



**TITLE:**                                    **Continuous Glucose Monitoring Devices for Patients with  
Diabetes Mellitus on Insulin**

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## **CONTINUOUS GLUCOSE MONITORING DEVICES FOR PATIENTS WITH DIABETES MELLITUS ON INSULIN**

*A Technology Assessment*

### **INTRODUCTION**

The California Technology Assessment Forum is requested to update its review of the published scientific literature on the use of continuous blood glucose monitoring (CGM) devices in patients with diabetes mellitus. There has been considerable literature published on this topic since the most recent CTAF assessment in 2003 which concluded that there was not yet sufficient evidence that CGM devices improved net health outcomes.<sup>1</sup> There are additional new devices which have U.S. Food and Drug Administration (FDA) since that time as well.

### **BACKGROUND**

#### **Diabetes Mellitus**

Diabetes is a disease condition of altered glucose metabolism, resulting in elevated blood glucose levels. Type I diabetes, which accounts for 5-10% of diagnosed cases, results from a deficiency in insulin production in the beta cells of the pancreas, and usually has its onset in children and young adults. Individuals with Type I diabetes must take exogenous insulin either via multiple daily injections or via an insulin pump. Type II diabetes, the most common form of diabetes in adults, results from disordered insulin action and insulin resistance. While much of Type II diabetes is treated with oral medication, it can ultimately result in the inability of the pancreatic beta cells to produce insulin, thus requiring treatment with exogenous insulin. Between 2004-2006, 13% of adults with diabetes were treated with both insulin and oral medication, while 14% were treated with insulin only.<sup>2</sup>

The U.S. Centers for Disease Control and Prevention estimates that in 2007, 7.8% (23.6 million people) of the population had diabetes. This prevalence differs by age group, with increasing prevalence for older age groups: 0.2% of the population under 20 has diabetes, while 10.7% of all adults over 20 and 32.1% of adults over 60 have diabetes.<sup>2</sup> Diabetes carries with it a significant risk of microvascular (retinopathy, nephropathy, neuropathy) and macrovascular complications (cardiovascular and cerebrovascular disease). Diabetes is the leading cause of new cases of

blindness among adults, and is the leading cause of kidney disease.<sup>2</sup> Among adults, those with diabetes have a 2-4 fold increased risk of cardiovascular disease.<sup>3</sup>

### **Intensive Glucose Control**

Randomized controlled trials (RCT) have shown that intensive glucose control, generally to a Hemoglobin A1C (HbA1C) <7%, in both Type I and Type II diabetes decreases risk for microvascular complications and possibly for macrovascular complications as well.<sup>4,5</sup> More recent RCTs with macrovascular endpoints were unable to demonstrate that very intensive control – with goal HbA1C in the normal range - reduced risk in Type II diabetes, and in fact results are concerning for increased mortality risk, possibly related to hypoglycemia.<sup>6,7</sup> Additionally, poorly controlled diabetes in pregnant women with Type I diabetes is associated with major birth defects, increased rates of spontaneous abortions, and high birth-weight babies.<sup>2</sup>

### **Self-monitoring Blood Glucose**

The standard of care for home glucose measurement is self-monitoring of blood glucose (SMBG) with a blood glucose meter and a lancet to collect a drop of blood for measurement. This type of glucose measurement provides a snapshot in time with considerable accuracy. Patients on multiple insulin injections per day as well as on insulin pumps are frequently provided with algorithms to adjust their insulin dose according to their blood glucose measurement. What SMBG cannot provide is insight into the blood glucose trajectory – e.g. if it is on its way up or down.

### **Continuous Glucose Monitoring**

Continuous glucose monitoring devices are intended to provide fairly continuous data (every one to ten minutes) over the time that the device is worn by an individual. Devices for CGM measure interstitial glucose concentration via sensors which are inserted subcutaneously. The newer generation of devices appear to have glucose measurements which are more highly correlated with plasma glucose than those from the older devices.<sup>8,9</sup> Yet, there is clearly still some variability among devices, particularly in the hypoglycemia range<sup>10,11</sup>, and there is evidence that interstitial glucose values may lag behind blood glucose whether glycemia is rising or falling.<sup>12</sup> The CGM sensors require regular calibration with SMBG, and it is still recommended that acute treatment decisions for hyper- or hypoglycemia be based on confirmatory SMBG.<sup>13</sup>



Theoretical advantages of CGM use include use of alarms for recognition of hypoglycemia, including nocturnal hypoglycemia which often goes unrecognized, particularly in children<sup>14</sup>, as well as use of intensive data for fine-tuned adjustment of insulin regimen by either injection or pump, leading to improved glycemic control.

## **TECHNOLOGY ASSESSMENT (TA)**

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

There are now at least four CGM devices available on the market.

The DexCom™ STS™ Continuous Glucose Monitoring System (DexCom, Inc., San Diego, CA) received FDA Premarket Approval (PMA) on March 23, 2005. On May 31, 2007 the STS-7 Continuous Glucose Monitoring System received FDA clearance.

The Guardian-RT (Real-Time) CGMS (Medtronic MiniMed, Northridge, CA) received FDA PMA in July 2005 - previous versions also received FDA clearance. Also by Medtronic, the MiniMed Paradigm® REAL-Time Insulin Pump and CGM System was approved in April 2006.

The Abbott FreeStyle Navigator Continuous Glucose Monitoring System (Abbott Diabetes Care, Alameda, CA) received FDA PMA on March 12, 2008.

