Washington State Health Care Authority

Continuous glucose monitoring - update

Clinical Expert

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Personal Data:

Place of Birth: Pomona, CA
Citizenship: USA

Education:

1991-1995	*Medical School (MDCM) Class of 1995* *McGill University, Faculty of Medicine, Montreal, Quebec, Canada*
1987-1991	*Graduate Studies Research, Faculty of Science* *McGill University, Montreal, Quebec*
1984-1987	*B.Sc. Immunology* *McGill University, Faculty of Science, Montreal, Quebec*

Postgraduate Training:

7/1999-6/2001	Fellow Metabolism, Endocrinology and Nutrition, University of Washington
7/1998-6/1999	Fellow Endocrinology and Metabolism, McGill University Hospital Centers, Montreal, Quebec, Canada Chief Medical Resident, Royal Victoria Hospital, Montreal, Quebec (12/98-6/99)
7/1995-6/1998	Resident Internal Medicine, Royal Victoria Hospital, Montreal, Quebec

Faculty Positions Held:

2008-	Associate Professor, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington, Harborview Medical Center, Seattle, Washington
2002-2008	Assistant Professor, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington, Harborview Medical Center, Seattle, Washington
2001-2002	Acting Instructor, Division of Metabolism, Endocrinology and Nutrition. University of Washington

Hospital Positions Held:

2001-	Attending Physician, Harborview Medical Center and University of Washington Medical Center
2007-	Director HMC Glycemic Control Service

Honors:

1987	B.Sc. with First Class Honors
1988-91	McGill Major Fellowship, FCAR Fellowship, MRC Fellowship
1992-94	McConnell Award for Academic Achievement in Medicine (three times)

1992	Leukemia Research Award
1995	MDCM, Dean's Honor List, Cushing Prize
1997	Resident Research Award
1998	Resident Teaching Award
2000	Endocrine Fellows Foundation Grant

Current Employment: N/A

Medical Certificates:

1998	ABIM, Board Certification in Internal Medicine
2001	ABIM, Board Certification in Endocrinology, Diabetes and Metabolism
2011	ABIM, Re-certification Endocrinology, Diabetes and Metabolism

Licenses:

Washington State Medical License	1999
US Medical License	1997

Professional Organizations:

North American Association for the Study of Obesity	2000
Endocrine Society	2001
Western Society of Clinical Investigation	2007

Teaching Responsibilities:
MCBD Block Director, teaching carbohydrate, protein and lipid metabolism
Energetics and Homeostasis Block - lecturer

Mentorship:
First year Endo Fellows clinical research project: (last 5 years)
Jean-Jacques Nya-Ngatchou, Jane-Frances Chukwu, Marisela Noorhasan, Jeff Vercollone, Jennifer Rosenbaum
Clinical research projects:
Luisa Duran, MD (Fellowship Research Project 2012-2013)
Glycemic Control projects (Liz Berggren, Sean McCliment, Rachel Thompson, Scott Binns)
Basic science research projects:
Carlos Campos, PhD (NCI R21) – post-doc with R. Palmiter

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Washington State Health Care Authority

Agency medical director comments

Continuous glucose monitoring - Update

Daniel Lessler, MD, Chief Medical Officer
Washington Health Care Authority
January 19, 2018

Continuous Glucose Monitoring (CGM)

CGM results provide real-time information about glucose levels that, when correlated with physical activity, diet, and insulin dose, may enable better blood glucose control in patients with diabetes

Continuous Glucose Monitoring (CGM)

- Continuous glucose monitoring systems (CGM) measure glucose in interstitial fluid
- Three components:
  - Glucose sensor, inserted subcutaneously
  - Transmitter
  - Receiver (type of monitor)
- Allows measurement of interstitial glucose every few minutes
  - Interstitial glucose correlates well with plasma glucose
  - CGM BG-levels lag plasma levels
- Flash CGM (FCGM) – no passive alerts; data/alert only if sensor scanned

Continuous glucose monitoring - update 3

Continuous Glucose Monitoring (CGM)

- Update to 2011 report which focused on self-monitoring of blood glucose (SMBG) in those 18 years old or younger who require insulin
- Update includes real-time continuous glucose monitoring in persons of any age with type 1 or type 2 DM; and, women with diabetes during pregnancy (pre-existing or gestational)

Continuous glucose monitoring - update 4

Agency Medical Director Concerns

- **SAFETY =** Medium
- **EFFICACY =** High
- **COST =** High

Continuous glucose monitoring - update

Key Questions

In persons with DM:

1. What is the evidence of efficacy and effectiveness of continuous monitoring?
2. What is the evidence of the safety of continuous glucose monitoring?
3. What is the evidence that glucose monitoring has differential efficacy or safety issues in subpopulations?
4. What is the evidence of cost-effectiveness of continuous glucose monitoring?

Continuous glucose monitoring - update 6

PICO Scope: Inclusion Criteria

- Population: Persons with DM; type 1, type 2, pregnant women with pre-existing diabetes or gestational diabetes
- Intervention: FDA-approved continuous glucose monitoring devices and FDA-approved combination devices integrating real-time continuous glucose monitoring with insulin pump/infusion
- Comparators: Self-monitoring using conventional blood glucose meters, attention control, blinded or sham CGM and usual care

CGM Costs

- CGM -- $1000 - $2000 for device
- Sensors and other supplies $350-$450 per month (though prices for supplies for newer devices are less)

2013 -2016 PEBB/ UMP
Paid Dollars by Year for CGM and Related Items
(CPT/HCPCS)

	Annual Unique Patients	**256**	**332**	**456**	**618**	
Proc Code HCPCS	**Description**	**2013**	**2014**	**2015**	**2016**	**TOTAL**
A9276	SENSOR; INVASIVE (E.G. SUBCUTANEOUS), DISPOSABLE, FOR USE WITH INTERSTITIAL GLUCOSE MONITORING	$183,610	$351,509	$570,434	$824,323	**$1,929,876**
A9277	TRANSMITTER; EXTERNAL, FOR USE WITH INTERSTITIAL CONTINUOUS GLUCOSE MONITORING	$46,396	$78,605	$122,773	$185,850	**$433,624**
A9278	RECEIVER (MONITOR); EXTERNAL, FOR USE WITH INTERSTITIAL CONTINUOUS GLUCOSE	$19,337	$22,884	$37,796	$57,752	**$137,769**
	Grand Total	**$249,343**	**$452,998**	**$731,003**	**$1,067,925**	**$2,501,269**

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2014 -2016 Medicaid MCO
Paid Dollars by Year for CGM and Related Items (CPT/HCPCS

Proc Code – HCPCS	Description	2014	2015	2016	Total
A9276	SENSOR	$719,681	$1,927,402	$3,255,554	**$5,902,637**
A9277	TRANSMITTER	$207,403	$347,211	$725,258	**$1,279,872**
A9278	RECEIVER	$67,185	$108,193	$250,292	**$425,670**
	Grand Total	**$994,269**	**$2,382,806**	**$4,231,104**	**$7,608,179**

Continuous glucose monitoring - update 10

Overall Summary: CGM in People with Type 1 DM

- Children and Adolescents (<18 yo): CGM improves HbA1C control short term (3 months), without worsening hypoglycemia; some evidence of improvement in HbA1C at 6 months (e.g. more recent cross-over trial, Battelino et al, 2012.)
- In adults, CGM improves HbA1C control up to 1 year, without worsening hypoglycemia
- In adults, CGM reduces the time spent with "biochemical" hypoglycemia at 3 and 6 months

Continuous glucose monitoring - update 11

Overall Summary: CGM in Adults with Type 2 DM

- Improvement in HbA1C control at 3 and 6 months
- No difference in minutes per day spent with "biochemical" hypoglycemia (BG < 70 mg/dl)

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CGM in Pregnancy

- Pre-existing Type 1 diabetes
  - Decreases C-section rate
  - Decreases admission to NICU
  - No effect on time spent in hypoglycemia
- Pre-existing Type 2 diabetes
  - Insufficient evidence to evaluate differences in outcome between CGM and SMBG (1 small trial)
- Gestational diabetes
  - Insufficient evidence to evaluate differences in outcome between CGM and SMBG (1 small trial)

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"Flash" CGM Evidence

- Strength of evidence insufficient for "Flash" CGM
  - Available data insufficient to determine effect on HbA1C control (1 study showed no difference)
  - Available data insufficient to determine effect on hypoglycemia (1 study associated with less time spent in hypoglycemic range $\leq$55 mg/dl)

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CGM Safety

- Most common adverse effects include skin related reactions/irritation that are generally not serious
- More serious adverse events include cellulitis and skin abscess, relatively rare across 9 trials (0% - 9%)
- Device malfunction (including those that are sensor related) is the other category of safety related adverse events
  - Wide variability in clinical trials
  - The overall incidence of device malfunction related adverse events is not known as numbers of CGM sold and operating is unknown
  - Nature of reporting varies across manufacturers (i.e. reporting not standardized)*

* Diabetologia (2017) 60:2319-2328

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Important Context

- Most trials conducted in “efficacy” context; “real world” outcomes may differ
- Which patients may benefit most from CGM is unclear
  - Available data suggests importance of patient regularly using the device (e.g. “most days” of the week)
  - Role of patient motivation, education, self-management plan and reinforcement/follow-up not well defined
- Longer term studies (>1 year) of the impact of CGM on HbA1C control and hypoglycemia are lacking
- No long term data on disease outcomes
  - Given the length of time and number of patients required for such studies, and the known relationship between HbA1C and clinical outcomes, HbA1C appears to be a reasonable surrogate
- Rapidly changing technology that out paces evaluative studies

Continuous glucose monitoring - update 16

CGM: Cost-Effectiveness

- Available CE models show wide range of results, depending on assumptions
- With favorable assumptions, CGM appears cost-effective for Type 1 DM and Type 2 DM, assuming willingness to pay <$100,00/QALY

CGM Clinical Guidelines: National Organizations

- Endocrine Society - Children
  - Recommends RT-CGM be used by children and adolescents with T1DM who have achieved HbA1C levels below 7.0% b/c it will assist in maintaining target HbA1C levels while limiting the risk of hypoglycemia
  - Recommends RT-CGM for children and adolescents with T1DM who have HbA1C levels ≥ 7.0% and are able to use devices on a near daily basis
  - No recommendation for or against the use of RT-CGM by children with T1DM who are < 8 y.o.

CGM Clinical Guidelines: National Organizations

- Endocrine Society – Adults
  - RT-CGM is recommended for adult patients with T1DM who have A1C levels above target and who are willing and able to use devices on a nearly daily basis
  - RT-CGM is recommended for adult patients with well-controlled T1DM who are willing and able to used devices on a nearly daily basis
  - It is suggested that short-term intermittent RT-CGM is used in adult patients with T2DM (not on prandial insulin) who have HbA1C levels ≥ 7.0% and are willing and able to use the device

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CGM Clinical Guidelines: National Organizations

- American Association of Clinical Endocrinologists and American College of Endocrinology
  - CGM should be considered for patients with T1DM and T2DM on intensive insulin therapy to improve A1C levels and reduce hypoglycemia
  - CGM may benefit patients not taking insulin

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CGM Clinical Guidelines: National Organizations

- Endocrine Society 2013 – Diabetes and pregnancy
  - CGM is suggested for use during pregnancy in women with overt or gestational diabetes when self-monitored glucose levels (or HbA1C values in women with overt diabetes) are not sufficient to assess glycemic control

Medicare National Coverage Decision

- "Non-Therapeutic" CGMs that are used as an adjunct to BGM (i.e. therapeutic decisions regarding diabetes treatment must be made with standard home BGM, not the CGM) are NOT covered as DME
- "Therapeutic CGMs," defined as a CGM used as a replacement for fingerstick glucose testing are covered as DME for patients with diabetes who have been performing SMBG $\geq$ 4X/day and is insulin treated with multiple daily injections or continuous infusion pump
  - Dexcom G5 and FreeStyle Libre are currently the only FDA-approved devices with a therapeutic (or "non-adjunctive") indication

CGM: Commercial Insurance Coverage Policies

- **Kaiser Washington**
  - Covered for people with type 1 and type 2 diabetes who, despite adherence to an appropriate glycemic management plan (customized basal-bolus insulin regimen; testing BG 4 ≥ per day; competent problem-solving skills; carbohydrate counting and appropriate meal management) have:
    - History of hypoglycemia unawareness within the past 3 yrs resulting in frequent and severe hypoglycemia; or
    - History within the past 3 yrs of frequent and severe hypoglycemia
    - Request must be made by an endocrinologist

CGM: Commercial Insurance Coverage Policies

- **Blue Cross – Blue Shield**
  - CGM may be considered medically necessary for:
    - Patients with type 1 DM who have demonstrated an understanding of the technology, are motivated to use the device, are expected to adhere to a comprehensive DM rx plan supervised by a qualified provider, and are capable of using the device to recognize alerts and alarms, or
    - Patients with type 1 DM who have recurrent, unexplained hypoglycemia (BG < 50 mg/dl), or impaired hypoglycemia awareness
    - Patients with poorly controlled type 1 DM who are pregnant

HTCC 2011: Glucose Monitoring for Insulin Dependent Individual Under 19 Years of Age

- Continuous glucose monitoring (CGM) is a covered benefit for diabetes mellitus (DM) patients under 19 using insulin when the following conditions are met:
  - Suffering from one or more severe episodes of hypoglycemia
  - Enrolled in an IRB approved trial

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AMDG CGM Recommendation: Children/Adolescents < 19 y.o.

- Continuous glucose monitoring (CGM) is a covered benefit for children/adolescents under 19 with Type 1 diabetes when the following conditions are met:
  - Unable to achieve target HbA1C despite adherence to an appropriate glycemic management plan (intensive insulin therapy; testing BG 4 or more times per day); OR
  - Suffering from one or more severe (BG < 50 mg/dl or symptomatic) episodes of hypoglycemia despite adherence to an appropriate glycemic management plan (intensive insulin therapy; testing BG 4 or more times per day) ; OR
  - Inability to recognize, or communicate about, symptoms of hypoglycemia

Continuous glucose monitoring - update

AMDG CGM Recommendation: Adults Type 1 Diabetes

- Continuous glucose monitoring (CGM) is a covered benefit for adults with type 1 diabetes patient when the following conditions are met:
  - Unable to achieve target HbA1C despite adherence to an appropriate glycemic management plan (intensive insulin therapy; testing BG 4 or more times per day); OR
  - Suffering from one or more severe (BG < 50 mg/dl or symptomatic) episodes of hypoglycemia despite adherence to an appropriate glycemic management plan (intensive insulin therapy; testing BG 4 or more times per day) ; OR
  - Inability to recognize, or communicate about, symptoms of hypoglycemia

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AMDG CGM Recommendation: Adults Type 2 Diabetes

- Continuous glucose monitoring (CGM) is a covered benefit for adults with type 2 diabetes patient when the following conditions are met:
  - Unable to achieve target HbA1C despite adherence to an appropriate glycemic management plan (intensive insulin therapy; testing BG 4 or more times per day); OR
  - Suffering from one or more severe (BG < 50 mg/dl or symptomatic) episodes of hypoglycemia (intensive insulin therapy; testing BG 4 or more times per day) ; OR
  - Inability to recognize, or communicate about, symptoms of hypoglycemia

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AMDG CGM Recommendation: Pregnant Women with Diabetes

- Covered for pregnant women with type 1 diabetes;
- Covered for pregnant women with type 2 diabetes on insulin prior to pregnancy;
- Covered for pregnant women with type 2 diabetes whose BG does not remain well controlled (HbA1C above target or experiencing episodes of hyperglycemia or hypoglycemia) on diet and/or oral medications during pregnancy and require insulin;
- Covered for pregnant women with gestational diabetes whose blood sugar is not well controlled (HbA1C above target or experiencing episodes of hyperglycemia or hypoglycemia) during pregnancy and require insulin

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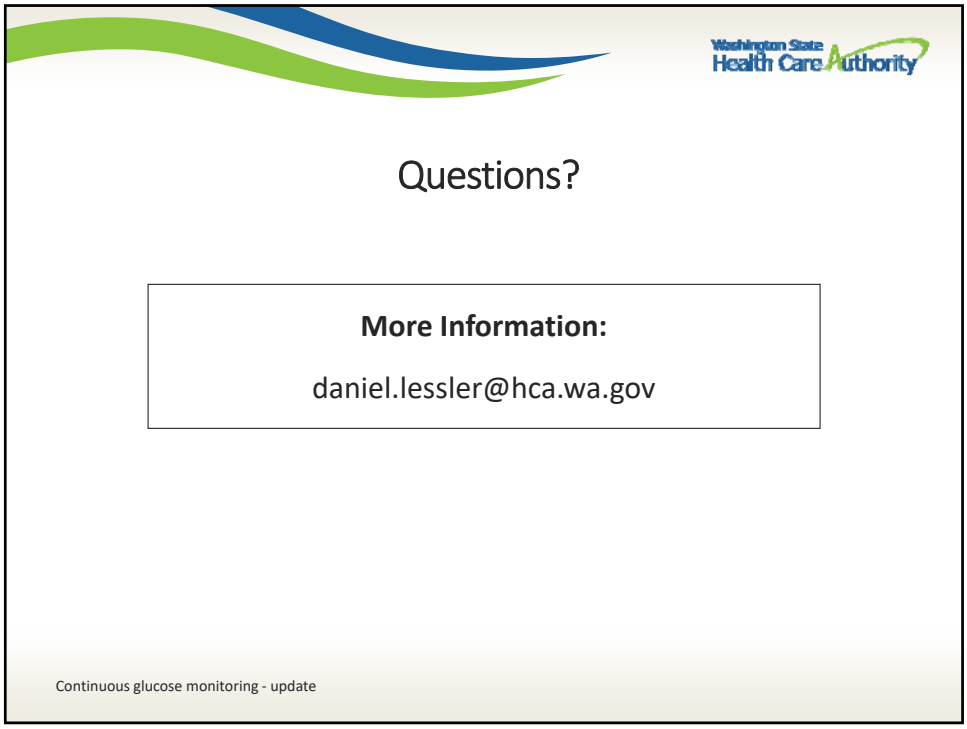
AMDG Recommendation: Flash CGM

- CGM with a “flash” device is not covered

Continuous glucose monitoring - update 30


Washington State Health Care Authority
Questions?
More Information:
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Order of scheduled presentations

Continuous glucose monitoring – update

	Name	Affiliation
1	Tomas Walker, MD	Dexcom
2	Catherine Pihoker, MD	Seattle Children's Hospital
3	Amy Bronstone, PhD	AB Medical Communications
4	Molly Carlson, MD	Division of Endocrinology, University of Washington School of Medicine
5	Refaat Hegazi	Abbott Diabetes Care
6	Zoe Alfaro	
7	Richard Hellmund	Abbott Diabetes Care
8	Irl Hirsch, MD	University of Washington School of Medicine

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.	X	
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.	X	

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am an employee of and stockholder in Dexcom , Inc.

I am the Senior US Medical Director for Dexcom, Inc.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	X	

If yes to #7, provide name and funding Sources:

I am an employee of and stockholder in Dexcom, Inc manufacturer of the Dexcom G5 Mobile Continuous Glucose Monitoring system.

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[redacted] 18 Dec 2017 Tomas C Walker, DNP, APRN

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: twalker @dexcom.com

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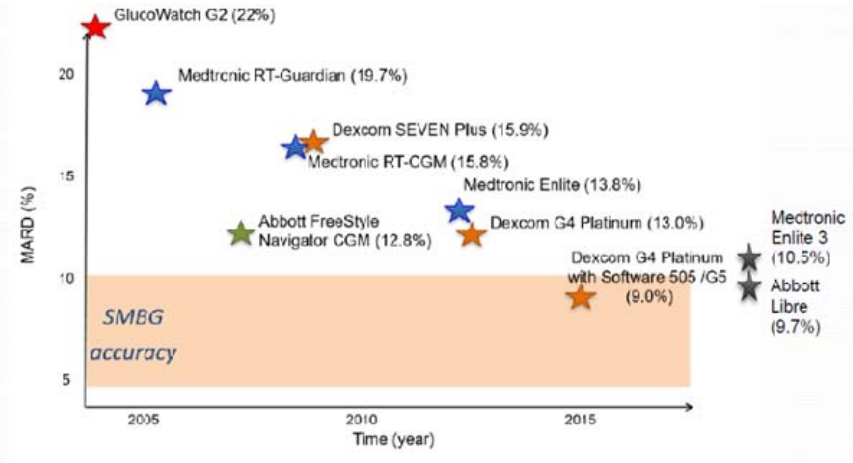
Meta-Analyses are Inappropriate Tools for Evolving Technology

1. CGM has evolved 4 generations since 2007
2. Accuracy, reliability, and performance are all significantly improved
   - CGM today is recognized as reliable and accurate enough to replace fingersticks for routine decision making
3. Health technology assessments should focus on current clinical trials with technology available today
   - Not pooling discontinued and current devices

Price, D., Graham, C., Parkin, C. G., & Peyser, T. A. (2016). Are systematic reviews and meta-analyses appropriate tools for assessing evolving medical device technologies?. Journal of diabetes science and technology, 10(2), 439-446.

