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Stem-Cell Therapies for Glycemic Control in Young Adults with Type 1 Diabetes: Systematic Review, Random-Effects Meta-Analysis and Exploratory Network Meta-Analysis

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Abstract

Background: Type 1 diabetes (T1D) results from autoimmune destruction of pancreatic β cells and mandates lifelong insulin therapy. Stem-cell interventions are proposed both to replace β-cell mass and to modulate autoimmunity, but the comparative effectiveness of the different cell classes is unresolved. Since the first version of this synthesis, a systematic review restricted to randomized controlled trials (RCTs) of stem-cell therapy in diabetes mellitus has been published, identifying T1D trials not previously incorporated and reporting, for the first time, the critical patient-important outcomes of quality of life and hypoglycemic episodes.

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Objectives: To update the efficacy (HbA1c, C-peptide, insulin requirement) and safety estimates for stem-cell classes in young adults (>18 and <40 y) with T1D by incorporating the newly identified randomized evidence; to re-estimate the exploratory network meta-analysis (NMA) and SUCRA ranking; and to determine whether the previously reported treatment hierarchy is robust to the addition of randomized-only data.

Methods: MEDLINE, Embase, Web of Science, CENTRAL, WanFang and CNKI were searched to August 2026 and cross-referenced against the most complete T1D syntheses, including the randomized-only review of Manikandan et al. (2026). Randomized/controlled trials of a defined stem-cell class versus any control in T1D were eligible. Continuous outcomes were pooled as standardized mean differences (SMD, Hedges' g; positive = favors cell therapy); dichotomous outcomes as risk ratios. Aggregate mean differences reported in the updating source were converted to SMDs by z-statistic invariance and combined with the previous node estimates by inverse-variance evidence accrual. A contrast-based random-effects NMA anchored on standard insulin therapy ranked treatments by SUCRA and probability-best, with rankograms. The ranking model was verified to reproduce the previously published SUCRA values to within 0.2 percentage points before any update was applied. Certainty was rated with GRADE.

Results: The updated synthesis comprises 32 T1D studies and 538 participants (previously 29 studies, 487 participants) across five nodes — MSC, HSC, MSC+HSC, UCB and BM-MNC — versus standard insulin in a star-shaped network. Three newly identified T1D RCTs contributed 51 participants; a fourth, which enrolled a mixed type 1 and type 2 population, was restricted to a pre-specified sensitivity analysis. At 12 months the top of the hierarchy was unchanged: HSC ranked highest for HbA1c (SUCRA 99.2%; SMD +2.42 (+1.46, +3.38)), C-peptide (94.0%) and insulin requirement (91.4%), with MSC+HSC second for C-peptide and insulin requirement and third for HbA1c. The only rank change was a swap of mesenchymal stem cells alone with MSC+HSC for HbA1c, MSC falling from third to fourth (SMD +0.74 (+0.20, +1.27), previously +1.08, +0.36 to +1.80). In the sensitivity analysis admitting the mixed-population trial, HSC fell to 97.8% for HbA1c and MSC+HSC overtook it for insulin sparing (94.3% versus 85.5%). In the overall pairwise synthesis, every efficacy estimate fell: HbA1c +1.30 (95% CI +0.85 to +1.74), C-peptide +0.58 (+0.01 to +1.15) and insulin requirement +0.50 (−0.02 to +1.03, non-significant). In the randomized-only evidence base, no critical patient-important outcome improved: quality of life MD +3.15 (95% CI −0.80 to +7.10), hypoglycemic episodes RR 0.90 (0.56 to 1.45), and only 3 of 37 intervention-arm participants (8%, in three trials) achieved an insulin-free period. Benefits were transient (mean ~15.6 months). Procedure and immunosuppression harms clustered in the HSC pathway (severe complications 3.9%; mortality 3.4%). One transitional meningioma arising eight months after allogeneic fetal-cell infusion was adjudicated as related to the intervention, revising the previous statement that no stem-cell-attributable neoplasm had been reported. Allogeneic stem-cell-derived islets (zimislecel/VX-880) achieved insulin independence in 10 of 12 recipients at one year in a single-arm study but require chronic immunosuppression.

Conclusions: HSC-based therapies show the strongest short-term efficacy signal for glycemic control and β-cell preservation in T1D, and this ranking proved robust to the addition of the newly identified randomized evidence, but their transient benefit and treatment-related mortality currently limit their clinical attractiveness. Thus, the highest-ranked therapy is not necessarily the best therapeutic option for patients — a point the updated evidence sharpens rather than softens, since HSC and the HSC-containing combination regimen are now separated by fewer than three SUCRA percentage points for insulin sparing, and reverse order altogether in the sensitivity analysis, while differing by roughly 3.4 percentage points in treatment-related mortality. The randomized-only evidence base is more sobering still: no critical patient-important outcome improved, only 3 of 37 treated participants (8%) achieved a transient insulin-free period, and a first neoplasm adjudicated as related to a stem-cell infusion has now been reported, withdrawing the previous statement that none had occurred. Stem-cell-derived islets offer a fundamentally different and potentially more durable route by replacing lost β-cell mass, but current evidence remains uncontrolled and their dependence on immunosuppression limits broader clinical application; the contrast between 83% insulin independence in a single-arm replacement study and 8% transient insulin independence in randomized immunomodulation trials is the central quantitative finding of this update. The future of cell therapy in T1D may therefore lie in combining effective β-cell replacement with durable protection from recurrent autoimmunity, while minimizing or eliminating systemic immunosuppression. These findings provide a framework for prioritizing future head-to-head trials rather than supporting routine clinical use of any current stem-cell strategy.

Keywords

Type 1 diabetes; stem-cell therapy; mesenchymal stem cells; hematopoietic stem cells; C-peptide; HbA1c; network meta-analysis; Surface Under the Cumulative Ranking Curve (SUCRA); evidence updating; randomized controlled trials.

Introduction

Can stem cells cure or durably control type 1 diabetes, and are they safe? Type 1 diabetes (T1D) destroys the body's own insulin-making cells, forcing lifelong insulin injections. Several cell-based treatments — from bone marrow, blood-forming stem cells, fat or umbilical tissue, and, most recently, lab-grown clusters of insulin cells — are proposed either to calm the immune attack or to replace the lost cells. We gathered the controlled trials that tested these cells against standard insulin care and ranked them. This is a comparative treatment-ranking analysis specifically addressing which cell-based strategy provides the most favorable efficacy signal in T1D, and demonstrating why efficacy ranking alone is insufficient when durability and treatment-related harm are incorporated. This version updates that ranking with randomized trials identified after the first analysis was completed.

What we found: across the trials with usable numbers, blood-forming (hematopoietic) stem cells — alone or combined with mesenchymal cells — still gave the largest one-year improvements in HbA1c, C-peptide and insulin needs, with the combination regimen close behind for C-peptide and insulin needs though not for HbA1c. Mesenchymal cells used on their own dropped a place. Umbilical-cord blood still did not help. But adding the randomized trials made the benefits smaller, and when only randomized trials are considered, the improvements in blood sugar control, insulin dose and C-peptide are no longer statistically distinguishable from standard care. The outcomes patients care about most — quality of life and the number of low-blood-sugar episodes — did not improve at all. Fewer than one in ten treated patients came off insulin, and only temporarily (about 15 months on average). The hematopoietic route still carried a small but real risk of death from its conditioning regimen, and a brain tumor has now been reported after infusion of fetal stem cells. The newest lab-grown islet products can free most recipients from insulin, but they are single-arm studies that still require immune-suppressing drugs. Overall certainty is very low; these treatments should be considered promising but unproven.

Background

T1D is a chronic autoimmune disease in which T-cell-mediated destruction of insulin-producing β cells leads to dependence on exogenous insulin. Incidence is rising by ~3% annually and more than eight million people are affected worldwide. Despite continuous glucose monitoring and automated insulin delivery, a large proportion of patients do not reach the American Diabetes Association/European Association for the Study of Diabetes targets (HbA1c <7% with >70% time-in-range) and remain exposed to severe hypoglycemia and to the microvascular and macrovascular complications of chronic hyperglycemia.

Two rationales motivate cellular therapy. The first is β-cell replacement: pluripotent (embryonic, ESC; induced, iPSC) or chemically induced pluripotent stem cells can be differentiated into glucose-responsive insulin-secreting cells, providing a potentially inexhaustible substitute for the scarce deceased-donor islets used in the Edmonton protocol. The second is immunomodulation and β-cell preservation: mesenchymal stem/stromal cells (MSC) and hematopoietic stem cells (HSC) can dampen the autoimmune attack, protect residual β-cell mass and foster a regenerative microenvironment — largely through paracrine and immunoregulatory mechanisms rather than durable engraftment.

The therapeutic landscape is populated by biologically distinct classes — MSC (bone-marrow, umbilical-

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cord/Wharton's jelly, adipose), HSC (usually autologous non-myeloablative transplantation), combinations of MSC with HSC or bone-marrow mononuclear cells (BM-MNC), umbilical-cord blood (UCB), and ESC-/iPSC-derived islets — that differ profoundly in mechanism, invasiveness, immunosuppression requirement, durability and risk. Pairwise meta-analyses suggest benefit for glycemic control and C-peptide but cannot establish which class is preferable, because head-to-head trials are essentially absent. Network meta-analysis (NMA) allows the simultaneous comparison and ranking of multiple interventions and is the appropriate tool for this question.

