

Neuroregenerative Therapies for Alzheimer's Disease, Parkinson's Disease and Related Dementias: A Scoping Review, Translational Evidence Map and a Neuroregenerative Readiness Index

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Abstract

Background: "Neuroregenerative therapy" is used with increasing frequency in both scientific and commercial communication about Alzheimer's disease (AD), Parkinson's disease (PD) and related dementias (ADRD), yet the term aggregates interventions whose biological rationale, manufacturing complexity, safety profile and clinical evidence differ by orders of magnitude. No published synthesis maps these heterogeneous platforms on a single, explicit and reproducible scale of translational readiness. The objectives of this scoping review were to (i) map the neuroregenerative platforms currently investigated in AD, PD and ADRD, (ii) chart their highest confirmed stage of human development and the status of their primary endpoints, and (iii) develop and apply a transparent, author-derived Neuroregenerative Readiness Index (NRI) that separates biological plausibility from demonstrated clinical benefit.

Methods and findings: We conducted a scoping review following the Joanna Briggs Institute (JBI) methodology and reported it according to the PRISMA Extension for Scoping Reviews (PRISMA-ScR). Eligible records were human clinical studies, registered trials, regulatory documents, methodological standards and pivotal preclinical reports concerning interventions with an explicit neuroprotective, neuroplastic, neurorestorative or cell-replacement rationale in AD, PD, mild cognitive impairment (MCI), dementia with Lewy bodies, vascular dementia and frontotemporal dementia.

Sixteen intervention families were charted across six domains — mechanistic plausibility, preclinical evidence, human clinical evidence, safety characterization, standardization/reproducibility and regulatory feasibility — each scored 0–3 (NRI range 0–18) independently by two reviewers with consensus adjudication. Pluripotent stem cell (PSC)-derived dopaminergic cell replacement in PD reached the highest readiness (NRI 16/18): a phase I trial of bemdaneprocel met its primary safety endpoint with no graft-induced dyskinesia or tumour formation and an 18-month OFF-state MDS-UPDRS Part III change of –23.0 points in the high-dose group, and a sham-controlled phase III trial (exPDite-2, ~102 participants) is ongoing. Multidomain lifestyle interventions ranked second (15/18) with the largest randomized datasets but small effect sizes (US POINTER: 0.029 SD/year, 95% CI 0.008–0.050, $P = .008$). Intermediate scores were assigned to gene therapy (13/18; only AAV2-GAD achieved a positive randomized sham-controlled result, $P = 0.04$, whereas CERE-110 and CERE-120 missed their primary endpoints and RESTORE-1 was placed on clinical hold), mesenchymal stromal cell therapy (12/18; phase 2a signals obtained under a prespecified $P < 0.10$ threshold), photobiomodulation (11/18; pooled cognitive SMD 0.66, 95% CI 0.23–1.08, but a null randomized motor trial in PD) and blood-derived products (11/18). Extracellular vesicle (EV) therapeutics scored 8/18, supported by a single uncontrolled first-in-human AD trial ($n = 9$) with no cognitive change at 12 weeks, whereas platelet-rich plasma (4/18) and in vivo astrocyte-to-neuron reprogramming (3/18) had no confirmed human efficacy data, the latter having failed stringent independent lineage-tracing replication. Main limitations are the absence of formal risk-of-bias appraisal inherent to the scoping design, the ordinal and non-validated nature of the NRI, and the rapid obsolescence of readiness scores in an actively evolving field.

Conclusions: Neuroregenerative medicine in AD, PD and ADRD is not a single therapeutic category but a readiness continuum. Only cell replacement in PD has entered pivotal sham-controlled testing; most other platforms — including the exosome and platelet-derived products most aggressively marketed to patients — remain at or below first-in-human safety stage. We propose the NRI as a communication and governance instrument to align clinical claims, informed consent, marketing and research prioritization with the actual maturity of each platform, and we recommend that future trials adopt standardized product characterization, sham-controlled designs and fluid biomarker endpoints (plasma NFL, GFAP, p-tau217) as minimum translational requirements.

Keywords

Neuroregeneration; Alzheimer's disease; Parkinson's disease; stem cell therapy; extracellular vesicles; translational medicine; Scoping review.

Introduction

Neurodegenerative disorders remain the paradigmatic unmet need of modern neurology: they are progressive, multifactorial, only partially responsive to symptomatic therapy, and — in the case of the dementias — increasingly targeted by disease-modifying strategies whose effect sizes remain modest relative to patient expectations. Against this background, the vocabulary of regenerative medicine has migrated rapidly into neurology and into direct-to-consumer health communication. Terms such as “neuroregeneration”, “brain rejuvenation”, “stem cell therapy for Alzheimer's” and “exosome therapy for Parkinson's” now circulate simultaneously in peer-reviewed journals, in conference programmes and in commercial advertising, frequently without any indication of which developmental stage the underlying technology has actually reached.

That semantic compression is scientifically consequential. Within the same conceptual umbrella one finds interventions as different as (i) surgical intraputaminar transplantation of pluripotent stem cell (PSC)-derived dopaminergic progenitors, now supported by two independent phase I trials published in *Nature* in 2025 and by a registrational sham-controlled phase III programme [1,2]; (ii) intravenous allogeneic mesenchymal stromal cells (MSC) evaluated in a randomized phase 2a trial in mild Alzheimer's disease [3]; (iii) intranasal MSC-derived extracellular vesicles tested in a single-arm first-in-human study of nine

patients [4]; and (iv) commercially promoted exosome and young-plasma infusions for which regulators have issued explicit public safety notifications stating that no such product is approved and that serious adverse events have occurred [5,6]. These interventions share a rhetorical family resemblance and almost nothing else.

At the same time, the non-pharmacological end of the field has produced the largest and methodologically strongest datasets in the entire space. The FINGER trial demonstrated that a two-year multidomain intervention improved a neuropsychological test battery composite score relative to control [8], and the US POINTER trial, reported in 2025 in 2,111 participants, confirmed a statistically significant but numerically small advantage of a structured over a self-guided multidomain lifestyle programme [7]. Whether such interventions should be labelled “regenerative” is itself a definitional question that the field has never resolved: they plausibly act through neuroplasticity, cerebrovascular health and metabolic resilience rather than through cell replacement.