Significant Evolutions in Performance

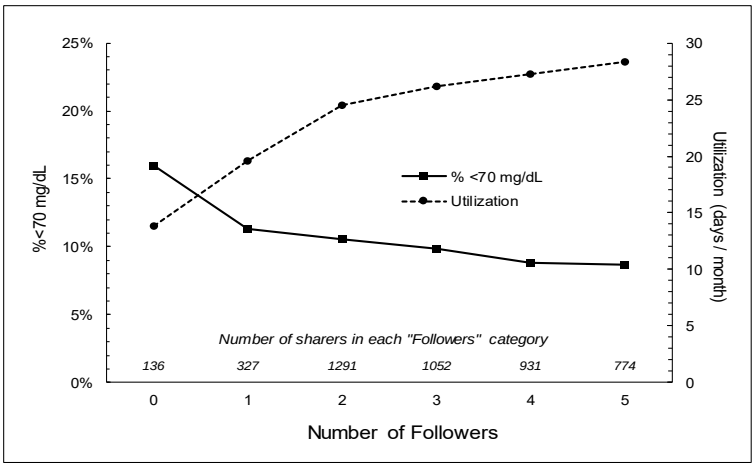


- Rapid evolution renders meta-analysis difficult
- Previous generations of technology are no longer available

Remote Monitoring

Allows parents or caregivers to monitor glucose remotely

Does Remote Monitoring Impact Care?



N=4511, Aged 2-10yo

Parker AS, Welsh JB, Hutchings M, Jimenez A, Walker T. Hypoglycemic exposure among children using the Dexcom Share Cloud. Poster presented at: Diabetes Technology Meeting; November 2, 2017; Bethesda, MD.

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		X
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.	X	
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

research funding from NIDDK, CDC

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources:

(Unsure if this is a conflict - I am on medical staff at Seattle Children's hospital + faculty at UW)

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 12/18/17 Catherine Pihoker MD

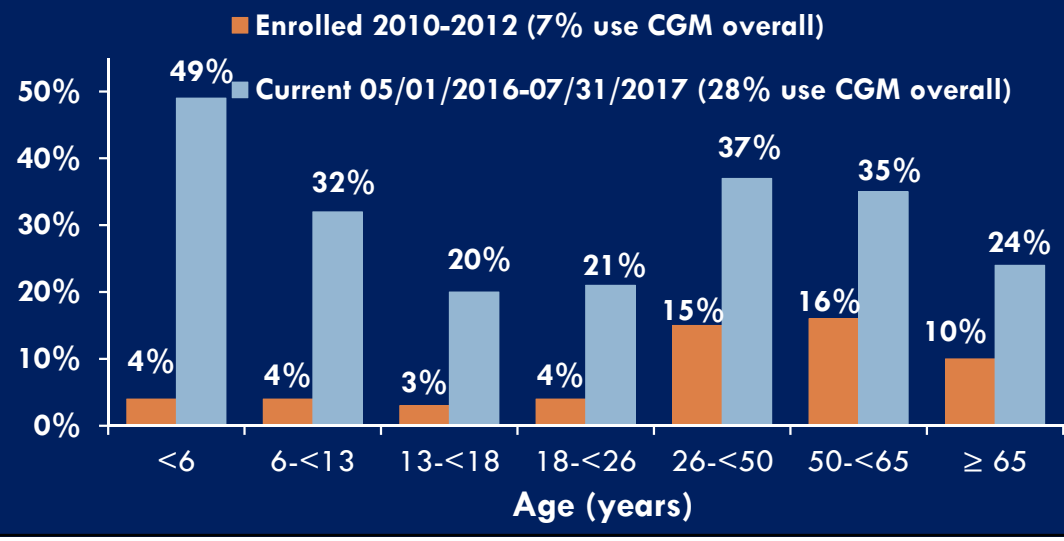
Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

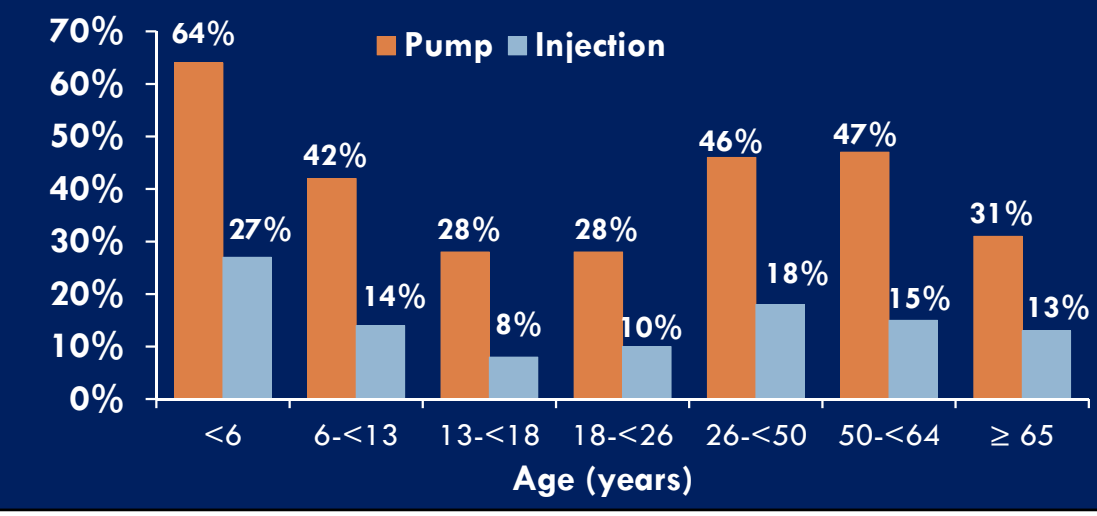
Email Address: catherine.pihoker@seattlechildrens.org

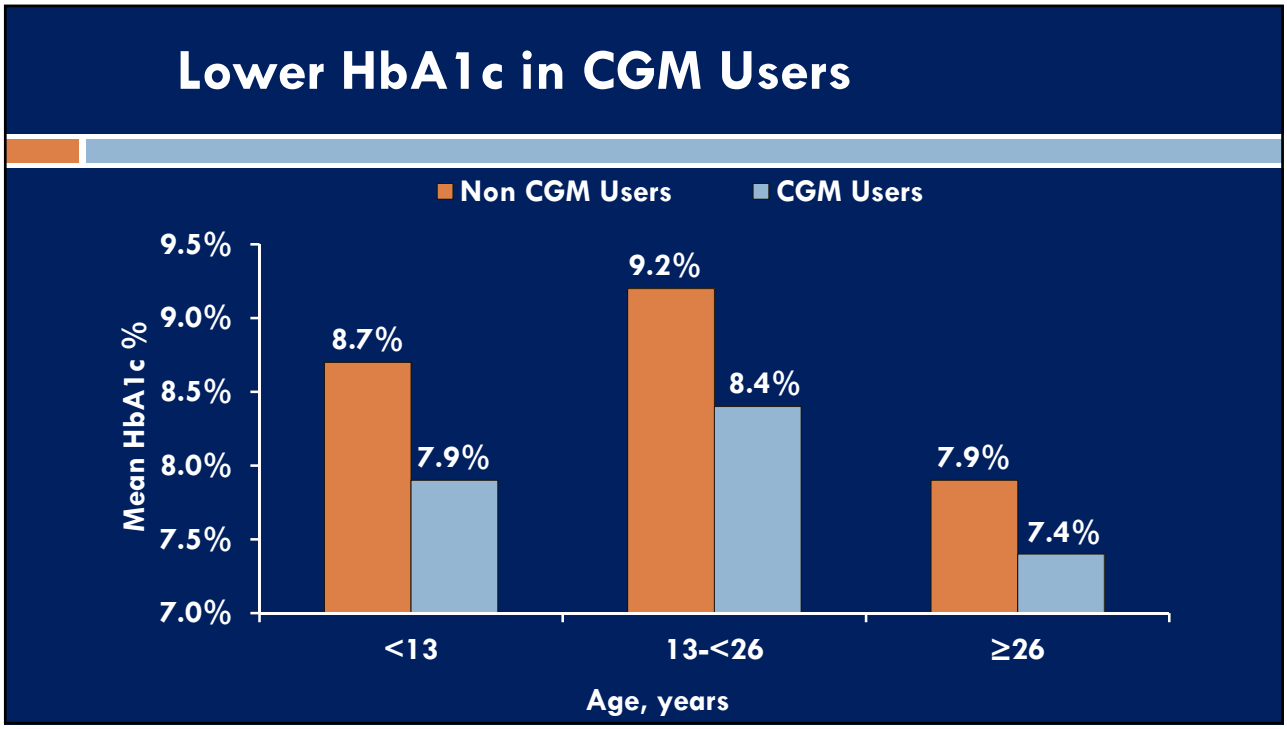
Phone Number: [redacted]

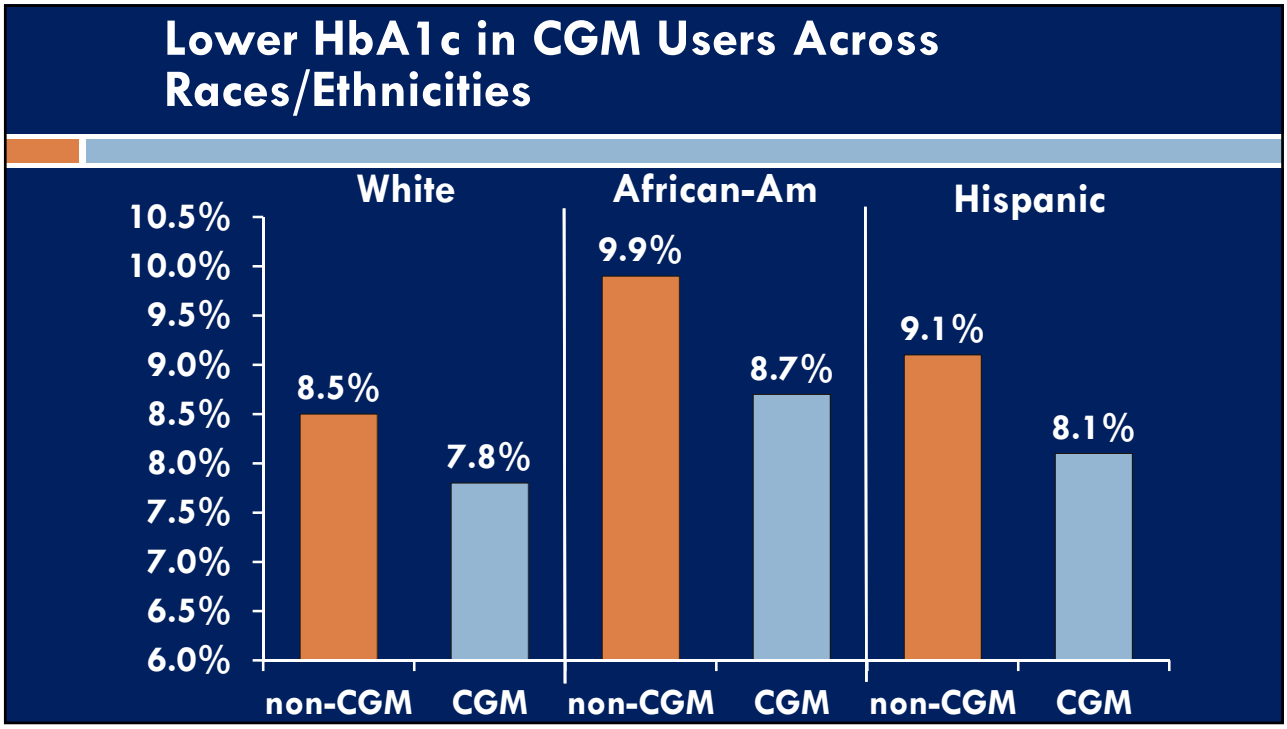
CGM Use Is Increasing But Still Low



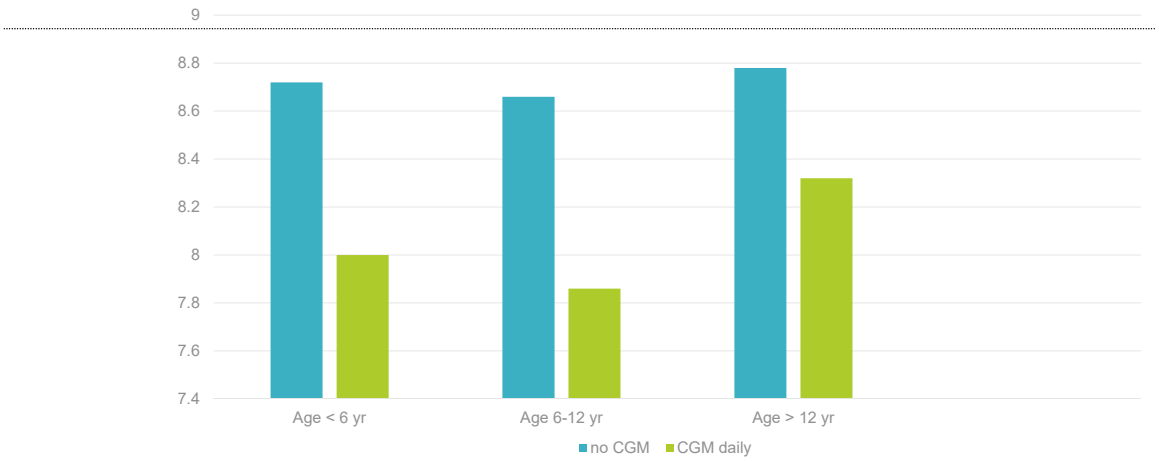
CGM Use by Insulin Delivery Method




Lower HbA1c in CGM Users
Non CGM Users
CGM Users
Mean HbA1c %
9.5%
9.0%
8.5%
8.0%
7.5%
7.0%
8.7%
7.9%
9.2%
8.4%
7.9%
7.4%
<13
13-<26
≥26
Age, years

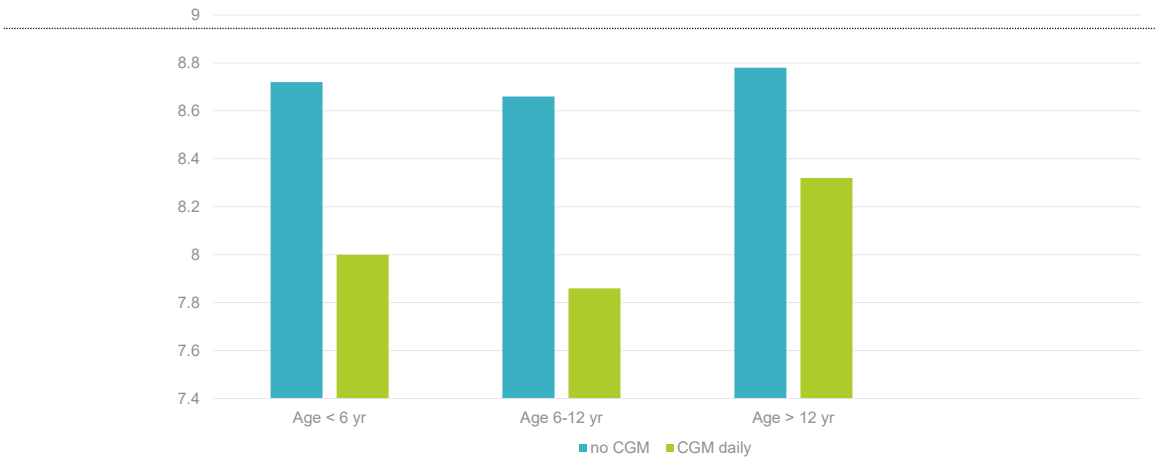

Lower HbA1c in CGM Users Across Races/Ethnicities
White
African-Am
Hispanic
10.5%
10.0%
9.5%
9.0%
8.5%
8.0%
7.5%
7.0%
6.5%
6.0%
8.5%
7.8%
9.9%
8.7%
9.1%
8.1%
non-CGM
CGM
non-CGM
CGM
non-CGM
CGM

HbA1C by CGM use by age group

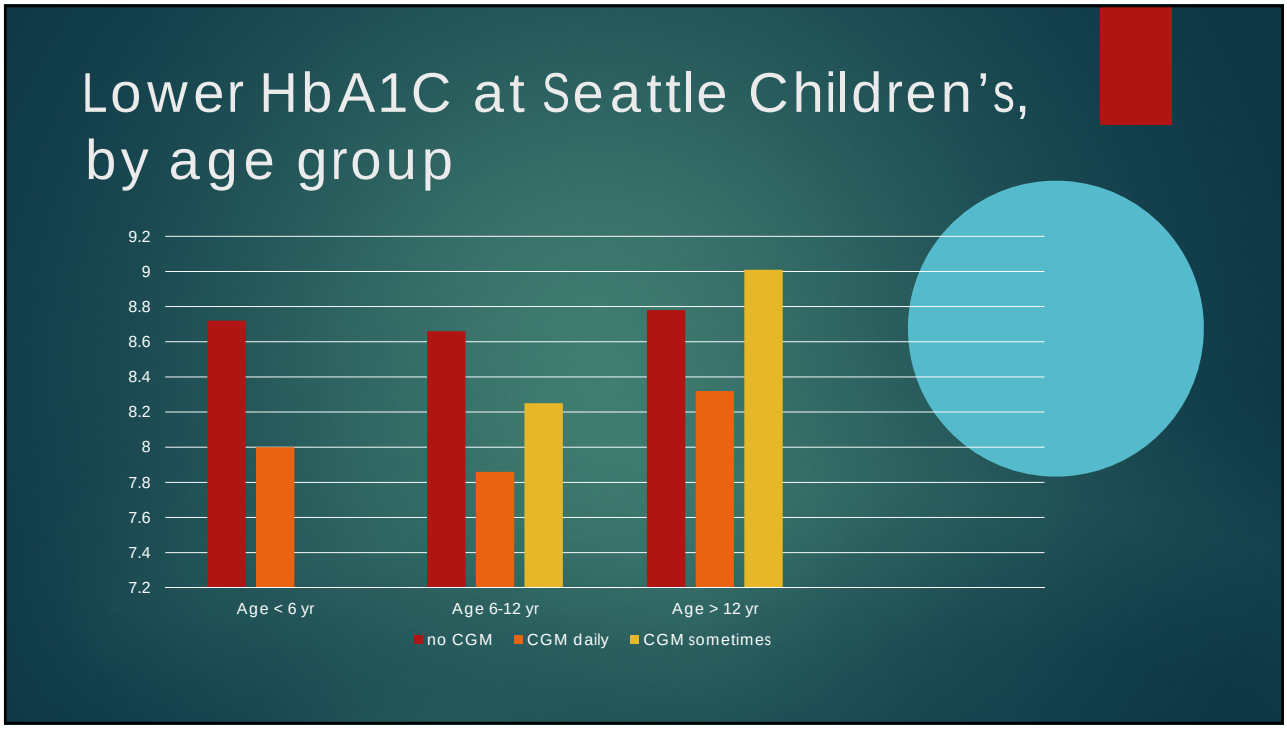


Seattle Children's HOSPITAL • RESEARCH • FOUNDATION | UW Medicine SCHOOL OF MEDICINE

HbA1C by CGM use by age group



Seattle Children's HOSPITAL • RESEARCH • FOUNDATION | UW Medicine SCHOOL OF MEDICINE


Lower HbA1C at Seattle Children's, by age group
9.2
9
8.8
8.6
8.4
8.2
8
7.8
7.6
7.4
7.2
Age < 6 yr
Age 6-12 yr
Age > 12 yr
no CGM
CGM daily
CGM sometimes

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I provide consulting services to Dexcom, Inc.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	X	

If yes to #7, provide name and funding Sources: Dexcom, Inc.

