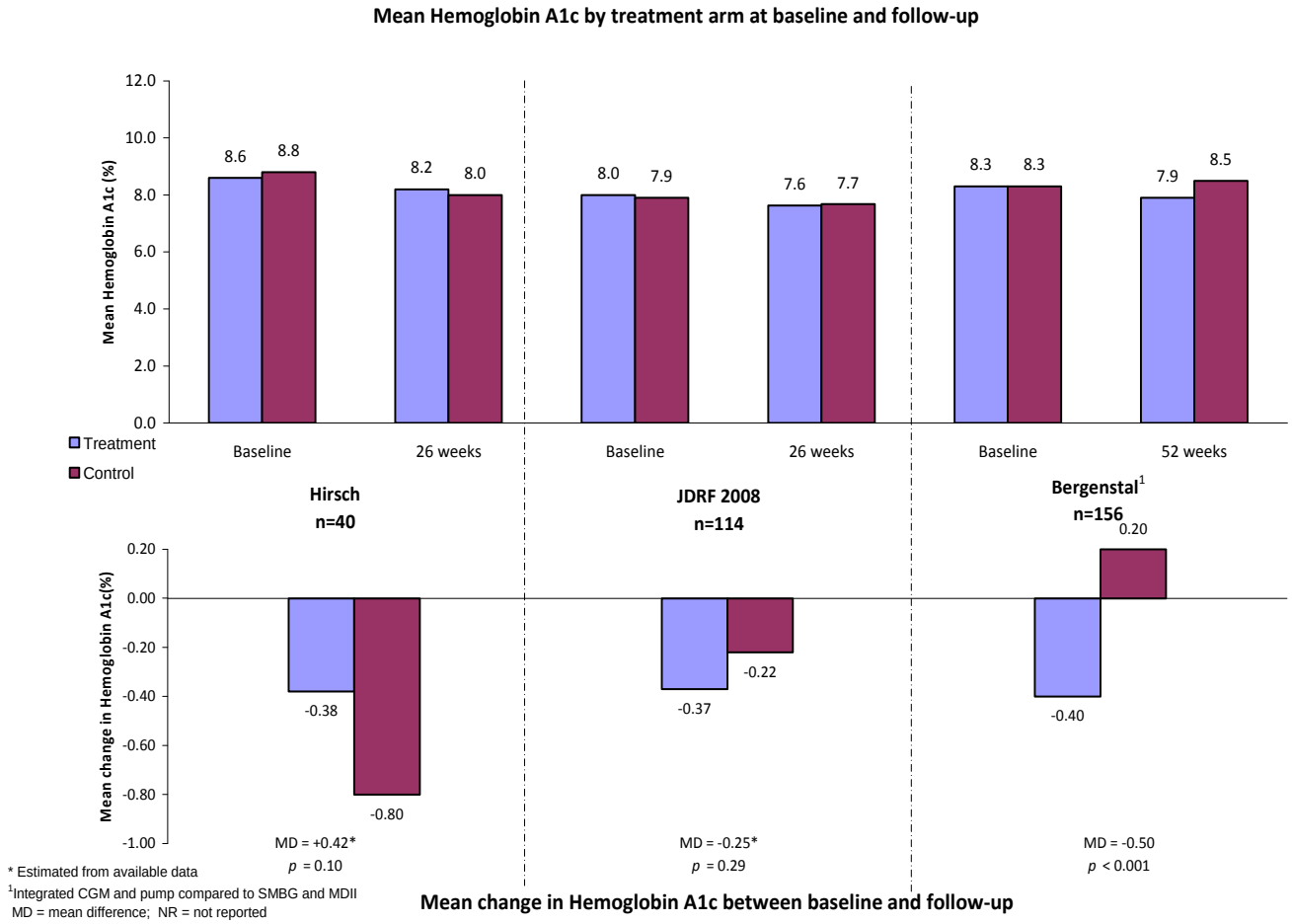
One additional RCT provides limited evidence to address the efficacy of CGM versus SMBG alone. This trial compared use of an integrated CGM and insulin pump system to SMBG with multiple daily insulin injections.[83]This study compares a combination of monitoring and treatment methods and is not able to directly address the question of comparative effectiveness of CGM with SMBG alone.

Figure 4. Mean A1C and mean change in A1C levels for RCTs comparing patient real-time use of CGM with SMBG alone*)*

Results across studies with regard to mean A1C (%) and mean change in A1C are provided in the figure below. For the studies that directly assessed CGM versus SMBG,[80,81] no significant differences in mean A1C or in changes in mean A1C were evident between groups at 26 weeks. While the Bergenstal study did demonstrate a significant difference for the change in means between groups at 52 weeks, this study is compares an integrated pump-CGM system with multiple injections plus SMBG.[83] Thus the independent influence of the mode of monitoring cannot be assessed.

Summary of mean A1C and mean change in A1C in RCTs that allowed participants to make use of the real-time features of CGM are provided in the figures below.

Figure 4. Mean A1C and mean change in A1C levels for RCTs comparing patient real-time use of CGM with SMBG alone



* Estimated from available data
[1]Integrated CGM and pump compared to SMBG and MDII
MD = mean difference; NR = not reported

Three RCTs compared participant use of a real-time continuous glucose monitor (rt-CGM) continuously for 26 weeks and reported on the effect on A1C[80-82]; however, only two provided results stratified by age. In the largest of these RCTs (N=114),[80] decreases in A1C levels between baseline and 26 weeks were greater in the CGM versus SMBG arms (-0.37 versus -0.22%); however, the difference in change between arms was not clinically significant (based on a cut point of greater than 0.5% as a measure of clinically meaningful change in A1C) nor was it statistically significant ($P = 0.29$).[80] In contrast, Hirsch et al. (N=40) reported a greater decrease in A1C levels in the SMBG with insulin pump arm compared to the integrated CGM arm (-0.80 versus -0.38%); however, the difference in change between arms was neither clinically nor statistically significant (p = 0.10).[81]

Two RCTs also reported the proportion of participants in CGM and SMBG arms achieving specified A1C targets and clinically significant differences in A1C levels.[80,81] In the largest RCT (N=114),[80] a greater proportion of participants in the CGM arm achieved target A1C levels < 7%

at 26 weeks (27% versus 12%, respectively suggesting that participants in the CGM arm were twice as likely as to achieve target A1c levels < 7% as participants in the SMBG arm. Participants in the CGM arm of the JDRF trial were also more likely to achieve a clinically significant difference in A1C levels, with 29% of CGM participants compared with 12% of SMBG participants achieving a relative decrease in A1C levels ≥ 10% (RR = 2.34 (95% CI 1.05, 5.31); RD = 17%; *P* = .0282), and 54% of CGM participants compared to 31% of SMBG participants achieving an absolute decrease in A1C levels ≥ 0.5% (RR = 1.72 (95% CI 1.10, 2.72); RD = 23%; *P* = .0148).[80] Hirsch et al. also reported a marginally significant difference in the proportion of participants achieving A1C levels < 7% between treatment arms at either 13 or 26 weeks (data not reported, *P* = 0.052).[81]

In the RCT comparing use of an integrated CGM and insulin pump system to SMBG with multiple daily insulin injections, Bergenstal et al. reported a statistically significant decrease (-0.4%) in A1C at 1 year for the integrated CGM and insulin pump arm and a slight increase (0.2%) for the SMBG plus insulin injection arm.The overall difference in change between groups was statistically significant (*P*< 0.001).[83] This study also reported that a greater proportion of participants in the integrated CGM arm achieved target A1C levels ≤ 7% at one year (Integrated CGM/pump:13% versus SMBG plus insulin injections: 5%; RR = 2.60 (95% CI 0.85, 7.93); RD = 8%; *P* = 0.0795), but statistical significance was not achieved. When ADA-recommended, age-appropriate target A1C levels were used (< 8% for 6-12 year olds and <7.5% for 13-19 year olds ,[18] 44% of participants in the integrated CGM arm achieved target A1C levels compared to 20% of participants in the SMBG plus insulin injections arm. The relative risk (RR = 2.27 (95% CI 1.37, 3.76); RD = 25%; *P* = 0.0007) indicates that roughly twice as many participants in the integrated CGM and insulin pump arm achieved age-specific target A1C levels compared with participants in the SMBG plus insulin injection arm.[83]

b) Maintaining target A1C levels

Although one RCT reported the effect of CGM on maintaining A1C levels among individuals with well-controlled type 1 diabetes (defined as A1C < 7% at baseline), A1C results were not stratified by age thus, are not reported.[82]

c) In conjunction with provider specific report cards for target (e.g. under 7/over 9)

No studies were found that reported on the effect of frequency or mode of glucose monitoring in conjunction with provider specific report cards for target.

d) Reduce hospitalizations or acute episodes of hypoglycemia, hyperglycemia, and diabetic ketoacidosis

Findings from the JDRF studies (direct comparison of CGM with SMBG versus SMBG alone) are summarized below and available data found in the following table.

- None of the RCTs reporting on episodes of hypoglycemia[80,82] found significant differences in the effect of CGM versus SMBG on episodes of hypoglycemia (as measured by proportion of participants with one or more severe hypoglycemia episode, the proportion of patents with one or more severe hypoglycemic episodes with seizure or coma, rate of severe hypoglcemic episodes, amount of time blood glucose levels were lower than either 70 mg/dl or 50 mg/dl). As noted previously, the goal of intensive

treatment is to maintain good glycemic control without increase in the frequency of hypoglycemic events.

- The only study that directly assessed CGM versus SMBG and reported on episodes of hyperglycemia in the age group of interest found no significant differences in the effect of CGM versus SMBG on episodes of hyperglycemia (as measured by the amount of time spent with blood glucose levels greater than either 180 mg/dl or 250 mg/dl).[80]
- There are very limited data available to assess the effect of CGM on episodes of diabetic ketoacidosis. One study reported one event[80] and two others[81,82] did not provide age-specific results.

The Bergenstal study did not directly compare CGM with SMBG as previously described. As seen in the table below, no statistical difference between treatment groups was seen with regard to rate of hypoglycemic events or AUC thresholds of < 70 mg/dL or <50 mg/dL. The AUC for both>180 mg/dL and 250mg/dL threholds in patients with the integrated CGM/pump was significantly less than for those in the MDI/SMBG group. [83]

Results related to hypoglycemia and hyperglycemia across studies that provided data are summarized in the table below.

Table 12.Results of RCT's using real-time CGM data: Effect of CGM versus SMBG on episodes of hypoglycemia and hyperglycemia

Measures of hypoglycemia

	Number or Time			AUC[a]		
	Measure	Results	*P*	Measure	Results	*P*
JDRF 2008[80] (n = 114)	No.# (%) with ≥ 1 severe event	CGM: 4 (7) SMBG: 6 (10)	0.74	NR	NR	
	No.# (%) with ≥ 1 severe event + seizure/coma	CGM: 0 SMBG: 0	NA	NR	NR	
	Rate of severe hypoglycemia	CMG: 17.9/100,000 py[b] SMBG: 24.4/100,000 py[b]	0.06	NR	NR	
	Mean time[c] ≤ 50 mg/dl	CGM: 10 SMBG: 13	0.50	NR	NR	
	Mean time[c] ≤ 70 mg/dl	CGM: 47 SMBG: 59	0.29			
Bergenstal[d] 2010[83] (n =156)	Rate of severe hypoglycemia	CGM+pump: 8.9/100,000 py[b] SMBG+MDI: 5.0/100,000 py[b]	0.35	AUC[a]< 70 mg/dl	CGM+pump: 0.23 SMBG+MDI: 0.25	0.79
				AUC[a]< 50 mg/dl	CGM+pump:	0.64

					0.01 SMBG+MDI: 10.02	
	Time			**AUC**		
	Measure	Results	*P*	Measure	Results	*P*
Measures of hyperglycemia						
JDRF 2008[80] (n =114)	Mean time[c] > 180 mg/ dl	CGM: 643 SMBG: 635	0.58	NR	NR	
	Mean time[c] > 250 mg/dl	CGM: 242 SMBG: 268	0.18	NR	NR	
Bergenstal[d] 2010[83] (n=156)	NR	NR		AUC[a]> 180 mg/dl	CGM+pump: 30.1 SMBG+MDI: 45.3	0.001
				AUC[a]> 250 mg/dl	CGM+pump: 9.2 SMBG+MDI: 17.6	0.001

[a]AUC = area under the curve
[b]py = person years
[c]Minutes/day
[d]The results of this study cannot be directly compared to JDRF 2008 since the treatment arms in this trial test two different modes blood glucose monitoring and two different modes of insulin delivery.