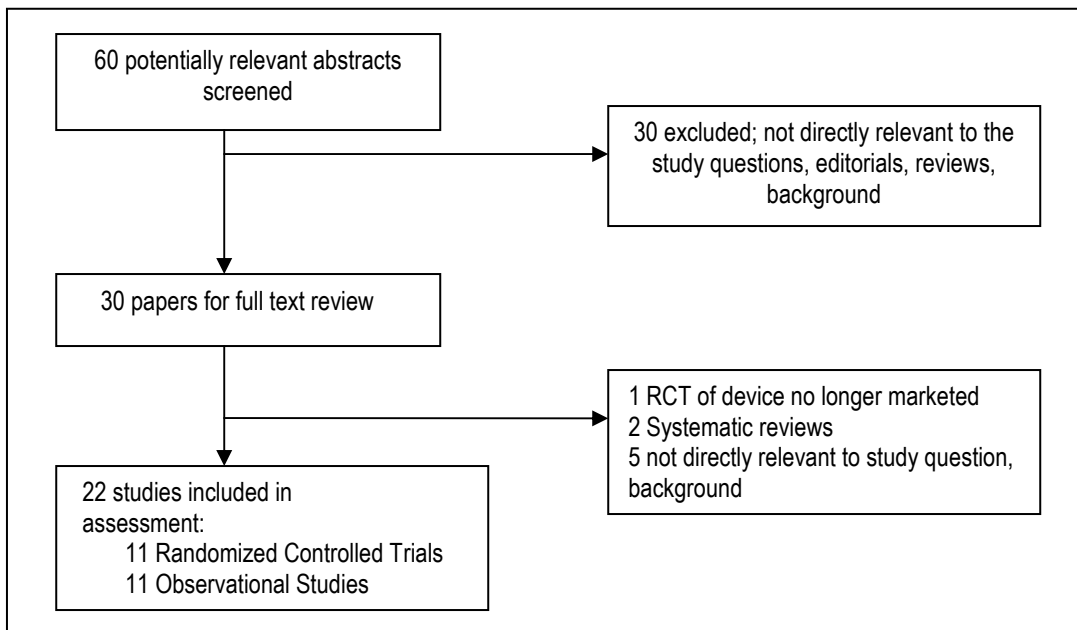
The GlucoWatch® Biographer family of CGM devices is no longer available. This device was included in the previous CTAF assessment but is not included in this assessment.

TA Criterion 1 is met.

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

The PubMed, Embase, and Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched for relevant references published since the previous CTAF review on this subject in 2003 through January 2009. (See appendix for search terms) The bibliographies of systematic reviews and key articles were manually searched for additional references. Abstracts of citations were reviewed and all relevant articles reviewed in full. Of 60 potentially relevant citations, we found 22 studies to include in this assessment. (See Figure below for study selection details) Of these 22 studies, 11 were randomized control trials, <sup>15-25</sup> and 11 were observational studies.<sup>9, 14, 26-36</sup>

Thirty-seven additional references were reviewed, but did not meet criteria for inclusion in this assessment. (References 38 –75).



**Figure: Study Selection Process**

Level of Evidence: 1, 2, 5  
TA Criterion 2 is met.

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

### ***Observational Studies***

Of the 11 observational studies included in this assessment, four focused on the **pediatric population**.<sup>31, 32, 35, 36</sup> All were small studies, ranging in size from ten to 60 participants. The largest, with 60 participants, found a statistically significant decrease from baseline in HbA1C after a three month study period (-.4%). This study did not find a difference in number of hypoglycemic episodes or daily insulin dose, but number and duration of hyperglycemic episodes were decreased.<sup>31</sup> Two smaller studies also found a modest decrease in HbA1C,<sup>32, 35</sup> and one of these also found a modest decrease from baseline in the time participants spent in a hypoglycemic and



hyperglycemic glucose range.<sup>32</sup> The fourth study was a feasibility study which found that children tolerated wearing a CGM sensor with wireless transmission for longer than three days.<sup>36</sup>

Five of the 11 observational studies focused on **non-pregnant adults**.<sup>26, 27, 29, 30, 33</sup> These studies ranged in size from five to 140 participants. Of the two largest studies, one found a significant reduction in HbA1C ( $-0.4 \pm .05\%$ ) and note that the greatest reductions in HbA1C were observed in those participants who had very poor glycemic control at baseline (HbA1C >9.0%), and for those who used the CGM more.<sup>26</sup> The other found a significant reduction in the time participants spent with clinically important hypoglycemia.<sup>27</sup> Two of the remaining smaller studies had similar findings of a modest reduction in HbA1C,<sup>29</sup> and reduced time spent in clinical significant hypoglycemia.<sup>30</sup> The final study was a small pilot measuring the ability of CGM to capture and alert for late onset hypoglycemia related to vigorous exercise.<sup>33</sup>

The remaining two observational studies were of **pregnant women**.<sup>28, 34</sup> These were feasibility studies of using CGM in pregnancy to adjust insulin regimens.

### ***Randomized Controlled Trials*** (Table)

Three of the 11 RCT's included in this assessment focused exclusively on the **pediatric population**.<sup>19, 25, 37</sup> These studies were all small, ranging from 27-36 participants, and none of them found any difference in glycemic control for the intervention group (CGM users) compared with the control group. A fourth study focused exclusively on **pregnant teens and adult women**.<sup>20</sup> This trial included 71 women with both Type I and Type II diabetes and also found no difference for the intervention group (CGM users) compared with the control group. It did find a moderately significant decrease in birth weight and borderline significant decrease in macrosomia for the intervention group.

Five RCT's focused exclusively on **non-pregnant adults**.<sup>15, 18, 21, 22, 24</sup> The largest of these, with 128 participants, found no difference in HbA1C or number of hypoglycemic episodes for the intervention (CGM) group, but did find a decrease in the duration of hypoglycemic episodes for the intervention group compared with the control group.<sup>24</sup> Two other trials also found that the CGM group either spent less time in severe hypoglycemic glucose range<sup>18</sup> or had decreased duration of



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hypoglycemic episodes.<sup>15</sup> Of the two remaining small studies, one found a decrease in HbA1C for the intervention group,<sup>22</sup> while the other – a pilot of an integrated pump-CGM system – found no

decrease in HbA1C, but increased satisfaction with the intervention system compared with multiple daily injections.<sup>21</sup>

Two RCT's included both **children and non-pregnant adults**.<sup>17, 23</sup> The earlier and smaller of the two, randomized within age group to two intervention arms, one with three months of ongoing CGM, and one with CGM for three days every two weeks over three months, and to a control group with conventional SMBG.<sup>17</sup> This study found a significant reduction in HbA1C only for the intervention group with ongoing CGM compared with the control group. This study adjusted for age group rather than presenting results for children and adults separately. The recently published and largest RCT (N=322), randomized stratified by three age groups (8-14yrs, 15-24, ≥25yrs), clinical site and baseline HbA1C to daily CGM or four times daily SMBG over 26 weeks.<sup>23</sup> The main outcome was glycemic control as measured by HbA1C at the end of 26 weeks. Only the ≥25 year old group had a significant decrease in HbA1C compared to the control group. There were very few severe hypoglycemic episodes in any age group, with no differences between intervention and control group. In secondary outcomes of relative decrease of HbA1C by ≥10%, absolute decrease by ≥.5%, and 26-week level of <7.0% with no severe hypoglycemic events, the intervention group (ages ≥25 and 8-14yrs) had significantly higher proportion achieve these goals than the control group. There were no differences in these outcomes for the 15-24 year old age group. Adherence to CGM sensor use varied by age group, with the ≥25 year old group having the highest rate of adherence and the 15-24 year old group the lowest rate of adherence.