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[redacted] 12-19-2017 Amy Bronstone

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: amy@abmedcom.com

Phone Number: 510-381-2498

Target Population

People with insulin-treated diabetes who have impaired awareness of hypoglycemia (IAH)

Enrollees with Diabetes **(107,170)**

Enrollees with Insulin-treated Diabetes **(34,756)**

Enrollees with Insulin-treated Diabetes with IAH **(4464)**

Model Parameters

Annual rate of severe hypoglycemia
(number per patient-year)

Patients without IAH		Patients with IAH	
Adults	1.0-1.1	Adults	5.0-6.2
Children	0.12-0.3	Children	0.5-0.6

% of severe hypoglycemia events requiring emergency treatment

% of severe hypoglycemic episodes requiring hospitalization	% of severe hypoglycemic episodes requiring an ER visit	% of severe hypoglycemic episodes requiring ambulance transport
Type 1 diabetes 5.0%	Type 1 diabetes 9.5%	Type 1 diabetes 23.3%
Type 2 diabetes 12.9%	Type 2 diabetes 20.7%	Type 2 diabetes 31.0%

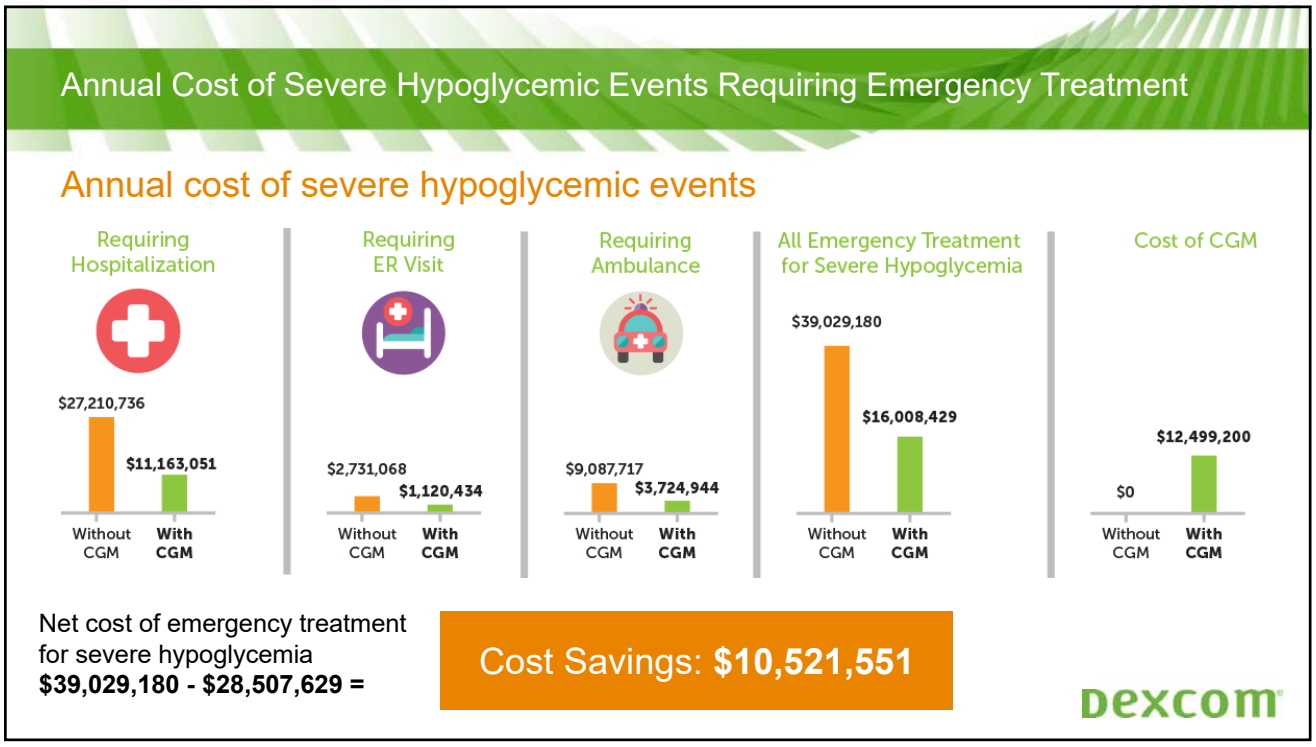
% reduction in severe hypoglycemic episodes conferred by CGM

AVERAGE COST of a Hypoglycemia-related:

Hospitalization	Ambulance Transport	ER visit
$12,787	$1704	$777

Annual cost of CGM per patient: **$2800**

Dexcom


Annual Cost of Severe Hypoglycemic Events Requiring Emergency Treatment
Annual cost of severe hypoglycemic events
Requiring Hospitalization
$27,210,736
$11,163,051
Without CGM
With CGM
Requiring ER Visit
$2,731,068
$1,120,434
Without CGM
With CGM
Requiring Ambulance
$9,087,717
$3,724,944
Without CGM
With CGM
All Emergency Treatment for Severe Hypoglycemia
$39,029,180
$16,008,429
Without CGM
With CGM
Cost of CGM
$0
$12,499,200
Without CGM
With CGM
Net cost of emergency treatment for severe hypoglycemia
$39,029,180 - $28,507,629 =
Cost Savings: $10,521,551
dexcom

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		X
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources:

If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may ***attach additional sheets*** *explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[redacted] 12/20/17 Molly Carlson, M.D.

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: mollyc@uw.edu

Phone Number: 206-598-4882

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.	X	
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Abbott Diabetes Care

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 12/29/17 Refaat Hegazi

Signature Date Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: refaat.hegazi@abbott.com

Phone Number: 614-208-9389

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	x	
2.	Equity interests such as stocks, stock options or other ownership interests.	x	
3.	Status or position as an officer, board member, trustee, owner.		x
4.	Loan or intellectual property rights.		x
5.	Research funding.		x
6.	Any other relationship, including travel arrangements.		x

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Abbott Diabetes Care

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		x

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 12/21/17 RICHARD HELLMUND

Signature *Date* *Print Name*

So we may contact you regarding this information, please provide the following:

Email Address: richard.hellmund@abbott.com

Phone Number: 510 520 8274

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		No
2.	Equity interests such as stocks, stock options or other ownership interests.		No
3.	Status or position as an officer, board member, trustee, owner.		No
4.	Loan or intellectual property rights.		No
5.	Research funding.		No
6.	Any other relationship, including travel arrangements.	Yes	

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am a part of the Dexcom ambassador program, Dexcom Warriors. With this relationship I help to spread diab
awareness and education. I am disclosing that my travel arrangements have been paid by Dexcom for this mee

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	Yes	

If yes to #7, provide name and funding Sources:

Dexcom, no funding sources applicable.

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X Zoe Alfaro (*Signature*) Dec 20 2017 (*Date*) Zoe Alfaro (*Print Name*)

So we may contact you regarding your presentation, please provide the following:

Email Address: zv1995@yahoo.com

Phone Number: 707-225-1398

Applicant Name	Irl Hirsch
Address	14310 SE 63rd St
	Bellevue, WA 98006

1. Business Activities

(a) If you or a member of your household was ***an officer or director of a business*** during the immediately preceding calendar year and the current year to date, provide the following:

Title	Business Name & Address	Business Type

(b) If you or a member of your household ***did business under an assumed business name*** during the immediately preceding calendar year or the current year to date, provide the following information:

Business Name	Business Address	Business Type

2. Honorarium and Research Funding

If you ***received an honorarium of more than $100*** during the immediately preceding calendar year and the current year to date, list all such honoraria:

Received From	Organization Address	Service Performed
Abbott Diabetes Care	1360 S Loop Rd, Alameda, CA 94502	Consultant
Roche	9115 Hague Road PO Box 50457 Indianapolis, IN 46250	Consultant
BigFoot	1561 Buckeye Drive Milpitas, CA 95035	Consultant
Adocia	115 avenue Lacassagne 69003 Lyon France	Consultant
Medtronic Diabetes	18000 Devonshire Street, Northridge, CA 91325	Research funding to UW

3. Sources of Income

(a) Identify ***income source(s) that contributed 10% or more of the combined total gross household income*** received by you or a member of your household during the immediately preceding calendar year and the current year to date.

Source Name & Address	Received By	Source Type

(b) Does any income source listed above relate to, or could it reasonably be expected to relate to, business that has, or may, come before the Committee?

☐ Yes ☐ No

If "yes", describe:

(c) Does an income source listed above have a legislative or administrative interest in the business of the Committee?

☐ Yes ☐ No

If "yes", describe:

4. Business Shared With a Lobbyist

If you or a member of your household ***shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist***, were employed by, or employed, a paid lobbyist during please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship which requires disclosure.)

Lobbyist Name	Business Name	Type Business Shared

Provide the information requested in items 5, 6, and 7 below only if:
(a) Your response involves an individual or business if you or a member of your household did business with, or reasonably could be expected to relate to business that has or may come before the Health Technology Clinical Committee.
(b) The information requested involves an individual or business with a legislative or administrative interest in the Committee.

5. Income of More Than $1,000

List each source (***not amounts***) of income over $1,000, other than a source listed under question 3 above, which you or a member of your household received during the immediately preceding calendar year and the current year to date:

Income Source	Address	Description of Income Source

6. Business Investments of More Than $1,000

(Do not list the amount of the investment or include individual items held in a mutual fund or blind trust, a time or demand deposit in a financial institution, shares in a credit union, or the cash surrender value of life insurance.)

If you or a member of your household had a personal, beneficial interest or investment in a business during the immediate preceding calendar year of more than $1,000, list the following:

Business Name	Business Address	Description of Business

7. Service Fee of More Than $1,000

(Do not list fees if you are prohibited from doing so by law or professional ethics.)

List each ***person for whom you performed a service for a fee of more than $1,000*** in the immediate preceding calendar year or the current year to date.

Name	Description of Service

I certify that I have read and understand this Conflict of Interest Form and the information I have provided is true and correct as of this date.

Print Name Irl Hirsch

Check One: ☐ Committee Member ☐ Subgroup Member ☒ Contractor

[redacted] 12/21/2017

Signature Date

Understanding CGM in 2018

Irl B. Hirsch, MD
Professor of Medicine
University of Washington School of Medicine

Average Glucose Versus A1C

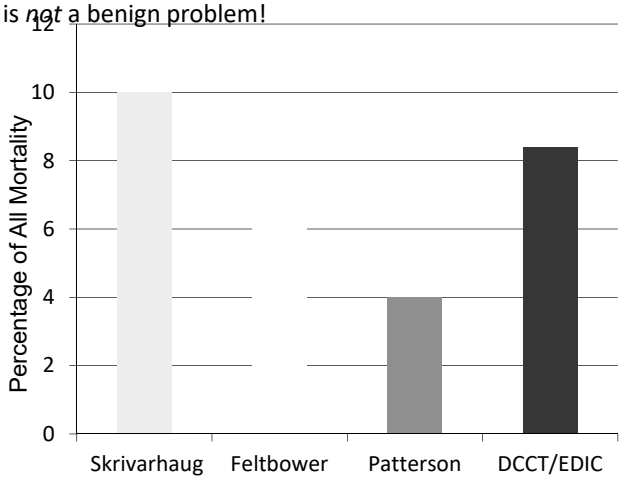
A1C (%)	AG (mg/dL [95% CI])
5	97 (76-120)
6	126 (100-152)
7	154 (123-185)
8	183 (147-217)
9	212 (170-249)
10	249 (192-282)
11	269 (217-314)
12	298 (240-347)

Historically, HbA1c has been our treatment target for the past 35 years. Is that appropriate? Is it safe?

Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. *Diabetes Care*. 2008;31:1473-1478.

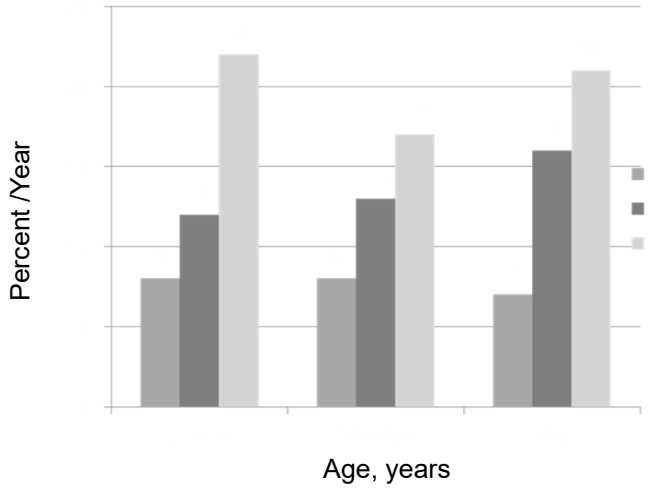
Hypoglycemia as the Cause of Death in Pediatric and Young Adult Type 1 Diabetes

This is *not* a benign problem!



Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. *Diabetologia*. 2006:49:298-305. Feltbower RG, Bodansky HJ, Patterson CC, et al. *Diabetes Care*. 2008;31:922-926.
Patterson CC, Dahlquist G, Harjutsalo V, et al. *Diabetologia*. 2007;50:2439-2442.
JAMA 2015;313:45-53

Frequency of Severe Hypoglycemia* Related to Type 1 Diabetes Duration

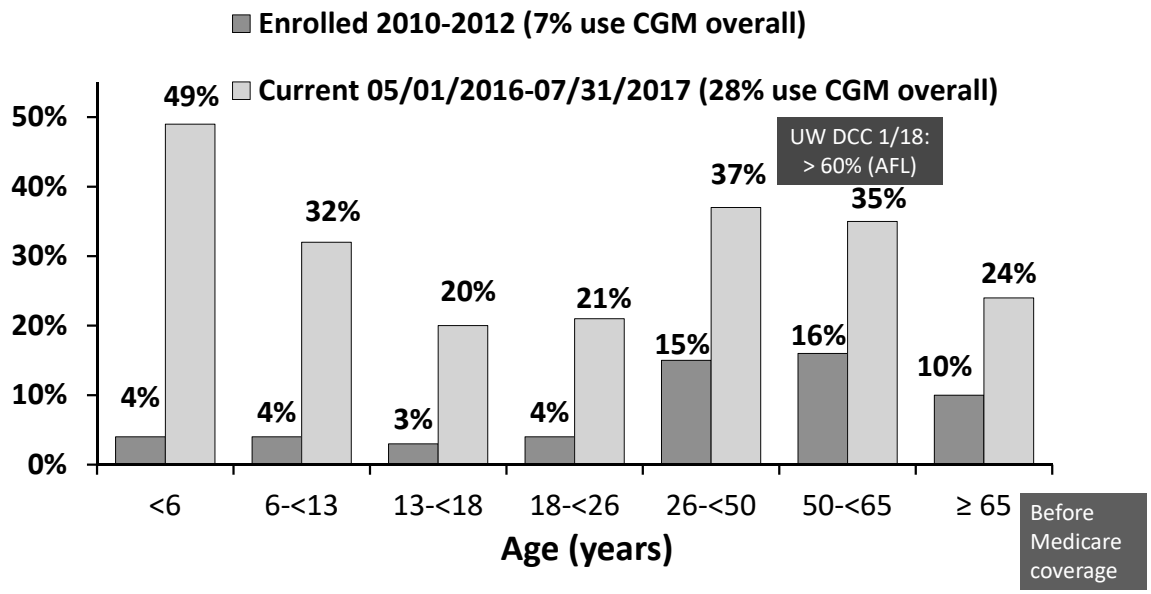


*Seizure or coma

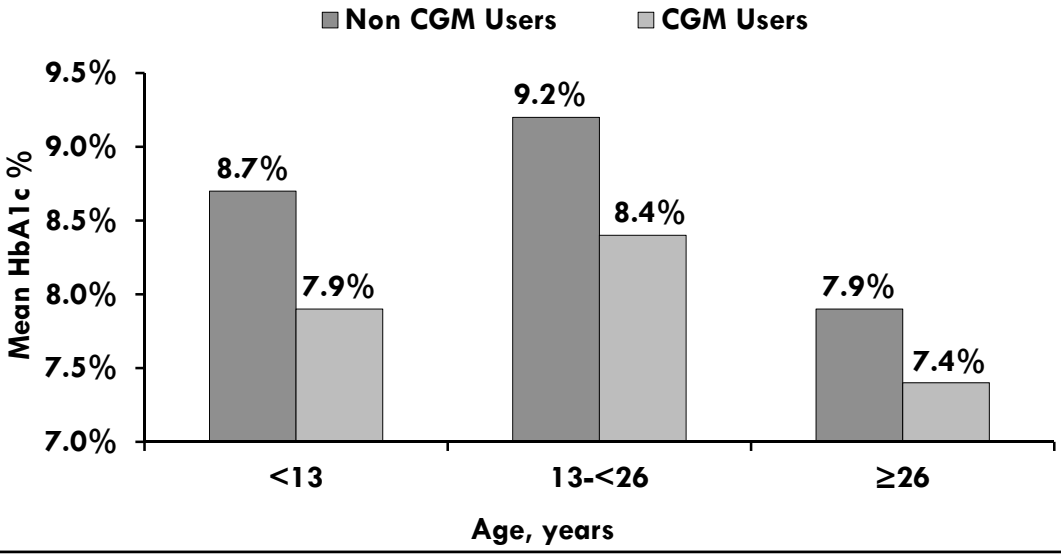
Given the limitations of HbA1c, and the dangers of hypoglycemia in both T1D and T2D taking insulin, wouldn't it make more sense to treat the glucose instead of the HbA1c?

Weinstock RS, Xing D, Maahs DM, et al. *J Clin Endocrinol Metab*. 2013;98:3411-3419.

CGM Use Is Increasing in the T1D Exchange

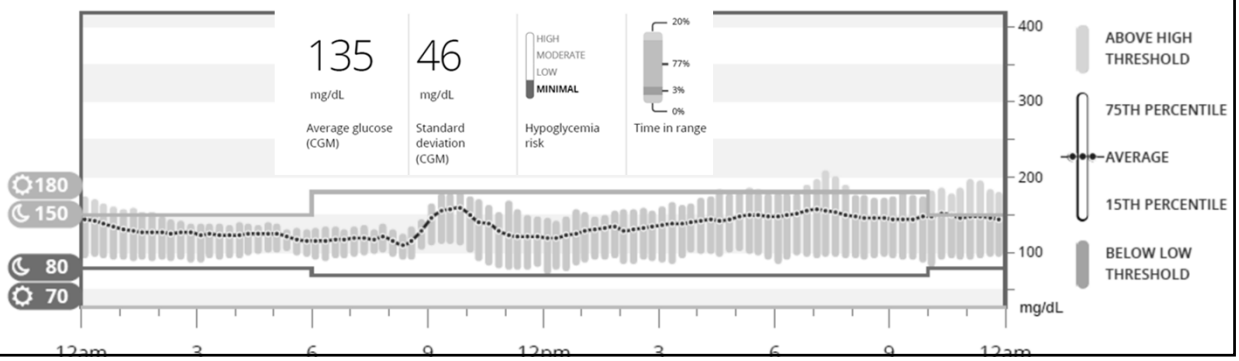


Lower HbA1c in CGM Users (N=16,656)



My UW Clinic, Jan 3, 2018

- 14 patients, 10 T1D, 3 T2D, 1 steroids after transplant
- CGM: 7/10 T1D, 1/3 T2D: 8/14 total
- First two patients: complete hypo unawareness. One 51y/o M, the other 71y/o M; both of them without a SH wearing CGM (total 12 yrs)



Take Home Points

- We treat the glucose, not the HbA1c
- "For every complex problem there is an answer that is clear, simple, and wrong" (HL Menckin)
  - Diabetes, especially type 1 diabetes is complex, and NOT having access to CGM in 2018 is wrong

Continuous Glucose Monitoring Re-Review

Presentation to

Washington State Health Care Authority

Health Technology Clinical Committee

Andrea C. Skelly, PhD, MPH
January 19, 2018

Report prepared by:
Andrea C. Skelly, PhD, MPH
Erika D. Brodt, BS
Cassandra Winter, BS
Aaron Ferguson, BS
Naomi Schwartz, BA
Mark Junge, BS

1

Scope, Update to 2011 Report

- **2011 Report**: self-monitoring of blood glucose (SMBG) and real-time continuous glucose monitoring (CGM) in those **18 years old or younger who require insulin**
- **Update report:**
  - Focus on real-time continuous glucose monitoring (CGM) in persons of **any age group with diabetes mellitus** (T1 or T2); women with diabetes during pregnancy (pre-existing or gestational)
  - Technological improvements in CGM technology; more widespread use
  - Insulin delivery (pumps vs. injections) **not** part of scope

2

Background - Diabetes Types

- **Diabetes mellitus (DM) is a serious chronic condition for which there is no definitive cure.**
- **DM is categorized into 3 major types, based on etiology**
  - **Type 1 (T1DM):** is an autoimmune disorder that destroys pancreatic beta cells which make insulin. It is the most common form in persons ≤ 18 years old. Insulin therapy is required.
  - **Type 2 (T2DM):** Is most common in adults, is caused by insulin resistance, disordered and inadequate insulin release and excessive glucose production by the liver. Diet, exercise and oral medications may be effective in the first years; however, it is progressive and insulin therapy may eventually be required.
  - **Gestational (GDM):** defined as glucose intolerance with pregnancy onset/first recognition of pregnancy.

