The Cost of Control: Cost-effectiveness Analysis of Hybrid Closed-Loop Therapy in Youth

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OBJECTIVE

Hybrid closed-loop (HCL) therapy is an efficacious management strategy for young people with type 1 diabetes. However, high costs prevent equitable access. We thus sought to evaluate the cost-effectiveness of HCL therapy compared with current care among young people with type 1 diabetes in Australia.

RESEARCH DESIGN AND METHODS

A patient-level Markov model was constructed to simulate disease progression for young people with type 1 diabetes using HCL therapy versus current care, with follow-up from 12 until 25 years of age. Downstream health and economic consequences were compared via decision analysis. Treatment effects and proportions using different technologies to define "current care" were based primarily on data from an Australian pediatric randomized controlled trial. Transition probabilities and utilities for health states were sourced from published studies. Costs were considered from the Australian health care system's perspective. An annual discount rate of 5% was applied to future costs and outcomes. Uncertainty was evaluated with probabilistic and deterministic sensitivity analyses.

RESULTS

Use of HCL therapy resulted in an incremental cost-effectiveness ratio of Australian dollars (AUD) $32,789 per quality-adjusted life year (QALY) gained. The majority of simulations (93.3%) were below the commonly accepted willingness-to-pay threshold of AUD $50,000 per QALY gained in Australia. Sensitivity analyses indicated that the base-case results were robust.

CONCLUSIONS

In this first cost-effectiveness analysis of HCL technologies for the management of young people with type 1 diabetes, HCL therapy was found to be cost-effective compared with current care in Australia.

Type 1 diabetes is challenging to optimally manage. Hypoglycemia poses an acute risk to health and may seriously impact quality of life and productivity, while prolonged exposure to hyperglycemia increases the risk of microvascular and macrovascular complications (1–6). Advancements in insulin pump therapy, continuous glucose monitoring, and educational strategies for self-management have the potential to improve glycemia and reduce complications of diabetes. However, only a minority of young people internationally are meeting glycemic targets despite the progress in technology (7,8). Furthermore, type 1 diabetes is still associated with

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

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increased mortality, with the highest risk among those with a younger age of onset (9–12).

Hybrid closed-loop (HCL) therapy is currently the most advanced management strategy available for type 1 diabetes. Current-generation HCL therapy integrates insulin pumps and continuous glucose monitoring devices with decision algorithms to automatically increase or decrease basal insulin to help correct hyperglycemia and mitigate hypoglycemia. While the automation of HCL therapy does not eliminate the need for fastidious user oversight, HCL systems do appear to provide the best potential for optimal glycemic outcomes among pediatric and adult populations (13–18).

The high acquisition cost of HCL therapy is a barrier to equitable access for people with type 1 diabetes (18–21). The cost of technology must also be weighed against the significant costs of diabetes and its complications for people with type 1 diabetes, their carers, health care systems, and society in general (22–25). At present, published economic data regarding HCL therapy are scarce (26). Two economic evaluations reported that HCL therapy was cost-effective compared with insulin pump therapy primarily among adults in Sweden and the U.K. (27,28). Our recent cohort-based cost-effectiveness analysis also reported that HCL therapy was likely cost-effective compared with insulin injections and capillary glucose testing among adults with type 1 diabetes in Australia (29). However, we are unaware of cost-effectiveness analyses regarding HCL therapy among young people or that consider a comparator group using insulin pumps or injections with any glucose monitoring system.

We thus aimed to evaluate the cost-effectiveness of HCL therapy compared with current care among young people with type 1 diabetes in Australia by using a patient-level simulation model. Facilitating and informing key aspects of our analyses were the results of an Australian, multicenter, parallel-group, randomized controlled trial (RCT) for the Australian JDRF Closed Loop Research Group (30).

RESEARCH DESIGN AND METHODS

Model Description

Development and reporting of our model followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement, the Diabetes Modeling Input Checklist, as well as the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) checklist (Supplementary "Reporting and validation," Supplementary Tables 4–6, and Supplementary Figs. 1 and 2) (31–33). A patient-level Markov model with annual cycles was constructed to evaluate the cost-effectiveness of HCL therapy compared with current care among young people aged 12 years, with follow-up until 25 years of age. This age range was chosen to mirror the Australian pediatric RCT that informed this economic analysis (30). A secondary analysis was performed to evaluate the cost-effectiveness of HCL therapy compared with current care from 12 years of age until death. Microsimulation was used to allow transition probabilities to vary based on different characteristics. The perspective was that of the Australian health care system. Future costs and outcomes were discounted by 5% annually based on guidelines by the Australian Government Department of Health (34). The primary outcome of interest was the incremental cost-effectiveness ratio (ICER) in terms of net cost per quality-adjusted life year (QALY) gained.