Acute episodes of hypoglycemia

All of the three RCTs comparing use of a rt-CGM to SMBG alone reported on the effects of CGM on hypoglycemia episodes [80-82]; however, in one trial, results were not stratified by age, thus results are not reported here.[80,81]reported no differences between CGM and SMBG arms in the proportion of participants with one or more severe hypoglycemia episode (CGM: 7% (n = 4) versus SMBG: 10% (n = 6); *P* = 0.74)in the rate of severe hypoglycemic events (CGM: 17.9 per 100,000 person years versus SMBG: 24.4 per 100,000 person-years), or in the proportion of participants with one or more severe hypoglycemic episodes with seizure or coma (0% for both arms). There were also no differences between CGM and SMBG arms in the amount of time blood glucose levels were either 50 mg/dl or lower (*P* = 0.50) or 70 mg/dl or lower (*P* = 0.29).[80] Among participants with well-controlled diabetes, no differences in time blood glucose levels were 70 mg/dl or lower within the stratum defined by age 8 to 14 years old were reported at 26 weeks.[82]

In the Bergenstal RCT[83] comparing use of integrated CGM and insulin pump with SMBG and multiple daily insulin injections, there were no differences in the number (CGM:7 (in 4 participants) versus SMBG: 4 (in 4 participants)) or rate (CGM: 8.9/100,000 person-years versus SMBG: 5.0/100,000 person-years) of severe hypoglycemia events between CGM plus insulin pump and SMBG arms (*P* = 0.53, *P* = 0.35, respectively). In addition, there were no differences between CGM plus insulin pump and SMBG arms in the change in area under the curve lower than 50 mg/dl or 70 mg/dl between baseline and 1 year. (*P* = 0.79, *P* = 0.64, respectively).

Acute episodes of hyperglycemia

Three RCTs comparing use of a rt-CGM to SMBG alone reported on the effects of CGM on hyperglycemic episodes[80-82]; however, in two trials, results were not stratified by age and thus, are not reported.[81,82] In the JDRF 2008 trial, no differences were reported between CGM and SMBG arms with respect to the amount of time blood glucose levels were greater than either 180 mg/dl ($P = 0.58$) or 250 mg/dl ($P = 0.18$) at 26 weeks.[80]
As seen in table 12, for the Bergenstal study, the AUC for both>180mg/dL and 250mg/dL thresholds in patients with the integrated CGM/pump was significantly less than for those in the MDI/SMBG group. [83]

Acute episodes of diabetic ketoacidosis
All three RCTs comparing use of a rt-CGM to SMBG alone assessed the effect of CGM on episodes of diabetic ketoacidosis; however, one reported no events in either treatment arm[80] and two reported events for participants of all ages combined; therefore, the results are not reported.[81,82] Limited information from the DCCT indirectly suggests that ketoacidosis was not reduced as a result of increased frequent monitoring with intensive treatment. The results of this trial are described for Key Question 1.

Among children in the Bergenstal trial, no differences in rates of ketoacidosis were seen, with rates for each group reported as 0.02 per 100 person-years.[83]

e) Reduce microvascular complications (retinopathy, nephropathy, neuropathy)
No studies were found that reported on the effect of frequency or mode of glucose monitoring on microvascular complications. Information from the DCCT (and the EDIC follow-up studies) in this population indirectly suggests that such complications are reduced as a result of frequent monitoring when combined with intensive treatment. The results of this trial are described for Key Question 1.

f) Reduce Mortality
Limited information on the effect of frequency or mode of glucose monitoring on mortality was reported in the RCTs. This information is included in Key Question 3.

g) Effect on medication or nutritional management
None of the RCTs in which patients used real-time features of CGM in conjunction with SMBG for daily management decisions[80-83] provided direct analysis of how CGM influenced participant-directed changes in medication or nutritional management, although results of these studies for glycemic control indirectly reflect changes made (or not) in response to the data. No other studies of decision making were found.

h) Quality of life (QOL)
One report of the JDRF trial evaluated the impact of CGM versus SMBG alone on Quality of Life (QOL), and found no differences in any QOL measures between either participants in CGM and SMBG arms or parents of participants in CGM and SMBG arms at baseline, 26 weeks or change from baseline to 26 weeks.[124]

As part of the JDRF trial [JDRF 2008], diabetes-specific measures of QOL (Hypoglycemia Fear Survey (HFS) worry subscale (scale 0 – 100 with higher score denoting more fear), Pediatric Quality of Life Inventory (PedsQL) Type -1 Diabetes module (scale 0 – 100 with higher score denoting higher QOL) and Problem Areas In Diabetes (PAID), aparent survey evaluating parental burden associated with diabetes care; norm-based score with higher score denoting better functioning)) and general assessments of QOL (PedsQL- Generic; scale 0 – 100 with higher score denoting higher QOL) were conducted at baseline and 26 weeks for all participants and parents of participants less than 18 years old. For participants, there were no differences in scores on any QOL measures between CGM and SMBG arms at baseline, 26 weeks or change from baseline to 26 weeks (see table below). For parents of participants, there were also no differences in scores on any QOL measures between CGM and SMBG arms at baseline, 26 weeks or change from baseline to 26 weeks (see table below). In addition, there were no differences in scores at any baseline or 26 weeks between CGM and SMBG in subgroups based on baseline A1C (≥ 7.0%, < 7.0%) and by CGM usage (< 6 days/week, ≥ 6 days/week) (no data provided).

Table 13.Baseline and 26-week values for QOL and HFS measures for participants and parents of participants in the CGM and control groups[124]

Measure	Results		*P*
Participants			
HFS* worry subscale	Baseline CGM: 25.7 ± 16.6 SMBG: 25.9 ± 14.9	26 Weeks CGM: 20.8 ± 13.1 SMBG: 22.6 ± 14.4	0.27
PedsQL†- - Generic	Baseline CGM: 78.5 ± 12.5 SMBG: 79.7 ± 11.7	26 Weeks CGM: 80.5 ± 12.4 SMBG: 81.4 ± 12.0	0.96
PedsQL – Diabetes-specific	Baseline CGM: 82.2 ± 12.2 SMBG: 81.6 ± 12.9	26 Weeks CGM: 81.7 ± 12.9 SMBG: 82.6 ± 13.2	0.28
Parents of Participants			
HFS worry subscale	Baseline CGM: 41.5 ± 16.0 SMBG: 42.2 ± 19.8	26 Weeks CGM: 37.0 ± 14.6 SMBG: 38.0 ± 17.2	0.88
PAID‡-parental	Baseline CGM: 46.3 ± 14.0 SMBG: 43.8 ± 15.9	26 Weeks CGM: 47.1 ± 12.7 SMBG: 43.8 ± 17.0	0.25
PedsQL - Generic	Baseline CGM: 76.7 ± 11.8 SMBG: 77.2 ± 13.7	26 Weeks CGM: 76.7 ± 12.6 SMBG: 77.5 ± 13.5	0.70
PedsQL – Diabetes-specific	Baseline CGM: 76.0 ± 12.1 SMBG: 75.7 ± 14.2	26 Weeks CGM: 76.5 ± 11.6 SMBG: 74.6 ± 13.3	0.28

* Hypoglycemia Fear Survey; range 0 to 100, higher score = higher fear
† Pediatric Quality of Life Inventory ; range 0 to 100, higher score = higher quality of life
‡ Problem Areas In Diabetes; norm-based score with higher score denoting better functioning

Overview of results for RCTS of periodic CGM use

As previously described, five trials comparing periodic use of CGM with SMBG were found.[84-88] In these trials, CGM data were gathered periodically and used by the researchers or clinicians retrospectively. An important contrast between these trials and the RCTs using the real-time CGM features is that these trials did not allow participant use of CGM data, based on study description. Although they did not meet the inclusion criteria for the evidence base for this report report and their results are not included as primary evidence in this report, they are briefly summarized for context. Details of on these studies are found in the Appendices. They are briefly summarized below:

- None of the five RCTs comparing periodic CGM use with SMBG reported significant differences in change in A1Clevels comparing baseline to follow-up between CGM and SMBG arms.[84-88] In addition, none of the differences in change in A1C levels between CGM and SMBG were clinically significant (based on a cutpoint of -0.5%)
- Only one RCT reported on the proportion of participants achieving specific A1C target levels, and found no difference between CGM and SMBG arms (53% versus 47%, respectively, $P = 0.50$).[86]
- Three RCTs studying the effect of CGM versus SMBG reported on episodes of hypoglycemia.[84,85,88] None reported significant differences in the effect of CGM versus SMBG on episodes of hypoglycemia (as measured by AUC < 70 mg/dl, number of events < 50, 60 or 70 mg/dl, time < 70 mg/dl)
- Two RCTs studying the effect of CGM versus SMBG reported on episodes of hyperglycemia. [84,85]Neither RCT reported significant differences in the effect of CGM versus SMBG on episodes of hyperglycemia (as measured by AUC > 180 mg/dl, number or time of episodes > 180 mg/dl).
- Three studies reported on the effect of CGM versus SMBG on medication or nutritional management with conflicting results.[84,86,88] Two reported significant differences between CGM and SMBG arms in insulin doses (number of participants altering insulin doses at day 3 CGM: 100% versus SMBG, 73%; p = 0.03[84]; number of insulin changes per month - CGM: 11.5 ± 1.5 versus SMBG: 5.2 ± 0.9, p = 0.001[88]), and one reported no difference in the change in insulin dose between treatment arms.[86]

3.2.3 Effectiveness of CGM and SMBG with respect to frequency of use

Information on effectiveness is taken from non-randomized studies.

Overview of findings
Three reports described the effect of frequency and consistency of CGM use on A1C, which consisted of subanalyses of the JDRF 2008 trial described above.[89,90] One reported adherence to CGM use during the trial (n = 56, 8–14 year olds) and the other reported continued use of CGM among those who had been randomized to CGM after the end of the trial up to one year (n = 80, 8–17 year olds); another among those who had been randomized to SMBG who were given CGM at the end of the trial for up to 26 weeks (n = 47, 8–14 year olds with A1C ≥ 7%). Since randomization is not preserved in such analyses, they are considered as prospective cohort

studies and were graded as LoE II. The other two RCTs described frequency of CGM use and association with A1c but did not stratify results based on age.[81,83]

A large (N = 26,723) registry study (LoE III) of persons 0-18 years old was the only study identified that had the primary purpose of evaluating the association between frequency of SMBG and glycemic control as measured by A1C and the frequency of hypoglycemia and ketoacidosis.[92] Five other non-randomized studies (LoE III) and one analysis from RCT data[98] looked at correlations (primarily univariate associations) between specific frequencies of SMBG and mean A1C.[93-97]

Evidence from these non-randomized studies suggests that:
For CGM

- Based on a subanalysis of the JDRF trial, in those who had been randomized to CGM, CGM use≥ 6 days per week for 6 months of the trial was associated with lower mean A1C values compared with baseline.
- A greater number of participants meeting targets of < 8.0% for 8−12 year olds and < 7.5% for 13−17 year olds compared with those who used it < 6 days per week during the trial. Those who continued use of CGM ≥ 6 days per week for 6 months after the trial's end (12 months total) maintained lower mean A1c values and an additional number achieved targets and decreased the time spent in the hyperglycemic range without increasing their time spent in the hypoglycemic range. The incidence of hypoglycemia remained low for all users.
- In an JDRF extension study of those initially randomized to SMBG who switched to CGM after the trial, no consistent pattern for improvement in A1C of ≥ 0.5% or achieving A1C <7% was seen at 6 months. Prior to CGM use, however, severe hypoglycemia occurred in 26.4 per 100 person-years compared with 13.0 per 100 person-years after 6 months of CGM use (p-value not stated).
- In of these reports, specific information on how data from CGM were used to influence management was not provided, thus the independent impact of monitoring itself cannot be determined. In the absence of additional studies in different populations the overall strength of evidence is low.

For SBMG

- Performing SMBG 4 to 5 times per day was associated with lower mean A1C, based on data from one large registry study and six prognostic studies. In these cross-sectional studies, however, it is not possible to determine out the extent to which lower A1C is causally related to the frequency of SMBG or if those who test more frequently tend to have lower A1C and may be more compliant with their treatment regimen in general. The overall strength of evidence is low.
- In 11 cross-sectional studies and one registry study (all LoE III), more frequent SMBG was associated with lower A1C, however specific data on frequency and A1C values were not provided. In nine of these studies, the correlation was significant. The presence of an association does not imply causality in cross-sectional studies.
- There is conflicting evidence regarding whether more frequent SMBG is associated with lower rates of hypoglycemia. One large registry reported hypoglycemia rates are higher with greater frequency of testing while one cohort study reported hypoglycemia rates are lower with greater frequency of testing. It is unclear whether the increase in events in the larger study may be due to increased frequency of testing in those more likely to have hypoglycemic events.

Detailed results

Consistency and frequency of CGM use
One LoE II follow-up (cohort) study, described frequency of CGM use among subjects randomized to CGM in the JDRF trial (JDRF 2008).[89]This analysis suggests that consistent, CGM use of ≥ 6 days per week during the six month trial may facilitate clinically significant decreases in A1C levels. Values estimated from the author's figure for the 56 participants 8 to 14 years old are summarized below. Associations were similar for all age groups.