Aggregate Analytics

3

Background-Diabetes Complications

- Chronic complications are strongly related to DM duration and glycemic control (T1 and T2DM):
  - Macrovasculsar complications (e.g. heart disease, stroke)
  - Microvascular complications (retinopathy, nephropathy, neuropathy)
  - Increased risk of infection, cancer, other autoimmune disorders (e.g. celiac sprue, thyroid disease)
- Hypoglycemia: 3 X more common in children (vs. adults), may be difficult to detect (unawareness); can damage brain, lead to seizures, coma, death; Severe hypoglycemia – rare event, generally in T1DM
- Diabetic ketoacidosis (DKA): severe hyperglycemia; leading cause of hospitalizations in children with T1DM nationally; can lead to coma, death

Aggregate Analytics

4

Background

- DM duration is associated with chronic complications, thus, younger persons may have the most to gain from maintaining good glycemic control yet have some of the greatest challenges in achieving and maintaining it.
- Goal: Achieve/maintain glucose and A1C levels as close to normal as possible while minimizing episodes of severe hypoglycemia
- Intensive management with tight control has become standard of care. Glucose monitoring plays an integral part:
  - Provides data for decision making
  - Assists in identifying and preventing hypoglycemia
  - Provides "peace of mind" to care givers
  - Influences activities and quality of life

Aggregate Analytics

5

Self-monitoring of blood glucose (SMBG)

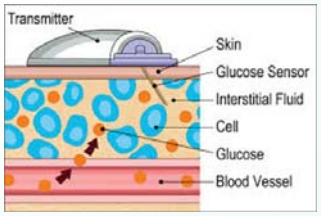
(intermittent monitoring)

- First FDA approval 1975
- Capillary blood drop placed on reagent-impregnated paper strips; monitor reads
- Provides "snap shot" of blood glucose levels
- Recommended: at least 4 times/day; individualized
- Barriers, adherence, use of data

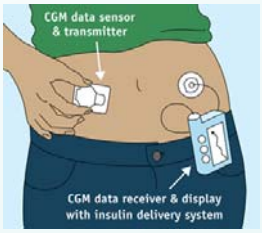
Aggregate Analytics

6

Traditional Real-time Continuous Glucose Monitor (TCGM)



http://www.nbdiabetes.org/news/continuous-glucose-monitoring-system-cgms



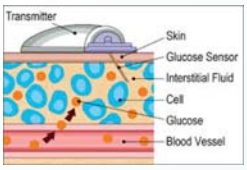
https://www.niddk.nih.gov/health-information/diabetes/overview/managing-diabetes/continuous-glucose-monitoring

- Subcutaneously placed, enzyme-embedded sensor samples interstitial fluid glucose; connected to transmitter
- Glucose data sent continuously to a receiver or smartphone app
- "Real-time" view of glucose level changes and trend information
- Threshold alarms for high, low glucose levels
- May be used with insulin pump (sensor augmented pump therapy)
- SMBG for calibration

Aggregate Analytics

7

Flash "Continuous" Glucose Monitor (FCGM)



http://www.nbdiabetes.org/news/continuous-glucose-monitoring-system-cgms

https://www.healthline.com/diabetesmine/newsflash-fda-oks-freestyle-libre-united-states#2

- Sensor (upper arm only) samples interstitial fluid glucose every minute; stores 8 hours of data
- Sensor must be scanned by separate reader; data are *not* continuously sent, no connectivity with mobile devices/smart phones
- No passive alerts; data, alerts, trends only if sensor scanned
- FDA approval >18 year olds only
- SMBG not *required* for calibration, treatment decisions

Aggregate Analytics

8

Real-time Continuous Glucose Monitor (CGM)

- Advances in traditional CGM technology:
  - Enhanced accuracy and precision
  - Timeliness and display of alarms (visual, audible)
  - Increased sensor durability, wear time; decreased size
- Some devices require SMBG for verification (adjunctive)
- Therapeutic device: *replacement* for fingerstick BG testing for treatment decisions (i.e. used as a primary system and not as an adjunct)
  - DexCom G5 Mobile CGM, Medtronic MiniMed 670G automates insulin delivery based on CGM);
  - SMBG required for calibration; may be recommended
- Patient education, support, adherence are important
- Flash GM differs from traditional CGM

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9

Key Questions

In persons with diabetes mellitus (DM):

1. What is the evidence of efficacy and effectiveness of continuous monitoring?
2. What is the evidence of the safety of continuous glucose monitoring?
3. What is the evidence that glucose monitoring has differential efficacy or safety issues in subpopulations?
4. What is the evidence of cost-effectiveness of continuous glucose monitoring?

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PICO Scope: Inclusion Criteria

- **Population**: Persons with diabetes mellitus; type 1, type 2, pregnant women with pre-existing diabetes or gestational diabetes
- **Interventions:** FDA-approved real-time continuous glucose monitoring devices and FDA-approved combination devices integrating real-time continuous glucose monitoring with insulin pump/infusion
- **Comparators:** Self-monitoring using convention blood glucose meters, attention control, blinded or sham CGM and usual care.

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PICO Scope: Inclusion Criteria

- **Study design**
  - Focus on high quality (low risk of bias) comparative studies (e.g., randomized controlled trials, crossover trials) for questions 1-3 as a basis for SoE.
  - Observational studies (e.g., longitudinal studies correlating intermediate outcomes (e.g., HbA1C) with long term clinical outcomes (e.g. macro or microvascular outcomes, maternal or fetal outcomes);observational studies of safety will be considered;
  - Formal, full economic studies
- **Publication**
  - Full-length studies published in English in peer-reviewed journals, FDA reports (EXCLUDED: meeting abstracts, proceedings)
  - Studies published subsequent to the 2011 report for persons <18 years old and studies published subsequent to the 2012 AHRQ report for adults, those with type 2 diabetes requiring insulin and pregnant women

12

Outcomes

Primary Clinical Outcomes (SoE)

- Microvascular complications (vision loss, kidney failure, peripheral neuropathy)
- Macrovascular complications (coronary artery, cerebrovascular or peripheral arterial disease)
- Fetal outcomes, cesarean section rates

Primary Intermediate Outcomes (SoE)

- Achieving target (age-appropriate) HbA1c level; "success", mean (Δ of 0.5% clinically meaningful)
- Maintaining target (age-appropriate) HbA1c level: "success", mean
- Acute episodes of hypoglycemia (events)

Secondary Intermediate Outcomes

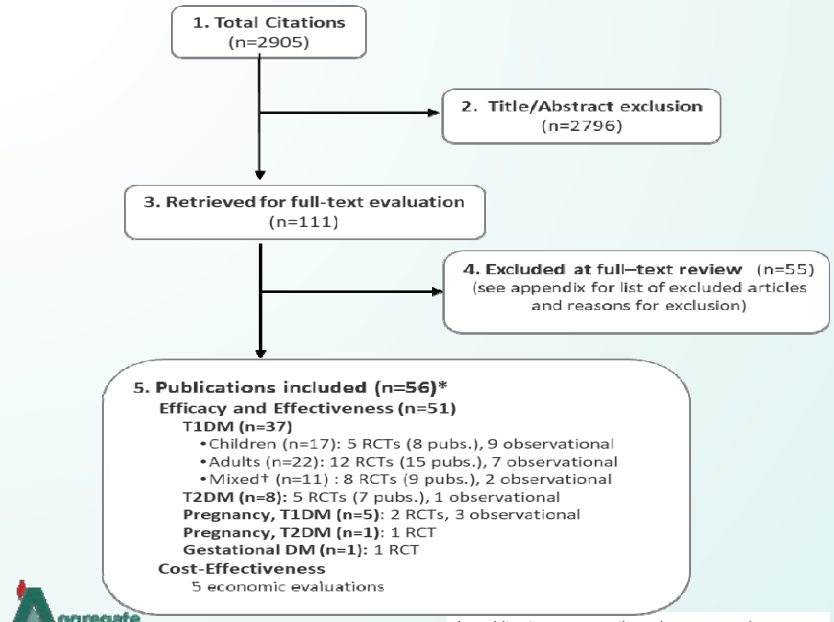
- Acute episodes of hyperglycemia
- Acute episodes of diabetic ketoacidosis
- Quality of life (validated instruments only)

Safety: Morbidity/adverse events from devices, mortality

Economic: ICER, cost savings for prevented morbid event

13

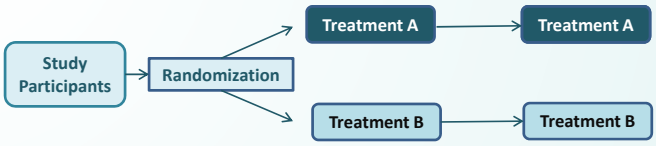
Literature Search Results



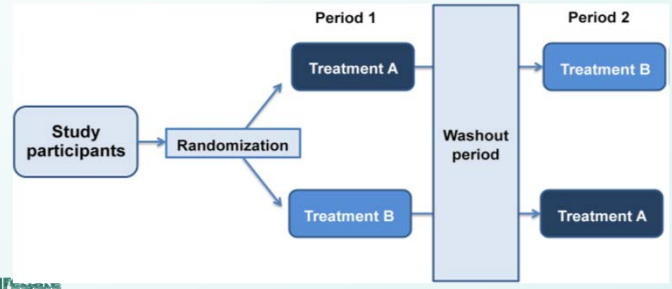
*A publication may contribute data to more than one type of diabetes or age group.

14

Parallel trial: Patients remain in groups as randomized



Cross-over trial: Patients receive different treatments at different time periods



15

Strength of Evidence (SoE) – Appendices D, E

Overall body of evidence for primary outcomes based on:

- **Risk of bias**: the extent to which the included studies protect against bias
  - Appropriate randomization
  - Allocation concealment
  - Intention to treat analysis
  - Blind assessment of outcomes
  - Co-interventions applied equally
  - Adequate follow-up (≥80%), <10% follow-up difference between groups
  - Control for confounding
  - Additional considerations for cross-over trials
- **Consistency:** degree to which estimates are similar in terms of range and variability.
- **Directness:** evidence directly related to patient health outcomes.
- **Precision:** level of certainty surrounding the effect estimates.
- **Publication/report bias**: selective reporting or publishing.

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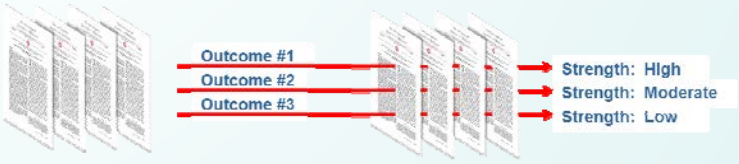
Systematic Review Process

Studies meeting eligibility criteria
- Efficacy: RCTs (possibly observational studies)
- Harms: RCTs, observational studies
- Economic studies

→ **Risk of Bias Appraisal (Study)**
Low, moderately low, moderately high, high
Synthesis/analysis

↓

Overall Strength of Evidence Determination (GRADE/AHRQ)



Strength of Evidence Ratings	
High	Very confident that effect is true.
Moderate	Moderately confident.
Low	Limited confidence.
Insufficient	No evidence or no confidence in effect.

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KQ1: Evidence base for persons with T1DM

Persons <18 years old with T1DM

5 RCTs (8 pubs.)	In previous report:	*Industry funding?*
8 observational	3 RCTs (4 pubs.)	2 Yes, 1 No
	3 observational	No
	New to report update:	
	2 RCTs (4 publications)	1 Yes, 1 No
	5 observational	2 Yes, 3 No

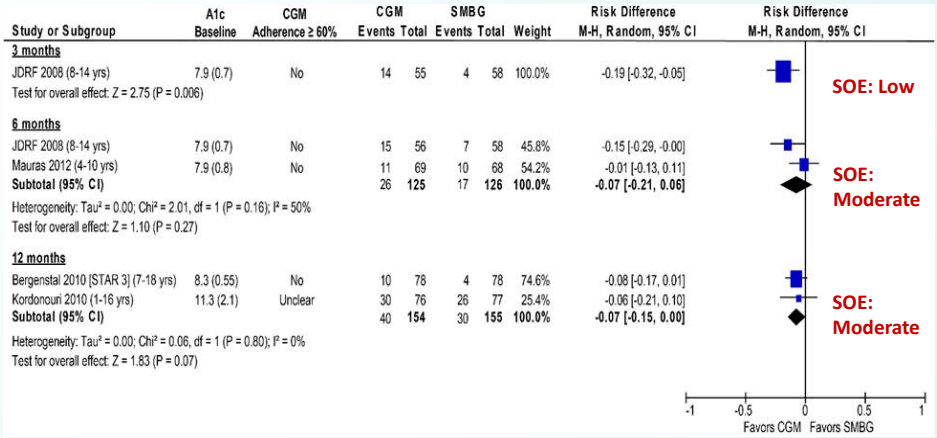
Adults with T1DM

	Industry funding?
12 RCTs (15 pubs.)	10 Yes, 2 No
6 observational	2 Yes, 4 No

18

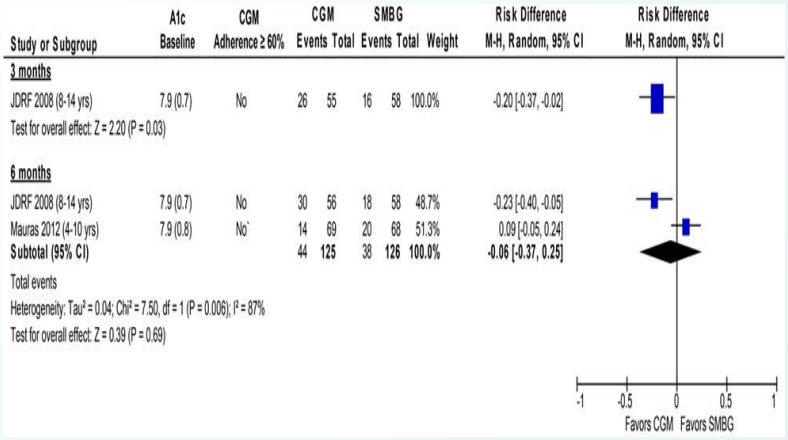
Persons <18 years old with Type 1 DM

KQ1:Persons <18 years old (children, adolescents) with T1DM Parallel trials, proportion achieving HbA1c % of <7%



3 months: More in CGM group achieved success (SOE Low)
6, 12 months: No clear difference between CGM and SMBG (SOE Moderate)

KQ1: Children, adolescents with T1DM: Parallel trials, proportion achieving absolute reduction of ≥ 0.5% for HbA1c



SOE: Low

3 months: More in CGM group achieved success (SOE Low)
6 months : No clear difference between CGM and SMBG (SOE Low)

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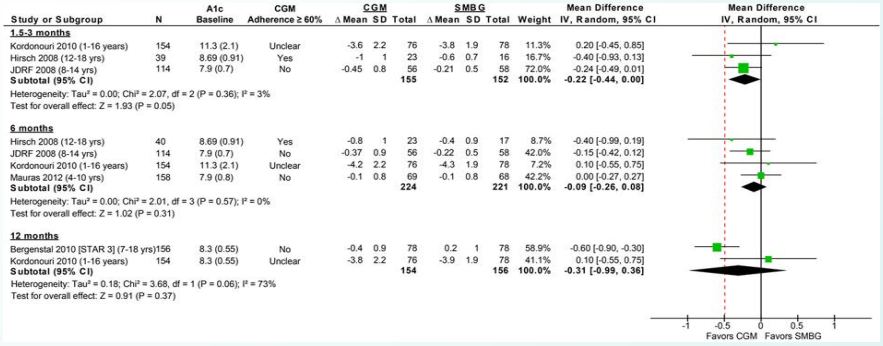
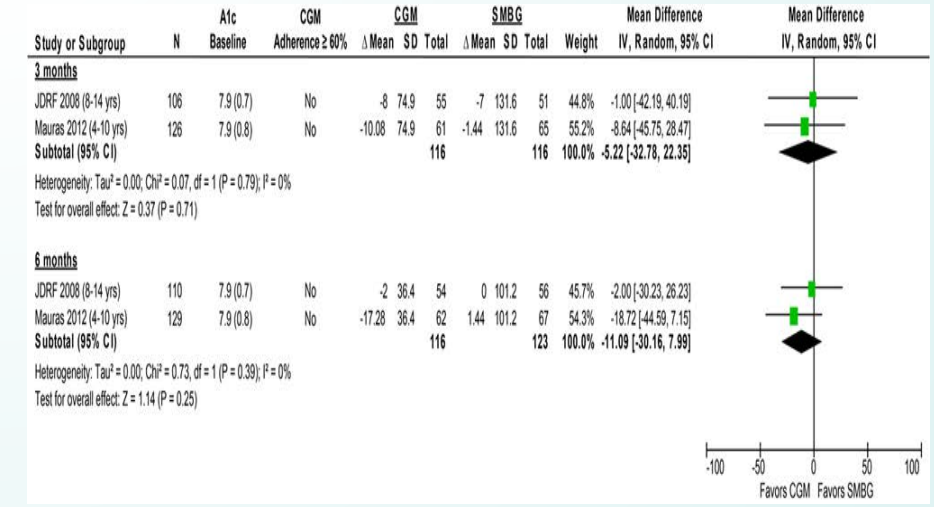
KQ1: Children, adolescents with T1DM
Between group difference in mean HbA1c change from baseline



3 months: Small reduction favoring CGM MD-0.22% (-0.44% to 0.0%, (SOE Low)
6 months: No clear difference in parallel RCTs; 1 cross-over trial (N = 72) significant difference during CMG periods: MD -0.46%, (-0.26 %to -0.66%) (SOE Moderate)
12 months: No difference (SOE Moderate)

22

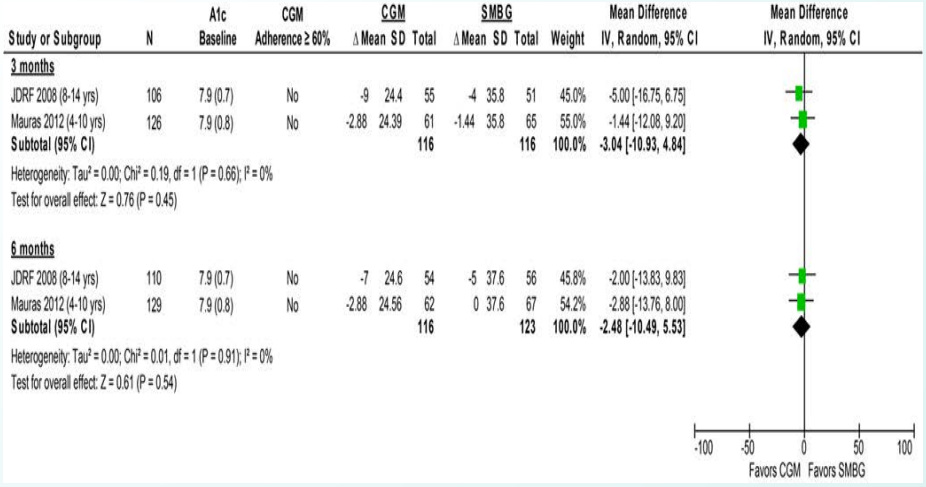
KQ1: Children, adolescents with T1DM
Time spent in hypoglycemic range < 70 mg/dL (min/day)



3 months, 6 months : No difference (SOE Low)

23

KQ1: Children, adolescents with T1DM
Time spent in hypoglycemic range <55mg/dL (min/day)

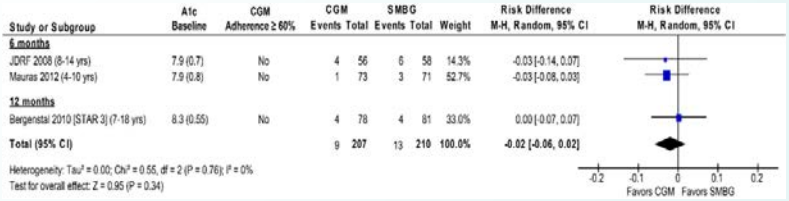


3 months, 6 months : No difference (SOE Low)

