WASHINGTON STATE HEALTH CARE AUTHORITY

Glucose Monitoring: Self-monitoring in patients under 18 years old

Health Technology Assessment

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Glucose Monitoring: Self-monitoring in patients under 18 years old

Provided by:

SPECTRUM RESEARCH

APPENDICES

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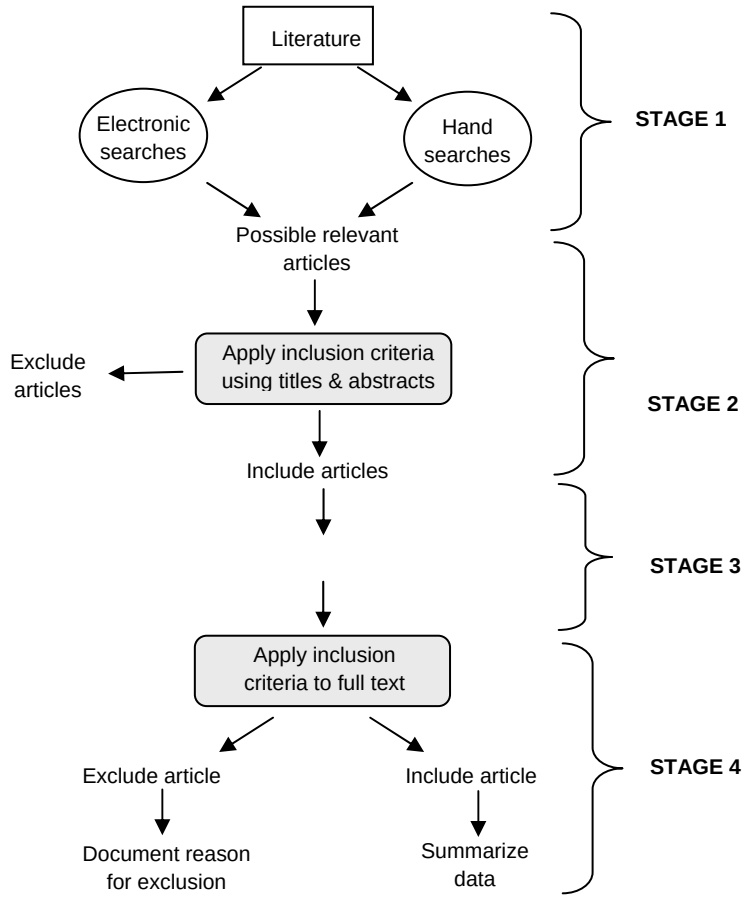
APPENDIX A. ALGORITHM FOR ARTICLE SELECTION



APPENDIX B: SEARCH STRATEGIES

Searches of primary bibliographic databases. In addition, hand searches of bibliographies, "related articles" and selective key word searches were used. Searches of the National Guideline Clearinghouse and INATHA were done as part of grey literature search.

MEDLINE Search Strategy (through July 8, 2010)

	Terms	Results	Possibly relevant
1	Diabetes Mellitus[MAJR:noexp] OR Diabetes, gestational[MH] OR diabetes mellitus, type 1[MH] OR diabetes mellitus, type i[MH] OR diabetes mellitus, type 2[MH] OR diabetes mellitus, type ii[MH] OR diabetes mellitus, juvenile onset[MH] OR diabetes mellitus, insulin dependent[MH]	154256	
2	Search blood glucose self monitoring[MH] OR continuous glucose monitor* OR continuous glucose measur* OR continuous blood glucose monitor* OR continuous blood glucose measur* OR continuous subcutaneous glucose monitor* OR ("continuous home monitoring" AND glucose[tiab]) OR continuous glucose sensor* OR cgms[tiab] OR cgm[tiab] OR chmg[tiab]	3889	
3	Search #1 AND #2	3889	
4	Search #3 Limits: only items with abstracts, Humans, English	1601	
5	Search (#4) NOT (editorial[PT] OR letter[PT] OR meta-analysis[PT] OR practice guideline[PT] OR review[PT]) Limits: only items with abstracts, Humans, English	1325	
6	Search #5 Limits: only items with abstracts, Humans, English, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years, Young Adult: 19-24 years	388	388
7	Search #4 AND (safety[MH] OR equipment safety[MH])	12	4
8	Search #4 AND economics[MH]	96	36
9	Search #4 AND (guideline[PT] OR clinical guideline)	32	12
10	Search #4 AND meta-analysis [PT]	11	5
11	Search #4 AND (registries OR registry OR clinical trial phase IV)	21	5

EMBASE 1988 to 2010 Week 28 (July 23, 2010)

Disease (D):

1. (diabetes mellitus OR insulin dependent diabetes mellitus OR juvenile diabetes mellitus OR pregnancy diabetes mellitus OR diabetic patient).mp [advanced search]

Intervention (I):

2. CGMS [basic search]

3. CGM* [basic search]

4. continuous glucose monitoring [basic search]

5. continuous subcutaneous glucose monitoring [basic search]

6. interstitial glucose [basic search]

7. subcutaneous monitor [basic search]

8. glucose sensor [basic search]

9. 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 [advanced search]

10. blood glucose monitoring [basic search]

11. blood glucose self monitoring [basic search]

12. blood glucose meter [basic search]

13. 10 OR 11 OR 12 [advanced search]

14. 9 OR 13 [advanced search]

Disease and Intervention:

15. 1 AND 14 [advanced search]

Disease and Intervention, limited to abstracts, human, and English (S):

16. 15

17. limit 16 to (abstracts AND human AND english language [advanced search]

The above set, not limited by publication type or age, will be used for subsearches. It retrieved 5270 citations.

Publication type (PT)

18. ((clinical trial) OR register).mp [advanced search]

Disease and Intervention, limited to abstracts, human, and English; and by publication type

19. 17 AND 18

20. (adolescent OR child OR newborn).mp [advanced search]

Disease and Intervention, limited to abstracts, human, and english; and by publication type; and by age (A)

21 . 19 AND 20 [advanced search]

22. *The above is the set of primary citations. This search retrieved 208 citations. Selected 19 as possibly relevant.*

Safety

23. (safety OR equipment).mp [advanced search]

25. 17 AND 23 [advanced search]

25. *This search retrieved 603 citations; selected 28 as possibly relevant.*

Cost-benefit

26. (economic evaluation OR cost-benefit analysis OR cost effectiveness analysis).mp [advanced search]

27. 17 AND 26

28. *This search retrieved 170 citations. selected 17 as possibly relevant.*

Clinical guideline

29. practice guideline.mp [advanced search]

30. 17 AND 29

31. *This search retrieved 238 citations; selected 13 as possibly relevant.*

Meta-analysis

32. meta analysis [advanced search]

33. 17 AND 32

34. *This search retrieved 100 citations;selected 8 as possibly relevant.*

Registry Studies

These should have been retrieved with clinical trials; Did a separate search without limitations by age.

35. (register OR (phase 4 clinical trial)).mp [advanced search]

36. 17 AND 35

37. *This search retrieved 38 citations. Selected 3 as possibly relevant.*

Clinical Decision Making

38. (evidence based medicine) OR (clinical decision making).mp [advanced search]

39. 17 AND 38

40. *This search retrieved 104 citations, 9 as possibly relevant.*

APPENDIX C: EXCLUDED ARTICLES (AND DUPLICATE CITATIONS)

Articles excluded as primary studies after full text review, with reason for exclusion. Articles included as background are not listed here. These articles were initially included by Spectrum's literature search and discussion by three investigators (JK, CO, and AS). This list does not include articles found only through other reviews.

Articles excluded as primary studies after full text review, with reason for exclusion.

Citation	Reason for Exclusion
(2007). "Self-monitoring of blood glucose in diabetes." Drug Ther Bull 45(9): 65-9	Age (adults)
Allen, K. D. and J. H. Evans (2001). "Exposure-based treatment to control excessive blood glucose monitoring." J ApplBehav Anal 34(4): 497-500	Design (case report)
Altamirano-Bustamante, N., L. Islas-Ortega, et al. (2008). "Economic family burden of metabolic control in children and adolescents with type 1 diabetes mellitus." J PediatrEndocrinolMetab**21**(12): 1163-8	Design (not full econ evaluation)
Ausili, E., F. Tabacco, et al. (2007). "Multidimensional study on quality of life in children with type 1 diabetes." Eur Rev Med PharmacolSci11(4): 249-55	Topic (does not mention glucose monitoring)
Banister, N. A., S. T. Jastrow, et al. (2004). "Diabetes selfmanagement training program in a community clinic improves patient outcomes at modest cost." J Am Diet Assoc104(5): 807	Age (adults)
Berg, C. A., M. Skinner, et al. (2009). "The fit between stress appraisal and dyadic coping in understanding perceived coping effectiveness for adolescents with type 1 diabetes." J FamPsychol23(4): 521-30	Topic (Not about glucose monitoring)
Bode, B., J. Shelmet, et al. (2004). "Patient perception and use of an insulin injector/glucose monitor combined device." Diabetes Educ30(2): 301-9	Age (mean age 42 [SD 14.3 y])
Bode, B. W., T. M. Gross, et al. (1999). "Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study." Diabetes Res ClinPract46(3): 183-90	Age (1 of 9 patients age 18, others older)
Bowker, S. L., C. G. Mitchell, et al. (2004). "Lack of insurance coverage for testing supplies is associated with poorer glycemic control in patients with type 2 diabetes." CMAJ 171(1): 39-43	Age, topic (patients had to by at least 30 y old and not use insulin)
Brown, J. B., G. A. Nichols, et al. (1999). "Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis." Diabetes Care 22(7): 1116-24.	Age (excluded px diagnosed before age 45)
Choleau, C., C. Aubert, et al. (2008). "High day-to-day glucose variability: a frequent phenomenon in children and adolescents with type 1 diabetes attending summer camp." Diabetes Metab34(1): 46-51	Topic (accuracy)
Coster, S., M. C. Gulliford, et al. (2000). "Self-monitoring in Type 2 diabetes mellitus: a meta-analysis" Diabet Med 17(11): 755-61	Age, topic (primary studies included adults; all but one had patients using only oral hypoglycemics)
Diabetes Research in Children Network Study, G., S. Weinzimer, et al. (2009). "Prolonged use of continuous glucose monitors in children with type 1 diabetes on continuous subcutaneous insulin infusion or intensive multiple-daily injection therapy." Pediatr Diabetes 10(2): 91-	Topic (comparison is continuous insulin infusion vs multiple daily

6	injections)
Eaton, S., S. Brent, et al. (2008). "Expenditure on diabetes treatments and achievement of glycaemic control: retrospective analysis." Diabet Med 25(6): 738-42	Age (not restricted to children, and children not reported separately)
Gagliardino, J. J., E. Olivera, et al. (2006). "PROPAT: a study to improve the quality and reduce the cost of diabetes care." Diabetes Res ClinPract72(3): 284-91	Age (age 56 =/- 16 y)
Gonder-Frederick, L., J. Zrebiec, et al. (2008). "Detection of hypoglycemia by children with type 1 diabetes 6 to 11 years of age and their parents: a field study." Pediatrics 121(3): e489-95	Topic (compares estimates of BG vs intermittent test by parents and children)
Gray, A., M. Raikou, et al. (2000). "Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). United Kingdom Prospective Diabetes Study Group." BMJ 320(7246): 1373-8	Age (subjects 25-65 y)
Halford, J. and C. Harris (2010). "Determining clinical and psychological benefits and barriers with continuous glucose monitoring therapy." Diabetes TechnolTher12(3): 201-5	Age (participants had to be > 18 y old)
Halvorson, M., S. Carpenter, et al. (2007). "A pilot trial in pediatrics with the sensor-augmented pump: combining real-time continuous glucose monitoring with the insulin pump." J Pediatr150(1): 103-105 e1	Design (only comparison is before/after)
Hovorka, R., J. M. Allen, et al. (2010). "Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial." Lancet 375(9716): 743-51	Topic: wrong comparison
Hsin, O., A. M. La Greca, et al. (2010). "Adherence and glycemic control among Hispanic youth with type 1 diabetes: role of family involvement and acculturation." J PediatrPsychol35(2): 156-66	Design (measured adherence by questionnaire)
Iafusco, D., F. Stoppoloni, et al. (2008). "Use of real time continuous glucose monitoring and intravenous insulin in type 1 diabetic mothers to prevent respiratory distress and hypoglycaemia in infants." BMC Pregnancy Childbirth 8: 23	Age (age range 18-28 y)
Icks, A., J. Rosenbauer, et al. (2004). "Direct costs of pediatric diabetes care in Germany and their predictors." ExpClinEndocrinol Diabetes**112**(6): 302-9	Design (not full econ evaluation)
Karter, A. J., M. R. Stevens, et al. (2003). "Out-of-pocket costs and diabetes preventive services: the Translating Research Into Action for Diabetes (TRIAD) study." Diabetes Care 26(8): 2294-9	Age (Subjects 18 y or older)
Kendrick, J. M., C. Wilson, et al. (2005). "Reliability of reporting of self-monitoring of blood glucose in pregnant women." J ObstetGynecol Neonatal Nurs34(3): 329-34	Age (age 18-42 y)
Kestila, K. K., U. U. Ekblad, et al. (2007). "Continuous glucose monitoring versus self-monitoring of blood glucose in the treatment of gestational diabetes mellitus." Diabetes Res ClinPract77(2): 174-9	Age (ages 32.6 +/- 4.7 y and 32.2 +/- 5.7 y)
Langova, K., H. Pribylova, et al. (2009). "Assessment of haemoglobin a1c evolution using two statistical approaches (survival analysis and linear regression) in persons with diabetes mellitus." Biomed Pap Med FacUnivPalacky Olomouc Czech Repub153(2): 137-43	Age (ages 19-69)
Logtenberg, S. J. J., N. Kleefstra, et al. (2009). "Use of short-term real-time continuous glucose monitoring in type 1 diabetes patients on continuous intraperitoneal insulin infusion: A feasibility study." Diabetes Technology and Therapeutics 11(5): 293-299	Age (patients were > 18 y old)
Madsen, S. D., G. I. Roisman, et al. (2002). "The intersection of adolescent development and	Topic