Chase (2010) is a follow-up study of the JDRF trial describing the continuation of CGM use for 6 months after completion of the JDRF trial.[90] This study describes the subset of 80 subjects 8 to 17 years old, and results were categorized according to whether participants used CGM < 6 days/week or ≥ 6 days/week in months 6 and 12. Seventeen participants (mean age 11.3 years and baseline A1C 8.2%) used CGM ≥ 6 days/week in month 6 (prior to the end of the JDRF trial) and used CGM use at this frequency in month 12 (6 months after the end of the trial); an additional 17 participants (mean age 12.7 years and baseline A1C 7.8%) used CGM ≥ 6 days/week in month 6, but used CGM < 6 days/week in month 12; while 46 participants (mean age 13.7 years and baseline A1c 8.0%) reported CGM use < 6 days/week in both months 6 and 12. In the analysis, authors adjusted for the differences in mean age and baseline A1C across groups.

JDRF 2010" Effectiveness" is also a follow-up extension of the JDRF 2008. [91] It describes 61 subjects aged 8 to 14 when the trial began who were randomized to SMBG in the JDRF study, completed the 6-months trial, and then were offered use of CGM for 6 months. Among the 47 subjects aged 8 to 14 with A1c ≥ 7.0% when they started using CGM, 11 used it 0 days/week; 15 used it > 0 but < 4 days/week; 10 used 4 to < 6 days/week, and 11 used it ≤ 6 days/week.

Table 14.Summary of studies reporting mean A1C and percent of subjects meeting target A1C by use of CGM at baseline, 6 months, and 12 months

Study (year), Design LoE				
Chase (2010)[90] Prospective Cohort LoE II	Group A: Use ≥ 6 days/week in month 12 (n = 17)	Group B: Use ≥ 6 days/week in month 6 but < 6 days/week in month 12 (n = 17)	Group C: Use < 6 days/week in both month 6 and month 12 (n = 46)	p
A1C, % mean				<0.001*
Baseline (JDRF trail)	8.2	7.8	8.0	
6 months	7.3	7.3	8.0	
12 months	7.4	7.7	8.1	
Percent of subjects meeting target A1C†				0.03*
Baseline (JDRF trail)	29	47	39	
6 months	65	76	35	
12 months	71	41	33	
JDRF (2009)[89] Prospective Cohort LoE II	Average use < 4 days/week in month 6 (n = 7)	Average use 4−6 days/week in month 6 (n = 21)	Average use ≥ 6 days/week in month 6 (n = 28)	
Change in A1C, %, age 8−14	+0.02‡	− 0.03‡	−0.72‡	<0.001§

NR = not reported
* authors report p-values from comparison across the 3 groups at 12 months (analysis of covariance for A1C, logistic regression for % meeting targets, adjusted for baseline A1c and age.
† A1C target was defined in this study as < 8.0% for 8−12 year olds and <7.5% for 13−17 year olds.
‡ Mean values were estimated from figure 1 in article.
§ p adjusted for baseline A1C.

Summary of extension study reporting on frequency of CGM use among those initially randomized to SMBG in the JDRF 2008 trial

JDRF (2010) [91] Prospective Cohort LoE II	Use 0 days/week in month 12 (6th month CGM) (n = 11)	Use > 0 to < 4 days/week in month 12 (6th month CGM) (n = 15)	Use 4 to < 6 days/week in month 12 (6th month CGM) (n = 10)	Use ≥ 6 days/week in month 12 (6th month CGM) (n=11)	P-value
A1C (%), mean					
Baseline ††	**7.8**	**7.6**	**7.9**	**7.8**	**NR**
Change, 6 months	**-0.1 ± 0.6**	**+0.2 ± 0.6**	**-0.2 ± 0.9**	**0.0 ± 0.6**	**NR**
Improved ≥ 0.5%, n(%)	**3 (27)**	**2 (13)**	**4 (40)**	**3 (27)**	**NR**
Worsened ≥ 0.5%, n(%)	**3 (27)**	**7 (47)**	**2 (20)**	**2(18)**	**NR**
A1C < 7.0%, n (%)	**2 (18)**	**1 (7)**	**3 (30)**	**2 (18)**	**NR**

††Baseline refers to the time of initiation of CGM use after the 6 months in the JDRF RCT SMBG group

Overall, in the Chase follow-up study, use of CGM ≥ 6 days a week was associated with better outcomes[90]:

- At the end of the JDRF trial (in month 6), participants who used CGM > 6 days/week experienced decreases in A1c of 0.9% (among participants who also reported CGM use > 6 days/week at 12 months – Group A) and 0.5% (among participants who reported CGM use < 6 days/week at 12 months – Group B), and participants who did not report GCM use > 6 days/week (Group C) experienced no change in A1C levels at 6 months (Table 14). This suggests that a clinically meaningful change in A1C with 6 months of consistent continued use of CGM may be possible based on a 0.5% criterion for clinically meaningful change.

- At the end of the extension study (in month 12), Group A (CGM used >6 days/week in months 6 and 12) maintained the reduction in A1c levels, while participants in Group B (CGM used >6 days/week in month 6 and < 6 days/week in month 12) had A1c levels that returned almost to baseline levels and participants in Group C (GCM used < 6 days/week in both months 6 and 12) had a slight increase in A1C levels. All statistical comparisons were adjusted for age. Differences were statistically significant for comparisons between those using the CGM ≥ 6 days a week in months 6 and 12 versus those using the CGM ≥ 6 days a week in month 6 but < 6 days/week in month 12 ($P = 0.01$). Differences were also statistically significant for comparisons between Group A participants versus Group C participants ($P< 0.001$). Differences were not statistically significant for the comparison between Groups B and C ($P = 0.19$).

- Based on A1c targets of < 8.0% for 8−12 year olds and < 7.5% for 13−17 year olds, the percentage of patients achieving those targets was assessed.

    - At 6 months, a larger percentage of participants in Group A achieved A1C targets (65% versus 29% at baseline) than participants in Group B (76% versus 47% at baseline) or Group C (35% versus 39% at baseline).

- At 12 months, 71% of participants in Group A, 41% of participants in Group B, and 33% of participants in Group C achieved target A1c levels. The comparison between those who continued using the CGM ≥ 6 days/week versus those who used the CGM < 6 days/week was statistically significant ($P = 0.02$) after adjustment for age. Other statistical comparisons between groups were not significantly different.

- Participants who continued to use the CGM ≥ 6 days/week in month 12 decreased their time spent in the hyperglycemic range without increasing their time spent in the hypoglycemic range. (Statistical comparisons between groups for hyper- and hypoglycemia were not provided.)

Overall, in the JDRF follow-up study of those originally randomized to SMBG but then switched to a CGM after the trial:

- Among the 47 eight to 14 year olds with A1c ≥ 7.0 when they started using a CGM, there was no significant change in A1c from beginning CGM use to 6 months (mean change in A1c +0.02; p = 0.85).
- Of the 47 participants who had A1C ≥ 7% at the start of the observational study, 26%improved A1C ≥ 0.5%, 30% had ≥ 0.5% worse A1C and 17% had an A1C < 7.0% at the end of the study.
- No consistent pattern for improvement in A1C of ≥ 0.5% or achieving A1C <7% was seen. (Data provided in table above.)
- Among all 61 eight to 14 year olds, the incidence of severe hypoglycemic episodes trended higher during the 6 months using SMBG than during the 6 months using CGM (26.4/100 person-years vs. 13.0/100 person-years; p not reported for individual age group).

Frequency of self-monitoring of blood glucose (SMBG)

A large registry study report (LoE III) by Ziegler was the only study found that evaluated the relationship between SMBG frequency and quality of treatment as measured by A1c levels and frequency of hypoglycemia and ketoacidosis.[92] Data for 26,723 persons age 0 to18 years (mean age 12.7 ± 4.1 years) were used from a standardized, prospective, computer-based documentation of diabetes care and clinical outcomes. These included patients from 233 centers in Germany and Austria who were seen for care between 1995 and 2006. Frequency of SMBG and mean A1c were associated with both age and treatment regimen, Table 15. The authors adjusted for these in multivariate analyses. There was also a small difference in the average frequency of SMBG measurements between males (4.7/d ± 1.60, n = 13877) and females (4.8/d ± 1.60, n = 12 843). In studies with large sample sizes, even small differences between groups may reach statistical significance but may not be clinically relevant.

Table 15. Summary of mean A1C and SMBG frequency by age and insulin regimen

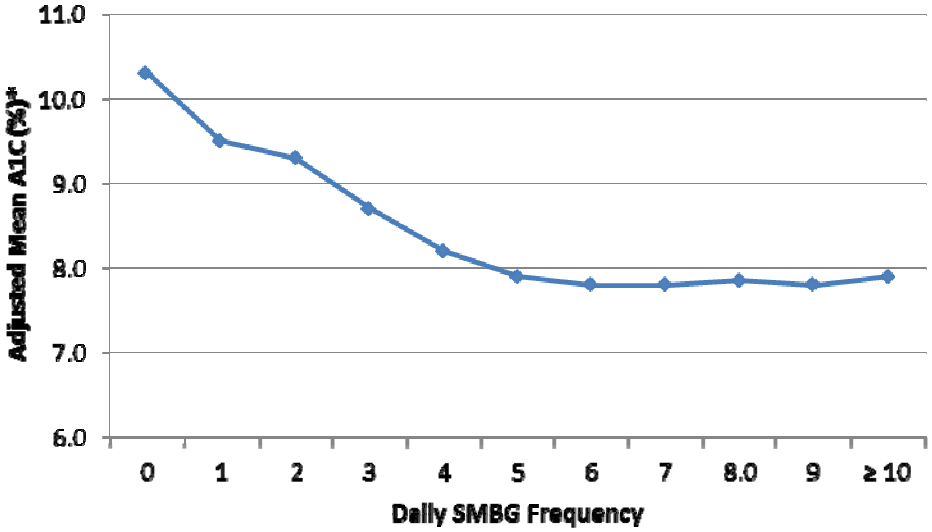
	0-5 years (n = 1989)	6-12 years (n = 7568)	> 12 years (n = 17,166)	P-value across age groups
Mean A1C	7.59% ± 1.34	7.61 ± 1.32	8.46 ± 1.85	*P*< .001
SMBG frequency	6.0/day ±1.9	5.3/day ± 1.6	4.4/day ± 1.4	*P*< .001
	CT (n = 5016)	**MDI (n = 18,565)**	**CSII (n = 3142)**	**P-value across treatment groups**
Mean A1C	7.64% ± 1.67	8.24% ± 1.75	8.01% ± 16.0	*P*< .001
SMBG frequency	5.3/day ± 1.8	4.7/day ± 1.5	5.3day ±1.8	*P*< .001

CT = Conventional treatment was defined as 3 or fewer daily injections; SCII = continuous subcutaneous insulin infusion, MDI = multiple daily injections

After adjusting for age, gender, diabetes duration, year of treatment, insulin dose, body mass index-standard deviation scores and clinical center, more frequent SMBG was associated with a significant improvement in metabolic control. The figure below provides information on the general trend for this association. (A1C values in the figure below were estimated from the author's figure.) The authors report that:

- An average decrease in A1c% (± SE) of 0.20% (± 0.007) was observed for one additional SMBG per day ($P < 0.001$). However, increasing SMBG frequency above 5/day did not, result in further improvements in metabolic control (i.e. decrease in A1c).
- When SMBG range was restricted to 0-5 measurements/day, A1c decreased by 0.46% (± 0.014) for one additional SMBG measurement ($P<0.001$).

Figure 5.General trend for the relationship between SMBG frequency and adjusted* mean A1C estimated from author's figure.[92]



*mean A1C (%) values adjusted for age, gender, diabetes duration, year of treatment, insulin dose, insulin regimen, BMI -standard deviation scores and clinical center. Values are estimated from the author's figure 2.

Six additional studies (five non-randomized studies and one cohort-like analysis of an RCT) provided some detail on specific numbers of SMBG tests in relation to A1C values as part of studies that were not directly focused on detailed evaluation of this relationship.[93-98] Evidence across these studies suggests that there may be an association between performing SMBG four to five times per day and lower A1C levels that are closer to target A1c levels (A1c range among participants with the highest SMBG frequency: 7.4%−8.3%) when indirectly compared with those who did not test or tested only 1-2 times per day (A1c range: 9.1%−9.9%). Although the studies analyzed relationship between frequency of SMBG and A1C using multivariate analysis, none reported direct comparisons between categories of SMBG frequency. Data from these studies are summarized below.

