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Stem-Cell Exhaustion, Cellular Rejuvenation and the Translational Frontier of Geroscience: A Structured Critical Evidence Review of Human and Preclinical Interventions Targeting Biological Aging

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Abstract

Background: Aging biology has become experimentally tractable, and private capital has entered the field at a scale without precedent in geriatric medicine. Whether that tractability has produced clinically meaningful human benefit is a separate question. Stem-cell exhaustion is a recognised hallmark of aging, and cell-based, reprogramming-based and vesicle-based products dominate both the scientific and the commercial imagination of the field.

Methods: This is a structured critical evidence review with protocol-informed narrative synthesis, not a completed systematic review. Retrieval drew on PubMed/MEDLINE-indexed literature, ClinicalTrials.gov (application programming interface version 2), regulatory and guideline documents, corporate securities filings, retraction registries and citation chaining,

with evidence current to 7 September 2026, and was organised by a four-part PICOS framework, a tiered outcome hierarchy, a registry-versus-publication audit and an integrity screen. Outcomes were classified as Tier 1 (clinical), Tier 2 (intermediate/physiological) or Tier 3 (molecular surrogate). Efficacy statements were restricted to primary trial reports and registry records; reviews, corporate disclosures and trade media were used only for context, financing and governance. Quantitative pooling was not performed because intervention classes, populations, product definitions, dose metrics and endpoint tiers were not commensurable. Four procedural limitations are stated at the outset and are not mitigated: the protocol was not registered or published in advance; independent multi-database export, deduplication and duplicate screening were not performed and no PRISMA flow counts exist; formal study-level risk-of-bias assessment was not completed and no domain-level judgements are reported; and certainty was not rated with GRADE.

Results: Within the evidence retrieved for this review, no intervention has been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency for an aging indication, and as of May 2026 the endpoint framework such an application would require was still the subject of expert consensus submissions to FDA rather than settled policy. Human evidence is concentrated in small, short, surrogate-endpoint studies. The largest cell-therapy dataset in aging — allogeneic mesenchymal stromal cells for frailty — comprises a 15-participant dose-escalation phase 1 cohort with a clean one-month safety result and larger phase 2 studies (150 and 158 participants) whose efficacy results remain unposted. The best-documented induced pluripotent stem cell (iPSC) efficacy dataset is a seven-patient open-label Parkinson's disease trial in which no tumorigenicity signal was detected over 24 months, alongside modest motor gains and a doubling of dyskinesia burden. Human partial epigenetic reprogramming is limited to one ongoing 18-participant ocular phase 1 trial with no efficacy data at the census date. Clinical-endpoint results are mixed rather than uniformly negative: a mechanistically supported phase 2b was followed by a failed phase 3 after a regulator-requested change to a patient-relevant endpoint, senolytic bone and randomised rapamycin healthspan trials missed their primary endpoints, and a fisetin trial was stopped for futility, whereas a two-year randomised metformin trial improved a frailty index while remaining null on the Fried criteria in the same population. Three epigenetic clocks disagreed within one randomised caloric-restriction trial; a telomerase gene-therapy publication was retracted; and a listed senolytics company dissolved after a primary-endpoint miss. Private financing is verifiable at large scale, yet no clinical-stage asset with an aging indication was identified at any of the largest privately financed platforms in the sources retrieved.

Conclusions: Biological plausibility, animal rejuvenation, phase 1 safety, surrogate change and demonstrated human efficacy are five distinct evidentiary states; on the evidence retrieved, the field occupies the first four. The binding constraints are endpoint ambiguity, unvalidated surrogates, product and potency definition, delivery and biodistribution, immunological burden, and incentives created by privately held datasets. Healthspan outcomes — autonomy, function, cognition and disease-free survival — should displace biomarker-only claims of age reversal. Journal classification as a critical review or structured evidence review is appropriate; classification as a systematic review would require prospective registration, independent multi-database screening in duplicate, a populated PRISMA flow diagram and completed study-level risk-of-bias assessment.

Keywords

Geroscience; Stem-cell exhaustion; Cellular reprogramming; Senolytics; Healthspan; Regenerative medicine.

Introduction

Aging is the dominant risk factor for the diseases that consume most of the world's clinical resources, and it has become an experimentally addressable process rather than an inert backdrop to pathology. Consolidation of the field around 12 hallmarks-from genomic instability, telomere attrition and epigenetic alterations through cellular senescence and stem-cell exhaustion to chronic inflammation and dysbiosis-supplied a shared target list, defining a hallmark by age-associated manifestation, acceleration of aging when experimentally accentuated, and the opportunity to decelerate, stop or reverse aging by intervening on it [1]. The third criterion is a research programme, not an empirical claim, and that distinction organises this review. For regenerative medicine the framework is not peripheral: stem-cell exhaustion is classified as an *integrative* hallmark, arising when accumulated primary and antagonistic damage can no longer be

compensated [1]. Regenerative failure is therefore a downstream integrator of aging rather than one lesion among many, which is why cell therapy, cellular reprogramming and extracellular-vesicle products have become the field's most visible translational bets and its most commercially exposed ones.

Two structural problems have travelled with the field from bench to clinic. The first is definitional. No single operational definition of aging exists; one geroscience review defines healthspan as maintenance of functional health with increasing age, cautions that lifespan extension does not necessarily demonstrate healthspan extension, and proposes integrative measures such as walking speed because they aggregate balance, strength, cognition and sensory function [2].

The second problem follows from the first. Because aging is not an approved indication, no conventional development pathway exists for an agent whose stated purpose is to slow it, and the regulatory-pathway literature frames the field as facing the absence of an obvious approval route for therapeutics that may slow aging and extend healthspan [3]. As recently as May 2026, a 27-author expert group convened under ARPA-H was still submitting to the US Food and Drug Administration (FDA) a consensus statement on how intrinsic capacity — across locomotor, cognitive, psychological, sensory and vitality domains — might be measured and used as a clinical endpoint and enrichment tool [4]. That document is a proposal to a regulator, not regulatory policy, and must not be read as evidence that such an endpoint has been accepted; its existence nonetheless locates the field's endpoint problem precisely. Around this uncertainty a financing environment has formed with few analogues in geriatric medicine: platform companies launched with multi-billion-dollar commitments, philanthropic funders operating at national-agency scale, and large proprietary datasets that remain unpublished. The popular framing of this environment as "secret science" is imprecise but points at something real — platform opacity, undisclosed negative results, delayed registry reporting, and asymmetric access to datasets that cannot be independently interrogated.

This review addresses four linked questions. What is the best available human evidence for each mechanistic class, and at what outcome tier does it sit? Where do cell-based and reprogramming-based platforms stand? What do the field's null, failed and retracted results teach about endpoint selection, surrogate validity and product definition? And how do capital structure, sponsorship and disclosure practice shape what is known? Its stance is that healthspan — autonomy, function and disease-free survival — is the outcome that matters, that biomarker-only claims of age reversal are hypothesis-generating measurements, and that the five evidentiary states in Section 7.1 are not interchangeable. No intervention discussed here ends aging, reverses aging clinically, or is approved for an aging indication anywhere in the retrieved record.

Methods

Design, reporting standard and registration status

This work is a structured critical evidence review with protocol-informed narrative synthesis. It is not a completed systematic review, and it is not presented as one. PRISMA 2020 was used as a reporting aid rather than as a compliance claim, its items being applicable to reviews with or without quantitative synthesis as well as to reviews of intervention effects [5]. Four procedural facts define what was and was not done, and they are repeated in Section 8 without mitigation. First, the protocol was not registered

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and not published in advance; the framework below was written to organise this review and is reported descriptively, not as evidence of prospective specification. Second, retrieval did not include independent record export and deduplication from Embase, Scopus, Web of Science or Cochrane CENTRAL, and screening was conducted by a single reviewer rather than in duplicate, so no PRISMA flow counts exist and none are reported. Third, formal study-level risk-of-bias assessment was not completed, and no domain-level judgements are reported for any included study. Fourth, certainty of evidence was not rated. Journal classification as a critical review or structured evidence review is therefore appropriate; reclassification as a systematic review would require prospective registration [6], independent multi-database screening in duplicate, a populated flow diagram and completed risk-of-bias assessment.

Review questions and outcome hierarchy

Because aging is not an approved indication, the review was organised around one master question and three sub-questions, each with its own eligibility rules.

Master question (PICOS): Population: humans with mean or median age of at least 18 years, in one of three populations — generally healthy older adults; adults with an age-related disease used as a tractable indication; or adults with a progeroid syndrome. Intervention: any intervention whose stated mechanism targets one or more of the 12 hallmarks [1], grouped into the mechanistic classes used in Section 3 and Table 1, from senolytics and cell-based therapies through partial epigenetic reprogramming to extracellular vesicles (EVs) and xenogeneic organ replacement; class boundaries are analytic conveniences rather than a validated taxonomy, and Table 1 reports individual interventions rather than a fixed class count. Comparator: placebo, sham, standard of care, active comparator, ad libitum control, or — for single-arm designs — within-participant baseline, recorded as "no comparator". Study designs: randomised, non-randomised and single-arm interventional studies, with animal work in a separately labelled preclinical stream that never contributes to human efficacy statements. Timing: at least four weeks of exposure or follow-up for pharmacological and biologic interventions, none for single-dose cell or gene therapies.

Outcome hierarchy. Tier 1 (clinical): mortality, incident age-related disease, disability, hospitalisation, validated physical function, visual acuity, forced vital capacity, cognition and frailty status. Tier 2 (intermediate/physiological): body composition, bone mineral density and turnover markers, insulin sensitivity, vascular measures and immune-cell subsets. Tier 3 (molecular surrogates, exploratory only): epigenetic-clock estimates with version specified, senescence markers including p16INK4a messenger RNA and senescence-associated secretory phenotype (SASP) panels, NAD+, telomere length and omics signatures. Safety: all adverse and serious adverse events by arm, with harms of interest including neoplasia or teratoma, thrombocytopenia, hepatotoxicity, infection, rejection, dyskinesia for central nervous system cell therapy, and QTc prolongation.

Sub-questions. Three organised the appraisal: whether any mammalian lifespan or healthspan effect is replicated across sites, sexes and genetic backgrounds [7]; whether the clock underlying any epigenetic-age claim is a validated surrogate measured with reliability-corrected principal-component versions [8,9,10]; and whether the intervention was delivered under an investigational new drug (IND) application or equivalent, prospectively registered, and consistent with International Society for Stem Cell Research

(ISSCR) Recommendations 3.1.1 and 3.5.1 [11].

Information sources, two-stream source rules and eligibility

Retrieval used three channels and closed on 7 September 2026, the census date for every status statement in this review: PubMed/MEDLINE-indexed records and publisher full texts; trial registries, principally ClinicalTrials.gov retrieved through its application programming interface version 2, with every value quoted from the record for the corresponding NCT identifier [12], supplemented by the WHO International Clinical Trials Registry Platform, which is not itself a registry and does not accept registrations [13], and Japanese and Chinese registry identifiers cited in primary publications; and primary institutional and corporate documents, comprising FDA announcements, warning letters and safety alerts, European Medicines Agency pages, ISSCR guidelines, WHO ICD-11–related literature, US Securities and Exchange Commission (SEC) EDGAR filings retrieved by central index key, company releases and retraction notices, with backward and forward citation chaining from anchor references in each class.

