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Nanofat and the Stromal Vascular Fraction in Regenerative Medicine: Biology, Preparation, Classification, and Clinical Applications

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Abstract

Background: Autologous adipose-derived products have moved rapidly from structural grafting to regenerative medicine, yet the labels nanofat, mechanically isolated stromal vascular fraction (SVF), enzymatically isolated SVF and adipose-derived stromal cells are often used interchangeably. These preparations differ materially in tissue architecture, cellular content, regulatory status and proposed mechanism. Their appeal rests on an abundant tissue source and plausible paracrine, angiogenic and immunomodulatory activity, but plausibility is not itself evidence of a reproducible clinical effect.

Objective: To provide a clinically useful, biologically grounded synthesis of nanofat and SVF that distinguishes product classes, links preparation to measurable composition, and appraises clinical findings against comparator strength, safety and methodological quality.

Methods: We undertook a narrative review of foundational biology, consensus nomenclature, preparation and analytical studies, and clinical evidence across musculoskeletal, reconstructive, dermatological and aesthetic indications. Particular attention was given to harvest site, donor phenotype, processing variables, viable nucleated-cell recovery, immunophenotyping, formulation-specific outcome reporting and controlled trials. Evidence was interpreted by separating uncontrolled improvement from incremental benefit over active or saline comparators and by considering published minimal clinically important differences where available.

Results: Adipose tissue contains a heterogeneous perivascular stromal ecosystem rather than a uniform stem-cell product. Fresh SVF commonly contains 15-30% stromal cells, 10-20% endothelial cells and 25-45% haematopoietic-lineage cells, while yields vary substantially with depot, donor and isolation method. Mechanical processing preserves a tissue-derived mixture but does not establish equivalence to enzyme-released SVF or culture-expanded cells. In clinical translation, early uncontrolled signals have contracted as comparators have strengthened. The MILES trial reported clinically notable improvement after microfragmented adipose tissue for knee osteoarthritis, whereas the 2025 saline-controlled Barfod trial was negative for its primary comparison. Across adipose-derived cell therapy studies, the pooled reported complication rate was approximately 4.2 percent, but adverse-event ascertainment and long-term surveillance were inconsistent. Evidence-quality assessments repeatedly identify small samples, heterogeneous products, incomplete cell characterisation and frequent absence of blinded comparator-controlled designs.

Conclusions: Nanofat and SVF should be treated as process-defined, compositionally variable products, not interchangeable proxies for stem-cell therapy. Their biological rationale supports further investigation, but clinical claims require matched product release criteria, transparent reporting of harvest and processing, adequate controls and outcomes interpreted against clinically meaningful thresholds. A taxonomy that connects nomenclature, manufacturing and measurement is essential before indication-specific efficacy can be judged with confidence in routine clinical practice.

Keywords

Adipose-derived stromal cells; Stromal vascular fraction; Nanofat; Microfragmented adipose tissue; Mesenchymal stromal cells; Regenerative medicine; Extracellular vesicles; Cell characterisation; Liposuction.

Abbreviations

AD-MSC, adipose-derived mesenchymal stromal cell; ADRC, adipose-derived regenerative cell; ADSC, adipose-derived stem cell; AE, adverse event; AIS, American Spinal Injury Association Impairment Scale; ALS, amyotrophic lateral sclerosis; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2; ANVISA, Brazilian Health Regulatory Agency; ARDS, acute respiratory distress syndrome; ASC, adipose-derived stromal/stem cell; ASERF, Aesthetic Surgery Education and Research Foundation; ATMP, advanced therapy medicinal product; BLA, biologics licence application; BMI, body mass index; BMC, bone marrow concentrate; CAT, Committee for Advanced Therapies; CEP/CONEP, Brazilian research ethics system; CGMP, current good manufacturing practice; CI, confidence interval; CMS, Centers for Medicare & Medicaid Services; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; cGvHD, chronic graft-versus-host disease; DTC, direct-to-consumer; EDSS, Expanded Disability Status Scale; EU, European Union; FDA, United States Food and Drug Administration; FSFI, Female Sexual Function Index; HCT/P, human cells, tissues, and cellular and tissue-based product; HFrEF, heart failure with reduced ejection fraction; HTA, Human Tissue Authority; I2, inconsistency statistic; ICIQ-SF, International Consultation on Incontinence Questionnaire Short Form; IIEF-5, International Index of Erectile Function-5; IND, investigational new drug; IRR, incidence rate ratio; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MACE, major adverse cardiovascular event; MCID, minimal clinically important difference; MHRA, Medicines and Healthcare products Regulatory Agency; MRI, magnetic resonance imaging; MSC, mesenchymal stromal cell; MSQOL-54, Multiple Sclerosis Quality of Life-54; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OA,

osteoarthritis; PFE, pulmonary fat embolism; PHQ-9, Patient Health Questionnaire-9; PRP, platelet-rich plasma; RCT, randomised controlled trial; RDC, Brazilian collegiate board resolution; ROBIS, Risk Of Bias In Systematic reviews; RR, risk ratio; SAE, serious adverse event; sCTMP, somatic cell therapy medicinal product; SoHO, substances of human origin; STEMI, ST-segment elevation myocardial infarction; SUSAR, suspected unexpected serious adverse reaction; SVF, stromal vascular fraction; TEP, tissue-engineered product; TGA, Therapeutic Goods Administration; VAS, visual analogue scale; VTE, venous thromboembolism; WADA, World Anti-Doping Agency; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Introduction

Autologous adipose tissue is increasingly presented as a readily available regenerative substrate, but the clinical object of interest is not a single biological entity. Lipoaspirate contains mature adipocytes, matrix, vessels, blood-derived cells and multiple stromal populations, and its manipulation can yield graftable tissue fragments, a mechanically enriched cellular suspension, an enzyme-released stromal vascular fraction (SVF), or a culture-expanded adherent cell population. Processed lipoaspirate was an early source from which multipotent adipose-derived cells were described, while marrow work established the reference framework for plastic-adherent mesenchymal populations and multilineage assays [1,2]. The cellular hierarchy therefore changes as the product moves from tissue to suspension to culture. A review of the field must name that transition rather than treat all adipose-derived material as a stable therapeutic category [3,4].

The terminology has not kept pace with product diversification. Nanofat commonly denotes mechanically emulsified and filtered adipose tissue intended for fine delivery; it is not synonymous with purified SVF, nor with adipose-derived stromal cells (ASC) expanded in culture. A term such as MSC is also insufficient without a tissue qualifier and a functional context: the International Society for Cell and Gene Therapy recommends interpreting MSC as mesenchymal stromal cells unless rigorous evidence establishes stemness, while the earlier nomenclature statement cautioned that unfractionated adherent populations should not be called stem cells by default [4,5]. The distinction is more than semantic because it determines the appropriate release tests, regulatory analysis and inference from preclinical studies. It also prevents a culture-derived phenotype from being retrospectively attributed to an uncultured clinical injectate.