Table 16.Summary of observational studies reporting mean A1C by frequency of SMBG

Study (year) Design LoE	Population	Results		
		Mean SMBG frequency	Mean A1C, % ± SD	Significance in multivariable analysis
Paris (2009)[95] Cross-sectional LoE III	N = 2743 Age: 13.2 ± 4.5 years Female: 50% DM duration: 5.0 ± 3.9 years	Cross-sectional data: *		NR
		0 to 2 times/day (n = 284)	9.5 ± 2.1†	
		3 times/day (n = 363)	9.0 ± 1.6	
		≥ 4 times/ day (n = 2063)	8.2 ± 1.3	
Moreland (2004)[97] Cross-sectional LoE III	N = 153 Age: 12.9 ± 2.3 years Female: 56% DM duration 6.3 ± 3.5 years	1 time/day (n = NR)	9.1††	*P* = .03††
		2 to 3 times/day (n = NR	8.4	
		4 to 5 times/day (n = NR)	8.1	
		≥ 6 times/day (n =NR)	7.4	
Laffel (2003) [98] Cross-sectional analysis of RCT LoE III	**N = 100 Age: 8-17 years Female: 47% DM duration: 2.7 years**	**1 time/day (n = NR)**	**11.5**¶**	***P* = 0.05**¶**
		2 times/day (n = NR)	**8.5**	
		3 times/day (n = NR)	**8.7**	
		4 times/day (n = NR)	**8.3**	
		5 times/day (n = NR)	**8.1**	
Anderson (2002)[94] Cross-sectional LoE III	8–12 years N = 69 Age 10.7 ± 1.47 Female: 51 DM duration: 2.7 ± 1.69 13–17 years N = 35 Age 14.7 ± 1.07 Female: 40 DM duration: 2.4 ± 1.32	Cross-sectional data:		
		0 to 3 times/day	8.6% ‡	*P*< .01‡
		4-5 times/day	8.2%	
Levine (2001)[96] Prospective cohort LoE III	N = 300 Age: 11.9 ± 2.5 Female: 56% DM duration: 5.2 y ± 3.0	Baseline/cross-sectional		
		1 time/day	9.1 ± 0.34§	*P*< .0001§
		3 times/day	8.9 ± 0.16	
		≥ 5 times/ day	8.0 ± 0.31	
Anderson (1997) [93] Cross-sectional LoE III	10–12 years N = 51 Age 11.7 ± 0.89 Female: 55	Cross-sectional data:		
		0 to 1 time/day	9.9 ± .044‖	p<0.02 ‖

DM duration: 5.3 ± 2.47 13–15 years N = 38 Age 14.0 ± 0.65 Female: 45 DM duration: 6.0 ± 2.67	2 times/day 3 times/day ≥ 4 times/ day	8.8 8.6 8.3 ± .022

DM is diabetes mellitus. NR is not reported.
* Some missing data.
†Mean A1C values were not adjusted for potential confounders.
†† Values are estimated from author's figure and adjusted for pubertal status and parental reports of family involvement in diabetes management tasks. P value is for independent association between SMBG and A1C.
‡Mean values were estimated from figure 4 in article. Mean A1C values were adjusted for age, gender, duration of diabetes, child conflict, and parent conflict.
§Mean A1C values were adjusted for duration of diabetes, pubertal state, and sex.
||Mean values for 2 and 3 times/day were estimated from figure 2 in article. Mean A1C values were adjusted for gender, pubertal stage, and duration of diabetes.
** Values are estimated from author's figure, presumably at 1 year. Model adjusted for age, diabetes duration, sex, daily insulin dose and teamwork intervention. The P-value appears to be for association between SMBG and A1C. It is unclear whether the SMBG used was from baseline or 1 year. Study was RCT of family intervention, not SMBG and this analysis is considered consistent a cohort study.

Eleven other cross-sectional studies and one registry study looked only at general correlation between SMBG frequency (as a continuous variable) and A1C and did not provide information on specific numbers of SMBG tests performed.[99-110]

SMBG was generally considered as one of many variables for multivariate analysis; therefore evaluation of the association between frequency of SMBG and A1C was not the primary goal of these studies. Seven of these studies reported a significant association between more frequent SMBG and lower A1C. Butler et al,[99] report a multivarate analysis including frequency of SMBG, youth knowledge, parent knowledge, youth negative affect, parent negative affect, and parent-perceived burden as predictors of A1c. Compared with SMBG four or more times day, SMBG zero to two times a day was significantly associated with A1c ($p = 0.01$); but compared with testing four or more times day, performing SMBG three times a day was not ($p = 0.46$). Associations may not be causal. All studies had LoE III. Strength of evidence is low. In an observational study of 229 children and adolescents, A1C decreased by 0.4% for each additional SMBG per day ($p = 0.006$).[100] [HALLER] It is unclear whether this estimate was adjusted for other factors: It appears that all factors (age, gender, insulin type and frequency, SMBG, diabetes duration) whether statistically significant or not were retained in the model. No data correlating specific numbers of SMBG with specific A1C levels were provided or any number below or above which correlated with optimal control. The authors also report an increase of 0.2% in A1C

Hypoglycemia and diabetic ketoacidosis (DKA)
In one registry study, performing SMBG ≥ 5/day was associated with higher rates of hypoglycemia but lower rates of diabetic ketoacidosis (DKA) (Table 17). [92]] Hypoglycemia was defined as severe if the child had altered mental status, was unable to assist in care, was semiconscious or unconscious or in coma, had convulsions, or might equire glucagon or intravenous glucose. DKA was defined as hospital admission for DKA (hyperglycemia > 11 mmol/L, (198 mg/dl) pH < 7.3).[92] In interpreting these findings, it must be remembered that the relationships may not be causal. For example, increased frequency of SMBG may avoid

individuals avoid hypoglycemic episodes; those with lower A1C who may be at increased risk for hypoglycemia may test more frequently.

Table 17.Rates* for hypoglycemic events and DKA from a registry 26,723 persons 0-18 years old by frequency of SMBG[92]

	Hypoglycemic events	Diabetic Keto-Acidosis (DKA) events
SMBG 0-4/day	13-20 events/100 person-years	6-12 events/100 person-years (except for 1SMBG/day)
SMBG ≥ 5/day	20-37 events/100 person-years	4-6 events/100 person-years
Comments:	Rate for severe hypoglycemia ↑ by 2.38/100 p-y ±0.54 for each additional glucose measurement and ↑0.62 events/100 p-y ± 0.301 for hypoglycemia with coma or convulsion	Rate ↓ by 0.38 events /100 p-y (± 0.144) per additional glucose measurement

As stated by the authors, rates (per 100 person-years) were estimated as the ratio of the total number of events during the most recent year and the total sum of person-years under risk, according to the person-years method under the assumption of a Poisson distribution for the events p-y is person-years

Only one other study of 2579 patients examined frequency of SMBG with respect to frequency of severe hypoglycemic episodes.[108] The study defined severe hypoglycemic episodes as events with loss of consciousness, seizures, or the need for glucagon injection. A negative correlation ($r = -0.20$) between frequency of SMBG and severe hypoglycemic episodes was reported: the more often patients tested their blood glucose, the fewer their hypoglycemic episodes. It is possible that those at increased risk for hypoglycemia may test more frequently

3.3 Key question 3: What is the evidence of the safety of glucose monitoring?

This section focuses on device-related safety, primarily for real time continuous glucose monitors (rt-CGM). Information on rates of hypoglycemia, hyperglycemia and ketoacidosis are described in the efficacy and effectiveness sections (Key Questions 1 and 2). A broader scope of studies is summarized in this question to better characterize the safety profile of CGM. Safety related information for SMBG is described at the end of this section. Safe disposal of sharp equipment and of biohazard materials is necessary for all monitoring types.

Summary for Continuous Glucose Monitors (CGM)

The possible device-related safety issues for CGMs relating to inserting the sensor into the skin include irritation, inflammation, infection, bleeding, bruising, blisters, edema, redness, and itching. Possible adverse events relating to inaccurate glucose readings or false alarms include subsequent inappropriate use of carbohydrates or insulin resulting in hyper- or hypoglycemia assuming that CMG data alone would be used without confirmatory SMBG reading.

Summary for CGM: The rate of events reported in RCTs, FDA reports, and nonrandomized studies varies widely. Some studies actively examined the insertion site to look for adverse events, while others did not. Studies categorized skin changes in different ways. In many studies, if no problems occurred they were not listed. With changes in technology and experience, the attachment between the sensor, the sensor mount, and the skin improved. Study

duration for CGM has been generally short (one year or less) and longer-term data on safety were not found.

CGMs currently marketed can set a threshold for alerting patients when glucose values have reached a specified low or high level, allowing patients to take appropriate action; therefore, the frequency of false alerts will depend on the threshold set. False alerts may be annoying and lead the patient to ignore subsequent alarms. More seriously, false alerts may cause patients to take inappropriate treatment actions. Because of the potential for false alerts, patients are not to base treatment decisions on the CGM reading alone. Instead, they should verify their glucose level with SMBG and base their treatment decision on that. Missed alerts, or occasions when the alarm should have sounded but did not, occur less frequently (at a rate depending on the specified threshold) but are more dangerous, because the patient is not alerted to take necessary action and may have a false sense of security.

Across the randomized and non-randomized studies, the range of the percent of subjects reported as having various problems with a CGM is shown.

Problems at insertion site:

- Cellulitis: 0%–4%
- Redness: 19%–45%
- Redness and itching: 16%
- Painful redness: 1%
- Pain: 2%
- Skin irritation: 3%–5%
- Scabbing: 32%
- Dry skin: 21%
- Changes in pigmentation: 7%
- Acute skin changes: severe 2%, moderate: 14%; mild: 14%
- Itching: 17%
- Rash: 2%
- Bruising: 3%
- Blisters: 2%–6%
- Edema: 2%–3%
- Bleeding at insertion site: 2%–10%
- Infection, bleeding, device failure or dislodgement: 0

- Irritation, bruising, or pain at insertion site: 0%–53%

Problems with sensor:

- Sensor alarms interfered with daily routine: 38%
- Irritation by alarms: 38%–50%
- Sensor too bulky: 22%–75%
- Sensor did not insert properly: 3%
- Sensor was pulled out accidentally: 10%–13%
- Disliked wearing sensor and dropped out or removed sensor: 3%–4%
- No deaths among participants ≤ 18 years old were reported in any study.

Summary of Self-monitoring of blood glucose (SMBG)

The only safety issue reported with modern SMBG devices is from the SMBG arm of one RCT, one patient reported dizziness while sampling blood. Reports of problems at the fingerstick site come from old studies, published 1983−1988. There were no data from studies using modern devices. Devices used for drawing blood have improved, with smaller lancets, less blood required, and test sites other than fingertips. With that caution, the range of the percent of subjects reported in RCTs and nonrandomized studies as having various problems related to SMBG is provided for context.

- Sore fingers: 58%
- Severe pain, bruising, or infection: 0
- Difficulty obtaining blood samples: 63%

Detail of studies

Summary of adverse events reported in RCTs of CGM

Overall, the primary events reported in RCTs using CGM were cellulitis at the CGM insertion site (0%–4%) and redness, itching, pain, irritation, or combinations of symptoms at the insertion site. (Table 18) [80,81,83-87] No deaths occurred in the age group for this report in any RCT.

Reporting of safety issues or adverse events varied across studies. If a study reported that there were no cases of a particular outcome, it is listed here as "0"; but if a study did not report an outcome, that outcome is not listed here. In some cases, authors did not report in that study arm an event occurred or whether events occurred in the population of interest for this report. These are noted in the comments column and in the text.

Table 18. Summary of adverse events reported in RCTs of CGM

Study (year)	CGM duration/ use	Adverse events	Comments
RCTs of patient real-time use of CGM data			
JDRF (2008)[80] N = 56 age 8–14 years in	26 weeks	CGM Group, age 8–14: Cellulitis at insertion site: 2	

CGM group N = 58 patients age 8–14 years in SMBG group Study duration: 26 weeks		(4%) Dizziness during blood draw: 0 Anxiety or depression: 0 SMBG Group, age 8–14: Cellulitis at insertion site: 0 Dizziness during blood draw: 1 (2%) Anxiety or depression: 0	
Hirsch (2008)[81] N = 23 patients age 12 to < 18 in CGM group N = 17 patients age 12 to < 18 in SMBG group Study duration: 26 weeks	26 weeks	CGM Group: None reported SMBG Group: None reported	Adverse events were not reported by age group. There were 2 abscesses in one patient at the *insulin infusion* site.
Bergenstal (2010)[83] N = 78 patients age 7–18 in pump-therapy group N = 78 patients age 7–18 in injection-therapy group Study duration: 1 year	1 year	*Pump-therapy group:* Death: 0 in those < 18 years old Cellulitis at insertion site requiring hospitalization: 0 *Injection-therapy group:* Death: 0	
RCT or crossover trials of periodic CGM use			
Deiss (2006)[84] N = 15 in open arm N = 15 in blinded arm Study duration: 6 months	3 days during 3 sessions over 6 months	Redness at insertion site: 23% Redness and itching at insertion site: 16% Painful redness at insertion site: 1%	N's were not reported Patients were randomized and crossed over to having data available or blinded to physicians
Lagarde (2006)[85] N = 27 Study duration: 4 months	3 sessions of up to 72 hours every 2 months for 4 months	Infection, bleeding, device failure, or sensor dislodgement: 0	Patients were randomized and crossed over to having data available or blinded to physicians
Yates (2006)[86] N = 19 in CGM group N = 17 in SMBG group Study duration: 12 weeks	19 subjects used for CGM 3 days every 3 weeks for 12 weeks.	*CGM group:* Skin irritation at insertion site: 1 (5%) *SMBGgroup:* Suicidal ideation: 1 (6%)	Patients were randomized to using a CGM giving periodic data or SMBG
Ludvigsson (2003)[87] N = 27 Study duration 6 months	72 hours at a time every 2 weeks for 6 months	Disliked wearing sensor and dropped out: 1 (4%)	Patients were randomized and crossed over to having

data available or blinded to physicians

There were three RCTs involving CGMs that gave real-time data and reported adverse events.[80,81,83]

The JDRF (2008) randomized 322 participants to wearing a CGM or using intermittent SMBG for 26 weeks.[80] The study was conducted among children, adolescents, and young adults, and reported adverse events by age group. Only results for the 114 in the 8- to 14-year old age group are included here. Collecting adverse events was part of the study design. In the CGM group, there were two cases of cellulitis related to using the monitor. One participant in the SMBG experienced dizziness during a blood sample. The study reported on deaths, anxiety, and depression, but found no case among the 8- to 14-year olds.

