Cost-effectiveness of Continuous Glucose Monitoring for Adults With Type 1 Diabetes Compared With Self-Monitoring of Blood Glucose: The DIAMOND Randomized Trial

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OBJECTIVE

This study evaluated the societal cost-effectiveness of continuous glucose monitoring (CGM) in patients with type 1 diabetes (T1D) using multiple insulin injections.

RESEARCH DESIGN AND METHODS

In the Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) trial, 158 patients with T1D and HbA_{1c} ≥7.5% were randomized in a 2:1 ratio to CGM or control. Participants were surveyed at baseline and 6 months. Within-trial and lifetime cost-effectiveness analyses were conducted. A modified Sheffield T1D policy model was used to simulate T1D complications. The main outcome was cost per quality-adjusted life-year (QALY) gained.

RESULTS

Within the 6-month trial, the CGM group had similar QALYs to the control group (0.462 ± 0.05 vs. 0.455 ± 0.06 years, $P = 0.61$). The total 6-month costs were $11,032 (CGM) vs. $7,236 (control). The CGM group experienced reductions in HbA_{1c} (0.60 ± 0.74% difference in difference [DiD]), $P < 0.01$), the daily rate of nonsevere hypoglycemia events (0.07 DiD, $P = 0.013$), and daily test strip use (0.55 ± 1.5 DiD, $P = 0.04$) compared with the control group. In the lifetime analysis, CGM was projected to reduce the risk of T1D complications and increase QALYs by 0.54. The incremental cost-effectiveness ratio (ICER) was $98,108 per QALY for the overall population. By extending sensor use from 7 to 10 days in a real-world scenario, the ICER was reduced to $33,459 per QALY.

CONCLUSIONS

For adults with T1D using multiple insulin injections and still experiencing suboptimal glycemic control, CGM is cost-effective at the willingness-to-pay threshold of $100,000 per QALY, with improved glucose control and reductions in nonsevere hypoglycemia.

Although the long-term health benefits of intensive glycemic control in patients with type 1 diabetes (T1D) have been well established (1), many patients continue to have suboptimal glycemic control (2–4). Suboptimal glycemic control invariably increases the risk of long-term complications, including microvascular and macrovascular complications

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(2,3), which greatly increase the costs of diabetes care (1,5). A barrier to delivering intensive glycemic management is the increased risk of hypoglycemia (severe and nonsevere), which negatively affects quality of life (QoL) and further increases treatment costs (6,7).

Achieving optimal glycemic control with intensive therapy necessitates frequent blood glucose monitoring (8). Unfortunately, the capillary finger-stick measurement does not adequately prevent hypoglycemia and hyperglycemia (8). Patients with T1D who test blood glucose levels as frequently as 9 times/day have been found to experience 2 h/day of clinical hypoglycemia (<70 mg/dL) and 7 h/day of clinical hyperglycemia (>180 mg/dL) (8). The availability of insulin pumps and insulin analogs has improved but not eliminated hyperglycemia and hypoglycemia (4). Only 30% of adults with T1D age >30 years achieve HbA_{1c} <7.0% (4).

Newer continuous glucose monitoring (CGM) technologies help optimize glucose control by significant improvements in the precise and accurate measurement of glucose levels, resulting in better informed diabetes management decisions (9–11). In a recently completed randomized controlled trial, the Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) study (12), Dexcom G4 CGM improved glucose control compared with self-monitoring of blood glucose (SMBG) in adult patients with T1D who had elevated HbA_{1c} levels while using multiple daily insulin injections.

The cost-effectiveness of CGM in populations with T1D with moderate to good glucose control was first reported in 2010 by the JDRF clinical trial. Insulin pump users comprised 80% of the patient population that was enrolled in the trial (13). However, >65% of patients with T1D use multiple daily injections of insulin rather than insulin pumps (3,14). The purpose of the current study was to evaluate the cost-effectiveness of using a newer CGM technology for the population of T1D patients using multiple daily injections, based on the DIAMOND trial results.