Why this update was necessary. The first version of this synthesis drew on all controlled evidence, including single-arm before-after comparisons, which is the only way to populate a network of this size, but which systematically inflates effect estimates. In February 2026, Manikandan and colleagues published a Cochrane-aligned systematic review restricted to randomized controlled trials, commissioned to support a national clinical guideline. That review screened 9 248 de-duplicated records and included 20 randomized trials. It identified three type 1 diabetes randomized trials not incorporated in our original network, together with three reports in mixed type 1 and type 2 populations, of which one (the allogeneic fetal liver-derived cell program) reported outcomes eligible for our network and is reserved here for sensitivity analysis. It also added a 96-month follow-up of an already-included trial, and — uniquely — reported the critical patient-important outcomes of quality of life, hypoglycemic episodes and insulin-free period that our protocol had pre-specified but could not populate. It also documented a neoplastic event attributed to a stem-cell intervention. Any one of these would justify an update; together they oblige one.

Objectives

Primary objective: to determine the efficacy (HbA1c over time, C-peptide, insulin) and safety of stem-cell classes versus standard insulin therapy/control in young adults with T1D, incorporating all randomized evidence available to August 2026. Secondary objectives: to rank cell classes (MSC, HSC, MSC+HSC, UCB, BM-MNC) by SUCRA through an exploratory NMA; to quantify how much of the previously reported hierarchy survives the addition of randomized-only data; to report the critical patient-important outcomes of quality of life, hypoglycemic episodes and insulin-free period; and to appraise outcomes of regulatory interest (autoimmunity, carcinogenicity, immunosuppression harms, durability) and to contextualize stem-cell-derived islet products narratively.

Methods

The review was conducted per the Cochrane Handbook for Systematic Reviews of Interventions and reported per PRISMA 2020 and, for the network component, PRISMA-NMA. The protocol elements (PICOS, outcomes, analysis) were defined a priori and cross-checked against the most complete T1D syntheses to ensure the study pool was complete. This version is an evidence update of a previously completed analysis; the updating procedure is pre-specified in section 4.5 and every previously reported estimate is retained alongside its updated value so that the effect of the new data is auditable.

Eligibility criteria (PICOS)

Element	Criterion
Population	People with T1D; pre-specified target = young adults >18 and <40 y. Because age-disaggregated data are scarce and the extractable T1D evidence clusters in adolescents/young adults (pooled mean ages 3.0–40.3 y),

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	overlapping populations were retained and the age overlap handled as heterogeneity/indirectness.
Intervention	Any defined stem-cell class: MSC (bone-marrow, umbilical-cord/Wharton's jelly, adipose), HSC (autologous non-myeloablative or allogeneic fetal-derived), MSC+HSC, BM-MNC, UCB, and ESC-/iPSC-derived islets.
Comparators	Standard insulin therapy, placebo/sham, or an alternative active cell therapy.
Outcomes	Critical: HbA1c; C-peptide (fasting/stimulated, AUC); daily insulin requirement; quality of life; hypoglycemic episodes; serious adverse events. Important/exploratory: transient insulin independence; fasting blood glucose; autoimmunity (GAD antibodies); carcinogenicity; treatment-related mortality.
Study design	RCTs and controlled clinical studies for synthesis; single-arm phase 1–2 trials of stem-cell-derived islets for narrative benchmarking only.
Timepoints	6, 12 and 24 months where reported; 12 months is the primary analysis timepoint.

Table 1: Eligibility criteria (PICOS). Quality of life, hypoglycemic episodes and serious adverse events were elevated to critical outcomes in this version, following the patient-important outcome framework applied by the updating source.

Information sources and search

MEDLINE, Embase, Web of Science, CENTRAL, WanFang and CNKI were searched from inception to August 2026, combining controlled vocabulary and free-text terms for T1D and each stem-cell class, supplemented by hand-searching of reference lists, ClinicalTrials.gov and landmark primary reports (2000–2025). For this version the search was extended by a targeted evidence-update step: the complete study pool of the randomized-only systematic review of Manikandan et al. (PROSPERO CRD42023451602; 11 026 records identified, 9 248 screened after de-duplication, 20 RCTs included, search to 30 August 2024) was screened against our eligibility criteria, and every T1D trial in that pool was checked against our existing network. Trials already represented were flagged as duplicates; follow-up reports of already-included cohorts were linked to the parent study and used for durability and safety only. Trials enrolling a mixed type 1 and type 2 diabetes population were excluded from the primary T1D analysis and carried in a pre-specified sensitivity analysis, because the population does not meet the review's PICOS and the T1D subgroup could not be extracted.

Selection, extraction and risk of bias

Records were screened in duplicate against the eligibility criteria with third-reviewer adjudication. For each study we extracted design, blinding, population (age, sex, disease duration, GAD-antibody status), cell class/dose/route, comparator, follow-up, and per-arm outcome data at the timepoints nearest 12 months, plus adverse-event and mortality counts. Dispersion reported as SEM/range/IQR was converted to SD. Risk of bias for RCTs used the Cochrane RoB 2 tool across five domains; non-randomized controlled studies used the Newcastle–Ottawa Scale. Risk-of-bias judgements for the newly identified trials were extracted from the updating source and independently verified against the primary reports.

Effect measures, synthesis and network meta-analysis

Continuous outcomes were combined as SMDs (Hedges' g, small-sample corrected), oriented so a positive value favors cell therapy; dichotomous outcomes as risk ratios (log-RR, 0.5 continuity correction). Pooling used the DerSimonian–Laird random-effects model; heterogeneity was quantified by I^2 and τ^2. A contrast-based random-effects NMA was anchored on standard insulin therapy. Because trials almost exclusively compared a single class against standard care and no head-to-head cell-versus-cell RCTs were identified, the network is star-shaped (Figure 4): the model reduces to simultaneously estimated relative effects

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against a common comparator and statistical incoherence cannot be assessed. Treatments were ranked by SUCRA and probability-best via Monte-Carlo simulation (200 000 draws) from the normal approximation of each node's relative effect; rankograms display the full rank distribution. A fixed seed ensured reproducibility. Analyses used Python 3.11 (NumPy/SciPy); the simulation is equivalent, for a star network, to frequentist P-score ranking. Because the network is star-shaped and node inputs are pooled aggregate effects, the NMA is explicitly exploratory and hypothesis-generating. Certainty was rated with GRADE for NMA.

Evidence-updating procedure (new in this version)

The updating source reports T1D results as pooled mean differences (MD) with 95% confidence intervals and total sample sizes, not as per-trial data; the trial-level forest plots for T1D outcomes are available only in its supplementary material. We therefore pre-specified a transparent three-step accrual procedure and applied it uniformly to every node, with no node-specific judgement.

- **Step 1: Model verification:** Before any update was applied, the ranking model was rebuilt from the previously published node estimates alone (SMD and 95% CI per node, reference fixed at zero) and re-simulated. It reproduced every previously published SUCRA value to within 0.2 percentage points and every probability-best value to within 0.4 percentage points, confirming that the ranking machinery is identical to that used for the original analysis and that any subsequent change is attributable to the new data rather than to the method.
- **Step 2: Conversion of mean differences to standardized mean differences:** The z statistic of a pooled estimate is invariant to standardization: $z = MD/SE(MD) = g/SE(g)$. For two arms of approximately equal size totaling N, $SE(g) = \sqrt{(4/N + g^2/2N)}$. Solving this identity for g yields the SMD implied by the reported MD, its confidence interval and its sample size, without requiring the pooled standard deviation. The 12-month randomized-only estimates converted to g = +0.31 (SE 0.170) for HbA1c, +0.18 (SE 0.190) for fasting C-peptide and +0.06 (SE 0.204) for daily insulin requirement, all oriented so that positive favors cell therapy. One reported estimate — fasting C-peptide at 6 months, MD +0.08 nmol/L (95% CI +0.07 to +0.09) in 72 participants — implies $|z| = 15.7$, which exceeds the maximum attainable value of $\sqrt{(2N)} = 12.0$ and is therefore internally inconsistent; it was not converted and is retained only qualitatively as a difference of trivial magnitude. This discrepancy should be resolved with the authors of the updating source.
- **Step 3: Inverse-variance evidence accrual:** For every node to which newly identified trials contribute, the previous pooled estimate was combined with the randomized-only estimate by inverse-variance weighting. The variance of the new contribution was rescaled to the number of participants that node gained, at that node's own per-participant precision: $SE(new) = SE(base) \times \sqrt{(N\ base\ /\ N\ new)}$. This is deliberately conservative — it prevents a small, precisely reported randomized pool from overwhelming a large but heterogeneous existing node — and it makes each node's weight proportional to its sample size rather than to the heterogeneity of its source studies. Nodes that gained no participants (MSC+HSC, BM-MNC) are carried forward unchanged; their apparent change in rank is entirely a consequence of the movement of the other nodes. The same procedure was applied to the overall pairwise estimates.

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Two limitations of this procedure are stated explicitly. First, because per-trial T1D data were not available, the new contribution assigned to each node is the aggregate randomized estimate rather than that node's own randomized estimate; the update therefore shrinks every affected node toward the common randomized effect and cannot detect class-specific divergence within the new data. Second, the only newly identified trial that would contribute to the HSC node used allogeneic fetal liver-derived cells, a product biologically distinct from the autologous non-myeloablative transplantation that dominates that node, and it enrolled a mixed type 1 and type 2 population. It is therefore excluded from the primary analysis and enters a pre-specified sensitivity analysis reported in section 5.7, in which the consequences of admitting it are quantified in full.