**Table. Randomized Controlled Trials of FDA Approved and Currently Marketed Continuous Glucose Monitoring Devices for Diabetes Mellitus**

Author/Year  Patient Population Device	Comparison Groups (N) / Intervention	Outcomes	Results	Comments
<b>Bode 2004</b> <sup>15</sup>  Adults Type I DM Guardian	Intervention: alert Group (N=35) – CGM alerts off (period one) CGM alerts on (period two)  Control group (N=36) – CGM alerts off (period one) CGM alerts off (period two)	<i>Accuracy:</i> Sensitivity & Specificity of sensor compared with home blood glucose meter readings  <i>Clinical Effectiveness</i> Number & duration of hypoglycemic excursions  Number & duration of hyperglycemic excursions	Low alert threshold of 80mg/dL: 83% sensitivity 86% specificity False alert rate of 51%  Low alert threshold of 70mg/dL; 67% sensitivity 90% specificity False alert rate of 47%  No significant difference in number of hypoglycemic excursions.  Duration decreased 27.8 min/excursion for alert group compared with 4.5 min/excursion for control group (p=.03)  No significant difference in number or duration of hyperglycemic excursions	Multicenter.  Small N overall & presumably per center.  No real-time CGM data given to patients.  Not an intention to treat analysis; 3 excluded from analysis in alert group; 2 excluded from analysis in control group
<b>Deiss 2006a</b> <sup>17</sup>  Children & Adolescents Type I DM CGMS, Medtronic	N=30; stratified by pubertal stage before randomization.  Randomized crossover trial Two arms: Intervention: display (CGM data/alerts);  Control: blinded (to CGM	Glycemic control HbA1C	At 3 months no significant difference between groups; display group HbA1C mean 7.8 ± 1.1 vs. blinded group HbA1C mean 8.3 ± 1.1 (p=.23); no significant change from baseline HbA1C.  Average 24hour glucose, hyperglycemia, and hypoglycemia also without significant difference. Similar findings after crossover.	More frequent changes in insulin therapy made in open group.  European study.



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	data/alerts);  CGM administered at baseline, 3 and 6 months; crossover after 3 months.			
<b>Deiss 2006b</b> <sup>16</sup>  Children & Adults Type I DM Guardian	N= 162 (81 children, 81 adults) Randomized within age-group  Arm 1: 3 months ongoing CGM;  Arm 2: CGM biweekly for 3-days every 2 weeks;  Arm 3: control, conventional self-monitoring blood glucose	Glycemic control HbA1c at 1 month and at 3 months.	Significant reduction in HbA1c for Arm 1 (ongoing CGM) compared to control group at 1 month (-.6 ± .8 vs. -.2 ± .8; p=.008), and at 3 months (-1.0 ± 1.1 vs. -.4 ± 1.0; p=.003). No significant difference between Arm 2 and control group.  At 3 months percent per group with ≥1% reduction HbA1c: Arm 1 (ongoing): 50% Arm 2 (intermittent): 37% Arm 3 (active control): 15%	Intention to treat, last value carried forward analysis. Age adjusted (children /adults).  Multicenter trial (8 European centers). No significant change from baseline in total insulin dose per day in any of the arms.  Did not present data for children and adults separately.
<b>Garg 2006</b> <sup>18</sup>  Adults Type I DM Type II DM DexCom STS	N=91 (75 Type I; 16 Type II) Intervention: display (CGM data/alerts);  Control: blinded (to CGM data/alerts);  3 consecutive 3-day periods of CGM for both groups	Time spent in high, low and target (81-140) glucose ranges	Display group spent 26% more time in the target glucose range of 81-140mg/dL than the control group (6.98 hours/day vs. 5.62 hours/day; p<.0001); 23% less time in highest glucose range of 241-400mg/dL (4.99 hours/day vs. 6.46 hours/day; p<.0001); 21% less time in the lowest glucose range of <55mg/dL (.74 hours/day vs. .94 hours per day; p<.0001). Both groups spent similar amounts of time in medium low (55-80mg/dL) and medium high (141-240mg/dL) ranges.	Multicenter trial (4 U.S. sites)  Combine results for Type I and Type II DM
<b>Lagarde 2006</b> <sup>19</sup>  Children	N=27 Intervention: display (CGM data/alerts) (N=18) ;	Glycemic control HbA1C	Intervention group with greater decrease in HbA1C at 6 months than control group (.61 ± .68% vs. .28 ± .78%; p=.13), but not statistically significant.	Small trial Single site Australian



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<p>Type I DM Medtronic MiniMed</p>	<p>Control: blinded (to CGM data/alerts) (N=9) ;  3 interval 3-day periods of CGM for both groups over 4 months</p>			
<p><b>Murphy 2008</b><sup>20</sup>  1<sup>st</sup> trimester pregnant teens &amp; women Type I DM Type II DM Medtronic MiniMed</p>	<p>N=71(46 Type I; 25 Type II)  Intervention group – (N=38) antenatal care plus CGM  Control group – (N=33) standard antenatal care</p>	<p>Glycemic control 2<sup>nd</sup> &amp; 3<sup>rd</sup> trimesters HbA1C Birth weight Risk of macrosomia</p>	<p>No statistical difference in mean HbA1C over course of pregnancy. Trend toward reduction in HbA1C in weeks 32-26 of pregnancy; Trend toward lower mean birth weight in CGM group (3340g vs. 3630g; p=.07); Mean birth weight centile lower in CGM group (69% vs. 93%; p.02); Fewer babies with macrosomia in CGM group (13% vs. 18%; p=.05).</p>	<p>All women seen in antenatal diabetes clinic.  No real-time CGM data given to patients.  No separation of results by type of diabetes (I or II) &amp; higher proportion of Type I diabetics in CGM group which could account for difference in birth weight and macrosomia.</p>
<p><b>Peyrot 2009</b><sup>21</sup>  Adults Type I DM Medtronic Paradigm 722 System</p>	<p>N=28. Intervention (N=14): integrated insulin pump with CGM  Control (N=14): multiple daily injections with home blood glucose monitoring  16 week study</p>	<p>Glycemic control HbA1C  Insulin Delivery System Ration Questionnaire (IDSRQ)  Blood Glucose</p>	<p>No difference in HbA1C change between intervention and control group at 16 weeks (-1.7% intervention vs. -1.0% control; p=.07).  Intervention participants reported significantly more convenience, blood glucose control, as well as less blood glucose burden, worry, social burden than the control group. Reports of interference and well-being were the same in both groups.</p>	<p>Small study Two-sites</p>



