C-peptide as a Health Economic Endpoint in Type 1 Diabetes (T1D): Systematic Review Evidence for Cost-Effectiveness Modelling of Disease-Modifying Therapies (DMTs)

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Introduction

- Type 1 diabetes (T1D) is a chronic autoimmune disease that destroys pancreatic β-cells, leading to complete insulin deficiency. T1D is associated with reduced quality of life (QoL), acute and long-term complications, shortened life expectancy, and substantial healthcare costs.[1]
- Approximately 2.1 million people in the United States live with T1D, including 1.8 million adults aged ≥ 20 years and ~314,000 children and adolescents.[2,3]
- C-peptide reflects β-cell function, with detectable levels associated with a lower risk of diabetic ketoacidosis (DKA), severe hypoglycaemia requiring hospitalisation and retinopathy in T1D.[4,5]
- Disease-modifying therapies (DMTs) like teplizumab rely on β-cell preservation and C-peptide retention as primary endpoint.
- However, Health Technology Assessment (HTA) bodies and payers require quantifiable C-peptide-to-outcomes links including healthcare resource utilisation (HCRU), QoL, etc. for robust DMT cost-effectiveness models.

Objective

- To conduct a systematic literature review (SLR) evaluating the evidence linking C-peptide levels with HCRU and QoL-relevant clinical outcomes in patients with T1D.
- Define dose-response thresholds of C-peptide levels parameterise state-transition and decision-tree cost-effectiveness models.

Method

- The SLR was conducted and reported in accordance with two established methodological frameworks.
- The process adhered to the standards outlined in the Cochrane Handbook for Systematic Reviews of Interventions,[6] ensuring methodological rigour throughout.
- Findings were subsequently reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[7] ensuring transparency and completeness in the presentation of results (**Figure 1**).

Figure 1. Overview of the SLR methodology

Phase 1: Search strategies
- The SLR was conducted to identify relevant experimental and observational studies reporting on the benefits of C-peptide preservation, the harms of C-peptide reduction, and its role in β-cell preservation among adults (≥18 years) or children with autoimmune T1D

Phase 2: Screening
- Relevant studies were identified by searching Embase and MEDLINE® from database inception to 22 May, 2025, using predefined search strategies. Conference proceedings from the past three years (2023 – 2025) were also searched

Phase 3: Inclusion and exclusion
- Abstract selection, full-text selection, and data extraction of included studies were performed. After full-text screening, a critical appraisal of eligible studies was conducted using a pre-defined critical appraisal tool which assessed the methodological quality, clinical relevance, and overall robustness of all studies included in the evidence base. Studies without a cap that did not meet the critical appraisal criteria were excluded

Phase 4: Appraisals and data extraction

Critical appraisal
- 2 independent reviewers
- Validated tools and standardised criteria

Data extraction (Microsoft Excel)
- Study characteristics: Authors, year, design, location, follow-up
- Patient characteristics: Age, sex, disease duration, BMI, HbA1c, C-peptide levels, insulin dose
- Outcomes: Severe hypoglycaemia, DKA, microvascular complications, glycaemic control, cost thresholds

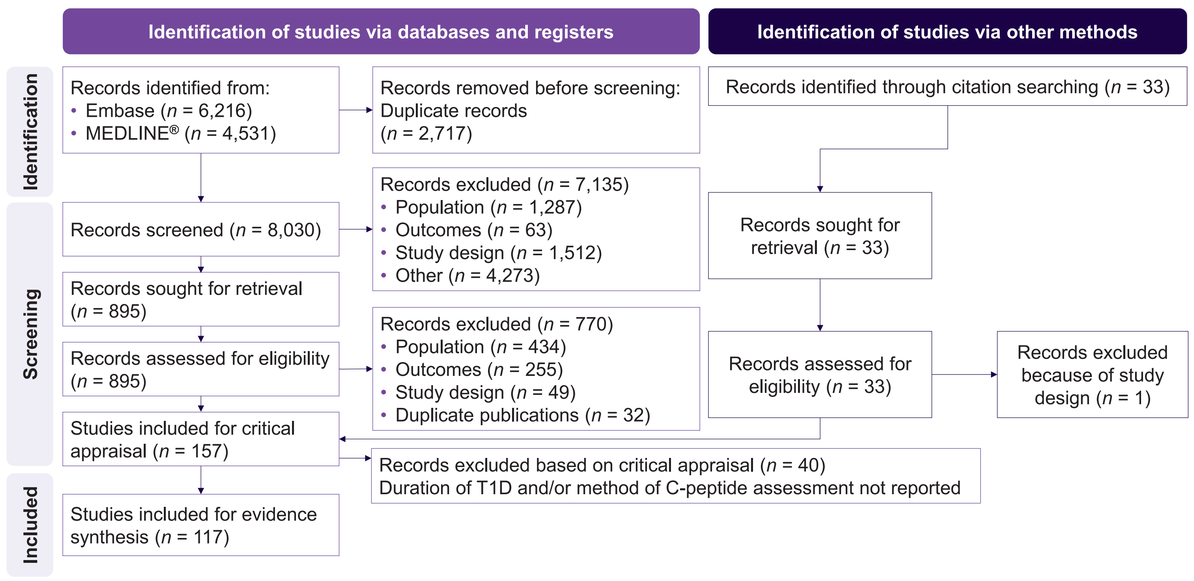
BMI, body mass index; DKA, diabetic ketoacidosis; Embase, Excerpta medica database; HbA1c, glycated haemoglobin; MEDLINE, Medical Literature Analysis and Retrieval System Online; SLR, systematic literature review; T1D, type 1 diabetes.