Model Structure

Health states considered by the model comprised type 1 diabetes with no complications or else any combination of diabetic eye disease, diabetic nephropathy, diabetic foot disease, acute myocardial infarction (AMI), stroke, congestive heart failure (CHF), unstable angina, and death. Diabetic eye disease was modeled with stages including "diabetic retinopathy" (level 20–35 according to the Early Treatment Diabetic Retinopathy Study [ETDRS] grading scale), "sight-threatening diabetic retinopathy" (level $\geq$43 on the ETDRS scale), "macular edema" (extrafoveal and/or clinically significant macular edema according to ETDRS classification), or blindness (both eyes) (35). Diabetic nephropathy was modeled with stages including moderately increased albuminuria, severely increased albuminuria, and end-stage renal disease. Regression of eye disease or renal disease was not modeled directly. Diabetic foot disease was modeled with health states including uncomplicated diabetic foot ulcer, complicated/infected diabetic foot ulcer, healed diabetic foot ulcer, minor amputation (at or below the ankle), infected amputation, major amputation (above the ankle), and healed amputation (36). The interrelated nature of complications was captured by transition probabilities for health states using the shared risk factor of HbA_{1c} as well as incorporating renal health states as part of annual cardiovascular risk prediction. Tracker variables were implemented to facilitate the independent modeling of different health states. Mortality was modeled to be a result of cardiovascular disease, renal causes, or "other" causes. Simulated individuals continued to cycle through the model until 25 years of age in the primary analysis and up to death with a theoretical limit of 100 years of age in the secondary analysis. Supplementary Fig. 2 graphically presents the model structure.

Transition Probabilities and Mortality Risk

Transition probabilities were derived from published sources to simulate disease progression (Supplementary Table 1). Contemporary published data were sought for each modeled health state, and age-specific all-cause mortality was drawn from published Australian data for people with type 1 diabetes (37).

Intervention Being Modeled

The treatment effect of HCL therapy on HbA_{1c} determined the difference in transition probabilities between treatment groups for all vascular complications. Rates of severe and nonsevere hypoglycemia were modeled to reflect the possibility of having multiple hypoglycemic events in a year rather than annual transition probabilities per event. All hypoglycemic events were assumed to be nonfatal. To predict the annual probability of the first macrovascular event, the Steno T1 Risk Engine model was used and involved the variables of age, sex, diabetes duration, systolic blood pressure, LDL cholesterol, HbA_{1c}, presence or absence of moderately or severely increased albuminuria, estimated glomerular filtration rate (eGFR) categorized as $>$40 or $<$40 mL/min/1.73 m^2, smoking status, and participation in regular exercise (38). Owing to the population-level data source for renal health states reporting on albuminuria or end-stage renal disease rather than eGFR levels, it was pragmatically

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assumed that eGFR was >40 mL/min/1.73 m^2 when using the Steno T1 Risk Engine model unless patients transitioned to end-stage renal disease. Recurrent cardiovascular events had to be preceded by a cardiovascular event at least 1 year earlier, and renal death could only occur in the presence of renal pathology arising at least 1 year prior. To predict the probability of recurrent cardiovascular events, the results of "A new model for 5-year risk of CVD in Type 1 diabetes" were annualized (39). This cardiovascular risk prediction model includes variables of age, diabetes duration, HbA_{1c}, systolic blood pressure, total cholesterol-to-HDL cholesterol ratio, smoking status, presence or absence of severe albuminuria, and the presence of a previous event (39). Random numbers were generated to determine patient sex, smoking status, and participation in regular exercise according to cohort-level probabilities as inputs for the cardiovascular risk prediction models. Results from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study were used to define the proportion of events comprising AMI, stroke, or CHF (40). Case fatality data were used to derive mortality rates for AMI, stroke, and CHF. Unstable angina and lower-extremity amputations were assumed to be nonfatal. Because projected cardiovascular and renal mortality rates were modeled separately in relation to glycemic control, previously reported estimates for these causes of death were subtracted from the published aggregate of Australian all-cause mortality data to avoid double counting.