A third development has changed the feasibility of the entire enterprise. Blood-based biomarkers have matured from research tools into regulated diagnostics: in May 2025 the United States Food and Drug Administration (FDA) cleared the first blood test for use in diagnosing Alzheimer’s disease, a plasma p-tau217/ β -amyloid 1-42 ratio assay [9], following primary-care validation studies reporting areas under the curve of approximately 0.97 for plasma p-tau217-based algorithms [10]. For the first time, regenerative trials in neurodegeneration can be designed around scalable, minimally invasive biological outcomes rather than around clinical scales alone.

What is missing is a framework. Systematic reviews exist for individual platforms — cell therapy in PD, MSC in AD, gene therapy in PD, photobiomodulation in cognitive impairment — but they are non-comparable, use different outcome hierarchies, and do not allow a clinician, a regulator, a journal editor or a patient to answer the single most practically important question: how close to legitimate clinical use is each of these technologies, and on what evidential basis?

This scoping review was designed to answer that question. Our objectives were:

1. To map the neuroregenerative intervention families currently under investigation for AD, PD, MCI, dementia with Lewy bodies (DLB), vascular dementia (VaD) and frontotemporal dementia (FTD).
2. To chart, for each family, the highest confirmed developmental stage in humans, the status of the primary endpoint of its most advanced completed trial, distinctive safety signals, regulatory milestones and programme discontinuations.
3. To construct and apply an explicit, reproducible **Neuroregenerative Readiness Index (NRI)** integrating mechanistic plausibility, preclinical evidence, human clinical evidence, safety characterization, standardization and regulatory feasibility.
4. To produce a “promise-versus-evidence” matrix capable of informing clinical communication, ethical consent, marketing governance and research prioritization.

The review deliberately does not attempt to estimate pooled efficacy. Its contribution is cartographic and evaluative: it maps a heterogeneous territory and provides an instrument for judging distance to the clinic.

Methods

Study design and reporting standards

We conducted a scoping review according to the framework of Arksey and O'Malley [11], as refined by Levac et al. [12] and operationalized in the updated JBI methodological guidance for scoping reviews [13]. Reporting follows the PRISMA Extension for Scoping Reviews (PRISMA-ScR) 20-item checklist plus the two optional items [14], and the JBI templates for population/concept/context definition and data charting [15]. A scoping design was selected deliberately: the research question concerns the breadth, maturity and heterogeneity of an intervention landscape rather than the pooled effect of a single intervention on a single outcome, which is the appropriate indication for a systematic review with meta-analysis.

Review question

Which neuroregenerative interventions are being investigated for Alzheimer's disease, Parkinson's disease and related dementias; what stage of translational development has each reached; and how do they compare on an explicit, multidimensional index of clinical readiness?

Eligibility criteria (PCC framework)

Population: Adults with AD, MCI due to AD, PD, DLB, VaD, FTD or mixed neurodegenerative dementia. Preclinical models were eligible only when required to characterize platforms without human data or to document failures of replication.

Concept: Interventions with an explicitly stated neuroprotective, neurorestorative, neuroplastic, immunomodulatory-regenerative or cell-replacement rationale, comprising: PSC-derived neural cell transplantation; fetal ventral mesencephalic tissue grafting; MSC therapy; viral-vector gene therapy; direct neurotrophic protein delivery; in vivo cellular reprogramming; extracellular vesicle (EV)/exosome therapeutics; photobiomodulation (PBM); non-invasive neuromodulation with a neuroplastic rationale (40 Hz gamma sensory stimulation, rTMS, tDCS); adaptive deep brain stimulation; MR-guided focused ultrasound blood–brain barrier (BBB) opening as an enabling delivery platform; multidomain lifestyle and structured exercise interventions; and blood-derived products (therapeutic plasma exchange, plasma fractions, platelet-rich plasma [PRP]).

Context: Any clinical or regulatory setting worldwide; publications in English, Portuguese or Spanish.

Exclusion criteria: Purely symptomatic pharmacotherapy without a regenerative rationale; anti-amyloid or anti-tau immunotherapy (a distinct and already extensively reviewed disease-modifying category, considered here only as a comparator); commercial claims unsupported by retrievable data; studies in acute stroke, spinal cord injury or psychiatric disorders except were used for mechanistic context; and any record from which the product, dose, route or outcome could not be determined.

Information sources and search

Records were identified through MEDLINE/PubMed, Europe PMC, PubMed Central, journal websites

(including Nature, Nature Medicine, Nature Biotechnology, Lancet and Lancet Neurology, JAMA and JAMA Neurology, Brain, Movement Disorders, Alzheimer's & Dementia, Journal of Extracellular Vesicles), the ClinicalTrials.gov registry, the Japan Registry of Clinical Trials (JRCT), the Australian New Zealand Clinical Trials Registry (ANZCTR), the Korean Clinical Research Information Service (CRiS), regulatory sources (US FDA), sponsor communications and the ISEV standards repository. Searches combined controlled and free-text terms for the diseases of interest with terms for each intervention family, and were supplemented by backward and forward citation tracking of pivotal trials and by targeted registry interrogation. The search covered the period from 1 January 2010 to the final search date, with earlier landmark trials retained when they constituted the historical benchmark for a platform (for example, fetal tissue grafting and first-generation neurotrophic factor infusion). Grey literature was restricted to regulatory notices, registry records and sponsor disclosures of trial holds, terminations or designations, all of which are unavailable in the peer-reviewed literature and materially affect readiness assessment.

Selection and charting of data

Screening was conducted in two stages (title/abstract, then full text) by two reviewers independently, with disagreements resolved by discussion. A structured charting form recorded: intervention family and specific product; disease and clinical stage; trial name and registration identifier; sponsor; phase; sample size; route, dose and treatment schedule; comparator (including sham surgery or sham device); follow-up duration; primary endpoint and whether it was met; principal secondary and biomarker outcomes; safety signals; regulatory designations; and programme status (ongoing, completed, held, terminated). Consistent with scoping review methodology, formal critical appraisal of individual studies was not performed; instead, methodological quality was captured descriptively as design attributes (randomization, blinding, sham control, prespecified alpha) that feed directly into the readiness index.

Development of the Neuroregenerative Readiness Index

The NRI was developed by the authors specifically for this review. It is not a validated psychometric instrument and should not be reported as such. It is a structured, transparent scoring heuristic designed to make explicit the judgements that narrative reviews usually leave implicit.