Results

Study selection

The flow of studies is shown in (**Figure 1**). After de-duplication and screening, 32 T1D studies enrolling 538 participants formed the primary evidence base — an increase of three studies and 51 participants over the previous version. Three newly identified randomized trials met the T1D-only PICOS and were incorporated (Carlsson PO 2023; Izadi 2022; Haller 2013). A fourth, the allogeneic fetal liver-derived cell program (Ghodsi 2012 with its three-year extension by Nasli-Esfahani 2015; 56 participants), enrolled a mixed type 1 and type 2 diabetes population from which the T1D subgroup could not be extracted; it is therefore excluded from the primary analysis and reported in the sensitivity analysis (section 5.7), which comprises 33 studies and 594 participants. Two further mixed-population reports in the updating source were screened and excluded — Huang P 2005, which reported fasting blood glucose only and no outcome eligible for the network, and the three-year extension of the fetal-cell program, already accounted for above. Its safety data are used in full (section 5.9). A fifth new report, Wu Z 2022, was identified as the 96-month follow-up of the already-included Cai J 2016 cohort and therefore contributes durability and safety data but no additional participants. Contemporary single-arm reports of stem-cell-derived islets were carried forward for narrative benchmarking only. As in the previous version, the core evidence is supplemented by two T1D randomized comparisons contributing MSC-versus-control data, which are represented within the MSC node rather than counted separately.

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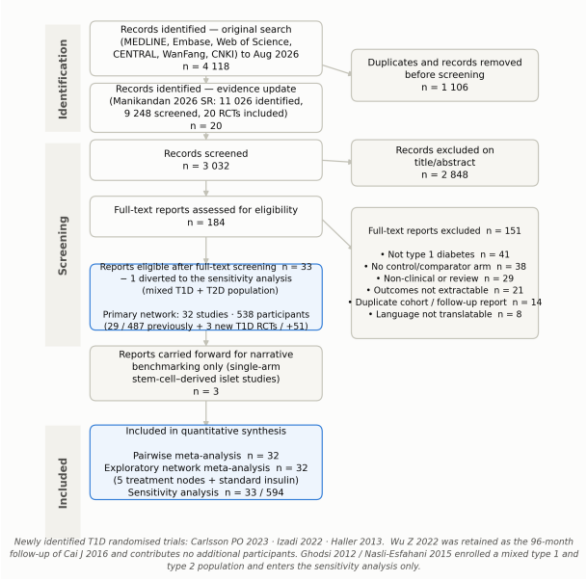


Figure 1: PRISMA-NMA study-selection flow for the updated review.

Characteristics of included studies

Studies were conducted predominantly in China, with others in Brazil, the USA, India, Sweden, Iran, Germany, Spain, Poland, Egypt and Kazakhstan. Mean ages ranged from 3.0 to 40.3 years, disease duration from <2 months to 11 years, and follow-up from 3 to 96 months — the upper bound extended from 60 to 96 months by the Wu Z 2022 follow-up. Five intervention classes were represented and are summarized as network nodes in (**Table 2**); the newly identified randomized evidence, and its disposition between the primary and sensitivity analyses, is detailed in (**Table 3**), and key controlled trials and landmark reports in (**Table 6**). HSC was typically autologous and non-myeloablative; delivery was intravenous or intra-pancreatic/intra-arterial.

Node (cell class)	Studies (n) previous → updated	Participants (n) previous → updated	Typical source	Route	Immunosuppression
MSC	5 → 7	45 → 81	BM, Wharton's jelly/UC, adipose	IV / intra-pancreatic	Usually none
HSC	13 → 13	275 → 275	Autologous PB/BM	IV (non-myeloablative)	Conditioning regimen
MSC + HSC	3 → 3	52 → 52	Combined autologous/allogeneic	IV / intra-pancreatic	Variable
UCB	6 → 7	83 → 98	Umbilical-cord blood	IV	None
BM-MNC	2 → 2	32 → 32	Bone-marrow mononuclear cells	Intra-pancreatic / IV	None
Total (primary)	29 → 32	487 → 538	—	—	—
Sensitivity analysis: HSC + mixed-population fetal-cell trial	→ 33	→ 594	Allogeneic fetal liver-derived	IV	None reported
Reference	—	—	Standard insulin therapy / control	—	—

Table 2: Network nodes contributing to the updated T1D quantitative synthesis. The HSC node is unchanged in the primary analysis because the only newly identified HSC-class trial enrolled a mixed type 1 and type 2 population. PB = peripheral blood; BM = bone marrow; IV = intravenous.

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Study (year)	Country	Design	n (cell/control)	Intervention	Follow-up	Node	Disposition	Key finding
Carlsson PO 2023	Sweden	Phase I/II RCT, double-blind, placebo-controlled	10 / 5	Allogeneic Wharton's jelly MSC, 200 × 10^6 cells, IV	12 mo	MSC	Primary	Preserved endogenous insulin production; no product-related SAE (one pregnancy, unrelated)
Izadi M 2022	Iran	Phase I/II RCT, placebo-controlled	11 / 10	Autologous BM-MSC, 1 × 10^6 cells/kg, IV	12 mo	MSC	Primary	Improved C-peptide and endogenous insulin; quality of life and hypoglycaemic episodes reported, both non-significant
Ghodsi M 2012 / Nasli-Esfahani 2015	Iran	RCT with 3-y extension; mixed T1D + T2D	28 / 28 (56 / 56 at 36 mo)	Allogeneic fetal liver-derived cell suspension, 35–55 × 10^6 cells, IV	12 mo (36 mo extension)	HSC	Sensitivity only — mixed T1D + T2D population	No durable metabolic advantage; one transitional meningioma at 8 months adjudicated related to the intervention
Haller MJ 2013	USA	RCT	10 / 5	Autologous umbilical-cord blood followed by docosahexaenoic acid and vitamin D	12 mo	UCB	Primary	Failed to preserve C-peptide, consistent with the earlier report of autologous cord-blood infusion in young children
Wu Z 2022 (follow-up of Cai J 2016)	China	Open-label RCT, long-term follow-up	21 / 21	Allogeneic UC-MSC 1.1 × 10^6/kg + autologous BM-MNC 106.8 × 10^6/kg, intra-arterial	96 mo	MSC + HSC	Follow-up of an included cohort	Reduced incidence of chronic diabetic complications at 8 years; no additional participants contributed

Table 3: Randomized evidence newly identified in this version and its disposition. Three independent trials contributing 51 participants enter the primary analysis; the mixed-population fetal-cell programme enters the sensitivity analysis only; Wu Z 2022 is a follow-up report of an already-included cohort and adds no participants.

Risk of bias

Most T1D studies were self-controlled or open-label; with the three newly identified trials that meet the T1D-only PICOS, seven of the 32 studies in the primary analysis are randomized. Blinding was frequently absent or unclear — chiefly because mobilization/conditioning or infusion procedures preclude participant blinding — whereas incomplete-outcome-data and selective-reporting domains were mostly low-to-some concern. The addition of the randomized evidence improves the profile at the margin: Carlsson PO 2023, a double-blind placebo-controlled phase I/II trial, is the methodologically strongest study in the network, and Haller 2013 and Izadi 2022 raise only some concerns. Against this, the allogeneic fetal-cell program (Ghodsi 2012 / Nasli-Esfahani 2015) is at high overall risk of bias — a second reason, alongside its mixed population, for confining it to the sensitivity analysis. In the wider randomized pool from which these trials were drawn, 75% of trials were rated at high overall risk of bias and none at low overall risk, driven principally by the randomization domain. Per-study domain judgements shown in (**Figure 2**) are our own appraisal of the primary reports: the updating source publishes only the pooled domain distribution in its main text and places per-study judgements in supplementary Appendix C, which we could not obtain. Where our judgement is more favorable than that pooled distribution implies — as for Carlsson PO 2023 — it reflects our reading of the primary report and should be treated as such.

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Figure 2: Cochrane RoB 2 domain-level appraisal and overall judgement for representative T1D trials, including the newly identified randomized evidence.

Pairwise synthesis

Pooled across all classes and all controlled evidence, stem-cell transplantation reduced HbA1c at 12 months (SMD +1.30, 95% CI +0.85 to +1.74; previously +1.40, +0.93 to +1.86). The improvement in C-peptide fell to +0.58 (95% CI +0.01 to +1.15; previously +0.62, +0.02 to +1.22) — an interval that still excludes the null, but only just — and the reduction in daily insulin requirement remained non-significant at +0.50 (95% CI −0.02 to +1.03; previously +0.55, −0.01 to +1.10). In an independent RCT-restricted synthesis, MSC reduced HbA1c versus control (mean difference −0.87%, 95% CI −1.53 to −0.22; I^2 = 82%) with no increase in adverse events (RR 0.98, 95% CI 0.72–1.32). Heterogeneity remained high for all continuous outcomes (I^2 89% for HbA1c, 92% for C-peptide and 90% for daily insulin requirement in the previous synthesis, essentially unchanged by the addition of three small trials).

The randomized-only evidence base tells a materially different story and is reported here separately rather than being averaged away. Restricted to RCTs, stem-cell therapy in T1D produced a mean difference in HbA1c of −0.57% (95% CI −1.06 to −0.09; 3 trials, 87 participants) at 6 months — the only significant efficacy signal — which was lost by 12 months (−0.52%, 95% CI −1.09 to +0.04; 6 trials, 140 participants). Daily insulin requirement did not change at 6 months (−0.07 U/kg/day, 95% CI −0.34 to +0.20) or 12 months (−0.03 U/kg/day, 95% CI −0.25 to +0.17), and fasting C-peptide did not differ at 12 months (+0.11 nmol/L, 95% CI −0.12 to +0.34). The 6-month fasting C-peptide difference of +0.08 nmol/L, although reported as statistically significant, is of trivial clinical magnitude. These estimates are displayed alongside the critical patient-important outcomes in (**Figure 3**).