This distinction is clinically consequential because a product can be labelled by its delivery format while its putative mechanism is attributed to a different preparation. Fresh SVF is a heterogeneous mixture with stromal, endothelial, pericytic and haematopoietic compartments; culture selection changes both its marker profile and its biological questions. The joint IFATS/ISCT statement therefore separates uncultured SVF stromal cells from culture-expanded ASC and specifies different phenotypic and viability expectations [3]. A final suspension that lacks its harvest, isolation and characterisation record is consequently not fully identifiable. The same label can conceal important variation in cells, matrix and residual tissue.

Claims of regenerative efficacy frequently outrun the measurement of what was injected. Published yield can be expressed per gram, per millilitre of lipoaspirate, per final millilitre or after variable culture

intervals, while flow panels, viability thresholds, colony-forming assays and release criteria are inconsistently reported. Even across two good-manufacturing-practice facilities, recovery, sterility and cell-subset distribution differed materially, showing why a device name or a volume of injectate cannot serve as a compositional surrogate [6]. Cell number may be necessary for batch description but cannot by itself establish cellular identity or mechanism. Comparisons of clinical outcomes should therefore begin with a compositional denominator.

The translational stakes extend beyond efficacy. Adipose-derived preparations have plausible angiogenic and immunomodulatory actions, but their heterogeneity also makes donor selection, tissue handling, culture history and oncological context relevant to benefit and risk. A systematic review of 70 clinical studies involving more than 1,400 recipients found that safety ascertainment was not described in 32 studies, illustrating that apparent procedural safety should not be mistaken for complete surveillance [7]. This reporting deficit is especially important where a product is proposed to alter angiogenesis, fibrosis or immune signalling. It limits confidence in both rare-event estimates and generalisability across indications.

This review therefore links nomenclature to preparation, composition and measured function before examining clinical applications. It asks which elements of adipose biology are supported by direct measurement, which properties change with processing or donor phenotype, and which claims remain extrapolations from in-vitro or uncontrolled clinical observations. The resulting taxonomy is intended to make explicit the boundary between a tissue-derived product, a defined cell preparation and a therapeutic assertion. It is also designed to expose when a clinical report has not supplied enough information to support a mechanistic claim. Subsequent sections apply this approach to harvest, classification, evidence and implementation.

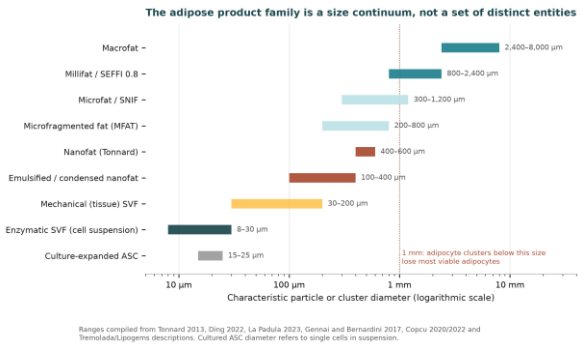

Figure 1: Taxonomy of adipose-derived products. Product names should specify tissue processing, cellular composition and culture status rather than implying biological equivalence [3,4].

Adipose Tissue as a Source: Depots, Composition and Donor Factors

Depot-specific biology and yields

Adipose tissue is anatomically regionalised rather than biologically uniform. In an eight-week overfeeding study of 28 healthy adults, abdominal subcutaneous adipocyte hypertrophy accompanied upper-body

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gain, whereas lower-body adipocyte number increased by 2.6 +/- 0.9 x 10^9 cells; baseline abdominal preadipocytes also expressed more PPARgamma2 and C/EBPalpha than femoral cells [8]. These observations support a depot-aware approach, but do not license a universal ranking because donor phenotype, harvest plane and endpoint differ across studies.

For procedural yield, lower abdominal lipoaspirate had a higher processed-cell concentration than most sites in a within-procedure study of 25 women, with no significant difference from inner thigh [9]. In a separate study, ASC frequency by limiting dilution and colony-forming assays was 5.1 +/- 1.1% in abdominal tissue versus 1.2 +/- 0.7% in hip/thigh tissue (P = 0.0009), despite no difference in total nucleated cells per volume and no difference in osteogenic potential within the colony-forming population [10]. Thus, absolute nucleated-cell recovery and progenitor frequency answer different questions and should be reported together.

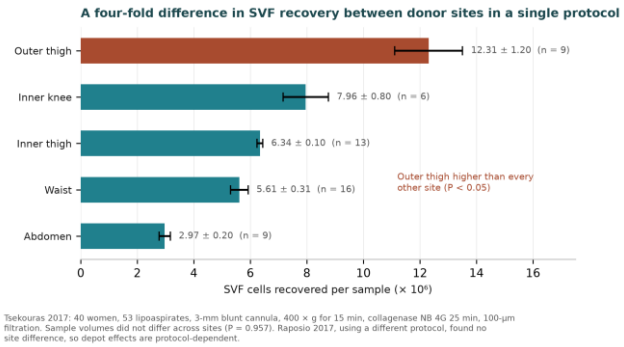

Figure 5: Anatomical depot is a biological variable. Abdominal and lower-body adipose tissue differ in cell frequency and growth biology, whereas total nucleated-cell yield may not track progenitor frequency [8,10].

Functional distinctions have also been observed among subcutaneous regions. In 12 female donors, superficial abdominal cells were more resistant to apoptosis than cells from four other depots, while arm-derived cells had the greatest stimulated glycerol release and persistent PPARgamma2 expression; proliferation-related differences tracked donor age more closely than site [11]. Dorsocervical tissue is an additional caution against simplistic labels: in antiretroviral-associated lipodystrophy its mitochondrial DNA content was 62% lower than in non-lipodystrophic dorsocervical tissue, yet it was relatively macrophage-poor and lacked meaningful UCP1 expression [12]. A separate transcriptomic study nevertheless detected UCP1 uniquely in buffalo-hump fat and described a distinct mitochondrial and proliferative signature, underlining that phenotype depends on the comparator and disease state [13].