Hirsch (2008) studied 146 participants (including 40 who were 12 to <18 years old) who used continuous subcutaneous insulin infusion (CSII).[81] Only the younger participants are described here. They were randomized to using a CGM integrated with a CSII or to SMBG (with CSII) and were followed up for six months. Adverse events were reported by subjects in their logs. Adverse events were not categorized by age group, and some may have occurred in the adult population. One participant had two abscesses at the *insulin infusion* site, but not at the CGM site; which monitoring group the participant was in was not reported.

Bergenstal (2010) studied 329 adult participants and 156 participants 7to 18 years old. Only results for the younger group are reported here.[83] All wore a CGM continuously for one year. Participants were randomized to using an insulin infusion pump integrated with the CGM ("sensor-augmented pump therapy") or to using frequent insulin injections with a CGM that did not display real-time data ("injection-therapy"). Collecting adverse events was part of the study design. Adverse outcomes were not stratified by age group.

No deaths occurred in participants < 18 years old.[126]

There were four randomized controlled trials involving an intervention in which participants wore a CGM for up to 72 hours on two or more occasions. All these studies used a CGM giving periodic (retrospective) data. The problems that developed during this short-term use may not be relevant to longer-term, consistent participant use. In three trials,[84,85,87] participants were randomized to using a CGM of which clinicians used the data to adjust treatment, or to using a CGM of which clinicians were blinded to the data, and did not use it to adjust treatment. This design accounts for effects of using the CGM itself, rather than using the data it provided. Another randomized controlled trial[86] randomized participants to intermittent blood glucose monitoring or to continuous glucose monitoring. These studies also provided data on suboptimal data collection. However, since data weren't given real-time, participants would not have been aware of the problems and would not have had a chance to correct them.

Deiss (2006) was a cross-over study of 30 participants.[84] All wore a CGM giving periodic (retrospective) data for three days at a time during three sessions over six months. They were randomized to having data from the CGM interpreted by physicians, or to having physicians blinded to the data. How adverse events were ascertained was not described. Among the 30

participants, 23% had redness, 16% had redness and itching, and 1% had painful redness at the insertion site. None of these adverse events caused the participants to remove their CGM early.

LaGarde (2006) was a cross-over study of 27 participants.[85] All wore a CGM giving retrospective data for three days at a time every two months for four months. They were randomized to having data from the CGM interpreted by physicians, or to having physicians blinded to the data. Participants recorded adverse events in their logs. There were no cases of infection, bleeding, device failure, or sensor dislodgement.

Yates (2006) randomized 36 participants ≤ 18 years old to SMBG or to CGM using monitors giving retrospective data.[86] Participants used the CGM for three days every three weeks for 12 weeks. How adverse events were ascertained was not described. One participant in the SMBG arm developed suicidal ideation. One participant in the CGM arm developed skin irritation at the sensor site and withdrew.

Ludvigsson (2003) was a cross-over study of 27 participants.[87] All wore a CGM giving periodic (retrospective) data for 72 hours at a time every two weeks for six months. They were randomized to having data from the CGM interpreted by physician, or to having physicians blinded to the data. How adverse events were ascertained was not described. One participant disliked wearing the sensor and dropped out; no other adverse events were reported.

Safety data from FDA Summaries of Safety and Effectiveness Data (SSED):

Only the Paradigm REAL-Time System and Guardian REAL-Time System (Pediatric Versions) are currently approved for use in persons ≤18 years old.[118] Studies of the FreeStyle Navigator® and DexCom™ devices are also described in this report and data are provided for context and since they were used in the JDRF trials.[119,120]

Overall, the rates of device-related adverse events among children using the Paradigm REAL-Time System or Guardian REAL-Time System was low (Table 19). The reported rates of bleeding at the insertion site was 2%; of rash, 2%; of pain, 2%; and of skin irritation, 3%. None of the adverse events was considered serious.

Among adults using the DexCom SEVEN PLUS or Freestyle Navigator, reported rates of bleeding at the insertion site were 2% − 3%; of bruising, 3%; of blisters, 2%−6%; of edema, 2%−3%; of redness, 19%−45%; and of itching, 17%. None of the adverse events in the DexCom SEVEN PLUS or Freestyle Navigator was considered serious.

Table 19.Overview of device-related adverse events rates for FDA-approved CGM devices* from FDA Summaries of Safety and Effectiveness Data

Device (year of SSED)	CGM Duration/use	Reported Adverse Events
Paradigm REAL-Time System and Guardian REAL-Time System* (Pediatric Versions) (2007)[118] N = 61: age 7-12 n =30; age 13-17 n = 31	6 days	• Bleeding at insertion site: 2% (1/61) • Rash: 2% (1/61) • Pain: 2% (1/61) • Skin irritation: 3% (2/61)

% completed: 93 Study duration: 6 days		
DexCom SEVEN PLUS (2006)[120]		
DexCom SEVEN PLUS Pilot study N = 31 Mean Age: 42 ± 13 y % completed: 100 Study duration: 12-24 h	12 hours: N = 16 24 hours: N = 15	*Pilot study* • Bleeding at insertion site: 3% (1/31) • Bruising: 3% (1/31) • Blisters: 6% (2/31) • Edema: 3% (1/31) • Redness: 45% (14/31)
DexCom SEVEN PLUS 72-hour study N = 42 Mean Age: 43 ± 12 y % completed: 100 Study duration: 72 h	72 hours	*72-hour study* • Bleeding at insertion site: 2% (1/42) • Blisters: 2% (1/42) • Edema: 2% (1/42) • Redness: 36% (15/42)
DexCom SEVEN PLUS Pivotal study N = 91 Mean Age: 44 ± 13 y % completed: 100 Study duration: 9 d	9 days	*9-day study* • Blisters: 2% (2/91) • Edema: 2% (2/91) • Redness: 19% (17/91)
FreeStyle Navigator (2008)[119] In-clinic study N = 58 Mean Age 40.5 ± 11.2 % completed: 98 Study duration: 5 days	5 days	*5-day study* • Blisters: 2% (1/58) • Redness: 28% (16/58) • Itching (17%) (10/58)

* Only the Paradigm REAL-Time System and Guardian REAL-Time System (Pediatric Versions) are currently approved for use in persons ≤18 years old. Age is reported as mean ± SD. Adverse events are reported as events/patients. More than one event may have occurred in each patient.

One theoretical benefit of rt-CGM is the ability to set a threshold for alerting patients when values are trending toward hypoglycemia or hyperglycemia, allowing for them to take the appropriate action. The FDA SSED reports related to device approval provide information on the false alarm rates for paired sets of data from CGM compared with the values from SMBG. (These evaluations assume that the SMBG provides an accurate indicator of the blood glucose level, which may not be true in all instances.) Although some of these reports were in patient populations older than 18 years old, they do add to the overview of the safety profile for these devices.

Hypoglycemia false alert rates are the percent of time when the device alarmed but the blood glucose level was above the alert setting. In other words, these are false positive alerts. False positive alerts for hypoglycemia may be annoying and lead the patient to ignore subsequent alarms. However, false positive alerts are not as dangerous as missed (false negative) alerts, i.e., times when the device did not alarm although the blood glucose level was below the alert setting.

Hyperglycemia false alert rates are the percent of time the device alarmed when the blood glucose level was actually below the alert level. These are false positive alerts. False positive alerts for hyperglycemia may be annoying and lead the patient to ignore subsequent alarms. However, false positive alerts are not as dangerous as missed (false negative) alerts, i.e., times when the device did NOT alarm although the blood glucose level was above the alert setting.

The false negative alert rate is captured in the TRUE alert rates: one minus the true alert rate gives the false negative rate. For hypoglycemia, the true alert rate is the percent of time when the glucose level was at or below the alert setting that the alert would have sounded. For hyperglycemia, the true alert rate is the percent of time when the glucose level was at or above the alert setting that the alert would have sounded.

Table 20.Overview of device-related true and false alarm rates for FDA-approved CGM devices* from FDA Summaries of Safety and Effectiveness Data

	Low Alerts				High Alerts			
	True Alert †		False Alert Rate (False positive)		True Alert †		False Alert Rate (False positive)	
	Threshold (mg/dL)	Rate, %	Threshold (mg/dL)	Rate, %	Threshold (mg/dL)	Rate, %	Threshold (mg/dL)	Rate, %
Paradigm REAL-Time and Guardian REAL-Time Systems (Pediatric Version)[118]	70	24.2	70	47.8	180	95.4	180	43.8
	75	41.0	75	44.1	185	94.8	185	41.8
	80	51.6	80	45.7	190	93.7	190	39.9
	85	61.1	85	49.3	195	92.7	195	37.9
	90	69.7	90	52.0	200	90.8	200	35.5
	95	77.9	95	54.6	205	89.9	205	32.7
	100	85.3	100	57.3	210	87.8	210	29.7
					215	86.1	215	26.6
					225	81.3	225	21.4
					250	63.9	250	13.1
DexCom SEVEN PLUS[120]	60	54	60	36	140	99	140	21
	70	57	70	24	180	98	180	24
	80	62	80	13	200	98	200	31
	90	68	90	9	240	96	240	43
					300	97	300	67
FreeStyle Navigator[119]	*Day*		*Day*		*Day*		*Day*	
	65	46	65	19	180	89	180	11
	70	56	70	16	240	78	240	12
	75	59	75	9	270	70	270	12
	85	61	85	7	300	61	300	12
	Night		*Night*		*Night*		*Night*	
	65	80	65	41	180	69	180	7
	70	79	70	40	240	41	240	25
	75	72	75	37	270	21	270	36
	85	65	85	33	300	12	300	33

* Only the Paradigm REAL-Time System and Guardian REAL-Time System (Pediatric Versions) are currently approved for use in persons ≤18 years old.

† True alert rate = sensitivity. 1 − true alert rate is missed alter (false negative) rate: the percent of times when the blood glucose level was below the alert setting for hypoglycemia that the device would NOT have alarmed; or the percent of times when the times when the blood glucose level was above the alert setting for hyperglycemia that the device would NOT have alarmed.

Device Recalls

Background: A manufacturer or distributor may recognize that a medical device has a problem that violates FDA law. If the problem is a defective device and/or a potential health risk, the device is recalled and the FDA is notified. The manufacturer or distributor typically recalls the devise voluntarily; otherwise, the FDA can force the recall. The recall may mean that the patient should stop using the device, return it, have it fixed, or simply have it checked. The problems with the highest risk are labeled Class I; those with the lowest risk are labeled Class III. The FDA posts recalls on its website and notifies health care providers and patients, if necessary.

As reported on the FDA website, in April 2010, Abbott Laboratories recalled 5449 FreeStyle Navigator CGMs. The monitors were recalled because the plastic housing near the battery could crack, allowing moisture to enter with the potential for device failure or inaccurate readings. This was considered a Class II recall.

In August, 2009, the FDA notified patients and clinicians that GDH-PQQ* glucose test strips (used with meters from various manufacturers) may give falsely elevated glucose readings. The strips did not distinguish between non-glucose sugars and glucose. A patient might use too high an insulin dose based on the falsely elevated reading. This was an alert, not a recall.

In January 2006, Roche Diagnostics voluntarily recalled some ACCU-CHEK Aviva glucose meters because they might give erroneous results or shut down completely.

In June 2005, Abbott Laboratories recalled several models of glucose meters. The meters were recalled because they could inadvertently switch units from mg/dL to mmol/L. The patient might not recognize the change in units and misinterpret the results, potentially leading to hyperglycemia. This was considered a Class I recall. In April 2005, LifeScan recalled several models of glucose meters for the same reason. This was also considered a Class I recall.

In August 2002, Roche Diagnostics recalled the Accu-Chek Inform Blood Glucose Monitoring System, which was sold only for professional use in hospitals. The meters were recalled because they could give inaccurate readings if the temperature icon had ever been displayed. This was considered a Class II recall.

Safety information available from non-randomized studies

Seven nonrandomized studies provide addition information regarding with regard to safety of CGM. The primary events reported in non-randomized studies were problems at the insertion site and problems with the sensor. The range of the percent of subjects reported as having a particular problem is included in the summary above.