Each intervention family is scored 0–3 on six domains (total 0–18):

Domain	0	1	2	3
P — Mechanistic plausibility	Mechanism speculative or contradicted	Plausible but unverified in the target tissue	Coherent mechanism with human biomarker or imaging support	Mechanism demonstrated in humans with target engagement evidence
Epre — Preclinical evidence	Absent or non-replicated	Single-laboratory positive data	Replicated in relevant models	Replicated across laboratories and species, including primates or large models
Ehum — Human clinical evidence	None	First-in-human safety only, uncontrolled	Randomized controlled data, endpoints mixed or exploratory	Positive randomized controlled trial(s) at phase 2b/3 on clinical endpoints
S — Safety characterization	Unknown or serious unresolved risk	Limited data or a documented programme-halting signal	Acceptable profile in small controlled samples	Well-characterized profile in large samples with long follow-up

Domain	0	1	2	3
Pad — Standardization and reproducibility	Product, dose or dosimetry not definable	Highly heterogeneous between centres	Partially standardized with published protocols	Fully specified product/dose with release criteria or device dosimetry
R — Regulatory feasibility	No viable pathway; marketed outside regulation	Early-stage pathway only	Formal expedited designation or pathway agreed	Approved product or approved device in the indication

$$[\text{NRI} = \text{P} + \text{E}_{\text{pre}} + \text{E}_{\text{hum}} + \text{S} + \text{Pad} + \text{R}]$$

Interpretive bands were prespecified as: **0–5**, exploratory/preclinical; **6–9**, early translation, human research only under regulated protocols; **10–13**, emerging clinical evidence, candidate for confirmatory trials; **14–18**, potential for regulated clinical implementation conditional on indication, safety and approval.

Two reviewers scored each domain independently using the charted evidence, with disagreements of ≥ 1 point resolved by consensus; a sensitivity analysis re-scored all families under a conservative rule in which any missed primary endpoint capped E_{hum} at 1.

Synthesis of results

Results are presented as (i) a narrative synthesis by platform, (ii) a disease × platform translational map, (iii) the NRI scoring table with domain-level justification, and (iv) a promise-versus-evidence matrix. No pooled statistical synthesis was performed; where meta-analyses already exist, their published effect estimates are reported verbatim with their confidence intervals.

Ethical statement

This study was conducted exclusively with previously published scientific texts, publicly accessible clinical trial registry records and public regulatory documents. It involved no recruitment of participants, no intervention, no access to medical records, no identifiable individual-level data and no human biological material. Under Brazilian National Health Council Resolution CNS No. 510/2016, Article 1, sole paragraph, item VI, research conducted exclusively with scientific texts for literature review is neither registered nor evaluated by the CEP/CONEP system [16]. The study therefore did not require ethics committee approval. The authors confirm adherence to the principles of the Declaration of Helsinki in the interpretation and reporting of the human studies discussed.

Results

Overview of the evidence landscape

Sixteen intervention families met inclusion criteria and were charted. They span the entire translational range, from an approved device technology to platforms whose founding preclinical claim has failed independent replication. Three structural observations organize the findings.

First, the most advanced neuroregenerative programme in neurology is anatomically and biologically specific: replacement of nigrostriatal dopaminergic neurons in Parkinson's disease. This is not accidental. PD offers a defined cellular target, a defined anatomical delivery site, a validated motor endpoint and a positron emission tomography marker of graft survival — conditions that Alzheimer's disease, a

distributed synaptic and network disorder, does not provide.

Second, the strength of evidence is inversely correlated with the intensity of commercial promotion. The platforms with the weakest human data — autologous adipose “stem cell” infusions, exosome preparations and platelet-derived products — are those most frequently marketed directly to patients, prompting explicit regulatory safety notifications [5,6].

Third, most positive signals in the field are safety and feasibility signals, not efficacy signals. Of the completed randomized trials charted, the majority either met a safety-only primary endpoint or missed their efficacy primary endpoint while reporting favourable secondary outcomes.

Platform 1 — Pluripotent stem cell-derived dopaminergic cell replacement in Parkinson’s disease

Two first-in-human trials published in *Nature* in 2025 redefined the ceiling of this field. In the phase I trial of bemdaneprocel (BRT-DA01/MSK-DA01), 12 participants received bilateral post-commissural putaminal transplantation of human embryonic stem cell-derived dopaminergic neuron precursors at two dose levels (0.9×10^6 and 2.7×10^6 cells per putamen, delivered in nine deposits) with one year of immunosuppression. The primary endpoint — absence of graft-related serious adverse events at 12 months — was met; no graft-induced dyskinesia and no tumour formation were observed. At 18 months, the change in MDS-UPDRS Part III in the OFF state was -23.0 points in the high-dose group versus -8.6 points in the low-dose group, and good ON time increased by 2.7 hours [1].

In the parallel Kyoto University phase I/II trial (jRCT2090220384), seven participants received allogeneic HLA-homozygous induced pluripotent stem cell-derived CORIN⁺ dopaminergic progenitors. No serious adverse events occurred; 73 adverse events were recorded, 72 of them mild, with no evidence of graft overgrowth. Among six evaluable participants, the OFF-state MDS-UPDRS Part III improved by 9.5 points (20.4%), and ¹⁸F-DOPA K_i increased by 44.7%, providing direct evidence of graft-derived dopaminergic function [2].

Two considerations temper these results. The trials were uncontrolled, and the pooled sham response in double-blind randomized trials of regenerative therapies for PD has been estimated at 4.3 UPDRS-III OFF units (95% CI 3.1–5.6) [23]. More instructively, the fetal-tissue benchmark trial TRANSEURO — in which only 11 of 36 randomized participants were ultimately grafted — reported no overall clinical effect three years after grafting, although major graft-induced dyskinesia was not observed [19]. The historical literature therefore contains a well-documented example of a promising open-label signal that did not survive controlled evaluation.

The field has nonetheless entered pivotal testing. exPDite-2 (NCT06944522) is a sham-controlled phase III trial of approximately 102 participants randomized 2:1, with ON time without troublesome dyskinesia at week 78 as the primary endpoint [17]. Bemdaneprocel holds FDA Fast Track (2021) and Regenerative Medicine Advanced Therapy (RMAT, 2024) designations and received Japan’s SAKIGAKE pioneering regenerative medical product designation in December 2025 [18]. The STEM-PD trial (NCT05635409) is separately evaluating hESC-derived dopaminergic progenitors at 3.54×10^6 and 7.08×10^6 cells per

putamen with 36-month follow-up and has advanced to the higher dose after acceptable safety [20]. Existing meta-analyses of cell transplantation in PD report favourable pooled motor changes — for example, a weighted mean difference in UPDRS of -14.86 (95% CI -16.62 to -13.10) across nine controlled trials and 129 patients [21], and a synthesis of 11 studies in 210 patients [22] — but these pool heterogeneous graft sources and largely pre-modern surgical protocols and should not be read as evidence for current products.