intensive intervention: age-related psychosocial correlates of treatment regimens in the diabetes control and complication trial." J PediatrPsychol27(5): 451-9	
McGarraugh, G. and R. Bergenstal (2009). "Detection of hypoglycemia with continuous interstitial and traditional blood glucose monitoring using the FreeStyle Navigator Continuous Glucose Monitoring System." Diabetes TechnolTher11(3): 145-50	Age (youngest was 18 y)
McGowan, K., W. Thomas, et al. (2002). "Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes." Diabetes Care 25(9): 1499-503	Device (CGM with retrospective data); topic (clinical research center)
Meier, J. L., A. L. Swislocki, et al. (2002). "Reduction in self-monitoring of blood glucose in persons with type 2 diabetes results in cost savings and no change in glycemic control." Am J Manag Care 8(6): 557-65	Age, topic (mean age 64 +/- 11 y; excluded patients receiving insulin; adults)
Miglani, S., R. Goswami, et al. (2004). "Glycaemic control and microvascular complication among patients with youth onset diabetes in India using differing types of insulin and methods of glucose monitoring." Diabetes Research and Clinical Practice 65(2): 183-185	Age (young adults & adolescents, not separated by age: mean age 27.3 +/- 9.4)
Murphy, H. R., G. Rayman, et al. (2008). "Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial." BMJ 337: a1680	Age (enrolled women 16-45; did not report outcomes for those ≤ 18 separately)
Neeser, K. and C. Weber (2009). "Cost impact of self-measurement of blood glucose on complications of type 2 diabetes: the Spanish perspective." Diabetes TechnolTher11(8): 509-16	Age (mean age 61.3 +/- 9.2 y)
Nwasuruba, C., M. Khan, et al. (2007). "Racial/ethnic differences in multiple self-care behaviors in adults with diabetes." J Gen Intern Med 22(1): 115-20	Age (youngest age group 18-34 y)
O'Connell, M. A., S. Donath, et al. (2009). "Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial." Diabetologia52(7): 1250-7	Age (ages 13-40; 52% age 13-19; results not reported separately for adolescents)
Oishi, M., H. Yokoyama, et al. (2007). "Time and cost involved in the care of newly registered patients with diabetes mellitus and other lifestyle diseases at diabetes clinics in Japan (JDDM 4)." Diabet Med 24(10): 1149-55	Age (mean age 57+/-12 y)
Palmer, A. J., S. Dinneen, et al. (2006). "Cost-utility analysis in a UK setting of self-monitoring of blood glucose in patients with type 2 diabetes." Curr Med Res Opin22(5): 861-72	Age (age range too old)
Patel, H., J. Srishanmuganathan, et al. (2007). "Trends in the prescription and cost of diabetic medications and monitoring equipment in England 1991-2004." J Public Health (Oxf) 29(1): 48	Age, topic (not restricted to children, and children not reported separately); not restricted to insulin-dependent diabetics)
Perwien, A. R., S. B. Johnson, et al. (2000). "Blood glucose monitoring skills in children with Type I diabetes." ClinPediatr (Phila) 39(6): 351-7	Topic
Rabiau, M. A., B. Knauper, et al. (2009). "Compensatory beliefs about glucose testing are associated with low adherence to treatment and poor metabolic control in adolescents with type 1 diabetes." Health Educ Res 24(5): 890-6	Design (treatment adherence by self-report)
Raccah, D., V. Sulmont, et al. (2009). "Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study." Diabetes Care 32(12): 2245-50	Age (39% of subjects children; results not reported separately for

	children)
Rosenberg, T. and C. G. Shields (2009). "The role of parent-adolescent attachment in the glycemic control of adolescents with Type 1 diabetes: a pilot study." FamSyst Health 27(3): 237-48	Design (correlates attachment with HgA1c, but not with glucose monitoring)
Rothman, R. L., S. Mulvaney, et al. (2008). "Self-management behaviors, racial disparities, and glycemic control among adolescents with type 2 diabetes." Pediatrics 121(4): e912-9	Topic (11% on insulin alone, 34% on insulin + oral agent; results not separated by medication type)
Schaepelynck-Belicar, P., P. Vague, et al. (2003). "Improved metabolic control in diabetic adolescents using the continuous glucose monitoring system (CGMS)." Diabetes Metab29(6): 608-1	Device (CGM with retrospective data), design (before-after)
Schiaffini, R., P. Ciampalini, et al. (2002). "The Continuous Glucose Monitoring System (CGMS) in type 1 diabetic children is the way to reduce hypoglycemic risk." Diabetes Metab Res Rev 18(4): 324-9	Device (CGM with retrospective data), design (before-after)
Soumerai, S. B., C. Mah, et al. (2004). "Effects of health maintenance organization coverage of self-monitoring devices on diabetes self-care and glycemic control." Arch Intern Med 164(6): 645-52	Age (patients at least 18 y)
St John, A., W. A. Davis, et al. (2010). "The value of self-monitoring of blood glucose: a review of recent evidence." Journal of Diabetes and its Complications 24(2): 129-141	Topic (type 2 DM)
Tansey, M. J., R. W. Beck, et al. (2005). "Accuracy of the modified Continuous Glucose Monitoring System (CGMS) sensor in an outpatient setting: results from a diabetes research in children network (DirecNet) study." Diabetes TechnolTher7(1): 109-14	Topic (accuracy)
Weber, C., B. Schneider, et al. (2007). "Cost impact of blood glucose self-monitoring on complications of type 2 diabetes: a Swiss perspective (ROSSO study No.11)." Swiss Med Wkly137(39-40): 545-50	Age, topic (mean age 61; 60% used insulin + oral agent)
Weinzimer, S. A., R. W. Beck, et al. (2005). "Accuracy of newer-generation home blood glucose meters in a Diabetes Research in Children Network (DirecNet) inpatient exercise study." Diabetes TechnolTher7(5): 675	Topic (accuracy of 2 glucose meters)
Willey, K. A., S. M. Twigg, et al. (1993). "Home blood glucose monitoring: How often?" Practical Diabetes 10(1): 22-25	Age (21-69 y)
Wiltshire, E. J., K. Newton, et al. (2006). Unrecognisedhypoglycaemia in children and adolescents with type 1 diabetes using the continuous glucose monitoring system: prevalence and contributors." J Paediatr Child Health 42(12): 758-63	Device (CGM with retrospective data); design (observational, no intervention)
Wysocki, T., H. P. Chase, et al. (2006). "Psychological aspects of continuous glucose monitoring in pediatric type 1 diabetes." Pediatric Diabetes 7(1): 32-38	Device (GlucoWatch)
Yoo, H. J., H. G. An, et al. (2008). "Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes." Diabetes Res ClinPract82(1): 73-9	Age (subjects were 20-80 y)
Ziegher, O., M. Kolopp, et al. (1993). "Self-monitoring of blood glucose and insulin dose alteration in type 1 diabetes mellitus." Diabetes Res ClinPract21(1): 51-9	Age (age 16-66; results not separated for those ≤ 18)

Key: Age: Wrong age group
Design: Wrong study design
Topic: Wrong topic
Device: Used device that is no longer marketed

Duplicate Citations

Each pair of duplicate citations was counted only once in the sum of included articles. Below is a list of duplicate citations (citations under both name of study group and name of first author):

Beck, R. W. (2009)."The effect of continuous glucose monitoring in well-controlled type 1 diabetes." Diabetes Care **32**(8): 1378-1383

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

Beck, R. W., B. Buckingham, et al. (2009)."Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes." Diabetes Care **32**(11): 1947-1953

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): 1947-53

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): 1464-76

Tamborlane, W. V., R. W. Beck, et al. (2008). "Continuous glucose monitoring and intensive treatment of type 1 diabetes." New England Journal of Medicine **359**(14): 1464-1476

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group (2008). "JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: research design and methods." Diabetes TechnolTher**10**(4): 310-21

Tamborlane, W. V., K. J. Ruedy, et al. (2008). "JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: Research design and methods." Diabetes Technology and Therapeutics **10**(4): 310-321

There were two citations describing the research design and methods for RCTs, without giving results. These were included as “background” articles

Davis, S. N., E. S. Horton, et al. (2010). "STAR 3 randomized controlled trial to compare sensor-augmented insulin pump therapy with multiple daily injections in the treatment of type 1 diabetes: research design, methods, and baseline characteristics of enrolled subjects." Diabetes TechnolTher**12**(4): 249-55

Design and methods for:
Bergenstal RM et al. (2010) Effectiveness of sensor-augmented insulin-pump therapy in Type 1 Diabetes. New Engl J Med 363:311-320.

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group (2008). "JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: research design and methods." Diabetes TechnolTher 10(4): 310-21.

Design and methods for:
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, W. V. Tamborlane, et al. (2008)."Continuous glucose monitoring and Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, W. V. Tamborlane, et al. (2008). N Engl J Med 359(14): 1464-76.

APPENDIX D: LEVEL OF EVIDENCE DETERMINATION

Each study was rated against pre-set criteria that resulted in an evidence rating (Level of Evidence I, II, III, or IV) and presented in a table. For therapeutic and prognostic articles, the criteria are listed in the Table below.

Definition of the different levels of evidence for articles on therapy and prognosis

	Studies of Therapy		Studies of Prognosis	
Level	**Study design**	**Criteria**	**Study design**	**Criteria**
I	Good quality RCT	• Concealment • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size	Good quality cohort	• Prospective design • Patients at similar point in the course of their disease or treatment • F/U rate of 80%+ • Patients followed long enough for outcomes to occur • Controlling for extraneous prognostic factors*
II	Moderate or poor quality RCT	• Violation of any of the criteria for good quality RCT	Moderate quality cohort	• Prospective design, with violation of one of the other criteria for good quality cohort study
	Good quality cohort	• Blind or independent assessment in a prospective study, or use of reliable data* in a retrospective study • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size • Controlling for possible confounding†		• Retrospective design, meeting all the rest of the criteria in level I
III	Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort	Poor quality cohort/cross sectional study	• Prospective design with violation of 2 or more criteria for good quality cohort, or • Retrospective design with violation of 1 or more criteria for good quality cohort • Cross-sectional study

	Case-control	• Any case-control design		Case-control	• Any case-control design
IV	Case series	• Any case series design		Case series	• Any case series design

*Reliable data are data such as mortality or reoperation.

†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Studies from Registries	
Study design	**Criteria**
Good quality registry	• Designed specifically for conditions evaluated • Includes prospective data only • Validation of completeness and quality of data • Patients followed long enough for outcomes to occur • Independent outcome assessment* • Complete follow-up of ≥ 85% • Controlling for possible confounding† • Accounting for time at risk‡
Moderate quality cohort	• Prospective data from registry designed specifically for conditions evaluated with violation of 2 of the rest of the criteria in level I
Poor quality cohort	• Prospective data from registry designed specifically for conditions evaluated with violation of 3 or more of the rest of the criteria in level I • Retrospective data or data from a registry not designed specifically for conditions evaluated

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.
† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
‡ Equal follow-up times or for unequal follow-up times, accounting for time at risk.

Methods for critical appraisal and level of evidence assessment

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,[1] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group,[2] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[3] Taking into account features of methodological quality and important sources of bias combines epidemiologic principles with characteristics of study design.

Procedures for determining adherence to level of evidence (LoE) criteria

Each study was rated against pre-set criteria that resulted in an evidence rating (Level of Evidence I, II, III, or IV) and presented in a table.For therapeutic articles, the criteria are listed in the Table below and an example is given.All criteria met are marked.A blank for the criterion indicates that the criterion was not met, could not be determined or was not reported by the author.

Example of methods evaluation for articles on therapy

Methodological Principle	Author 1	Author 2	Author 3	Author 4
Study design				
Randomized controlled trial	√	√		
Cohort Study			√	
Case-series				√
Statement of concealed allocation*	√	√		
Intention to treat*	√	√		
Independent or blind assessment	√		√	
Co-interventions applied equally	√	√	√	
Complete follow-up of ≥85%	√			√
Adequate sample size	√	√	√	
Controlling for possible confounding	√	√	√	
Evidence Level	**I**	**II**	**III**	**IV**

* Applies to randomized controlled trials only.

Assessment of economic studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al.[4] QHES embodies the primary components relevant for critical appraisal of economic studies.[4, 5] It

also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (e.g., with respect to age, gender, medical conditions, etc)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc)?
- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:

- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim selection, patient population considerations and other factors listed above consistent with a high quality design?
- Number of formal analyses (3 or more)
- Consistency of findings and conclusions from analyses across studies.