Table 21. Summary of adverse-events reported in non-randomized studies of CGM*

	CGM duration/	Adverse events	Comments

	use		
Cemerglu (2010)[111] LoE III N = 34 with short-term use Mean age 14.6 ± 0.9 years 94% completed questionnaire† Study duration: 4 weeks N = 9 with long-term use Mean age 13.4 ± 1.6 years 89% completed questionnaire † Study duration: 2–18 months	Short-term group: 4 week trial Long-term group: 2–18 months	*4-week trial group:* † Sensor alarms interfered with daily routine: 38% Irritation by alarms: 50% Sensor too bulky: 22 % Sensor site irritation/ bruising/ pain: 53 % *Long-term use group:* † Sensor alarms interfered with daily routine: 38% Irritation by alarms: 38% Sensor too bulky: 75 % Sensor site irritation/ bruising/ pain: 0%	Subjects in long-term use group were self-selected for satisfaction with CGM. CGM gave real-time data. Questionnaire asked about problems with alarms and sensor site.
Messer (2009)[112] LoE III Using CSII N = 30 Mean Age 11.2 ± 4.1 years % completed: 100 Study duration: 13 weeks Using MDI N = 27 Mean Age 11.0 ± 3.9 years % completed: 100 Study duration: 13 weeks	13 weeks	*CSII group:* Sensor did not insert properly: 3% Too much bleeding at sensor insertion site: 8% Sensor was pulled out accidentally: 13% Participant removed sensor due to discomfort: 3% Other problems unrelated to sensor insertion or adhesion: 39% *MDI group:* Sensor did not insert properly: 3% Too much bleeding at sensor insertion site: 10 % Sensor was pulled out accidentally: 10% Participant removed sensor due to discomfort: 4% Other problems unrelated to sensor insertion or adhesion: 48%	CGM gave real-time data Diabetes educators asked participants about problems.
DRCN (2007)[113] LoE III N = 33 enrolled, 28 completed Mean Age 11.2 ± 4.1 years % completed: 85 Study duration: 13 weeks	13 weeks	Severe skin reactions: 2 (7%) Moderate acute skin changes: 14% Mild acute skin changes: 14% Scabbing: 32% Dry skin: 21% Changes in pigmentation: 7%	CGM gave real-time data Skin was inspected at clinic visits at 3, 7, and 13 weeks
Gandrud (2007)[114] LoE III	3 days	"Occasional" mild irritation and rash at the insertion site	CGM worn 4-6 times for 3 days over 6 months; total

N = 19 Mean age: 4.8 years % completed: 100 Study duration: 6 months		Infection: 0	102 wearings from all 19 participants CGM gave retrospective data How adverse events were ascertained was not reported.
Wong (2006)[115] LoE III N = 20 Mean age: 12.2 ± 4.6 years % completed: 100 Study duration: 7 days	7 days	Itching: 30-40% ‡ Edema: 0 Pain: 2 (10%) Dryness: 2 (10%) ≤ 3 mm induration: 92% ≤ 5 mm redness: 90% Infection: 1 (2%)	CGM gave retrospective data Participants completed a questionnaire about adverse effects and insertion site was inspected.
Jeha (2004)[116] LoE III N = 10 Mean age: 3.65 years % completed: 90 Study duration: 1 month	70 hours (median) on 2 occasions 1 month apart	Local irritation: 0 Infection: 0	CGM gave retrospective data How adverse events were ascertained was not reported.
Boland (2001)[117] LoE III N = 56 Mean age: 11.6 years % completed: 89 Study duration: 3 days	3 days	Inflammation: 0 Infection: 0	CGM gave retrospective data After 3 days, family was asked about problems and insertion site was inspected.

*Ages are reported a mean ± SD. Adverse events are reported as events/participants. More than one event may have occurred in each participant.
† Only 32 in 4-week trial group answered questionnaire; only eight with long-term use answered questionnaire.
‡ Numbers estimated from figure.
CSII is continuous subcutaneous insulin infusion; DRCN is Diabetes Research in Children Network; MDI is multiple daily injections

Those studies that actively sought adverse events by questionnaires or inspecting the insertion site typically reported higher rates of problems than those studies that passively learned of adverse events.

Cemerglu (2010) was a retrospective chart review of patients who tried using a real-time CGM for four weeks before using it long term.[111] After the trial period, patients and their parents completed a questionnaire about the CGM. The questionnaire included items about sensor alarms and problems with the sensor site. These investigators described the answers received from 32 patients who used the CGM for only four weeks; and from eight patients who continued using the CGM long-term (two to 18 months). Those patients who liked the CGM during the trial period were the ones most likely to continue using it long term, so they were self-selected for being satisfied with the monitor.

Messer (2009) assessed the process of educating participants and their families on using a real-time CGM.[112] Part of that process was asking participants whether they had any problems with the CGM. Their answers provide the data for adverse events. The study included 57 participants, 30 of whom were using an insulin pump and 27 of whom were using multiple daily insulin injections.

DRCN [Diabetes Research in Children Network] (2007)[113]: This prospective observational study enrolled 33 participants. However, three withdrew during a run-in phase and two dropped out after seven weeks (85% continued). The other 28 wore a CGM giving real-time data for 13 weeks. During clinic visits at three, seven, and 13 weeks, the insertion sites were inspected. Two participants had severe skin reactions from adhesive. These were avoided by placing a bandage between the sensor mount and the skin. At 13 weeks, two (7%) had severe acute skin changes, 14% had moderate acute skin changes, and 14% had mild acute skin changes. In addition, 11 (39%) had nonacute changes: scabbing (32%), dry skin (21%), and changes in pigmentation (7%).

In Gandrud (2007),[114] 19 participants wore CGMs for three days four to six times over six months. Although the CGMs gave only retrospective data, clinicians used that information to adjust the treatment regimen. The method of ascertainment of adverse events was not reported Wong (2006) assessed the performance, safety, and tolerance for 20 participants wearing CGMs up to seven days.[115] The CGMs gave retrospective data, which was shared with the participants at the end of the week. At the end of seven days, participants completed a questionnaire that included items about adverse effects and the insertion site was inspected.

In Jeha (2004),[116] ten participants wore a CGM for 72 hours during two sessions one month apart. The CGM gave retrospective data, which clinicians used to adjust the insulin dosage. How adverse events were ascertained was not reported.

In Boland (2001),[117] 56 participants wore a CGM for up to three days. The CGM gave retrospective data, which was compared with data obtained from twice-daily SMBG. At the end of the three days, insertion sites were inspected and participants and family were asked about problems with the CGM.

Two observational studies of participants using CGMs (Chase 2010, JDRF 2010) included as evidence for Key Question 2 did not report adverse events.[90]

Summary of adverse-events reported in randomized and non-randomized studies using SMBG

Limited information about adverse effects from SMBG is available from two very old (published 1983 to 1988) randomized and one old nonrandomized study. Devices requiring less blood and smaller implements for obtaining the blood sample have been developed since then. Thus, the results in the tables below are most likely not representative of currently available devices and are provided primarily for context. Information is available from three more recent studies (published 2006 to 2008) that randomized some participants to using SMBG or CGM.[80,81,86]

The only events reported among those using SMBG was dizziness during a blood draw. Additional adverse events from those studies such as hypoglycemia and hyperglycemia are reported in the table with adverse events with CGMs.

Table 22. Summary of adverse-events reported in randomized studies comparing SMBG to urine testing and in non-randomized study of SMBG

	Adverse events*	Comments
Randomized studies		
Daneman (1985)[74] N = 16 LoE II Mean age 4.1 years Study duration: 26 weeks	Severe pain, bruising, or infection at fingerstick sites: none Preferred SMBG to urine testing: 11 (69%)	Participants were "divided" into two groups—not necessarily randomized. How adverse events were ascertained was not described.
Miller (1983)[75] LoE II Mean age: NR N = 19 Study duration: 5 months	Difficulty obtaining blood samples: 12 (63%) Sore fingers: 7 (58%)	Attitude about testing was assessed by interview.
Non-randomized study		
Belmonte (1988)[121] LoE III N = 219 Mean age 12.6 ± 5.2 years 86 (39%) had fingertips examined Study duration: 3 years	Fingertip exam:† No stab marks: 23% < 10 stab marks: 23% ≥ 10 stab marks: 55%	A random sample of participants who performed SMBG 2-3 times/day had fingertips examined

LoE = level of evidence; NR = not reported.
* Adverse events are reported as events/participants. More than one event may have occurred in each participant.
† Percents do not sum to 100 because of rounding.

3.4 Key question 4: What is the evidence that glucose monitoring has differential efficacy or safety issues in sub-populations?

Include consideration of:

a) Gender
b) Age (differential within the 18 and under population)
c) Psychological or psychosocial co-morbidities
d) Other patient characteristics or evidence based patient selection criteria
e) Provider type, setting or other provider characteristics
f) Benefit provider/payer type, including worker's compensation, Medicaid, state employees

No comparative studies that directly assessed differential outcomes of either rt-CGM or SMBG by gender, provider type, setting or characteristics, or benefit provider type were found. While a number of studies were found that explored relationships between various psychological, and psychosocial factors and glycemic control (based on A1C), none directly evaluated how such factors modify the relationship between SMBG or CGM and outcomes such that differential efficacy or safety could be assessed.

Evidence from one RCT (LoE II) [80] comparing CGM with SMBG and one large registry study (LoEIII) that evaluated specific frequencies of SMBG[92] provide the only direct evidence to answer this question based on analyses in the same underlying population.

The overall strength of evidence for these findings is low. Overall, these studies suggest that For CGM:

- Participants 8 to14 years old and participants 15 to 24 years old had similar results with regard to A1C levels and the proportions achieving A1c targets between CGM and SMBG arms, and no evidence of differential efficacy by age was demonstrated, based on one RCT.

For SMBG:

- There appears to be differential effectiveness for frequency of SMBG by age. For 13 to18 years olds, an average improvement in A1c of 0.3% ± 0.011 ($P < 0.001$) for each additional SMBG was reported. This appears to apply up to tests five per day. For ages 0 to 5 and 6 to12 years, there was little improvement in A1C beyond one test per day. Results for these younger age groups were described as only a minor improvement by the study authors. Evidence is from one large registry study.[92]
- There may be some differential effectiveness for frequency of SMBG by insulin regimen. Patients using continuous subcutaneous insulin infusion (CSII) experienced a mean reduction of 0.27% in A1C for one additional SMBG per day. This group came closest to approaching A1C targets of between 7.0% and 7.5%. Those using multiple daily injections (MDI) experienced a 0.24% decrease in A1C. Evidence is from one large registry study.

Findings with respect to age

Randomized studies-CGM (with SMBG) versus SMBG alone

One RCT (LoEII)[80] provided data for comparison of outcomes by age group. In addition to the 8-14 year old group reported in KQ2, the JDRF trial also included participants aged 15 to 24 years old. Results were not included above because less than 80% of the group was ≤ 18 years old (mean age for stratum, 18.8 ± 3.0 years) and therefore didn't strictly meet inclusion criteria for this HTA. None-the- less the data provide limited insight into outcomes for persons in their late teens. The results are similar to what are reported for the 8 to 14 year olds in KQ2:

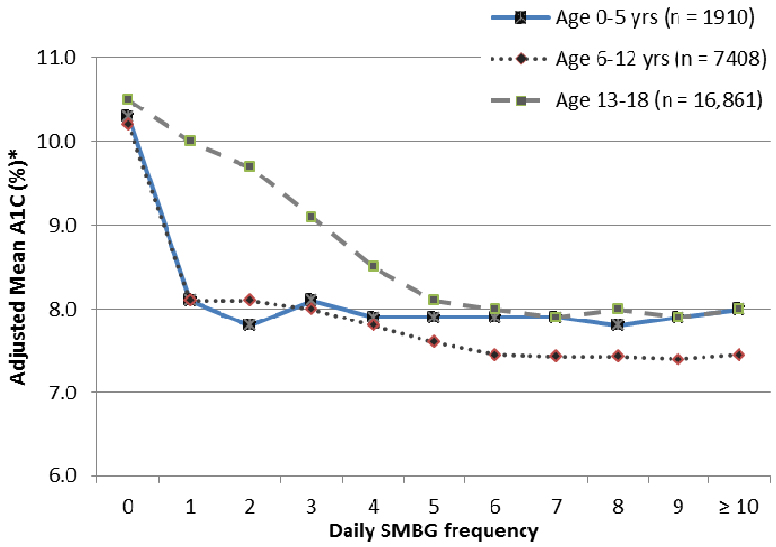
- Among 15 to 24 year olds, there was no significant difference in the change in A1C levels from baseline to 6 months between the CGM and SMBG arms among 15 to 24 year olds (−0.18% vs. −0.21%, respectively; $P = 0.52$).
- Among 15 to 24 year olds, at 26 weeks, there were no significant differences between CGM and SMBG arms in the proportion of participants achieving target A1C levels < 7% (14% versus 18%, p = 0.80), a relative reduction in A1C levels ≥ 10% (14% versus 10%, $P = .46$), or an absolute reduction in A1C levels ≥ 0.5% (36% versus 37%, $P = 0.5784$).
- Among 15 to 24 year olds, at 26 weeks there was no statistically significant difference between the CGM and SMBG arms in the mean minutes per day at glucose levels 71–180 mg/dL, > 180 mg/dL or > 250mg/dL.