Depot or context	Yield / cellular signal	Proliferation or differentiation	Clinical implication
Lower abdomen	Higher processed-cell concentration than most sites; exact value not reported	Abdominal ASC frequency 5.1 +/- 1.1% in one comparison	Favourable candidate when a progenitor-enriched harvest is required [9,10]
Hip / thigh	ASC frequency 1.2 +/- 0.7%; total nucleated cells per volume similar to abdomen	Osteogenic fraction within CFU population similar to abdomen	Low progenitor frequency does not prove lower lineage competence [10]

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Superficial abdomen	No universal absolute yield estimate	Greater apoptosis resistance in one 12-donor series	Site effects should be separated from donor-age effects [11]
Dorsocervical in lipodystrophy	62% lower mitochondrial DNA than non-lipodystrophic comparator	Distinct inflammatory and regional transcriptional programmes	Disease-altered depots should not be treated as interchangeable with routine subcutaneous fat [12,13]

Table 1: Anatomical adipose depots and biological implications. Yield, proliferative behaviour and differentiation are endpoint-specific and cannot be collapsed into a single hierarchy.

CFU, colony-forming unit; ASC, adipose-derived stromal cell. Values reflect the cited study designs and are not universal release specifications.

Cellular composition of the stromal vascular fraction and ISCT/IFATS immunophenotype criteria

SVF should be understood as the non-adipocyte cellular and matrix-associated fraction released or concentrated by a specified process, not as a homogeneous stem-cell dose. In intact and aspirated fat, adipocytes constituted less than 20% of total cellularity, whereas endothelial and adipose stromal cells together represented more than one half; aspiration disrupted the capillary network, ruptured more than 30% of adipocytes versus 5% in excised tissue, and yielded roughly half as many viable ASC [14]. The preparation method is therefore part of the biological identity.

The IFATS/ISCT framework defines uncultured SVF stromal cells as CD45-negative, CD235a-negative, CD31-negative and CD34-positive, expected to comprise at least 20% of SVF cells. Its tabulated resident populations are stromal cells 15-30%, haematopoietic-lineage cells 25-45%, endothelial cells 10-20% and pericytes 3-5%; recommended release expectations include viability above 70%, stromal-cell frequency above 20% and leukocytes below 50% [3]. These are pragmatic identity and release anchors, not proof that each injected cell is a self-renewing therapeutic stem cell.

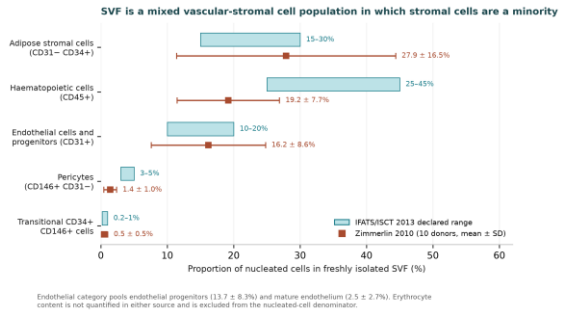

Figure 2: SVF is a multicellular vascular-stromal ecosystem. Fresh SVF includes stromal, endothelial, pericytic and blood-derived compartments whose proportions change with isolation and gating [3,15].

SVF population	Typical immunophenotype	Reported frequency	Interpretive point
Stromal cells	CD45-/CD235a-/CD31-/CD34+; CD13/CD73/CD90 positive	15-30% total nucleated cells; >=20% expected for release	Fresh phenotype is not identical to expanded ASC [3]
Supra-adventitial ASC	CD31-/CD34+/CD146-	27.9 +/- 16.5% of nucleated cells	Predominant non-haematopoietic stromal subset in abdominoplasty samples [15]
Endothelial progenitors	CD31+/CD34+	13.7 +/- 8.3% of nucleated cells	Vascular component should not be counted as stromal cells [15]

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Mature endothelium	CD31+/CD34-	2.5 +/- 2.7% of nucleated cells	Frequency depends on dissociation and gating [15]
Pericytes	CD31-/CD146+; often alpha-SMA+	3-5% expected; 1.41 +/- 0.97% reported in one series	Perivascular identity overlaps functionally with stromal populations [3,15]
Haematopoietic / immune cells	CD45+; macrophages often CD14+/CD31+	25-45% expected; macrophages 11% in one flow study	Immune composition is donor- and inflammation-sensitive [3,16]

Table 2: Cellular composition of SVF. Reported frequency ranges require the accompanying isolation, viability, denominator and flow-cytometry gating strategy.

ASC, adipose-derived stromal cell; SVF, stromal vascular fraction. Percentages are not directly interchangeable across processing protocols.

Detailed flow cytometry reinforces this heterogeneity. In ten abdominoplasty samples, supra-adventitial ASC represented 27.9 +/- 16.5% of nucleated cells, endothelial progenitors 13.7 +/- 8.3%, mature endothelial cells 2.5 +/- 2.7% and pericytes 1.41 +/- 0.97%; debris, doublets, autofluorescent and haem-positive events together excluded 70.0 +/- 13.3% of acquired events [15]. A different multicolour study reported CD146-dim and CD146-bright populations at 9.9% and approximately 39.3%, respectively, and endothelial cells at approximately 7.7%, illustrating the effect of marker definitions and denominators [17].

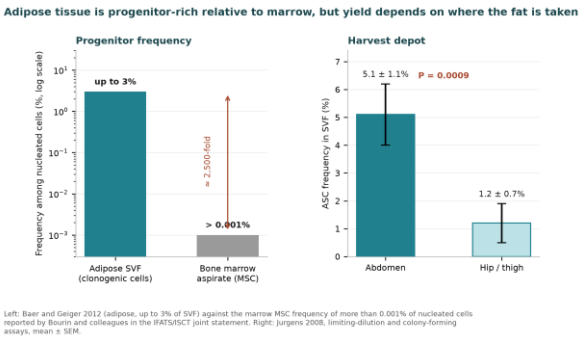

Figure 3: Frequency estimates depend on the denominator. Cell proportions in SVF vary with digestion, event exclusion and marker panel, so percentage alone is an incomplete release metric [3,15,17].

Fresh and culture-selected populations should not be conflated. In lipoaspirate, ASC, endothelial progenitors and pericytes can be separated by CD31, CD34, CD45, CD90, CD105 and CD146 patterns, while both fatty and fluid fractions change substantially after adherence [18]. Fresh SVF contained colony-forming fibroblasts, adipocytes and osteoblasts at frequencies of 1:32, 1:28 and 1:16, respectively, in one report; stromal-marker expression increased with adherence whereas CD34 peaked in fresh or early-passage cells [19]. Obesity further complicates composition because macrophage abundance correlates with BMI and macrophage-associated transcripts were strongly linked to adiposity [16,20].

Perivascular origin and pericyte biology

The perivascular niche provides a biologically coherent, but not monolithic, explanation for much of the stromal activity in adipose tissue. Native ASC activity was concentrated in the CD34-positive SVF fraction,

and immunohistology placed these cells in the stroma rather than assigning them a stable mature-pericyte phenotype; CD34 declined during culture while pericytic markers could emerge [21]. By contrast, the majority of freshly isolated CD34-positive, CD31-negative, CD144-negative adipose stromal cells co-expressed mesenchymal, pericytic and smooth-muscle-associated markers and stabilised endothelial networks in co-culture [22].