RESEARCH DESIGN AND METHODS

Study Design

In this unblinded multicenter trial, 158 patients with T1D and HbA_{1c} ≥7.5% using multiple insulin injections were randomly assigned in a 2:1 ratio to CGM or SMBG, usual care (control), stratified by clinical site and HbA_{1c} level (<8.5% and ≥8.5%). Patients who were assigned to the CGM group initiated CGM use for 6 months. All patients were surveyed at baseline and at 6 months regarding their health-related QoL, health care services utilization outside of the study, medications, test strip use, work productivity if employed, and number of hours per day devoted to self-management diabetes care. Time devoted by trial personnel for training and counseling participants was also collected through staff surveys for both treatment groups. More details of the DIAMOND trial, including its design, study populations, and clinical results, can be found in Beck et al. (12).

Our cost-effectiveness analyses (CEAs) included a within-trial CEA using observed trial data and a lifetime CEA using a modified Sheffield T1D policy model. We adopted the societal perspective for both of these analyses. All of the collected data were analyzed to determine the clinical factors that would potentially influence the CEAs. According to the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine (15) and of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (16), we provide an impact inventory table and reporting checklist in Supplementary Tables 1 and 2.

Costs

All costs are expressed in 2015 U.S. dollars. Total costs included all direct costs associated with clinical care provided by trial personnel, CGM device use, health care services, test strip use, and medications and also indirect costs associated with patients' reduced work productivity and daily hours devoted to diabetes care. All cost assumptions are provided in Supplementary Tables 3 and 4.

Direct Clinical Personnel Costs

During the trial, clinical staff members (including physicians, advanced nurse practitioners, nurses, educators, and others) reported nonscheduled encounters with patients via phone, email, and/or clinic visit outside of the study-specific visits. We included staff time devoted to CGM training and counseling and excluded research time. The costs of staff time were calculated using the U.S. Bureau of Labor Statistics median hourly wage per job category.

CGM Costs

The CGM cost was estimated to be $15.20 per day, which includes the costs of its three components (i.e., G4 sensor, receiver, and transmitter). This price was the estimated average allowable price in the U.S. marketplace.

Non-CGM Medical Care Costs

Health care service utilizations included routine office visits, after-hour clinic visits (urgent care), 911 calls, ambulance use, emergency department visits, and hospitalizations, as well as average daily test strip use and glucose-lowering medications for the prior 6 months. To calculate the 6-month costs of utilization at baseline and 6 months, the median prices of each health care service were multiplied by the number of each service use in the past 6 months.

Indirect Costs

Patients were also surveyed at baseline and 6 months on the number of missed workdays due to diabetes and the number of workdays with underperformance (defined as <50% productivity) (13). A workday with underperformance was considered a half-day of missed work. The costs of missed work and time for self-diabetes care were calculated based on median hourly wage per job category of patients through well-established references (provided in Supplementary Table 3).

Measurements of QoL

The 5-Level EuroQol 5-Dimension (EQ-5D-5L) questionnaire was used to measure health-related QoL. This QoL measure was converted into a utility score, ranging from 0.0 ("death") to 1.0 ("perfect life") (17). For the long-term CEA, we used previously published disutilities for microvascular and cardiovascular complications and for severe and nonsevere hypoglycemia. The utilities were then incorporated into a simulation model of long-term outcomes.

Quality-adjusted life years (QALYs), a measure of health outcomes and disease burden, were calculated by the area under the curve method using the calculated utility scores. The incremental cost effectiveness ratio (ICER) was calculated as the ratio of the difference in costs to the difference in QALYs between the two groups.

Nonsevere Hypoglycemic Events

Nonsevere hypoglycemic events (NSHEs), self-treated hypoglycemia (18), may be experienced by 24–85% of patients with diabetes, particularly among insulin users (18–20). Each patient in the DIAMOND trial was required to wear a blinded CGM device to record glucose concentration

(invisible to the patients) for 2 weeks before randomization and for a week before the 12- and 24-week visits. NSHEs were defined as the detection of a glucose value <3.0 mmol/L (<54 mg/dL) for at least 20 consecutive minutes, considered to be clinically significant biochemical hypoglycemia according to the International Hypoglycemia Study Group recommendations (21). A daily rate of NSHE was obtained based on the number of NSHEs observed during each period of blinded CGM use. The numbers of NSHEs at 6 months were pooled from 12- to 24-week visits because the NSHE rates did not differ between the two visits (12).