Costs

All costs were reported in 2021 Australian dollars (AUD), with adjustment for inflation using the health consumer price index (41). Multiple sources were used to estimate costs (Supplementary Table 2). For type 1 diabetes without any complications, costs were sourced from the largest Australian cost-of-illness study comprising 2,200 people with type 1 diabetes selected from an Australian diabetes register (National Diabetes Services Scheme [NDSS]) (22). For diabetic retinopathy among those with type 1 diabetes in Australia, costs were estimated based on Medicare Benefits Schedule item numbers, the Pharmaceutical Benefits Scheme for medications, and the intensity of monitoring and intervention was based on clinical guidelines, landmark clinical trials, and the expert opinion of ophthalmologists. For diabetic nephropathy, costs were derived from Australian economic projections published by Kidney Health Australia reflecting the cost of kidney disease for the general population (42,43). For diabetic foot disease, costs were derived from an Australian cost-effectiveness analysis regarding the optimal care for diabetic foot ulcers among those with type 1 or type 2 diabetes (36). Costs for the inpatient and subsequent outpatient management of stroke, regardless of diabetes status, were derived from Australian cost-effectiveness analyses (44,45), and the costs for other cardiovascular diseases among the general population were derived from a report by the Australian Heart Foundation (46). A conservative 50% reduction was applied to costs for fatal cardiovascular events to account for only 50% of deaths occurring in hospitals throughout Australia, regardless of diabetes status (47,48). For severe hypoglycemia, an Australian economic evaluation was used that comprised costs for ambulance callout, hospital admission, accident and emergency visit, glucagon injection, and follow-up visits (49). Nonsevere hypoglycemic events were assumed to have no associated costs, but an annual disutility was applied.

Regarding intervention costs, the analysis included incremental costs of an HCL system over current care, which was defined by the baseline utilization rates of insulin pump therapy or multiple daily injections of insulin with either capillary glucose testing or continuous glucose monitoring in the Australian pediatric RCT (30). The only commercially available HCL systems in Australia at the time of writing comprised the MiniMed 670G/770G (Medtronic), infusion sets, reservoirs, batteries, Guardian Sensor 3 (Medtronic), transmitter, and transmitter charger. Twice-daily capillary glucose testing was assumed for calibration when using the HCL system or continuous glucose monitoring compared with eight tests per day for capillary glucose testing. Among those in the comparator arm using continuous glucose monitoring apart from HCL therapy, it was assumed that available and subsidized brands (AMSL Diabetes and Medtronic Diabetes Australia) were used in equal proportions. Cohort-level utilization rates of insulin pumps, injections, capillary glucose testing, and continuous glucose monitoring of those ≤25 and >25 years of age derived an overall weighted cost for management in the comparator arm. The previously described Australian cost of illness study presented aggregated costs of type 1 diabetes that captured the cost of multiple daily injections and capillary glucose testing. Consistent with current government subsidies, the cost of insulin pump consumables, but not insulin pumps, was added to the aggregated cost of type 1 diabetes among those using insulin pump therapy in the comparator arm.

Utilities

Utilities for the health state of type 1 diabetes without complications were drawn from the same Australian cost of illness study described above (22). In the absence of Australian data sources and sparsity of detail internationally, utilities for the different stages of diabetic eye disease were drawn from Japanese and Canadian patient preference-based time trade-off analyses that informed prior cost-effectiveness analyses (50–52). To facilitate the inclusion of separate utilities for albuminuria as well as hemodialysis and peritoneal dialysis, European analyses of people with type 2 diabetes or on chronic dialysis were implemented and were consistent with the available more general data regarding people with type 1 diabetes (53–55). To facilitate the inclusion of separate utilities for diabetic foot ulceration, infection, as well as minor or major amputations, with or without infection, European time trade-off analyses were chosen that had been used previously in Australian cost-effectiveness analyses (36,56). Disutilities for AMI, stroke, CHF, and angina were taken from a population-based time trade-off analysis among people with type 2 diabetes in the U.K. (57). Annual disutilities of −0.0475 and −0.0041 were used for severe and nonsevere hypoglycemia, respectively. Disutility for hypoglycemia was derived as the average of daytime and nocturnal events from a large Canadian time trade-off survey among people with type 1 diabetes (58). Disutilities for multihealth conditions were summed. See Supplementary Table 3 for a list of utilities/disutilities used in the analysis.