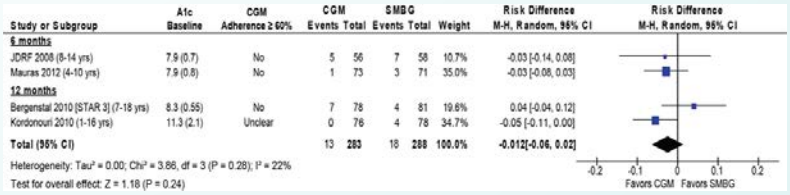
24

KQ1: Children, adolescents with T1DM
Severe Hypoglycemic Events

Proportion with ≥1 severe hypoglycemic event



Number of severe hypoglycemic *events*

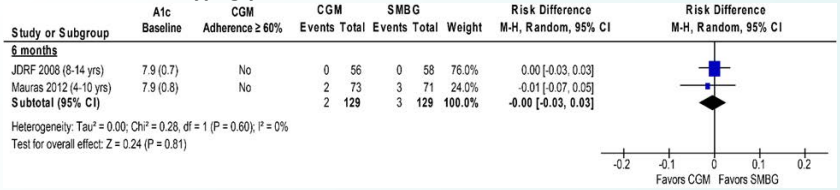


To 12 months: Studies likely underpowered to detect a difference; no difference (SOE Low)

25

KQ1: Children, adolescents with T1DM - Severe Hypoglycemic Events

Number of severe hypoglycemic events with seizure, coma or loss of consciousness



Incidence of severe hypoglycemic events

Author, Year(age range)	Follow-up	Incidence: CGM vs. SMBG (p-value)
Severe hypoglycemic events		
JDRF 2008 [64] (8-14 years)	6 mos	events per 100 person years 17.9 vs. 24.4, p=0.64
Bergenstal 2010, STAR 3 [15] (children 7-18 years); ITT w/LOCF	12 mos	rate per 100 person-yr, 8.98 vs. 4.95, p=0.35
Kordonouri 2010 [70] (1-16 years)	12 mos	P= 0.46
Severe hypoglycemic events with seizure, coma or loss of consciousness		
Mauras 2012 [78] (4 to <10)	6 mos	rate per 100 person-years 8.6 vs. 17.6*

To 12 months: Studies likely underpowered; no difference (SOE Low)

26

Children with Type 1 DM: Other Outcomes (SOE not assessed; detail in full report)

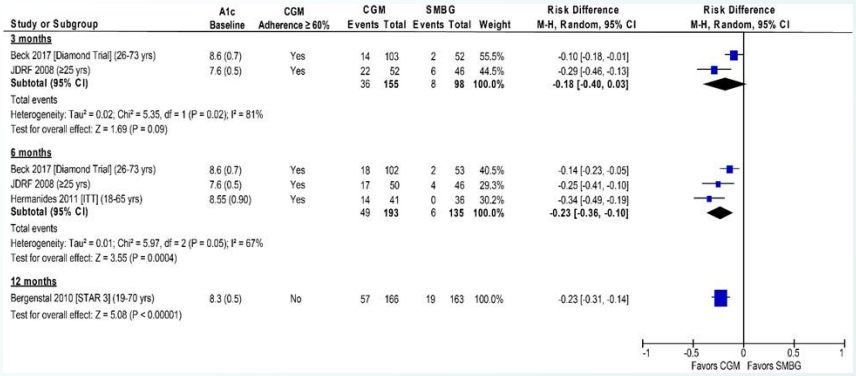
- **Adherence:**
  - Single-arm extensions (case series) generally found that greater CGM adherence/use was associated with better HbA1c levels
  - Comparative data: Unclear
- **Satisfaction and QOL:**
  - Satisfaction: Generally ↑ with CGM vs, SMBG in children, parents; ↑ satisfaction with ↑ use
  - QOL: Generally, no statistical differences (children or parent's proxy)

27

Adults with Type 1 DM

28

KQ1: Adults with T1DM
Parallel trials, proportion achieving HbA1c % of <7%



SoE Low (all time periods)
3 months: More adults achieved success with CGM in individual trials
6, months: More adults achieved success with CGM pooled RD: -23%, 95%CI -36% to -10%
12 months: More adults achieved success with CGM; RD -23%, 95%CI -31% to -14%)

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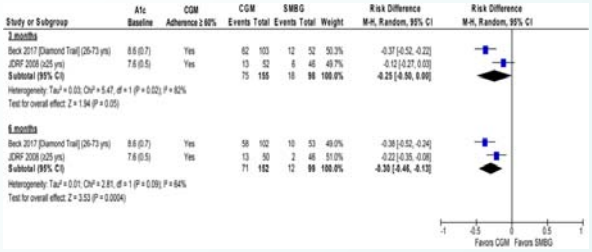
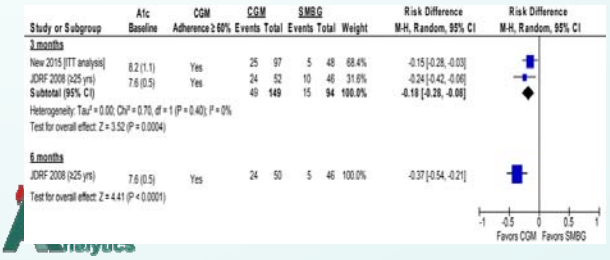
KQ1, Adults with T1DM: Parallel trials proportion achieving specific A1c changes: Low to Moderate Evidence

Relative reduction >10% from baseline in HbA1c



More achieved success w/CGM
3 months, SoE Low : RD -25% (-50% to 0%)(Beck, significant)
6 months, SoE Moderate : RD-30%, 95% (-46% to -13%)

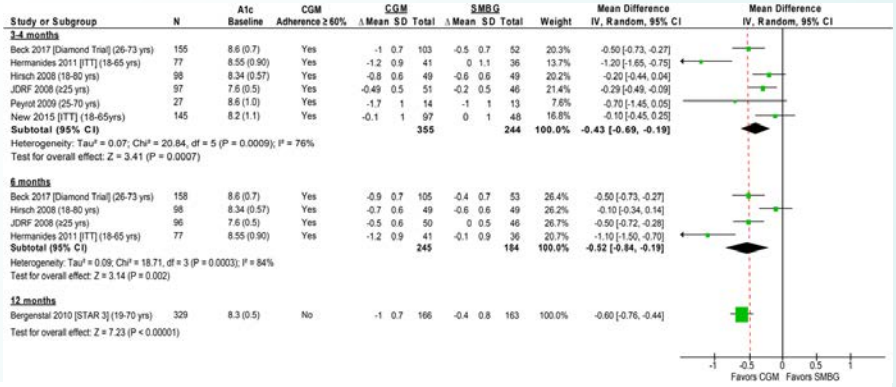
Absolute reduction of ≥ 0.5% from baseline in HbA1c %



More achieved success w/CGM
3 months, SoE Moderate:
RD -18% (-28% to -8%)
6 months, SoE Low:
RD -37% (-54% to 21%)

30

KQ1: Adults with T1DM – Parallel trials
Between group difference in mean HbA1c change from baseline



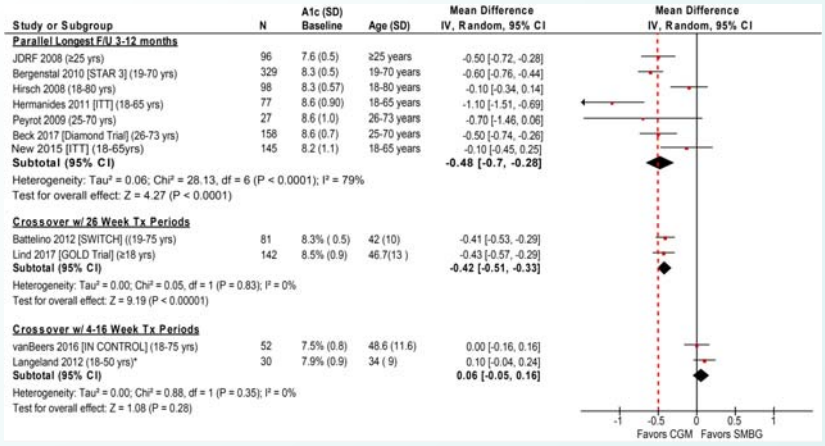
Traditional GCM (plot) was associated with significant improvement in mean change in HbA1c % from baseline vs. SMBG- (SoE Low)

- **3-4 months:** Pooled MD – 0.43% (-0.69% to -19.0%)
- **6 months:** Pooled MD -0.52% (-0.84% to -0.19%),
- **12 months**: MD-0.6% (-0.76% to -0.44%)

Flash CGM vs. SMBG: No difference between groups at 3 or 6 months (1 trial, SOE Insufficient) MD 0% (-0.17% to 17%) at both times; Baseline A1c 6.79 and 6.78

31

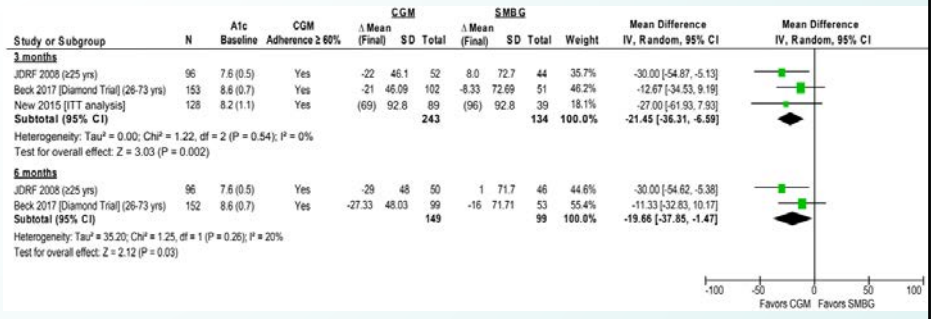
KQ1: Adults with T1DM - difference in mean HbA1c% at last follow-up: Parallel and cross-over trials



Traditional GCM was associated with clinically and statistically significant improvement mean HbA1c % at final follow-up vs. SMBG across parallel trials, statistically significant in cross-over trials of at least 26 weeks treatment periods (SoE Low) in adults; Findings from 2 trials with newer devices (GOLD and DIAMOND) were similar to those from other trials; 1 showed NS difference (IN CONTROL)

32

KQ1: Adults with T1DM
Time spent in hypoglycemic range < 70 mg/dL (min/day)



Traditional CGM – Most parallel and cross-over trials, CGM appears to be associated with decreased time spent in this range vs. SMBG (SOE Low)

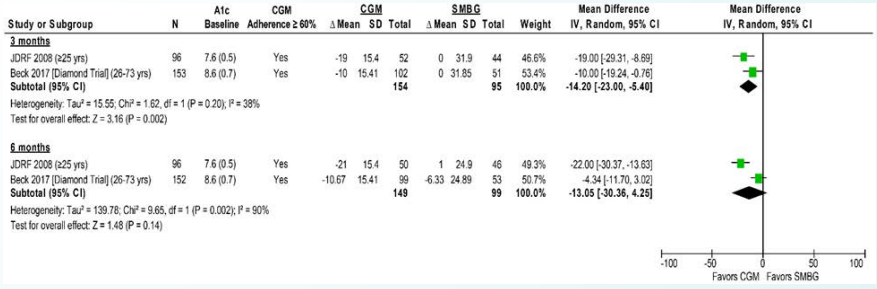
Parallel trials (Plot): 3 months (MD -21.5 minutes/day (-36.3 to -6.6), 6 months (MD -19.7 m/d (-37.9 to -1.5)

Cross-over Trials: 16 week periods, MD -1.1 hours/day (-1.4 to -0.8); 26 week periods, MD -2.0% (-2.83% to -1.17%) percent of time spent in range

Flash CGM associated with less time in this range (SOE Insufficient):
3 months MD -1.09 (±0.18) hours/d, 6 months, MD -1.24 (±0.24) hours/d

33

KQ1: Adults with T1DM
Time spent in hypoglycemic range < 55 mg/dL



Traditional CGM – Parallel trials- minutes/day (SOE Low 3 months, insufficient, 6 months)

3 months: decrease in the mean min/d with CGM, MD -14.2 minutes/d, (-23 to -5.4)

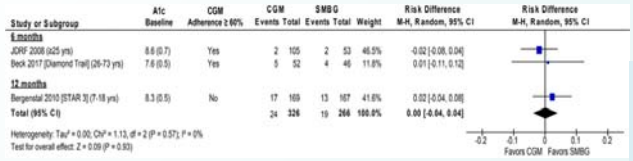
6 months: No difference, newest trial failed to reach statistical significance

Flash CGM associated with less time in this range (1 trial) (SOE Insufficient):
Adjusted MD (SD): 3 months: -0.68 ± 0.13 hours/d, 6 months, -0.82 ± 0.74 hours/d

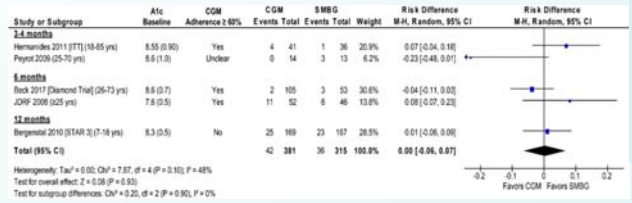
34

KQ1: Adults with T1DM
Severe hypoglycemic events

Proportion with ≥1 severe hypoglycemic event, parallel trials



Number of severe hypoglycemic events, parallel trials



SoE Low
Studies were likely underpowered to detect differences between groups; no statistical differences between groups in most trials;

3 Cross-over trials: Only one small trial reported statistically fewer events with CGM
FCGM: 2% (n =2) of participants in the FCGM and 2% (n=3) in the SMBG group

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Adults with Type 1 DM: Other Outcomes (SOE not assessed; detail in full report)

- **Adherence:**
  - Single arm (case series) extensions of RCTs generally found that greater CGM adherence/use was associated with better HbA1c levels
  - Comparative evidence: Unclear
- **Satisfaction and QOL:**
  - Satisfaction: 2 RCTs (1 newer device) ↑ satisfaction with CGM vs. SMBG; ↑ satisfaction with ↑ use
  - QOL: Results varied across measures

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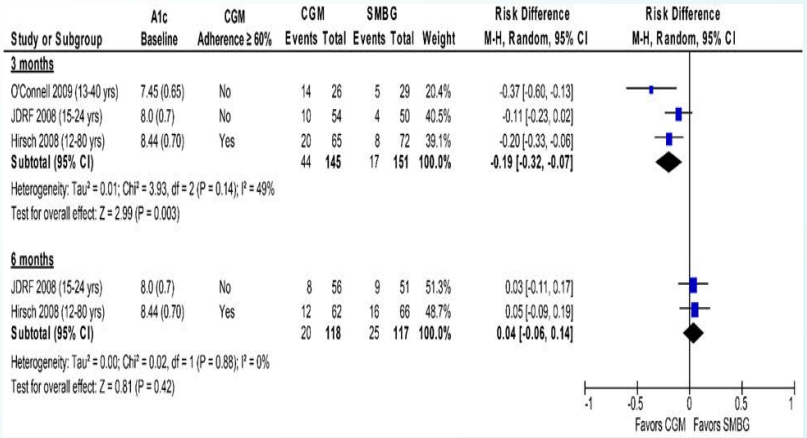
Mixed Populations (Adults and Children) with Type 1 DM

- **Evidence base:**
  - 8 RCTs (9 publications); 7 were industry funded
  - 2 observational studies; (not industry funded

37

KQ1: Mixed populations (children and adults) with T1DM
Parallel trials, proportion achieving HbA1c % of <7%

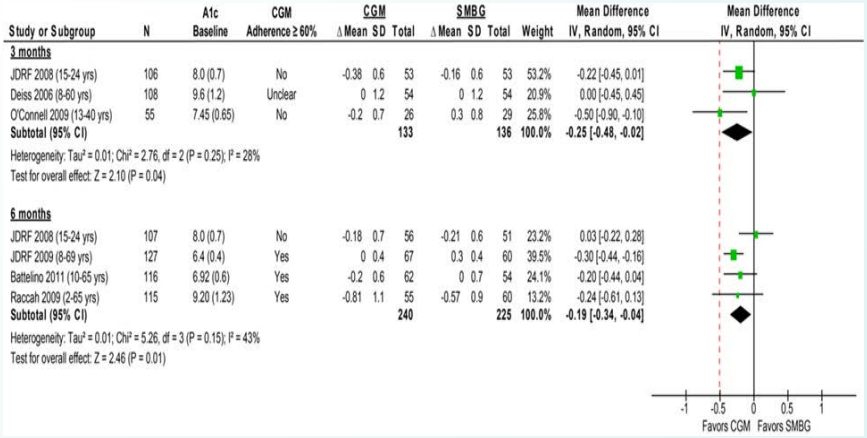


3 months: Significantly more patients in the CGM group achieved target: RD -19% (95%CI, -32% to 7%)

6 months: No difference between groups

38

KQ1: Mixed populations (children and adults) with T1DM
Between-group differences in HbA1c change from Baseline:



Small reductions favoring CGM (SoE Moderate)

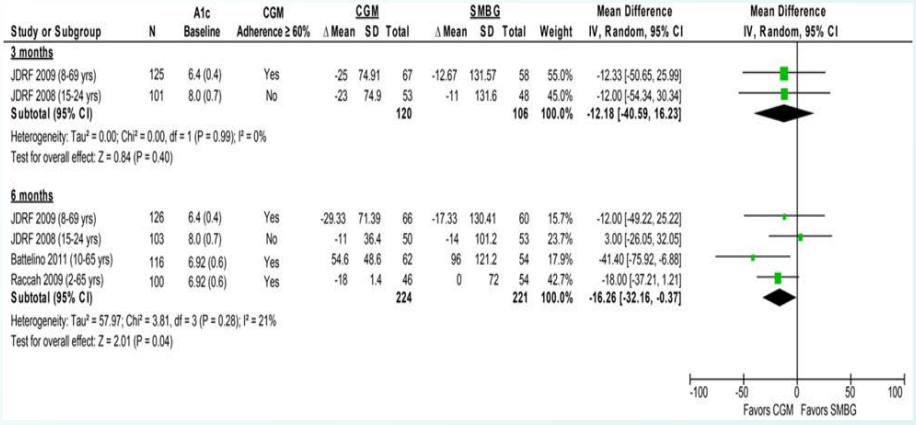
3 months: 3 parallel trials (MD -0.25%, 95%CI -0.48% to -0.02%)

6 months: 4 parallel trials (MD -0.19%, 95%CI -0.34% to -0.04%);
1 cross over trial, MD -0.43, 95%CI -0.32 to -0.55) N=153

Unclear if differences are clinically important

39

KQ1: Mixed population (children, adults) with T1DM
Time spent in hypoglycemic range < 70 mg/dL (min/day)

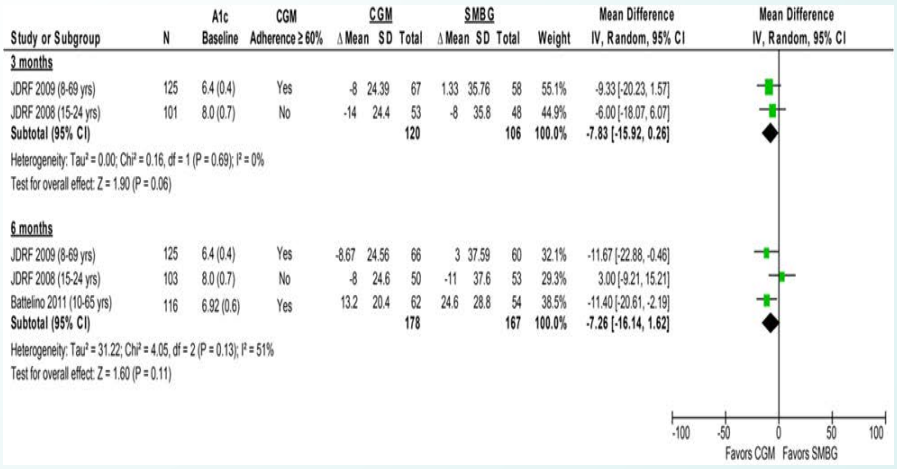


3 months: No difference (SOE Low)

6 months: Less time in range with CGM, Pooled MD: -16.26 (-32.16 to -0.37)

40

KQ1: Mixed population (children, adults) with T1DM
Time spent in hypoglycemic range < 55 mg/dL (min/day)

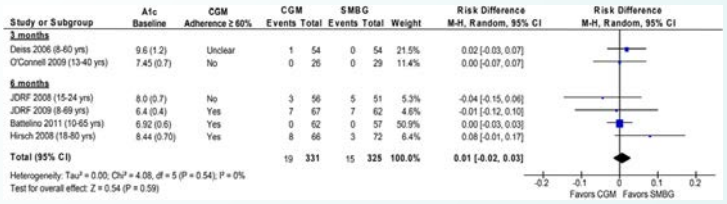


3 months, 6 months: No difference (SOE Low)