These findings are better interpreted as evidence of a perivascular continuum than as a single definitive marker signature. Pericytes from several human organs, including adipose tissue, were prospectively identified by CD146, NG2 and PDGFRbeta expression with exclusion of haematopoietic, endothelial and myogenic markers, and displayed clonal adipogenic, chondrogenic and osteogenic potential [23]. In subcutaneous adipose tissue, the CD34-positive, CD31-negative subset was the fraction selectively enriched during adipogenesis, whereas CD34-positive, CD31-positive endothelial cells and CD14-positive, CD31-positive macrophages were distinct populations [24]. The practical implication is to measure a panel and function rather than infer potency from CD34, CD146 or vessel proximity alone.

Secretome, immunomodulation and extracellular vesicles

For many intended indications, the proposed active mechanism is paracrine rather than durable engraftment. Human adipose stromal cells secreted, per 10^6 cells, 1,203 +/- 254 pg vascular endothelial growth factor (VEGF), 12,280 +/- 2,944 pg hepatocyte growth factor and 1,247 +/- 346 pg transforming growth factor-beta; hypoxia increased VEGF secretion five-fold to 5,980 +/- 1,066 pg per 10^6 cells [25]. Growth-factor exposure is itself a modifier: bFGF or EGF increased HGF secretion, with a further increase after ascorbic acid, and inflammatory stimulation induced both haematopoietic and pro-inflammatory cytokines [26].

Adipose and marrow stromal cells share some paracrine outputs but are not interchangeable. ASC showed higher IGF-1, VEGF-D and IL-8 messenger RNA than marrow MSC in one comparative analysis, while VEGF-A and angiogenin were comparable; ASC-conditioned medium increased endothelial tubulogenesis and neutralisation implicated VEGF-A and VEGF-D [27]. Mixed preparations are also not reducible to a cell count: SVF-adipocyte co-culture produced higher concentrations of all 26 measured cytokines than adipocytes alone, with G-CSF increasing by 14,242 pg/mL (174-fold) [28].

Extracellular vesicles (EV) are a plausible component of this paracrine system, but their dose and cargo require direct measurement. Proteomic analysis identified 4,937 proteins in adipose-MSC EV, with proteins enriched for angiogenesis, coagulation, apoptosis, matrix remodelling and inflammation-regulation pathways compared with the parent cells [29]. PDGF altered ASC EV secretion and cargo, and PDGF-conditioned EV increased endothelial vessel-like structure formation, an effect reduced by c-kit or stem-cell-factor blockade [30]. These laboratory data support mechanistic hypotheses but do not validate an EV-mediated mechanism for an uncharacterised clinical nanofat or SVF product.

Immunomodulation is likewise contextual and inducible. ASC inhibited lymphocyte proliferation in contact and transwell systems, and IFN-gamma-induced indoleamine 2,3-dioxygenase was required for the observed suppression in mechanistic experiments [31]. In age-matched comparisons, adipose-derived MSC suppressed peripheral-blood mononuclear-cell proliferation and immature dendritic-cell

differentiation more potently than marrow-derived MSC at equal cell numbers, with higher IL-6 and TGF-beta1 secretion [32]. Such observations identify testable modes of action; they do not establish that any preparation with a matching surface phenotype will have the same in-vivo effect.

Donor age, sex, body mass index, comorbidity, smoking, irradiation and chemotherapy

Donor factors affect both recoverable cells and their measured fitness. In 189 women, the stromal-cell-to-adipocyte relationship was approximately constant across age and BMI, but differentiation capacity declined with increasing BMI and obesity was accompanied by greater total stromal-cell and adipocyte numbers [33]. A separate lipoaspirate study reported 404,000 +/- 206,000 cells per mL, with a negative association between yield and BMI but not age in female donors, whereas a single-platform series of 52 women found a mean 7.19 x 10^5 +/- 2.11 x 10^5 nucleated cells per mL and a significant age-related decline in SVF yield [34,35]. In 62 cultured samples from a 64-donor cohort, the yield was 375 +/- 142 x 10^3 ASC per mL over 4.1 +/- 0.7 days, demonstrating that culture duration can be embedded in a value called yield [36]. Different denominators and processing methods prevent these values from being pooled as a universal benchmark.

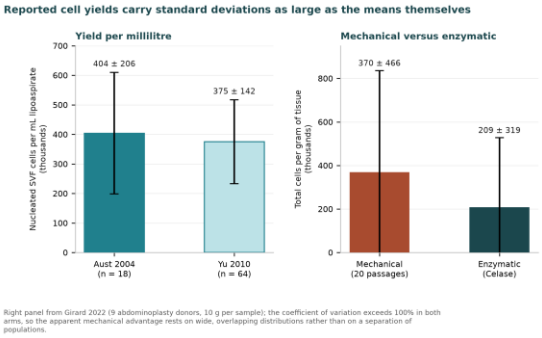

Figure 4: Yield is process- and donor-dependent. Published recovery differs by denominator, isolation platform, donor age and BMI, so a single cell-count target cannot establish equivalence [34,35,37].

Factor or process	Direction of effect	Magnitude / measured outcome	Source
Increasing donor age	Decreases	SVF yield declined in 52 female donors; aged cells had lower expansion, viability and differentiation	[35,38]
Higher BMI / obesity	Generally, decreases potency	Lower proliferation, CFU potential and osteogenesis; fewer CD90+ cells and lower proangiogenic capacity	[39,40]
Diabetes	Decreases	Reduced proliferation, migration and HGF, VEGF-A and IGF-1 release in a diabetic model	[41]
Smoking	Decreases	Viability 92.0 +/- 3.2% versus 95.6 +/- 1.9% in non-smokers; lower metabolic activity	[42]
Gamma irradiation	Dose-dependent decrease	10 and 30 Gy, but not 5 Gy, reduced viability at 24-168 h in five donor cultures	[43]
Neoadjuvant chemotherapy	No clear decrease in yield	No significant difference by exposure; cancer-side yield lower than contralateral tissue	[44]
Mechanical versus enzymatic isolation	Method-dependent	Literature ranges: mechanical 10,000-240,000 versus enzymatic 100,000-1,300,000 nucleated cells/cc	[37]

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Table 3: Donor and processing factors modifying SVF yield or potency. Effect direction is endpoint-specific; reported magnitudes should not be extrapolated across platforms or clinical indications.

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CFU, colony-forming unit; SVF, stromal vascular fraction. Evidence includes in-vitro, ex-vivo and disease-model studies and should be interpreted accordingly.