Non-randomized studies and frequency of SMBG

A database study (LoE III) by Ziegler was the only study found that had the primary purpose of evaluating the relationship between frequency of SMBG with quality of treatment as measured by A1C and the frequency of hypoglycemia and ketoacidosis, as reported in KQ 2.[92] They also explored the modification of the relationship between SMBG frequency and A1C by patient age and insulin regimen.

In patients 13–18 years old, greater SMBG frequency was associated with lower A1C levels after accounting for (i.e. statistically adjusting for) the effects of gender, diabetes duration, year of treatment, insulin regimen, insulin dose, BMI -standard deviation scores and clinical center. The authors report an average improvement in A1C of −0.30% ± 0.011($P = .001$) for 13–18 years old for each additional SMBG test per day. This appears to apply to up to five tests per day. By contrast, the authors report that those in the younger age groups showed only minor improvement in A1C for each additional SMBG test over once per day. Among those 0 to 5 years old, for each additional SMBG test, there was an average improvement in A1c of 0.04% ± 0.018, $P = 0.031$. Among those 6 to 12 years old, for each additional SMBG test over once per day, there was an average improvement in A1c of 0.12% ± 0.010, $P< 0.001$. Although statistically significant it is unclear that these smaller changes in A1C for the 0-5 year olds are clinically significant. (Mean A1C values are estimated from the author's figure.)

Figure 6. General trend for the relationship between frequency of SMBG and adjusted* mean A1C by age group.

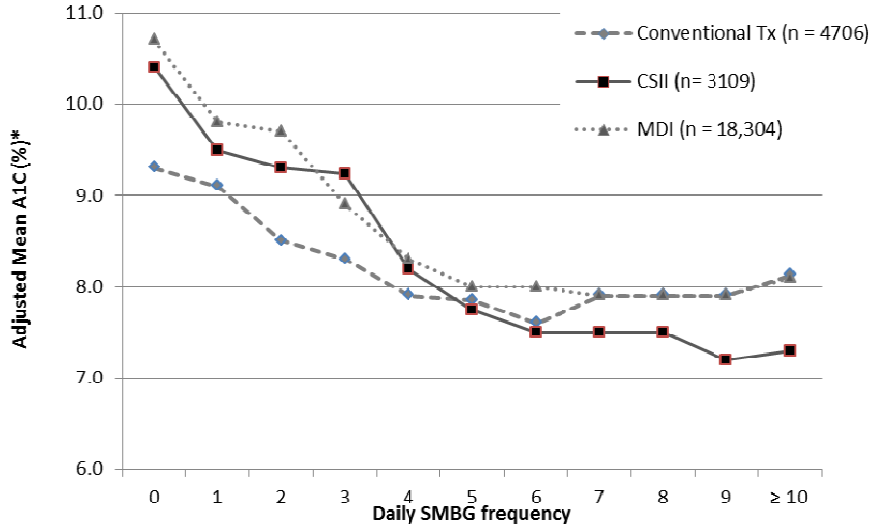


*mean A1C (%) values adjusted for gender, diabetes duration, year of treatment, insulin dose, insulin regimen, BMI -standard deviation scores and clinical center. Values are estimated from the author's figure 4.

Findings with respect to insulin regimen

In the same report by Ziegler, insulin regimen also appeared to modify the relationship between SMBG frequency and mean A1C after adjusting for age, gender, diabetes duration, year of treatment, insulin dose, BMI-standard deviation scores and clinical center. Patients using CSII experienced a mean reduction of 0.27% (± 0.017, $P< .001$) in A1C for one additional SMBG per day. A more modest incremental benefit appeared to continue beyond doing five tests per day for this group and they appeared to get closer to targets of between 7.0% and 7.5%. For participants using MDI (4 or more daily injections) a 0.24% (± 0.009, $P< .001$) decrease in A1C for each additional SMBG test per day was reported. For those using conventional therapy, defined as three or less daily injections, a 0.09% (± 0.016, $P< .001$) decrease in A1C for each additional SMBG test per day was reported.

Figure 7. General trend for the relationship between SMBG frequency and adjusted* mean A1C by insulin regimen estimated from author's figure.



CSII = continuous subcutaneous insulin infusion, MDI = multiple daily injections; Conventional treatment was defined as 3 or fewer daily injections
*mean A1C (%) values adjusted for age. gender, diabetes duration, year of treatment, insulin dose, BMI -standard deviation scores and clinical center.

Associations with glycemic control: Psychological and psychosocial factor, patient-related factors and race/ethnicity

A number of factors in addition to frequency and type of glucose monitoring influence whether a child achieves and maintains glycemic control including: diet, exercise, insulin regimen and its adjustment for stress, infection and exercise. Physiological, social, cognitive, developmental and emotional changes that occur in those 0-18 year old as they grow also play a role. While a number of studies were found that explored relationships and associations between various factors and glycemic control (based on A1C), none evaluated how they modify the relationship between SMBG or CGM and outcomes.[63,122] It appears that many of these factors may influence adherence to diabetes management regimens, which in turn influences glycemic control. The relationships are complex and multidimensional and beyond the scope of this report.

Without explicit, direct comparison of how the outcomes differ between groups of patients with and without the various factors and with respect to specific frequency of SMBG (or comparison with CMG), no conclusions can be drawn from these studies with regard to differential efficacy or effectiveness.

Examples of patient and provider characteristics associated with HgA1C in a selection of studies are only briefly summarized here.

In unadjusted analyses, diabetes stress,[122] depression,[123] conflicts between the mother and patient,[102] discrepancies between the mother and patient about the patient's decision-making

autonomy,[102] and more negative patient communication[103] were associated with higher A1C. In another unadjusted analysis, a mother's recall of better diabetes management was associated with the patient's lower A1C.[104] Finally, in an adjusted analysis, lower family income[127] was associated with higher A1C. Other studies found no relationship between A1C and depression[105] or adolescent's decision-making autonomy.[106] Nordly 2005 examined clinic factors associated with A1C.[107]No associations between A1C and diabetes team, clinical practice guidelines or written guideline for families, telephone hotline service or center size were noted in this Danish registry study. Rosilio 1998 examined medical and social factors associated with A1C in French children.[108] Factors associated with lower A1C included university-affiliated hospital use and number of patients in a center and family support.

Again, these studies do not provide sufficient information to describe differential efficacy or effectiveness of SMBG or CGM.

3.5 Key question 5: What is the evidence of cost implications and cost-effectiveness of self-glucose monitoring?

Including consideration of:

a. Costs (direct and indirect) in the short term and over the expected duration of use
b. Estimates of costs saved by preventing morbid events

There is no evidence available to assess the cost effectiveness of SMBG or CMG persons with diabetes ≤18 years old who require insulin. No full economic studies that focused on the cost-effectiveness of CGM or the frequency of SMBG were found.

Discussion

For this technology assessment, only cost effectiveness or cost utility studies, consistent with other decision-making organizations such as the National Institute for Clinical Excellence (NICE) in the United Kingdom, were considered. Studies that report only costs or do not compare alternatives are not considered full economic evaluations. Economic evaluations identify and compare appropriate alternatives, their incremental impact on health outcomes, and their incremental costs. There are several types of economic evaluation. Cost minimization studies consider the cost differences between alternatives of equal effectiveness. Cost benefit studies consider both costs and benefits in monetary terms. Cost effectiveness studies consider differences in costs and differences in effectiveness, but effectiveness is measured variably between studies (e.g. can be survival or a condition-specific outcome such as symptom-free days). Cost utility studies consider differences in costs and outcomes for quality-adjusted survival, most often using the quality adjusted life year (QALY). Cost utility studies have the advantage of providing an incremental cost effectiveness ratio (ICER) expressed as 'cost per quality adjusted life year' (cost per QALY) that eases comparison across multiple studies.

4. Summary by key question

Information on determination of overall strength of evidence is found in the appendices.

Summary of evidence and implications

Key question 1: Efficacy and effectiveness of monitoring.

Efficacy

No randomized controlled trials or observational studies which directly evaluated current methods of SMBG testing, as an independent component of management were found. The Diabetes Complications and Control Trial (DCCT) provides indirect evidence regarding the efficacy of SMBG as part of a package of comprehensive, intensive diabetes care, which included SMBG four or more times per day and education on how to use the information to adjust insulin, diet and exercise compared with the then standard of care (urine or SMBG once/day, only periodic insulin adjustment). The long-term intervention (mean 7.4 years) allowed for evaluation of diabetes-related complications.

Overall, participants 13-17 years old (N=195) at baseline (N = 195, mean age 15 years) in the intensive treatment group (across both cohorts over the entire study period) experienced:

- Significantly lower mean A1C levels by 6-12 months that remained lower for the remainder of the 7.4 year trial, (8.06% intensive treatment versus 9.76% conventional treatment; (P value for test of medians was < 0.0001, loss to follow-up unclear).
- Lower average daily blood glucose concentrations ($P< 0.0001$)
- A higher rate of hypoglycemia resulting in coma or seizures (RR 2.93; 95% CI, 1.75, 4.90; P < 0.001).
- A 61% risk reduction in sustained ≥ three-step retinopathy (95% CI 30% to 78%; p=0.02) after adjusting for baseline retinopathy
- No statistical difference in rate of ketoacidosis (18% for intensively treated, 20% for conventionally treated).
- No significant differences in nephropathy in the primary prevention cohort or the combined cohorts. (Participants in the secondary prevention cohort who were intensively treated experienced a statistically significant reduction in risk (55%) of having microalbuminuria (95% CI 3, 79%, P = 0.042) compared with those in this cohort who were conservatively treated.)
- Significantly higher peripheral motor and sensory nerve conduction velocities compared with the conventionally treated group at 5 years. No statistically significant difference in neuropathy between treatment groups were seen in the combined cohort.

Effectiveness

Indirect evidence on the effectiveness of SMBG is based on (the Epidemiology of Diabetes Interventions and Complications (EDIC) the observational follow-up to the DCCT at four and ten years. All participants in the conventional treatment arm were offered instruction in the use of intensive therapy and intensive treatment group patients were encouraged to continue such treatment.

Overall, in those who were <18 years old at the start of the DCCT and followed in the EDIC:

- Mean A1C values were similar between the former intensive and former conventional groups at the end of years 4 and 10.
- Among the former intensive treatment group, the prevalence a ≥ 3 step progression of retinopathy and of progression to proliferative or severe nonproliferative retinopathy were significantly reduced by compared with the former conventional groups at year four. At year 10, however, there were no significant differences among former intensive and conventional treatment groups in the progression of retinopathy (≥ 3 step progression of retinopathy, severe nonproliferative retinopathy, proliferative retinopathy clinically significant macular edema or photocoagulation therapy.
- No differences in nephropathy were seen at the end of either follow-up period.

At 10 years of observation following the completion of the DCCT, the progression of retinopathy ≥3 levels and proliferative retinopathy was less in the prior intensive group of adolescents compared with the conventional group, but the difference was not statistically significant. However, the entire EDIC cohort (including all ages) who had been in the DCCT intensive treatment group experienced a statistically significant reduction at 10 year follow-up. The authors suggest that the waning effect in the adolescent cohort may have been because the adolescents did not achieve as low an A1c during the DCCT as the older study subjects, and thus the "memory effect" was less. It should also be noted that the adolescent EDIC sample size was much smaller. The long term impact of intensive treatment on the cardiovascular complications for those who were adolescents at entry to DCCT is not yet fully known as even after 10years of follow-up, this group would be young adults. A delay in observed benefit would be consistent with current understanding of the cumulative damage and thus may take more years to become clinically evident. This is also true for retinopathy, neuropathy and nephropathy outcomes.

Key question 2: Efficacy and effectiveness by frequency or mode of testing.

Efficacy

There were no randomized controlled trials (RCT) that directly evaluated the efficacy of SMBG frequency. Indirect evidence from the DCCT (described above) provides information with respect to frequency in that the intensive group was instructed to test at least four times per day compared with the conventional care group's once per day.

The bulk of the evidence on efficacy of mode of self-monitoring comes from RCT's of continuous glucose monitors (CGM) where patients had real-time access to data comes. Data from one primary JDRF 2008 report that provided result stratified by age (n = 114, 8-14 year olds) and one smaller RCT (n = 40, 12-18 year olds) that also stratified by age, form the primary basis for the overall evidence summary. The other JDRF (2009) report has few outcomes stratified by age. In all studies, CMG was used in conjunction with SMBG (for calibration and verification per FDA recommendations) and was compared with SMBG alone. In the JDRF studies, 84% of both CGM and SMBG groups used insulin pumps (which did not communicate with the CMG) and 100% of patients in the Hirsch study used pumps integrated with the CMG device in the CGM arm only. This heterogeneity in study design precluded pooling of data. There are currently no long-term comparative studies on these devices for evaluation of benefits, complications or diabetes-related comorbidities on those ≤ 18 years old.

The overall strength of evidence for efficacy is low. Results for follow-up to 26 weeks in these studies on the efficacy of CGM (in conjunction with SMBG) over SMBG include the following:

- Two RCTs reported A1c results stratified by age. Differences in the change in mean A1C between treatment arms were not statistically significant in the larger JDRF 2008 study or the smaller (Hirsch) RCT (P = 0.29, P = 0.10, respectively). Differences in the change in mean A1C between groups were of questionable clinical significance (based on 0.5% as a threshold) across two RCTs. In the JDRF 2008 RCT, changes in A1C levels were -0.37 in the CGM arm and -0.22% in the SMBG arm. In the smaller RCT, change in A1C levels were -0.80% in the SMBG arm and -0.38% in the CGM arm.