Within-Trial CEAs

We followed the intent-to-treat principle in our analyses. A Wilcoxon rank sum test was used to compare the two groups in QALYs, utility, and other continuous outcomes. The Fisher exact test was used for each categorical outcome. An ANCOVA was performed to model the change from baseline in utility, HbA_{1c}, daily rate of NSHEs, and daily strip test use, and to compare the two groups, adjusting for their baseline effects. A repeated ANOVA via a linear mixed model (LMM) was also performed to test the effects of treatment, time, and their interaction. Age, sex, and duration of T1D were treated as potential covariates in each model, and site was considered as a random effect. A test of the interaction between the baseline outcome and treatment arm was also conducted through an ANCOVA or LMM to assess homogeneity of the treatment effect. Because ANCOVA and LMM produced similar results, we only present the ANCOVA results. All *P* values were two-sided, and *P* values <0.05 were considered significant. Analyses were conducted with SAS version 9.4 software.

Lifetime CEAs

To evaluate the cost-effectiveness of CGM, we simulated the natural history of T1D over the projected lifetime of patients by extrapolating the within-trial findings. Among the existing T1D simulation models in the literature, we selected the patient-level Sheffield T1D policy model (22) based on the following features: the model was constructed solely using T1D studies and trials, it includes HbA_{1c}, a risk factor significantly modified by CGM, in most risk equations, it was validated against major T1D trial studies, and it is completely transparent and hence reproducible. The simulation model is characterized by the simultaneous progression of T1D through major microvascular and macrovascular complications as well as short-term complications (hypo- and hyperglycemia) and their associated costs and health utilities. The risk parameters for the microvascular- and macrovascular-related complications and mortalities of the Sheffield model were taken directly from Tables 1 and 2 in Thokala et al. (22).

We modified the Sheffield model with respect to severe and nonsevere hypoglycemic events. The original hypoglycemia module assumed that the risk of severe hypoglycemic events increases as the HbA_{1c} level decreases. This relationship is altered by CGM, as described in the systematic review and meta-analysis conducted on behalf of Agency for Healthcare Research and Quality (11) and as we found in the DIAMOND trial: patients are able to achieve normoglycemia without an increased risk of hypoglycemia. As an alternative to the Sheffield hypoglycemia module, we used the observed hypoglycemia event rates from the DIAMOND trial. In the model, we also incorporated NSHEs and their QoL and costs effects, which were not considered in the original Sheffield model. All base-case model parameters, including clinical inputs, costs, and health utilities, are described in Supplementary Tables 5–7. A 3% annual discount rate was applied to costs and health utilities (23). We used bootstrapping of simulation samples to calculate 95% CIs for the key outcomes.

Projected CGM Effects

The simulation base-case model carried forward the CGM effects on HbA_{1c} reduction and NSHEs rate found in the trial through the lifetime of patients (Supplementary Table 5). Other risk factors, such as systolic blood pressure, HDL cholesterol, and total cholesterol, which were only measured at the baseline in the trial, were assumed not to change over time in the simulations (Supplementary Table 5). Similar modeling assumptions have been used in prior CEAs of new interventions for diabetes, including CGM (13).

One-Way Sensitivity and Subgroup Analyses

We performed subgroup analyses per baseline HbA_{1c} with a cutoff of 8.5%. We also conducted one-way sensitivity analyses on selected model parameters. Several scenarios were considered, including changes in CGM effects and costs and reflecting CGM technology advancements such as Dexcom's G5 CGM. The Dexcom G5 CGM was approved by the U.S. Food and Drug Administration to allow for replacement of finger-stick blood glucose testing (24). In the G5 scenarios, we assumed that patients use as few as 2.8 test strips per day (25). Because smartphones can be used as a G5 receiver (26), we assumed that 50% of the CGM patients use their phones as the receiver from the 2nd year of obtaining CGM onwards (the U.S. Food and Drug Administration requires that a CGM receiver should be included in the CGM package). Because the lifetime of device sensors can be prolonged from the recommended 7 days to 10 days (27) without compromising safety (28), we also conducted sensitivity analyses for the real-world use of G4 and G5 CGMs (see Supplementary Table 4). Details of all subgroup and sensitivity analyses scenarios are provided in Supplementary Table 8.

In the base-case analysis, we assumed that patients continued to use and benefit from CGM over their lifetime. In clinical practice, patients may in fact discontinue use of CGM over time. To account for this phenomenon, we considered alternative assumptions and evaluated scenarios where CGM was used for different periods of 5, 10, 15, 20, and 25 years. In each scenario, patients accrued the benefits and the costs of CGM only during periods of use.