		<p>Monitoring System Rating Questionnaire (BGMSRQ)</p> <p>User Acceptance Questionnaires (UAQs)</p>	<p>Intervention participants reported significantly more blood glucose control than the control group, but reports of convenience, interference and blood glucose burden were not different between groups.</p> <p>Intervention participants had high acceptability ratings for the new system. No comparison was made with control group.</p>	
<p><b>Rigla 2008<sup>22</sup></b></p> <p>Adults Type I Medtronic MiniMed</p>	<p>N=10 All on insulin pumps. Crossover trial: 4 weeks each phase, 6 week washout period between.</p> <p>Intervention phase: CGM for 3 days/week.</p>	<p>Glycemic control HbA1C</p>	<p>Significant decrease in HbA1C after intervention phase (mean decrease .8g/dL) compared to no change in the control phase.</p>	<p>Small trial.</p> <p>All subjects also used telemedical assistance to follow glucose readings and changes in therapy throughout the trial.</p>
<p><b>Tamborlane 2008<sup>23</sup></b></p> <p>Adults &amp; children Type I DexCom Medtronic MiniMed FreeStyle Navigator</p>	<p>All on insulin pumps or ≥3 injections per day N=322; (98 ≥25yrs; 110 15-24yrs; 114 8-14yrs) Randomization stratified by 3 age groups, clinical site, HbA1C level.</p> <p>Intervention: daily CGM (change device every 3-7 days);</p> <p>Control: 4xdaily home blood glucose monitoring.</p> <p>26-week study; visits at 1,4,8,13,19 &amp; 26 weeks and phone visits between in-person visits.</p>	<p>Glycemic control</p> <p>Change in HbA1C from baseline to 26 weeks.</p> <p>Mean minutes per day in target glucose range, hyperglycemic and hypoglycemic ranges. Number of severe hypoglycemic episodes.</p> <p>2ndary outcomes: Relative decrease of HbA1C by ≥10%, absolute decrease by ≥.5%, 26-week level &lt;7.0%</p>	<p>Significant decrease for ≥25 year old age group for intervention group compared to control group (-.50 ± .56 vs. .02 ± .45; p&lt;.001). No significant difference in primary outcome for other age groups (age 15-24yrs, age 8-14yrs).</p> <p>In ≥25 year old age group, intervention group spent significantly more minutes in the target glucose range and significantly fewer minutes in the hyperglycemic range than the control group. There was no difference in mean minutes spent in the hypoglycemic range. There was no difference between intervention and control groups in the other two age ranges.</p> <p>There were very few severe hypoglycemic episodes in any age group, with no differences between intervention and control group.</p>	<p>Multicenter.</p> <p>Largest study to date; Intention to treat analysis; Adjusted significant p-value level (.0167) to analyze primary outcome.</p> <p>Adherence to sensor use was much higher in ≥25 year old age group (83% with at least 6 days/week of use) than in the 15-24 year old age group (30% with at least 6 days/week of use) or</p>



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		with no severe hypoglycemic events, relative increase by $\geq 10\%$ , absolute increase by $\geq .5\%$ .	In secondary outcomes of relative decrease of HbA1C by $\geq 10\%$ , absolute decrease by $\geq .5\%$ , 26-week level $< 7.0\%$ with no severe hypoglycemic events, the intervention group (ages $\geq 25$ and 8-14yrs) had significantly higher proportion achieve these goals than the control group. No differences for the 15-24 year old age group.	in the 8-14 year old age group (50% with at least 6 days/week of use).
<p><b>Tanenberg 2004<sup>24</sup></b></p> <p>Adults IDDM Medtronic MiniMed</p>	<p>N=128; all on insulin pumps or multiple injections / day with baseline HbA1C <math>&gt; 7.9\%</math>.</p> <p>Intervention (N= 62/51 analyzed): CGM 3days/week x 12 weeks;</p> <p>Control (N=66; 54 analyzed): 4xdaily home blood glucose monitoring;</p> <p>12-week study; at the end both groups with 3 days CGM for hypoglycemia measurement</p>	<p>Glycemic control HbA1C</p> <p>Number of hypoglycemic (<math>\leq 60\text{mg/dL}</math>) episodes per day.</p> <p>Mean minutes per hypoglycemic episode.</p>	<p>No difference in HbA1C change between intervention and control group at 12 weeks (<math>-.74\% \pm .95\%</math> vs. <math>-.73\% \pm 1.17\%</math>; <math>p=.7</math>).</p> <p>No difference in number of hypoglycemic episodes per day (Intervention <math>1.4 \pm 1.1</math> vs. control <math>1.7 \pm 1.2</math>; <math>p=.3</math>). Fewer mean minutes per hypoglycemic episode for intervention group (<math>49.4 \pm 40.9</math> vs. <math>81.0 \pm 61.1</math>; <math>p=.009</math>).</p>	<p>Multicenter</p> <p>Due to drop-out in both groups, study underpowered for primary HbA1C outcome.</p>
<p><b>Yates 2006<sup>25</sup></b></p> <p>Children Type I Medtronic</p>	<p>N=36; all on insulin pumps or multiple injections / day.</p> <p>Intervention (N=19): CGM for 3 days every 3 weeks x 3 months;</p> <p>Control (N=17): 4-6x daily home blood glucose monitoring.</p>	<p>Glycemic control HbA1C</p>	<p>No difference in HbA1C change between intervention and control group at 12 weeks (<math>p=.83</math>) or at 6 months (<math>p=.87</math>).</p>	<p>Small trial Single site</p>

DM: diabetes mellitus

HbA1c: hemoglobin A1C

IDDM: insulin dependent diabetes mellitus

CGM: continuous glucose monitor



TA Criterion 3 is met for non-pregnant adults.

TA Criterion 3 is not met for children or for pregnant women.

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

The standard of care for home glucose measurement is SMBG with a blood glucose meter and a lancet to collect a drop of blood for measurement. It is evident from the RCT's that the use of CGM devices is no worse than standard frequent SMBG measurement. Indeed it appears to have benefit above usual care for those non-pregnant adults who are able to adhere to continual use of CGM sensors and to change their insulin regimen in conjunction with their physician based on CGM data. However, the CGM devices all require regular calibration with blood glucose via SMBG. Thus, even patients utilizing CGM devices must use SMBG for calibration as well as for confirmation of alarm-triggering hypo- and hyper-glycemia. Most of the RCTs of children have been underpowered to detect a difference in benefit for CGM; and in the most recent and largest RCT,<sup>23</sup> while children did no worse, they did not benefit more from CGM use, in part because adherence to continual sensor use may be just too difficult in this population. There has not been an adequately powered RCT of pregnant women to draw conclusions of CGM devices compared to SMBG in this population.