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Simulation Cohort and Treatment Effects

The model was populated by convention with 10,000 individual patient-level simulations profiled largely from a 6-month Australian pediatric RCT of HCL therapy compared with current care (30). Individuals entered the model at 12 years of age, with diabetes duration of 7 years, and with no vascular complications. Rates of severe and nonsevere hypoglycemia among the pediatric population and those modeled to continue through adulthood were drawn from large registries, the DCCT/EDIC study, cohort studies as well as the 6-month Australian RCT (2,30,59–67). Treatment effects for HCL therapy on HbA_{1c} and nonsevere hypoglycemia reduction were drawn from the same Australian pediatric RCT and were assumed to be constant over follow-up for primary and secondary analyses (30). HCL therapy was also conservatively assumed to reduce severe hypoglycemia by 50% in the base-case. Baseline utilization of technology types among participants in the Australian pediatric RCT defined the comparator arm for our economic evaluation, were assumed to remain constant until 25 years of age, and comprised insulin pump therapy (81%), multiple daily injections of insulin (19%), continuous glucose monitoring (59%), and capillary glucose testing (41%) (30). For the secondary analyses that followed up individuals until death, clinical profiles and utilization rates of technology types after 25 years of age were based on data from the Australian National Diabetes Audit, which has reported that 27% and 23% of adults with type 1 diabetes used insulin pumps and continuous glucose monitoring, respectively, and were also assumed to remain constant over time (20). Cohort-level mean (±SD) values for biomarkers required for cardiovascular risk prediction in adulthood were also derived from the Australian National Diabetes Audit and were assumed to be equivalent in the treatment and comparator groups (68). Broadly in keeping with current funding initiatives in Australia, those using continuous glucose monitoring were assumed to receive no government subsidy after 25 years of age, unless part of the modeled intervention of HCL therapy (20). Those using insulin pumps apart from HCL therapy were also assumed to receive the current government subsidy that is limited to consumables (reservoirs and cannulas) and insulin regardless of age. A detailed profile of the simulated individuals and treatment effects is provided in Table 1.

Sensitivity Analyses

Probabilistic sensitivity analyses with 10,000 iterations were performed to account for uncertainty across the input parameters. Univariate scenario analyses were also considered to explore model assumptions that comprised extending the horizon from 13 years to a lifetime; reducing discount rates for future costs and outcomes to 3.5%, 1.5%, and 0%; increasing and decreasing the cost of HCL therapy by 10%; reducing the treatment effect of HCL therapy on nonsevere hypoglycemia by 25% and 50%; increasing the baseline rate of nonsevere hypoglycemia to 104 events per person/year; reducing the treatment effect of HCL therapy on severe hypoglycemia by 50% and 100%; assuming no treatment effect on HbA_{1c}; assuming the baseline HbA_{1c} was 7.0% (53 mmol/mol) or 9.0% (75 mmol/mol); assuming the baseline incidence of severe hypoglycemia was 16.6 or 6.7 per 100 person-years based on local population studies (64,69); and assuming the treatment effect on HbA_{1c} increased from 0.3% (3.3 mmol/mol) to 1.0% (10.9 mmol/mol) over a lifetime horizon with the baseline HbA_{1c} unchanged or else increased to 9.0% (75 mmol/mol). All univariate scenario analyses were replicated over a lifetime horizon, except for assuming reduced base rates of severe hypoglycemia based on results reported among a pediatric population. In addition, the treatment effect of HCL therapy on HbA_{1c} was only increased from 0.3% (3.3 mmol/mol) to 1.0% (10.9 mmol/mol) among adults over a lifetime horizon based on results of meta-analyses among adults (13,14). Microsoft Excel (Microsoft Corp., Redmond, WA) and TreeAge Pro Healthcare 2021 R1.1 (TreeAge Software LLC, Williamstown, MA) were used for the economic analyses.

RESULTS

Compared with current care, the use of HCL therapy was associated with gains of 1.15 (discounted) QALYs per person until 25 years of age, at a net cost (discounted) of AUD $37,827, resulting in an ICER of AUD $32,789 per QALY gained. At the commonly accepted willingness-to-pay (WTP) threshold of AUD $50,000 per QALY gained in Australia (70–72), 93.3% of simulations predicted the HCL system to be cost-effective.