Probabilistic Sensitivity Analysis

To examine the combined effects of model parameter uncertainty, we performed a probabilistic sensitivity analysis (PSA) by varying multiple parameters simultaneously. All input parameters in the base-case model, including costs, utilities, and parameters in risk equations, were sampled using distributions described in the Sheffield model (22). A total of 200 PSA scenarios were generated, and the same simulation method as in the base-case analysis was performed for each scenario. The simulation results were summarized in a cost-effectiveness acceptability curve (CEAC).

RESULTS

The 6-month visit for outcome collection was completed by 102 participants (97%) in the CGM group and all 53 participants (100%) in the control group. The CGM

group was younger than the control group (mean ± SD: 45.7 ± 13.6 vs. 51.4 ± 10.9, $P < 0.01$) (Table 1). No other significant differences were found for the other baseline characteristics.

Within-Trial CEA

During the trial, the two groups had similar utility ratings (mean ± SD: control: 0.91 ± 0.12 vs. CGM: 0.92 ± 0.10, $P = 0.78$) and QALYs (control: 0.46 ± 0.06 vs. CGM: 0.46 ± 0.05), both close to 0.5, the maximum QALY attainable in a half-year (Table 2). From a societal perspective, the average 6-month total costs were $11,032 for the CGM group and $7,236 for the control group ($P < 0.01$). The difference in total costs was primarily attributable to CGM device costs of $2,554. We found no other difference between the groups in other major cost categories such as direct personnel costs, non-CGM medical care costs, and all indirect costs associated with work productivity (all $P > 0.4$). CGM reduced daily strip use (0.55 ± 1.5 difference in difference [DiD], $P = 0.04$), resulting in a reduction in costs of strip use (CGM: $612; control: $750). CGM patients had no significant difference from control patients in their frequency of interactions with trial personnel or other forms of health care utilization (Supplementary Table 9), even though they were granted one additional visit at week 1 to review CGM use instructions. No within-trial ICER was calculated due to the lack of difference in QALYs. CGM was dominated by control in the within-trial CEA.

In addition to the key CEA results, a number of clinical outcomes were evaluated. CGM lowered HbA_{1c} (reduction from baseline: CGM: −1.0 ± 0.8% vs. control: −0.4 ± 0.7%) and the daily rate of NSHEs (CGM: −0.12 ± 0.29 vs. control: −0.06 ± 0.27, $P = 0.02$). In the subgroup with high baseline HbA_{1c} (≥8.5%), CGM reduced HbA_{1c} (0.76% DiD, $P < 0.01$), with no change in the daily rate of NSHEs ($P = 0.27$) compared with the control group (Table 2). In the subgroup with low baseline HbA_{1c} (<8.5%), CGM reduced HbA_{1c} (0.41% DiD, $P < 0.01$) and the daily rate of NSHEs (0.15 DiD from raw means, 0.125 DiD from adjusted means; $P = 0.03$). There were no significant differences in insulin dosing, BMI, number of severe hypoglycemic events, and number of patients who changed noninsulin glucose–lowering medicines. With the exception of one CGM patient who stopped using metformin during the trial, all the other patients remained on the same glucose-lowering medicines as at baseline. Age was not significantly associated with any of the clinical outcomes (results not shown).

Table 1—Baseline characteristics of the study populations

	Control (n = 53)	CGM (n = 105)	P value
Demographic characteristics			
Female sex, n (%)	23 (43)	47 (45)	1
Race, n (%)			0.5
White	50 (94)	95 (90)	
Black	3 (6)	6 (6)	
Other	0 (0)	4 (4)	
Age (years)			<0.01
Mean ± SD	51.4 ± 10.9	45.7 ± 13.6	
Range	25–73	25–72	
T1D duration (years)			0.1
Mean ± SD	23.1 ± 14.5	19.6 ± 13.1	
Range	4–56	2–56	
Clinical outcomes at baseline			
HbA_{1c} (%)			0.6
Mean ± SD	8.6 ± 0.6	8.6 ± 0.7	
Range	7.5–9.9	7.5–9.9	
Daily strip tests (n)			0.4
Mean ± SD	4.1 ± 1.6	3.9 ± 1.3	
Range	1–9	1–7	
Insulin (units)			0.4
Mean ± SD	60.2 ± 32.7	66.0 ± 36.7	
Range	12–185	24–155	
Daily event rate of NSHEs			0.5
Mean ± SD	0.35 ± 0.33	0.30 ± 0.29	
Range	0–1.34	1–1.33	
Utility			0.6
Mean ± SD	0.91 ± 0.13	0.93 ± 0.10	
Range	0.26–1.0	0.38–1.0	
BMI (kg/m^2)			0.2
Mean ± SD	26.8 ± 4.6	27.9 ± 5.9	
Range	18.2–38.4	16.9–62.6	
Patients using noninsulin glucose–lowering medication, n (%)	8 (8)	4 (8)	1.0
Patients having severe hypoglycemia in previous 12 months, n (%)	8 (8)	9 (17)	0.1
Patients having severe hyperglycemia in previous 12 months, n (%)	1 (2)	1 (<1)	1.0