Two source streams were kept separate, and the distinction governs what any given citation may support. In the efficacy stream, every quantitative human efficacy or safety statement is drawn from a primary trial report, a registry record, or a regulatory document reporting trial result; systematic reviews are cited for their own screening and appraisal output, not for human effect estimates. In the preclinical stream a narrower allowance operates: narrative reviews may be cited for contextual synthesis — the shape of a literature, the range of reported outcomes, the presence or absence of a reported harm — but never as sole support for a pivotal effect size, and any review-only figure is labelled as such where used. Where a value was first located through a review or commentary, the primary publication was retrieved and cited in its place — most consequentially for the mTOR-inhibitor infection-prevention programme, whose phase 2b and phase 3 results are cited to the primary randomised report [14] and its phase 2a predecessor [15], with the commentary cited only for editorial interpretation [16]. Where a primary source could not be verified, the quantitative assertion was removed or reduced to a qualitative statement. In the context stream — financing, corporate status, governance and market structure — securities filings, company statements, law-firm announcements and trade media are cited, each labelled by evidence category in (**Table 5**). Context-stream sources are never used to support a claim about clinical efficacy or safety. Retracted publications are catalogued separately and contribute to no effect estimate.

The PubMed/MEDLINE strategy combined a population/concept block of controlled vocabulary and free-text terms for aging, healthspan, longevity, frailty, senescence, geroscience and stem-cell exhaustion, an intervention block enumerating each class and its principal agents, and a design block applied only to the clinical stream; the animal stream was run separately. No language restriction was applied, a deliberate departure from the English-only restriction of the principal published systematic review of rapamycin in humans, because the iPSC and cell-therapy literature is substantially Japanese- and Chinese-registered [17]. Registry retrieval ran 21 query terms and deduplicated by NCT identifier, extracting status, reason stopped, phase, enrolment count and type, allocation, masking, sponsor, interventions, conditions, primary outcomes, dates and the results-posted flag [12].

Eligible were human interventional studies of any design and language, including single-arm designs, with at least five participants — a threshold aligned with that systematic review, so that the two remain

comparable [17] — together with registered trials carrying posted results but no publication, mammalian lifespan or healthspan studies for the preclinical stream, and regulatory and guideline documents for the governance stream. Excluded were smaller case series, unless they constitute the only human evidence for a modality and are labelled as such; oncology and transplant-rejection indications, unless the outcome was an aging biomarker; and narrative reviews and commentaries as sources of effect estimates.

Data extraction, registry audit, appraisal approach and readiness framework

Extraction covered registration and authorisation identifiers, sponsor class, funding and competing interests verbatim, enrolment and its actual-versus-estimated flag, masking, product identity including cell source, dose unit and potency assay, compounding status, registered versus published primary endpoint, effect estimates, harms by arm, and clock version. A registry-versus-publication discrepancy audit sought numerical divergence between registered and published values, and reporting lag, defined as a record whose primary completion date has passed without posted results; both were found and are reported in Section 3.1.

Formal risk-of-bias assessment was not completed: No RoB 2, ROBINS-I or SYRCLE domain judgement was made for any study, and none is reported; the appraisal in this review is narrative and study-level bias is discussed qualitatively where the design makes a specific threat evident. The tools appropriate to each stream for the confirmatory version are Cochrane RoB 2 [18], ROBINS-I, noting the revised V2 draft released on 30 November 2025 [19], and SYRCLE's tool [20]. Five recurring features were treated narratively as reasons for caution: compounded or non-good-manufacturing-practice product; no concurrent control where the claim is biological-age reversal; a single non-principal-component clock used as an efficacy endpoint; positive findings confined to post hoc subgroups; and sponsor identity coinciding with the consumer vendor. GRADE was not applied, because it requires duplicate assessment and outcome-level pooling that were not performed; where it is applied in the confirmatory version, indirectness should be rated serious or very serious for any Tier 3 surrogate [10].

A five-level translational-readiness scale summarises class-level maturity: TR1, mechanism in vitro or invertebrate only; TR2, rodent efficacy with unresolved reproducibility questions; TR3, rodent efficacy replicated across sites or supported by non-human primate data, with an unclear route to good-manufacturing-practice production; TR4, IND or authorisation cleared with phase 1 or 2 studies on surrogate endpoints; TR5, randomised clinical-endpoint evidence in an approvable indication. This scale is a conceptual organising framework created for this review, not a validated instrument, and it maps imperfectly onto behavioural and nutritional interventions, as noted in (**Table 1**).

Intervention class	Best human evidence (design, n)	Primary endpoint and key result	Principal limitation	Status	TR
Senolytics, dasatinib + quercetin (bone)	Open-label phase 2 RCT, n = 60 postmenopausal women, senescence-enriched [25]	CTx at 20 weeks −4.1% vs −7.7% control, **P = 0.611 — primary endpoint not met**; P1NP +16% at 2 and 4 weeks	Open-label; Tier 2 surrogate; AEs 77% vs 17%; positive findings tertile-restricted	H2, primary not met	TR4

Senolytics (pulmonary fibrosis)	Phase 1 randomised placebo-controlled pilot, n = 12 [45]	No meaningful between-group difference in frailty, pulmonary or physical function	Authors state study under-powered; 3-week exposure	H2, null	TR4
Senolytics (Alzheimer's disease)	Phase 1 open-label, 5 completers [46]	Cognitive and neuroimaging endpoints unchanged; CSF IL-6 ↑ (P = 0.008) and GFAP ↑ (P = 0.028)	n = 5, no control; quercetin undetectable in CSF; adverse biomarker direction	H1	TR4
Fisetin	Phase 2, n = 20 (NCT04537299) [12]	**Stopped for futility** by DSMB and NIA	No efficacy signal; several ongoing trials unreported	H-neg	TR4
BCL-xL senolytic, intravitreal	Phase 2b active-controlled RCT, n = 52 actual (NCT06011798) [12]	**No efficacy or safety value reported: the only accounts of the results are corporate documents, and no publication or posted registry results table was retrieved**	Programme discontinued and sponsor dissolved 26 Sep 2025 [93]; earlier knee-OA failure, press-reported [78]	Results not available in any evidentiary source	TR4 (discontinued)
Senomorphics	None identified	—	No human trial verified	n.a.	TR1
MSC therapy for aging frailty	Phase 2b RCT, n = 150 (NCT03169231) [12]; published phase 1, n = 15 [26]	Phase 1: no treatment-emergent SAEs at 1 month at 20–200 × 10^6 cells; **phase 2b efficacy unavailable — no posted results**	Largest trials unreported; heterogeneous products; no potency standard	H2/H3 with unreported outcomes	TR4
iPSC-derived dopaminergic cells	Open-label phase I/II, 7 transplanted / 6 evaluated [32]	MDS-UPDRS III OFF −9.5 points (−20.4%); putaminal ^{18}F-DOPA K_i +44.7%; **UDysRS +12.3 points (+116.4%)**; 0 tumours	No control; 6 evaluable; immunosuppression AEs 42.9%; not an aging indication	H1	TR4
Partial epigenetic reprogramming (OSK)	Phase 1 recruiting, 18 estimated (NCT07290244) [12]	**No human data exist**; primary completion projected May 2027	Ocular route only; preclinical claims from small, largely single-laboratory studies	H1 ongoing; otherwise P	TR4
Plasma exchange / plasma dilution	Uncontrolled clinical study [60]	Proteomic and senescence-marker shifts; C3 and C1q fall by ~half then return within ~1 month with no lasting effect	No control; small heterogeneous sample; published correction; registry records stale	H1	TR3
Young-donor plasma	No credible trial; 2,120-participant record inactive since 2018 (NCT03353597) [12]	No efficacy evidence; IND required for these indications [61]	Commercially offered without evidence	DTC	TR1
Telomerase gene therapy	None legitimate; patient-paid AAV-hTERT record with blank design fields (NCT04133649) [12]	Mouse: longevity increase without increased cancer [62]	Retracted human-adjacent publication [64]; human genetics complicates "longer is better" [63]	P + DTC + RETRACTED	TR2
Rapamycin / rapalogs (healthspan)	Phase 2 double-blind RCT, 114 analysed (NCT04488601) [12,23]	**Visceral adipose tissue P = 0.942 — primary endpoint not met**; lean tissue mass in women on 10 mg +6.19 (95% CI 0.88–11.51)	Decentralised; compounded drug at ~⅓ exposure; DTC sponsor; subgroup-only positives	H2, primary not met	TR4

mTOR inhibition for immune function	Phase 2b n = 652 positive; **phase 3 n = 1,024 failed** [14]	Phase 2b OR 0.601 (90% CI 0.391–0.922), P = 0.02; **phase 3 OR 1.07 (90% CI 0.80–1.42), P = 0.65, primary endpoint not met**	Endpoint changed at regulator's request [16]; target engagement retained [15]	H3 → H-neg	TR4 (dormant)
Metformin	2-year double-blind RCT, 141 analysed [51]	Frailty index −0.0494/month (95% CI −0.0918 to −0.0071), P = 0.0222; **Fried criteria null**	Instruments discordant; blunts resistance-training adaptation [50]	H2, mixed	TR4
NAD precursors	Crossover RCT, 24 completers [52]; phase 1 RCT n = 20 [53]	Up to 5-fold blood NAD^+ rise; no moderate or severe AEs at 3,000 mg/day	No clinical healthspan endpoint met; gait-speed trial reports 2027	H2, pharmacodynamic	TR4
Caloric restriction (25% prescribed)	Phase 2 RCT, 218 started [54]; methylation analysis n = 197 [55]	Achieved restriction 11.9%; −7.5 kg; LDL and TC:HDL fell P < 0.0001; DunedinPACE d = −0.29/−0.25; **PhenoAge and GrimAge null**	Achieved dose half of prescribed; clocks disagree; young cohort; **no clinical-event endpoint**	H2 (randomised, Tier 2 intermediate outcomes only)	Not classifiable on the TR scale: behavioural intervention without an IND pathway; **TR5 not met, since no approvable clinical endpoint was tested**
Autophagy induction (spermidine)	Phase 2b RCT, n = 100 [57]	Dose ~0.9 mg spermidine/day; **primary cognitive outcome and P value not captured in this evidence set — no efficacy conclusion drawn**	Dose orders of magnitude below preclinical regimens; single centre	H2, outcome not extracted	TR3
Taurine	Trials completed without posted results (NCT06613542) [12]	Biomarker premise refuted by cross-species longitudinal analysis [59]	Foundational claim contradicted [58]	P, premise refuted	TR2
Urolithin A	Sponsor RCT n = 66 (NCT03283462); NIA RCT n = 180 recruiting (NCT06274749) [12]	Sponsor trial results not posted	Sponsor-dominated evidence; no aging endpoint	H2, unreported	TR4
Immune / thymic rejuvenation	Uncontrolled, n = 9 [66]; extension trial NCT04375657 unreported [12]	Epigenetic age ≈ −1.5 y; thymic fat-free fraction improved in 7/9 (P = 8.57×10^{-17})	No control; not preregistered; multi-drug; extreme baseline clock offsets; extension trial unreported	H1	TR3
Gene therapy / editing for aging	Ocular OSK phase 1 (NCT07290244); 12-participant AAV-follistatin study (NCT07443826) [12]	No efficacy data	Vector dose translation unresolved (~6×10^{13} vg/kg in mice) [39]; retracted precedent [64]	P / H1	TR3–TR4
Mitochondrial interventions	Human transplantation only in acute cerebral ischaemia (NCT04998357) [12]	MitoQ male median lifespan +2% (P = 0.91) in reference platform [7]	No aging indication in humans	P	TR2
Microbiome (faecal transfer)	None in human aging	Progeroid mice: healthspan and lifespan extension [70]	Progeroid models only	P	TR2
Extracellular vesicles / exosomes	7 published clinical studies, 14 ongoing as of Sep 2022, **none in aging** [21]	No dose consensus (μg vs particles vs cell equivalents)	No FDA-approved exosome product; documented serious AEs [68]	H1/H2 in other indications; DTC in aging	TR2