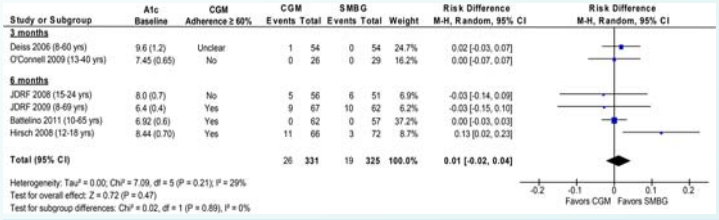
41

KQ1: Mixed population (children, adults) with T1DM
Severe Hypoglycemic Events

Proportion with ≥1 severe hypoglycemic event



Number of severe hypoglycemic events

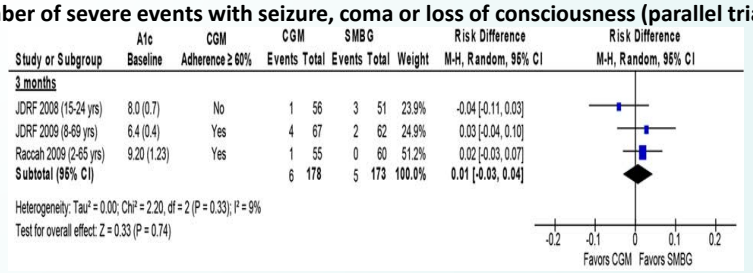


To 6 months: Studies likely underpowered to detect a difference; No difference (SOE Low);

42

KQ1: Mixed population (children, adult) with T1DM
Severe Hypoglycemic Events

Number of severe events with seizure, coma or loss of consciousness (parallel trials)



Cross-over trial: Number and rate of severe hypoglycemic events

Author year	Outcome	Timing	CGM Periods	SMBG Periods	MD (95% CI) Effect Size (SE)	p-value
SWITCH Battelino 2012 Treatment periods: 6 months Washout phase: 4 months *Moderately low*	Episodes of severe hypoglycemia: requiring assistance, or neurological recovery in response to restoration of plasma glucose to normal)	Across both treatment periods†	4 (5.7 per 100 patient-years)	2 (2.83 per 100 patient-years)	NR	0.40

No difference (SOE Low); studies likely underpowered

43

Mixed Populations (children and adults) with Type 1 DM
Other Outcomes (SOE not assessed; see report)

- Adherence:
  - Greater adherence was associated with improved HbA1c
  - Comparative: unclear
- Satisfaction and QOL:
  - Not reported in any included trials or observational studies

44

Adults with Type 2 DM

- Evidence base:
  - 5 RCTs (7 publications); 4 RCTs were industry funded
  - 1 observational study (Industry funded)

45

KQ1: Adults with T2DM

Outcome Definition	Studies Risk of Bias	Reasons for Downgrading	Conclusion	Quality
Success (Achieving HbA1c % <7.0%)	1 RCT (Beck 2017[b]) N = 152 Moderately Low RoB	Imprecision (-1)	**3 months:** CGM 22%, SMBG 12% Adjusted RD: 10%, 95% CI −2% to 23% **6 months:** CGM 11%, SMBG 9% Adjusted RD: 3%, 95% CI −9% to 14% **Conclusion:** No clear difference at 3 months; no difference at 6 months.	⊕⊕○○ LOW
HbA1c%: Absolute reduction of ≥0.5% from baseline	3, 6 mos.		Absolute reduction **3 months:** CGM 61%, SMBG 38% Adjusted RD: 31%, 95% CI 5% to 57% **6 months:** CGM 56%, SMBG 37% Adjusted RD: 26%, 95% CI 0% to 50% **Conclusion**: More CGM patients achieved ≥0.5% reduction in HbA1c at both time points.	⊕⊕○○ LOW

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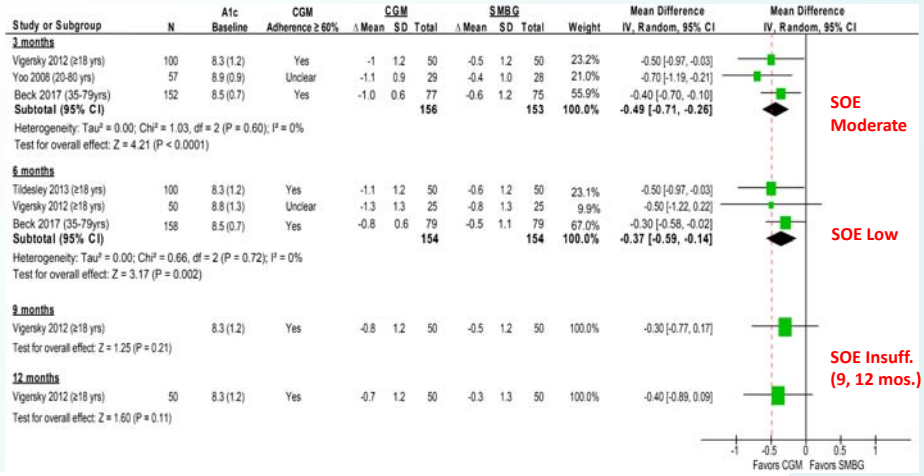
KQ1: Adults with T2DM
Between-group differences in HbA1c change from baseline



3 months: Clinically and statistically sig. reduction with CGM
6 months: Statistically sig. reduction with CGM
9, 12 months: No difference (1 small trial)
FCGM: adjusted MD at 6 months: 0.03 (SE 0.114), p=0.822 (SOE Insufficient)

47

KQ1: Adults with T2DM
Hypoglycemia, range <50 and < 70 mg/dl

No differences between CGM and SMBG in *minutes per day, % of readings per day, or % of time* spent in either range:

Hypoglycemia <50 mg/dL

- 3 months (2 RCTs, N=242)
- 6 months (1 RCT, N=146)

SOE Low for both time points

FCGM (1 RCT, N=224): <55 mg/dl
6 months MD -13. 2 min/d favoring FCGM vs. SMBG **SOE Insufficient**

Hypoglycemia <70 mg/dL

- 3 months (2 RCTs, N=242)
- 6 months (1 RCT, N=146)
- 12 months (1 RCT, N=92)

SOE Low for 3 and 6 mos., **Insufficient** for 12 mos.

FCGM (1 RCT, N=224): <70 mg/dl
6 months MD -28.8 min/d favoring FCGM vs. SMBG **SOE Insufficient**

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KQ1: Adults with T2DM
Episodes of Severe Hypoglycemia

Outcome	Studies RoB	Reasons for Downgrading	Conclusion	Quality
Episodes of Severe Hypoglycemia	3 RCTs N=264 (Beck 2017[b], Tildesley 2013, Yoo 2008) 3-6 mos	Imprecision (-2)	No episodes (defined as requiring third party assistance) in one trial over 6 months Two trials did not define severe hypoglycemia: one reported no events over 3 months; second reported frequency in both CGM and SMBG group was "negligible with no serious events" (data NR, 6 months). **Conclusions**: Trials underpowered; no differences between groups.	⊕⊕◯◯ LOW

Flash CGM (N=224, Haak 2016): **No difference, study underpowered, SOE Insufficient:** FCGM, 3 patients (2%) vs. SMBG, 1 patient (1%) (event requiring third party assistance).

49

Adults with Type 2 DM
Other Outcomes (SOE not assessed, see report)

- **Adherence**: Greater sensor use associated with greater reduction in HBA1c % to 12 months (1 RCT)
- Comparative data unclear
- **Satisfaction and QOL:**
  - Satisfaction: CGM usage associated improved satisfaction in trials of traditional CGM and flash CGM.
  - QOL: NS differences in any measure for TCGM (1 trial in newer device, 1 trial in older device) or in most measures for FCGM (1 trial)

50

Diabetes in Pregnancy

Pre-existing Type 1 DM

- 2 RCTS (industry funded)
- 3 observational (1 industry funded, 1 not, 1 unclear)

Pre-existing Type 2 DM

- 1 RCT (industry funded)

Gestational Diabetes

- 1 RCT (funding unclear)

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KQ1: Pregnancy, Preexisting T1DM

Statistically significant, clinically important difference favoring CGM for the following outcomes (wide CIs):

- **Caesarean section (2 RCTs, N=325), *SOE Moderate***:
  CGM 50.9%, SMBG 62.3%
  Pooled RD: -11.0%, 95% CI -21.0% to -1.0%, I^2 = 0%

- **Admission to NICU, >24 hours (1 RCT, N=200), *SOE Low*:**
  CGM 27%, SMBG 43%
  RD -16%, 95% CI -29% to -3%

Satisfaction: favorable ratings with CGM; NS difference in QOL measures

52

KQ1: Pregnancy, Preexisting T1DM, cont.

No statistically significant difference (studies may have lacked power for some outcomes) between CGM and SMBG for the following outcomes:

SOE Moderate (2 RCTs):

- Gestational age; Birthweight; Miscarriage; Preterm Delivery; Preeclampsia (SOE Moderate, RCTs)

SOE Low (1 to 2 RCTs):

- Large for gestational age; Episodes of severe neonatal and severe maternal hypoglycemia; Hypoglycemia (neonatal, maternal); Still birth; Birth trauma; and HbA1c% measures (success, ≤6.5%; mean change from baseline)

SOE Insufficient (1 to 2 RCTs):

- Major congenital anomalies; Time spent in hypoglycemia (≤70 or <63 mg/dl range)

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KQ1: Pregnancy, Preexisting T2DM

No difference between CGM and SMBG in any outcome measured in one small trial (N=31) due at least in part to small sample size; all evidence considered. **Insufficient SOE**:

- Gestational age
- Birth weight
- Large for gestational age
- Neonatal hypoglycemia
- Miscarriage
- Perinatal mortality
- Caesarean section
- HbA1c%
- Hypoglycemia (% of SMBG values ≤70 mg/dl)
- Severe Hypoglycemia (episodes requiring 3rd party help)

54

KQ1: Gestational Diabetes

No difference between CGM and SMBG in any outcome measured in one trial (N=106); Study was likely underpowered to detect most outcomes; all evidence considered **Insufficient**:

- Gestational age
- Birth weight
- Large for gestational age
- Macrosomia
- Neonatal hypoglycemia
- Perinatal mortality
- Caesarean section
- HbA1c% (mean change from baseline)

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KQ2: Safety and Harms: AEs leading to discontinuation

Outcome, f/u Studies	Downgrade	Conclusion	Quality
Adverse events leading to discontinuation 3-6.5 months Traditional CGM 8 RCTs (N=25 to 142) 2 observational (N=83 to 1714)	Inconsistent -1 Imprecise -1	**Frequency (RCTs): 0% to 24%.** **Older devices**, from 2% to 24%; most common • Difficulty operating device and/or sensor (3% to 8%, 3 RCTs) • Alarms too frequent (6% , 2 RCTs) • Discomfort or inconvenience; (20%, 1 small RCT, n=25) **Newer devices** (2 trials, N=52, 142): • Allergic reaction to sensor (1%) • Could not upload CGM data (4%) **Observational studies**: 61%, 44%, similar reasons **Conclusion**: Discontinuation not uncommon; most were due to difficulty operating the device or bothersome alarms	⊕⊕◯◯ LOW
Flash CGM 2 (N=269) 6 months	Risk of bias -1 Inconsistent -1 Imprecise -1	**Frequency 2% to 5%** included: itching, rash, erythema, weeping at insertion site; severity of events unclear/not defined. **Conclusion:** Site-related AE discontinuation was not common;	⊕◯◯◯ INSUFFICIENT

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KQ2: Serious device-related AE (proportion with ≥ 1 event)

Outcome, f/u Studies	Downgrade	Conclusion	Quality
Serious device related adverse events (proportion with ≥1 event) 6-12 months TCGM: 11 RCT (N=14 to 244)	Inconsistent -1 Imprecise -2	Frequency (all RCTs) 0% to 7%, Excluding very small trial (n=14), frequency 0%-3%. **Older devices (9 RCT):** 0% to 7%, included: • Hospitalization for DKA (2% to 7%, 2 trials); *2% (1/44) caused by pump failure.* • Serious skin reactions (0% to 6%, 2 trials) • Diabetes-related hospitalization (3%, 1 trial) • Insertion site infections resulting in cellulitis, skin abscess (1% each, 3 trials) • Serious device or study related AE not otherwise specified (0%, 2 trials) **Newer (2 RCT, N=52 ,142**): 0% - 1%; Retinal detachment (1%) **Conclusion**: Serious device-related AE (as reported by authors) were relatively rare. Sample size may be too small to detect	⊕⊕◯◯ LOW
Flash CGM 2 (N=269)	Risk of bias -1 Inconsistent -1 Imprecise -1	Frequency, 1% to 3%: Sensor site allergic, reaction necrosis or infection; rash, erythema, pain, itching **Conclusion**: AEs appear to be rare; severity not defined	⊕◯◯◯ INSUFFICIENT

Analytics

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KQ2: Technical or mechanical issues

Outcome, f/u Studies	Downgrade	Conclusion	Quality
Technical or mechanical issues 3 months 4 (N=27 to 157)	Risk of bias -1 Imprecise -1	Frequency (3 RCTs) 1% to 16% • Sensor-related, loss of all glucose readings (15%) • Mechanical problems, not further specified (16%) • "Device issue" (1%) (newer CGM device; Lind) Women with preexisting T1DM during pregnancy (1 RCT, n=103 CGM), older CGM device (Feig): • 81% reported issues related to transmitter/receiver connection, various sensor problems; others (not specified) • 78% did not use the device (alarms too frequent, inaccurate readings, too difficult to operate, sensor errors, calibration issues, other) **Conclusion:** Definitions and reporting of technical or mechanical issues varied and were not well reported across trials	⊕⊕◯◯ LOW

Aggregate Analytics

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KQ2: Non serious device-related AE (proportion with ≥1 event)

Non serious device-related adverse events (proportion with ≥1 event) 3 to 8.5 months 7 RCT (N=25 to 157) 1 prospective cohort (n=83)	Risk of bias -1 Imprecise -1	Frequency 0% to 45% (RCTs). **Sensor or insulin infusion site skin-related AE** accounted for most (e.g., erythema, inflammation, rash/allergic reaction, mild infection) Excluding trial of preexisting type 1 DM during pregnancy which reported 45% with skin change range was 0% to 24%. **Newer device** (N= 142, Lind): 3% skin-related problems, including allergic reaction to sensor, inflammation, itching, and rash at application site. **Cohort study** local skin reaction/irritation(36%) **Conclusion:** Non-serious device related adverse events, especially skin-related problems, are common	⊕⊕◯◯ LOW
Flash CGM 2 (N=269)	Risk of bias -1 Inconsistent -1 Imprecise -1	Frequency 4% to 8%; allergic reaction at sensor site, rash, erythema, pain, itching, edema, site infection Also reported "expected sensor-insertion site symptoms" (not considered AEs by the authors) in up to 40% of subjects; Events similar to those reported as "non-serious device-related"; unclear how outcomes differ and if there is overlap between them. **Conclusion:** Definitions of adverse events/distinction between events and symptoms was unclear.	⊕◯◯◯ INSUFFICIENT

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KQ3: Differential Efficacy and Harms

RCTs Exposure	Outcome (F/U)	Downgrade	Conclusion	Quality
T1DM 1 RCT N = 155 (Beck 2017[a]) **T2DM** 1 RCT N = 152 (Beck 2017[b]) **Exposures** **Baseline HbA1c;** **Age;** **Percent CGM time <70 mg/dL;** **SMBG frequency;** **Education;** **Hypoglycemia Unawareness Score;** **Diabetes Numeracy Score;** **Hypoglycemia Fear Total Score;** **Clinical site (T1DM only)**	Δ baseline HbA1c % 6 months	Consistency (Unknown) Indirect (-1) Imprecise (-1) HTE (-1)	**T1DM** No factors modified effect. **T2DM** Baseline Hypoglycemia Unawareness Survey scores: greater ↓ in mean HbA1c % levels in subjects with **reduced awareness or uncertainty (score ≥3)**, vs. higher awareness (score ≤2), following **CGM** but not SMBG (interaction p=0.031). No other factors modified **Conclusion:** Insufficient evidence precludes drawing firm conclusions.	⊕◯◯◯ INSUFFICIENT

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KQ 4: Full Economic Studies – Adults T1DM, non U.S. Studies

	Chaugule 2017 Canada QHES 86/100	Roze 2014 Sweden QHES 93/100
Population Adults	Mean 46 y.o., 53% Male Baseline HbA1c = 8.6% MDI	Mean 27 y .o., 54.5% Female Baseline A1c = 8.6% Assumed 13 yrs. since diagnosis, CSII
Clinical data	DIAMOND Trial	IMS CORE Diabetes Model, DCCT, pubs
Time horizon	50 years	70 years
ICER	$43,926/QALY	$57,433 / QALY
SA Range	$42,552 to $84,972	$43,751 to $92,759
Author's Conclusion	**At WTP threshold of $50,000 CGM robustly, cost effective vs. SMBG**	**CGM is a cost–effective option in the treatment of T1DM in Sweden**
Limitations	• **Canadian societal perspective stated; only direct costs reported** • **SA for long-term micro- and macrovascular complications not presented** • **Lifetime horizon; RCT data to 12 months. Change in HbA1C based on DIAMOND trial; Unclear if 1% change over lifetime sustainable.** • **Industry funded**	• **Swedish societal perspective** • **Limited acknowledgment of modeling, study limitations** • **Lifetime horizon; RCT data provide information up to 12 months.** • **Industry funded**

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KQ 4: Full Economic Studies – Adults T1DM, U.S. Studies

	Huang 2010 U.S. QHES 85/100	McQueen 2011 U.S. QUES 93/100
Population Adults	Two A1c cohorts : Mean 43 y.o. (25-73) 57% Female; Baseline A1c = 7.6 (SMBG), 7.1% (CGM): A1c <7.0% (age 31y.o., 8-65); MDI and CSII	Mean 40 y.o. Baseline HbA1c = 7.6% 20 yrs. since diagnosis MDI and CSII
Clinical	JDRF, DCCT, pubs	C.D.C. CE group; experts, DCCT, pubs
horizon	Lifetime	33 years
ICER	$98,679 /QALY	$45,033 / QALY
SA Range	$70,000 to $701,397	$12, 000 to $300,000; CE in 48% Monte Carlo simulations at < $50,000; 70% of simulations < $100,000/QALY
Author's Conclusion	**Wide CI (CGM dominating, being dominated by SMBG); Immediate QOL of CGM responsible majority of projected lifetime benefits**	**CGM cost effective in more circumstances than not at WTP of $100,000.**
Limitations	• **CV complications From T2DM CV model** • **Lifetime horizon (RCT data to 12 months)** • **High baseline utilities - ceiling on potential OQL benefit of CGM** • **Unclear if models for microvascular and CV complications reflect current care** • **JDRF grant**	• **Some costs were extrapolated from studies that include all age groups.** • **Time horizon; sustainability of improved A1C unclear** • **Substantial variation in ICER based on SA/modeling of complications based on probabilities from different populations**

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KQ 4: Full Economic Studies – Adults T2DM, non U.S. Studies

Type 2 Studies:	Fonda 2016[37] U.S. QHES 75/100
Population Adults	57.8 y.o.; T2DM least 3 months. Not taking prandial insulin. Initial A1C of between 7% and 12% ; MDI and CSII
Perspective	Third-party payer (direct costs only)
Time horizon	Lifetime
Clinical data	Risk adjustments from UKPDS, DCCT Framingham Heart Study, literature, CORE Diabetes Model
ICER	$8,898 / QALY
SA	Probabilistic cost-effectiveness analysis: likelihood CGM CE 70% at the willingness-to-pay threshold of $100,000/QALY.
Author's Conclusion	**CGM offers a cost-effective alternative to populations matching that the trial specifically: short-term, intermittent use in people with type 2 diabetes.**
Limitations	• **Small sample size of trial (n = 100) to estimate effectiveness parameters.** • **Limited sensitivity analyses presented; results of one-way SA not discussed** • **Used older CGM device that has since been update.** • **Life-time horizon used; Few RCT data on long-term CGM use in type 2 DM.** • **Unclear if DCCT, USPKD, Framingham complications data reflect current care** • **Industry funding (Dexcom Grant)**

Analytics

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Summary: KQ1, Efficacy in Children with T1DM