Long-Term CEA

Base-Case Analyses

The results of the lifetime analysis indicate that CGM is expected to reduce the average incidence rates of all major T1D complications (Table 3). In particular, the use of CGM may lead to reductions in the lifetime risks of end-stage microvascular complications, including blindness (1.9 → 1.8%), end-stage renal disease (11.7 → 10.1%), and amputation (8.1 → 7.1%). Similarly, CGM reduced the lifetime risk of macrovascular complications, including myocardial infarction (37.8 → 37.0%), stroke (7.2 → 7.0%), and heart failure (11.1 → 10.7%). Further, life expectancy improved by 0.72 years on average under CGM (24.29 → 25.01). The improvement in quality-adjusted life expectancy was 0.54 QALYs. The ICER in the base-case was estimated at $98,108 per QALY, and its 95% CI was $90,298–$105,144 per QALY.

One-Way Sensitivity and Subgroup Analyses

Figure 1 shows ICER values for one-way sensitivity and subgroup analyses. The most notable changes in ICER were influenced by the price of CGM. In the real-world scenarios with extended use of CGM components (price justification provided in Supplementary Table 4), the ICERs were $33,459 per QALY for G4 and $41,464 per QALY for G5, whereas a 25% increase in the CGM price increased the ICER to $159,679 per QALY. The second key factor was HbA_{1c} reduction produced by CGM. If the HbA_{1c} reduction observed during the trial was 50% higher, the ICER would be

Table 2—Within-trial cost-effectiveness results

	Control (n = 53)		CGM (n = 103)		
	Mean (SD)	Median (range or IQR)	Mean (SD)	Median (range or IQR)	
Utility and QALYs					P value[b]
Utility change from baseline	0.0 (0.08)	0 (−0.27, 0.26)	−0.01 (0.09)	0 (−0.33, 0.32)	0.78
QALYs	0.46 (0.06)	0.47 (0.13, 0.50)	0.46 (0.05)	0.47 (0.24, 0.50)	0.61
Costs, $					P value[b]
Total direct costs	3,118 (3,120)	2,565 (1,928, 3,277)	5,336 (3,070)	5,092 (4,485, 5,726)	**<0.01**
Direct trial personnel	96 (205)	47 (0, 94)	60 (77)	47 (0, 94)	0.41
Medical care	3,022 (3,088)	2,478 (1,880, 3,122)	2,921 (3,065)	2,509 (1,909, 3,095)	0.86
CGM	0 (0)	0	2,554 (0)	2,554	**<0.01**
Total indirect costs[a]	36 (121)	0 (0, 0)	54 (314)	0 (0, 0)	0.85
Missed work	26 (101)	0 (0, 0)	36 (307)	0 (0, 0)	0.65
Poor performance	10 (40)	0 (0, 0)	18 (70)	0 (0, 0)	0.63
Self-management	4,012 (5,529)	2,829 (0, 5,610)	5,473 (10,300)	2,829 (2,259, 5,658)	0.86
Total costs	7,236 (6,097)	5,287 (4,586, 8,223)	11,200 (11,300)	8,178 (6,864, 10,300)	**<0.01**
Total costs[a]	3,154 (3,122)	2,565 (1,999, 3,513)	5,593 (3,083)	5,105 (4,496, 5,780)	**<0.01**
Clinical outcomes: reduction from baseline					P value[b]
HbA_{1c}	−0.39 (0.70)	−0.30 (−3.20, 0.90)	−0.99 (0.77)	−1.00 (−3.00, 0.70)	**<0.01**
Daily strip tests	0.1 (1.5)	0 (−4, 3)	−0.5 (1.5)	0 (−5, 3)	**0.04**
Insulin dose	1.0 (11)	1 (−23, 25)	−2.3 (22)	0 (−145, 52)	0.31
Daily rate of NSHEs	−0.06 (0.27)	0 (−0.93, 0.47)	−0.12 (0.29)	−0.08 (−1.07, 0.63)	**0.02**[c]
BMI	0.27 (1.07)	0.15 (−2.22, 2.80)	0.59 (1.38)	0.56 (−3.42, 5.28)	0.16
Patients having severe hyperglycemic events, n (%)	1 (2)		0 (0)		0.34
Patients having severe hypoglycemic events, n (%)	2 (4)		2 (2)		0.6
Subgroup analyses: reduction from baseline					P value[c]
In the subgroup with high baseline HbA_{1c} (≥8.5%)					
HbA_{1c}	−0.53 (0.60)	−0.50 (−1.5, 0.8)	−1.29 (0.77)	−1.30 (−3, 0.3)	**0.02**
Daily rate of NSHEs	−0.10 (0.29)	−0.07 (−0.93, 0.47)	−0.08 (0.27)	−0.07 (−1.03, 0.63)	0.27
In the subgroup with low baseline HbA_{1c} (<8.5%)					
HbA_{1c}	−0.22 (0.78)	−0.10 (−3.20, 0.90)	−0.63 (0.59)	−0.60 (−1.80, 0.70)	**0.01**
Daily rate of NSHEs	−0.02 (0.25)	0.01 (−0.86, 0.32)	−0.17 (0.32)	−0.14 (−1.07, 0.44)	**0.03**