Xenogeneic organ replacement	Two phase 1/2 trials recruiting (NCT06878560, NCT07224763), 50 estimated each [12]	No results yet	Heavy immunosuppression; addresses organ supply, not aging	H1 ongoing	TR4
AI-discovered agent in an age-related disease	Phase 2a RCT, n = 71 [72]	**Primary endpoint was safety**; exploratory FVC +98.4 mL (95% CI 10.9–185.9) at 60 mg QD	Liver-injury discontinuations up to 22.2%; 22 missing spirometries; single-country cohort	H2	TR4

Table 1: Evidence hierarchy by intervention class: best human evidence, primary endpoint, principal limitation, status and translational readiness.

Synthesis approach and integrity screen

Quantitative pooling was not performed. Structured narrative synthesis was used because the material is non-commensurable along several axes simultaneously: classes differ mechanistically; populations range from healthy volunteers to patients with end-stage organ disease; two studies nominally testing the same cell or vesicle product may not be testing the same product; dose metrics are non-interchangeable, most acutely for EVs [21]; and pooling a Tier 3 methylation estimate with a Tier 1 functional outcome would produce a number with no interpretable referent. Within-class pooling would be defensible where at least three randomised trials share a Tier 1 or Tier 2 outcome, and on the retrieved record no intervention class meets that bar for a Tier 1 outcome. Synthesis therefore proceeds by mechanistic class, with outcome tier, comparator type, primary-endpoint status and product definition tabulated, and preclinical lifespan changes reported with sex- and site-specific values rather than pooled [7].

Three integrity procedures were applied throughout. Retracted publications were identified through Retraction Watch and journal notices and catalogued separately. Corporate identity was verified against SEC central index keys before any financial statement was attributed, since EDGAR contains two registrants trading under variants of the name "Unity" and only Unity Biotechnology, Inc., central index key 0001463361, is the senolytics developer [22]. Claims appearing only in secondary media were classified as media narrative and excluded from all clinical-evidence statements; the most consequential example is discussed in Section 4.6.

Results

Numerical detail for each class is tabulated in (**Tables 1–4**); the prose reports only decisive values and their interpretation. All registry statements are quoted from records retrieved on 7 September 2026 [12].

The shape of the human evidence base

Five structural features recur across every mechanistic class, and the underlying records are tabulated in (**Table 2**). Enrolment is small: only three studies in the curated registry sample recorded 140 or more actual participants — allogeneic MSCs in aging frailty at 150 (NCT03169231) and 158 (NCT04919135) and metformin at 141 (NCT02570672), the next largest being rapamycin at 129 (NCT04488601) — and the modal trial enrols under 60 for under a year. Reporting is sparse and asymmetric: posted results cluster among academic senolytic and industry ophthalmology studies, while the two largest cell-therapy studies in frailty and the largest randomised rapamycin study carry none. Phase labels are unreliable as a quality signal: a direct-to-consumer combination study is recorded as phase 3 with 30 estimated participants

(NCT07475546) and a plasma-exchange study as phase 3 with 40 and status "unknown" (NCT06534450); enrolment, masking and comparator fields should be read instead. Stale and abandoned records are common: a young-plasma study registered with 2,120 estimated participants was last updated in January 2018, and three aging-directed studies were withdrawn before enrolling anyone [12]. Registry and publication diverge: the rapamycin trial's record lists 129 actual participants against 114 completers in the publication and 123 in the preprint [12,23,24], and the senolytic bone trial's record lists 74 against 60 randomised [25]. Reporting lag is equally concrete: a thymic-regeneration extension trial and an everolimus aging study have both passed primary completion without results [12].

Trial / identifier	Intervention	Phase and status	Enrolment (type)	Population	Primary endpoint	Key result or reporting status
NCT02065245, CRATUS [12,26]	Allogeneic bone-marrow MSC, 20/100/200 × 10^6 IV	Phase 1/2, completed	**Registry 65 (actual); published safety findings derive from the 15-participant phase 1 cohort only**	Aging frailty, 60–95 y	Treatment-emergent SAEs at 1 month	**In the 15-participant phase 1 cohort:** no treatment-emergent SAEs at 1 month; no donor-specific immune reaction to 6 months. No outcome data are available for the remaining registry participants
NCT03169231 [12]	Allogeneic MSC	Phase 2b, completed	150 (actual)	Aging frailty, 70–85 y	Not extractable from public record	**No results posted**; primary completion Sep 2021
NCT04919135 [12]	MSC therapy	Phase 1/2, completed	158 (actual)	Frailty, 60–85 y	Not extractable from public record	**No results posted**
jRCT2090220384 / UMIN000033564 [32]	Allogeneic iPSC-derived dopaminergic progenitors	Phase I/II, open-label, completed	7 transplanted (6 evaluated)	Parkinson's disease, 50–69 y	Safety over 24 months	73 AEs (72 mild); 0 tumorigenicity signals; MDS-UPDRS III OFF −9.5 points; UDysRS +12.3 points
NCT07290244 [12]	ER-100, OSK partial reprogramming, ocular	Phase 1, recruiting	18 (estimated)	Open-angle glaucoma or NAION, 40–85 y	Safety	**No data**; primary completion projected May 2027
NCT04488601, PEARL [12,23]	Compounded rapamycin 5 or 10 mg/week, 48 weeks	Phase 2, completed	129 registry (actual); 114 analysed	Healthy adults 50–85 y	Visceral adipose tissue	**Primary endpoint not met**, P = 0.942; lean tissue mass benefit in women on 10 mg only
RTB101 phase 3 [14]	mTORC1 inhibitor	Phase 3	1,024	Adults ≥ 65 y, non-smokers without COPD	Clinically symptomatic respiratory illness	**Primary endpoint not met: OR 1.07 (90% CI 0.80–1.42), P = 0.65**
NCT04313634 [25]	Intermittent dasatinib + quercetin	Phase 2, completed	74 registry (actual); 60 randomised	Postmenopausal women 60–90 y, senescence-enriched	CTx at 20 weeks	**Primary endpoint not met**, P = 0.611
NCT04537299, COVID-FIS [12]	Fisetin	Phase 2, terminated	20 (actual)	Nursing-home residents ≥ 65 y	—	**Stopped for futility** by DSMB and NIA

NCT06011798, ASPIRE [12,94]	Foselutoclax (UBX1325) vs aflibercept, intravitreal	Phase 2b, completed	52 (actual)	Diabetic macular oedema	BCVA, average of weeks 20 and 24	**No results posted; outcome described only in sponsor communications, from which no value is taken** at primary analysis; non-inferior at week 36
NCT00427193, CALERIE [54,55]	25% prescribed caloric restriction, 2 years	Phase 2 RCT	218 started	Healthy adults 21–50 y	Cardiometabolic risk factors (exploratory outcomes reported)	Achieved 11.9% restriction; LDL and TC:HDL fell $P < 0.0001$; clocks discordant
NCT02570672 (**registry record consistent with, not confirmed identical to, the publication, which states no registration number**) [12,51]	Metformin up to 2,000 mg/day, 24 months	Phase 2, completed	141 (actual)	Adults ≥ 65 y with glucose intolerance	Frailty	Frailty index $P = 0.0222$; **Fried criteria null**
NCT04375657, TRIIM-X [12]	rhGH + DHEA + metformin	Phase 2, recruiting	85 (estimated)	Adults 40–80 y	Thymic and immune measures	**No results posted**; listed completion Dec 2025
NCT06208527, NADage [12]	Nicotinamide riboside 2,000 mg/day, 52 weeks	Phase 2, recruiting	100 (estimated)	Adults ≥ 75 y	**Change in 6-m gait speed** (Tier 1)	Primary completion projected Dec 2027
Rentosertib phase 2a [72]	Generative-AI-discovered TNIK inhibitor	Phase 2a RCT	71 randomised	Idiopathic pulmonary fibrosis, ≥ 40 y	Proportion with ≥ 1 treatment-emergent AE	TEAEs 70.6–83.3%; liver-injury discontinuations up to 22.2%; exploratory FVC +98.4 mL at 60 mg QD

Table 2: Representative human trials in aging-directed intervention research (registry values retrieved 7 September 2026).

Stem-cell exhaustion and cell-based regenerative interventions

Mesenchymal stromal cells in aging frailty are the largest human cell-therapy dataset directed at an aging phenotype, and the clearest illustration of the reporting problem. The published phase 1 was a non-randomised dose-escalation study in 15 frail patients given allogeneic bone-marrow MSCs at 20, 100 or 200 million cells intravenously, five per dose; the primary outcome, treatment-emergent serious adverse events at one month, occurred in none, and no clinically significant donor-specific immune reaction occurred within six months [26]. These findings derive from that 15-participant phase 1 cohort, not from the 65 participants recorded as actual enrolment for the parent registry record NCT02065245 [12]. Beyond that the record thins abruptly: the phase 2b of the same product enrolled 150 participants, reached primary completion in September 2021 and carries no posted results, and a phase 1/2 on vaccine response (62), an Alzheimer's extension (50) and a Vietnamese phase 1/2 (158) likewise have none [12]. For the three largest MSC-in-frailty studies — 150, 158 and 62 participants — no efficacy effect size is available from the registry, and none was verified from a peer-reviewed publication.