TA Criterion 4 is met for non-pregnant adults.

TA Criterion 4 is not met for children and pregnant women.

**TA Criterion 5: The improvement must be attainable outside of the investigational setting.**

All of the studies included in this assessment had patients use the CGM device at home, with intermittent follow-up with study investigators. In order to ensure appropriate use of CGM devices patients must be taught how to apply and replace the sensors, how to respond to alarms, and the need to confirm glucose excursions using SMBG. All of this can be done in the non-investigational clinical setting. Certainly, it appears that adherence is a very important component of successful CGM device use, thus teaching and ongoing support will likely play a very important role in clinical use of CGM devices outside the investigational setting. The RCT's also all focused on patients already requiring multiple daily insulin injections or an insulin pump; this population is likely already



conducting SMBG multiple times per day (in the studies four to six times daily), and are the appropriate population in which to consider use of a CGM device in part because they are likely already receiving close follow-up for their diabetes. However, because CGM devices have not been proven in clinical trials to improve net health outcomes for children and pregnant women, that benefit also, cannot be obtained outside the investigational setting.

TA Criterion 5 is met for non-pregnant adults.

TA Criterion 5 is not met for children and pregnant women.

## **CONCLUSION**

In summary, the largest RCT to date of CGM devices for adults and children was well designed and analyzed, and it found conclusive benefit only for adults 25 years and older. While in this study, and in other smaller RCT's there is evidence that both children and adults spend less time in a hypoglycemic glucose range when using a CGM device compared to usual care frequent SMBG, there is little evidence that use of a CGM device confers an ultimate health benefit as measured by HbA1C as a marker of overall glycemic control. It may be that for children and adolescents this is in large part due to difficulty with device adherence and not with the device itself. However, a health technology is only as good as its actual clinical application, and the evidence has not yet shown conclusive benefit for children, adolescents, and even young adults. Likewise, while the small studies that exist of pregnant women show the feasibility of CGM device use during pregnancy, they do not yet demonstrate conclusive benefit in this population either. Future study of these devices should incorporate more research on how the devices can be made more acceptable and user-friendly for children and adolescents with Type I diabetes in order to optimize potential clinical benefit for this population. Larger studies of pregnant women which are limited to those women requiring multiple insulin injections per day are needed in order to adequately assess potential benefit in this population.



## RECOMMENDATION

It is recommended that: continuous glucose monitoring devices *meet* CTAF criteria 1-5 for safety, effectiveness and improvement in health outcomes for the management of type I diabetes mellitus in non-pregnant adults requiring multiple ( $\geq 3$ ) daily insulin injections and frequent ( $\geq 3$ ) self-monitoring blood glucose checks.

It is further recommended that continuous glucose monitoring devices *do not* meet CTAF criteria 3-5 for safety, effectiveness and improvement in health outcomes for the management of diabetes mellitus in children, adolescents and pregnant women.

### **March 11, 2009**

A previous assessment of this technology was reviewed by CTAF in October 2003.

*The California Technology Assessment Forum voted to accept the recommendation as presented.*



## RECOMMENDATIONS OF OTHERS

### **Blue Cross Blue Shield Association (BCBSA)**

The BCBSA Technology Evaluation Center has not conducted a review of this technology since 2003 when it was determined that TEC criteria were not met.

### **Centers for Medicare and Medicaid Services (CMS)**

CMS does not have a NCD specific to the use of this technology.

### **American Association of Clinical Endocrinologists (AACE)**

A representative of the California Chapter of the AACE attended the meeting to provide testimony and engage in discussion with the CTAF panel and other experts.

### **American Diabetes Association (ADA)**

The ADA was invited to attend the meeting to provide testimony. The ADA Standards of Medical Care in Diabetes – 2009 were recently published in the January 2009 issue of Diabetes Care.

## ABBREVIATIONS USED IN THIS REVIEW

CTAF	California Technology Assessment Forum
CGM	Continuous blood glucose monitoring
FDA	U.S. Food and Drug Administrations
RCT	Randomized controlled trials
HBA1C	Hemoglobin A1C
SMBG	Self-monitoring of blood glucose
DARE	Database of Abstracts of Reviews of Effects

## APPENDIX I: Detailed search criteria

### Pubmed Search

Search	Most Recent Queries	Time	Result
#22	Search #21 OR #18	16:47:41	<u>87</u>
#18	Search #11 AND SYSTEMATIC REVIEW*	16:46:42	<u>2</u>
#21	Search #12 NOT (REVIEW[PT] OR EDITORIAL[PT] OR LETTER[PT] OR NEWS[PT] OR NEWSPAPER ARTICLE[PT])	16:46:13	<u>85</u>
#12	Search #11 AND (CONTINUOUS[TI] OR CGMS[TI] OR CGM[TI] OR CHMG[TI])	16:26:46	<u>95</u>
#11	Search #9 NOT #10	16:26:14	<u>143</u>
#10	Search #9 Limits: Animals	16:26:02	<u>6</u>
#9	Search #7 OR #8	16:24:08	<u>149</u>
#8	Search #6 Limits: Research Support, N I H, Extramural, Research Support, N I H, Intramural, Research Support, Non U S Gov't, Research Support, U S Gov't, Non P H S, Research Support, U S Gov't, P H S	16:21:37	<u>130</u>
#7	Search #6 AND (CLINICAL TRIAL OR CLINICAL TRIALS AS TOPIC[MH] OR RANDOMIZED CONTROLLED TRIAL*)	16:18:22	<u>65</u>
#6	Search #2 AND #3 Limits: Publication Date from 2003 to 2008	16:17:57	<u>261</u>
#5	Search #2 AND #3 Limits: English	16:17:15	<u>326</u>
#3	Search CONTINUOUS GLUCOSE MONITOR* OR CONTINUOUS GLUCOSE MEASUR* OR CONTINUOUS BLOOD GLUCOSE MONITOR* OR CONTINUOUS BLOOD GLUCOSE MEASUR* OR CONTINUOUS SUBCUTANEOUS GLUCOSE MONITOR* OR ("CONTINUOUS HOME MONITORING" AND GLUCOSE[TIAB]) OR CONTINUOUS GLUCOSE SENSOR* OR CGMS[TIAB] OR CGM[TIAB] OR CHMG[TIAB]	16:11:16	<u>803</u>
#2	Search DIABETES MELLITUS, TYPE 1[MH] OR DIABETES MELLITUS[MAJR:noexp] OR TYPE 1 DIABETES OR TYPE I DIABETES OR JUVENILE DIABETES	16:08:19	<u>100003</u>