All costs data were summarized by interquartile range (IQR) and other continuous outcomes were summarized by range. Bold P values indicate statistical significance ($P < 0.05$). [a]Both total indirect costs and total costs did not include the costs from diabetes self-management due to its 20% missing data and huge variability; that is, ∼20% patients reported unknown daily number of hours of self-management and seven patients from both groups reported ≥12 h/day and two of CGM users reported 24 h/day. [b]P value was from the Wilcoxon rank sum test to compare the two groups. [c]P value was from an ANCOVA model adjusting for its baseline outcome and site as a random effect.

$61,586 per QALY, whereas a 50% reduction of the glycemic benefit would increase the ICER to $177,268 per QALY. Assumptions regarding the QoL effects of NSHEs also had a substantial effect on the ICERs. The major reason behind this observation is that the frequencies of NSHEs are very high (annual rates observed in the trial: CGM: 85.9 vs. control: 131.4 in patients with low baseline HbA_{1c}). As a result, any small change in the per-episode QoL disutility can lead to large changes in the annual NSHE-related QoL disutilities. For example, by multiplying the per-episode disutility of −0.00045 in the base-case model with the annual frequencies of NSHEs, the annual NSHE disutilities are −0.0387 (CGM) and −0.0591 (control), causing a difference of +0.02 in annual utilities.

Sensitivity Analysis on Duration of CGM Use

Prolonged use of CGM increased the differences between CGM and control in lifetime costs, life expectancy, and QALYs (Supplementary Table 10). Because costs increased at a higher rate than QALYs, ICERs also increased with longer CGM use. The key CEA outcomes at 25 years of CGM use approach those under the base-case assumption, demonstrating the consistency of our base-case analysis.

PSA

The CEAC (in Supplementary Fig. 1) revealed the consistency of our base-case results. For example, in ∼90% of the PSA scenarios, CGM use was cost-effective at a willingness-to-pay threshold of $100,000 per QALY.

CONCLUSIONS

We assessed the cost-effectiveness of CGM use compared with usual care with SMBG in adults with T1D with elevated HbA_{1c} levels (≥7.5%). Within the trial, CGM increased costs without immediately improving QoL as measured by the EQ-5D. However, CGM reduced HbA_{1c} (0.6% DiD), daily strip test use (201 strips/year DiD), and NSHEs (25 episodes/year DiD). When these clinical benefits were extrapolated over a lifetime, CGM emerged as a cost-effective intervention with an ICER of $98,108 per QALY, with patients gaining 0.54 QALYs. This base-case result was robust to most of the sensitivity analyses. Most of the incremental cost was attributable to the CGM costs ($5,548 per annum). With reasonable extended use of CGM components, the annual cost of CGM could be reduced to $3,271, and the ICER would decrease to $33,459 per QALY. Similarly, the ICER for G5 declines from $96,376 per QALY to $41,464 per QALY with real-world use of components. The base-case ICER for this device is below acceptable ICER thresholds ($109,000 and $297,000 per QALY), which are estimated from existing