Haematopoietic stem cells supply the field's most striking recent preclinical rejuvenation result and its most instructive retraction. Antibody-mediated depletion of myeloid-biased HSCs rejuvenated aged

immunity in mice, with functional challenge by vaccination and by pathogenic Friend retrovirus [27]. In the same compartment, Nature retracted in its entirety a 2010 report that systemic signals regulate ageing and rejuvenation of blood stem-cell niches, three authors requesting retraction after re-examination raised serious concerns with reported data on osteopontin-positive niche cells, the first author declining to sign [28].

Neural, muscle and epithelial compartments are preclinical throughout: neural stem-cell rejuvenation is supported across several niches, within a review that also records conflicting human hippocampal-neurogenesis findings [29]; ageing deregulates muscle satellite cells through cell-intrinsic and niche axes [30]; and aging reduces intestinal stem-cell self-renewal with reduced canonical Wnt signalling, while aged human organoids respond to WNT3a [31]. No human rejuvenation trial was identified in any of these three compartments, so the clinical marketing of stem-cell interventions for neurological and musculoskeletal aging has no corresponding human efficacy evidence.

Induced pluripotent stem cell–derived therapies

iPSC-derived products have reached patients for neurodegenerative disease, not aging, and no iPSC product with an aging indication was identified in the registry. The best-documented efficacy dataset is an open-label, single-centre, uncontrolled phase I/II trial of allogeneic iPSC-derived dopaminergic progenitors in Parkinson's disease (jRCT2090220384, UMIN000033564), in which seven patients were transplanted and six evaluated over 24 months [32]. Doses were 2.1–2.6 × 106 cells per hemisphere in three patients and 5.3–5.5 × 106 in four; adverse events occurred in 7 of 7, totalling 73 events, 72 mild and one moderate, with no serious event requiring hospitalisation or resulting in death. No tumorigenicity signal was detected on any measure applied over 24 months: no tumour-like enlargement, no increased 18F-fluorothymidine accumulation, no appreciable translocator-protein tracer uptake, and in corresponding rat grafts Ki-67 positivity below 1.0% with no overgrowth [32]. This is limited reassurance from seven patients over 24 months, not evidence that the tumorigenicity risk of pluripotency-derived products is resolved. The product was characterised as approximately 60% dopaminergic progenitors and 40% dopaminergic neurons with no TPH2-expressing cells — composition reporting that should be the norm and frequently is not.

Efficacy was modest and mixed: MDS-UPDRS part III OFF improved in 4 of 6 evaluable patients (mean −9.5 points) and total putaminal 18F-DOPA Ki rose 44.7%, with a dose gradient of +7.0% against +63.5%. Against these gains the Unified Dyskinesia Rating Scale total worsened by 12.3 points (+116.4%) in 6 of 7 patients, and potentially tacrolimus-associated adverse events occurred in 3 of 7 (42.9%), including two renal-impairment events [32]. The single-patient autologous precedent is instructive chiefly for its regulatory route, an FDA expanded-access IND [33]; eight further phase 1 or 1/2 iPSC-derived neural programmes were identified, none with an aging indication [12]. iPSC-derived therapy has therefore produced limited 24-month reassurance on tumorigenicity in seven patients; it has not demonstrated efficacy in a controlled design, its benefit carries a large increase in dyskinesia burden, and its immunosuppression requirement imports a quantifiable harm; extrapolation to an aging indication would be unjustified.

Partial epigenetic reprogramming

Preclinical. In vivo partial reprogramming ameliorates hallmarks of aging and prolongs lifespan in premature-aging mice [34], restores vision in glaucoma, optic-nerve-crush and aged-mouse models when OSK is delivered virally with c-Myc omitted [35], and shifts multi-tissue molecular profiles in wild-type mice, with explicitly small group sizes [36]. An inducible-epigenomic-change model further showed that faithful DNA repair itself advances aging at physiological, cognitive and molecular levels — including exdifferentiation, senescence and clock advancement — reversibly by OSK [37]. Two strategies address exposure rather than dose: restricting OSK to stressed and senescent cells through a Cdkn2a-promoter construct [38], and systemic dual adeno-associated virus serotype 9 delivery in 124-week-old mice at approximately 6 × 1013 vector genomes/kg [39]. A narrative review describes lifespan extension in progeroid and very old wild-type mice with frailty-index improvement, and no teratoma formation under prolonged induction [40]; it is used only for contextual synthesis, and no pivotal effect size rests on it. The lifespan, frailty and multi-tissue findings are attributed to their primary reports [34,36,39], none of which displays a complete set of group sizes and exact lifespan values publicly — which is why a review-level summary circulates in place of primary numbers. Two cautions follow: these are small, largely single-laboratory studies, and progeroid gains measure correction of a monogenic defect rather than modification of normative aging.

Human. Human partial reprogramming consists of one trial. Life Biosciences reports that its OSK platform's ER-100 is the first epigenetic-reprogramming therapy cleared to enter human trials, with authorisation to proceed on 15 January 2026 and the phase 1 beginning in early 2026 in open-angle glaucoma and non-arteritic anterior ischaemic optic neuropathy [41]. The registry record (NCT07290244) describes a recruiting phase 1 with 18 estimated participants aged 40–85, primary completion projected May 2027 [12]. This is the field's pivotal human data point, and it contains no efficacy information. Within the evidence retrieved for this review to 7 September 2026, no human efficacy data for partial epigenetic reprogramming were identified in any tissue or at any dose, and no retrieved source supports a claim that reprogramming has rejuvenated a human being. Because the search was not an exhaustive multi-database screen (Section 8.1), this is an absence in the retrieved record rather than a demonstrated absence in the world literature.

Cellular senescence, senolytics and senomorphics

Senescent cells enter an essentially irreversible cell-cycle arrest while remaining viable, accumulate with aging and frailty, and act largely through the SASP, which comprises pro-inflammatory, pro-apoptotic and pro-fibrotic factors in 30–70% of senescent cells; above a threshold, self-amplifying spread is proposed to outpace immune clearance, producing inflammaging [42]. The counterweight is explicit in the hallmark's synthesis: limited, spatially confined senescence suppresses oncogenesis and improves wound healing, so senolysis is a trade-off rather than a subtraction [1].

Dasatinib plus quercetin shows a consistent pattern across four indications — feasibility met, mechanism partially demonstrated, clinical endpoints not met (Tables 1 and 4) [43,44,45]. The most instructive is an open-label phase 1 in mild Alzheimer's disease with five completers, in which quercetin was not detected in cerebrospinal fluid at all, cognitive and neuroimaging endpoints did not differ from baseline, and cerebrospinal-fluid interleukin-6 and glial fibrillary acidic protein both increased (P = 0.008 and P = 0.028) [46] — a warning against assuming that a peripherally validated senolytic mechanism transfers to the

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brain.

The most rigorous senolytic trial here is a 20-week open-label randomised phase 2 in postmenopausal women, enriched by T-cell p16INK4a messenger RNA above the 95th percentile of young controls, under IND 145558 [25]. The primary endpoint was missed: CTx at 20 weeks changed by −4.1% against −7.7% in controls, P = 0.611. P1NP rose 16% at two and four weeks before falling at 20 weeks, and in the highest senescence-burden tertile P1NP rose 34% at two weeks and radius bone mineral density rose 2.7% at 20 weeks (P = 0.004). Adverse events occurred in 77% of treated women against 17% of controls, with one withdrawal for QTc prolongation [25]. The National Institute on Aging's summary records no between-group difference in either bone marker by 20 weeks [47].

A phase 2 of fisetin in nursing-home residents was terminated, the registry recording that the data and safety monitoring board and the National Institute on Aging stopped it for futility (NCT04537299), while other fisetin trials remain active [12]. The intravitreal BCL-xL senolytic programme, analysed in Section 4.4, carries an on-target class liability, since BCL-xL inhibition causes thrombocytopenia, which is why proteolysis-targeting chimeras were developed and a local route chosen [48]. No human senomorphic trial was verified; the class is a gap in the human record rather than a body of negative evidence.

Nutrient-sensing pharmacology

mTOR inhibition. The strongest preclinical dataset in geroscience is the multi-site heterogeneous-mouse lifespan programme, in which microencapsulated rapamycin at 42 ppm begun at 20 months extended median lifespan by 11% in males (P = 0.0007) and 15% in females (P < 0.0001), while a three-month exposure gave 11% in males (P = 0.024) but only 4% in females (P = 0.15, not significant) [7]. Two features matter as much as the headline: four comparator compounds on the identical platform were null (17-DMAG +9%, P = 0.12; minocycline +5%, P = 0.99; β-guanidinopropionic acid −1%, P = 0.73; MitoQ +2%, P = 0.91, all in males), and site heterogeneity was large, the male cycled-rapamycin median change ranging from −5% to +41% across three sites [7]. A double-masked randomised placebo-controlled canine trial is under way but embargoed [49].

The human record is thinner by orders of magnitude: a published systematic review included 19 articles from 11,717 deduplicated records, rating risk of bias high in four and of some concern in 11 [17]. The largest randomised rapamycin healthspan trial analysed 114 completers over 48 weeks under a direct-to-consumer sponsor, and its interpretation is dominated by product definition, since the compounded drug achieved approximately one-third the blood concentration of commercial rapamycin at 24 hours; the primary endpoint was not met (visceral adipose tissue, P = 0.942), a lean-tissue subgroup finding in women on 10 mg carried a confidence interval spanning 2.42 to 323.7 and so estimates nothing, and no other significant effects were observed [23].

The decisive human lesson comes from a different agent, and it is taken here from the primary randomised report rather than from commentary. In the phase 2b of the mTORC1 inhibitor RTB101, the proportion of participants with one or more laboratory-confirmed respiratory tract infections was lower on RTB101 10 mg once daily than on pooled placebo (34 of 176, 19%, versus 50 of 180, 28%; odds ratio 0.601, 90% confidence interval 0.391 to 0.922, P = 0.02), while the RTB101-plus-everolimus comparison did not reach

significance [14]. FDA then requested a change in primary endpoint before phase 3, on the stated concern that laboratory confirmation of an infection was not relevant to how patients feel and function [16]; in the phase 3, RTB101 10 mg once daily did not reduce clinically symptomatic respiratory illness (134 of 511, 26%, versus 125 of 510, 25%; odds ratio 1.07, 90% confidence interval 0.80 to 1.42, P = 0.65) [14]. The phase 2a predecessor had shown reduced reported infections and improved influenza-vaccination response with low-dose TORC1 inhibition [15], so target engagement was not the failure point.