QHES Instrument[4] **Study** _____

Questions	Points	Yes	No
1. Was the study objective presented in a clear, specific, and measurable manner?	**7**		
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	**4**		
3. Were variable estimates used in the analysis from the best available source (i.e., randomized controlled trial - best, expert opinion - worst)?	**8**		
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	**1**		
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	**9**		
6. Was incremental analysis performed between alternatives for resources and costs?	**6**		
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	**5**		
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	**7**		
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	**8**		
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	**6**		
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	**7**		
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	**8**		
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	**7**		
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	**6**		
15. Were the conclusions/recommendations of the study justified and based on the study results?	**8**		
16. Was there a statement disclosing the source of funding for the study?	**3**		
TOTAL POINTS	**100**		

1. Oxford Centre for Evidence-based Medicine Levels of Evidence. 2009. (Accessed 9/27/10, at http://www.cebm.net/?o=1025.)
2. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
3. West S, King V, Carey TS, et al. Systems to Rate the Strength Of Scientific Evidence. Rockville, MD: Agency for Healthcare Research and Quality; 2002.
4. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9:53-61.
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Determination of Overall Strength of Evidence

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. Methods for determining the overall strength of evidence are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the primary domains of quality (LoE), quantity of studies and consistency of results across studies as described by AHRQ [West].

SRI establishes a strength-of-evidence baseline using the following definitions to determine whether or not the body of evidence meets the criteria for each domain:

Domain	Definition/Criterion
Quality	• At least 80% of the studies are LoE I or II
Quantity	• There are at least three studies which are adequately powered to answer the study question
Consistency	• Study results would lead to a similar conclusion (similar values, in the same direction) in at least 70% of the studies (assumes at least 3 studies available)

Based on the criteria described above, the possible scenarios that would be encountered are described below. Each scenario is ranked according to the impact that future research is likely to have on both the overall estimates of an effect and the confidence in the estimate. This ranking describes the overall "Strength of Evidence" (SoE) for the body of literature on a specific topic. The method and descriptions of overall strength are adapted for diagnostic studies from system described by the GRADE Working Group [Atkins] for the development of clinical guidelines.

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	High	Very unlikely to change confidence in effect estimate	+	+	+
2	Moderate	Likely to have an important impact on confidence in estimate and *may* change the estimate	+	-	+
			+	+	-
3	Low	Very likely to have an important impact on confidence in estimate and *likely* to change the estimate	+	-	-
			-	+	+
4	Very Low	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Limitations or special strengths can modify the quality of the evidence from the baseline as follows:

Factors that can reduce the quality of the evidence 1 or 2 levels:

- Limitations in study design or execution
- Indirectness of evidence
- Imprecision

Factors that can increase the quality of the evidence: 1 or 2 levels:

- Large magnitude of effect
- Dose response gradient

APPENDIX E. LEVEL OF EVIDENCE FOR COMPARATIVE STUDIES

Level of Evidence (LoE) evaluation for included RCTs (Key questions 1 and 2)

Methodological Principle	DCCT (1994)	JDRF 2008	JDRF 2009	JDRF 2010	Hirsch 2008	Bergenstal 2010
Study design						
Randomized controlled trial	■	■	■	■	■	■
Cohort Study						
Prospective						
Retrospective						
Statement of concealed allocation*	■					
Intent-to-treat*	■	■	■	■		■
Independent or blind assessment	■	■	■	■	■	■
Co-interventions applied equally		■	■	■	■	■
Complete follow-up of ≥80%		■	■	■	■	■
Adequate sample size	■	■	■	■		■
Controlling for possible confounding	■	■	■	■	■	■
Evidence Level	**II**	**II**	**II**	**II**	**II**	**II**

* Applies to randomized controlled trials only.

Level of Evidence assessment: Observational Studies of SMBG

Methods evaluation for prognostic studies assessing the association between frequency of SMBG andA1c levels which provided information on frequency of SMBG and specific A1C values.

METHODOLOGICAL PRINCIPLE	Anderson (2002)	Anderson (1997)	Levine (2001)	Moreland (2004)	Paris (2009)	Laffel (2003)
Study design						
Prospective cohort design			■			
Retrospective cohort/cross-sectional	■	■		■	■	■
Case-control design						
Case-series						
Patients at similar point in the course of their treatment	■	■	■	■	■	■
Complete follow-up of ≥80% *						
Patients followed long enough for outcomes to occur						
Controlling for extraneous risk factors†	■	■	■	■		■
Evidence Level	**III**	**III**	**III**	**III**	**III**	**III**

*Not applicable (NA) for case-control design; May refer to response rate for cross-sectional studies
Blank box indicates criterion not met or information not reported by author.
†For these studies, credit is given if the authors assessed the association between SMBG and A1C (or other outcomes) and controlled for confounding factors related to assessment of this association.

Methods evaluation for prognostic studies assessing the association between frequency of SMBG andA1c levels which *did not* provide specific information on frequency of SMBG and specific A1C values.

Methodological Principle	Butler 2008	Dorchy 1997	Haller 2004	Lewandowski 2007	Marvicsin 2008	McGrady 2009	Mehta 2009	Miller 2003	Miller 2007	Nordly 2005	Rosilio 1998
Study design											
Prospective cohort											
Retrospective/Cross-sectional	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Case-Control											
Case-series											
Patients at similar point in the course of their treatment											
Complete follow-up of ≥80% *	☒	☒	☒		☒					☒	
Patients followed long enough for outcomes to occur											
Controlling for extraneous risk factors†	☒					☒		☒		☒	☒
Evidence Level	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**

*Not applicable (NA) for case-control design; May refer to response rate for cross-sectional studies
Blank box indicates criterion not met or information not reported by author.
†For these studies, credit is given if the authors assessed the association between SMBG and A1C (or other outcomes) and controlled for confounding factors related to assessment of this association.

Methodological quality of registry studies assessing frequency of SMBG

Methodological principle	Ziegler (2010)
Designed specifically for conditions evaluated	■
Includes prospective data only	■
Validation of completeness and quality of data	
Patients followed long enough for outcomes to occur	■
Independent outcome assessment*	
Complete follow-up of ≥ 85%	
Controlling for possible confounding†	■
Accounting for time at risk‡	■
Evidence level	**III**

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.
† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
‡ Equal follow-up times or for unequal follow-up times, accounting for time at risk.

Level of evidence for analyses from EDIC (DCCT follow-up study) in those who were 18 years or younger at DCCT enrollment.**

Methodological Principle	White (2001)	White (2010)
Study design		
Randomized controlled trial		
Cohort Study		
Prospective	■	■
Retrospective		
Concealed treatment allocation*		
Intention to treat analysis*		
Independent or blind assessment	■	■
Complete follow-up of ≥80%	■	■
Adequate sample size	■	■
Controlling for possible confounding	■	■
Evidence Level	**II**	**III**

*Applies only to RCTs
**Both reports are on the same study population. Since participants were no longer required to follow RCT protocol, these studies are considered observational studies

Level of evidence for observational/sub-analyses from RCTs evaluating the effectiveness of CGM in children with type 1 diabetes.

Methodological Principle	Chase (2010)	JDRF (2009) "Factors"	JDRF (2009) "Effectiveness"	Hirsch (2008)	Bergenstal (2010)
Study design					
Randomized controlled trials					
Cohort Study					
Prospective	■	■	■	■	■
Retrospective					
Independent or blind assessment					
Complete follow-up of ≥80%	■		■	■	■
Adequate sample size*	■	■	■	■	■
Controlling for possible confounding*	■	■	■		■
Evidence Level	**II**	**III**	**III**	**III**	**II**

*For these studies, credit is given if the authors assessed the association between SMBG or CGM and A1C (or other outcomes), had adequate sample size in the population of interest and controlled for confounding factors related to assessment of this association

LoE tables: Observational studies not included elsewhere - related to Key Question 3

Methodological Principle	Belmonet 1988	Boland 2001	Cemeroglu 2010	DRCN 2007	Gandrud 2007	Jeha 2004	Messer 2009	Wong 2006
Study design								
Randomized controlled trial								
Cohort Study								
Prospective	■	■		■	■	■	■	■
Retrospective			■					
Case-series								
Independent or blind assessment						■		
Co-interventions applied equally	■			■	■	■	■	■
Complete follow-up of ≥85%		■	■	■	■	■	■	■
Adequate sample size	■	■	■	■	■		■	■
Controlling for possible confounding					■			
Evidence Level	**III**	**III**	**III**	**III**	**II**	**III**	**III**	**III**

LoE tables – Periodic CGM studies (cited in safety section)

Methodological Principle	Chase 2001	Deiss 2006	Lagarde 2006	Ludvigsson 2003	Yates 2006
Study design					
Randomized controlled trial	■	■	■	■	■
Cohort Study					
Prospective					
Retrospective					
Statement of concealed allocation*			■		
Intent-to-treat*		■			
Independent or blind assessment		■	■	■	■
Co-interventions applied equally	■	■		■	■
Complete follow-up of ≥85%	■	■	■	■	■
Adequate sample size		■			■
Controlling for possible confounding			■		
Evidence Level	**II**	**II**	**II**	**II**	**II**

APPENDIX F: DATA TABLES- DEMOGRAPHICS, STUDY CHARACTERISTICS AND RESULTS OF RCTS

Characteristics of RCTs of at real-time CGM in children.

Author (year)	Study design (LoE) Study period	Demographics	Follow-up (% followed)	Inclusion/exclusion criteria	Interventions	Outcomes	Funding
Bergenstal (2010)	RCT Multicenter January 2007 to December 2008	Pump Therapy (PT) n = 78 male: 59% mean age (± SD): 11.7 ± 3.0 years Injection Therapy (IT) n = 78 male: 53% mean age (± SD): 12.7 ± 3.1	1 year (91.3%; n = 443/485)	Inclusion: • Type 1 diabetes • Age 7–70 years • Received multiple daily injections that included a long-acting analogue insulin during the previous 3 months • HbA1c 7.4%–9.5% • Under the care of the principal investigator or a referring physician for ≥ 6 months • Computer access • History of testing blood glucose an average of ≥ 4x/day for pervious 30 days Exclusion: • Use if insulin-pump therapy within previous 3 years • History of ≥ 2 severe glycemic events in the year before enrollment • Use of a pharmacologic noninsulin treatment for diabetes during the previous 3 months • Pregnancy or the intention to become pregnant	PT • Sensor-augmented insulin pump therapy (MiniMed Paradigm REAL-Time System, Medtronic) • insulin pump therapy for 2 weeks, then glucose sensors introduced • used insulin aspart (NovoLog or NovoRapid, Novo Nordisk) IT • Multiple daily insulin injections • with continuous glucose monitoring (Guardian REAL-Time Clinical, Medtronic) • used both insulin glargine (lantus, Sanofi-Aventis) and insulin aspart All patients received training in intensive diabetes management including carbohydrate counting and the administration of correction doses of insulin	Primary: • Change from baseline in HbA1c at 1 year Secondary: • Rates of severe hypoglycemia (< 50 mg/dl) and DKA	Supported by Medtronic, Bayer Healthcare, and Becton Dickinson
Beck (2009) JDRF trial	RCT Multicenter February 2007 to December 2007	CGM* n = 18 female: NR age: 8–14 years Control* n = 11 female: NR age 8–14 years	26 weeks (CGM: 99%, n = 66/67; Control: 98%, n = 61/62) Phone f/u: CGM: 98% Control: 95%	Inclusion: • Age ≥ 8 years • Type-1 diabetes for at least 1 • Year • Use of either an insulin pump or at least three daily insulin injections • Baseline A1C level < 7.0% Successfully completion of a run-in phase of "blinded" CGM use	CGM • Instructed to use device on a daily basis and to verify accuracy with a home blood glucose meter • Used the Dex Com SEVEN (DexCom, San Diego, CA), the MiniMed Paradigm REAL-Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic MiniMed, Northridge, CA), or the FreeStyle Navigator (Abbott Diabetes Care, Alameda,	Primary: • Change in HbA1c levels Secondary: • Severe hypoglycemia, • Hyperglycemia resulting in DKA • Unexpected study-related or device-related events • Serious adverse events	Funding provided by the JDRF (grants 22-20006-1107, 22-2006-1117, 22-2006-1112, 22-2006-1123, 01-2006-8031) Home glucose meters and test strips were

Author (year)	Study design (LoE) Study period	Demographics	Follow-up (% followed)	Inclusion/exclusion criteria	Interventions	Outcomes	Funding
					CA) Control • Home monitoring with a blood glucose meter only • Instructed to perform SMBG ≥ 4x daily	regardless of causality	provided by LifeScan and Abbott Diabetes Care
JDRF Trial (2008)	RCT Multicenter February 2007 to December 2007	CGM* n = 56 female: 48% mean age (± SD): 11.4 ± 2.0 Control* n = 58 female: 50% mean age (± SD): 11.6 ± 2.1	26 weeks (100%) Crossover occurred in 2 patients in the control group before end of study period	Inclusion: • 3x/daily glucose monitoring • Age > 8 years • HbA1c < 10.0% • Not pregnant or planning pregnancy • Naïve to sensor use	CGM • Instructed to use device on a daily basis and to verify accuracy with a home blood glucose meter • Used the Dex Com SEVEN (DexCom, San Diego, CA), the MiniMed Paradigm REAL-Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic MiniMed, Northridge, CA), or the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA) Control • Home monitoring with a blood glucose meter only • Instructed to perform SMBG ≥ 4x daily	Primary: • Change in HbA1c levels Secondary: • Hypoglycemia (time per day, < 70 mg/dl, < 50 mg/dl) • Hyperglycemia resulting in DKA (time per day, > 180 mg/dl, > 250 mg/dl) • Unexpected study-related or device-related events • Serious adverse events regardless of causality	Funding provided by the JDRF (grants 22-20006-1107, 22-2006-1117, 22-2006-1112, 22-2006-1123, 01-2006-8031) Authors received consultation fees and/or devices and equipment from several device companies
Hirsch (2008)	RCT Multicenter	Sensor Group† n = 17 female: NR age (years): 12 to <18 Control† n = 23 female: NR age (years): 12 to <18	26 weeks (100%)	Inclusion: • Age 12–72 years • HbA1c ≥ 7.5% • Type-1 diabetes diagnosed > 1 year prior to study • Previously treated with CSII ≥ 6 months	Sensor Group • Sensor-augmented insulin pump therapy using the Paradigm 722 System (Medtronic) Control • Self-monitored blood glucose measurements and a Paradigm 715 insulin pump • Blinded CGM Both groups received intensive diabetes management training	Primary • Change in A1c from baseline to 6 months Secondary • Percentage of subjects achieving 7% A1c • Hypoglycemia (< 70 mg/dl) and hyperglycemia (> 180 mg/dl) areas under the curve • Incidence and frequency of severe hypoglycemic and hyperglycemic events • Safety • Compliance	Supported by a grant from Medtronic, Inc. All authors have received grant support from one or more device company