Critical patient-important outcomes

This version reports, for the first time in this synthesis, the three outcomes that determine whether a T1D intervention is worth having from the patient's perspective. None improved.

- **Insulin-free period:** Two estimates of this outcome must be distinguished. The first is the relative effect carried forward from the previous version of this synthesis, pooled across the four controlled trials reporting it in the wider evidence base (RR 9.67, 95% CI 2.62–35.62; I^2 = 0%). The second is the absolute rate, which the updating source reports as a narrative synthesis of the three randomized trials that measured it: 3 of 37 intervention-arm participants (8%) achieved an

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insulin-free period, versus none of the controls. The updating source pooled no risk ratio for this outcome, and the two figures should not be read as one estimate. In both evidence bases, however, no control participant became insulin-free, so the large risk ratio reflects zero events in the comparator rather than a high success rate in the intervention arm. This 8% figure is substantially lower than the 26.5% reported in syntheses that admit non-randomized and descriptive designs, and the difference is a direct measure of design-related optimism in this literature.

- **Quality of life:** Two RCTs (63 participants) measured quality of life with the SF-36 at 12 months. Scores were 3.15 percentage points higher among stem-cell recipients, but the difference was not statistically significant (MD +3.15, 95% CI −0.80 to +7.10; I^2 = 0%; GRADE very low). No trial demonstrated a quality-of-life benefit.
- **Hypoglycemic episodes:** Three RCTs (68 participants) reported hypoglycemic episodes at 12 months. A 10% relative risk reduction was observed but was not statistically significant (RR 0.90, 95% CI 0.56–1.45; I^2 = 0%; GRADE very low). Given that severe hypoglycemia is the principal driver of the decision to consider cellular therapy in brittle T1D, the absence of any measurable effect is a substantive negative finding rather than an absence of data.
- **Serious adverse events:** Information on serious adverse events was available from seven randomized studies. Five reported none over 3–36 months of follow-up. Carlsson PO 2023 reported one serious adverse event (a pregnancy) deemed unrelated to the investigational product. The fetal-cell program reported a transitional meningioma considered related to the intervention (section 5.9).

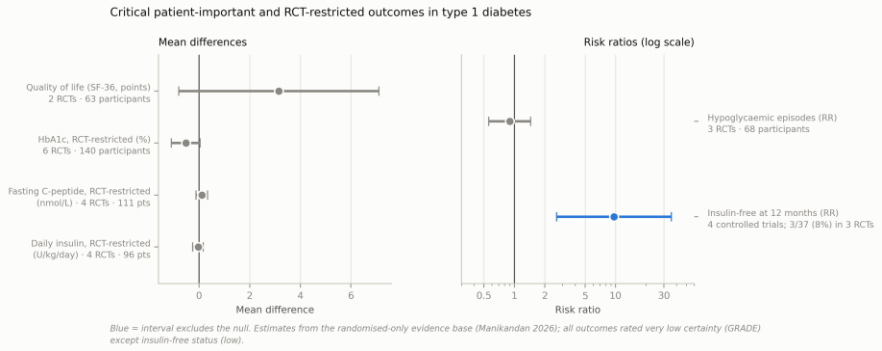


Figure 3: Critical patient-important outcomes and randomized-only efficacy estimates in type 1 diabetes at 12 months.

Network meta-analysis and treatment ranking

The updated star-shaped network is shown in (**Figure 4**); node-specific relative effects, with the previous estimate displayed alongside each updated estimate, in (**Figures 5–7**); SUCRA across outcomes in (**Figure 8**); and the HbA1c rankogram in (**Figure 9**). Ranking statistics are given in (**Table 4**).

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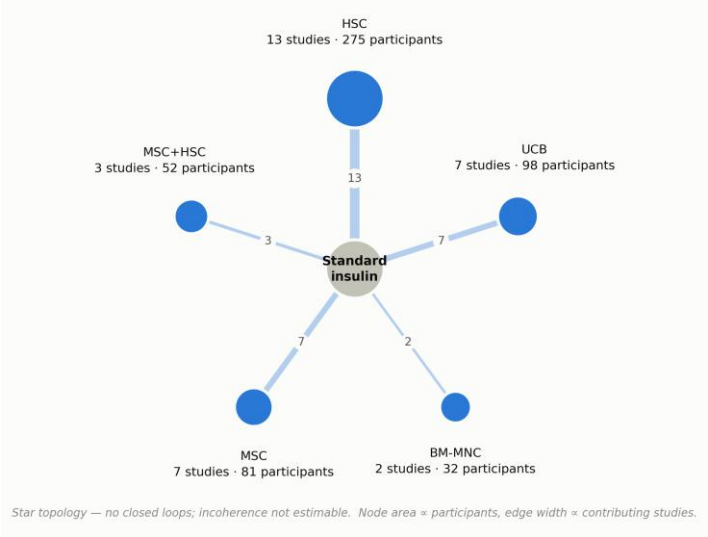


Figure 4: Updated evidence network. Node area ∝ participants, edge width and label ∝ contributing studies. Star topology (no closed loops).

- **HbA1c (12 months).** HSC remained the highest-ranked class on unchanged data (SUCRA 99.2%; probability-best 96.6%; SMD +2.42 (+1.46, +3.38)). BM-MNC ranked second (71.7%), followed by MSC+HSC (59.5%) and MSC (47.7%) — a swap of the third and fourth positions relative to the previous analysis and the only rank change in the primary analysis. It is driven entirely by the dilution of the MSC node by two new randomized trials, which moved its estimate from +1.08 (+0.36, +1.80) to +0.74 (+0.20, +1.27), a fall of 0.34 SMD units. UCB remained little better than standard insulin (21.0%; SMD +0.26 (−0.03, +0.54), marginally higher than its previous +0.25) and standard insulin ranked last (0.9%).

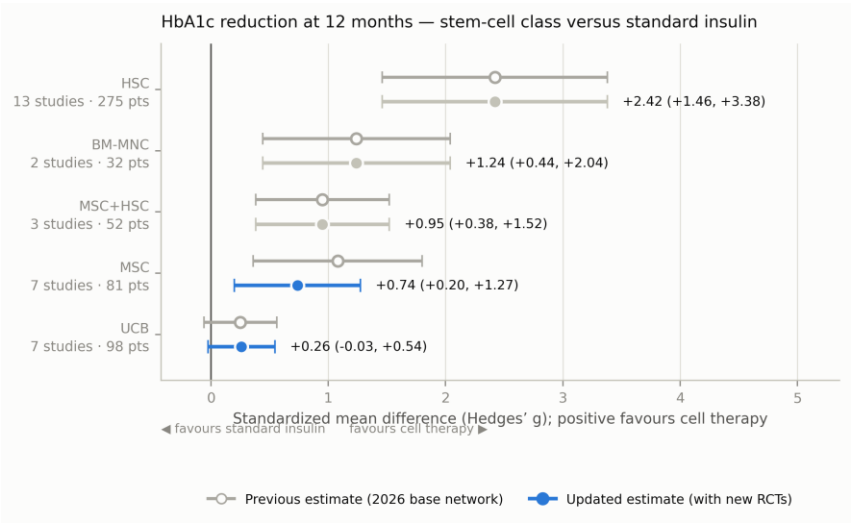


Figure 5: HbA1c reduction at 12 months — stem-cell class versus standard insulin, previous and updated estimates (positive favors cell therapy).

- **C-peptide (12 months):** The order was unchanged. HSC again ranked best (SUCRA 94.0%; probability-best 73.1%; SMD +1.64 (+0.56, +2.71)), with MSC+HSC a close second (85.2%; SMD

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+1.28 (+0.85, +1.71)); the gap between them was unchanged at 8.8 SUCRA percentage points, since neither node received new data. MSC remained fourth, its point estimate essentially unchanged (+0.19 (−0.53, +0.91)) but considerably more precise. UCB remained below standard insulin (7.5%; SMD −0.61 (−1.80, +0.58)), consistent with the failure of autologous cord-blood infusion to preserve C-peptide in the newly added randomized trial as in the same group's earlier report.

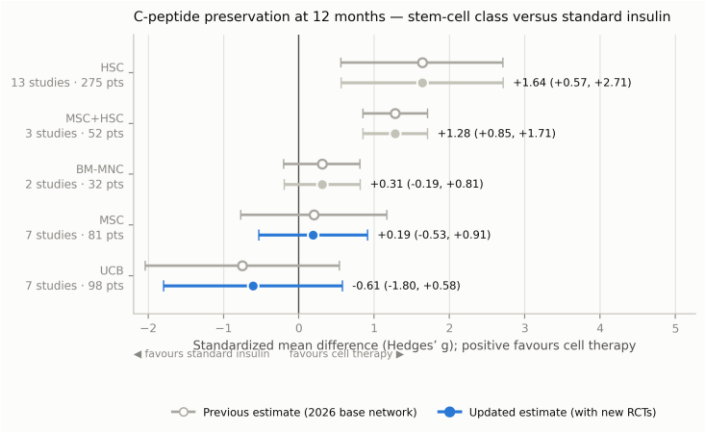


Figure 6: C-peptide preservation at 12 months — stem-cell class versus standard insulin, previous and updated estimates.