Sensitivity analyses found that results were most sensitive to the base rate and treatment effect on nonsevere hypoglycemia, the cost of HCL systems, the time horizon, and the treatment effect of HCL therapy on HbA_{1c}. Assuming the base rate of nonsevere hypoglycemia was increased to 104 events per person/year in keeping with the rates reported by the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines for hypoglycemia (66), led to an ICER of AUD $18,436 per QALY gained while reducing the treatment effect of HCL therapy on nonsevere hypoglycemia by 50% increased the ICER to AUD $54,668 per QALY gained. In contrast, assuming no treatment effect on severe hypoglycemia for people aged 12 to 25 years increased the ICER only slightly to AUD $37,452 per QALY gained. Reducing or increasing the cost of HCL therapy by 10% led to ICERs of AUD $24,234 or AUD $40,864 per QALY gained, respectively.

Extending the time horizon to a lifetime increased the ICER to AUD $48,882 per QALY gained. In the context of a lifetime horizon, increasing the relative treatment effect of HCL therapy on HbA_{1c} from −0.3% (3.3 mmol/mol) to −1.0% (10.9 mmol/mol) reduced the ICER to AUD $42,271 per QALY gained, or AUD $43,136 per QALY gained if the baseline HbA_{1c} was also increased to 9.0% (75 mmol/mol). Results over a lifetime were also particularly sensitive to the cost of HCL therapy as well as the base rate of nonsevere hypoglycemia and the treatment effect of HCL therapy on nonsevere hypoglycemic events. Reducing the recommended 5% discount rate for future costs and health outcomes increased the ICER. Results of the base-case and scenario analyses are presented in Tables 2 and 3, respectively.

The cost-effectiveness plane and scatter plot (Fig. 1) presents the variation in modeled outcomes, with HCL therapy tending to offer greater effectiveness in QALYs but at a greater cost than current care. The ellipse in Fig. 1 represents the 95% confidence for modeled results. The cost-effectiveness acceptability curves for the primary and secondary analyses

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Table 1—Characteristics of patient-level simulations

Cohort characteristics	Mean (variance)	α	β	Distribution	Reference
Initial age, years	12.00			Fixed	Abraham et al. (30)
Duration of diabetes, years	7.00			Fixed	Abraham et al. (30)
Female sex, %	55.00			Fixed	Abraham et al. (30)
Total-to-HDL cholesterol ratio	3.09			Fixed	Pease et al. (68)
LDL cholesterol, , mean (SD), mmol/L	2.55 (0.95)			Normal	Pease et al. (68)
HbA_{1c} (age ≤21 years), mean (SD), %	8.0 (1.0)			Normal	Abraham et al. (30)
HbA_{1c} (age ≤21 years), mmol/mol	64 (10.9)			Normal	Abraham et al. (30)
HbA_{1c}, (age >21 years), mean (SD), %	8.5 (1.5)			Normal	Pease et al. (68)
HbA_{1c}, (age >21 years), mean (SD), mmol/mol	69 (16.4)			Normal	Pease et al. (68)
Systolic blood pressure, mmHg	124 (17)			Normal	Pease et al. (68)
Smoker, %	38.50	397	634	β	Pease et al. (68)
Regular exercise, %	68.20	2,937	1,369	β	Vistisen et al. (38)
Nonsevere hypoglycemia (overall), *n*/person/year	55.70	100.00	0.56	γ	Ratzki-Leewing et al. (60)
Severe hypoglycemia, *n*/person/year					
Total—age ≤21 years	0.38	100.00	0.00	γ	Gubitosi-Klug et al. (67)
Total—age >21 years*	1.98	100.00	0.02	γ	Pease et al. (29), Geddes et al. (59)
Hypoglycemia awareness—age >21 years					
Normal	1.00				
Impaired	6.00				
Proportion with impaired hypoglycemia awareness (age >21 years), %	19.50				
Treatment effects of HCL therapy					
HbA_{1c} reduction, %,	0.3			Fixed	Abraham et al. (30)
HbA_{1c} reduction, mmol/mol	3.3			Fixed	Abraham et al. (30)
Nonsevere hypoglycemia reduction, %	54			Fixed	Abraham et al. (30), Pease et al. (29)
Severe hypoglycemia reduction, %					
Age ≤25 years	50			Fixed	Assumption
Age >25 years	95			Fixed	Pease et al. (29)

*The number of severe hypoglycemic events per person/year represented the average weighted number of events estimated from the prevalence of impaired hypoglycemia awareness (19.5%) and the number of severe hypoglycemic events for adults >21 years of age with and without impaired awareness of hypoglycemia.

(Supplementary Fig. 3 and 4, respectively) present the proportion of 10,000 iterations that were cost-effective for HCL therapy and current care at various WTP thresholds. Tornado diagrams of sensitivity analyses of HCL therapy compared with current care are presented in Supplementary Figs. 5 and 6 and provide further support for our choice of variables and scenarios for deterministic sensitivity analyses presented in Table 3.