Other nutrient-sensing agents contribute one methodological lesson each (Table 1). Metformin altered skeletal-muscle transcriptome adaptations to resistance training — an interference signal, not a benefit [50] — and over two years improved a frailty index (P = 0.0222) while remaining null on the Fried criteria in the same randomised population 51: a discordance between instruments rather than a drug failure. The publication does not state a registration number; the registry record NCT02570672 is consistent with, not confirmed identical to, the published trial, and is described that way throughout [12]. No registry record was retrieved for the Targeting Aging with Metformin trial, and no facts about it are asserted [12]. Nicotinamide riboside is safe to 3,000 mg/day but unproven on any clinical endpoint, its first Tier 1 test reporting from December 2027 [12,52,53]. Caloric restriction at 25% prescribed, achieving 11.9%, lowered weight and lipids [54] yet produced discordant clocks in one randomised sample — principal-component PhenoAge and GrimAge null, DunedinPACE d = −0.29 and −0.25 — with the investigators stating that effects were small and a conclusive test requires long-term disease and mortality follow-up [55,56]. Spermidine was tested at approximately 0.9 mg/day, orders of magnitude below rodent regimens; the primary cognitive outcome and its P value were not captured in the evidence set assembled for this review, so no efficacy conclusion is drawn, and an exposure at that level would not test the mechanism in any case [57]; and taurine's founding premise was refuted by longitudinal cross-species data showing that circulating taurine often increased or remained constant with age, although trials proceeded and results are unposted [12,58,59].

Systemic milieu, telomeres, and immune and thymic rejuvenation

Plasma. Therapeutic plasma exchange with 5% albumin replacement was studied in individuals aged 46–77 with proteomics of 507 proteins; complement C3 and C1q fell by roughly half immediately after a procedure but returned to baseline about a month later, with no significant lasting effects across three rounds [60]. The study is uncontrolled, small and heterogeneous and carries a published correction; its title claims biological-age reduction while its strongest findings are proteomic. FDA stated in February 2019 that establishments were offering young-donor plasma infusions at up to thousands of dollars per infusion for indications ranging from normal aging to dementia, and that administration outside the recognised Circular of Information requires an active IND [61].

Telomeres. Telomerase gene therapy in aged mice was reported to delay aging without increasing cancer [62], but Mendelian randomisation in 379,758 UK Biobank participants found genetically determined telomere length associated with age-related outcomes in both directions, so "longer is better" is not defensible [63]. The human translational record here is dominated by an integrity failure and a governance failure. A 2022 report of intranasal and injectable gene therapy for healthy life extension was retracted after the sponsoring university requested it following internal review of data discrepancies; the article discloses that the work was fully funded by a commercial sponsor owning the pending patent, with an

author on that sponsor's board, and reporting on the retraction records that in 2021 the company sent six dementia patients to Mexico for injections of the experimental treatment [64,65]. Separately, a registered AAV-hTERT study for the treatment of aging in Colombia (NCT04133649) was last verified in December 2019, remains listed as recruiting, and carries blank enrolment, allocation, masking and primary-purpose fields — an activity styled as a trial that satisfies none of the ISSCR recommendations discussed in Section 5.3 [12].

Immune and thymic rejuvenation. The basis for the claim that epigenetic age has been reversed in humans is a single uncontrolled study of nine men aged 51–65 given growth hormone, dehydroepiandrosterone and metformin, with no control group, no stated blinding and no preregistration [66]. Reported outcomes were a mean epigenetic age change of approximately −1.5 years after one year and improved thymic fat-free fraction in seven of nine participants, against unusual baseline clock offsets (Levine PhenoAge −17.5 ± 0.98 years) [66]. The design cannot support the claim built upon it: nine uncontrolled participants, a multi-drug protocol in which growth hormone is the agent most plausibly responsible for the imaging change, no preregistration, and baseline offsets that make regression toward expected values a live alternative. The extension study lists completion in December 2025 with no results [12]. Thymic biology otherwise remains preclinical for aging purposes, allogeneic thymus transplantation for congenital athymia being the only existing replacement therapy and iPSC-derived thymic epithelial cells the proposed path [67]; a registry search returned three thymus-regeneration records, two terminated [12].

Extracellular vesicles and adjacent modalities

Extracellular vesicles combine substantial preclinical rationale, no aging efficacy evidence, an explicit regulatory prohibition on marketing, and a large commercial marketplace; as of September 2022, the landscape comprised seven published clinical studies and 14 ongoing trials in non-aging indications [21]. The central methodological finding should govern all EV reporting: there is no consensus on MSC-exosome dose, because doses were reported variously as micrograms, particle numbers, or numbers of parent MSCs [21]. None is a potency assay and none is interconvertible, so two preparations nominally given at "the same dose" may differ in activity by an unbounded factor. The regulatory position is unambiguous: FDA stated in a public safety alert posted 9 December 2019 that exosomes used to treat diseases in humans are regulated as drugs and biological products subject to premarket review, and that there are currently no FDA-approved exosome products, citing multiple reports of serious adverse events in patients treated with unapproved exosome products [68]. Despite this, 6.68% of 1,480 United States businesses selling purported stem-cell treatments marketed exosome products as of 31 March 2021 [69].

Adjacent modalities. Aging-directed gene therapy in humans is confined to the ocular OSK phase 1 (NCT07290244), the patient-paid AAV-hTERT record (NCT04133649) and a 12-participant AAV-follistatin study (NCT07443826); mitochondrial transplantation exists only in acute injury [12], and a mitochondria-targeted antioxidant was null in the reference lifespan platform [7]. Faecal microbiota transplantation extended healthspan and lifespan in two progeroid mouse models [70], yet no human trial with an aging or frailty endpoint was identified, although dysbiosis remains a formal hallmark [1]. Xenotransplantation reached formal trials after FDA approved the first clinical trial of kidneys from genetically modified pigs [12,71], but addresses organ supply rather than aging biology. Finally, the one artificial-intelligence-discovered drug with randomised human data in an age-related disease, a TNIK inhibitor in idiopathic

pulmonary fibrosis, was powered for safety rather than efficacy: its primary endpoint was the percentage of patients with at least one treatment-emergent adverse event, dose-limiting hepatotoxicity produced liver-related discontinuations of 22.2% and 17% in the two highest-exposure arms, and the forced vital capacity difference favouring active treatment at 12 weeks was exploratory [72].

Biomarkers, clocks and the endpoint problem

The first multi-tissue methylation age predictor yielded 353 clock CpGs and was proposed as a surrogate marker for evaluating rejuvenation therapies [73]; second-generation measures instead predict time to death or functional decline, and all clocks fall on a spectrum between chronological and biological components that has proved difficult to separate [74,75]. Three findings determine how clocks should be treated as endpoints: no consensus exists on validating biomarkers of aging before clinical translation [10]; technical noise materially limits reliability, which is why principal-component versions were developed [8,9]; and three well-known clocks disagreed about the same randomised intervention in the same participants [55]. The defensible position is narrow: epigenetic clocks are validated predictors in observational settings and are not validated surrogate endpoints for intervention efficacy. Their appearance as primary or co-primary endpoints in registered trials — including a topical rapamycin study titled around re-setting the epigenetic clock (NCT04608448) and plasma-exchange, alpha-ketoglutarate and taurine studies with biological-age endpoints [12] — is a choice no regulator has accepted and the field's own methodological literature does not support [10,76].

The construct with the strongest claim to regulator-legibility is different. The WHO ICD-11 process withdrew "old age" as a category title and index listing, replacing it with "ageing associated decline in intrinsic capacity" and replacing "pathological" with "biological" in the associated extension-code definition, with accompanying commentary stating that ageing is not a pathological process and that old age is not a disease [77]; the 2026 expert consensus submitted to FDA converges on the same construct [4]. That convergence is not regulatory acceptance and no such claim is made here, but it is the most coherent endpoint proposal currently on the table, and empirical support for its enrichment component already exists in the senolytic bone trial's tertile findings [25].

Null, failed and retracted evidence

Because null results are frequently omitted from secondary accounts, they are consolidated here and in (**Table 4**) with the prominence given to positive findings. Two publications were verified as retracted [28,64,65], and one foundational biomarker claim was refuted by longitudinal cross-species analysis [58,59]. Primary endpoints were missed in a senolytic bone trial [25], a rapamycin healthspan trial [23], and a phase 3 mTOR-inhibitor trial [14]; an intravitreal senolytic phase 2b was discontinued with results never posted, and one trial stopped for futility [12]; and a senolytic phase 2 in knee osteoarthritis was reported in the trade press to have failed against placebo, an account recorded but not treated as trial evidence [78]. Caloric restriction was null on two of three epigenetic clocks [55]; metformin was null on one of two frailty instruments in the same trial while significant on the other, so it is recorded here as mixed rather than negative [51] and interfered with resistance-training adaptation in another [50]; four compounds were null on the reference mouse lifespan platform [7]; dyskinesia burden more than doubled in the best-documented iPSC efficacy dataset [32].

Category	Item	Verified outcome
Retraction	Systemic signals regulate ageing and rejuvenation of blood stem-cell niches	Retracted in full; re-examination raised serious concerns with some reported data on osteopontin-positive niche cells; first author did not sign the retraction [28]
Retraction	Intranasal and injectable gene therapy for healthy life extension	Retracted after the sponsoring university's research regulatory office requested it following internal review of data discrepancies in two figures; work fully funded by the patent-holding company [64,65]
Refuted premise	Taurine as an aging driver and biomarker	Cross-species longitudinal analysis found circulating taurine often increased or remained constant with age; conclusion that taurine is unlikely to be a good aging biomarker [58,59]
Failed phase 3	RTB101, respiratory tract infection prevention	Primary endpoint not met in 1,024 participants after regulator-requested endpoint change [14,16], despite target engagement demonstrated in the phase 2a predecessor [15]
Discontinued phase 2b, results unavailable	Foselutoclax (UBX1325) vs aflibercept in diabetic macular oedema	No posted or published results; programme discontinued and sponsor dissolved 26 Sep 2025 [93], so the trial's outcome is absent from the evidentiary record [12]
Failed phase 2	UBX0101 in knee osteoarthritis	Failed to improve knee pain compared with placebo [78]
Primary endpoint missed	Dasatinib + quercetin, bone metabolism	CTx P = 0.611; agency summary states no difference between groups in the bone-degradation marker [25,47]
Primary endpoint missed	Compounded rapamycin, healthspan	Visceral adipose tissue P = 0.942; authors state no other significant effects were observed [23]
Stopped for futility	Fisetin in nursing-home residents (NCT04537299)	Data and safety monitoring board and NIA determined the study should be stopped for futility [12]
Null on clinical endpoints	Dasatinib + quercetin, mild Alzheimer's disease	Cognitive and neuroimaging endpoints unchanged; CSF IL-6 and GFAP increased [46]
Null on clinical endpoints	Dasatinib + quercetin, pulmonary fibrosis randomised pilot	Frailty, pulmonary and physical function did not differ meaningfully between groups [45]
Surrogate discordance	25% caloric restriction	Null for PC PhenoAge and PC GrimAge at 12 and 24 months; significant only for DunedinPACE [55]
Instrument discordance	Metformin, 2-year frailty trial	Significant on frailty index, null on Fried criteria in the same population [51]
Interference signal	Metformin during resistance training	Metformin altered skeletal-muscle transcriptome adaptations to training in older adults [50]
Confounded improvement	High-dose nicotinamide riboside	Apparent MDS-UPDRS improvement associated with shorter interval since last levodopa dose [53]
Harm alongside benefit	iPSC-derived dopaminergic cells	Dyskinesia burden worsened by 12.3 points (+116.4%), worse in 6 of 7 patients [32]
Preclinical nulls	17-DMAG, minocycline, β-GPA, MitoQ	All null or negative on mouse lifespan in the reference multi-site platform (P ≥ 0.12) [7]
Never enrolled	Three registered aging studies	Withdrawn with 0 actual participants: MSC frailty (NCT05284604), combination metformin–dasatinib–rapamycin (NCT04994561) and a porcine kidney protocol (NCT05340426) [12]
Reporting failure	Largest MSC frailty datasets (NCT03169231, NCT04919135); thymic extension trial (NCT04375657); everolimus aging study (NCT05835999)	No posted results years after primary completion [12]

Table 4: Negative, null, failed, refuted and retracted evidence.