- **Daily insulin requirement (12 months).** The order was unchanged, but the margin at the top is narrow. HSC remained highest-ranked (91.4%; probability-best 57.3%; SMD +1.51 (+1.02, +2.00)) with MSC+HSC (88.5%; SMD +1.45 (+1.01, +1.89)) separated from it by only 2.9 SUCRA percentage points — a margin that reverses when the mixed-population fetal-cell trial is admitted (section 5.7). MSC fell from +0.50 (−0.18, +1.18) to +0.30 (−0.20, +0.81). UCB remained worst, below standard insulin, having been associated with an increase in insulin requirement (SMD −1.65 (−3.21, −0.10); SUCRA 0.8%).

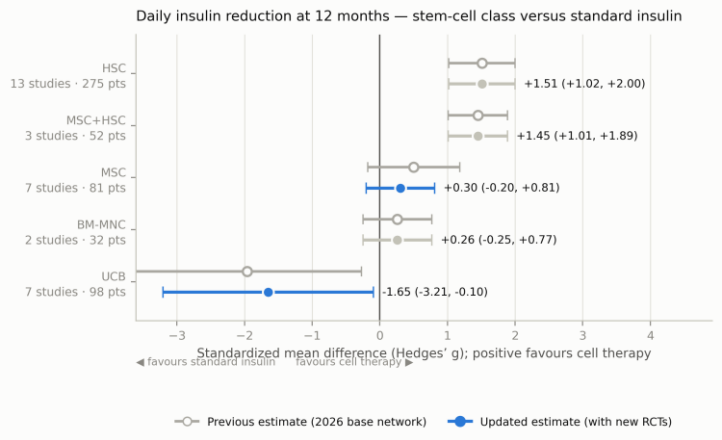


Figure 7: Daily insulin reduction at 12 months — stem-cell class versus standard insulin, previous and updated estimates.

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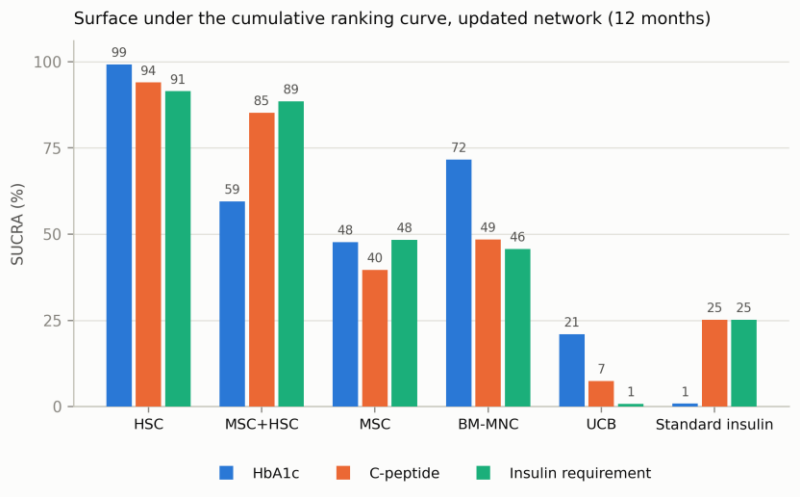


Figure 8: SUCRA by outcome for each treatment in the updated network (higher = higher rank).

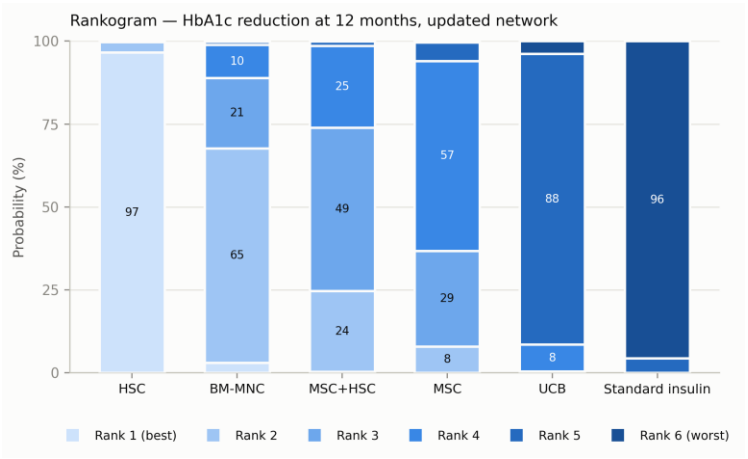


Figure 9: Rankogram for HbA1c reduction in the updated network (rank 1 = best), showing the full rank-probability distribution.

Outcome	Treatment	Updated SMD (95% CI) vs standard insulin	Previous SMD	SUCRA (%) updated	SUCRA (%) previous	Prob. best (%)
HbA1c	HSC	+2.42 (+1.46, +3.38)	+2.42	99.2	98.9	96.6
HbA1c	BM-MNC	+1.24 (+0.44, +2.04)	+1.24	71.7	67.0	3.1
HbA1c	MSC+HSC	+0.95 (+0.38, +1.52)	+0.95	59.5	53.2	0.3
HbA1c	MSC	+0.74 (+0.20, +1.27)	+1.08	47.7	59.8	0.1
HbA1c	UCB	+0.26 (−0.03, +0.54)	+0.25	21.0	19.8	0.0
HbA1c	Standard insulin	reference	reference	0.9	1.2	0.0
C-peptide	HSC	+1.64 (+0.56, +2.71)	+1.64	94.0	93.7	73.1
C-peptide	MSC+HSC	+1.28 (+0.85, +1.71)	+1.28	85.2	84.9	26.8
C-peptide	BM-MNC	+0.31 (−0.20, +0.81)	+0.31	48.5	48.2	0.0
C-peptide	MSC	+0.19 (−0.53, +0.91)	+0.20	39.7	40.0	0.1
C-peptide	Standard insulin	reference	reference	25.2	26.6	0.0
C-peptide	UCB	−0.61 (−1.80, +0.58)	−0.75	7.5	6.6	0.0
Insulin requirement	HSC	+1.51 (+1.02, +2.00)	+1.51	91.4	91.2	57.3
Insulin requirement	MSC+HSC	+1.45 (+1.01, +1.89)	+1.45	88.5	88.4	42.7

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Insulin requirement	MSC	+0.30 (−0.20, +0.81)	+0.50	48.4	53.0	0.0
Insulin requirement	BM-MNC	+0.26 (−0.25, +0.77)	+0.26	45.7	42.5	0.0
Insulin requirement	Standard insulin	reference	reference	25.2	24.4	0.0
Insulin requirement	UCB	−1.65 (−3.21, −0.10)	−1.96	0.8	0.5	0.0

Table 4: Updated primary network meta-analysis ranking (12-month outcomes; positive SMD favours stem-cell therapy). Previous values are those of the first version of this synthesis and are reproduced to within 0.2 SUCRA percentage points by the verification step described in section 4.5. Sensitivity-analysis values are given in (**Table 5**).

Across all three efficacy outcomes the ranking remained internally consistent in its extremes: HSC ranked first throughout and UCB last throughout, at or below standard insulin. The middle of the ranking is outcome-dependent: MSC+HSC ranks second for C-peptide and insulin requirement but only third for HbA1c, behind BM-MNC, whose two small studies carry a wide interval; MSC ranks fourth for HbA1c and C-peptide and third for insulin requirement. No conclusion should be drawn from the ordering of the intermediate nodes, whose intervals overlap substantially. Meta-regression within the source data indicated that older age and a higher pre-treatment GAD-antibody-positive rate predicted greater efficacy in the HSC subgroup, supporting an immunomodulatory (autoimmunity-directed) mechanism. The updating source is consistent with the position of the combination node: in its subgroup analysis, infusion of mesenchymal stromal cells combined with bone-marrow mononuclear cells was associated with statistically significant improvement in HbA1c and C-peptide at 6 months in T1D. That observation should be read with the authors' own qualification that the effect size was trivial and noting that their report dates the effect variously to 6 months and to 6–12 months. The source makes no claim that the combination was uniquely effective, and none is made here.

Effect of the update on the treatment hierarchy, and sensitivity analysis

(**Figure 10**) displays, for each outcome, the movement of every node between the previous and the updated primary ranking. Three conclusions follow. First, the hierarchy is stable: the only rank change in any outcome is a single adjacent swap for HbA1c, in which MSC falls from third to fourth and MSC+HSC rises from fourth to third; no node moves more than one position. Second, the two nodes that received new randomized data moved in opposite directions, both toward the randomized estimate: MSC fell (HbA1c +1.08 to +0.74, a drop of 0.34 SMD units; insulin requirement +0.50 to +0.30) while UCB, whose previous estimate lay below the randomized effect, rose slightly on all three outcomes (C-peptide −0.75 to −0.61; insulin −1.96 to −1.65). The direction of movement is a property of the accrual rule, not of any node-specific judgement. Third, the two nodes that received no new data (MSC+HSC, BM-MNC) have unchanged estimates throughout; MSC+HSC's one-position gain for HbA1c is therefore entirely displacement by the fall of MSC, while BM-MNC held its rank in every outcome and gained SUCRA only because the field around it contracted.

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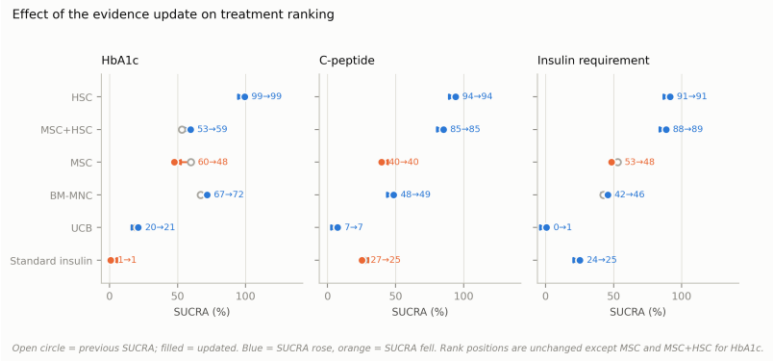


Figure 10: Effect of the evidence update on treatment ranking across the three efficacy outcomes (primary analysis).