CONCLUSIONS

Our modeled economic evaluation produced an ICER of AUD $32,789 per QALY gained for HCL therapy relative to current care. HCL therapy is thus likely to be cost-effective compared with current care among young people with type 1 diabetes in Australia based on the commonly accepted WTP threshold of AUD $50,000 per QALY gained (70–72). Sensitivity analyses demonstrated the results were robust.

Our analyses regarding HCL therapy had a unique focus on young people as well as the comparison with a range of preexisting management devices. However, results were consistent with the few published economic evaluations, primarily among adults, that similarly reported HCL therapy to be cost-effective despite different health care systems, WTP thresholds, modeling perspectives, models, and different clinical comparators (27–29). HCL therapy has been consistently modeled

Table 2—Overall base-case results

Results	Current care	HCL therapy
Costs, mean (SD), $	90,507 (11,391)	128,334 (12,611)
QALYs, mean (SD)	6.56 (0.81)	7.71 (0.82)
Incremental cost, $		37,827
Incremental QALYs		1.15
ICER, $		32,789

The results represent discounted values reported in 2021 AUD.

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Table 3—Deterministic scenario analyses

Scenarios	ICER (mean), $
Primary analysis (12 to 25 years of age)	
Discount rate 3.5% for costs and outcomes	32,816
Discount rate 1.5% for costs and outcomes	32,102
Discount rate 0% for costs and outcomes	31,952
Assuming the cost of HCL therapy increased by 10%	40,864
Assuming the cost of HCL therapy decreased by 10%	24,234
Assuming treatment effect on nonsevere hypoglycemia was reduced by 25%	41,110
Assuming treatment effect on nonsevere hypoglycemia was reduced by 50%	54,668
Assuming baseline rate of nonsevere hypoglycemia was 102 per person/year	18,436
Assuming treatment effect on severe hypoglycemia was reduced by 50%	35,184
Assuming treatment effect on severe hypoglycemia was reduced by 100%	37,452
Assuming baseline rate of severe hypoglycemia was 16.6 per 100 person/years	35,469
Assuming baseline rate of severe hypoglycemia was 6.7 per 100 person/years	36,817
Assuming no treatment effect on HbA_{1c}	32,928
Assuming baseline HbA_{1c} was 1.0% (10.9 mmol/mol) lower	32,928
Assuming baseline HbA_{1c} was 1.0% (10.9 mmol/mol) higher	32,990
Over a lifetime horizon:	48,882
Discount rate 3.5% for costs and outcomes	50,454
Discount rate 1.5% for costs and outcomes	57,909
Discount rate 0% for costs and outcomes	63,691
Assuming the cost of HCL therapy increased by 10%	61,885
Assuming the cost of HCL therapy decreased by 10%	43,501
Assuming treatment effect on nonsevere hypoglycemia was reduced by 25%	65,443
Assuming treatment effect on nonsevere hypoglycemia was reduced by 50%	82,920
Assuming baseline rate of nonsevere hypoglycemia was 102 per person/year	27,882
Assuming treatment effect on severe hypoglycemia was reduced by 50%	49,662
Assuming treatment effect on severe hypoglycemia was reduced by 100%	53,748
Assuming no treatment effect on HbA_{1c}	51,302
Assuming the treatment effect on HbA_{1c} was −1% (10.9 mmol/mol)	42,271
Assuming baseline HbA_{1c} was 1.0% (10.9 mmol/mol) lower	49,609
Assuming baseline HbA_{1c} was 1.0% (10.9 mmol/mol) higher	48,939
Assuming baseline HbA_{1c} was 1.0% higher and the treatment effect on HbA_{1c} was −1%	43,136

The results represent discounted values with annual discounting of 5% for costs and outcomes unless otherwise stated. All costs are reported in 2021 AUD.

to increase QALYs over a lifetime, with the increment ranging from 1.73 and 1.90 compared with insulin pump therapy (27,28), through to 3.72 compared with insulin injections (29) in the U.K., Sweden, and Australia, respectively. This is in keeping with our sensitivity analyses over a lifetime horizon that modeled an increment of 2.15 QALYs compared with current care. However, prior modeled cohorts have been much older, with analyses starting at 18 years of age in Australia (29), or a mean age of 37.8 (SD 16.5) years in the U.K. and Sweden (27,28). Previous analyses have also limited their comparison of HCL systems to insulin pump therapy or insulin injections. Therefore, our focus on the cost-effectiveness of HCL therapy among young people compared with current care adds important breadth to the growing landscape of economic evidence.