Outcome		3 months	6 months	12 months
Success (HbA1c% <7%)	Effect	RD -19% (-32% to -5%) 1 RCT	NS 2 RCTs	NS 1 RCT
	SoE	⊕⊕	⊕⊕⊕	⊕⊕⊕
Mean HbA1C% change	Effect	MD -0.22% (-44% to 0.0%)* 3 RCTs	NS 4 Parallel RCTs	NS 2 RCTs (heterog)
	SoE	⊕⊕	⊕⊕⊕	⊕⊕⊕
Hypoglycemia (Time at <70 or <55mg/dL)	Effect	NS 2 RCTs	NS 2 RCTs	NS 1 RCT
	SoE	⊕⊕	⊕⊕	⊕⊕
Severe Hypoglycemic Events	Effect	↓ power, NS	↓ power, NS	↓ power, NS
	SoE	⊕⊕	⊕⊕	⊕⊕

*MS=marginally significant, clinical significance unclear; 6 months 1 cross-over trial MD -0.46% favored CGM

Aggregate Analytics

Favors CGM Moderate	Favors CGM Low	NS difference Moderate	NS difference Low	INSUFFICIENT

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Summary: KQ1, Efficacy in Adults with T1DM: HbA1c%

Parallel Trials

Outcome		3 months	6 months	12 months
Success (HbA1c% <7%) (TCGM)	ES	1RCT RD -10% (-18% to -1%)* 1RCT RD -29% (-46% to -13%) Heterogeneous	RD -23% (-36% to -10%) 3 RCTs	RD -23% (-31% to -14%) 1 RCT
	SoE	⊕⊕	⊕⊕	⊕⊕
Mean HbA1C% change (TCGM)	ES	MD -0.43 (-69 , -19) 6 RCTs (Heterogeneous)	MD -0.52 (-0.84, -0.19) 4 RCTs (Heterogeneous)	MD -0.60 (-0.76, 0.44) (1 RCT)
	SoE	⊕⊕	⊕⊕	⊕⊕
Mean A1C % change (FCGM, 1 RCT)	ES	NS	NS	NR
	SoE	INSUFF	INSUFF	NR

Cross-over Trials

TCGM Difference in final mean A1C % (SOE LOW)	
6 Parallel RCTs (3-12 months)	Pooled MD -0.48 (-0.7 to -0.28)
2 Cross-over (26 weeks)	Pooled MD -0.42 (-0.51 to -0.33)
2 Cross-over (4-16 weeks)	NS

Aggregate Analytics

Favors CGM Moderate	Favors CGM Low	NS difference Moderate	NS difference Low	INSUFFICIENT

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Summary: KQ1, Efficacy, adults with T1DM: Hypoglycemia

Outcome		3-4 months*	6 months*
Hypoglycemia (↓ Time at <70 mg/dL) TCGM	ES	MD -21m/d (-36.3, -6.6) 2 PRCT MD -66 m/d (-84m, -48) 1 CRCT	MD -19.7 m/d (-37.9, -1.5) 2 PRCT MD -2.0% time (-2.8, - 1.2) 1 CRCT
	SoE	⊕⊕	⊕⊕
Hypoglycemia (↓ Time <70 mg/dL) Flash CGM (1 trial)	ES	MD -65.4 m/d	MD -74.4 m/d
	SoE	INSUFF	INSUFF
Hypoglycemia (↓ Time <55mg/dL) TCGM	ES	MD -14 m/d (-23 to -5.4) 2 trials	MD -22m/d(-30.4, -13,63) 1 PRCT MD -4.3m/d (-11.7, 3.0) 1 PRCT (Heterogeneous)
	SoE	⊕⊕	INSUFF
Hypoglycemia (↓ Time at <55mg/dL) Flash CGM (1trial)	ES	MD - 40.8 m/day	MD -49.2 m/d
	SoE	INSUFF	INSUFF
Severe Hypoglycemic Events	ES	↓ power, NS	↓ power, NS
	SoE	⊕⊕	⊕⊕

*Includes parallel and cross-over trials

Aggregate Analytics

Favors CGM Moderate	Favors CGM Low	NS difference Moderate	NS difference Low	INSUFFICIENT

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Summary: Efficacy, mixed populations (children, adults) with T1DM:

Outcome		3 months	6 months
Success (HbA1c% <7%)	ES	RD-19% (-32%, -7%) 3 RCTs	NS 2 RCTs
	SoE	⊕⊕	⊕⊕
Mean A1C% change	ES	MD -0.25%* (-0.48%, -0.02%) 3 RCTs	MD -0.19% (-0.34%, -0.04%) 4 PRCTs* MD -0.43 (-0.32%, -0.55%) 1 CRCT
	SoE	⊕⊕⊕	⊕⊕⊕
Hypoglycemia (↓Time at <70 mg/dL)	ES	NS 2 RCTs	MD -16.3 m/d (-32.2, -0.37) 4 RCTs
	SoE	⊕⊕	⊕⊕
Hypoglycemia (↓Time at <55mg/dL)	ES	NS 2 RCTs	NS 3RCTs
	SoE	⊕⊕	⊕⊕
Severe Hypoglycemic Events	ES	↓ power, NS, 4 RCTs	↓ power, NS, 6 RCTs
	SoE	⊕⊕	⊕⊕

*clinical significance unclear

Favors CGM Moderate	Favors CGM Low	NS difference Moderate	NS difference Low	INSUFFICIENT

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Summary: KQ1, Adults with T2DM, HbA1c % outcomes

Outcome		3 months	6 months	9, 12 months
Success (HbA1c% <7%)	ES	adj. RD 10% (-2% , 23%) (1 trial)	adj. RD 3% (-9%, 14% (1 trial)	NR
	SoE	⊕⊕	⊕⊕	
HbA1c% absolute reduction ≥0.5%	ES	adj. RD 31% (1 trial)	adj. RD 31% (1 trial)	NR
	SoE	⊕⊕	⊕⊕	
Mean HbA1C% change TCGM	ES	MD -0.49% (-0.71, -0.2) (3 trials)	MD -0.37% (-0.59, -0.14) (3 trials)	9 mos (NS) 12 mos (NS) 1 trial
	SoE	⊕⊕⊕	⊕⊕⊕	
Mean HbA1C% change, FCGM	ES	NR	NS, 1 trial	NR
	SoE		INSUFF	

Favors CGM Moderate	Favors CGM Low	NS difference Moderate	NS difference Low	INSUFFICIENT

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KQ1 Summary: Adults with T2DM, Hypoglycemia Outcomes

Outcome		3 months	6 months
<50 mg/dl: min/day, % of readings, or % time TCGM	ES	NS 2 RCT	NS 1 RCT
	SoE	⊕⊕	⊕⊕
<55 mg/dl: minutes/ day FCGM (1 trial)	ES	NR	Adj. MD -13.2 min/d (SE 4.1)
	SoE		INSUFF
<70 mg/dl: min/day, % readings day, or % time, TCGM	ES	NS 2 RCT	NS 1 RCT
	SoE	⊕⊕	⊕⊕
<70 mg/dl: min/day FCGM (1 trial)	ES	NR	Adj. MD -28.2 minutes (SE 8.0)
	SoE		INSUFF
Episodes, severe hypoglycemia, TCGM	ES	↓ power, NS (3 RCTs)	↓ power, NS (3 RCTs)
	SoE	⊕⊕	⊕⊕
Episodes, severe hypoglycemia, FCGM	ES	↓ power, NS,	↓ power, NS
	SoE	INSUFF	INSUFF

Favors CGM Moderate	Favors CGM Low	NS difference Moderate	NS difference Low	INSUFFICIENT

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KQ 2 Summary: Safety

Inconsistent definitions, classification, reporting of AEs make conclusions challenging. There are limited data on newer devices. Most AEs relate to sensor-related skin problems. AEs for CGM only

Outcome		
AEs leading to discontinuation TCGM	Effect	**Older devices (8 RCT):** Operation (3%), alarm frequency (6%), discomfort, inconvenient (5/25pts) **Newer (2 RCT):** Allergic rx (1%), cannot upload data (4%) **2 Observational studies** 44%, 61%
	SoE	⊕⊕
AEs leading to discontinuation Flash CGM	Effect	2% to 5%: itching, rash, erythema, weeping at insertion site; severity of events unclear/not defined.
	SoE	Insufficient
Serious device related AE (≥1 AE) TCGM	Effect	**Older (9 RCT):** Hospitalization (DKA 2%-7%, other (3%); Skin reaction (0-6%), infection (leading to cellulitis, abscess 1%) **Newer (2 RCT):** 0% - 1%; Retinal detachment (1%)
	SoE	⊕⊕
Serious device related AE (≥1 AE) Flash CGM	Effect	1-3% Site allergic reaction, necrosis, infection, rash, erythema, pain, itching
	SoE	Insufficient

Moderate	Low	INSUFFICIENT

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KQ 2 Summary: Safety

Inconsistent classification, reporting of AEs make conclusions challenging; limited data on newer devices

Outcome		
Technical, mechanical issues (3 months)	**Effect**	• **4 RCTs:** 1% (not defined, new device) to 16% (sensor issues w/data loss, mechanical problems) • **1 RCT:** T1DM in pregnancy: 81% (transmitter/receiver connection, sensor problems); 78% didn't use (alarm frequency, sensor or reading errors, calibration, difficulty operating)
	SoE	⊕⊕
Non-serious AE (≥1 AE) TCGM	**Effect**	• 0% to 45% (7 RCTs), Excluding RCT of T1DM in pregnancy range was 0% to 24%. Sensor or insulin infusion site skin-related AE accounted for most • Newer device (1RCT: 3% skin-related problems); • Cohort study: 36% (local skin reaction/irritation)
	SoE	⊕⊕
Non-serious AE (≥1 AE) Flash CGM	**Effect**	4% to 8%; allergic reaction, infection at sensor site, rash, erythema, pain, itching, edema; reported "expected sensor-insertion site symptoms" (not considered AEs by the authors) in up to 40% of subjects; distinction between events and symptoms was unclear
	SoE	Insufficient

Moderate	Low	INSUFFICIENT

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Summary: KQ1, Preexisting T1DM in Pregnancy

Outcome		Up to 36 gest. weeks
Caesarean section	**ES**	RD -11% (-21%, -1%), 2 trials
	SoE	⊕⊕⊕
Admission to NICU	**ES**	RD -16% (-29%, -3%) 1 trial
	SoE	⊕⊕
Gestational age; Birthweight; Miscarriage; Preterm Delivery; Preeclampsia; Studies may be underpowered to detect some outcomes	**ES**	NS (2 trials)
	SoE	⊕⊕⊕
Large for gestational age; episodes of severe neonatal and severe maternal hypoglycemia; Hypoglycemia (neonatal, maternal); Still birth; Birth trauma; and HbA1c% measures (success, ≤6.5%; mean change from baseline); Studies may be underpowered to detect some outcomes	**ES**	NS (1-2 trials)
	SoE	⊕⊕
Major congenital anomalies; Time spent in hypoglycemia (≤70 or <63 mg/dl range)	**ES**	NS (1-2 trials)
	SoE	⊕

Favors CGM Moderate	Favors CGM Low	NS difference Moderate	NS difference Low	INSUFFICIENT

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Summary: KQ1, Preexisting T2DM in Pregnancy

Outcome		Up to 36 gest. weeks
Gestational age; Birth weight; Large for gestational age; Neonatal hypoglycemia; Miscarriage; Perinatal mortality; Caesarean section; HbA1c%; Hypoglycemia (% of SMBG values ≤70 mg/dl); Severe Hypoglycemia (episodes requiring 3rd party help); low power	Effect	NS (1 small trial)
	SoE	⊕

Summary: KQ1, Gestational Diabetes

Outcome		Up to 36 gest. weeks
Gestational age; Birth weight; Large for gestational age; Macrosomia; Neonatal hypoglycemia; Perinatal mortality; Caesarean section; HbA1c% (mean change from baseline); low power	Effect	NS (1 trial)
	SoE	⊕

Favors CGM Moderate	Favors CGM Low	NS difference Moderate	NS difference Low	INSUFFICIENT

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Summary: Full economic studies

Cost-effectiveness:

- **Adults with T1DM (4 studies):** CGM may be cost-effective at WTP $100,000/QALY; ICERs ranged from $43,926/QALY to $98,679 /QALY; wide range of ICERs from sensitivity analyses; long time horizon
- **Adults with T2DM (1 study):** CGM may be cost-effective 70% at WTP $100,000/QALY. Long time horizon
- **No Evidence**: Children/adolescents, patients with pre-existing DM in pregnancy, those with GDM or those >65 years old or FCGM

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Considerations and remaining questions

- Baseline HbA1c% for most studies of TCGM in T1DM was ≥ 8%; only trial of FCGM in T1DM baseline A1c was <7%
- Impact of CGM data and how it is used in daily decision making is unclear
- Which patients may benefit most from CGM is unclear
- Daily sensor use/adherence in trials vs. real world
- Trial data to 12 months; efficacy and safety of daily use for longer periods of time is unclear
- Few studies with newer devices, none in children; some results across newer and older devices are similar
- Use in >65 years olds not described in comparative studies of traditional CGM
- No long term data on macro or microvascular disease

Aggregate Analytics

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Washington State Health Care Authority

FINAL key questions and background

Continuous glucose monitoring

Background

Diabetes mellitus (DM), or diabetes, is a serious metabolic disease characterized by chronic elevation of blood glucose (i.e., hyperglycemia) resulting from defects in insulin secretion, insulin action, or both. No definitive cure is known at this time. Diabetes is generally categorized into three major types based on etiology: Type 1 diabetes (T1DM) (formerly called juvenile diabetes or insulin-dependent diabetes mellitus [IDDM]), Type 2 diabetes (T2DM) (formerly called adult onset diabetes mellitus [AODM] or non-insulin dependent diabetes [NIDDM]), and gestational diabetes mellitus (GDM).

Diabetes is a leading cause of morbidity and mortality and is associated with substantial healthcare and societal costs. An estimated 29.9 million Americans (9.3% of the population) had diabetes in 2015 and, by 2050, the prevalence of diabetes in the U.S. adult population is projected to increase to between 21% and 33%. Serious complications related to diabetes include diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic nonketotic syndrome (HHNS), as well as longer term morbidity due to microvascular (e.g., retinopathy, nephropathy, neuropathy) and macrovascular (e.g., heart disease, stroke) complications; other diabetes related complications include increased risk of infections, cancer and other autoimmune disorders including celiac sprue, thyroid disease, rheumatoid arthritis, and vitiligo.

Intensive insulin therapy, a term used to describe tight management of blood glucose levels, has been shown to reduce the risk of long-term diabetic complications by lowering average blood sugar levels, but also increases the risk of hypoglycemia, which can result in serious morbidity and even death, and causes fear of hypoglycemia which is a major barrier to optimal glucose control.

Real-time continuous glucose monitoring (CGM) is advanced glucose monitoring technology that continuously measures interstitial glucose levels, displays the current blood glucose level as well as the direction and rate of change, and uses alarms and alerts to inform patients when blood glucose is exceeding or falling below specified thresholds. Conventional fingerstick self-monitoring of blood glucose (SMBG), sometimes called intermittent monitoring, is a technique for testing blood glucose using a portable glucose meter designed for home use. SMBG provides an instantaneous reading of current blood glucose levels at single points in time, but cannot indicate whether the glucose level is on its way up or down. CGMs were designed to aid in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long term therapy adjustments, which may minimize these excursions. With the exception of one FDA-approved device (Dexcom G5 Mobile CGM System), CGMs are intended to complement, not replace, information obtained from a standard home glucose monitoring device; they are not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a fingerstick may be required. CGMs can be used as stand-alone devices or in conjunction with compatible insulin pumps.

Policy context

This topic was originally reviewed in 2011. It is proposed for re-review based on new evidence and newly expanded indications for continuous glucose monitoring (CGM). New evidence and indications are identified that support re-reviewing the evidence for continuous glucose monitoring.

Objectives

The first aim of this report is to update the 2011 HTA on glucose monitoring in children and adolescents by systematically reviewing, critically appraising and analyzing new research evidence on the safety and efficacy of continuous glucose monitoring in persons under 18 years old with insulin requiring diabetes mellitus. The second aim is to systematically review, critically appraise and analyze research evidence on the safety and efficacy continuous glucose monitoring in persons with type 1 or type 2 diabetes (regardless of insulin requirement), including pregnant women with pre-existing or gestational diabetes. SMBG as a stand-alone means of monitoring blood glucose will not be included as an intervention.

Key questions

In persons with diabetes mellitus (DM):

1. What is the evidence of efficacy and effectiveness of continuous monitoring?
2. What is the evidence of the safety of continuous glucose monitoring?
3. What is the evidence that glucose monitoring has differential efficacy or safety issues in sub-populations?
4. What is the evidence of cost-effectiveness of continuous glucose monitoring?

Scope

Population: Persons with diabetes mellitus, including those with type 1 and type 2, and pregnant women with pre-existing diabetes or gestational diabetes

Interventions: FDA-approved real-time continuous glucose monitoring devices and FDA-approved combination devices integrating real-time continuous glucose monitoring with insulin pump/infusion (including sensor augmented insulin pumps).

Comparators: Self-monitoring using convention blood glucose meters, attention control, blinded/sham CGM, and usual care.

Outcomes:

Primary clinical outcomes:

- Microvascular complications (e.g., vision loss, kidney failure, peripheral neuropathy, objectively assessed)
- Macrovascular complications (e.g., coronary artery, cerebrovascular or peripheral arterial disease, objectively assessed)
- Fetal outcomes, cesarean section rates

Primary intermediate outcomes:

- Achieving target (i.e. age-appropriate) HgA1C level
- Maintaining target (i.e. age-appropriate) HgA1C level
- Acute episodes of hypoglycemia

Secondary intermediate outcomes

- Acute episodes of hyperglycemia
- Acute episodes of diabetic ketoacidosis
- Quality of life (validated instruments only)

Safety outcomes:

- Mortality
- Morbidity from glucose meters or monitors

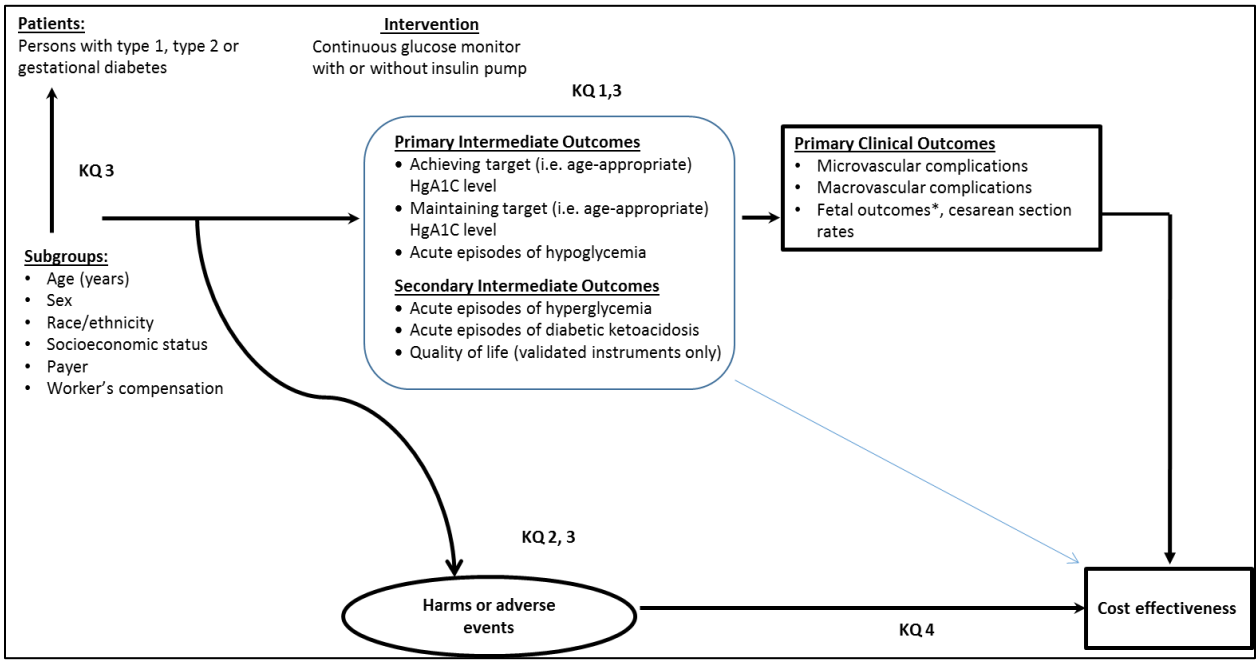
Economic outcomes:

- Long term and short term comparative cost-effectiveness measures

Studies:

Only high quality (low risk of bias) comparative studies will be considered for Key Questions 1-3. Observational studies with longer term clinical outcomes or safety outcomes will be considered for Key Questions 1 and 3. Full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be sought for Key Question 4; studies using modeling may be used to determine cost-effectiveness over the full duration of glucose monitoring, which is a lifetime. Observational studies of safety will be considered.