Author (year)	Study design (LoE) Study period	Demographics	Follow-up (% followed)	Inclusion/exclusion criteria	Interventions	Outcomes	Funding
DCCT (1994)	RCT Multicenter 1983 to 1993	Primary prevention (PP cohort)‡ N = 125 IT, n = 56 female: 44% mean age (± SD): 15 ± 1.0 years CT, n = 70 female: 53% mean age (± SD): 15 ± 1.0 years Secondary intervention (SI cohort)§ N = 70 IT, n = 37 female: 51% mean age (± SD): 15 ± 1.0 years CT, n = 33 female: 61% mean age (± SD): 15 ± 1.0 years Overall ages: 13–14 years: 41% 15–16 years: 47% 17 years: 12%	7.4 years (4–9) (98%)	Inclusion: PP Cohort • IDDM for 1 - 5 yrs • no retinopathy • urinary albumin excretion <40 mg/24 hr SI Cohort • IDDM for 1 - 15 yrs • very mild to moderate nonproliferative retinopathy • urinary albumin excretion <200 mg/24 hr"	Intensive therapy (IT): • ≥3 insulin injxn/day using specific insulin regimen (pump or injxn) • ≥4 SMBG/day • Clinic visits monthly Coventional therapy (CT): • 1–2 insulin injxn/day (not adjusted daily) • 1 SMBG/day • Clinic visits every 3 months	• HbA1c • Retinopathy • Nephropathy	Supported by the NIDDK, NHLBI, NEI, and NCRR

BMI: body mass index; CGM: continuous glucose monitoring; DKA: diabetic ketoacidosis; JDRF: Juvenile Diabetes, Research Foundation; NCRR: National Center for Research Resources.NEI: National Eye Institute; NHLBI: National Heart, Lung and Blood Institute; NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases; NIH: National Institute of Health; SMBG: self-monitoring of blood glucose.
*Demographics are reported for children age 8–14 years only.
†Demographics are reported for adolescents age 12 to < 18 only.
‡Subjects with insulin-dependent diabetes mellitus but with no retinopathy at baseline.
§Subjects with mild retinopathy.

Results of RCTs looking at real-time CGM in children

Study	HbA1c %	Hypoglycemia	Hyperglycemia	Ketoacidosis	Adverse events/other
Bergenstal (2010)	**HbA1c% (mean ± SD)** Baseline PT: 8.3 ± 0.6 IT: 8.3 ± 0.5 1 year values NR Difference b/t baseline and 1 year PT: -0.4 ± 0.9 IT: +0.2 ± 1.0 *P*< .001 (Change from baseline to 1 year between arms) **Achieving target HbA1c < 7%** PT: n = 10 (13%) IT: n = 4 (5%) *P* = .15 **Achieveing target HbA1c < 8% (in 6–12 year olds); < 7.5% (in 13–19 year olds)** PT: n = 35 (44%) IT: n = 16 (20%) *P* = .005	**Rate of severe hypoglycemia at 1 year** PT: 8.98/100 person-yea IT: 4.95 person-year *P* = .35 **Severe hypoglycemia events** PT: 7 events in 4 patients IT: 4 events in 4 patients *P* = .53 **AUC < 70 mg/dl*min (mean ± SD)*** Baseline PT: 0.26 ± 0.40 IT: 0.23 ± 0.44 1 year PT: 0.23 ± 0.41 IT: 0.25 ± 0.41 *P* = .79 (Change baseline to 1 year; PT vs. IT) **AUC< 50 mg/dl*min (mean ± SD)*** Baseline PT: 0.01 ± 0.04 IT: 0.02 ± 0.05 1 year PT: 0.02 ± 0.07 IT: 0.01 ± 0.05 *P* = .64 (Change baseline to 1 year; PT vs. IT)	**AUC > 250 mg/dl*min (mean ± SD)*** Baseline PT: 13.89 ± 11.04 IT: 16.23 ± 10.46 1 year PT: 9.2 ± 8.08 IT: 17.64 ± 14.62 *P*< .001 (Change baseline to 1 year; PT vs. IT) **AUC > 180 mg/dl*min (mean ± SD)*** Baseline PT: 39.36 ± 21.70 IT: 44.68 ± 20.34 1 year PT: 30.11 ± 17.34 IT: 45.29 ± 25.57 *P*< .001 (Change baseline to 1 year; PT vs. IT)	Data not stratified by age	Data not stratified by age **PT group** 2 hospital admissions for cellulitis, insertion site infections **IT group** 1 death from sudden cardiac attack
Beck (2009) JDRF trial	Data not stratified by age	**Minutes/day < 70 mg/dl** Data within age strata similar to overall analysis: There was a greater decrease in median time per day < 70 mg/dl in the CGM compared to SMBG only arm (-37 minutes/day versus -5 minutes/day; *P* =.16 [ranks]; *P* = .04 [outliers truncated]; *P* = .06 [square root transformation])	Data not stratified by age	NR	NR
JDRF Trial (2008)	**HbA1c% (mean ± sd)** Baseline: CGM: 8.0 ± 0.7 Control: 7.9 ± 0.6 Difference between baseline and 26 weeks: CGM: -0.37 ± 0.9 Control: -0.22 ± 0.54 *P* = .29 (change baseline to 26	**Rate of severe hypoglycemia** CGM: 17.9/100 person-year Control: 24.4 person-year *P* = .64 **>1 severe hypoglycemic event** CGM: n = 4 (7%) Control: n = 6 (10%) *P* = .74	**Minutes/day >180 mg/dl (mean)** Baseline CGM: 745 Control: 671 26 weeks CGM: 643 Control: 635 *P* = .58 (change from baseline to 26 weeks between arms)	CGM: n = 0 Control: n = 0	**Cellulitis related to censor use:** CGM: n = 2 Control: n = 0 **Dizziness during blood draw:** CGM: n = 0 Control: n = 1

Study	HbA1c %	Hypoglycemia	Hyperglycemia	Ketoacidosis	Adverse events/other
	weeks between arms) **Relative decrease by > 10%** CGM: n = 16 (29%) Control: n = 7 (12%) **Absolute decrease at 26 weeks > 0.5%** CGM: n = 30 (54%) Control: n = 18 (31%) **Relative increase at 26 weeks > 10%** CGM: n = 5 (9%) Control: n = 2 (3%) **Absolute increase at 26 weeks > 0.5%** CGM: n = 12 (21%) Control: n = 7 (12%) **< 7% at week 26** CGM: n = 15 (27%) Control: n = 7 (12%) **<7% w/o severe hypoglycemic events at week 26** CGM: n = 14 (25%) Control: n = 6 (10%)	**>1 severe hypoglycemic event with seizure/coma** CGM: n = 0 Control: n = 0 **Minutes/day < 70 mg/dl (mean)** Baseline CGM: 49 Control: 59 26 weeks CGM: 47 Control: 59 *P* = .29 (CGM vs. control at 26 weeks) **Minutes/day < 50 mg/dl (mean)** Baseline CGM: 17 Control: 18 26 weeks CGM: 10 Control: 13 *P* = .50 (CGM vs. control at 26 weeks)	**Minutes/day >250 mg/dl (mean)** Baseline CGM: 343 Control: 282 26 weeks CGM: 242 Control: 268 *P* = .18 (change from baseline to 26 weeks between arms)		
Hirsch (2008)	**HbA1c % (mean ± sd)** Baseline CGM: 8.59 ± 0.80 Control: 8.82 ± 1.05 13 weeks CGM: 7.97 ± 0.59 Control: 7.86 ± 0.97 (*difference between baseline and 13 weeks calculated by hand) 26 weeks CGM: 8.21 ± 0.97 Control: 8.02 ± 1.11 (*difference between baseline and 26 weeks given in table) *P* = .57 for change 0–26 weeks in CGMs (-0.37 ± 0.95) *P* = .01 for change 0–26 weeks in controls (-0.79 ± 0.65) *P* = .10 for change 0–26 weeks between CGM vs. control	Data not stratified by age "severe hypoglycemic events" CGM, n = 11 Control, n = 3	Data not stratified by age	Data not stratified by age CGM, n = 1 Control, n = 1	Adverse events reported were not stratified by age: **skin abscess (twice) at insulin infusion site**, n = 1 (treatment arm not stated)

Study	HbA1c %	Hypoglycemia	Hyperglycemia	Ketoacidosis	Adverse events/other
	% achieving 7% by 13 weeks Data not reported *P* = .052 (CGM vs. control)				
DCCT (1994)	**HbA1c% (mean ± sd)** Baseline PP cohort IT: 9.3 ± 1.9 CT: 9.2 ± 1.8 SI cohort IT: 9.8 ± 1.8 CT: 10.1 ± 1.8 F/U HbA1c only provided in Figure A - no data Table IV may have overall average HbA1c for combined cohorts: **Overall average follow-up HbA1c for combined cohorts:** IT: 8.06 ± 0.13 CT: 9.76 ± 0.12 *P* = NR for change from baseline	**Severe hypoglycemia events requiring assistance (combined cohorts)** IT: 603 events in 75 patients (82%) CT: 207 events in 46 patients (45%) **Rate of severe hypoglycemia requiring assistance (combined cohorts)** IT: 85.7/100 patient-year CT: 27.8/100 patient-year RR = 2.96 (1.90, 4.62); *P*< .001 **Severe hypoglycemia events resulting in coma/seizure (combined cohorts)** IT: 188 events in 58 patients (63%) CT: 72 events in 26 patients (25%) **Rate of hypoglycemia resulting in coma/seizure (combined cohorts)** IT: 26.7/100 patient-year CT: 9.8/100 patient-year RR = 2.93 (1.75, 4.90); *P*< .001 **Hospitalizations to treat severe hypoglycemia** IT: n = 14 CT: n = 5 *P* = NR	NR	**Ketoacidosis events (combined cohorts)** IT: 20 events in 17 patients (18%) CT: 35 events in 21 patients (20%) **Rate of ketoacidosis (combined cohorts)** IT: 2.8/100 patient-year CT: 4.7/100 patient-year RR=0.62 (0.32, 1.23); *P* = .174	RETINOPATHY **Rate of any sustained retinopathy at 6 months** PP cohort IT: 18/100 patient-year CT: 23/100 patient-year 30% reduction (-9, 55); P > .05 SI cohort NA since everyone had retinopathy **Rate > 3-step sustained retinopathy over entire study period** PP cohort IT: 6.3/100 patient-year CT: 3.2/100 patient-year 53% reduction (-78, -1); *P* = .048 SI cohort IT: 2.9/100 patient-year CT: 734/100 patient-year 70% reduction (-88, -25); *P* = .01 Combined cohort: 61% reduction (-78, -30); *P* = NR ≥3-step sustained retinopathy over entire study period† PP cohort IT: n = 10 CT: n = 24 SI cohort IT: n = 8 CT: n = 16 PP cohort: Too few #'s of nonproliferative retinopathy (n = 4), clinically significant macular edema (n = 2), or required photoagulation (n= 4) SI cohort: Proliferative or severe nonproliferative retinopathy (CT: n = 7, IT: n =

Study	HbA1c %	Hypoglycemia	Hyperglycemia	Ketoacidosis	Adverse events/other
					2; *P* = .087 [4 in CT required laser treatmemt vs. 2 in IT) NEPHROPATHY‡ **Rate of nephropathy over entire study period** PP cohort IT: 5.8/100 patient-year CT: 7.1/100 patient-year 10% reduction (-70, 52); *P* = .75 SI cohort IT: 6.6/100 patient-year CT: 12.7/100 patient-year 55% reduction (-79, -3); *P* = .04 Combined cohort: 35% reduction (-7,60); *P* = NR Entire cohort: Too few #'s of clinical-grade albuminuria (IT: n = 3, CT: n = 6; *P* = ns), 0 had impaired renal function NEUROPATHY **clinical neuropathy cases over entire study period** (combined cohorts) IT: n = 3 CT: n = 7 Peripheral motor and sensory nerve conduction velocities were significantly slower in CT than IT at 5 years of study (No data provided)

AUC: area under the curve; CGM: continuous glucose monitoring; NR: not reported; PP cohort: primary prevention cohort (adolescents with no evidence of retinopathy); SI cohort: secondary intervention cohort (adolescents with evidence of retinopathy).
*AUC is a measure of the duration and severity of hypoglycemia or hyperglycemia (units = mg/dL*min/day).
†Worsening of at least 1 micro-aneurysm on two consecutive 6 months fundus photographs.
‡Urinary albumin > 40 mg/24 hr.