Platform 2 — Mesenchymal stromal cell therapy

MSC therapy is the most widely tested regenerative platform in neurodegeneration and the most heterogeneous in quality.

The strongest dataset is the CLEAR MIND phase 2a randomized, double-blind, placebo-controlled trial of laromestrocel (Lomecel-B), an allogeneic bone marrow-derived MSC product, administered intravenously to 49 participants with mild AD. The primary safety endpoint was met, with treatment-emergent serious adverse event rates of 0–9.1% and no amyloid-related imaging abnormalities (ARIA). The composite Alzheimer's Disease Score (CADS) favoured treatment by 0.38 ($P = 0.091$) against a prespecified significance threshold of $P < 0.10$; MoCA change reached $P = 0.009$, and whole-brain atrophy was slowed by 48.4% ($P = 0.005$) [3]. The product holds FDA RMAT and Fast Track designations for mild AD [24]. The prespecified use of a liberal alpha is methodologically legitimate in a phase 2a trial but means the cognitive result should be described as a signal to be confirmed, not as demonstrated efficacy.

In Parkinson's disease, a phase 2 randomized trial of allogeneic bone marrow-derived MSC (10×10^6 cells/kg intravenously, three infusions; $n = 45$) met its prespecified Bayesian threshold with a posterior probability of 93.7% [25,26].

Against these, the negative and opaque record is substantial. NEUROSTEM-AD, delivering allogeneic umbilical cord blood-derived MSC intracerebroventricularly via an Ommaya reservoir, missed its ADAS-Cog primary endpoint [27]. AstroStem, an autologous adipose-derived MSC product given as ten intravenous infusions to 21 participants with AD (NCT03117738), has never been published; results were filed 356 days late and no significant efficacy has been demonstrated [28,29,30]. A 2026 systematic review of MSC trials in AD identified 17 clinical trials, 70.6% using the intravenous route [28] — a route for which the fraction of cells reaching the brain parenchyma remains the central unresolved pharmacological question. Randomized data also exist for autologous adipose MSC in PD [31] and for umbilical cord MSC in vascular dementia, the latter in small single-centre studies [32].

Platform 3 — Viral vector gene therapy

Gene therapy in PD has the most instructive success-and-failure record in the entire review.

AAV2-GAD, delivered to the subthalamic nucleus, remains the only randomized, double-blind, sham-surgery-controlled CNS gene therapy trial in PD to report a positive primary result: OFF-state UPDRS improved by 8.1 points versus 4.7 points with sham surgery, a between-group difference of $P = 0.04$ [33].

The subsequent record is more sobering. VY-AADC01/NB1b-1817 (AAV2-hAADC) achieved putaminal

coverage of 21–42% and a 30% reduction in levodopa-equivalent daily dose in the highest-dose cohort [34], but the pivotal RESTORE-1 trial was placed on FDA clinical hold after MRI abnormalities were identified, and the PD programme was subsequently terminated [35]. The lentiviral ProSavin produced a 12-month improvement in OFF-state UPDRS Part III from 38 to 27 ($P = 0.0001$) in an open-label phase 1/2 trial of 15 patients [36], but its successor AXO-Lenti-PD was terminated after six participants and discontinued in 2023 [37]. AB-1005 (AAV2-GDNF) achieved 63% putaminal coverage in 11 participants with a met safety endpoint and an 18-month OFF-state MDS-UPDRS III change of -18.8 ± 6.6 points in the moderate cohort, with five serious adverse events all adjudicated unrelated [38]; the phase 2 REGENERATE-PD trial (NCT06285643, ~127 participants, primary endpoint at month 18) is ongoing [39].

In Alzheimer's disease, results have been uniformly negative on clinical endpoints. CERE-110 (AAV2-NGF) delivered to the nucleus basalis of Meynert in 49 participants missed its 24-month ADAS-Cog primary endpoint (14.52 versus 9.11, $P = .17$) [40], mirroring the failure of CERE-120 (AAV2-neurturin) in PD [41]. A phase 1 trial of AAV2-BDNF in AD/MCI is ongoing, with a reported FDG-PET signal in three of six participants in interim analysis [42].

Platform 4 — Direct neurotrophic protein delivery

Direct protein delivery illustrates the gap between compelling preclinical neuroprotection and clinical translation. In the Bristol randomized trial, intermittent intraputamenal GDNF by convection-enhanced delivery (120 μ g per putamen every four weeks for ten infusions; $n = 41$) did not meet its primary endpoint: OFF-state UPDRS-III improved 17.3% versus 11.8% with placebo, least-squares difference -4.9% (95% CI -16.9 to 7.1), $P = 0.41$ [43], despite an open-label extension and PET evidence of biological effect [44]. A randomized phase 1 trial of intraputamenal CDNF in 17 patients found the approach safe but produced no significant secondary changes, with severe adverse events attributable to the delivery procedure [45]. In AD, NGF encapsulated cell biodelivery to the cholinergic basal forebrain reached only phase Ib ($n = 6$, then $n = 4$ with a second-generation device), demonstrating feasibility and continued NGF release from 13 of 16 explanted devices [46]. A meta-analysis of GDNF and neurturin brain infusion reported a non-significant pooled motor effect of -1.37 (95% CI -6.02 to 3.29) alongside a significant excess of serious adverse events (1.18, 95% CI 0.05 – 2.30) [47].

Platform 5 — In vivo cellular reprogramming

The proposal that knockdown or deletion of *Ptbp1* converts astrocytes into functional neurons generated substantial enthusiasm as a route to endogenous neuronal replacement. Stringent independent lineage tracing using *Aldh1l1*-creERT2/*Sun1*-GFP reporters found no GFP⁺/NeuN⁺ or HuC/HuD⁺ cells at 2, 4 or 8 weeks after *Ptbp1* deletion in cortex, striatum or substantia nigra, including in 6-OHDA-lesioned animals [48]. Current interpretations attribute the reported functional benefits to anti-inflammatory or neuroprotective mechanisms rather than to astrocyte-to-neuron transdifferentiation [49]. No human trial exists. This platform is included precisely because it demonstrates the value of an explicit readiness framework: a technology can generate high-profile publications, media coverage and clinical expectation while its central mechanistic claim remains unreplicated.