Table 3—Results of base-case lifetime CEA

	Control		CGM
Lifetime probability of			
Diabetic retinopathy, %			
Background	33.5		27.3
Proliferative	28.9		24.6
Macular edema, %	8.4		6.4
Blindness, %	1.9		1.8
Macroalbuminuria, %	19.7		17.2
End-stage renal disease, %	11.7		10.1
Neuropathy, %	33.2		27.3
Amputation, %	8.1		7.1
Myocardial infarction, %	37.8		37.0
Stroke, %	7.2		7.0
Angina, %	20.6		20.6
Heart failure, %	11.1		10.7
Expected life–years	24.29		25.01
Difference in expected life-years		0.72	
Discounted QALYs, means	12.78		13.32
Difference in QALYs, mean		0.54	
Discounted total costs, mean	305,278		360,486
Difference in costs, mean		55,208	
ICER, mean (95% CI*)	98,108 (90,298–105,144)		

*CI of the mean. The CI was calculated by bootstrapping simulation samples (each simulation scenario consists of 2,000,000 simulation samples (1,000,000 for each study arm), which were created by first generating 1,000 sample patients and then simulating their lifetime each 1,000 times per study arm).

coverage decisions for medical services by U.S. insurance plans, reflecting the societal preferences in the U.S. (29).

Our findings are consistent with the results of prior CEA studies of CGM in patients with T1D. In the JDRF trial, the ICER of CGM versus usual care in the trial adults with HbA_{1c} ≥7.0% (80% insulin pump users) was $98,679 per QALY (13). The incremental cost was solely due to CGM and not to the pump. Building on the original JDRF trial results, a subsequent CEA study found that the ICER of CGM use versus SMBG in the broader T1D adult population with a full range of HbA_{1c} was $45,033 per QALY (30). CGM has also been evaluated as a combined intervention with the insulin pump. A CEA study of sensor-augmented pump therapy (CGM + continuous subcutaneous insulin infusion [CSII]) versus CSII in Danish patients with a mean HbA_{1c} of 8.1% found that the ICER was $24,751 per QALY (31). In a study of sensor-augmented pump therapy versus usual care in adults with inadequately controlled glucose, the ICER was $168,104 per QALY (32). In a similar study in the Swedish health care setting, the ICER of CGM+ CSII versus usual care was $41,000 per QALY (23). A meta-analysis study (33) concluded that CGM was likely to be cost-effective in patients with T1D, particularly in those with poor glucose control.

From a policy perspective, because the total cost of diabetes care for the U.S. population has been steadily rising in an unsustainable fashion, carefully evaluating the clinical and economic values of new glucose-control technologies is critically important. From 2007 to 2012, the total cost of diabetes care in the U.S. rose from $174 billion to $245 billion, a 41% increase (5). Newer CGM technology has been found to significantly improve the precise and accurate measurement of glucose levels and to help optimize glucose control. As such, CGM can be a useful clinical