- Two of the three RCTs reported on proportions of patients achieving A1C targets: In the JDRF 2008 participants in the CGM group were roughly twice as likely to achieve A1C targets of <7% (RD = 15%), relative A1C decreases of ≥ 10% (RD = 17%) and absolute decreases of ≥ 0.5% (RD = 23%). These changes were achieved without significant differences in hypoglycemic events. In the other RCT [Hirsch 2008], the difference in reaching A1C targets did not reach significance (p=0.052) perhaps as a function of sample size.
- Neither of two JDRF RCTs found significant differences in the effects of CGM versus SMBG alone on episodes of hypoglycemia (measured as the proportion of participants with one or more severe hypoglycemia episode, rate of severe hypoglycemic episodes (CGM: 17.9/100,000 person-years versus SMBG: 24.4/100,000 person-years), amount of time blood glucose levels were lower than either 70 mg/dl (CGM: 47 min/day versus SMBG: 59 min/day) or 50 mg/dl (CGM: 10 min/day versus SMBG: 13 min/day)).
- Hyperglycemia rates were reported in one RCT: No significant differences in episodes of hyperglycemia (measured as the amount of time spent with blood glucose levels greater than either 180 mg/dl (CGM: 643 min/day versus SMBG: 635 min/day) or 250 mg/dl (CGM: 242 min/day versus SMBG: 268 min/ day)).
- There were no differences in any QOL measures between participants in either treatment arm or parents of participants at 26 weeks or in change from baseline to 26 weeks in the one RCT reporting on this.
- No RCTs of the effect of monitoring mode on any of the following outcomes were found for the following: a) maintaining A1C levels, b) achieving target A1C levels in conjunction with provider specific report cards, c) acute episodes of diabetic ketoacidosis, d) microvascular complications, or e) medication or nutritional management.
- No studies relating specifically to pregnant patients ≤ 18 years old or patients ≤ 18 years old with type 2 diabetes who require insulin were found.
- Specific information regarding how data were used for management decisions was not provided in any trial, thus conclusions regarding the direct, independent impact of monitoring on decision making are not possible.

Effectiveness

Frequency of CGM use: Subanalyis and extended follow-up studies of the JDRF 2008 RCT population provide the primary evidence. In the absence of additional studies evaluating frequency and consistency of CGM use in different patient populations, the overall strength of evidence is low.

- Based on a subanalysis of the JDRF 2008 trial, consistent use of CGM ≥ 6 days per week for 6 months was associated with lower mean A1c values compared with baseline. In an extension study of the group who had been randomized to CGM, a greater number of participants meeting targets of < 8.0% for 8−12 year olds

and <7.5% for 13−17 year olds compared with those who used it < 6 days per week. Those who continued use of CGM ≥ 6 days per week for 6 months after the end of the trial (i.e. a total of12 months). maintained lower mean A1C values and an additional number achieved targets. These improvements in A1c were achieved while the incidence of hypoglycemia remained low for all users.

- In another JDRF extension study of those initially randomized to SMBG who switched to CGM after the trial, no consistent pattern for improvement in A1C of ≥ 0.5% or achieving A1C <7% was seen at 6 months in those 8-12 years old. Prior to CGM use, severe hypoglycemia occurred in 26.4 per 100 person-years compared with 13.0 per 100 person-years after 6 months of CGM use (p-value not stated).
- In these reports, specific information on how data from CGM or SMBG were used to influence management was not provided, thus the independent impact of monitoring itself cannot be determined.

Frequency of SMBG. The overall strength of evidence is low.

- Performing SMBG 4 to 5 times per day was associated with lower mean A1C, based on data from one large registry study and six prognostic studies (all LoE III). In these cross-sectional studies, however, it is not possible to sort out the extent to which lower A1c is causally related to the frequency of SMBG. It is not known, if those who test more frequently tend to have lower A1c and may be more compliant with their treatment regimen in general.
- In 11 cross-sectional studies and one registry study (all LoE III), more frequent SMBG was associated with lower A1C, however specific data on frequency and A1C values were not provided. In nine of these studies, the correlation was significant.
- There is conflicting evidence regarding whether more frequent SMBG is associated with lower rates of hypoglycemia. One large registry reported hypoglycemia rates are higher with greater frequency of testing while one cohort study reported hypoglycemia rates are lower with greater frequency of testing. It is unclear whether the increase in events in the larger study may be due to increased frequency of testing in those more likely to have hypoglycemic events.
- The presence of an association in cross-sectional studies does not infer that the relationship is causal as temporal sequence and other relevant factors are unknown.

Key question 3: Safety

Safety issues related to CGM or SMBG device design and implementation are described as safe use is a function of both design and implementation. The overall strength of evidence is moderate based on the number and quality of studies. No major adverse events were reported. Hypoglycemia and hyperglycemia are described under Key Questions 1 and 2.

CGM: Data from RCTs, observational studies and FDA SSED reports were used. There were no major adverse events reported.

- The most frequent insertion site problems included redness and/or itching (16%-45%), dry skin (21%), mild and moderate acute skin changes (14% each) and irritation, bruising or pain (0-53%) based on information across RCTs and observational studies, some of which had small sample sizes.
- The most frequent sensor/device related concerns were alarms interfering with daily routine (38%), irritation by alarms (38%-50%), sensor too bulky (22%-75%) and sensor pulled out accidentally (10-13%) based on information across RCTs and observational studies, some of which had small sample sizes.
- Thresholds can be set for alerting patients when glucose values have reached a specified low or high level, allowing patients to take appropriate action. The primary safety concerns for CGM relate to false alerts and missed alerts (occasions when the alarm should have sounded but did not). The rates for these varied across blood glucose thresholds and across devices, based on FDA Summaries of Safety and Efficacy Data

used for FDA approval. False positive alerts may be annoying and lead the patient to ignore subsequent alarms. False negative alerts, i.e., times when the device did NOT alarm may be more problematic as the person is not prompted to consider action and may give him/her a false sense of security. While these are human/behavioral factors, they have the potential to lead to adverse events and therefore are considered in the context of safe device implementation.

- No deaths among participants ≤ 18 years old were reported in any study.

SMBG: Reports of problems at the finger stick site come from old studies, published 1983−1988, and devices used for drawing blood have improved. The primary concerns reported were sore fingers and difficulty obtaining blood in these studies. These are related to the device used for drawing blood, rather than the glucose monitor itself.

Key question 4: Differential efficacy or safety in sub-populations

One RCT and one large registry study directly assessed differential outcomes for either CGM or SMBG by subpopulations. The overall strength of evidence is low.

CMG compared with SMBG: One RCT

- Patients 8-14 years old and those 15-24 years old had similar results with regard to A1C and achieving targets for CGM and SMBG with no evidence of differential efficacy by age was demonstrated, based on one RCT.

SMBG frequency: Evidence is from one large registry study.

- There is limited evidence for differential effectiveness for frequency of SMBG by age. For 13-18 year olds an average improvement in A1C of 0.3% ± 0.011 for each additional SMBG was reported. This appears to apply up to tests five per day. In contrast, for ages 0-5 and 6-12, beyond one test per day, improvement in A1C was much less and averaged 0.04% ± 0.018 and 0.12% ± 0.010 respectively beyond one SMBG per day.
- There may be some evidence differential of effectiveness for frequency of SMBG by insulin regimen. Patients using continuous subcutaneous insulin infusion (CSII) experienced a mean reduction of 0.27% in A1C (%) for one additional SMBG per day. This group came closest to approaching A1C targets of between 7.0% and 7.5%. Those using multiple daily injections (MDI) experienced a 0.24% decrease in A1C.

Key question 5: Economic studies

There is no evidence available to assess the cost effectiveness of SMBG or CMG in persons with diabetes ≤18 years old who require insulin. No full economic studies which focused on the cost-effectiveness of CGM or the frequency of SMBG were found.

Summaries of overall strength of evidence by key question

Table 23. Summary of evidence for Key Question 1: Efficacy and effectiveness of monitoring

Key Question 1: What is the evidence of efficacy and effectiveness of self-monitoring of blood glucose?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
• Intensive diabetes care package (SMBG ≥ 4/day, education on how adjust insulin, diet and exercise)	• Standard care (urine or SMBG up to 1/day, no daily changes in insulin, diet)	**Low**	**Efficacy** No RCTs or observational studies directly evaluating current SMBG methods. Indirect evidence from DCCT (n = 195) on SMBG as part of intensive program for tight control: • <u>In the short-term</u> (6-12 months) Intensive program participants had lower A1C and average daily blood glucose levels • <u>In the longer-term</u> (to mean 7.4 years. Intensive program participants sustained lower A1C and average daily blood glucose levels (177 ± 31 mg/dL vs. 260 ± 52 mg/dL; *P*< .0001), had risk reduction of 61% for retinopathy but no differences in ketoacidosis or nephropathy in the primary or combined cohorts. A55% reduction in microalbuminuria was seen in intensively treated participants in the secondary prevention cohort (P = 0.042). Nerve conduction velocities were significantly higher in the intensively treated group.	+	-	-

Key Question 1: What is the evidence of efficacy and effectiveness of self-monitoring of blood glucose?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
• Prior participation in DCCT Intensive treatment arm; Participants encouraged to continue intensive treatment	• Prior participation in DCCT conventional treatment arm; Participants provided education on intensive treatment	Low	**Effectiveness** No observational studies directly evaluating current SMBG methods. Indirect evidence from EDIC observational follow-up of DCCT: • 4 years after the end of DCCT (n=175): Adolescents who were in the intensive treatment arm had significantly lower rates of retinopathy progression and no difference in mean A1c%. Prevalence of microalbuminuria and albuminuria were lower in those in the former intensive treatment group statistical significance was not achieved. • 10 years after the end of DCCT (n=156): Adolescents who were in the Intensive treatment arm no difference in mean A1c% or retinopathy progression. There were no differences in microalbuminuria or albuminuria	+	-	-

Table 24. Summary of Evidence for Key Question 2: Efficacy and effectiveness by mode or frequency

Key Question 2: What is the evidence of efficacy and effectiveness by mode or frequency?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
• CGM (in conjunction with SMBG)	• SMBG alone	Low	**Efficacy** JDRF 2008 RCT (n = 114; 8-14 year olds) and one small RCT (n = 40, 12-18 year olds) form basis for the overall evidence summary. A third RCT provided limited data. • In the short-term (to 26 weeks) No clinically meaningful differences in mean A1C or mean change, hypoglycemia or hyperglycemia. Limited evidence (1 report) that CGM participants were twice as likely to achieve ADA age-specific A1C targets. • In the longer-term : There are no long-term studies or follow-up studies to RCTs in the long term	+	-	-
• Consistent CGM use (in conjunction with SMBG)	• Less frequent use	Low	**Effectiveness** Sub-analysis of JDRF RCT: More frequent CGM use was associated with a greater reduction in A1c from baseline to 6 months ($p < 0.001$ among 8-14 year olds) Extension studies of JDRF RCT: • Among those randomized to CGM, those who continued use of CGM ≥ 6 days per week for an additional 6 months (12 months total) maintained lower mean A1C values and an additional number achieved ADA age-specific targets compared with those who didn't continue past the 6 month trial end or those who used it < 6 days/week. Improvements in A1c were achieved while the incidence of hypoglycemia remained low for all users. • Among those randomized to SMBG, who switched to CGM after the trial, no consistent	+	-	-

Key Question 2: What is the evidence of efficacy and effectiveness by mode or frequency?						
Mode/Method	**Comparator**	**SoE**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
			pattern in improvement in A1C of ≥ 0.5% or achieving A1C <7% was seen at 6 months in those 8-12 years old . Prior to CGM use, incidence of severe hypoglycemia was higher than the incidence after 6 months of CGM use			
• Higher SMBG frequency	• Lower SMBG frequency	Low	One large registry and six prognostic studies (all cross-sectional) suggest an association between greater SMBG frequency and lower A1C. Causality cannot be inferred from cross-sectional studies. • SMBG 4 to 5 times per day was associated with lower mean A1C across reports. Causality cannot be inferred. • Eleven cross-sectional studies and one registry study found an inverse correlation between frequency of SMBG and A1C. • Conflicting evidence regarding whether more frequent SMBG is associated with lower rates of hypoglycemia: the large registry's rates of hypoglycemia are higher with greater frequency of testing while one cohort study reported lower rates. Causality cannot be inferred.	-	+	+

Remaining questions

There are a number of questions that remain with regard to rt-CMG use in particular. It is not clear from the evidence available what precise role these devices may play in those 18 years old or younger or which individuals may most benefit from this technology. It is not clear to what extent improvements in overall glycemic control within CMG groups is clinically meaningful or how they may translate long-term into other health outcomes. The short follow-up time in the trials to date preclude making conclusions about the long-term benefits of CGM.

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