Platform 6 — Extracellular vesicle and exosome therapeutics

Despite the volume of preclinical literature and commercial activity, human therapeutic evidence for EVs

in neurodegeneration consists of a single completed trial. In an open-label 3 + 3 dose-escalation phase I/II study at Ruijin Hospital (NCT04388982), nine patients with mild-to-moderate AD received intranasal allogeneic human adipose MSC-derived exosomes at 2×10^8 , 4×10^8 or 8×10^8 particles in 1 mL twice weekly for 12 weeks, with follow-up to week 48. The safety primary endpoint was met — no treatment-related adverse or serious adverse events, no hepatic or renal toxicity, and the maximum tolerated dose was not reached. Exploratory efficacy at week 12 showed no benefit: ADAS-Cog +1.4 (SD 5.4, $P = 0.500$), MoCA-B -1.1 ($P = 0.510$) and MMSE unchanged ($P = 1.000$) [4,50]. A second-generation umbilical cord MSC exosome trial (NCT07457125, $n = 33$, with a randomized placebo-controlled expansion phase) is registered but not yet recruiting [51]. No registered EV therapeutic trial in Parkinson's disease was identified, which is itself a notable gap in the translational map.

Reporting and manufacturing standardization remains the rate-limiting barrier. Dose for the same registry record has been reported both as particle counts and as protein mass in different publications [4,58], precisely the discrepancy that MISEV2023 was written to eliminate; that guidance, built on 1,025 survey responses, also formalizes the preference for “extracellular vesicle” over “exosome” and for size-based nomenclature [52]. Position papers from ISEV and from the EVOLVE France group, and recent regulatory-science analyses, converge on unresolved requirements for potency assays, biodistribution, batch release and comparability [53,54,55]. In parallel, the FDA's public safety notification of December 2019 states that no exosome product is approved and documents serious adverse events following administration of unapproved products [5].

The strongest current role for EVs in this field is diagnostic rather than therapeutic. Neuronally derived EV α -synuclein discriminated individuals at risk of PD with derivation and validation areas under the curve of 0.85 (95% CI 0.79–0.91) and 0.91 (95% CI 0.86–0.96) in 576 participants [56], and exosomal p-tau181 in AD showed a pooled standardized mean difference of 1.75 (95% CI 1.16–2.35) [57].

Platform 7 — Photobiomodulation

Photobiomodulation occupies an intermediate and internally contradictory evidential position: positive in cognition, null in Parkinsonian motor function.

In a randomized, double-blind, placebo-controlled confirmatory trial in MCI due to AD ($n = 80$; 808 nm bilateral dorsolateral prefrontal stimulation, six sessions weekly for 12 weeks), the MoCA-K changed by $+3.87 \pm 2.51$ versus -0.74 ± 2.85 with sham ($P < 0.001$), with no device-related adverse events [59]; an earlier sham-controlled study from the same group ($n = 26$) reported a consistent effect [60]. Two meta-analyses support a moderate pooled cognitive effect: 24 randomized trials in 820 participants yielded a standardized mean difference of 0.66 (95% CI 0.23–1.08, $P = 0.003$) [63], and an earlier synthesis of 11 trials reported 0.51 (95% CI 0.162–0.864, $P = 0.004$), with a larger effect for multi-wavelength (0.648) than single-wavelength (0.385) protocols [64].

In Parkinson's disease the picture is different. The PDNeuro randomized feasibility trial ($n = 40$; 810 nm plus 630–670 nm, 20 sites, 24 minutes, six sessions weekly for 12 weeks, 1,137 J per session) found no significant between-group difference in MDS-UPDRS Part III [61]. An extended-treatment randomized trial combining transcranial with abdominal and neck delivery ($n = 63$) found no difference in Hoehn–Yahr

stages 1–2, with a difference in Timed Up and Go confined to stage 3 (9.8 versus 12.0 seconds, $P = 0.016$) [62]. The mechanistic constraint is explicit: transcranial penetration is approximately 20–30 mm, so the substantia nigra pars compacta cannot be directly irradiated, which is the principal rationale offered for remote (abdominal/gut) delivery [65]. Parameter heterogeneity — wavelength, irradiance, fluence, site, session number and total dose — remains the dominant limitation of the entire literature.

Platform 8 — Non-invasive neuromodulation with a neuroplastic rationale

40 Hz gamma sensory stimulation. In the OVERTURE phase 2 trial (NCT03556280), 76 participants were randomized 2:1 to audiovisual 40 Hz stimulation for one hour daily over six months. The primary MADCOMS endpoint was not met (least-squares difference -0.23 , SE 0.568 , 95% CI -1.38 to 0.91 , $P = 0.6825$). Secondary outcomes favoured treatment: MMSE $+2.10$ ($P = 0.0417$; 76% less decline) and ADCS-ADL $+6.61$ ($P = 0.0004$; 77% less decline), with no ARIA [66], and a companion MRI analysis reported reduced corpus callosum atrophy [67]. The pivotal HOPE study (NCT05637801) randomized 670 participants across 68–70 US sites with an estimated primary completion in June 2026 [68]. Earlier MIT GENUS feasibility studies established tolerability of the stimulation parameters [69].

rTMS and tDCS. A meta-analysis of 31 randomized trials in AD and MCI reported immediate cognitive effects of SMD 0.930 (95% CI 0.638 – 1.222 , $P < 0.001$) and long-term effects of 0.42 (95% CI 0.13 – 0.70), with dorsolateral prefrontal targeting outperforming other targets (1.28 versus 0.52) [70]. In PD, pooled UPDRS-III improvement across 32 articles was SMD 0.64 (95% CI 0.47 – 0.80) [71]. For tDCS in AD, 14 studies in 211 patients yielded SMD 1.640 (95% CI 0.782 – 2.498) for general cognition and 1.031 for memory, with no significant effect on attention [72].

Adaptive deep brain stimulation. In February 2025 the FDA approved the first adaptive DBS system for Parkinson's disease, supported by the ADAPT-PD randomized crossover trial against conventional stimulation [73,74]. This is the only approved technology charted in this review — and it is functional and symptomatic rather than regenerative, a distinction of considerable importance for honest classification.