### Embase Search

No.	Query	Results
#12	'continuous *4 monitor' OR 'continuous *4 monitors' OR 'continuous *4 monitoring' OR 'continuous *4 measurement' OR 'continuous *4 measurements' OR 'continuous *4 sensor' OR 'continuous *4 sensors' OR cgms:ti,ab OR cgm:ti,ab OR chmg:ti,ab	14,311
#13	'insulin dependent diabetes mellitus'/de OR 'diabetes mellitus'/mj OR ((diabetes:ti,ab OR diabetic:ti,ab) AND ('type 1' OR 'type i')) OR 'juvenile diabetes'	139,780
#14	#12 AND #13	584
#15	#14 AND ('clinical trial'/exp OR 'clinical study'/de OR 'major clinical study'/de OR 'controlled study'/de OR random*:ti,ab)	297



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#16	#15 AND [english]/lim	275
#17	#15 AND [english]/lim AND [animals]/lim	7
#18	#16 NOT #17	268
#19	#16 NOT #17 AND [2003-2008]/py	204
#20	#16 NOT #17 AND ([editorial]/lim OR [letter]/lim OR [review]/lim OR [short survey]/lim)	38
#21	#19 NOT #20	175
#22	#21 AND (continuous*:ti or cgms:ti or cgm:ti or chmg:ti)	122

## Cochrane Search

ID	Search	Hits	Edit	Delete
#1	<u>(TYPE 1 NEAR DIABET*) OR (TYPE i NEAR DIABET*) OR JUVENILE DIABETES OR JUVENILE DIABETIC OR "INSULIN DEPENDENT" and (CONTINUOUS NEAR MONITOR*) OR (CONTINUOUS NEAR MEASUR*) OR (CONTINUOUS NEAR SENSOR*) OR CGMS OR CGM OR CHMG</u>	47	<a href="#">edit</a>	<a href="#">delete</a>
#2	<u>(TYPE 1 NEAR DIABET*) OR (TYPE i NEAR DIABET*) OR JUVENILE DIABETES OR JUVENILE DIABETIC OR "INSULIN DEPENDENT" and (CONTINUOUS NEAR MONITOR*) OR (CONTINUOUS NEAR MEASUR*) OR (CONTINUOUS NEAR SENSOR*) OR CGMS OR CGM OR CHMG and (CONTINUOUS* OR CGMS OR CGM OR CHMG):ti, from 2003 to 2008</u>	26		

## Search Results

### Show Results in:

[Cochrane Reviews \[1\]](#) | [Other Reviews \[0\]](#) | [Clinical Trials \[23\]](#) | [Methods Studies \[0\]](#) | **[Technology Assessments \[2\]](#)** | [Economic Evaluations \[0\]](#) | [Cochrane Groups \[0\]](#)

**Please note: exported CLINICAL TRIALS [23 REFS] & TECHNOLOGY ASSESSMENTS [2 REFS] only; COCHRANE REVIEWS [1 ref] not relevant.**

## REFERENCES

1. Tice JA. *Continuous Glucose Monitoring Devices in Diabetes Mellitus (including the Continuous Glucose Monitoring System and GlucoWatch Biographer)* San Francisco: Blue Shield CA Foundation California Technology Assessment Forum; October 8, 2003.
2. CDC. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007.: Department of Health and Human Services, Centers for Disease Control and Prevention; 2008.
3. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *J Am Coll Cardiol.* Jan 20 2009;53(3):298-304.
4. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med.* Sep 30 1993;329(14):977-986.
5. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* Sep 12 1998;352(9131):837-853.
6. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* Jun 12 2008;358(24):2545-2559.
7. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* Jun 12 2008;358(24):2560-2572.
8. The accuracy of the CGMS in children with type 1 diabetes: results of the diabetes research in children network (DirecNet) accuracy study. *Diabetes Technol Ther.* 2003;5(5):781-789.
9. Mastrototaro J, Shin J, Marcus A, Sulur G. The accuracy and efficacy of real-time continuous glucose monitoring sensor in patients with type 1 diabetes. *Diabetes Technol Ther.* Oct 2008;10(5):385-390.
10. Clarke WL, Anderson S, Farhy L, et al. Evaluating the clinical accuracy of two continuous glucose sensors using continuous glucose-error grid analysis. *Diabetes Care.* Oct 2005;28(10):2412-2417.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

11. Kovatchev B, Anderson S, Heinemann L, Clarke W. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. *Diabetes Care*. Jun 2008;31(6):1160-1164.
12. Boyne MS, Silver DM, Kaplan J, Saudek CD. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes*. Nov 2003;52(11):2790-2794.
13. ADA. Standard of medical care in diabetes - 2009. *Diabetes Care*. January 2009;32(Supplement 1).
14. Wiltshire EJ, Newton K, McTavish L. Unrecognised hypoglycaemia in children and adolescents with type 1 diabetes using the continuous glucose monitoring system: prevalence and contributors. *J Paediatr Child Health*. Dec 2006;42(12):758-763.
15. Bode B, Gross K, Rikalo N, et al. Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: the guardian continuous monitoring system. *Diabetes Technol Ther*. Apr 2004;6(2):105-113.
16. Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care*. Dec 2006;29(12):2730-2732.
17. Deiss D, Hartmann R, Schmidt J, Kordonouri O. Results of a randomised controlled cross-over trial on the effect of continuous subcutaneous glucose monitoring (CGMS) on glycaemic control in children and adolescents with type 1 diabetes. *Exp Clin Endocrinol Diabetes*. Feb 2006;114(2):63-67.
18. Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care*. Jan 2006;29(1):44-50.
19. Lagarde WH, Barrows FP, Davenport ML, Kang M, Guess HA, Calikoglu AS. Continuous subcutaneous glucose monitoring in children with type 1 diabetes mellitus: a single-blind, randomized, controlled trial. *Pediatr Diabetes*. Jun 2006;7(3):159-164.
20. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. *BMJ*. 2008;337:a1680.
21. Peyrot M, Rubin RR. Patient-reported outcomes for an integrated real-time continuous glucose monitoring/insulin pump system. *Diabetes Technol Ther*. Feb 2009;11(1):57-62.
22. Rigla M, Hernando ME, Gomez EJ, et al. Real-time continuous glucose monitoring together with telemedical assistance improves glycemic control and glucose stability in pump-treated patients. *Diabetes Technol Ther*. Jun 2008;10(3):194-199.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

23. Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. Oct 2 2008;359(14):1464-1476.
24. Tanenberg R, Bode B, Lane W, et al. Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. *Mayo Clin Proc*. Dec 2004;79(12):1521-1526.
25. Yates K, Hasnat Milton A, Dear K, Ambler G. Continuous glucose monitoring-guided insulin adjustment in children and adolescents on near-physiological insulin regimens. *Diabetes Care*. July 2006;29(7).
26. Bailey TS, Zisser HC, Garg SK. Reduction in hemoglobin A1C with real-time continuous glucose monitoring: results from a 12-week observational study. *Diabetes Technol Ther*. Jun 2007;9(3):203-210.
27. Bode B, Silver M, Weiss R, Martin K. Evaluation of a continuous glucose monitoring system for home-use conditions. *Manag Care*. Aug 2008;17(8):40-45.
28. Chen R, Yogev Y, Ben-Haroush A, Javanovic L, Hod M, Phillip M. Continuous glucose monitoring for the evaluation and improved control of gestational diabetes mellitus. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2003;14:256-260.
29. Garg SK, Kelly WC, Voelmle MK, et al. Continuous home monitoring of glucose: improved glycemic control with real-life use of continuous glucose sensors in adult subjects with type 1 diabetes. *Diabetes Care*. Dec 2007;30(12):3023-3025.
30. Garg SK, Schwartz S, Edelman SV. Improved glucose excursions using an implantable real-time continuous glucose sensor in adults with type 1 diabetes. *Diabetes Care*. Mar 2004;27(3):734-738.
31. Gorska A, Starzyk J, ANazim J. Continuous glucose monitoring is a helpful tool for the modification and assessment of such a modified treatment of type 1 diabetes mellitus in children and adolescents. *Pediatr Pol*. 2008;83(6):634-639.
32. Halvorson M, Carpenter S, Kaiserman K, Kaufman FR. A pilot trial in pediatrics with the sensor-augmented pump: combining real-time continuous glucose monitoring with the insulin pump. *J Pediatr*. Jan 2007;150(1):103-105 e101.
33. Iscoe KE, Campbell JE, Jamnik V, Perkins BA, Riddell MC. Efficacy of continuous real-time blood glucose monitoring during and after prolonged high-intensity cycling exercise: spinning with a continuous glucose monitoring system. *Diabetes Technol Ther*. Dec 2006;8(6):627-635.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

34. McLachlan K, Jenkins A, O'Neal D. The role of continuous glucose monitoring in clinical decision-making in diabetes in pregnancy. *Aust N Z J Obstet Gynaecol*. Jun 2007;47(3):186-190.
35. Weinzimer S, Xing D, Tansey M, et al. FreeStyle navigator continuous glucose monitoring system use in children with type 1 diabetes using glargine-based multiple daily dose regimens: results of a pilot trial Diabetes Research in Children Network (DirecNet) Study Group. *Diabetes Care*. Mar 2008;31(3):525-527.
36. Wong LJ, Buckingham BA, Kunselman B, Istoc E, Leach J, Purvis R. Extended use of a new continuous glucose monitoring system with wireless data transmission in children with type 1 diabetes mellitus. *Diabetes Technol Ther*. Apr 2006;8(2):139-145.
37. Deiss D, Hartmann R, Hoeffe J, Kordonouri O. Assessment of glycemic control by continuous glucose monitoring system in 50 children with type 1 diabetes starting on insulin pump therapy. *Pediatr Diabetes*. Sep 2004;5(3):117-121.
38. Alemzadeh R, Palma-Sisto P, Parton EA, Holzum MK. Continuous subcutaneous insulin infusion and multiple dose of insulin regimen display similar patterns of blood glucose excursions in pediatric type 1 diabetes. *Diabetes Technol Ther*. Aug 2005;7(4):587-596.
39. Bode BW, Steed RD, Schleusener DS, Strange P. Switch to multiple daily injections with insulin glargine and insulin lispro from continuous subcutaneous insulin infusion with insulin lispro: a randomized, open-label study using a continuous glucose monitoring system. *Endocr Pract*. May-Jun 2005;11(3):157-164.
40. Burdick J, Chase P, Faupel M, Schultz B, Gebhart S. Real-time glucose sensing using transdermal fluid under continuous vacuum pressure in children with type 1 diabetes. *Diabetes Technol Ther*. Jun 2005;7(3):448-455.
41. Chetty VT, Almulla A, Oduyungbo A, Thabane L. The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HBA1c) levels in Type I diabetic patients: a systematic review. *Diabetes Res Clin Pract*. Jul 2008;81(1):79-87.
42. Deiss D, Kordonouri O, Hartmann R, Hopfenmuller W, Lupke K, Danne T. Treatment with insulin glargine reduces asymptomatic hypoglycemia detected by continuous subcutaneous glucose monitoring in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. Jun 2007;8(3):157-162.
43. Dungan KM, Buse JB, Largay J, et al. 1,5-anhydroglucitol and postprandial hyperglycemia as measured by continuous glucose monitoring system in moderately controlled patients with diabetes. *Diabetes Care*. Jun 2006;29(6):1214-1219.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