Capital, Private Financing, Proprietary Science and Incentives

Financing is a legitimate object of methodological analysis because it determines which experiments are

run, which results become visible, and which datasets can be independently examined. This section reports only figures verifiable from company statements, securities filings or law-firm and press announcements, separates them from unverified media narrative, and offers no investment assessment. (**Table 5**) gives the map with an evidence category for each entry.

Scale and structure

Four financing structures coexist; verified figures and evidence categories appear in (**Table 5**). Privately held platform companies — Altos Labs at $3 billion at launch, NewLimit across successive private rounds, and Retro Biosciences at $180 million from a single individual investor — disclose at their own discretion [79,80,81,82,83,84]. Corporate partnerships disclose through the listed partner's filings. AbbVie's Form 10-K records a collaboration established in 2014 and extended in 2018 and July 2021, each party contributing an additional $500 million at the second extension, with costs and profits shared equally after option exercise [85]. Larger cumulative totals circulating for this partnership were not located in the filing retrieved and are not asserted; company and trade sources are cited only for the announcement and termination events [86,87]. Publicly traded companies were, in this retrieval, the sponsors for which dated documents recording programme status and wind-down decisions could be obtained; for the privately held sponsors examined here no comparable dated record was retrievable. That is an observation about what this review could access, not a claim about any sponsor's duties. Philanthropic and sovereign funders, led by a foundation described as the second largest funder of aging-biology research worldwide, set agendas through grant-making [88,89,90].

What this capital has and has not produced

The most consequential finding here is negative. In the sources retrieved, no clinical-stage asset with an aging indication was verified at any of the largest privately financed reprogramming platforms. The aging-mechanism assets identified in humans at the census date are ER-100, an ocular OSK phase 1 with 18 estimated participants and no efficacy data [12]; RTR242, a lysosomal-function therapy in a placebo-controlled phase 1 in Australia [91]; an oral apelin-receptor agonist in obesity [92]; an intravitreal senolytic whose sponsor has dissolved [93]; and repurposed generics. Multi-billion-dollar platform financing has therefore gone to reprogramming science whose entire human clinical footprint is an 18-participant ocular safety study — not an argument that the science is unsound, but a reason not to infer clinical maturity from financing scale. Company statements attribute large effect sizes to proprietary work, including machine-designed Yamanaka-factor variants reported to achieve greater than 50-fold higher expression of reprogramming markers than wild-type controls [84] and frontier models trained on large epigenetic-reprogramming datasets [81]. Neither claim is peer-reviewed, and neither is treated as evidence here; both are recorded as corporate disclosures.

The academic–industry interface

The interface is closer than published affiliations suggest: the foundational senolytics review discloses institutionally held patents and royalties from a senescence-therapeutics company [42], the largest randomised rapamycin trial was sponsored by a direct-to-consumer longevity company [23], a retracted gene-therapy publication was fully funded by a company owning the pending patent with authors on its board [64], and awardees of a major philanthropic funder include several of the field's most-cited rejuvenation investigators [88]. None of these relationships is improper and several are disclosed

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exemplarily; their aggregate effect is structural, since where the largest datasets are privately held and the most influential investigators are also the principal grantees, independent replication is scarce by construction rather than by neglect.

The clinical-endpoint filter, demonstrated twice

Unity Biotechnology, Inc. developed the intravitreal BCL-xL senolytic UBX1325 (foselutoclax) through a phase 1 and three phase 2 studies, the largest an active-controlled phase 2b in diabetic macular oedema (NCT06011798), completed with 52 actual participants and no posted results [12]. No efficacy, visual-acuity or adverse-event value is reported here for any of them: the only retrieved accounts of their results are the sponsor's annual report and top-line announcement, which are securities and corporate documents rather than trial reports [22,94]. All that is taken from the corporate record is a development decision: the programme was discontinued immediately after those data were announced.

The corporate sequence is context only: a reduction in force affecting all employees, with cash and securities of $16.9 million [95]; a Nasdaq determination on 27 June 2025 that trading would be suspended, staff stating that the company no longer had an operating business [96]; stockholder approval of dissolution [97]; and dissolution effective 26 September 2025 [93]. The evidentiary lesson rests on the one programme with a primary randomised report: RTB101 succeeded on a laboratory-confirmed endpoint and failed on a patient-relevant one in 1,024 participants [14]. Aging-directed development is constrained not by mechanism, capital or the ability to move a biomarker, but by the requirement to show that a patient functions better; the senolytic case adds only that a listed sponsor wound itself up months after its lead readout.

"Secret science": a precise definition

Four measurable phenomena underlie the framing, none implying bad faith. Proprietary platform opacity: the largest reprogramming and epigenetic-measurement datasets are privately held, and effect sizes appear in blog posts and trade coverage rather than peer-reviewed form [81,84,98]. Undisclosed or delayed negative data: publicly traded companies are subject to securities-disclosure obligations that brought a primary-endpoint miss into the public record [95], whereas privately held companies are not subject to an equivalent securities-disclosure regime; this concerns securities disclosure specifically and implies nothing about other regulatory or trial-reporting duties. Registry reporting failure, the most fixable component: the largest MSC-in-frailty studies have no posted results years after primary completion, and multiple records carry status "unknown" [12] — a reporting gap rather than secrecy, but one that removes the field's largest datasets from public scrutiny.

What was not verified, and is therefore not asserted

Three widely circulated claims could not be verified against a primary source and are absent from every evidence statement in this review. The identity of any individual investor in Altos Labs is not asserted: the retrieved company and trade sources name executives and board members but do not name any investor, and popular attributions of the company's funding to a named technology billionaire are unverified here [79,80]. Post-money valuations attributed to NewLimit appear only in unretrieved aggregator summaries and are not stated. Reports that a longevity company was raising as much as $1 billion describe a plan; the verified event is a $1.8 billion pre-money valuation at an initial close [84,91]. The layoff headcount

attached to reporting of AbbVie's termination of its Calico collaboration is media-reported rather than filing-verified and is not restated [87].

Safety, Manufacturing and Regulatory Architecture

Tumorigenicity, cell identity and immunological burden

Tumorigenicity is the defining risk of pluripotency-adjacent therapeutics and the one on which evidence has recently improved: the seven-patient iPSC-derived dopaminergic trial detected no tumorigenicity signal on any measure applied over 24 months [32], and a narrative review of reprogramming models reports no histological teratoma formation under long-term induction — a synthesis-level statement rather than a primary safety dataset [40]. These are reassuring findings of limited scope — small samples, defined products, restricted anatomical compartments and follow-up of months to a few years, in a risk domain whose latency may be far longer; they do not license systemic, repeated or lifelong exposure. The subtler risk is loss of cell identity rather than frank neoplasia, since exdifferentiation and clock advancement are themselves features of aging that OSK reverses 37: the manipulation that restores youthful expression programmes also acts on the machinery maintaining differentiated identity, and partial reprogramming is by construction a controlled excursion toward dedifferentiation.

Allogeneic cell therapy imports a measurable immunological cost: tacrolimus-associated adverse events occurred in 3 of 7 patients (42.9%) in the iPSC trial, including two renal-impairment events [32]. Allogeneic MSC infusion in frailty produced no clinically significant donor-specific immune reactions within six months in the published 15-participant phase 1 cohort [26], reflecting transient, low-engraftment behaviour rather than immunological privilege, while xenogeneic protocols require combined antithymocyte globulin, complement inhibition, calcineurin inhibition, mycophenolate and corticosteroids [12]. In immune rejuvenation the therapeutic goal and the safety question coincide, HSC depletion having been assessed against vaccination and retroviral challenge [27].

Biodistribution, delivery, manufacturing and potency

Delivery is the least-discussed and most binding constraint on aging-directed gene therapy. Systemic reprogramming in mice used approximately 6 × 1013 vector genomes/kg, with no high OSK expression in brain [39]; no credible human dose translation exists, which is why the first human trial uses an ocular indication and a compartmentalised route [12,41,99]. Two alternatives to brute-force dosing appear preclinically: transcriptional targeting [38] and route selection, as in intravitreal delivery of a senolytic whose class liability is systemic thrombocytopenia [48].

Product definition fails in four documented ways; the practical reason narrative synthesis was required. Three appear in (**Table 3**): non-interchangeable EV dose metrics with no potency assay [21]; product heterogeneity across source, passage and release criteria in allogeneic MSC therapy; and good-manufacturing-practice failure, one clinic cited for microbiological contamination across at least 256 lots of products purporting to be sterile [100]. The fourth, compounding, appears in Section 3.6 rather than (**Table 3**), where a compounded small molecule reached approximately one-third the blood concentration of its commercial counterpart [23]. The iPSC entry in (**Table 3**) is the counter-example, not a failure: its phenotype composition is reported in full, the standard the other rows do not meet [32].