APPENDIX G: DATA TABLES –OBSERVATIONAL STUDIES

Characteristics and Results of Observational Studies of CGM OR SMBG.

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
Studies of Self-Monitoring of Blood Glucose						
White (2010)	Prospective cohort (II)	Epidemiology of Diabetes Interventions and Complications (EDIC) Intensive (INT – participants from intensive treatment arm of DCCT) N =73 Female: 47% Mean age (±SD) at DCCT entry: 15.1 ± 1.3 years DM duration (±SD) at DCCT entry: 5.5 ± 3.5 years Conventional (CON – participants from conventional treatment arm of DCCT) N =83 Female: 57% Mean age (±SD) at EDIC entry: 14.8 ± 1.4 years DM duration (±SD) at EDIC entry: 4.8 ± 3.4years	*Primary prevention cohort of DCCT* • Type 1 diabetes for 1–5 years • No retinopathy • Urinary albumin excretion<40mg/24 hrs. *Secondary prevention cohort of DCCT* • Type 1 diabetes for 1–15 years • Mild/moderate retinopathy • Urinary albumin excretion≤ 200mg/24 hrs.	To assess whether the benefits of intensive diabetes therapy (for 7.4 years during the DCCT) persist after the end of the DCCT	A1c (mean) *Average over10 years of EDIC* INT: 8.2 ± 1.3 % CON: 8.2 ± 2.1 % Progression of ≥ 3 step retinopathy (%) *From DCCT start to EDIC yr 10* INT: 50.9% CON: 53.4% RR=0.9; P=0.84 *From DCCT end to EDIC yr 10* INT: 40% CON: 40% RR=1.0; *P* = .95 Progression of ≥ 3 step retinopathy (cumulative incidence) *From DCCT end to EDIC yr 10* INT: NR CON: NR RR=0.68; *P* = .13 Progression to severe NPDR or worse (%) *From DCCT end to EDIC yr 10* INT: 11.6 % CON: 19.5 % RR=0.54; *P* = .26 Progression proliferative retinopathy (%) *From DCCT end to EDIC yr 10* INT: 11.6 % CON: 18.2 % RR=0.59; *P* = .36 Progression macular edema(%) *From DCCT end to EDIC yr 10* INT: 11.6 %	After completion of the DCCT, the beneficial effects of intensive treatment waned over time and were no longer significantly different from conventional treatment after 10 years of follow-up.

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
					CON:6.9 % RR=1.75; *P* = .39 Laser therapy (%) *From DCCT end to EDIC yr 10* INT: 7.3% CON:17.7 % RR=0.36; *P* = .08 Nephropathy Year 10 AER >40 mg/24 h (%) INT : 20.8%, CON: 20.7% AER >300mt/24h INT 5.6%, CON: 4.9%	
White (2001)	Prospective cohort (II)	Epidemiology of Diabetes Interventions and Complications (EDIC) Intensive (INT – participants from intensive treatment arm of DCCT) N=81 (age 13-17 at start of DCCT) Female: 48% Mean age (±SD) at year 4: 27.2 ± 2.4 years DM duration (±SD) at year 4: 17.4 ± 4.2 years Conventional (CON – participants from conventional treatment arm of DCCT) N = 89 (age 13-17 at start of DCCT) Female: 60% Mean age (±SD) at year 4: 26.3 ± 2.2 years DM duration (±SD)) at year 4: 16.3 ± 4.3years	*Primary prevention cohort of DCCT* • Type 1 diabetes for 1–5 years • No retinopathy • Urinary albumin excretion<40mg/24 hrs. *Secondary prevention cohort of DCCT* • Type 1 diabetes for 1–15 years • Mild/moderate retinopathy • Urinary albumin excretion≤ 200mg/24 hrs.	To assess whether the benefits of intensive diabetes therapy (for 7.4 years during the DCCT) persist after the end of the DCCT	A1c (mean) *Baseline(start of EDIC)* INT: 8.4 % CON: 8.4 % *Average over 4 years of EDIC* INT: 8.38% CON: 8.45 % Coma or Seizure INT: 16.6/ 100 person-years CON: 26.8/ 100 person-years RR = 0.62; *P* = .358 Events requiring assistance INT: 51.0/ 100 person-years CON: 57.0/ 100 person-years RR = 0.90; *P* = .749 Progression of ≥ 3 step retinopathy (%) *From DCCT baseline to EDIC yr 4* INT: 65% CON: 32% RR = 0.26; *P*<.001 *From DCCT end to EDIC yr 4* INT: 7.1 % CON: 25.4 % RR=0.23; *P*=.004 Progression to severe NPDR or worse (%) *From DCCT end to EDIC yr 4*	After completion of the DCCT, the beneficial effects of intensive treatment persisted for an additional 4 years even though the beneficial effect on A1c was no longer sustained.

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
					INT: 1.4 % CON: 14.5 % P=0.005 <u>Progression proliferative retinopathy (%)</u> *From DCCT end to EDIC yr 4* INT: 1.4 % CON: 8.7 % *P* = .07 <u>Progression macular edema(%)</u> *From DCCT end to EDIC yr 4* INT: 2.9% CON:5.5 % *P* = .69 <u>Laser therapy (%)</u> *From DCCT end to EDIC yr 4* INT: 0.0% CON:5.6 % *P* = .12 <u>Retinopathy high risk (%)</u> *From DCCT end to EDIC yr 4* INT: 0.0% CON:7.0 % *P* = .06 <u>Progression to proliferative or severe NPDR (%)</u> *From DCCT baseline to EDIC yr 4* INT: 5.4% CON:20.3 % RR= 0.22; *P* = .007 <u>Progression to microalbuminuria (%)</u> *From DCCT end to EDIC yr 4* INT: 8.1% CON:13.6 % RR = 0.52; *P* = .28 <u>Progression to albuminuria (%)</u> *From DCCT end to EDIC yr 4* INT: 1.3% CON:9.9 % RR= 0.15; *P* = .08	

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
Studies of Continuous Glucose Monitoring						
Chase (2010)	Prospective cohort (II)	<u>Group A</u> (CGM use ≥ 6 days/week in month 12) n = 17 Female: 53% Mean age (±SD): 11.3 ± 2.9 years DM duration (±SD): 5.8 ± 3.1 years <u>Group B</u> (CGM use ≥ 6 days/week in month 6 and < 6 at month 12) n = 17 Female: 59% Mean age (±SD): 12.7 ± 2.8 years DM duration (±SD): 6.0 ± 3.3 years <u>Group C</u> (CGM use < 6 days/week in both month 6 and 12) n = 46 Female: 46% Mean age (±SD): 13.7 ± 2.8 years DM duration (±SD): 7.2 ± 3.2 years	• Type-1 DM for ≥ 1 year • Use of either an insulin pump or ≥ 3 daily insulin injections • HbA1c level 7.0% to < 10.0%	To assess ongoing use of CGM over the course of 12 months and its association with glycemic outcomes in pediatric patients 8–17 years of age upon study entry	<u>A1c (mean)</u> *Baseline* Group A: 8.2 Group B: 7.8 Group C: 8.0 *6 months* Group A: 7.3 Group B: 7.3 Group C: 8.0 *12 months* Group A: 7.4 Group B: 7.7 Group C: 8.1 *P*< .001 for the 3-group comparisons* <u>Percent of subjects meeting target A1c†</u> *Baseline* Group A: 29% Group B: 47% Group C: 39% *6 months* Group A: 65% Group B: 76% Group C: 35% *12 months* Group A: 71% Group B: 41% Group C: 33% *P*< .03 for the 3-group comparisons*	Continued use of CGM ≥ 6 days/week through months 6 and month 12 was associated with lower A1c values
JDRF (2010)	Prospective cohort (II)	N = 47 Using CGM in month 6: 0 days/ week, n = 11 > 0 to < 4 days/week, n = 15 4 to <6 days/week, n=10	• Randomized to SMBG in JDRF RCT • Crossed-over to CGM in extension	To determine whether CGM is effective when used in a typical clinical care environment	<u>Mean change from baseline to 6 months, by use of CGM:</u> • 0 days/ week: -0.1 • > 0 to < 4 days/week: +0.2 • 4 to <6 days/week: - 0.2	Greater CGM use was associated with a great A1c decrease (*P* = .01 adjusted for age-group)

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
		≥ 6 days/week, n = 11	study		• ≥ 6 days/week: 0 Rate of severe hypoglycemia: • 6 months using SMBG during trial: 26.4/100 person years • 6 months using CGM after trial: 13.0 person-years	The incidence of severe hypoglycemia trended lower in all age groups. There were no significant differences in adjusted glycemic indices between baseline and month 6.
JDRF (2009)	Prospective cohort (II)	n = 74‡ Female: 50% Age: 8–14 years DM duration < 5 years: 41%	• Age ≥ 8 years • Type-1 DM for ≥ 1 year • Use of either an insulin pump or ≥ 3 daily insulin injections • HbA1c level < 10.0%	To investigate factors associated with successful use of CGM among subjects with intensively treated DM	Change in A1c (%) based on average CGM use in month 6 • < 4 days/week (n = 7): + 0.02§ • 4–6 days/week (n = 21): -0.03§ • ≥ 6 days/week (n = 28): -0.72§ *P*< .001**	Near daily CGM use is associated with a similar reduction in A1c regardless of age. Frequency of blood glucose meter monitoring and initial CGM use may help predict the likelihood of long-term CGM benefit in all ages
Studies assessing frequency of SMBG						
Ziegler (2010)	Registry study (III)	N = 26,723 Female: 48% Mean age (± SD): 12.7 ± 4.1 years 0–5 years: n = 1989 (7%) 6–12 years: n = 7568 (28%) > 12 years: n = 17,166 (65%) Duration DM (± SD): 4.8 ± 3.8 years	• Documented from years 1995–2006 • Age 0–18 years • Type-1 DM	Evaluate whether the frequency of SMBG is related to the quality of treatment as measured by hemoglobin A1c (HbA1c), the frequency of hypoglycemia and ketoacidosis, and if the associations between SMBG and these outcomes are influenced by the patient's age or treatment regime.	Age, A1c, and SMBG frequency • *0–5 years* Mean A1c: 7.59% ± 1.34 SMBG frequency: 6.0x/day ± 1.9 • *6–12 years* Mean A1c: 7.61% ± 1.32 SMBG frequency: 5.3x/day ± 1.6 • *>12 years* Mean A1c: 8.46% ± 1.85 SMBG frequency: 4.4x/day ± 1.4 *P*< .001 for A1c comparisons across age groups *P*< .001 for SMBG frequency across age groups Insulin regimen, A1c, and SMBG frequency • *CT (n = 5016)* Mean A1c: 7.64% ± 1.67 SMBG frequency: 5.3x/day ± 1.8	A higher frequency of SMBG was related to better metabolic control Metabolic control depended significantly on age and was significantly different between all three treatment regimens A significant positive relationship was seen between the rate of hypoglycemia and SMBG frequency Frequency of DKA was significantly and inversely related to SMBG frequency

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
					• *MDI: (n = 18,565)* Mean A1c: 8.24% ± 1.75 SMBG frequency: 4.7x/day ± 1.5 • *CSII (n = 3142)* Mean A1c: 8.01% ± 16.0 SMBG frequency: 5.3x/day ± 1.8 *P*< .001 for A1c comparisons across regimen groups *P*< .001 for SMBG frequency across regimen groups <u>Hypoglycemic events, DKA, and SMBG frequency</u> • *Hypoglycemicevents* SMBG 0–4 x/day: 13–20 events/100 person-years; SMBG ≥ 5x/day: 20–37 events/100 person-years (Rate for severe hypoglycemia ↑ by 2.38/100 p-y ±0.54 for each additional measurement and ↑0.62 events/100 p-y ± 0.301 for hypoglycemia with coma or convulsion) • *DKA* SMBG 0–4 x/day: 6–12 events/100 person-years (except for 1 SMBG/day); SMBG ≥ 5x/day: 4–6 events/100 person-years (Rate ↓ by 0.38 events /100 p-y (± 0.144) per additional glucose measurement)	
Paris (2008)	Cross-sectional (III)	N = 2743 Female: 50% Mean age (± SD): 13.2 ± 4.5 years DM duration (±SD): 5.0 ± 3.9 years	• Age < 20 years • Type-1 DM ≥ 1 year • No episodes of DKA during the previous month • Insulin-dependent	To describe the insulin regimens used to treat type-1 DM) in youth in the United States, to explore factors related to insulin regimen, and to describe the associations	<u>Mean SMBG frequency; mean A1c (% , ± SD)</u>†† • 0–2 x/day (n = 284): A1c: 9.5 ± 2.1 • 3x/day (n = 363): A1c: 9.0 ± 1.6 • ≥ 4x/day (n = 2063):	The frequency of SMBG was associated with A1C, with those who checked their blood glucose infrequently (≤ 2x/daily) showing higher A1C levels than those who checked