Focused ultrasound BBB opening. In the first-in-human study, five participants underwent 220 kHz MR-guided BBB opening; the primary safety and reversibility endpoint was met, without significant amyloid change [75]. A subsequent trial combined focused ultrasound with six monthly infusions of aducanumab in three participants, reporting numerically greater amyloid reduction in sonicated regions [76]. Focused ultrasound is therefore best classified as an enabling delivery platform for regenerative and disease-modifying agents rather than as a therapy in itself.

Platform 9 — Multidomain lifestyle and structured exercise

These interventions have the largest randomized datasets in the review. FINGER randomized 1,260 at-risk older adults to a two-year multidomain programme, with a neuropsychological test battery Z-score difference of 0.022 per year (95% CI 0.002 – 0.042 , $P = 0.030$) and more adverse events in the intervention arm (46 [7%] versus 6 [1%]), predominantly musculoskeletal [8]. US POINTER randomized 2,111 participants and reported a structured-intervention advantage of 0.029 SD per year (95% CI 0.008 – 0.050 , $P = .008$), with no interaction by APOE status ($P = .95$) but an interaction with baseline cognition ($P = .02$) [7]. In Parkinson's disease, the Park-in-Shape trial ($n = 130$) demonstrated that six months of home aerobic

cycling increased anterior putamen connectivity and reduced global brain atrophy relative to stretching [78], and the phase 3 SPARX3 trial (n = 370 planned; high-intensity 80–85% versus moderate 60–65% HRmax) is testing whether exercise intensity modifies MDS-UPDRS Part III at 12 months [77].

The interpretive tension is clear: these are the best-evidenced interventions in the field and simultaneously the ones with the smallest per-year effect sizes and the least mechanistic specificity regarding “regeneration”.

Platform 10 — Blood-derived products

The AMBAR trial evaluated therapeutic plasma exchange with albumin replacement in 347 randomized patients with AD. One co-primary endpoint was met (ADCS-ADL, 52% less decline, $P = 0.03$) while the other was not (ADAS-Cog, 66%, $P = 0.06$); in the moderate subgroup (MMSE 18–21) both co-primaries reached significance (61%, $P = 0.002$ and $P = 0.05$), with CDR-sb 71% ($P = 0.002$) and ADCS-CGIC 100% ($P < 0.0001$) [79,80]. The PLASMA trial (NCT02256306) of young fresh frozen plasma in 18 participants met its safety and tolerability primary endpoint, with 71 adverse events (21 likely related) and no related serious adverse events [81]. GRF6019, a plasma fraction, was safe across two dose levels in 47 participants, with MMSE change of -1.0 (100 mL) versus $+1.5$ (250 mL) at 24 weeks in an underpowered comparison [82,83]. The FDA advisory of February 2019 against for-profit young-donor plasma infusions for ageing or dementia remains in force [6].

For platelet-rich plasma and platelet lysates, no human clinical trial in AD, PD or dementia was identified; the available literature is preclinical [84]. Given that PRP is among the most widely marketed “regenerative” products in general practice, this absence is one of the most policy-relevant findings of this review.

Fluid biomarkers as trial outcomes

Trial design in this field is being transformed by blood biomarkers. The FDA cleared the first blood test for use in diagnosing Alzheimer’s disease in May 2025 (plasma p-tau217/A β 42 ratio; validation n = 499, with 91.7% of positive results amyloid-positive and 97.3% of negative results amyloid-negative, and fewer than 20% indeterminate) [9]. Plasma p-tau217 achieved an AUC of 0.97 (95% CI 0.95–0.99) with a positive predictive value of 91% in primary care in 1,213 participants [10], with concordant diagnostic accuracy in independent immunoassay validation [85]. Plasma neurofilament light has been validated multicentrically as a marker of neuroaxonal injury [86], and plasma GFAP is elevated in cognitively normal older adults at risk of AD [87]. Together these markers make it feasible — and, we argue, obligatory — for early-phase neuroregenerative trials to report objective biological outcomes alongside clinical scales.

Translational evidence map

Platform	Alzheimer’s disease / MCI	Parkinson’s disease	Vascular dementia	DLB / FTD
PSC-derived neural cell replacement	No human trial identified	Phase III ongoing (sham-controlled) [1,17]	None	None
Fetal ventral mesencephalic grafting	None	Phase II completed; primary outcome not achieved [19]	None	None
Mesenchymal stromal cells	Phase 2a randomized, safety met, cognition exploratory [3]	Phase 2 randomized, Bayesian threshold met [25]	Small randomized single-centre studies [32]	None

Platform	Alzheimer's disease / MCI	Parkinson's disease	Vascular dementia	DLB / FTD
AAV/lentiviral gene therapy	Phase 2 completed, primary missed [40]; phase 1 ongoing [42]	Phase 2 positive (AAV2-GAD) [33]; phase 2 ongoing (AB-1005) [39]; programme holds/terminations [35,37]	None	None
Neurotrophic protein delivery	Phase Ib [46]	Phase 2, primary not met [43]	None	None
In vivo reprogramming	Preclinical, replication failure [48]	Preclinical, replication failure [48]	None	None
Extracellular vesicles	Phase I/II, n = 9, uncontrolled [4]	No registered therapeutic trial identified	None	None
Photobiomodulation	Randomized sham-controlled, positive [59,63]	Randomized, primary not met [61,62]	Not established	Not established
40 Hz gamma sensory stimulation	Phase 2 primary missed; phase 3 pending [66,68]	None	None	None
rTMS / tDCS	Meta-analytic benefit, heterogeneous [70,72]	Meta-analytic motor benefit [71]	Limited	Limited
Adaptive DBS	Not applicable	Approved device (2025) [73]	Not applicable	Not applicable
Focused ultrasound BBB opening	Phase 1 safety met; delivery-enabling [75,76]	Investigational	None	None
Multidomain lifestyle intervention	Phase 3 positive, small effect [7,8]	Phase 3 ongoing (exercise intensity) [77]	Indirect (vascular risk)	Limited
Structured aerobic exercise	Supportive within multidomain trials [7,8]	Randomized, imaging effects [78]	Limited	Limited
Therapeutic plasma exchange / plasma fractions	Phase 2b/3, co-primary partially met [79]	None	None	None
Platelet-rich plasma / platelet lysate	No human trial identified [84]	No human trial identified	None	None

Table 1: Disease × platform translational map: highest confirmed stage of human development.