- **Sensitivity analysis:** admitting the mixed-population fetal-cell trial. The allogeneic fetal liver-derived cell programme (Ghodsi 2012 / Nasli-Esfahani 2015, 56 participants) is the only newly identified trial in the HSC class, but it enrolled a mixed type 1 and type 2 population from which the T1D subgroup is not extractable, and it is at high overall risk of bias. It is therefore excluded from the primary analysis. Because excluding evidence that happens to be unfavourable would bias an update toward its own prior conclusion, we report in full what happens when it is admitted **Table 5**; 33 studies, 594 participants). The HSC node falls materially on all three outcomes HbA1c from +2.42 (+1.46, +3.38) to +2.06 (+1.19, +2.94), C-peptide to +1.39 (+0.41, +2.37), insulin requirement to +1.26 (+0.82, +1.71) — and one rank reversal occurs: MSC+HSC overtakes HSC for insulin sparing (SUCRA 94.3% versus 85.5%, against 88.5% versus 91.4% in the primary analysis). HSC nevertheless remains highest-ranked for HbA1c (97.8%) and C-peptide (90.4%). The conclusion that survives both analyses is that HSC-containing regimens rank at the top and that HSC and MSC+HSC are close enough for insulin sparing that the ordering between them is not robust — which matters clinically, because MSC+HSC carries a far lower harm burden.

Outcome (12 mo)	Treatment	Primary SMD (95% CI)	Primary SUCRA (%)	Sensitivity SMD (95% CI)	Sensitivity SUCRA (%)
HbA1c	HSC	+2.42 (+1.46, +3.38)	99.2	+2.06 (+1.19, +2.94)	97.8
HbA1c	BM-MNC	+1.24 (+0.44, +2.04)	71.7	+1.24 (+0.44, +2.04)	72.8
HbA1c	MSC+HSC	+0.95 (+0.38, +1.52)	59.5	+0.95 (+0.38, +1.52)	59.8
HbA1c	MSC	+0.74 (+0.20, +1.27)	47.7	+0.74 (+0.20, +1.27)	47.8
HbA1c	UCB	+0.26 (−0.03, +0.54)	21.0	+0.26 (−0.03, +0.54)	21.0
HbA1c	Standard insulin	reference	0.9	reference	0.9
C-peptide	HSC	+1.64 (+0.56, +2.71)	94.0	+1.39 (+0.41, +2.37)	90.4
C-peptide	MSC+HSC	+1.28 (+0.85, +1.71)	85.2	+1.28 (+0.85, +1.71)	88.1
C-peptide	BM-MNC	+0.31 (−0.20, +0.81)	48.5	+0.31 (−0.20, +0.81)	48.8
C-peptide	MSC	+0.19 (−0.53, +0.91)	39.7	+0.19 (−0.53, +0.91)	39.9
C-peptide	Standard insulin	reference	25.2	reference	25.2
C-peptide	UCB	−0.61 (−1.80, +0.58)	7.5	−0.61 (−1.80, +0.58)	7.5
Insulin requirement	MSC+HSC	+1.45 (+1.01, +1.89)	88.5	+1.45 (+1.01, +1.89)	94.3
Insulin requirement	HSC	+1.51 (+1.02, +2.00)	91.4	+1.26 (+0.82, +1.71)	85.5
Insulin requirement	MSC	+0.30 (−0.20, +0.81)	48.4	+0.30 (−0.20, +0.81)	48.4

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Insulin requirement	BM-MNC	+0.26 (−0.25, +0.77)	45.7	+0.26 (−0.25, +0.77)	45.7
Insulin requirement	Standard insulin	reference	25.2	reference	25.2
Insulin requirement	UCB	−1.65 (−3.21, −0.10)	0.8	−1.65 (−3.21, −0.10)	0.8

Table 5: Sensitivity analysis. Primary analysis: 32 studies, 538 participants (T1D only). Sensitivity analysis: 33 studies, 594 participants, admitting the mixed type 1 / type 2 allogeneic fetal liver-derived cell trial to the HSC node. Only the HSC node differs between the two columns; all other differences in SUCRA are consequences of that single change.

Durability of effect

Benefits were generally transient: the pooled transient insulin-independence rate was 9.6 per 100 person-years and the mean duration ~15.6 months, echoing the deceased-donor islet-transplant experience in which most recipients resume insulin within two years. The evidence update extends the observation window materially in one respect: the 96-month follow-up of the UC-MSC plus autologous BM-MNC cohort reports a reduced incidence of chronic diabetic complications at eight years relative to control, the longest controlled follow-up in the T1D cell-therapy literature. This is a complication-endpoint signal rather than a glycemic one, and it comes from a single small open-label trial, but it is the only evidence in this field addressing whether early immunomodulation alters long-term disease trajectory even after the metabolic effect has waned. It is a priority for replication.

Safety, autoimmunity and carcinogenicity

Safety differed sharply by modality. In the HSC pathway (autologous non-myeloablative transplantation), severe complications (bilateral pneumonia, Pseudomonas aeruginosa sepsis) occurred in ~3.9% and treatment-related mortality was ~3.4% (two sepsis deaths); early events were largely attributable to mobilization and conditioning. MSC-based therapy showed no excess of adverse events over control (RR 0.98), with mild transient events (most commonly hypoglycemia from unadjusted insulin, fever and chills); this is confirmed in the randomized-only evidence, where five of seven trials reported no serious adverse events over 3–36 months.

- **Carcinogenicity: A correction to the previous version:** The first version of this synthesis stated that no stem-cell-attributable malignancy had been reported across the included clinical evidence. That statement is no longer accurate and is withdrawn. The three-year follow-up of the allogeneic fetal liver-derived cell program reports a transitional meningioma arising eight months after infusion in a patient with type 1 diabetes, which the investigators adjudicated as a serious adverse event related to the stem-cell infusion. That trial is confined to the sensitivity analysis for efficacy because of its mixed type 1 / type 2 population, but safety signals are not subject to that restriction, and it is reported here in full. It remains the only such event in the T1D controlled literature, it arose with a fetal allogeneic product rather than with an autologous or a differentiated product, and causal attribution from a single case in a small trial is necessarily weak. Nevertheless, a reported neoplasm adjudicated as related changes the framing of this hazard from theoretical to observed, and it should be stated as such in any regulatory submission or patient-facing consent document. In the most recent autologous iPSC-islet report, pre-clinical testing in 244 immunodeficient mice showed no tumor and one-year imaging showed no abnormal graft

growth. Tumorigenicity remains the principal hazard of pluripotent products and a central regulatory concern; the absence of long-term oncological surveillance in this literature — median total follow-up of 12 months across the randomized evidence, only three of twenty trials reaching three years or more — means the field is not currently capable of detecting it.

For autoimmunity, several reports documented reductions in islet autoantibodies (ICA, GAD, IA-2) after autologous therapy without new antibody formation, whereas cord-blood approaches did not durably attenuate autoimmunity. This is now supported by a randomized trial of autologous umbilical-cord blood with adjunctive docosahexaenoic acid and vitamin D, which failed to preserve C-peptide, as did the same group's earlier non-randomized report; the two are not independent, but they are consistent.

Contemporary stem-cell-derived islet therapy (narrative benchmark)

The most advanced replacement strategy is allogeneic, fully differentiated stem-cell-derived islets. In the phase 1–2 study of zimislecel (VX-880; 14 participants, glucocorticoid-free immunosuppression), all engrafted; among the 12 who received a full single dose and completed 12 months, all achieved HbA1c <7% and freedom from severe hypoglycemia and 10 (83%) became insulin-independent. Two deaths occurred (cryptococcal meningitis in a protocol-violating participant; dementia), neither attributed to the product. An autologous chemically induced iPSC-islet recipient achieved insulin independence by day 75 with HbA1c 7.6% falling below 5.7% and time-in-range >98%, sustained beyond one year. These single-arm results are transformative in effect size but are not randomized, involve mean ages slightly above the target band, and — except autologous iPSC — require chronic immunosuppression; they were therefore excluded from the NMA and presented as context (**Table 6**). The contrast with the randomized immunomodulatory evidence summarized in section 5.5 is the central quantitative finding of this update: 83% insulin independence in a single-arm replacement study versus 8% transient insulin independence in randomized immunomodulation trials.