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
			with complete data on insulin regimen • Baseline A1c measurement	between insulin regimen and clinical outcomes, particularly glycemic control.	A1c: 8.2 ± 1.3 *P* = NR	more often (≥ 4x/ daily) regardless of insulin regimen
Moreland (2004)	Cross-sectional (III)	N = 153 Female: 66% Mean age (± SD): 12.9 ± 2.3 years DM duration (± SD): 6.3 ± 3.5 years	Age 8–16 years Type-1 DM • Duration of DM1 ≥ 6 months • ≥ 3 outpatient visits in the past 2 years • Residence in the USA • Fluency in English or Spanish • Stable living environment • No major psychiatric or neurocognitive disability, and no significant medical disease other than DM1	To evaluate the relative impact of physiological, therapeutic, and psychosocial variables of glycemic control in youth with type-1 DM	Mean SMBG frequency; mean A1c (%)‡‡ • 1 x/day: A1c: 9.1 • 2–3x/day: A1c: 8.4 • 4–5x/day: A1c: 8.1 • ≥ 6x/day : A1c: 7.4 *P* = .03‡‡	SMBG frequency significantly predicted A1c levels, with more frequent monitoring related to more optimal control Patient report of DM-specific family conflict, frequency of SMBG, and pump uses were all independent and significant predictors of A1c after controlling for pubertal status and parent report of family involvement in DM management tasks.
Anderson (2002)	Cross-sectional (III)	8-12 years n = 69 Female: 51% Mean age (± SD): 10.7 ± 1.47 years DM duration (± SD): 2.7 ± 1.69 years 13-17 years n = 35 Female: 40% Mean age (± SD): 14.7 ± 1.07 years DM duration (± SD): 2.4 ± 1.32 years	• Age 8–17 years • Duration of type-1 DM > 2 months, but < 6 years • Residence in New England or New York • ≥ 1 outpatient medical visit in the past year	To investigate the relationship between diabetes-related parental behaviors (conflict around and involvement in treatment tasks), adherence to SMBG, and glycemic control in youth with short duration Type 1 DM	Mean SMBG frequency; mean A1c (%)§§ • 0–3x/day: A1c: 8.6 • 4–5x/day: A1c: 8.2 *P*< .01§§	Early in the course of diabetes, diabetes-specific conflict and adherence to SMBG is strongly linked to glycemic control
Levine (2001)	Prospective cohort (II)	N = 300 Female: 56% Mean age (± SD): 11.9 ± 2.5 years	• Age 7–16 years • Duration of diabetes > 6	To examine predictors of glycemic control and to assess how glycemic	Mean SMBG frequency; mean A1c (%, ± SD)*** • 1x/day:	SMBG frequency was the sole modifiable predictor of A1c

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
		DM duration (± SD): 5.2 ± 3.0 years	months • ≥ outpatient visit between January 1997 and January 1998 (the year before the start of the study) • Residence in New England or New York • No documented serious medical or psychiatric condition or unstable living environment.	control affects the incidence of short-term adverse outcomes in a pediatric population with type 1 diabetes.	A1c: 9.1 ± 0.34 • 3x/day: A1c: 8.9 ± 0.16 • ≥ 5x/day A1c: 8.0 ± 0.31 *P*< .0001***	The incidence of short-term adverse events in children with type 1 diabetes remains high, particularly in those with poorest glycemic control
Anderson (1997)	Cross-sectional (III)	<u>10-12 years</u> N = 51 Female: 55% Mean age (± SD): 11.7 ± 0.89 years DM duration (± SD): 5.3 ± 2.47 years <u>13-15 years</u> N = 38 Female: 45% Mean age (± SD): 14.0 ± 0.65 years DM duration (±SD): 6.0 ± 2.67 years	• Age 10–15 years • Duration of insulin-dependent DM > 1 year • Reasonable metabolic control (A1c 6.6%–10.4%) • No documented serious medical or psychiatric condition • Residence in New England or New York • ≥ 1 outpatient medical visit in the previous year	To identify parental behaviors that relate to adherence and metabolic control in a population of young adolescents with insulin-dependent diabetes mellitus, and to understand the interrelationships among the variables of parental involvement, adherence to blood glucose monitoring, and glycemic control.	<u>Mean SMBG frequency; mean A1c (%, ± SD)</u>††† • 0–1 x/day A1c: 9.9 ± .044 • 2 x/day A1c: 8.8 • 3 x/day A1c: 8.6 • ≥ 4 x/day A1c: 8.3 ± .022 *P*< .02†††	Parental involvement in SMBG supports more frequent monitoring in 10- to 15-year-old patients with insulin-dependent DM. This increased adherence to SMBG is associated with better metabolic control (i.e. lower A1c levels)
Studies reporting safety and adverse events for CGM						
Cemerglu (2010)	Retrospective cohort (III)	<u>Short term use (4 weeks)</u> N = 34 Female: NR Mean age (± SD): 14.6 ± 0.9 years (3–25 years)	• Expressed interest in using a real-time CGM • Duration of diabetes ≥ 1 year	To assess the patient's and the caregiver's perception of benefits and disadvantages of real time CGM in children or	*4-week trial group*‡‡‡: • Sensor alarms interfered with daily routine: 38% • Irritation by alarms: 50% • Sensor too bulky: 22 %	The most common perceived benefits of real-time CGMs are prevention of hypoglycemia and decrease in

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
		DM duration: NR <u>Long term use (≥ 2 months)</u> N = 9 Female: NR Mean age (± SD): 13.4 ± 1.6 years(7–21 years) DM duration: NR	• Have been on insulin pump therapy ≥ 6 months	young adults with type I DM.	• 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%	hypoglycemia-related anxiety. Negative effects are uncommon and seem to be unlikely to affect the decision to use real-time CGMs for the long-term.
Messer (2009)	Prospective cohort (III)	<u>CSII</u> N = 30 Female: 40% Mean age(± SD): 11.2 ± 4.1 years DM duration(± SD): 5.8 ± 3.0 years <u>MDI</u> N = 27 Female: 52% Mean age (± SD): 11.0 ± 3.9 DM duration (± SD): 4.0 ± 3.1 years	• Age 4–18 years • Type I diabetes, duration of < 1 year • Stable insulin regimen • Excluded: asthma medically treated in the prior 6 months; cystic fibrosis; other medical conditions that could affect completion of any aspect of the protocol	To describe the process of educating families and children with type I diabetes on real-time CGM and to note the similarities and differences of training patients using CSII versus MDI	*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%	Educators who teach real-time CGM should emphasize lag time and calibration techniques, technical device training, and sensor insertion. Follow-up focus should include insulin dosing adjustments and skin issues.
DRCN (2007)	Prospective cohort (III)	N = 33 Female: 40% Mean age (± SD): 11.2 ± 4.1 years	• Age between 3 and <18 years • Diagnosis of	To examine the feasibility and short-term efficacy of daily use of	• Severe skin reactions: 7% • Moderate acute skin changes: • 14%	Incorporating real-time continuous glucose monitoring into the daily

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
		DM duration (± SD) 5.8 ± 3.0 years	T1D,of ≥1 year duration • Stable insulin regimen using a pump for at least six months prior • Home computer with e-mail access • Primary caregiver (and subject if ≥9 years of age) comprehend written English • Excluded: asthma that was medically treatedin the prior six months; cystic fibrosis; inpatient psychiatric treatment in the past 6 months(patient or primary caregiver); current use ofglucocorticoids; a medical condition or use of a medication that in the judgment of the investigator could affect wearing of the sensors or the completion of any aspect of the protocol.	CGM in children with type 1 DM receiving insulin pump therapy and to determine if there were any limitation on its use based on patient age or other clinical factors	• Mild acute skin changes: 14% • Scabbing: 32% • Dry skin: 21% • Changes in pigmentation: 7%	management of T1D in children is feasible and viewed as helpful by both patients and parents.
Gandrud (2007)	Prospective cohort (II)	N = 19 Female: 47% Mean age (± SD): 4.8 ± 1.4 years (1.6–6.8) DM duration: NR	• Age < 7 years • Diagnosis of DM	To assess the incidence of hypoglycemia as well as postprandial glycemic patterns in this age group utilizing continuous	• "Occasional" mild irritation andrash at the insertion site • Infection: 0	Frequent mild nocturnal hypoglycemia and significant postprandial hyperglycemia was observed, with a rapid rise

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
				glucose monitoring.		in glucose following the meal. The most rapid rate of rise and the most severe postprandial hyperglycemia occurred after breakfast.
Wong (2006)	Prospective cohort (III)	Overall N = 20 Female: 40% Mean age (± SD): 12.2 ± 4.6 years(5–17) DM duration: NR Group 1 (initial sensors) N = 10 Female: 60% Mean age (± SD): 13.7 ± 4.5 years (5–17) DM duration: NR Group 2 (cable-modified sensors) N = 10 Female: 20% Mean age (± SD): 10.8 ± 4.3 years (5–17) DM duration: NR	• Diagnosis of type 1 DM • No skin abnormality, history of tape allergies, or evidence of chronic infection • Not on chronic corticosteroid therapy • Not enrolled in other investigational studies in the 4 weeks prior to study	To evaluate the performance, safety, and patient tolerance of using a CGM for 7 continuous days in children with type 1 DM who were encouraged to participate fully in their usual sports and activities in their home environment.	• Itching: 30%-40%§§§ • Edema: 0 • Pain: 10% • Dryness: 10% • ≤ 3 mm induration: 92% • ≤ 5 mm redness: 90% • Infection: 2%	CGMS has been shown to be safe and provide clinically useful data well beyond its label use of 3 days. Using the described protocol, 5 days seems to be an optimal length of sensor wear.
Jeha (2004)	Prospective cohort (III)	N = 10 Female: 80% Mean age (± SD): 3.7 ± 1.3 years (1.8–5.7) DM duration (± SD): 1.9 ± 1.4 years	• Age < 6 years • Diagnosis of type 1 DM for > 6 months • Excluded: on continuous subcutaneous insulin infusion therapy or medication that alter glucose metabolism	To determine using the whether twice-daily insulin injection therapy using CGM achieves adequate control in preschool children with type 1 DM and whether the CGM is more informative than SMBG regarding glucose control and if it is well tolerated by preschool children andtheir families.	• Local irritation: 0 • Infection: 0	Preschool children with type 1 DM have suboptimal control on twice-daily insulin injection therapy, with frequent and prolonged hypoglycemia, especially at night, lasting up to 1 hour per day. CGM is well tolerated by patients and has the advantage of revealing daily glucose trends missed by SMBG.

Author (year)	Study design (LoE)	Demographics	Inclusion/exclusion criteria	Study purpose	Results	Conclusions
Boland (2001)	Prospective cohort (III)	N = 56 Female: 55% Mean age(± SD): 11.6 ± 4.6 years (2–18) DM duration (± SD): 5.0 ± 3.0 years	• < 18 years of age • No other health problem expect for treated thyroid disease • Treated with insulin for ≥ 1 year	To evaluate the efficacy of using CGM to obtain glucose profiles in children with type 1 DM and to examine limitations of conventional monitoring.	• Inflammation: 0 • Infection: 0	Despite excellent HbA1c levels and target pre-prandial glucose levels, children often experience nocturnal hypoglycemia and postprandial hyperglycemia that are not evident with routine monitoring. Repeated use of the CGMS may provide a means to optimize basal and bolus insulin replacement in patients with type 1 DM.
Studies reported safety and adverse events for SMBG						
Belmonte (1988)	Prospective cohort (III)	N = 219 Female: 48% Mean age (± SD): 12.6 ± 5.2 years DM duration (± SD): 5.0 ± 3.9 years	• NR	To assess the effects of SMBG on the long-term glycemic control in children with type 1 DM	Fingertip exam:**** • No stab marks: 23% • < 10 stab marks: 23% • ≥ 10 stab marks: 55%	Simple teaching and a physician's recommendation to use SMBG are not sufficient to improve glycemic control.

CGM: continuous glucose monitoring; CSII: continuous subcutaneous insulin infusion; CT: conventional therapy (i.e. ≤ 3 daily injections); DKA: diabetic ketoacidosis; DM: diabetes mellitus; DRCN: Diabetes Research in Children Network Study; MDI: multiple daily injections; NR: not reported; SD: standard deviation; SMBG: self-monitoring of blood glucose.
*Adjusted for baseline A1c value and age.
†A1c target < 8.0% for 8−12 year olds and < 7.5% for 13−17 year olds.
‡Demographics and results are reported for the 8–14 year age group only. In total there were 232 subjects, 53% female, age range 8–72 years.
§Mean values were estimated from figure 1 in article.
**Adjusted for baseline A1c.
††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.
‡‡‡Only 32 in 4-week trial group answered questionnaire; only eight with long-term use answered questionnaire.
§§§Numbers estimated from figure.
****Percentages do not sum to 100 due to rounding.