Neuroregenerative Readiness Index

Platform	P	Epre	Ehum	S	Pad	R	NRI	Band
PSC-derived dopaminergic replacement (PD)	3	3	2	2	3	3	16	Implementation-capable, pending phase III
Multidomain lifestyle intervention	2	3	3	3	2	2	15	Implementation-capable
Adaptive DBS (functional, non-regenerative comparator)	1	2	3	2	3	3	14	Approved, but not regenerative
AAV gene therapy (PD)	3	3	2	1	3	1	13	Emerging clinical evidence
40 Hz gamma sensory stimulation	2	3	1	3	3	1	13	Emerging clinical evidence
rTMS / tDCS	2	2	2	3	2	1	12	Emerging clinical evidence
Mesenchymal stromal cells	2	2	2	3	1	2	12	Emerging clinical evidence
Focused ultrasound BBB opening (enabling platform)	2	3	2	2	2	1	12	Emerging clinical evidence
Photobiomodulation	2	2	2	3	1	1	11	Emerging clinical evidence
AAV neurotrophin gene therapy (AD)	2	2	1	2	3	1	11	Emerging clinical evidence
Plasma exchange / plasma fractions	2	2	2	2	2	1	11	Emerging clinical evidence
Neurotrophic protein delivery (GDNF/CDNF)	3	3	1	1	2	0	10	Emerging clinical evidence
Fetal ventral mesencephalic grafting	3	3	1	2	0	0	9	Early translation (historical benchmark)
Extracellular vesicles / exosomes	2	2	1	2	1	0	8	Early translation only
Platelet-rich plasma / platelet lysate	1	1	0	1	1	0	4	Exploratory / preclinical
In vivo astrocyte-to-neuron reprogramming	1	1	0	0	1	0	3	Exploratory / preclinical

Table 2: NRI domain scores by platform (0–3 per domain; total 0–18).

P = mechanistic plausibility; Epre = preclinical evidence; Ehum = human clinical evidence; S = safety characterization; Pad = standardization and reproducibility; R = regulatory feasibility. Bands: 0–5 exploratory/preclinical; 6–9 early translation; 10–13 emerging clinical evidence; 14–18 potential for regulated clinical implementation.

In the prespecified sensitivity analysis capping Ehum at 1 for any platform whose most advanced completed trial missed its efficacy primary endpoint, the rank order was unchanged for the top and bottom quartiles; AAV gene therapy in PD fell from 13 to 12 and MSC therapy from 12 to 11, while PSC-derived replacement and multidomain intervention retained their positions. The index is therefore reasonably robust to the single most contestable scoring judgement.

Promise-versus-evidence matrix

Category	Platforms	Defining feature	Appropriate clinical language
A. Confirmatory stage	PSC-derived dopaminergic replacement; multidomain lifestyle intervention	Randomized pivotal evidence available or imminent	“Under regulated pivotal evaluation” / “recommended within programmes”
B. Signal-generating stage	MSC therapy; AAV gene therapy; photobiomodulation; gamma sensory stimulation; rTMS/tDCS; focused ultrasound; plasma exchange	Randomized data exist; endpoints mixed, exploratory or dependent on liberal alpha	“Investigational; encouraging but unconfirmed”
C. First-in-human stage	Extracellular vesicles; NGF encapsulated cell biodelivery; AAV2-BDNF	Safety demonstrated; efficacy untested	“Experimental; no efficacy evidence in humans”
D. No human evidence	Platelet-rich plasma in neurodegeneration; in vivo reprogramming	Preclinical only, and in one case failed replication	“Not supported for clinical use outside research”
E. Regulatory-cautioned commercial offerings	Unapproved exosome products; for-profit young-donor plasma	Marketed despite explicit regulatory warnings [5,6]	“Not approved; associated with documented harms”

Table 3: Classification by the relationship between clinical promotion and demonstrated evidence.

Discussion

Principal findings

This scoping review demonstrates that “neuroregenerative therapy” is not a therapeutic class but a readiness continuum spanning 13 index points, from an exploratory score of 3 for in vivo reprogramming to 16 for PSC-derived dopaminergic replacement in Parkinson’s disease. Three findings deserve emphasis.

First, cell replacement in PD has legitimately entered the pivotal era. Two independent phase I trials reported acceptable safety, absence of graft-induced dyskinesia and imaging evidence of graft-derived dopaminergic function [1,2], and a sham-controlled phase III trial is under way [17]. Should exPDite-2 succeed, it will be the first demonstration in neurology that engineered human cells can produce a durable, controlled, clinically meaningful functional benefit. Should it fail — as TRANSEURO did on clinical endpoints [19] — the failure will nonetheless be informative because it will be controlled.

Second, the fields most visible to patients are the least mature. Extracellular vesicle therapeutics rest on a single uncontrolled trial in nine patients with no cognitive signal at 12 weeks [4], no registered PD trial, unresolved potency and biodistribution requirements [54,55] and an active FDA safety notification [5]. Platelet-rich plasma, marketed globally as a regenerative therapy, has no human neurodegeneration trial at all [84]. The distance between the marketing and the evidence is, in these two cases, the widest in the entire map.

Third, the interventions with the strongest evidence are the least glamorous. Multidomain lifestyle programmes, structured aerobic exercise and non-invasive neuromodulation carry the largest randomized samples and the most reproducible safety profiles [7,8,70,71,72], though their effect sizes are small and

their mechanism is neuroplastic and vascular rather than restorative in the cell-replacement sense.

Why Parkinson's disease leads and Alzheimer's disease lags

The asymmetry between diseases is structural rather than accidental. PD offers a discrete cellular target (nigrostriatal dopaminergic neurons), a stereotactically accessible delivery site (the putamen), a validated and responsive motor endpoint, and a molecular imaging readout of graft function (^{18}F -DOPA) [2]. AD offers none of these: the pathology is distributed across cortical networks, the relevant cell populations are heterogeneous, and cognitive endpoints are noisy over the timescales feasible for early-phase trials. It is therefore predictable that every AD-specific regenerative programme charted here — CERE-110, NEUROSTEM-AD, AstroStem, intranasal exosomes — either missed its primary endpoint, remained unpublished, or was safety-only [4,27,28,40]. Investigators proposing regenerative interventions for AD should be explicit that they are pursuing neuroprotection, immunomodulation or synaptic resilience, not neuronal replacement.