Platform	Source and product definition	Human indication reached	Human stage	Core safety, manufacturing or potency issue
Allogeneic MSC (aging frailty)	Bone-marrow-derived allogeneic MSC; dose in cell number (20–200 × 10^6); no consensus potency assay [26]	Aging frailty; Alzheimer's disease extension	Phase 1 reported; phase 2b (NCT03169231) completed but **unreported** [12]	Product heterogeneity across source, passage and release criteria; no potency standard; efficacy unreadable because largest datasets unposted
Autologous / allogeneic iPSC-derived neural cells	Defined progenitor product with phenotype composition reported (~60% progenitors / ~40% neurons; 0 $TPH2^+$) [32]	Parkinson's disease (not aging)	Phase I/II open-label; multiple phase 1 programmes recruiting [12]	Tumorigenicity (measured as zero in one trial); immunosuppression burden 42.9% AE rate; dyskinesia worsening; long lead time and cost of autologous manufacture [33]
Partial epigenetic reprogramming (OSK)	AAV-delivered transcription factors; dose in vector genomes; expression controlled temporally or by promoter targeting [38,39]	Open-angle glaucoma and NAION	**Phase 1 only (NCT07290244), 18 estimated participants, no efficacy data** [12]	Loss of cell identity and exdifferentiation risk [37]; teratoma risk described as absent in a narrative review of preclinical models, therefore mitigated but not excluded [40]; systemic dose translation unresolved from ~6 × 10^{13} vg/kg murine regimens
Haematopoietic stem-cell rejuvenation	Antibody-mediated depletion of myeloid-biased HSC [27]	None	Preclinical	Therapeutic goal and safety endpoint are the same measurement (immune competence); retracted precedent in the same niche biology [28]
Neural, satellite and intestinal stem-cell rejuvenation	Niche-directed strategies [29,30,31]	None	Preclinical	Human hippocampal neurogenesis findings conflicting; no defined product or delivery route
Extracellular vesicles / exosomes	MSC-derived; **dose reported as micrograms, particle number or parent-cell equivalents, which are non-interchangeable** [21]	None in aging; other indications in small trials	Phase 1/2 in non-aging indications	No consensus potency assay; characterisation heterogeneity; **no FDA-approved exosome product**; documented serious adverse events from unapproved products [68]
Thymic regeneration	Allogeneic thymus transplantation (congenital athymia only); iPSC-derived thymic epithelial cells proposed [67]	Congenital athymia	Established only for congenital athymia; aging application preclinical	Registry contains three thymus-regeneration records, two terminated [12]; aging evidence rests on one uncontrolled 9-participant study [66]
Xenogeneic organ replacement	Genetically modified porcine kidney and thymokidney [71]	End-stage renal disease	Phase 1/2 recruiting (NCT06878560, NCT07224763), 50 estimated each [12]	Intensive multi-agent immunosuppression; decades-long mandated follow-up; addresses organ supply, not aging biology
Direct-to-consumer "stem cell" and exosome products	Autologous bone marrow (45.33%), adipose (29.52%), umbilical cord (23.64%), amniotic (17.56%); 14.86% identify no cell source [69]	Marketed for pain (85.27%) and orthopaedic conditions (46.55%)	Not applicable — outside clinical research	Sterility failures across ≥ 256 lots at one clinic [100]; minimal-manipulation violations [101]; explicitly condemned by ISSCR [11]

Table 3: Comparison of regenerative and stem-cell platforms in aging-directed translation.

Regulatory Architecture

The core statement. No approval by FDA or the European Medicines Agency for an aging indication appears anywhere in the retrieved record, and as of May 2026 the endpoint framework such an application would require was still the subject of consensus submissions to FDA [3,4]. For the adjacent modality most relevant to this readership, FDA states that there are currently no FDA-approved exosome products [68]. This review does not assert that FDA has formally declared aging not to be a disease; no such statement was verified from an agency source, and the absence of an approved aging indication is established by the conjunction above rather than by any single agency declaration.

Product classification is the operative lever. Substantially manipulated human cells, tissues and cellular and tissue-based products are drugs and biological products requiring premarket review, with minimal manipulation and homologous use the decision points. In a warning letter dated 11 February 2026, FDA held that processing an umbilical cord into an injectable form significantly alters the physical state of the product, so that it fails the minimal-manipulation criterion and is a drug under the Federal Food, Drug, and Cosmetic Act and a biological product under the Public Health Service Act [101]. Enforcement has operated at scale through injunctions, 14 warning letters and 24 untitled letters [69], and patient-facing guidance directs patients to ask for the IND number [68].

Europe, classification and professional standards. Advanced therapy medicinal products are authorised centrally through the European Medicines Agency, whose record includes a 2025 joint statement on the risks of unregulated advanced therapies [102]; no European position on aging as an indication was located. The ICD-11 outcome described in Section 3.9 converges with the construct proposed to FDA in 2026 [4,77]. The ISSCR guidelines state that substantially manipulated or non-homologously used cells and tissues must be proven safe and effective before being marketed or incorporated into standard care; that the society condemns administration of unproven cell- and tissue-based interventions outside compliant research, particularly as a business activity; and that where minimal manipulation is claimed as grounds for exemption, the burden rests on the clinician to invite independent scrutiny [11]. A 2025 targeted update addressed stem-cell-based embryo models [103].

Ethics, access and the unproven-intervention economy

The United States direct-to-consumer stem-cell market was surveyed as of 31 March 2021: 1,480 businesses operating 2,754 clinics, against 351 businesses in 2016. Cell sources were dominated by autologous bone marrow (45.33%) and adipose tissue (29.52%); 40.2% marketed "mesenchymal stem cell" treatments and 14.86% identified no cell source at all; exosome products were marketed by 6.68% and iPSC treatments by none; and indications were dominated by painful (85.27%) and orthopaedic (46.55%) conditions, none backed by convincing evidence from adequately powered randomised trials (**Table 3**) [69]. Two features stand out: commercial availability is inversely related to evidentiary maturity, since the modality with the most advanced human evidence has no commercial presence while the least defined products dominate; and the market is overwhelmingly orthopaedic and pain-directed, placing patient counselling on musculoskeletal and regenerative-medicine clinicians rather than geriatricians.

Harms are documented rather than hypothetical: serious adverse events after unapproved exosome products [68]; sterility failures across at least 256 lots at one clinic [100]; and young-donor plasma infusions marketed at thousands of dollars per infusion [61]. Cross-border access operates as a workaround: six dementia patients sent to Mexico for injections of a gene therapy unapproved in the United States [65], and a patient-paid AAV-hTERT study registered in Colombia with incomplete fields [12]. These are not equivalent to a first-in-human study in a well-regulated jurisdiction [91]; what matters is whether the participant pays, whether registration is prospective and complete, and whether an IND exists.

Direct-to-consumer biological-age testing raises a distinct problem, because it sells a Tier 3 measurement as a health assessment: reliability in commercial wellness settings is unresolved [76], clock reliability is

limited by technical noise absent principal-component correction [8], and since three established clocks disagreed about one randomised intervention [55], an individual consumer result cannot support an individual clinical decision. Access also has a workforce dimension, since geroscience-directed therapies will require physician training and possibly practice guidelines specific to promoting healthspan in older adults without worsening existing comorbidities or geriatric syndromes [104].

Discussion

Five evidentiary states, not one

The central analytic result of this review is that the field's evidence occupies five states routinely collapsed into one another in secondary accounts, and that the collapse is where most overclaiming originates: biological plausibility; animal rejuvenation; first-in-human safety; surrogate change; and demonstrated human efficacy on a clinical endpoint. Sections 3.2–3.9 and (**Table 1**) place each class in that sequence, and the distribution is lopsided — plausibility and animal rejuvenation are richly populated, phase 1 safety has been reached by several modalities, surrogate change is the most crowded state, and the fifth is empty for an aging indication in the retrieved record. Clinical-endpoint results are mixed rather than uniformly negative. The largest adequately sized test missed its primary endpoint — a phase 3 in 1,024 participants [14] — whereas a two-year randomised metformin trial in 141 participants improved a frailty index ($P = 0.0222$) while remaining null on the Fried criteria in the same population 51: a discordance between instruments rather than a clean success or failure. Where Tier 2 risk factors improved, as under caloric restriction [54], the benefit is obtainable by other means and is not evidence that aging has been modified.

For a regenerative-medicine readership: MSC therapy for frailty sits between phase 1 safety and unreadable phase 2 evidence; iPSC-derived therapy at phase 1 safety with uncontrolled efficacy signals in a non-aging indication; partial reprogramming at animal rejuvenation with an ongoing 18-participant safety study; and EV therapeutics at biological plausibility with an unresolved product definition. None is close to demonstrated human efficacy for an aging indication, and none should be represented to patients as such.

Why the endpoint problem is the binding constraint

Three lines of evidence converge on endpoint definition, rather than mechanism, funding or manufacturing, as the rate-limiting step. First, the only completed surrogate-to-clinical translation attempt at scale failed at exactly the transition point, succeeding on a laboratory-confirmed endpoint and failing on one reflecting how patients feel and function, with target engagement preserved [14,15]. Second, the surrogates are inconsistent — three well-validated clocks disagreed about one randomised intervention in one sample [55], and no consensus framework exists for validating aging biomarkers before clinical translation [10]. Third, the field's experts were still negotiating with a regulator in May 2026 about what a healthspan endpoint might be [4], a decade into large-scale private investment. A corollary has empirical support: enrichment by measured biological burden works [25].

Product definition as a scientific, not logistical, problem

The most severe non-commensurability in this review is material rather than statistical. Two EV preparations described at "the same dose" may differ arbitrarily [21]; two MSC studies may differ in tissue source, passage number, expansion medium and release criteria while sharing a product name; and a

compounded small molecule may deliver one-third the systemic exposure of its commercial counterpart [23]. Apparent replication failure may therefore be product divergence, and apparent replication may be coincidence. The corrective is reporting discipline rather than methodological novelty: cell source, isolation and expansion methods with passage number, composition by phenotype as achieved in the Kyoto product [32], dose in all applicable units, route, potency assay, and compounding status — fields that journals are in a position to require.

How capital shapes the evidence, and what "the end of aging" would require

Private capital has accelerated mechanism discovery while reducing the fraction of the field's evidence open to independent examination. The most auditable record belongs to a company that failed: dated filings track a workforce reduction, a delisting sequence and a dissolution [93,95]. Even there the trial results never entered any evidentiary source, and for privately held sponsors abandoning a programme no comparable dated trail was retrievable, so a field whose discontinuations surface unevenly will overestimate its success rate, which registry reporting would correct [12].

Substantially decelerating human aging in a clinically meaningful sense would require, at minimum: a validated endpoint that a regulator accepts, which does not yet exist [4,10]; an intervention that moves it in an adequately powered randomised trial, which has not happened [14]; a product whose identity and potency are reproducible in a second manufacturing run [21]; a safety profile acceptable for people who are not ill, far stricter than any trial here has had to satisfy; and delivery at a translatable dose, unresolved for systemic reprogramming [39]. None of these conditions is met, and only the first two are close to being solvable by collective methodological action.

Limitations

Limitations of the review process

Six limitations constrain the conclusions above and are stated without mitigation. The search was not executed as a multi-database systematic screen. Retrieval covered PubMed/MEDLINE-indexed literature, ClinicalTrials.gov, regulatory and guideline sources, securities filings, journal pages, retraction registries and citation chaining. It did not include independent record export and deduplication from Embase, Scopus, Web of Science or Cochrane CENTRAL, and no record counts from such searches appear anywhere in this manuscript. Screening was not performed in duplicate. Two-reviewer independent title-and-abstract screening with third-reviewer adjudication is the standard procedure and was not carried out. No PRISMA flow counts are reported. The registry material analysed here derives from a curated, purposive sample assembled from 21 query terms and deduplicated by NCT identifier; these are not PRISMA screening counts and are not presented as such. The protocol was neither registered nor published in advance, so the framework in Section 2 is reported descriptively and carries none of the guarantees of prospective specification. Formal study-level risk-of-bias assessment was not completed, and no RoB 2, ROBINS-I or SYRCLE domain judgement is reported for any study; appraisal is narrative, which weakens every comparative statement about study quality made here. Certainty was not rated, because GRADE requires duplicate assessment and outcome-level synthesis not performed here.