Observational studies reporting an association between frequency of intermittent blood glucose monitoring

Study	*Confounders adjusted for*	*Association*	*Direction of association*
McGrady 2009	Depression; patient's age, sex, ethnicity, duration of diabetes, mode of insulin delivery; caregiver's education, insurance, and marital status; clinical site; availability of meter download	Lower levels of SMBG were associated with higher A1c ($\beta = -0.39$; $p < 0.001$)	The more often patients tested their blood glucose, the lower their A1c.
Marvicsin 2008	None	The number of blood glucose tests in the past month negatively correlated with metabolic control $r = -0.71$; $p< 0.01$	The more often patients tested their blood glucose, the lower their A1c.
Miller 2007	None	Frequency of SMBG correlated with A1c ($r = -0.36$; $p < 0.01$)	The more often patients tested their blood glucose, the lower their A1c.
Lewandowski 2007	None	Frequency of SMBG correlated with A1c ($r = -0.09$; NS)	The more often patients tested their blood glucose, the lower their A1c.
Miller 2003	None	Frequency of SMBG correlated with GHg ($r = -0.17$; NS)	The more often patients tested their blood glucose, the lower their A1c.
Studies reporting association between A1c and frequency of SMBG (assessed by physician or patient report)			
Nordly 2005	Age, sex, duration of diabetes, interaction between parents' ethnic background and occupational status	Increased frequency of SMBG was associated with lower A1c (P=0.02)	The more often patients tested their blood glucose, the lower their A1c. The association was significant.
Rosilio 1998	For A1c: Age, duration of diabetes, BMI, insulin daily dose, number of insulin injections, number of clinic visits, number of inpatient days, parents' age, number of hypoglycemic episodes. For hypoglycemia: none	For relationship between SMBG and A1c: $r = -0.21$; $p < 0.0001$ For relationship between SMBG and hypoglycemic episodes: $r = -0.20$	The more often patients tested their blood glucose, the lower their A1c. The more often patients tested their blood glucose, the fewer their hypoglycemic episodes.
Studies reporting association between A1c and frequency of SMBG (method of assessing not reported)			
Dorchy 1997	None	Frequency of home SMBG was negatively correlated with A1c ($Z = -2.8$; $p = 0.004$)	The more often patients tested their blood glucose, the lower their A1c.
Registry study reporting association between A1c and frequency of SMBG (assessed by meter download or patient report)			
Svensson	None	An inverse relationship between number of SMBG and A1c (statistic NR)	The more often patients tested their

2008 blood glucose, the lower their A1c.

APPENDIX H:SUMMARIES OF PERIODIC CMG AND HISTORICAL SMBG STUDIES

Studies of periodic, retrospective-CGM use

Description of Randomized Controlled Trials of Continuous Glucose monitors use retrospectively

RCTs of periodic use of CGM data		
Lagarde 2006 (N=27)	**CGM arm:** CGM worn at baseline, 8 and 16 weeks for 3-days; SMBG before meals and bedtime, 1 weekly 2:00am SMBG **SMBG arm:** SMBG before meals and bedtime, 1 weekly 2:00am SMBG; blind CGM worn at baseline, 8 and 16 weeks for 3-days	**CGM:** CGM data were collected and reviewed at each visit (baseline, 2 and 4 months); therapeutic changes were based on analysis of both CGM and SMBG data **SMBG:** Therapeutic changes were based on SMBG only
Deiss 2006[1] **(N=31)**	**CGM arm:** CGM for 3 days at 0 and 12 weeks **SMBG arm:** CGM for 3 days at 0 and 12 weeks	**CGM arm:** Therapeutic changes were based on CGM **SMBG:** No information provided by authors with respect to whether or not therapeutic changes were recommended in this arm
Ludvigsson 2010 [2] **(N=27)**	**CGM arm:** CGM worn every 2 weeks for 3-days for a total of 12 weeks; plus ≥ 2 SMBG/day and 1, 7-point SMBG/week **SMBG arm:**≥ 2 SMBG/day and 1, 7-point SMBG/week; blind CGM worn every 2 weeks for 3-days for a total of 12 weeks	**CGM arm:** No information provided by authors with respect to how or if CGM data was used to make therapeutic changes; standardized insulin injection protocol and dietary recommendations **SMBG arm**: No information provided by authors with respect to how SMBG data was used to make therapeutic changes, standardized insulin injection protocol and dietary recommendations
Chase 2001 (N=11)	**CGM arm:** CGM worn for 6, 3-day periods within 30 day period plus ≥ 4 SMBG/day **SMBG arm:**≥ 4 SMBG/day	**CGM arm:** Diabetes team used CGM in conjunction with SMBG data for therapeutic changes at after each meter use; participants were asked to not change dietary practices during the study **SMBG arm:** diabetes team used SMBG data only for therapeutic changes; no information was provided b authors with respect to how often SMBG data was reviewed
Yates 2006 (N=39)	**CGM arm:** CGM worn for 3-day periods every 3 weeks for 12 weeks plus ≥ 4 SMBG/day **SMBG arm:** ≥ 4 SMBG/day	**CGM arm:** Every 3 weeks therapeutic changes suggested by investigator based on CGM and SMBG; standardized recommendations given to participants for adjustments to insulin doses based on diet, activity and blood glucose levels **SMBG arm:** Every 3 weeks therapeutic changes suggested by investigator based on SMBG only; standardized recommendations given to participants for adjustments to insulin doses based on diet, activity and blood glucose levels

[1]Cross-over trial; arms crossed over at 12 weeks without wash-out period
[2]Cross-over trial; arms crossed over at 3 months without wash-out period

Overview and appraisal

Five RCTs compared periodic use of CGM (in conjunction with SMGB) with SMBG alone and did not have patients use CGM data in real-time. These trials only provide information on use of CGM data retrospectively by providers to recommend therapeutic changes [Diess, Lagarde, Ludvigsson, Yates, Chase 2001]. 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. All are LoE II.

Lagarde et al. is also LoE II RCT comparing intermittent use of rt-CGM (CGM device not reported) as a supplement to SMBGwith SMBG alone among 27 participants age 5 to 17 years with Type 1 diabetes. In this 16-week trial, participants in the CGM arm of this trial wore an unblinded CGM and participants in the control arm wore a blinded CGM for 72-hours at weeks 0, 8 and 16 during the trial. At each visit (0, 8 and 16 weeks), therapeutic changes were made based on rt-CGM data in the CGM arm, and on SMBG data only in the control group. The primary outcomes included A1c (laboratory derived), and several measures of hyper- and hypoglycemia (Mean daily area under the CGM curve and time spent below/above target for glucose < 70 or > 180 mg/dl), which were calculated using 72-hour CGM data from unblinded meters in the CGM and blinded meters in the SMBG arm.

Two small, randomized controlled cross-over trials also compared rt-CGM to SMBG alone (Deiss, Ludvigsson). Deiss et al., a LOE II trial compared a single use of rt-CGM (MiniMed Medtronic) as a supplement to SMBGwith SMBG alone among 30 participants age 2 to 16 years with Type 1 diabetes. Participants were randomly assigned to either receive the open (unblinded) CGM (Arm A) or closed (blinded) CGMS first (Arm B). After 12 weeks, open and blinded switched. All Participants were asked to self-monitor ($\geq$ 5 times per day), and received CGM (open for CGM arm and blinded for control arm) for 3 days at baseline, 12 and 24 months. It was also not stated whether or how participants used the CGM data (during the open arm) to make therapeutic changes. This study has several important limitations. First, because of the very short duration of CGM use in this intervention, by the end of each arm (12 weeks), an intervention effect may have waned. Another limitation is the lack of wash-out period between the open and blinded arms. There is evidence that a 'carry-over' effect was present after cross-over [Deiss]; therefore, the results presented for this study exclude data after treatment arm cross-over. Lastly, it is unclear the values reported for some glucose level outcomes represent the median for a 24- or 72-hour period; therefore, it is difficult to compare these estimates across studies.

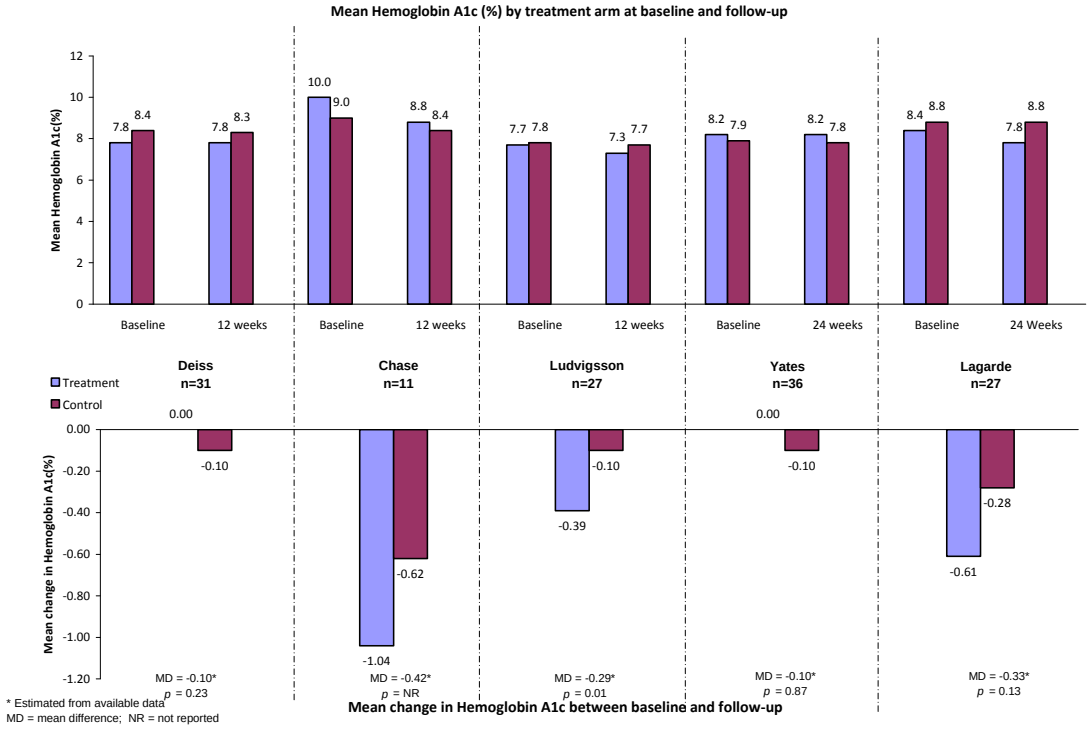
Ludvigson et al. is also a LOE II randomized controlled cross-over trial comparing compared intermittent use of rt-CGM (MiniMed, Medtronic) as a supplement to SMBGwith SMBG alone among 27 participants age 5 to 19 years with Type 1 diabetes. Participants were randomly assigned to either receive the open (unblinded) CGM or closed (blinded) CGMS first. After 12 weeks, open and blinded switched. Participants were asked to self-monitor ($\geq$ 2 times per day), and received CGM (open for CGM arm and blinded for control arm) for 3 days every two weeks throughout the trial; however, it was not stated whether or how, if, or when participants used the CGM data (during the open arm) to make therapeutic changes. Similar to Deiss et al, this study had no wash-out period before cross-over. However, in contrast to Deiss et al., the results were combined for all participants irrespective of the order in which they were randomized to treatment. Given the carry-over effect documented in Deiss et al.(REF) it is possible that results were biased by a the lack of wash-out period (REF); thus, the interpretation of this study is limited.

Yates et al. is a LoE II randomized controlled trial comparing intermittent, delayed use of CGM (MiniMed Medtronic) as a supplement to SMBGwith SMBG alone among 36 participants age 18 years old or less. Participants in the CGM arm wore a CGM for 3 days, every 3 weeks for 12 weeks total, and participants in the control group were asked to complete SMBG 4 to 6 times daily. All participants received standardized instruction about modifying insulin doses based on SMBG levels. Every 3 weeks during the trial the therapeutic changes were made based on CGM and SMBG data in the CGM arm, and on SMBG data only in the control group. Eligibility criteria includes A1c $\leq$ 10%, diabetes for at least 1 year on either SII or an MDI regimen that included glargine for at least 3 months.

Chase et al. is a LoE II randomized controlled trial comparing intermittent, delayed use of CGM (MiniMed brand, specific device not named) as a supplement to SMBGwith SMBG alone among 12 participants 10 to 17 years of age. Participants in the CGM arm wore a CGM for a total of 18 censor days within a 30-day period, and participants in the control group were asked to complete SMBG at least 4 times daily. Therapeutic changes were made based on CGM data in the CGM arm, and on SMBG data only in the control group, although it is unclear how often therapeutic changes were made for participants. Eligibility criteria includes A1c > 8% for at least 6 months prior to the trial.

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

a) Hemoglobin A1c Results across studies with regard to mean A1C (%) and mean change in A1C are provided in the figure below.



Three of five RCTs comparing periodic use of CGM to SMBG, reported greater decreases in Alc levels in CGM versus SMBG arms[Chase, Lagarde, Ludvigsson]. One small study (n=11) [Chase] reported a larger decrease in A1c levels between baseline and 12 weeks in the CGM arm (-1.04 in CGM versus –-0.62 in SMBG); however the difference in change between arms was not statistically significant (p = 0.10, calculated from available data). Although this small trial reported the largest difference in change in A1c between CGM and SMBG arms, power was limited due to the large variance in A1c levels and small sample size (n=11). Lagarde et al. also reported a larger decrease in A1c levels between baseline and 24 weeks in the CGM versus SMBG arms; however, the difference in change between baseline and follow-up between arms was not statistically significant (p = 0.13, Figure 1). In addition, (Ludvigsson et al.) reported a larger decrease in A1c levels in the CGM versus SMBG arm at 12 weeks (CGM: -0.39% versus SMBG: -0.10%); however, results were combined for all participants irrespective of the order in which they were randomized to treatment. Given the carry-over effect documented in Deiss et al.(Deiss) it is possible that results were biased by a the lack of wash-out period [Cummings 2010]; thus, the interpretation of this data is limited.

Furthermore, based on a cutpoint of greater than 0.5% as a measure of clinically meaningful change in A1c [JDRF 2008], neither of the differences in change in A1c levels between CGM and SMBG were clinically significant; although the reduction in A1c levels in the CGM arm only of the JDRF did reach the threshold of clinical significance.