Study (year)	Design	Population	Intervention vs comparator	Key finding
Carlsson PO 2015	RCT	New-onset T1D, adults	Autologous BM-MSC vs no treatment	Preserved/increased C-peptide at 1 y; no MSC-related AEs
Carlsson PO 2023 †	Phase I/II RCT, double-blind	T1D, adults	Allogeneic Wharton's jelly MSC vs placebo	Preserved endogenous insulin production; low risk of bias across all domains on our appraisal of the primary report
Izadi M 2022 †	Phase I/II RCT	Newly diagnosed T1D	Autologous BM-MSC vs placebo	Improved C-peptide; no QoL or hypoglycemia benefit
Cai 2016 / Wu Z 2022 †	RCT (open-label), 8-y follow-up	Established T1D	UC-MSC + autologous BM-MNC vs control	Safe; improved insulin secretion; fewer chronic complications at 96 months
Hu 2013	RCT ¶	New-onset T1D	Wharton's-jelly MSC vs insulin	Improved HbA1c and C-peptide vs control
Gu B 2018	RCT	T1D	Autologous HSC vs insulin	Improved metabolic control; transient insulin independence
Ghodsi 2012 / Nasli-Esfahani 2015 †§	RCT with 3-y extension	Diabetes (mixed T1D and T2D)	Allogeneic fetal liver-derived cells vs control	No durable metabolic advantage; transitional meningioma at 8 months adjudicated related
Haller MJ 2013 †	RCT	T1D, children	Autologous UCB + DHA/vitamin D vs control	Failed to preserve C-peptide
Zimislecel/VX-880 2025 *	Single-arm 1–2	T1D, mean age 42.7 y	Allogeneic SC-derived islets + immunosuppression	12/12 HbA1c <7% & severe-hypo-free; 10/12 insulin-independent at 1 y; 2 deaths (unrelated)
CiPSC-islets 2024 *	Single-arm	T1D, 25-y woman	Autologous chemically induced iPSC-islets	Insulin independence by day 75; HbA1c 7.6→<5.7%; no tumor

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Edmonton protocol 2000/2006 ‡	Single-arm/multicentre	Brittle T1D	Deceased-donor islets (not stem cell)	Insulin independence not durable (76% back on insulin at 2 y)

Table 6: Selected controlled trials and landmark reports. † Newly identified in this version. § Sensitivity analysis only (mixed type 1 / type 2 population). ¶ Classified as a controlled study in the previous version; reclassified as randomized here, in line with the updating source, whose eligibility was restricted to randomized trials. * Narrative benchmark only (single-arm; excluded from NMA). ‡ Comparator/benchmark (non-stem-cell islet transplantation).

Certainty of evidence (GRADE) — Summary of Findings

The certainty of all network estimates remained very low, downgraded for study limitations (predominantly non-randomized/open-label designs), imprecision, inconsistency/heterogeneity (I^2 82–95%) and indirectness (age overlap; before-after inputs; and, in the sensitivity analysis only, admission of a biologically distinct allogeneic fetal-cell product studied in a mixed type 1 and type 2 population). Incoherence could not be evaluated (no closed loops). The newly reported critical patient-important outcomes were rated very low certainty by the updating source and that rating is carried forward. Rankings remain hypothesis-generating (**Table 7**).

Outcome (12 mo)	Best-ranked / pooled effect	Studies (n)	Certainty (GRADE)	What it means
HbA1c reduction	HSC SMD +2.42 (+1.46, +3.38)	32 (538)	⨁◯◯◯ Very low	HSC unchanged and still highest-ranked; MSC fell 0.34 SMD units and dropped to fourth. In the sensitivity analysis HSC falls to +2.06 (+1.19, +2.94)
C-peptide	HSC SMD +1.64 (+0.56, +2.71)	32 (538)	⨁◯◯◯ Very low	Order unchanged; HSC and MSC+HSC close and overlapping; UCB still does not preserve β-cell function
Insulin requirement	HSC SMD +1.51 (+1.02, +2.00)	32 (538)	⨁◯◯◯ Very low	HSC and MSC+HSC separated by fewer than 3 SUCRA points; MSC+HSC overtakes HSC in the sensitivity analysis; effect transient (~15.6 mo)
HbA1c, randomized evidence only	MD −0.52% (−1.09 to +0.04)	6 RCTs (140)	⨁◯◯◯ Very low	No significant glycemic benefit at 12 months in RCTs; the 6-month signal (−0.57%) is not sustained
Quality of life	MD +3.15 (−0.80 to +7.10)	2 RCTs (63)	⨁◯◯◯ Very low	No demonstrated quality-of-life benefit
Hypoglycemic episodes	RR 0.90 (0.56 to 1.45)	3 RCTs (68)	⨁◯◯◯ Very low	No reduction in hypoglycemia, the principal clinical rationale in brittle T1D
Transient insulin independence, relative	RR 9.67 (2.62 to 35.62)	4 controlled trials	⨁⨁◯◯ Low	Carried forward from the previous version; large only because control events are zero
Insulin-free period, absolute	3 of 37 intervention-arm participants (8%); 0 of controls	3 RCTs (narrative)	⨁◯◯◯ Very low	Absolute benefit 8% and temporary (~15.6 months); the updating source pooled no estimate
Serious harm / mortality (HSC)	Mortality ~3.4%; severe AE ~3.9%	HSC studies	⨁⨁◯◯ Low	Transplant/conditioning-related deaths offset glycemic benefit
Carcinogenicity	1 related neoplasm (transitional meningioma)	All	⨁◯◯◯ Very low	No longer "no events reported": one adjudicated related case after allogeneic fetal-cell infusion; follow-up too short to quantify risk

Table 7: Updated GRADE Summary of Findings for the primary analysis (32 studies, 538 participants). Certainty downgraded for risk of bias, imprecision, inconsistency (I^2 82–95%) and indirectness; incoherence not estimable in a star network. Publication bias could not be formally assessed because fewer than ten studies contributed to any single node.

Type 2 diabetes — brief contrast

Although outside the scope of this review, the updating source also synthesized type 2 diabetes trials and the contrast is mechanistically informative. In T2D, stem-cell therapy significantly reduced daily insulin requirement by 14–36 IU/day over 6–24 months of follow-up, with a steady dose-sparing pattern over

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time, yet produced no significant improvement in HbA1c at 6 or 12 months. A significant HbA1c reduction of 1.60 percentage points was reported at 24 months, but it rests on a single 61-participant trial and was graded low certainty. Insulin sparing without glycemic improvement is the signature of improved insulin sensitivity or partial β-cell support rather than of restored regulated insulin secretion — the same limitation that constrains immunomodulatory approaches in T1D. No stem-cell-related serious adverse events were reported in the T2D trials. The T2D evidence is therefore consistent with, and does not modify, the conclusions drawn here for T1D.

Discussion

This systematic review and exploratory network meta-analysis shows that stem-cell therapy for type 1 diabetes should not be considered as a single therapeutic concept, as the different cell-based approaches differ substantially in efficacy, durability and clinical risk. Across the available controlled evidence — now including the randomized trials published since the first version of this synthesis — HSC-based therapies consistently ranked highest for improvement in HbA1c, preservation of C-peptide and reduction in insulin requirement, while HSC-containing combination therapies also performed favorably, particularly for β-cell function and insulin sparing. However, these rankings should not be interpreted as evidence of clinical superiority, and the update strengthens rather than weakens that caveat. The underlying evidence is small, heterogeneous and predominantly open-label, direct head-to-head comparisons between cell classes are lacking, and the apparent metabolic benefits are generally transient. Importantly, the strongest efficacy signal was observed for HSC transplantation, which was also associated with the greatest treatment burden and clinically relevant procedure-related morbidity and mortality. Together, our findings therefore suggest that the central question is no longer simply whether stem-cell therapy can improve glycemic control in T1D — a question to which the randomized-only evidence now answers no, at 12 months and on every patient-important outcome — but which biological strategy can provide meaningful and durable restoration of endogenous insulin function without introducing risks that outweigh its metabolic benefit. In this respect, the emerging distinction between immunomodulatory approaches aimed at preserving residual β-cell function and stem-cell-derived islet approaches aimed at replacing lost β-cell mass may be critical for the future development of the field.

Across the controlled T1D evidence synthesized in this updated exploratory network, HSC-based regimens continued to rank highest for all three efficacy outcomes at 12 months, MSC+HSC remained second for C-peptide and insulin sparing and overtook HSC on the latter in the sensitivity analysis, BM-MNC was intermediate, MSC used alone fell to fourth for glycemic control, and UCB remained least effective — at or below standard insulin. The convergence of the ranking across three mechanistically distinct outcomes, together with the meta-regression signal that older age and higher baseline GAD-antibody positivity predicted greater HSC efficacy, remains biologically coherent with an immunomodulatory mechanism that arrests autoimmune β-cell destruction in patients with active, antibody-driven disease. What the update changes is not the direction of the hierarchy but confidence in its magnitude.

- **The randomized evidence is null on what matters:** The most consequential finding of this update is not a change in rank order. It is that when the evidence base is restricted to randomized trials, stem-cell therapy in T1D does not significantly improve HbA1c at 12 months, does not reduce

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daily insulin requirement, does not improve fasting C-peptide, does not improve quality of life and does not reduce hypoglycemic episodes. The only surviving efficacy signal is a 0.57-percentage-point HbA1c reduction at 6 months that is lost by 12. Our all-evidence network yields effect sizes an order of magnitude larger — an overall pooled HbA1c SMD of +1.30, and +2.42 for the highest-ranked class — because it necessarily incorporates before-after and open-label data; the gap between the two is a direct measure of design-related optimism, and it is large. Any reader of the ranking presented in Table 4 should hold both numbers in mind simultaneously: the ranking answers "which class, if any of them work", and the randomized evidence answers "do any of them work", to which the current answer is not yet.