Results

Study Selection

- **Figure 2** illustrates the PRISMA flow diagram of the study selection process. The SLR identified 10,747 abstracts through search of Embase and MEDLINE® database searches.
- Title and abstract screening excluded 7,135 records. Subsequently, 895 full-text articles underwent detailed assessment, and 770 excluded for the following reasons: ineligible population (*n* = 434), irrelevant outcomes (*n* = 255), inappropriate study design (*n* = 49), and duplicate publications (*n* = 32).
- Citation searching yielded an additional 32 studies. Ultimately, 157 studies met the eligibility criteria and were included in the critical appraisal.

Figure 2. PRISMA flow diagram of study identification, screening, and inclusion



n, number of studies; Embase, excerpta medica database; MEDLINE, medical literature analysis and retrieval system online; PRISMA, preferred reporting items for systematic reviews and meta-analyses; T1D, type 1 diabetes.

Critical Appraisal

- Of the 157 studies included in the critical appraisal, 40 studies that did not report either the duration of autoimmune T1D since diagnosis or the method of C-peptide assessment or both were excluded as they did not meet the minimum criteria for methodological and reporting quality.
- In total, 117 studies were included in the SLR (**Figure 2**).

Acute Cost Drivers (Hypoglycaemia and DKA), Daily Resource Use, and Chronic Microvascular Complications

- As shown in **Table 1,** preserved C-peptide levels (≥ 0.2 nmol/L) versus minimal C-peptide levels (< 0.2 nmol/L) only demonstrated a strong correlation between clinical benefits across acute complications, daily management, lower cost of strips/ continuous glucose monitoring cost, glycaemic control, and chronic complications.
- These improvements correspond to substantial cost savings through reduced emergency care, hospitalisations, drug costs, monitoring resources, and specialist procedures.

Table 1. Clinical outcomes and potential health economic relevance of preserved versus minimal C-peptide levels

Domain	Outcome	Clinical effect (C-peptide preserved/minimal)	Cost/HCRU impact
Acute complications	Severe hypoglycaemia	↓ 51% (95% CI: 44–57; p < 0.0001)[8]	↓ Inpatient hospitalisations, emergency care interventions, and lost workplace productivity
	DKA incidence	↓ 56% (HR: 0.44; 95% CI: 0.29–0.67, p = 0.0001)[9]	↓ Hospital admissions, acute inpatient costs
Daily management	Exogenous insulin	↓ 28% (0.49 vs 0.69 U/kg/day, p < 0.001)[10]	↓ Drug and supply costs
Glycaemic control	Time-in-range	↑ +11.4% (95% CI: 4.75–18.08, p = 0.001)[11]	↓ Test strip/CGM usage
Chronic complications	Retinopathy	↓ 50% progression (95% CI: 12–72, p = 0.017)[8]	↓ Specialist/procedure costs
	Diabetic nephropathy	↓ OR: 0.61 (95% CI: 0.38–0.96, p = 0.033)[12]	↓ Renal care and dialysis costs
	Diabetic neuropathy	↓ Prevalence across long-term cohorts	↓ Neurology/pain management costs

CGM, continuous glucose monitoring; CI, confidence interval; DKA, diabetic ketoacidosis; HCRU, healthcare resource utilisation; HR, hazard ratio; OR, odds ratio.

Model Parameterisation and Threshold Analysis

- Two C-peptide thresholds may be utilized as cost-effectiveness parameters for modeling.The intermediate threshold (0.02–0.2 nmol/L) achieves an 11.4% (95% CI: 4.75–18.08) improvement in time-in-range (p = 0.001),[10] with lower monitoring costs, while the optimal threshold (≥ 0.2 nmol/L) represents the primary health economic threshold, with the lowest healthcare-related costs.
- These thresholds may provide critical decision points for health economic modelling and treatment optimisation strategies.