Only one RCT comparing periodic use of CGM to SMBG, reported the proportion of participants in CGM and SMBG arms achieving specified A1c targets. In Yates et al., a larger proportion of participants in the CGM arm had a final A1c levels equal to or less than 7.5% (CGM: 53% versus SMBG: 47%); however, the difference between arms was not statistically significant (p=0.5).

b) Maintaining target A1c levels

All of the 5 RCTs comparing period use of CGM with SMBG were conducted in populations with mean A1c > 7% at baseline; therefore, none were able to report the effect of CGM on maintaining A1c levels.

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

None of the 5 RCTs comparing periodic use of CGM with SMBG 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

Acute episodes of hypoglycemia

Four of the 5 RCTs comparing periodic use of CGM with SMBG reported on the effect of frequency or mode of glucose monitoring on hypoglycemia.[Lagarde, Chase, Ludvigsson, Deiss] Two of these trials reported no differences between CGM and SMBG arms in the median number of excursions in blood glucose levels below 60 mg/dl (CGM:1 versus SMBG:0; p =

0.36)[Deiss], or the mean number of symptomatic episodes below 70 mg/dl (CGM:1.2 ± 2.2 versus SMBG:0.67 ± 1.0; p = 0.24)[Lagarde]. Chase et al. also reported no significant difference in the number of excursions in blood glucose levels below 60 mg/dl (CGM: 12.8 ± 1.6 versus SMBG: 6.7 ± 1.1); however, the control arm in this trial did not wear a blinded CGM thus the mean number of excursions is likely influenced by the number of actual blood glucose measures collected. Ludvigsson et al. also reported no difference in the number of excursions below 54.0 mg/dl between CGM and SMBG arms (no data provided).

In addition, two trials reported no difference between CGM and SMBG in the amount of time blood glucose levels were lower than a specific threshold.[Deiss, Lagarde] No differences were reported between CGM and SMBG arms in the amount of time blood glucose levels were lower than 60 mg/dl (CGM (median: 30 min versus SMBG: 0 minutes, p = .603)[Deiss] or lower than 70 mg/dl (CGM (mean minutes/day: 133 ± 111 versus SMBG: 84 ± 66, p = .24)[Lagarde].

Two trials also reported no differences between CGM and SMBG arms in the area under the curve for blood glucose levels lower than 60 mg/dl (CGM (median of 1 day):0 versus SMBG:0; p = 0.42)[Deiss] or 70 mg/dl (CGM (mean of 3 days): 2061 ± 1778 versus SMBG:1415 ± 1256; p = 0.18)[Lagarde].

Acute episodes of hyperglycemia

Three of the 5 RCTs comparing periodic use of CGM with SMBG reported on the effect of frequency or mode of glucose monitoring on hypoglycemia[Lagarde, Ludvigsson, Deiss]; however, one did not stratify results by treatment arm thus results were not reported for this study[Ludvigsson]. Deiss et al. reported no difference in the median number of excursions for blood glucose levels greater than 180 mg/dl between CGM and SMBG arms (CGM: 4 versus SMBG: 3; p = 0.242). Two studies also reported no differences between CGM and SMBG arms in the area under the curve for blood glucose levels greater than 180 mg/dl (CGM (median of 1 day): 620 versus SMBG:720; p=0.191[Deiss] and CGM (mean of 3 days):662 ± 229 versus SMBG:656 ± 243; p = 0.95[Lagarde]), and no difference in the amount of time blood glucose levels were greater than 180 mg/dl (CGM (median minutes): 620 versus SMBG:720 minutes; p=0.191[Deiss].

Acute episodes of diabetic ketoacidosis

None of the 5 RCTs comparing periodic use of CGM with SMBG reported on the effect of frequency or mode of glucose monitoring on diabetic ketoacidosis.

e) Reduce microvascular complications (retinopathy, nephropathy, neuropathy)

None of the 5 RCTs comparing periodic use of CGM with SMBG reported on the effect of frequency or mode of glucose monitoring on microvascular complications.

f) Reduce Mortality

None of the 5 RCTs comparing periodic use of CGM with SMBG reported on the effect of frequency or mode of glucose monitoring on mortality.

g) Effect on medication or nutritional management

With regard to clinical decision making on the part of providers, the five trials that used CGM for periodic intermittent data collection provide only limited insight into how such data impacted provider-directed changes in medication management. Three trials reported on the effect of CGM on medication management.[Deiss, Chase, Yates], two of which reported increases in medication changes during CGM compared to SMBG alone[Deiss, Chase]. Deiss et al. reported a significant difference in the number of participants altering insulin doses by day 3 of the trial (100% of CGMS versus 73% of SMBG; $p = 0.03$); however, by 3 months, the number of participants altering insulin doses was no longer statistically significant ($p > 0.10$) (Deiss). In addition, Chase et al. reported that participants in the CGM arm had a significantly greater number of insulin changes than the SMBG arm (11.5 ± 1.5 versus 5.2 ± 0.9 per month, respectively; $p = 0.001$). In contrast, Yates et al. reported no difference in the change in insulin dose between treatment arms at 12 weeks (+0.01 versus 0.03 units/kg/day, respectively; $p = 0.69$).

h) Quality of life

Only one trial comparing periodic use of CGM with SMBG alone reported on the effect on quality of life.[Chase] Chase et al. reported no significant differences in Hypoglycemia Fear Survey or Quality of Life survey scores between CGM and SMBG participants at 1 or 3 months (no data provided). There were also no significant differences in HFS or QOL scores within treatment arm between baseline and 1 or 3 months (no data provided), although the mean HFS score within the CGM arm decreased slightly between baseline and 3 months (baseline HFS score: 61.8 and 3 month HFS score: 56.6; $p>0.05$).[Chase]

SUMMARY OF HISTORICAL RCTS OF SMBG

Four clinical trials comparing urine testing with SMBG published between 1975 (when the first home glucose meter was approved) and 1987 (when the ADA published its first clinical recommendation that SMBG should replace urine glucose testing) were found. The studies and their results are shown in the tables below. Overall these studies are considered more feasibility and acceptance types of investigations. Both the urine testing and the methods for SMBG are considered to be out dated.

These studies are limited in a number of ways. The sample sizes were small (N = 16 to 86) and were highly selected from the author's clinical practice. Two studies used a double crossover design [Daneman 1985, Miller 1983], considered at that time to be a powerful study design, but each used only a t-test, a substandard analytic method, on the pre-post outcomes for each treatment group and interval. (Current recommendation for the analysis of a crossover study is to use a repeated measures ANOVA, but that computerized assessment tool was not widely available at the time.) Only one of the studies randomized the subjects into treatment groups [Miller 1983]; two used a stratified assignment based on age, sex and duration of diabetes [Daneman 1985, Mann 1984]. The fourth study recruited patients from the three physicians that were recommending SMBG and matched them to controls from patients who saw the two physicians in the practice who did not advocate SMBG [Carney].

The interventions in these studies varied. The two crossover studies provided education on SMBG technique and glucose control to the entire study population [Daneman 1985, Miller 1983], and one provided education on diabetes management to both the SMBG and urine testing group [Mann 1984], while the fourth provided education only to the SMBG group [Carney 1983]. The study by Mann was conducted in the UK and provided nurse home visits every 6 weeks to all study subjects. Structured follow-up was not mentioned in the other studies. Follow-up times ranged from 6.5 months to 18 months. Three of the four studies delineated inclusion and/or exclusion criteria and all three excluded patients diagnosed with diabetes less than 12 months prior to the start of the study in order to control for patients in their "honeymoon" phase of their diabetes [Mann 1984, Carney 1983, Miller 1983].

Summary of results

The results from these studies may show a trend toward improved glycemic control but no statistically significant improvement in A1c. 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. 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 was valuable to these children and their parents and that the pain of glucose testing and hassle of working with the meter was not a significant obstacle.

Mean glycosylated hemoglobin A_{1c} (HbA_{1c}) levels across four RCTs comparing self-monitoring blood glucose testing to standard urine testing in children.

Study/demographics		Glucose monitoring		*P*-value
		SMBG	Urine testing	
Daneman 1985				
N = 16	*Group 1**			
Male: 31.2%	baseline	10.5 ± 0.6	10.5 ± 0.6	
Age (mean): 13.1 years	3 months	10.9 ± 0.6	10.7 ± 0.6	ns
Diabetes duration (mean): 4.1 years	*Group 2**			
	baseline	9.5 ± 0.3	9.5 ± 0.3	
	3 months	10.1 ± 0.4	10.2 ± 0.4	ns
Miller 1983				
N = 19	*Group 1†*			
Male: NR	baseline	11.0	11.0	
Age (median): 13 years‡	5 months	10.5	10.5	ns
Diabetes duration: NR	*Group 2†*			
	baseline	11.2	11.2	
	5 months	10.4	11.0	ns
Mann 1984				
N = 39	baseline	14.1 ± 1.3	12.7 ± 2.0	ns
Male: 59.0%	3 months	13.5 ± 1.6	12.6 ± 2.3	ns
Age (range): 6–16 years	6 months	14.9 ± 3.0	13.6 ± 2.5	ns
Diabetes duration (mean): 5.8 years	9 months	15.4 ± 2.1	14.3 ± 2.8	ns
	12 months	14.9 ± 2.8	13.0 ± 2.8	ns
	15 months	14.8 ± 3.1	13.3 ± 2.8	ns
	18 months	14.3 ± 1.9	12.8 ± 2.4	ns
Carney 1983				
N = 86	*All patients*			
Male: NR	baseline	11.88 ± 0.28	12.04 ± 0.31	ns

Age (mean): 14.1 years	6 months	11.0 ± 0.26	11.88 ± 0.32	< .05
Diabetes duration (mean): 6.5 years	*≥ 6 months§*			
	baseline	12.18 ± 0.27	12.21 ± 0.31	ns
	9 months	10.80 ± 0.26	11.82 ± 0.35	< .01

NR = not reported; SMBG = self-monitoring blood glucose.
*Group1did urine testing plus SMBG during weeks 1–13, then urine testing only during weeks 14–26; Group 2did urine testing only during weeks 1–13, then urine testing plus SMBG during weeks 14–26.
†Group 1 did 5 months of urine testing followed by 5 months of SMBG; Group 2 did 5 months of SMBG followed by 5 months of urine testing.
‡Age given only for the initial 25 children asked to participate in the trial.
§Subgroup of patients (n = 34, 81%) who continued to test at least 2x/day 6 months or more after training.

Mean change from baseline* in glycosylated hemoglobin A_{1c} (HbA_{1c}) levels across four RCTs comparing self-monitoring blood glucose testing to standard urine testing in children.

Study/demographics		Glucose monitoring		*P*-value
		SMBG	Urine testing	
Daneman 1985				
N = 16	*Group 1*†			
Male: 31.2%	3 months	0.4 ± 0.0	0.2 ± 0.0	ns
Age (mean): 13.1 years	*Group 2*†			
Diabetes duration (mean): 4.1 years	3 months	0.6 ± 0.1	0.7 ± 0.1	ns
Miller 1983				
N = 19	*Group 1*‡			
Male: NR	5 months	-0.5 ± 2.3	-0.5 ± 2.3	ns
Age (median): 13 years§	*Group 2*‡			
Diabetes duration: NR	5 months	-0.8 ± 1.3	-0.2 ± 1.3	ns
Mann 1984				
N = 39	3 months	-0.6 ± 0.3	-0.1 ± 0.3	ns
Male: 59.0%	6 months	0.8 ± 1.7	0.9 ± 0.5	ns
Age (range): 6–16 years	9 months	1.3 ± 0.8	1.6 ± 0.8	ns
Diabetes duration (mean): 5.8 years	12 months	0.8 ± 1.5	0.3 ± 0.8	ns
	15 months	0.7 ± 1.8	0.6 ± 0.8	ns
	18 months	0.2 ± 0.6	0.1 ± 0.4	ns
Carney 1983				
N = 86				
Male: NR	6 months	-0.88 ± 0.02	-0.16 ± 0.01	< .05
Age (mean): 14.1 years	9 months**	-1.38 ± 0.01	-0.39 ± 0.04	< .01
Diabetes duration (mean): 6.5 years				

NR = not reported; SMBG = self-monitoring blood glucose.
*A negative number indicates a decrease in HbA_{1c} from baseline score.
†Group1 did urine testing plus SMBG during weeks 1–13, then urine testing only during weeks 14–26; Group 2 did urine testing only during weeks 1–13, then urine testing plus SMBG during weeks 14–26.
‡Group 1 did 5 months of urine testing followed by 5 months of SMBG; Group 2 did 5 months of SMBG followed by 5 months of urine testing.
§ Age given only for the initial 25 children asked to participate in the trial.
**Subgroup of patients (n = 34, 81%) who continued to test at least 2x/day 6 months or more after training.

APPENDIX I . PEER REVIEWERS

The individuals listed below have agreed to provide clinical and/or peer review.

This role should not be construed to mean that the individuals were authors or contributors to the formulation of the draft, nor does it imply endorsement, approval, or disapproval of the process or report.

Individual	Expertise/Experience
Dace Trence, MD, FACE Director, Diabetes Care Center, University of Washington Endocrine Fellowship Director, University of Washington	▪ MD, University of Minnesota Medical School ▪ Endocrine Fellowship, University of Minnesota, Minneapolis, Minnesota ▪ Board Certifications: American Board of Internal Medicine, American Board of Endocrinology and Metabolism ▪ Over 30 years of experience in medicine, teaching and professional activity related to diabetes ▪ Over 20 years of experience in direction/management of clinical departments
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