Ageing influences more than the initial count. ASC from donors older than 60 years showed fewer cells, lower cumulative population doublings, reduced viability and differentiation, and higher senescence-associated beta-galactosidase, p16INK4a and p21 expression [38]. Across BMI 18.5-32.8, higher BMI correlated inversely with proliferation and colony formation and was associated with less mineralisation and lower alkaline-phosphatase expression [39]. Obese-donor tissue also yielded fewer CD90-positive cells with reduced differentiation and proangiogenic capacity, alongside mitochondrial and self-renewal abnormalities in human and experimental samples [40,45]. ASC from obese donors have additionally polarised macrophages and microglia towards a pro-inflammatory phenotype in experimental work, which complicates generic claims of anti-inflammatory action [46].

Comorbidity and prior exposure require separate assessment rather than exclusion by convention. Diabetic ASC had lower proliferation, migration and release of HGF, VEGF-A and IGF-1, and their SVF-mediated wound benefit was blunted in a diabetic model [41]. In smoking donors, viable cells measured 92.0 +/- 3.2% versus 95.6 +/- 1.9% in non-smokers ($P < 0.01$), with lower colony formation and metabolic activity [42]. In five donor cultures, 10 and 30 Gy gamma irradiation reduced viability at each measured time point whereas 5 Gy did not, while breast ASC yield and in-vitro proliferation did not differ appreciably after neoadjuvant chemotherapy in a small clinical comparison [43,44]. Sex is frequently underpowered or unreported in these datasets; it should be recorded as a prespecified source variable rather than

assumed irrelevant.

The isolation pathway adds another layer of variation. A literature comparison reported mechanical recovery of 10,000-240,000 nucleated cells per cc versus 100,000-1,300,000 per cc for manual collagenase digestion, although viability, CFU frequency and study protocols varied widely [37]. Conversely, one modified mechanical protocol reported 369,557 +/- 466,220 cells per gram after 20 passes and 291,272 +/- 394,588 after 30 passes, both higher than its enzyme comparator but with declining phenotype frequency and CFU-F after additional passes [47]. In a recent mechanically isolated product co-administered with platelet-rich plasma, 23 knee osteoarthritis patients had 49.7 +/- 22.9 x 10^6 viable nucleated cells per final mL; the unusually high per-final-volume count cannot be compared directly with per-tissue-volume studies [48].

Differentiation potential and comparison with bone-marrow stromal cells

Culture-expanded ASC can meet many of the ISCT minimal criteria for multipotent mesenchymal stromal cells, including plastic adherence, CD105/CD73/CD90 expression and in-vitro trilineage differentiation, but fresh adipose stromal cells are characteristically CD34-positive and therefore do not map perfectly onto a culture-derived criterion set [49,50]. Adipose-derived adherent cells express a broad stromal surface profile and differ from marrow cells in markers such as STRO-1, while their transcriptome includes angiogenesis and extracellular-matrix programmes that are reproducible but not identical across donors [51,52]. This is why product identity needs both time point and assay context.

Adipose tissue is attractive partly because progenitors are more frequent than in marrow. The IFATS/ISCT statement places CFU-F progenitor frequency at 1-10% of SVF nucleated cells, compared with more than 0.001% of marrow nucleated cells, and a review estimated that uncultured adipose stem/progenitor cells reach up to 3% of whole cells, approximately 2,500-fold the marrow frequency [3,53]. Isolation success was 100% for both adipose and marrow samples in one comparison, with higher colony frequency in adipose tissue, while white adipose tissue contained on average 263 times more CD45-negative, CD34-positive cells per mL than marrow in another study [54,55]. More cells, however, does not imply superior differentiation in every target tissue.

Patient-matched comparisons favour marrow for some skeletal endpoints. Marrow-derived aggregates expressed 500- to 5,000-fold more type II collagen than adipose-derived aggregates, despite 68% higher DNA content in the latter [56]. In another study, marrow cells had greater osteoblastic differentiation and a higher chondrogenesis score than adipose cells (6.5 +/- 1.3 versus 4.3 +/- 1.6), whereas a further comparison found greater adipogenic differentiation and colony formation in adipose cells but greater osteogenesis in marrow cells [57,58]. These differences argue against a source-agnostic MSC claim and for indication-specific potency assays.

Culture can further change the relevant phenotype. ASC retained adipogenic and osteogenic differentiation through 10 passages in one series, but growth slowed after passage 5 and late cultures showed evidence of osteogenic drift [59]. In eight donor cultures, proliferative arrest occurred between passages 5 and 14 and cumulative population doublings ranged from 8.03 to 28.97, with strongly donor-specific loss of clonogenicity and differentiation [60]. Consequently, a culture-expanded product should

report passage, population doublings, cryopreservation and functional potency rather than adopting the presumed properties of fresh SVF.

Finally, the regenerative niche is not biologically neutral in all contexts. Adipose CD34-positive progenitors promoted tumour growth and metastasis in experimental breast-cancer models, and ASC increased primary metastatic breast-cancer-cell proliferation 5.1-fold in vitro; in one xenograft experiment, active CD90-positive tumour cells formed tumours at 17 of 40 sites only when co-injected with ASC [55,61]. In a separate triple-negative breast-cancer model, ASC-conditioned medium stimulated migration and co-injection increased metastasis, with donor-dependent effects on primary growth [62]. These studies do not establish clinical harm from every local autologous application, but they support careful oncological history, indication-specific follow-up and restraint in claiming that an angiogenic stromal product is intrinsically regenerative.

Harvest and Infiltration: Variables That Determine What Is in the Syringe

Infiltrate is a processing variable, not background anaesthesia

The harvested product is determined before aspiration begins: carrier fluid, vasoconstrictor, local anaesthetic, infiltration-to-aspirate ratio, dwell time and temperature all alter the relative amounts of blood, extracellular fluid, intact adipose parcels and recoverable stromal cells [63–65]. Coleman described either Ringer's lactate with epinephrine 1:400,000 or 0.5% lidocaine with epinephrine 1:200,000 at approximately 1 mL infiltrate per mL fat, whereas the original nanofat protocol used modified Klein solution containing lidocaine 800 mg/L and adrenaline 1:1,000,000 [63,66]. A modern Klein-type protocol may include saline, lidocaine, bicarbonate and adrenaline, but the exact concentrations and temperature are often not reported with the product data [67,68]. This omission matters because ASCs exposed to lidocaine or prilocaine for 2 h showed reduced metabolic activity, and by 6 h both agents reduced metabolic activity and cell number in vitro [69]. Conversely, an 11-patient lipotransfer study used 0.6 mg/mL lidocaine with epinephrine and could not detect significant inter-patient variability, which does not establish that anaesthetic exposure is biologically neutral across concentrations or dwell times [68].