Critical Appraisal: Evidence Heterogeneity and Future Validation

- As presented in **Table 2**, the current evidence base, primarily comprising observational cohorts and early experimental studies, is characterised by heterogeneity in C-peptide assessment methods, patient populations, and outcome definitions. This heterogeneity limits the uniformity of findings across all investigated clinical and economic outcomes.

Table 2. Key drivers of heterogeneity in the C-peptide literature

Category	Details
Nature of literature base	
Foundational evidence	Primarily observational cohorts and early experimental studies
Evidence clarity	Overall trends favour C-peptide preservation; the relationship with all outcomes is not uniformly clear-cut across trials
Key drivers of heterogeneity	
Methodological variations	Diverse C-peptide assessment methods (fasting, post-prandial, and stimulated); varying assay sensitivities
Study population differences	Wide variation in patient age, disease duration, and background standard of care
Outcome definitions	Differing criteria for microvascular and macrovascular event progression

Policy and HTA Implications

- **Table 3** demonstrates that C-peptide preservation as a clinically meaningful and valid endpoint for health economic decision-making, given its established link to β-cell function and glycaemic outcomes. This relevance underpins its use in Markov models that translate β-cell function into health utility and cost savings.
- However, prospective studies with standardised assays are needed to confirm these findings and refine cost-effectiveness parameters.

Table 3. Policy and HTA implications

Category	Details
Validation of surrogate endpoint	C-peptide preservation is associated with lower rates of cost-driving clinical outcomes. These findings represent an initial step toward exploring its potential role as a surrogate endpoint in health economic evaluations; further studies are needed to establish a causal link between C-peptide preservation, microvascular complications, and associated cost reductions
HTA modelling strategy	Enables health economists to build reliable Markov models using C-peptide tiers (≥ 0.2 nmol/L, 0.02–0.2 nmol/L, and < 0.02 nmol/L) and to connect β-cell preservation directly to health utility gains and HCRU savings
Baseline framework	This SLR provides foundational evidence to inform initial health economic models
Need for prospective confirmation	Well-designed prospective studies using standardised C-peptide assays and modern glycaemic technology are required to confirm these findings and refine the parameters of cost-effectiveness models

HCRU, healthcare resource utilisation; HTA, health technology assessment; SLR, systematic literature review.

Limitations

- Heterogeneous measurement methods and patient characteristics limit cross-study comparability.
- Experimental studies with small sample sizes restrict statistical power and generalisability.
- The evidence is largely observational or early-stage experimental studies.
- C-peptide effects cannot be disentangled from endogenous insulin; likely reflects preserved β-cell function.
- Excluding non-English studies may have introduced publication bias.

Conclusions

- C-peptide preservation demonstrates quantifiable associations with cost-driving clinical outcomes, supporting its potential relevance as a surrogate endpoint.
- Established C-peptide thresholds (≥ 0.2 nmol/L for major benefits; ≥ 0.02 nmol/L for intermediate benefits) offer standardised benchmarks for DMT cost-effectiveness modelling.
- These thresholds facilitate rigorous health economic evaluation of β-cell preservation strategies.
- These findings enable evidence-based economic modelling of β-cell preservation interventions, supporting HTA submissions and reimbursement decisions for emerging T1D therapies.

References

1. Gregory GA, *et al. Lancet Diabetes Endocrinol* 2022;10(10):741–760.
2. CDC. National Diabetes Statistics Report. 2024. [Available from: https://www.cdc.gov/diabetes/php/data-research/index.html]
3. Tönnies T, *et al. Diabetes Care* 2023;46(2):313–320.
4. Alan MS, *et al. J Diabetes Complications* 2025;39(3):108867.
5. Mellor JC, et al. *Diabetes Care 2026*;49(8):1348–1356.
6. Higgins JPT, *et al. Cochrane* Handbook for Systematic Reviews of Interventions version 6.5. Updated August 2024. [Available from: https://training.cochrane.org/handbook/]
7. Page MJ, *et al. BMJ* 2021;372:n71.
8. Lachin JM, *et al. Diabetes* 2014;63(2):739–748.
9. Jeyam A, *et al. Diabetes Care* 2021;44(2):390–398.
10. *Ann Intern Med* 1998;128(7):517–523.
11. Lopes V, *et al. Arch Endocrinol Metab* 2024;68:e230503.
12. Harsunen M, *et al. Lancet Diabetes Endocrinol* 2023;11(7):465–473.

Conflicts of Interest
OG, AJOA, and **MB** are employees of Sanofi and may hold stocks and/or stock options in the company. **DP, JPC**, and **JZ** are employees of Evidinno Outcomes Research Inc.

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