Standardization as the true rate-limiting step

Across platforms, the recurring obstacle is not biological plausibility but product definition. Cell-replacement programmes have advanced precisely because they specify cell identity, dose per putamen, deposit number and immunosuppression duration [1,2]. EV programmes have not advanced, in part because the same registry record has been reported in two incompatible dose units [4,58] — the exact failure mode MISEV2023 was designed to eliminate [52]. Photobiomodulation shows the same pathology in device form: wavelength, irradiance, fluence, session number and anatomical target vary so widely between trials that the pooled cognitive effect of SMD 0.66 [63] cannot be translated into a prescribable protocol. Standardization is not a bureaucratic afterthought; it is the difference between a therapy and an anecdote.

Control design and the placebo problem

Neuroregenerative interventions are unusually susceptible to expectancy effects: they are procedural, novel, expensive and accompanied by intensive clinical attention. The pooled sham response in randomized regenerative PD trials is 4.3 UPDRS-III OFF units [23], a magnitude comparable to some reported open-label “successes”. The OVERTURE trial is instructive in the opposite direction: an intervention can miss its primary endpoint while producing consistent, clinically plausible secondary benefits [66], and only an adequately powered pivotal trial can adjudicate between signal and noise [68]. Sham-controlled design should therefore be the default expectation for any procedural neuroregenerative intervention beyond first-in-human safety testing.

Regulatory and ethical implications

Only one technology charted in this review holds marketing approval in the target indications — adaptive DBS, which is not regenerative [73]. Everything else is investigational, several products carry expedited designations that are frequently misrepresented in promotional communication as evidence of efficacy [18,24], and two categories are subject to active regulatory warnings [5,6]. The practical consequence for clinicians is straightforward: designations describe a pathway, not a proof. Informed consent for any regenerative intervention in neurodegeneration should state the platform's developmental stage explicitly, and we suggest that the NRI band provides a usable vocabulary for that disclosure.

A proposed minimum reporting standard for neuroregenerative trials

Based on the deficiencies charted here, we propose that trials of neuroregenerative interventions in AD, PD and ADRD report, at minimum: (i) complete product characterization (cell identity and viability, EV particle count and protein content with MISEV2023-compliant nomenclature [52], vector serotype, genome copies and coverage, or full device dosimetry); (ii) route, dose and anatomical target with imaging confirmation where applicable; (iii) a sham or active control beyond first-in-human studies; (iv) prespecified alpha, with any liberalized threshold declared in the abstract; (v) at least one fluid biomarker outcome from plasma NfL, GFAP or p-tau217 [9,10,85,86,87]; (vi) safety follow-up proportionate to the persistence of the product, including graft survival, immunogenicity and tumorigenicity where relevant; and (vii) public posting of results within the statutory window — a requirement demonstrably violated in at least one charted AD programme [30].

Research agenda

Four priorities follow directly from the map. First, PD cell replacement requires completion of sham-controlled pivotal testing and, thereafter, comparative work on immunosuppression duration and autologous versus allogeneic sourcing. Second, EV therapeutics require a randomized, placebo-controlled trial with MISEV2023-compliant characterization and a biomarker primary endpoint before any further scaling; the absence of any registered PD trial is an obvious opportunity. Third, photobiomodulation requires a dose-finding programme establishing wavelength–fluence–site relationships before further efficacy trials, since the current literature cannot specify a protocol. Fourth, the field needs transdiagnostic, biomarker-stratified trials testing whether patients with a predominantly inflammatory-glial profile (high GFAP, high NfL, low amyloid-tau burden) respond differently to regenerative interventions than patients with predominant proteinopathy — a hypothesis that the maturation of plasma biomarkers now makes testable at scale [9,10,86,87].

Limitations

Several limitations qualify these findings. As a scoping review, no formal risk-of-bias appraisal or GRADE assessment was performed, consistent with JBI methodology [13] but limiting inference about the reliability of individual results. The NRI is an author-derived heuristic, not a validated instrument; its domains are weighted equally without empirical justification, its ordinal scores are not interval-scaled, and different reviewers could plausibly assign scores differing by one to two points, although the sensitivity analysis suggests rank stability. Grey literature was included selectively (regulatory notices, registry records and sponsor disclosures), which introduces potential asymmetry because negative corporate results are systematically less visible than positive ones — the AstroStem programme is a concrete example [29,30]. The review is a snapshot of a rapidly moving field: readiness scores for at least three platforms (PD cell replacement, gamma sensory stimulation, AAV-GDNF) will change when ongoing pivotal trials report [17,39,68]. Finally, language restriction to English, Portuguese and Spanish may have excluded relevant regional evidence, particularly from China, Japan and Korea, where several of the charted programmes originate.

Conclusions

Neuroregenerative medicine for Alzheimer's disease, Parkinson's disease and related dementias is best

understood not as a therapeutic category but as a spectrum of maturity. Applying an explicit six-domain readiness index across sixteen intervention families, we found a single platform approaching regulated clinical implementation — pluripotent stem cell-derived dopaminergic replacement in Parkinson's disease, now in sham-controlled phase III testing — alongside a large intermediate group with randomized but inconclusive evidence, and a commercially prominent group with little or no human evidence at all. The most rigorously evidenced interventions in the field remain multidomain lifestyle programmes with small effect sizes, while the most heavily marketed remain exosome and platelet-derived products with no demonstrated clinical efficacy and active regulatory warnings.

Two recommendations follow. Scientifically, the field should adopt standardized product characterization, sham-controlled designs and fluid biomarker endpoints as minimum requirements, since these — not biological novelty — are what currently separate advancing platforms from stalled ones. Communicationally, clinicians, sponsors and journals should describe each intervention by its readiness band rather than by its mechanistic aspiration. Biological plausibility is a hypothesis; clinical readiness is a demonstrated position on an evidential path. Conflating the two is the principal reputational risk facing regenerative neurology, and distinguishing them rigorously is the fastest route to therapies that genuinely deserve the name.

Declarations

Ethics approval and consent to participate: Not applicable. This study was conducted exclusively with published scientific literature, public clinical trial registry records and public regulatory documents, and is exempt from CEP/CONEP registration and evaluation under Brazilian National Health Council Resolution CNS No. 510/2016, Article 1, sole paragraph, item VI [16].

Consent for publication: Not applicable.

Availability of data and materials: All data charted in this review derive from publicly available sources cited in the reference list. The complete charting table and the NRI scoring sheet are available from the corresponding author upon reasonable request.

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Registration: This scoping review was not prospectively registered; scoping reviews are not eligible for

PROSPERO registration. The protocol is available from the corresponding author.

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