44. Fiallo-Scharer R. Eight-point glucose testing versus the continuous glucose monitoring system in evaluation of glycemic control in type 1 diabetes. *J Clin Endocrinol Metab.* Jun 2005;90(6):3387-3391.
45. Franklin VL, Wilson AW, Butler RA, Greene SA. A predictive tool for the self-management of diabetes (Librae): evaluation using a continuous glucose monitoring system. *Diabet Med.* Jan 2006;23(1):21-25.
46. Gandrud LM, Xing D, Kollman C, et al. The Medtronic MiniMed Gold continuous glucose monitoring system: an effective means to discover hypo- and hyperglycemia in children under 7 years of age. *Diabetes Technol Ther.* Aug 2007;9(4):307-316.
47. Garg SK, Kelly WC, Voelmlle MK, et al. Continuous home monitoring of glucose: improved glycemic control with real-life use of continuous glucose sensors in adult subjects with type 1 diabetes. *Diabetes Care.* Dec 2007;30(12):3023-3025.
48. Garg SK, Jovanovic L. Relationship of fasting and hourly blood glucose levels to HbA1c Values: Safety, accuracy, and improvements in glucose profiles obtained using a 7-day continuous glucose sensor. *Diabetes Care.* Dec 2006;29(12):2644-2649.
49. Geiger MC, Ferreira JV, Hafiz MM, et al. Evaluation of metabolic control using a continuous subcutaneous glucose monitoring system in patients with type 1 diabetes mellitus who achieved insulin independence after islet cell transplantation. *Cell Transplant.* 2005;14(2-3):77-84.
50. Golicki DT, Golicka D, Groele L, Pankowska E. Continuous Glucose Monitoring System in children with type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetologia.* Feb 2008;51(2):233-240.
51. Gorska A, Starzyk J, ANazim J. Continuous glucose monitoring is a helpful tool for the modification and assessment of such a modified treatment of type 1 diabetes mellitus in children and adolescents. *Pediatr Pol.* 2008;83(6):634-639.
52. Halvorson M, Carpenter S, Kaiserman K, Kaufman FR. A pilot trial in pediatrics with the sensor-augmented pump: combining real-time continuous glucose monitoring with the insulin pump. *J Pediatr.* Jan 2007;150(1):103-105 e101.
53. Heptulla RA, Allen HF, Gross TM, Reiter EO. Continuous glucose monitoring in children with type 1 diabetes: before and after insulin pump therapy. *Pediatr Diabetes.* Mar 2004;5(1):10-15.
54. Hirsch IB, Bode BW, Garg S, et al. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. *Diabetes Care.* Mar 2005;28(3):533-538.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

55. Howorka K, Pumprla J, Gabriel M, Thoma H, Schabmann A. Computerized generation of circadian sensor modal days with continuous glucose monitoring for comparison of various insulin regimens based on insulin glargine in type 1 diabetes. *Int J Artif Organs*. Aug 2003;26(8):728-734.
56. Iscoe KE, Campbell JE, Jamnik V, Perkins BA, Riddell MC. Efficacy of continuous real-time blood glucose monitoring during and after prolonged high-intensity cycling exercise: spinning with a continuous glucose monitoring system. *Diabetes Technol Ther*. Dec 2006;8(6):627-635.
57. Jones SM, Quarry JL, Caldwell-McMillan M, Mauger DT, Gabbay RA. Optimal insulin pump dosing and postprandial glycemia following a pizza meal using the continuous glucose monitoring system. *Diabetes Technol Ther*. Apr 2005;7(2):233-240.
58. Kollman C, Wilson DM, Wysocki T, Tamborlane WV, Beck RW. Limitations of statistical measures of error in assessing the accuracy of continuous glucose sensors. *Diabetes Technol Ther*. Oct 2005;7(5):665-672; discussion 673-664.
59. Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A. Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. *Diabetes Technol Ther*. Dec 2005;7(6):849-862.
60. Kovatchev BP, Gonder-Frederick LA, Cox DJ, Clarke WL. Evaluating the accuracy of continuous glucose-monitoring sensors: continuous glucose-error grid analysis illustrated by TheraSense Freestyle Navigator data. *Diabetes Care*. Aug 2004;27(8):1922-1928.
61. Kovatchev BP, King C, Breton M, Anderson S, Clarke W. Clinical assessment and mathematical modeling of the accuracy of continuous glucose sensors (CGS). *Conf Proc IEEE Eng Med Biol Soc*. 2006;1:71-74.
62. Lee SW, Cao M, Sajid S, et al. The dual-wave bolus feature in continuous subcutaneous insulin infusion pumps controls prolonged post-prandial hyperglycaemia better than standard bolus in Type 1 diabetes. *Diabetes Nutr Metab*. Aug 2004;17(4):211-216.
63. Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics*. May 2003;111(5 Pt 1):933-938.
64. Manuel-y-Keenoy B, Vertommen J, Abrams P, et al. Postprandial glucose monitoring in type 1 diabetes mellitus: use of a continuous subcutaneous monitoring device. *Diabetes Metab Res Rev*. Nov-Dec 2004;20 Suppl 2:S24-31.
65. McCall AL, Cox DJ, Crean J, Gloster M, Kovatchev BP. A novel analytical method for assessing glucose variability: using CGMS in type 1 diabetes mellitus. *Diabetes Technol Ther*. Dec 2006;8(6):644-653.

66. McDonnell CM, Donath SM, Vidmar SI, Werther GA, Cameron FJ. A novel approach to continuous glucose analysis utilizing glycemic variation. *Diabetes Technol Ther. Apr 2005;7(2):253-263.*
67. McLachlan K, Jenkins A, O'Neal D. The role of continuous glucose monitoring in clinical decision-making in diabetes in pregnancy. *Aust N Z J Obstet Gynaecol. Jun 2007;47(3):186-190.*
68. Prevention CfDca. *National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2008.
69. Sparacino G, Zanderigo F, Corazza S, Maran A, Facchinetti A, Cobelli C. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. *IEEE Trans Biomed Eng. May 2007;54(5):931-937.*
70. Weintrob N, Schechter A, Benzaquen H, et al. Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs. continuous subcutaneous insulin infusion. *Arch Pediatr Adolesc Med. Jul 2004;158(7):677-684.*
71. Weinzimer S, Xing D, Tansey M, et al. FreeStyle navigator continuous glucose monitoring system use in children with type 1 diabetes using glargine-based multiple daily dose regimens: results of a pilot trial Diabetes Research in Children Network (DirecNet) Study Group. *Diabetes Care. Mar 2008;31(3):525-527.*
72. Weinzimer SA, DeLucia MC, Boland EA, Steffen A, Tamborlane WV. Analysis of continuous glucose monitoring data from non-diabetic and diabetic children: a tale of two algorithms. *Diabetes Technol Ther. 2003;5(3):375-380.*
73. Wentholt IM, Vollebregt MA, Hart AA, Hoekstra JB, DeVries JH. Comparison of a needle-type and a microdialysis continuous glucose monitor in type 1 diabetic patients. *Diabetes Care. Dec 2005;28(12):2871-2876.*
74. Wong LJ, Buckingham BA, Kunselman B, Istoc E, Leach J, Purvis R. Extended use of a new continuous glucose monitoring system with wireless data transmission in children with type 1 diabetes mellitus. *Diabetes Technol Ther. Apr 2006;8(2):139-145.*
75. Yogev Y, Chen R, Ben-Haroush A, Phillip M, Jovanovic L, Hod M. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. *Obstet Gynecol. Apr 2003;101(4):633-638.*