In addition to the primary analysis among young people, a secondary analysis using a lifetime horizon was included due to the lifelong nature of type 1 diabetes. Consistent between the primary and secondary analyses was that nonsevere hypoglycemia and the cost of technology remained key drivers for cost-effectiveness. The important role of utility gains from reduced hypoglycemia or "fear" of hypoglycemia as well as technology costs have also been reported by the few other economic evaluations of HCL therapy to date (27–29). Furthermore, because most vascular complications develop in adulthood, the relative impact of HbA_{1c} reductions from HCL therapy on ICER values was also much greater over the lifetime horizon compared with the primary analysis over 13 years. Our conservative analyses over a lifetime horizon produced an ICER of AUD $48,882 per QALY gained. Combined with our primary analysis, the results suggest that HCL therapy may be cost-effective in young people and across the life span compared with current care in Australia. Any reductions in technology costs over time would also be predicted to decrease the ICER further. However, base rates of nonsevere hypoglycemia and treatment effects of HCL therapy on HbA_{1c} and nonsevere hypoglycemia over a lifetime may impact these conclusions.

The strengths of our study included patient-level simulations providing more granular detail than cohort-based models and a diverse multidisciplinary team developing the model and ensuring face validity (Supplementary File; Reporting and validation). Treatment effects of HCL therapy for HbA_{1c} and nonsevere hypoglycemia were derived from an Australian RCT (30). The comparator arm used for our analyses may also be more generalizable than other studies because participants and their clinicians were free to use any management technology apart from HCL therapy throughout the trial, reflecting real-world clinical practice (30). In addition, conservative estimates for baseline glycemia were implemented, and extensive sensitivity analyses for key drivers of cost-effectiveness supported our base-case results. Costs and utilities for the baseline health state of type 1 diabetes without complications were sourced from Australia's largest cost of illness study (22), and all other cost data were taken from Australian sources.

We also acknowledge that there were limitations of the available data sources and model assumptions. Outcome projections over a number of years were extrapolated from short-term clinical data in the absence of long-term studies for modern technologies. Like most economic evaluations, generalizability of results may be limited by the implementation of RCT data with recruited and often highly motivated participants. Treatment effects and base rates of severe hypoglycemia were also unclear in the literature. However, data from the landmark DCCT/EDIC study were implemented for base rates of severe hypoglycemia as they were considered conservative compared with population studies and meta-regression of RCTs (1,2,64–67,73,74). Sensitivity analyses also considered lower baseline rates of severe hypoglycemia as reported by other Australian studies (64,69).

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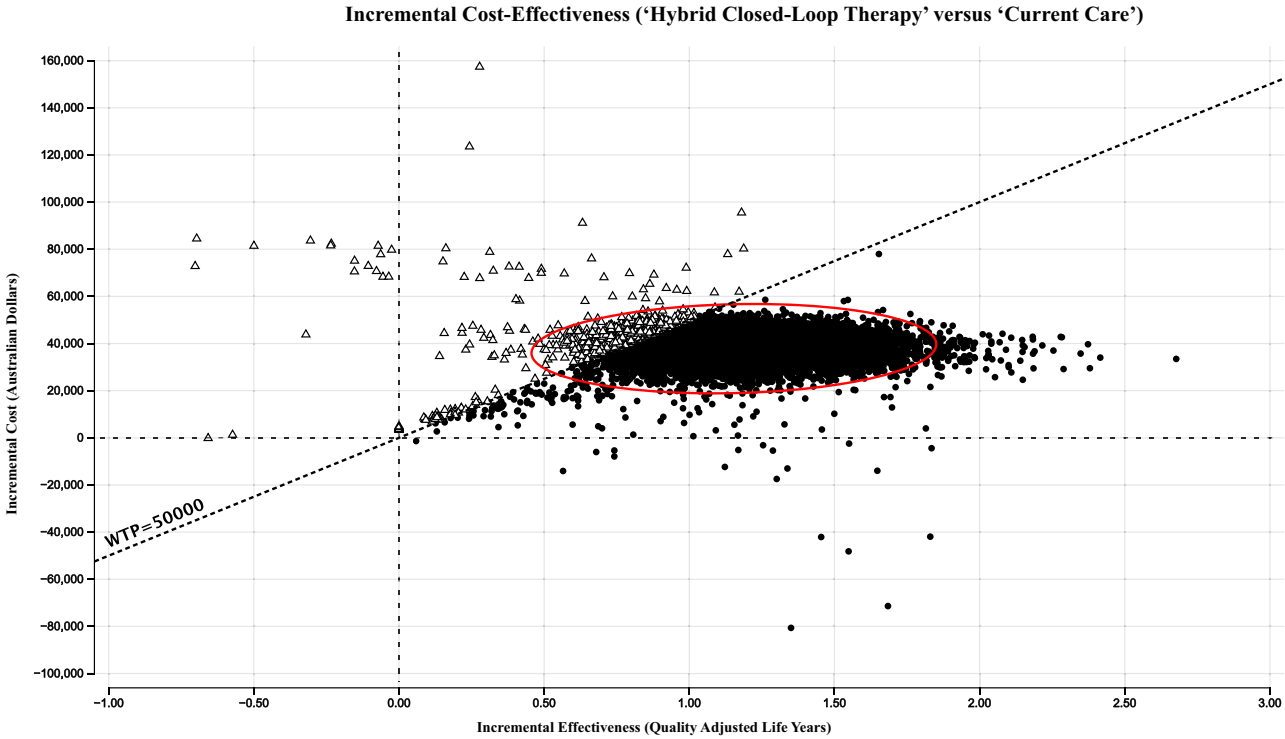