Analytic framework



*Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, admission to a neonatal intensive care unit, stillbirth, and neonatal and perinatal mortality.

Public comment and Response

See ***Draft key questions: Public comment and response*** document published separately.

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical Committee Findings and Decisions

Efficacy Considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next Step: Cover or No Cover

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions

If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
    - Refer to evidence identification document and discussion.
    - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
    - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
    - What are the known conditions/criteria and evidence state
    - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical Committee Evidence Votes

First Voting Question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety Outcomes	Importance of Outcome	Safety Evidence / Confidence in Evidence
Morbidity/adverse events from devices		
Mortality		

Efficacy – Effectiveness Outcomes	Importance of Outcome	Efficacy / Effectiveness Evidence
Achieving target HbA1c level		
Mean change HbA1c		
Hypoglycemic events (acute)		
Vision loss		
Kidney failure		
Peripheral neuropathy		
Coronary artery disease		
Cerebrovascular disease		
Fetal outcomes		
Caesarean section rates		
Acute episodes hyperglycemia		
Acute episodes diabetic ketoacidosis		
Quality of life		
Pregnancy related outcomes Gestational age Birth weight Large for gestational age Neonatal hypoglycemia Miscarriage Perinatal mortality Caesarean section HbA1c %		

Cost Outcomes	Importance of Outcome	Cost Evidence
Costs of testing		
Cost effectiveness		

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Special Population / Considerations Outcomes	Importance of Outcome	Special Populations/ Considerations Evidence
Baseline HbA1c		
Age		
% CGM time<70 mg/dL		
SMBG frequency		
Education level		
Hypoglycemia unawareness score		
Diabetes numeracy score		
Hypoglycemia fear total score		
Clinical site		

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

For Safety: Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Efficacy/Effectiveness: Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Cost Outcomes/Cost-Effectiveness: Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not Covered _____ Covered Unconditionally _____ Covered Under Certain Conditions

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next Step: Proposed Findings and Decision and Public Comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?

2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next Step: Final Determination

Following review of the proposed findings and decision document and public comments:

Final Vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.

Medicare and Coverage Guidelines

[From page 54 of the Final Evidence Report]

Medicare

Medicare does not have an NCD on CGM systems; however there is an NCD on home blood glucose monitors. These and related accessories and supplies are considered medically necessary and are covered as long as certain criteria are met by the patient or the patients' care giver. CMS updated their policy on CGM devices in a ruling (CMS Ruling 1682R) published on January 12, 2017. This ruling separated CGM devices into therapeutic and non-therapeutic devices, and allows for therapeutic devices to be considered as durable medical equipment (DME). Therapeutic devices are those used as a replacement for fingerstick BG testing for diabetes treatment decisions (i.e. used as a primary system and not as an adjunct) and must meet five criteria used to classify DMEs. The ruling does not establish CGM broadly as medically necessary but does allow for claim-by-claim payment for devices approved for therapeutic uses.

Guidelines

[From page 27-35 of Final Evidence Report]

Table 2. Summary of clinical guidelines

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
American Diabetes Association (ADA)* [7] Standards of Medical Care in Diabetes (2017)	1 meta-analysis 4 RCTs 1 registry study 3 studies, type NR	CGM **may be a useful tool** in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. Individual readiness **should be assessed** prior to prescribing CGM. Robust diabetes education, training, and support **are required** for optimal CGM implementation and ongoing use. *Adult population* CGM, when used properly and in conjunction with intensive insulin regimens, **is a useful tool** for lowering A1C levels in selected adults (aged 25 years or older) with T1DM. People who have been using CGM successfully **should have continued access** after they turn 65 years old.	C† E† E† A† E†

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
		Pediatric population CGM **may be helpful** for lowering A1C levels in children, teens, and younger adults.	B†
Joslin Diabetes Center and Joslin Clinic (Shahar et al.) [140] Clinical guideline for adults with diabetes (2015, revised 2017)	1 RCT 2 studies, type NR	For patients using RT-CGM to treat hypoglycemia, blood glucose levels should be checked 15 minutes post treatment using a finger stick and not the sensor reading. CGM **can be considered** if the patient has a history of severe recurrent hypoglycemia or hypoglycemia unawareness.	1B‡ NR
Peters et al. [118] Diabetes Technology—Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline (2016)	<u>T1DM in adults</u> 7 studies, type NR <u>T2DM in adults</u> 1 RCT 1 study, type NR	RT-CGM **is recommended** for adults patients with T1DM who have A1C levels above target and who are willing and able to use devices on a nearly daily basis. RT-CGM **is recommended** for adult patients with well-controlled T1DM who are willing and able to use devices on a nearly daily basis. **It is suggested** that short-term, intermittent RT-CGM is used in adult patients with T2DM (not on prandial insulin) who have A1C levels at 7% or greater and are willing and able to use the device. **It is suggested** that adults with T1DM and T2DM who use CSII and CGM receive education, training, and ongoing support to help achieve and maintain individualized glycemic goals.	1, A§ 1, A§ 2, C§ Ungraded Good Practice Statement
Handelsman et al. [60] American Association of Clinical Endocrinologists and American College of Endocrinology—Clinical Practice Guidelines for Developing a Diabetes	2 RCTs	CGM **should be considered** for patients with T1DM and T2DM on intensive insulin therapy to improve A1C levels and reduce hypoglycemia. CGM **may benefit** patients not taking insulin.	Grade B, BEL 2** Grade D, BEL 4**

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
Mellitus Comprehensive Care Plan (2015)			
Blumer et al. [21] Diabetes and pregnancy: an Endocrine Society clinical practice guideline (2013)	NR	CGM **is suggested** for use during pregnancy in women with overt or gestational diabetes when self-monitored blood glucose levels (or HbA1C values in women with overt diabetes) are not sufficient to assess glycemic control	2++††
Klonoff et al.‡‡ [86] Continuous Glucose Monitoring: An Endocrine Society Clinical Practice Guideline (2011)	<u>T1DM in children and adolescents</u> 3 RCTs 11 studies, type NR <u>T1DM in adults</u> 2 RCT 5 studies, type NR	RT-CGM **is recommended** for children and adolescents with T1DM who have achieved HbA1c levels below 7.0%. RT-CGM **is recommended** for children and adolescents with T1DM with T1DM who have HbA1c levels of 7.0% or higher who are able to use devices on a nearly daily basis. **No recommendations are made for or against** the use of RT-CGM in children with T1DM who are less than 8 years old.	1, A§ 1, B§ NA§
NICE [112] Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) (2016)	NR	The MiniMed Paradigm Veo system **is recommended** as an option for managing blood glucose levels in people with T1DM only if: • They have episodes of disability hypoglycemia despite optimal management with CSII *and* • The company arranges to collect, analyze, and publish data on the use of the MiniMed Paradigm Veo system The MiniMed Paradigm Veo system **should be used under** the supervision of a trained multidisciplinary team who are experienced in CSII and CGM for managing T1DM only if the person or their carer:	NR

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
		• Agrees to use the sensors for at least 70% of the time • Understands how to use it and is physically able to use the system *and* • Agrees to use the system while having a structured education program on diet and lifestyle, and counselling People who start using the MiniMed Paradigm Veo system **should only continue use it** if there is a sustained decrease in the number of hypoglycemic episodes. There is **insufficient evidence** for the Vibe and G4 PLATINUM CGM to support routine adoption in the National Health Service for managing blood glucose levels in people with T1DM.	
NICE (National Clinical Guideline Centre) [108] Type 1 diabetes in adults: diagnosis and management (2015)	NR	**Do not offer** RT-CGM routinely in adults with T1DM. RT-CGM **can be considered** for adults with T1DM willing to commit to using at least 70% of the time and to calibrate the device as needed, and who have any of the following characteristics despite optimized use of insulin therapy and conventional BGM: • > 1 episode of severe hypoglycemia per year with no obviously preventable precipitating cause • Complete loss of awareness of hypoglycemia • Frequent (>2) episodes per week of asymptomatic hypoglycemia that causes problems with daily activities	NR

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
		• Extreme fear of hypoglycemia • Hyperglycemia (HbA1c levels of 9% or higher) that persists despite testing at least 10 times per day. RT-CGM **should only be continued** if HbA1c can be sustained at or below 7% and/or there has been a fall in HbA1c levels of 2.5% or more Adults with T1DM using RT-CGM should use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or CSII therapy. RT-CGM should be provided by a center with expertise in its use, as a part of strategies to optimize a person's HbA1c levels and reduce frequency of hypoglycemic episodes.	
National Collaborating Centre For Women and Children's Health [109] Diabetes (type 1 and type 2) in children and young people: diagnosis and management (2015)	NR	Offer ongoing RT-CGM with alarms to children and young people with T1DM who have at least 1 of the following: • Frequent severe hyperglycemia • Impaired awareness of hypoglycemia associated with adverse consequences (e.g. seizures or anxiety) • Inability to recognize or communicate about symptoms of hypoglycemia (e.g. cognitive or neurological disabilities) Offer ongoing RT-CGM for: • Neonates, infants, and pre-school children • Children and young people who have undertaken high levels of physical activity	NR

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
		• Children and young people who have comorbidities or who are receiving treatments that can make blood glucose control difficult CGM **can be considered** to help improve blood glucose control in children and young people who continue to have hyperglycemia despite insulin adjustment and additional support.	
National Collaborating Centre For Women and Children's Health [110] Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period (2015)	NR	**Do not offer** CGM routinely to pregnant women with diabetes. CGM **can be considered** for pregnant women on insulin therapy if one of the following applies: • Problematic severe hypoglycemia (with or without impaired awareness of hypoglycemia) • Unstable blood glucose levels (to minimize variability) • To gain information about variability in blood glucose levels **Ensure that support is available** for pregnant women who are using continuous glucose monitoring from a member of the joint diabetes and antenatal care team with expertise in its use.	NR
Wright et al. [161] A Practical Approach to the Management of Continuous Glucose Monitoring (CGM) / Real-Time Flash Glucose Scanning (FGS) in Type 1 Diabetes Mellitus in Children and Young	1 SR 2 RCTs 13 studies, type NR	Continuous CGM **can be considered** for any patient irrespective of age, sex, socioeconomic status, ethnic, or educational background who meet NICE criteria§§. Continuous CGM **can be considered** in children on CSII or MDI therapy.	B*** A*** B***

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
People Under 18 Years (2017)		Continuous CGM with alarms **should be considered** in any child of any age who has had a hypoglycemic seizure. Continuous CGM with alarms **should be considered** in all young children. Continuous CGM with alarms **should be considered** in all children of any age with neurodevelopmental or cognitive problems that impair their ability either to recognize or respond to hypoglycemia. CGM with alarms **should be considered** in frequent hypoglycemia and in nocturnal hypoglycemia. CGM with alarms **should be considered** in situations with individuals who have unawareness of hypoglycemia. CGM with alarms **should be considered** in individuals where anxiety or fear of hypoglycemia is high. CGM **can be considered** for improving diabetes control in children and young people by reducing HbA1c and/or reducing the time spent in hypoglycemia, with any HbA1c < 10%. CGM **is not recommended** for use to reduce HbA1c or hypoglycemia in children with HbA1c > 10%.	A*** D*** B*** B*** D*** B*** D***
Choudhary et al. [31] Evidence-Informed Clinical Practice Recommendations for Treatment of Type 1 Diabetes Complicated by Problematic Hypoglycemia (2015)	2 SRs 4 RCTs 1 observational study 4 studies, type NR	CSII or CGM **should be added** to the treatment regimen of patient's with T1DM and problematic hypoglycemia if glycemic and hypoglycemia targets are not met though an education or hypoglycemia-specific education program.	NR
Working Group of the Clinical Practice	NR	CGM **can be used** as an instrument to improve or maintain metabolic	A***

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
Guideline on Diabetes Mellitus Type 1 [159] Clinical practice guidelines for diabetes type 1 (2012)		control in patients motivated and trained in intensive care. However, CGM **is not recommended for universal use** for people with T1DM.	

BGM, blood glucose monitoring; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HbA1c, hemoglobin A1c (glycated hemoglobin); MDI, Multiple Daily Injection; NICE, National Institute for Health and Care Excellence; NR, not reported; RCT, randomized controlled trial; RT-CGM, real-time continuous glucose monitoring; SR, systematic review; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus

* Chamberlain 2016 details the ADA Standards of Medical Care from 2016. The paper supports the use of CGM for the reduction of severe hypoglycemia risk but gives no additional recommendations for CGM
†ADA evidence-grading systems for "Standards of Medical Care in Diabetes"

A: Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including

- Evidence from a well-conducted multicenter trial
- Evidence from a meta-analysis that incorporated quality ratings in analysis

Compelling nonexperimental evidence, i.e. "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford.
Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including

- Evidence from well-conducted trials at one or more institutions
- Evidence from meta-analysis that incorporated quality ratings in the analysis

B: Supportive evidence from well-conducted cohort studies

- Evidence from a well-conducted prospective cohort study or registry
- Evidence from a well-conducted meta-analysis of cohort studies

Supportive evidence from a well-conducted case-control study

C: Supportive evidence from poorly controlled or uncontrolled studies

- Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
- Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)
- Evidence from case series or case reports

Conflicting evidence with the weight of evidence supporting the recommendation

E: Expert consensus or clinical experience

‡ Strength of recommendation grading:
1A: strong recommendation and high quality of evidence
1B: Strong recommendation and moderate quality of evidence
1C: Strong recommendation and low quality of evidence
2A: Weak recommendation and high quality of evidence
2B: Weak recommendation and moderate quality of evidence
2C: Weak recommendation and low quality of evidence
§GRADE Strength of Recommendation:
1: Strong for an intervention
2: Weak for an intervention
3: Weak against an intervention
4: Strong against an intervention
GRADE Quality of Evidence rating:
A: High quality of evidence
B: Moderate quality of evidence
C: Low quality of evidence
D: Very low quality of evidence
** Strength of recommendation grading:

A: Strong
B: Intermediate
C: Weak
D: Not evidence based

Best evidence level (BEL) grading:
1: Meta-analysis of randomized controlled trials (MRCT) OR randomized controlled trials (RCT)
2: Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT) OR nonrandomized controlled trial OR prospective cohort study (NRCT) OR prospective cohort study (PCS) OR retrospective case-control study (RCCS)
3: Cross-sectional study (CSS) OR surveillance study (SS) OR consecutive case series (CCS) OR single case reports (SCR)
4: No evidence; based on theory, opinion, consensus, review, or preclinical study (NE)

††Quality of evidence and strength of recommendation grading:
Quality of evidence:
+ denotes very low quality evidence
++ denotes low quality evidence
+++ denotes moderate quality evidence
++++ denotes high quality evidence
Strength of recommendation:
1-indicates a strong recommendation
2-indicates a weak recommendation

‡‡Recommendations for adult populations were not included because updated guidelines from the Endocrine Society for adult populations are in Peters et al.

§§NICE criteria was stated as patients with the following indications: hypoglycemic seizures, frequent severe hypoglycemia, impaired awareness of hypoglycemia, anxiety regarding hypoglycemia, inability to recognize hypoglycemia due to cognitive or neurological disabilities, young children who may not be able to recognize and respond, patients undertaking high levels of physical activity, to reduce HbA1c, to improve glycemic control, or to reduce glycemic variation

***Strength of recommendation grading:
A: At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or*
A body of evidence consisting principally or studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 1++ or 1+
C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 2++
D: Evidence level 3 or 4; *or*
Extrapolated evidence from studies rated as 2+

Table 3. Summary of consensus statements

Consensus statement	Evidence Base	Recommendation	Rating/Strength of Recommendation
Danne et al. International Consensus on Use of Continuous Glucose Monitoring (2017)	**Type 1** 12 studies, type NR **Type 2** 3 studies, type NR **Gestational diabetes** 1 study, type NR	CGM **should be considered** in conjuction with HbA1c for glycemic status assessment nd therapy adjustment in all patients with type 1 and patients with type 2 diabetes treated with intesnsive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia Al patients **should receive training** in how to interpret and respond to their glucose data. Patient education and training for CGM	NR

Consensus statement	Evidence Base	Recommendation	Rating/Strength of Recommendation
		should utilized standardized programs with follow-up to improve adherence and facilitate appropriate use of data and diabetes therapies. CGM data **should be used** to assess hypoglycemia and glucose variability	
Bailey et al. [12] American Association of Clinical Endocrinologists and American College of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement (2016) **Fonseca et al.*** [50] Continuous Glucose Monitoring: A Consensus Conference of the American Association of Clinical Endocrinologists and American College of Endocrinology (2016)	<u>T1DM</u> 1 study, type NR 1 nonrandomized study 2 RCT <u>T2DM</u> 2 RCTs <u>Gestational Diabetes</u> 1 study, type NR 3 RCTs	CGM **should be available** to all insulin-using patients regardless of diabetes type, although **data on CGM is limited** in patients with T2DM receiving insulin/sulfonylureas or glinides. **No recommendation** can be made for CGM in patients with T2DM that have a low risk of hypoglycemia *Adult population* CGM is **recommended** in adults with T1DM, particularly in patients with history of severe hypoglycemia, hypoglycemia unawareness, and to assist in the correction of hyperglycemia in patients not at goal. *Pediatric population* CGM is **recommended** in children with pediatric T1DM, particularly in patients with history of severe hypoglycemia, hypoglycemia unawareness, and to assist in the correction of hyperglycemia in patients not at goal. More in-depth training and more frequent follow-up is recommended. *Pregnant population* CGM **can be used** during pregnancy as a teaching tool, to evaluate glucose patterns, and to fine-tune insulin dosing.	NR

Consensus statement	Evidence Base	Recommendation	Rating/Strength of Recommendation
		CGM in pregnancy **can supplement BGM** particularly to monitor nocturnal hypoglycemia or hyperglycemia and postprandial hyperglycemia.	
Rewers et al. [128] ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Assessment and monitoring of glycemic control in children and adolescents with diabetes (2014)	2 RCTs 8 studies, type NR	CGM devices are becoming available that **may particularly benefit** those with hypoglycemic unawareness.	A†
Kesavadev et al. [83] Consensus guidelines for glycemic monitoring in type 1/type 2 & GDM (2014)	<u>T1DM in adults and adolescents</u> 2 studies, type NR <u>T1DM in youth</u> 5 studies, type NR	CGM **may be a supplemental tool** to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. *Adult population* CGM in conjunction with intensive insulin regimens **can be useful** in lowering A1C in selected adults (age ≥25 years) with type 1 diabetes. *Pediatric population* CGM **may be helpful** in children, teens, and younger adults in lowering A1C levels. CGM **is recommended** in children and adolescents with T1DM who have achieved HbA1c levels less than 7.0%. CGM **is recommended** in youth with T1DM who have HbA1c levels 7.0% or higher and are able to use the device on a near-daily basis. *Pregnant population* Pregnant patients with T1DM **should be offered** CGM	D‡ A‡ C‡ D‡ D‡ Rating NR

Consensus statement	Evidence Base	Recommendation	Rating/Strength of Recommendation
Scaramuzza et al. [135] Recommendations for self-monitoring in pediatric diabetes: a consensus statement by the ISPED (2013)	2 SRs 3 RCTs 9 studies, type NR	Patients should fulfill the following criteria to be a candidate for CGM: • Children with no awareness of hypoglycemia or frequent episodes of severe hypoglycemia • Children and adolescents with impaired metabolic control (HbA1c > 8.5%) on intensive insulin therapy CGM **could be helpful** in the following circumstances: • To improve metabolic control regardless of HbA1c value • To reduce SMBG measurements, especially if > 10 times per day • To help patients undergoing competitive sports • To start insulin pump therapy	NR

BGM, blood glucose monitoring; CGM, continuous glucose monitoring; GDM, gestational diabetes mellitus; HbA1c, hemoglobin A1c (glycated hemoglobin); ISPAD, International Society for Pediatric and Adolescent Diabetes; ISPED, Italian Society of Pediatric Endocrinology and Diabetology; NR, not reported; RCT, randomized controlled trial; SMBG, self-monitoring blood glucose; SR, systematic review; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus

*Fonseca et al. was associated with the same consensus conference as Bailey et al; emphasis for information on recommendations was placed on Bailey et al. while Fonseca et al. was used for background information and context.
† System for rating strength of recommendation was not reported
‡ Strength of recommendation grading:
A: Type of evidence supporting recommendation is based on randomized controlled trials, meta-analyses, or systematic reviews
B: Type of evidence supporting recommendation is based on non-randomized controlled trials or uncontrolled randomized clinical trials
C: Type of evidence supporting recommendation is based on observational trials or evidence based reviews or case studies
D: Type of evidence supporting recommendation is based on opinion of expert panel