Adrenaline limits bleeding and therefore changes the non-adipose fraction entering later filtration or density separation, but it should be reported as a component of the manufacture rather than treated as a generic operative detail [65,70]. The 2019 breast-grafting consensus recorded the Klein formulation of saline, lidocaine 0.1% and epinephrine 1:1,000,000 in 39% of panel practice, while a contemporary trial protocol specified 40 mL Carbocain 1%, 250 mL saline, 0.5 mg adrenaline and bicarbonate before manual harvest [65,70]. Such heterogeneity precludes attributing a downstream CD34-positive frequency to a device alone when the drug exposure, dwell interval and aqueous carry-over differ [71,72].

Cannula, port geometry, vacuum and donor site

Cannula external diameter is an incomplete descriptor because side-port diameter, number, edge sharpness, distribution, length and aspiration method together set local shear and parcel geometry [73–75]. The original nanofat harvest used a 3-mm multiport cannula with sharp 1-mm side holes, whereas SEFFI used a 2-mm cannula with fifteen 0.8- or 0.5-mm ports and MicroSEFFI fifteen 0.3-mm ports, all aspirated manually into 10-mL syringes [66,73]. In 10 donors, a 5-mm single-opening cannula followed by

micronisation generated 0.20 cm3 SVF from 5 cm3 fat, greater than the 0.11 cm3 after direct 1-mm harvesting; direct 5-mm harvesting yielded 0.23 cm3, illustrating that harvest aperture and post-harvest reduction are not interchangeable manipulations [76]. Rheological modelling also found lower inlet static pressure and maximum velocity with a 2.5-mm than a 2-mm three-hole cannula at 6 x 10^4 Pa suction, although the experiment was small and does not identify a clinical optimum [74].

Vacuum is likewise a dose, not a binary choice. With a 3-mm cannula in three patients, -350 mmHg pump or power-assisted liposuction produced greater SVF yield than -700 mmHg and significantly more than manual syringe aspiration; however, the power advantage at -350 mmHg appeared in only two of three patients [77]. In a separate 10-patient comparison, -30 +/- 5 kPa produced more than twice the SVF-cell number obtained at -55 +/- 5 kPa and was associated with smaller particles, fewer red cells, better early growth, greater bFGF and VEGF secretion and greater adipogenic differentiation [78]. Observational and consensus sources point in the same direction, with low-pressure suction below 250 mmHg considered favourable to adipocyte viability and -700 mmHg associated with more than 10% damage, but their underlying endpoints and harvest systems differ [65,79]. The manuscript should therefore report measured pressure at the cannula, syringe or pump setting, not merely 'manual' or 'low suction' [80,81].

Donor-site effects cannot be generalised from a single harvest region. In 40 women, outer thigh yielded 12.31 +/- 1.2 x 10^6 SVF cells, exceeding abdomen (2.97 +/- 0.2 x 10^6), waist (5.61 +/- 0.31 x 10^6), inner thigh (6.34 +/- 0.1 x 10^6) and inner knee (7.96 +/- 0.8 x 10^6) cells under one isolation protocol [82]. In contrast, 22 donors had a higher ASC frequency in abdominal tissue than hip/thigh tissue, 5.1 +/- 1.1% versus 1.2 +/- 0.7% of SVF, and a 30-patient study found no overall regional difference in total cells despite a lumbar versus inner-thigh pairwise difference [10,83]. Harvest method itself confounds site comparisons: paired studies have shown significant method-associated differences in total SVF and ASC yield, and an older comparison reported distinct immunophenotypes after manual Coleman versus pump-assisted collection [79,84].

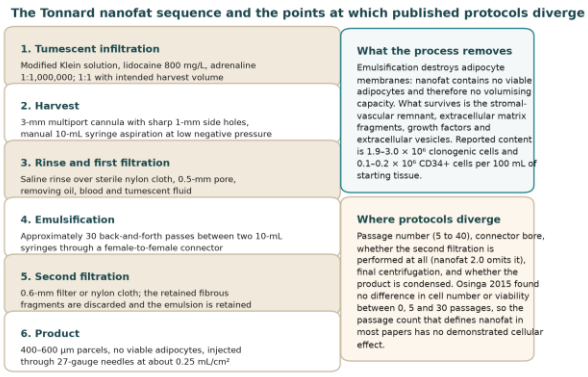

Figure 6: From infiltrate to injectable derivative. Harvest, separation and size-reduction steps each select a different combination of cells, matrix, oil and fluid; report the sequence rather than the final label alone [66,72,85].

Assisted harvesting techniques

Water-jet-assisted lipoaspiration couples fluid infiltration and aspiration, and should be documented by

flow, fluid temperature, cannula and vacuum. In 13 patients treated at 90-130 mL/min with 37-38 C solution and 500 mbar negative pressure, mean total SVF yield was 6.1 x 10^5 cells/mL aspirate and 43% of SVF cells were CD34-positive [86]. A within-donor comparison combined water-jet collection with automated Sepax-2 processing in 10 donors, but the accessible report provides no quantitative yield or viability that would permit a claim of superiority [87]. Ultrasound-assisted liposuction did not compromise the measured regenerative potential of CD45-negative/CD31-negative/CD34-positive cells in a three-patient comparison, whereas laser-assisted harvest in seven patients initially reduced viable stem-cell numbers and increased apoptosis indicators before the difference had reversed at 72 h [88,89]. These small mechanistic studies support technique-specific description, not equivalence claims across energy-assisted platforms [88,89].

Processing: From Coleman Fat to Nanofat

Separation of fluid, oil, viable tissue and matrix

Coleman-style processing separates a lipoaspirate into an upper oil layer, a middle adipose layer and an aqueous or blood-rich lower layer, then removes oil by decanting and wicking. The original convention was 3,000 rpm for 3 min, with 10 mL harvested fat yielding 4-6 mL refined fat; Coleman discouraged washing, whereas subsequent closed washing and filtration platforms deliberately remove blood, free lipid and tumescent fluid [63,64,90]. Decantation is a lower-force alternative but does not standardise time, temperature or residual fluid. In comparative work, 20-min room-temperature decantation, 1,200 g for 3 min, REVOLVE and PureGraft were all used as distinct processing conditions, so a manuscript that reports only 'processed fat' cannot be reproduced [91]. Gauze rolling is also an active fluid-removal intervention: it usually takes 2-4 min and in one comparison gave 90% concentrated fat, similar to 91% after 1,200 g centrifugation, with similar ASC content and mouse graft retention [92,93].

Evidence does not identify a universal best separation method. A systematic review found no compelling evidence for a single superior lipoaspirate-processing technique, and another found that only 42% of included studies adequately described inclusion criteria while insufficient centrifuge information prevented RCF calculation in 11 studies [80,94]. The physiological target should be stated: maximal volume concentration, retained adipocyte viability, recoverable nucleated cells, matrix-rich injectability or a combination of these endpoints are not the same product specification [95,96]. Large oil droplets and large graft diameters carry a distinct graft-survival problem, as the viable and regenerating zones are limited by diffusion and oil drops greater than 8 mm may form cysts [95].