Figure 1—Incremental cost-effectiveness plane and scatter plot (12 to 25 years of age). The solid circles and open triangles represent iterations for which HCL therapy compared with current care was the optimal and suboptimal strategy in relation to the WTP threshold, respectively. The bold dotted line represents the WTP threshold, and the ellipse represents 95% confidence.

Regarding the treatment-effect of HCL therapy on severe hypoglycemia, the majority of recent trials have been of short duration and reported zero events among young people, although similarly low rates were present in comparator arms as well. In contrast to other economic evaluations that assumed HCL therapy completely prevented severe hypoglycemia over a lifetime in the base-case (27,28), we were more conservative and considered a treatment effect of 50% with sensitivity analyses ranging from 0 to 95%. As with other published economic models, utility values derived from populations with type 2 diabetes and/or from different countries were implemented when comparable detail was not available for those with type 1 diabetes in Australia. Experienced ophthalmologists also assisted with the development of model assumptions regarding the investigation and management of diabetic eye disease in the absence of adequate publicly available data. Owing to limited available data sources, a number of assumptions were made during model development. The costs of end-stage renal disease and of CVD were based on populations irrespective of comorbid diabetes status, and the cost of diabetic foot disease was based on a population with any diabetes type. Fatal cardiovascular event costs were conservatively reduced by 50% to account for only 50% of deaths occurring in hospitals throughout Australia (47,48); however, assuming no adjustment for death costs or assuming zero costs for death had minimal impact on the primary or secondary analysis (data not shown). Results were limited to the health care system perspective, although any societal benefits from HCL therapy would likely reduce the ICER further. Similar to other validated models, historical results from the DCCT/EDIC study were used to apportion modeled cardiovascular events as AMI, unstable angina, stroke, or CHF. In addition, eGFR was assumed to be $<$40 mL/min/1.73 m^2 only for those modeled to have end-stage renal disease. Deterministic and probabilistic sensitivity analyses addressed uncertainty in the model, but it was not feasible to address all clinically relevant scenarios.

In addition to cost-effectiveness analyses, further research is needed into the indirect costs and budget impact of HCL therapy as well as real-world and patient-relevant outcomes. Clinical trials and existing diabetes registries could be leveraged to collect standardized economic data to strengthen models, address economic uncertainty, and appraise implementation strategies. The increasing focus on time-in-range over HbA_{1c} as a metric of glycemic control also requires longer-term data regarding the complications of diabetes and quality of life to facilitate inclusion in future economic modeling. Furthermore, while most economic evaluations focus on the perspective of the health care system for funding decisions, the burden of health care costs on people with type 1 diabetes and their carers should also drive further research into health equity.

Overall, HCL therapy is likely cost-effective compared with current care by reducing HbA_{1c} and the incidence of hypoglycemia among those with type 1 diabetes in Australia. This first positive finding among young people adds to the weight of growing international economic evidence among adults that HCL therapy appears to represent good value for money in a relatively short time frame and across the life span. Future research into diabetes management technologies

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should also focus on budget impact and incorporating health equity into funding decisions.

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