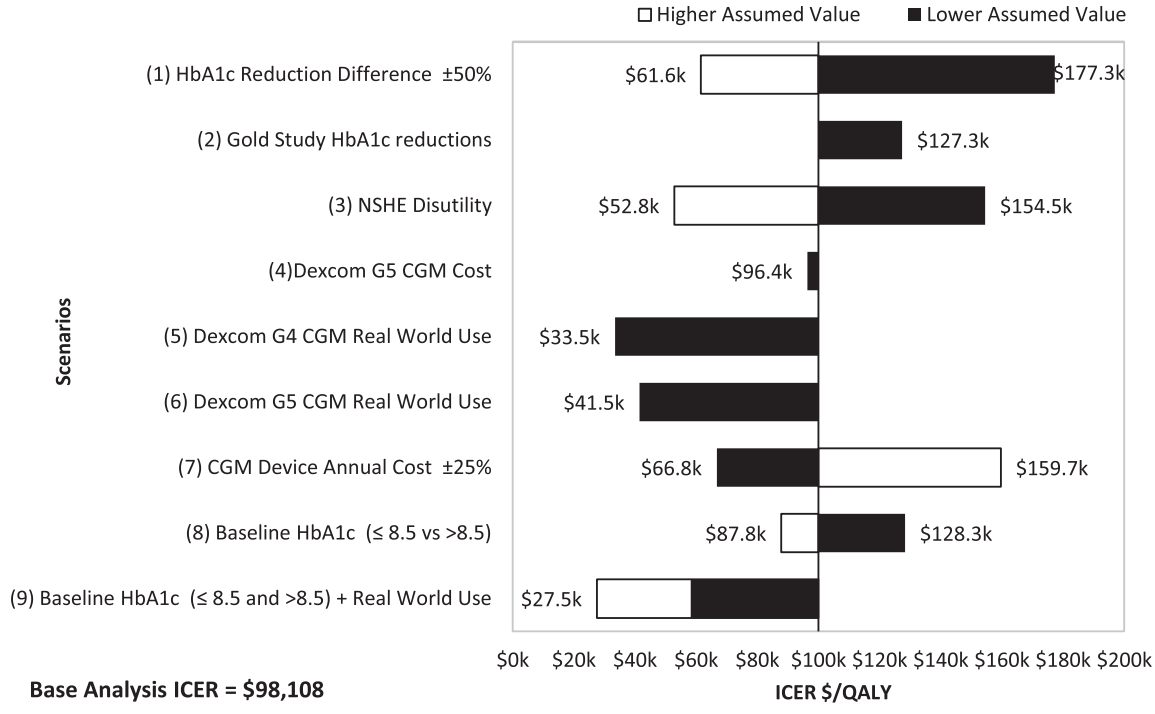

Figure 1—Results of subgroup and one-way sensitivity analyses.

and lifestyle aid for patients with T1D (9,10). Our study provides an important expanded view on the contemporary economic value of CGM in T1D. The prior JDRF trial and its economic study did not have substantial representation by patients with T1D using multiple daily injections of insulin (13). Our study based on the DIAMOND trial confirms that CGM is equally valuable in this large and important segment of the population with T1D.

An important strength of our study is that we selected and modified the Sheffield model (22), one of the most rigorous and thoroughly reported T1D models (34). The Sheffield model is the only model that features all the following properties: ability to account for all major complications, estimation of model parameters solely based on T1D trial data, HbA_{1c} as a predictor in most risk equations, validation with major T1D studies, capable of sensitivity analysis, and full transparency. Based on the trial findings, we modified the Sheffield model by removing the interdependency between rates of severe hypoglycemic events and HbA_{1c} levels.

Another strength of this study is that we were able to capture and model NSHEs in our economic model. The cost of a NSHE episode used in the study was $20.32, including $11.09 in direct medical costs and $9.23 in indirect costs (35,36). Lowering NSHEs not only reduces the risk of subsequent severe hypoglycemia (37) but also improves QoL, including psychological well-being, adherence to treatment regimens, work productivity, and quality and quantity of sleep (6,18,19).

Our study has some limitations. The disutility value of a NSHE was difficult to ascertain due to diverse definitions of NSHEs within a limited literature. Prior studies of the QoL effects of NSHE (38,39) were based on life with and without symptomatic hypoglycemia or on the experience of a single symptomatic hypoglycemic event. These patient-reported definitions are distinct from the new international definition of <54 mg/dL for ≥ 20 successive minutes (21), attainable by CGM device, which has a higher frequency than those based on past definitions and is frequently asymptomatic. The EQ-5D is widely accepted and regularly used for indirect utility assessment in clinical trials but may not be sensitive enough to reflect changes in QoL that are caused by reductions in NSHEs (40). Future work should pursue translating the QoL effects of NSHEs into health state utilities. Although the trial found that CGM reduced the daily rate of NSHEs, most of the CGM patients still experienced NSHEs. This indicates that reducing NSHEs should be an important goal of future interventions. Whether a 6-month treatment effect will be sustained over a person's lifetime is not clear. Our other study limitation is related to the possible inaccuracy of number of missed workdays, number of workdays with $<50\%$ productivity, and daily hours devoted to self-management diabetes care. Because patients were surveyed at baseline and 6 months, a 6-month recall period may be too long to recall this information accurately.

Despite higher within-trial costs, for adults with T1D multiple insulin injections and suboptimal glycemic control, CGM is cost-effective at the $100,000 per QALY willingness-to-pay threshold with improved glucose control and reductions in nonsevere hypoglycemia. With real-world use, CGM can be highly cost-effective.

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