Centrifugation: rpm is not a biological dose

Revolutions per minute is rotor speed, whereas relative centrifugal force is the acceleration delivered at a specified radius. The conversion is RCF = 1.12 x 10^-5 x radius in cm x rpm^2; hence rpm alone cannot specify the biological dose or enable cross-study comparison [80]. Coleman 3,000 rpm for 3 min has been reported as 1,200 g in one protocol, 1,500 g in another and approximately 1,811 g in a third, demonstrating quantitatively why the convention is not a transferable g-force [97–99]. Reviews of 54 centrifugation papers identify this g-versus-rpm confusion, along with inconsistent harvest, transfer and survival methods, as a central cause of discordant findings [81]. Every report should provide rotor type, radius, RCF, duration, temperature, fill volume, braking and what was removed after the spin [72,80].

Biological findings vary with the comparator and endpoint. Ferraro et al. found low viability and fat-cell damage at 3,000 rpm reported as 1,500 g for 3 min, while 1,300 rpm reported as 250 g for 5 min improved density with good viability and progenitor preservation relative to simple decantation [98]. In contrast, Son et al. found no change in viable adipocytes or ASCs after 1,000, 3,000 or 4,000 rpm for 3 min, and the broader review records both no acceleration effect in one study and harmful effects at higher forces in others [92,100]. Thus, a nominal speed should not be used to infer viability, nor should a p value from one rotor be converted into a device recommendation. For SVF-oriented work, low, medium and high bands of 400-600 g, 1,200-1,500 g and 2,000-2,500 g for 5-20 min are descriptive categories, not validated release criteria [96].

Emulsification, filtration and the nanofat family

Tonnard's 2013 nanofat was not simply small-volume fat. It was a sequence of 3-mm, 1-mm-side-port harvest, rinse, 0.5-mm nylon-cloth filtration, 30 transfers through a female-to-female Luer-Lok connector between 10-mL syringes, and repeat filtration, yielding approximately 1 mL nanofat per 10 mL lipoaspirate [66]. The product was intended for 27-gauge injection and is commonly described as a 400-600-micrometre emulsion, although later papers variously state particles below 0.1 mm or describe a 95% volumetric reduction in mature adipocytes [101–103]. These measurements are not interchangeable because particle diameter, viable adipocyte content and isolated-cell composition depend on the analytical route as well as the preparation [104,105].

Subsequent variants changed each of the decisive steps. Nanofat 2.0 retained 30 passes but omitted final filtration and was reported to have higher ADSC content and differentiation potential; a no-filtration mechanical series used 20, 30 or 40 passes and reported 369,557 +/- 466,220 cells/g after 20 passages and 291,272 +/- 394,588 cells/g after 30 [101,106]. Yet a six-donor study found no difference after 0, 5 or 30 intersyringe shifts in cell number, viability, clonogenicity or adipogenic differentiation, showing that the number of passages alone is an inadequate process descriptor [107]. Connector bore changes tissue stress: with 30 transfers at approximately 2.5 mL/s, oil release rose from 13.6 +/- 6.2% at 3.76 mm to approximately 84% at 0.80 mm, and simulation located the highest stress in the 0.80-mm group [108].

Filtration is similarly an intervention, not a neutral final sieve. Tonnard's protocol used 0.5-mm nylon cloth, whereas a Tulip sequence used 2.4-, 1.4- and 1.2-mm connectors followed by 500-micrometre mesh; the latter reduced SVF and MSC recovery, leading the authors to suggest pores above 600 micrometres [66,109]. A device comparison contrasts LipocubeNano's 10 passes and single 500-micrometre filter with NanoTransfer's 30 transfers and double 400 plus 600-micrometre filters; it found 2.24 x 10^6 versus 1.44 x 10^6 viable cells/cc and 96.05-96.75% viability, but this should be interpreted as an inseparable device-process comparison rather than evidence that one filter pore is causal [110]. Fluidic testing likewise found 898,525 +/- 329,107 cells/mL in microfat, 130,613 +/- 103,428 in manual nanofat and 271,450 +/- 58,106 after a 1-mm-membrane fluidic device, at viabilities around 91-93% [111].

Technique	Key steps	Passages	Filtration	Reported output	Source
Original nanofat	Rinse, intersyringe emulsification	30	0.5-mm cloth before and after	About 1 mL from 10 mL lipoaspirate	[66]

Nanofat 2.0	Tonnard-like emulsification	30	Final filtration omitted	Higher ADSC content and differentiation reported	[101,103]
No-filter mechanical SVF	Intersyringe emulsification	20, 30 or 40	None	20 passes: 369,557 +/- 466,220 cells/g	[106]
Tulip NanoTransfer	Sequential narrowing connectors	30	Single 500-micrometre mesh in filtration arm	Filtration reduced SVF and MSC amount	[109]
LipocubeNano	Port reduction and inter-port transfer	10	Single 500-micrometre filter	2.24 x 10^6 viable cells/cc; 96.05-96.75% viability	[110]
Hy-Tissue Nanofat	Coupled-syringe mixing	30	120-micrometre inner bag	Connective-tissue fragments injectable through 27-30 G	[112]

Table 4: Nanofat and mechanical-SVF variants. The shared label conceals material differences in shear history, passages and sieve steps.

ADSC, adipose-derived stromal/stem cell; SVF, stromal vascular fraction.

Protocol	RCF or rpm as reported	Duration	Effect on cell yield or viability	Source
Coleman structural fat	3,000 rpm; reported elsewhere as 1,200-1,811 g	3 min	Clinical convention; refined fat 4-6 mL from 10 mL harvest	[63,97,99]
Ferraro comparison	3,000 rpm = 1,500 g; 1,300 rpm = 250 g; 500 rpm = 50 g	3 or 5 min	High force damaged fat cells; 250 g/5 min improved density with good viability	[98]
Son donor study	1,000, 3,000 or 4,000 rpm	3 min	No change in viable adipocytes or ASCs; RCF not stated	[100]
Gauze versus spin	1,200 g	3 min	91% concentrated fat versus 90% with mesh/gauze; ASC counts and mouse retention similar	[93]
Nanofat filtration study	1,200 g	1 min	Pre-transport concentration before 30 passes and 500-micrometre filtration	[109]

Table 5: Centrifugation and processing parameters reported across studies. Rpm cannot be compared without rotor radius; each row retains the authors' own reporting convention.

RCF, relative centrifugal force. Where an RCF is absent, it should not be inferred from rpm alone.