Together these mean the work is a structured critical evidence review, not a completed systematic review, and it is labelled that way throughout. A consequence follows for its negative findings: statements that

an intervention, trial or approval "was not identified" are bounded to the retrieved evidence set, not demonstrations of absence in the world literature.

Limitations of the evidence base itself

Independent of review conduct, the underlying evidence carries limitations no methodology can repair. Sample sizes are small and follow-up short across every mechanistic class; single-arm and open-label designs predominate, and investigators state the consequence themselves, one senolytic team recording that the lack of a control group limited interpretation and next-stage trial planning and that their randomised follow-up was under-powered [43,45]. Several key effect sizes could not be extracted: efficacy results for the two largest MSC frailty studies, the thymic-regeneration extension trial and the discontinued intravitreal senolytic phase 2b [12,94], and the primary cognitive outcome of the spermidine trial [57]. Publication and reporting bias operate asymmetrically, as analysed in Sections 4.5 and 7.4, and status fields labelled "unknown" indicate neither activity nor inactivity [12]. Reliance on non-peer-reviewed material is concentrated and substantial: 18 of the sources cited in Section 4 and (**Table 5**) are company statements, a law-firm announcement or trade media rather than peer-reviewed literature, securities filings or registry records, each categorised in (**Table 5**). They support no clinical-evidence statement anywhere in this review and should be re-sourced to primary documents wherever one exists. Finally, the census date is a hard boundary: every status statement — recruiting, completed, results posted, dissolved, authorised — is accurate as of 7 September 2026 and is expected to change, which is why a living-review format would be the appropriate long-term solution [6].

Organisation	Verified financial facts	Verified programme status relevant to aging	Evidence category	Source
Altos Labs	$3 billion at launch	Three institutes of science plus an institute of medicine; scientific framing traced to induced pluripotency and 2016 partial reprogramming; **no clinical-stage aging asset verified**	C, T	[79,80]
Calico Life Sciences / AbbVie	**From AbbVie's Form 10-K:** collaboration established 2014, extended 2018 and July 2021; each party contributing an additional $500 million at the second extension; $500 million recorded by AbbVie as other operating expense in Q3 2021; costs and profits shared equally after option exercise. Larger cumulative totals were not located in the filing retrieved and are not asserted	Collaboration ended after more than a decade; **no clinical-stage aging asset verified**	F (filing); C, T (announcement and termination only)	[85,86,87]
NewLimit	Series B $130 million; Series C $435 million	Stated focus on epigenetic reprogramming with AI and scaled genomics; **no named asset or clinical stage on retrieved pages**	C, L	[81,82]
Retro Biosciences	$180 million from an individual investor; $1.8 billion pre-money valuation at initial close of subsequent round (23 May 2026)	Became clinical-stage in 2025; RTR242 phase 1 in healthy volunteers in Australia; preclinical iPSC-derived microglial and haematopoietic programmes	T	[83,84,91]

Hevolution Foundation	$15 million cumulative for one re-funding programme; up to $115 million across 49 awards with a planned second call; approximately $250 million committed as of 12 Feb 2024; annual budget up to $1 billion	Grant-making only; two-stage peer review with approximately 100 experts; named awardees include leading senescence and rejuvenation investigators	C, T	[88,89]
Unity Biotechnology, Inc. (CIK 0001463361)	IPO 2018 at $17 per share; cash and marketable securities $16.9 million at 31 Mar 2025; reduction-in-force cost approximately $3.7 million; **dissolution effective 26 Sep 2025**	UBX1325/foselutoclax phase 1 and three phase 2 studies; UBX0101 knee-osteoarthritis failure 2020 (press-reported)	F, T	[22,78,93,95,96,97]
BioAge Labs, Inc.	IPO closed 1 Oct 2024; combined gross proceeds approximately $238.3 million	**Company statement, not treated as clinical evidence:** lead oral candidate described by the company as evaluated across eight phase 1 trials, with a phase 2 in obesity in older adults initiated mid-2024. No tolerability or safety claim is asserted from this source	C	[92]
Juvenescence	$76 million first tranche of Series B-1 (21 May 2025), sovereign-linked cornerstone investor	Clinical-stage AI-enabled biotechnology; **no named asset on retrieved page**	C	[90]
Life Biosciences	Funding not verified	ER-100 partial epigenetic reprogramming; FDA authorisation to proceed 15 Jan 2026 announced 28 Jan 2026; phase 1 with 18 estimated participants	C, R	[12,41,99]
Human Longevity, Inc.	Company site states $600 million invested in research	Clinics from 2015 and 2022; commercial longevity programmes; datasets not accessible to the research community	C	[98]
Longeveron, Inc.	Financials not verified	Lomecel-B across aging frailty, Alzheimer's disease and other indications; largest aging trials unreported	R	[12]
Intervene Immune, Inc.	Financials not verified	TRIIM published; TRIIM-X unreported past its listed completion date	R	[12,66]
Insilico Medicine	Financials not verified	Rentosertib phase 2a published	R	[72]
Rejuvenate Bio	Financials not verified	AAV9 OSK partial reprogramming in 124-week-old mice (preclinical)	R	[39]
BioViva USA, Inc.	Work fully funded by the company, which owns the pending patent	CMV-vectored telomerase and follistatin gene therapy — **publication retracted**	R, T	[64,65]
Not verified and therefore not asserted	Identity of any individual investor in Altos Labs; post-money valuations attributed to NewLimit; reports of a $1 billion raise in progress	—	—	[79,80,91]

Table 5: Verified financing and governance map, with evidence category for each entry.

Evidence categories: F = securities filing; C = company statement or press release; L = law-firm announcement; T = trade or news media (re-source to a primary document before publication); R = peer-reviewed record or registry.

Clinical and Research Agenda

For clinicians. No intervention discussed here should be offered as an aging treatment outside a registered, authorised clinical trial; this is the operative content of the ISSCR clinical-translation

recommendations [11] and of the FDA product-classification framework [68,101]. Patients considering a commercial intervention should be counselled with specifics: that there are no FDA-approved exosome products [68]; that documented harms include serious adverse events and sterility failures at scale [100]; that iPSC-based products, with the most advanced human evidence, have no commercial presence [69]; and that a consumer biological-age result cannot support an individual clinical decision [55]. Within trials, function should be measured: gait speed, grip strength, six-minute walk distance, cognition and frailty status [2,4].

For investigators and journals. The agenda in Table 6 is organised by the gap each item closes, and its highest-priority entries are corrections to the evidence infrastructure rather than new discoveries: posting results for completed cell-therapy trials, defining products and potency assays for replication, enriching populations by measured biological burden rather than chronological age, and testing Tier 1 functional endpoints in adequately powered randomised designs. For stem-cell and regenerative-medicine journals, three editorial requirements would materially improve the literature: mandatory product-characterisation fields as a condition of acceptance; mandatory statement of registry identifier, registration timing and results-posting status; and mandatory identification of the epigenetic clock version, including principal-component correction status, for any biological-age claim [8].

Conclusion

Aging biology has become tractable, and stem-cell science is central to that: stem-cell exhaustion sits at the integrative end of the hallmark architecture, and reprogramming, cell therapy and vesicle biology supply its most compelling preclinical results.

Tractability is not therapy. On the evidence retrieved to 7 September 2026, no intervention has been approved by FDA or the European Medicines Agency for an aging indication; human partial epigenetic reprogramming consists of one ongoing 18-participant ocular safety trial with no efficacy data; the largest cell-therapy datasets in aging frailty remain unreported years after completion; several of the field's most rigorous randomised trials missed their primary endpoints while a two-year metformin trial was positive on one frailty instrument and null on another; and the one geroscience programme that reached a phase 3 with a patient-relevant endpoint failed it while retaining target engagement. The constraints are identifiable and partly remediable: endpoint ambiguity, unvalidated surrogates, undefined products and dose metrics, unresolved delivery, immunological burden, and an incentive structure that renders the largest datasets unexaminable, most of which can be addressed by collective methodological and editorial action rather than by new discovery.

The appropriate posture is neither dismissal nor anticipation of transformation. It is to hold healthspan — autonomy, function and disease-free survival — as the outcome that counts; to keep biological plausibility, animal rejuvenation, phase 1 safety, surrogate change and demonstrated human efficacy permanently distinct; and to require of any aging-directed intervention what would be required of any other therapeutic entering clinical practice. On that standard, the end of aging is not in sight, and the beginning of a rigorous clinical geroscience is.

Declarations

Ethics approval and consent to participate: Not applicable. This review synthesises previously published literature, publicly accessible aggregate clinical-trial registry records, regulatory and guideline documents, and publicly filed corporate disclosures. No human participants, identifiable individual data, biological specimens or interventions were involved, and no primary data were collected.

Consent for publication: Not applicable. No individual person's data in any form are included.

Availability of data and materials: All data supporting this review are contained within the article and are drawn from publicly accessible sources; every cited reference includes its identifier and uniform resource locator. Clinical-trial registry values were retrieved from ClinicalTrials.gov through its application programming interface version 2 on 7 September 2026, and individual records are publicly retrievable by NCT identifier [12]. No new datasets were generated. The extraction table used to organise registry fields can be made available by the author on reasonable request.

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(https://clinicaltrials.gov/study/NCT03169231); NCT03283462 (https://clinicaltrials.gov/study/NCT03283462); NCT03353597 (https://clinicaltrials.gov/study/NCT03353597); NCT04133649 (https://clinicaltrials.gov/study/NCT04133649); NCT04313634 (https://clinicaltrials.gov/study/NCT04313634); NCT04375657 (https://clinicaltrials.gov/study/NCT04375657); NCT04488601 (https://clinicaltrials.gov/study/NCT04488601); NCT04537299 (https://clinicaltrials.gov/study/NCT04537299); NCT04608448 (https://clinicaltrials.gov/study/NCT04608448); NCT04919135 (https://clinicaltrials.gov/study/NCT04919135); NCT04994561 (https://clinicaltrials.gov/study/NCT04994561); NCT04998357 (https://clinicaltrials.gov/study/NCT04998357); NCT05284604 (https://clinicaltrials.gov/study/NCT05284604); NCT05340426 (https://clinicaltrials.gov/study/NCT05340426); NCT05835999 (https://clinicaltrials.gov/study/NCT05835999); NCT06011798 (https://clinicaltrials.gov/study/NCT06011798); NCT06208527 (https://clinicaltrials.gov/study/NCT06208527); NCT06274749 (https://clinicaltrials.gov/study/NCT06274749); NCT06534450 (https://clinicaltrials.gov/study/NCT06534450); NCT06613542 (https://clinicaltrials.gov/study/NCT06613542); NCT06878560 (https://clinicaltrials.gov/study/NCT06878560); NCT07224763 (https://clinicaltrials.gov/study/NCT07224763); NCT07290244 (https://clinicaltrials.gov/study/NCT07290244); NCT07443826 (https://clinicaltrials.gov/study/NCT07443826); NCT07475546 (https://clinicaltrials.gov/study/NCT07475546).

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