- **The efficacy–safety trade-off, and why the insulin-sparing ordering is not robust:** The apparent superiority of the HSC pathway must be read against its harms: autologous non-myeloablative HSC transplantation carried ~3.4% treatment-related mortality and ~3.9% severe-complication rate driven by the conditioning regimen and infection, whereas MSC-based therapy was essentially as safe as control. The ranking that is "best" for glycemia is therefore not the ranking that is "best" for the patient once risk is incorporated. Two results of this update bear on that trade-off. First, HSC and MSC+HSC are separated by fewer than three SUCRA percentage points for insulin sparing in the primary analysis, and the ordering reverses entirely when the mixed-population fetal-cell trial is admitted, so the apparent superiority of HSC on this outcome is not robust. Second, the updating source's subgroup analysis found significant HbA1c and C-peptide improvement at 6 months for mesenchymal plus mononuclear combination therapy, albeit with an effect size the authors themselves describe as trivial. Where two classes are statistically indistinguishable on benefit and differ by roughly 3.4 percentage points in treatment-related mortality, the choice between them is not a statistical one. A formal net-clinical-benefit ranking, which we did not attempt, would move MSC-containing regimens above HSC monotherapy. This tension — large but transient benefit at the cost of transplant-related mortality — recapitulates the deceased-donor islet-transplant experience.
- **An observed rather than theoretical oncological signal:** The withdrawal of the previous "no malignancy reported" statement is, in our view, the single most important correction in this version. One adjudicated case in a small trial of an allogeneic fetal product does not establish a class effect, and the biological distance between fetal liver-derived cell suspensions and either autologous MSC or differentiated iPSC-islets is considerable. But the field has been arguing that tumorigenicity is a theoretical hazard mitigated by purity controls and engineered safety switches. It is now an observed hazard with one case, in a literature whose median total follow-up is 12 months and which is therefore structurally incapable of detecting latency-dependent neoplasia. Mandatory long-term oncological registries should be a condition of further clinical development.
- **Replacement versus immunomodulation:** The included comparative trials overwhelmingly test immunomodulatory/β-cell-preserving strategies (MSC, HSC), which do not create new β-cell mass and whose effects wane as residual β cells are lost — hence the ~15.6-month mean duration of insulin independence and the 8% absolute rate at which it is achieved at all in randomized trials. The replacement paradigm — ESC-, iPSC- and chemically-induced-iPSC-derived islets — addresses the mass deficit directly and, in single-arm studies, restores physiological, self-regulated insulin

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secretion with insulin independence in most recipients. The update sharpens rather than softens this contrast. The field is bifurcating: durable cure will likely require replacement, while immunomodulation may best serve early, antibody-positive disease, possibly as a complication-prevention rather than a glycemic intervention — a reading now supported by the eight-year complication data from the combination cohort. Combination or sequential strategies (immune-tolerance induction plus replacement) are a logical next step.

- **Comparison with prior work and regulatory/cost considerations:** Prior pairwise meta-analyses concluded that stem-cell transplantation lowers HbA1c and improves C-peptide, with MSC+HSC and HSC subgroups clearest; our NMA extends this by providing a single coherent ranking with quantified uncertainty, and both agree that UCB does not preserve β-cell function. The randomized-only review used for this update disagrees with the magnitude of those conclusions and agrees with their direction, and it reports an 8% insulin-free rate against the 26.5% obtained in a synthesis admitting non-randomized designs — a threefold discrepancy that is itself a finding. Outcomes of regulatory interest — tumorigenicity, autoimmunity recurrence, immunosuppression-related infection/malignancy and durability — remain incompletely characterized; pluripotent products in particular carry an intrinsic teratoma hazard mandating rigorous purity and, increasingly, engineered safety switches and hypoimmunogenic designs. On cost, autologous MSC is inexpensive and low-risk but modest and transient; autologous iPSC-islet manufacture is highly effective but bespoke and costly; allogeneic "off-the-shelf" islets offer scalability at the recurring cost and risk of lifelong immunosuppression. A formal cost-effectiveness analysis was not feasible from available data and is a research priority — although the null randomized effect on patient-important outcomes means that, for immunomodulatory approaches, the appropriate current answer to a cost-effectiveness question is that effectiveness has not yet been established.
- **Strengths and limitations:** Strengths include a Cochrane-aligned protocol, RoB and GRADE appraisal, a transparent random-effects synthesis, probability-based ranking with full rank distributions, integration of efficacy with modality-specific safety and autoimmunity/carcinogenicity signals, and — new in this version — an auditable updating procedure whose first step verifies that the ranking model reproduces the previously published results before any new data are introduced, so that every change is attributable to evidence rather than to method. Limitations are substantial and temper every conclusion: (i) the network remains star-shaped — no head-to-head cell-versus-cell RCTs, no closed loops, so incoherence cannot be assessed; (ii) node inputs are pooled aggregate (largely before-after) effects rather than individual-participant data; (iii) the new randomized contribution had to be entered as an aggregate rather than per-node estimate because trial-level T1D data were reported only in supplementary material, so the update moves affected nodes toward a common effect and cannot detect class-specific divergence within the new data; (iv) the HSC node received no new randomized data in the primary analysis, because the only candidate trial enrolled a mixed type 1 and type 2 population — so the class that ranks highest is also the class this update was least able to test, and the sensitivity analysis indicates that when it is tested the estimate falls substantially; (v) most contributing studies were small, single-centre and open-label; (vi) heterogeneity was high (I^2 82–95%); (vii) age-disaggregated data for the 18–40-year band were rarely available

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(indirectness); (viii) most estimates are at one year and do not capture later loss of effect or latent harm; and (ix) the most effective modern therapies (stem-cell-derived islets) are single-arm and could not enter the network. We also note an internal inconsistency in the updating source's reported 6-month fasting C-peptide confidence interval (section 4.5), which we could not resolve and therefore did not use. GRADE certainty is very low and the rankings are hypothesis-generating.

Conclusions and Implications

In the available T1D evidence relevant to young adults — now including the randomized trials published since the first version of this synthesis — HSC-based and HSC-containing regimens rank highest for short-term glycaemic control, preservation of β-cell function and reduction in insulin requirement, whereas UCB consistently ranks lowest. The hierarchy proved robust to the update: the only rank change in any outcome was a single adjacent swap for HbA1c, in which mesenchymal stem cells used alone fell from third to fourth. These findings should, however, not be interpreted as evidence of clinical superiority. The underlying evidence is of very low certainty, benefits are generally transient, and the apparent efficacy advantage of HSC transplantation is offset by clinically relevant conditioning- and transplant-related morbidity and mortality — an advantage that, for insulin sparing, is now smaller than the uncertainty around it and reverses when the mixed-population fetal-cell trial is admitted.

The randomized-only evidence base adds a further and more fundamental caution. Restricted to randomized trials, stem-cell therapy in T1D did not significantly improve HbA1c at 12 months, did not reduce daily insulin requirement, did not improve fasting C-peptide, did not improve quality of life and did not reduce hypoglycemic episodes; only 3 of 37 treated participants (8%) achieved a transient insulin-free period, lasting about 15 months. Two consequences follow immediately. For practice, no stem-cell therapy should currently be offered to patients with type 1 diabetes outside a clinical trial, and patients presented with a "stem-cell cure" should be told these numbers alongside the 3.4% treatment-related mortality of the hematopoietic pathway. For regulation, trials must be powered for patient-important outcomes — quality of life, severe hypoglycemia, time-in-range — and not for C-peptide alone, since the surrogate has repeatedly moved without the patient-important outcome following; and the report of a neoplasm adjudicated as related to a stem-cell infusion converts tumorigenicity from a theoretical to an observed hazard, which a literature with a median total follow-up of 12 months cannot detect. Long-term oncological registries should be a condition of authorization for any cellular product in this indication.

More importantly, our findings highlight a fundamental distinction between two therapeutic strategies. Immunomodulatory approaches such as HSC and MSC therapy may preserve residual β-cell function and temporarily reduce insulin dependence but are unlikely to overcome the progressive loss of functional β-cell mass — and the updated randomized evidence indicates that, at the doses, products and follow-up durations tested so far, they do not reliably achieve even that. Stem-cell-derived islet therapies directly address this deficit and therefore represent a potentially more durable route towards restoration of endogenous insulin secretion; the contrast between 83% insulin independence in a single-arm replacement study and 8% transient insulin independence across randomized immunomodulation trials is the clearest expression of that difference in the current literature. Their future clinical value will,

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however, depend on whether durable graft function can be achieved without chronic immunosuppression and its associated risks. Ultimately, successful cell therapy for T1D may therefore require not simply the most effective cell product, but a strategy that combines restoration of β-cell mass with durable protection from recurrent autoimmunity.

Future studies should move beyond comparisons with standard insulin therapy alone. Adequately powered, blinded, head-to-head trials are required to directly compare cell-based strategies, stratify participants by disease duration, residual β-cell function and autoantibody status, and report standardized, time-resolved measures of HbA1c, stimulated C-peptide, insulin requirement and time-in-range. Without such trials this network will remain star-shaped and its rankings uninterpretable, and individual-participant-data pooling would remove the aggregate-input limitation that constrains both this analysis and its update. Among immunomodulatory approaches, the combination of mesenchymal with bone-marrow mononuclear cells is the priority candidate: it ranks second for β-cell preservation and insulin sparing with a safety profile indistinguishable from control and now has eight-year complication data warranting replication. Longer follow-up is essential to distinguish transient metabolic improvement from durable disease modification and to adequately capture tumorigenicity, recurrent autoimmunity and treatment-related adverse effects. For replacement therapies in particular, development of hypoimmunogenic cells, encapsulation or other immune-protective strategies that reduce or eliminate the need for systemic immunosuppression may ultimately determine whether the impressive biological potential of stem-cell-derived islets can be translated into a safe, scalable and durable treatment for T1D.

The honest summary is that stem-cell therapy for type 1 diabetes remains promising and unproven, and that the promise has migrated. It no longer rests principally on immunomodulation, whose randomized evidence is null on all outcomes patients care about, but on replacement — where a small number of single-arm recipients of stem-cell-derived islets have achieved what four decades of β-cell preservation research has not. The next version of this synthesis should be able to place those products in the network. Until it can, the ranking presented here describes the relative order of interventions whose absolute benefit has not been established.

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Registration: (To be registered at PROSPERO).

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