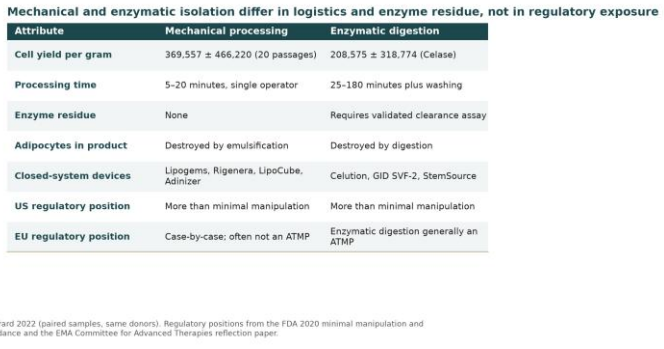

Figure 7: Mechanical and enzymatic paths do not yield the same analyte. Mechanical products retain variable extracellular matrix and tissue fragments, whereas enzymatic digestion liberates a cell suspension [3,113,114].

Condensed nanofat, SVF gel and mechanical versus enzymatic isolation

Condensed or matrix-enriched products add a second concentration step after shear. In one SVF/ECM-gel protocol, fat was spun at 1,200 g for 3 min, sheared for 1 min at 10 mL/s through a 2.4-mm connector, then spun at 2,000 g for 3 min; the resulting gel retained significantly more volume than Coleman fat at

3, 14, 28 and 60 days in mice [115]. In a 28-donor cellular study using the same broad sequence, the gel retained about 80.5% of ADSCs and 74.2% of endothelial cells and enriched the density of CD45-negative/CD31-negative/CD34-positive and CD45-negative/CD31-positive/CD34-positive cells while reducing CD45-positive cells [116]. 'SVF gel' therefore describes a shear-and-concentration product containing matrix, not an enzymatically isolated cell pellet [117,118].

Mechanical and enzymatic isolation answer different questions. Enzymatic SVF typically digests minced tissue with collagenase, dispase, trypsin or related enzymes at 37 C for 30 minutes to more than 1 hour followed by differential centrifugation; mechanical approaches use washing, filtration, centrifugation, vibration, mincing or shear and retain variable tissue architecture [3,117]. A systematic review reported mechanical and enzymatic ranges of 0.03-26.7 x 10^5 versus 2.3-18.0 x 10^5 cells/mL and 46-97.5% versus 70-99% viability, while mechanical procedures were faster at 8-20 versus 50-210 min [113]. An older review reported 10,000-240,000 mechanically recovered versus 100,000-1,300,000 enzymatically recovered nucleated cells/cc and cautioned that point-of-care mechanical speed trades against cell recovery [37]. These overlapping ranges invalidate a generic claim that 'mechanical SVF' is a defined cell dose; paired split-sample studies, rather than cross-study means, are necessary for a fair yield comparison [114,119].

Enzyme concentration, loading, agitation, stop conditions and clearance assay also change the reference standard. With 0.02% collagenase for 1 h, a 0.4 loading-volume ratio produced 2.65 +/- 0.98 x 10^5 total nucleated cells/mL and 72.96 +/- 4.64% viability, whereas the 0.8 ratio produced 1.58 +/- 0.96 x 10^5 cells/mL and 57.70 +/- 3.88% viability [120]. Commercial comparisons have reported residual collagenase differences of 5.1-, 13.0- and 57-fold relative to Celution for three other systems, while a later four-device comparison found negligible residual collagenase but viability from 50.3% to 84.02% and CFU-F from 0.495% to 1.704% [121,122]. Any enzymatic report should specify enzyme identity, activity or units, tissue-to-enzyme ratio, incubation time and temperature, neutralisation, washing, residual-enzyme assay and its detection limit [3,67].

Closed systems, devices and storage

Closed or functionally closed systems may improve handling consistency and reduce open transfers, but the term should not be conflated with a standardised biological output. Celution processes up to 360 mL in about 1.5 h to 5 mL using Celase, reporting 3.6 +/- 1.8 x 10^5 cells/g and 84.7% viability across 31 donors; its ultrasound mechanical comparator recovered only 11.2-13.7% of Celution yield and higher energy caused more than 90% cell death [123]. PureGraft washing and filtration reduced blood cells and free lipid and improved glycerol-release viability relative to gravity separation and Coleman centrifugation in a 22-donor study, whereas closed REVOLVE filtration completes in approximately 10 min using a 200-micrometre mesh and repeated lactated-Ringer washes [90,124,125]. Device choice also changes recovery: AutoPose and Lipogems recovered 74% and 42% of decanted-fat mass, respectively, and their direct outgrowth yields diverged despite non-significant initial enzymatically liberated cell counts [105].

Device	Mechanism	Processing time	Reported yield or concentration	Regulatory framing	Source
Celution	Closed enzymatic Celase digestion and separation	About 1.5 h	3.6 +/- 1.8 x 10^5 cells/g; 84.7% viability	Functionally closed cell-processing system	[123]

Device	Mechanism	Processing time	Reported yield or concentration	Regulatory framing	Source
MultiStation, LipoKit, GID SVF-2, StemSource	Commercial cell-separation systems	65.4-120.8 min	1.01-6.24 x 10^5 cells/mL; viability 50.3-84.02%	Device comparison; enzyme clearance must be assayed	[122]
REVOLVE ENVI 600	Active filtration, 200-micrometre mesh and washes	About 10 min	Yield not reported in accessible extract	Closed active filtration product	[125]
Lipogems	Saline-immersed mechanical microfragmentation	6 min agitation reported	5 x 10^5 hADSCs/mL product in one study	Disposable closed mechanical device	[70,126]
Beauty-Stem / Duo	Wash and dual filtration without centrifugation	5-45 min	Up to 400 mL harvest; about 200 mL purified fat	Mechanical purification device	[127]
Rigeneracons	Mechanical disaggregation with 50-micrometre cut-off	About 2 min	73% viability in 3 patients; 96-100% across mixed samples	Micro-graft filtration device	[128]

Table 6: Commercial and closed-system devices. Mechanism, processing time and analytical method must accompany the device name because nominally similar platforms yield different products.

hADSC, human adipose-derived stromal/stem cell. Regulatory status is jurisdiction- and intended-use-dependent; the table describes process framing, not marketing authorisation.

Comparative device literature reinforces the need to report the actual workflow. A 30-patient breast study required approximately 12 min for PureGraft to prepare 300 cm3 of injectable graft, whereas its centrifugation comparator used 3,000 rpm for 3 min; a five-donor comparison separately evaluated decantation, centrifugation, Macrofill, PureGraft and Adipure from 50-150 mL aliquots [129,130]. In a preliminary paired investigation, a 180-min collagenase protocol and Lipogems mechanical processing produced different short-term cell counts, further illustrating that a device name cannot replace a material description [131].

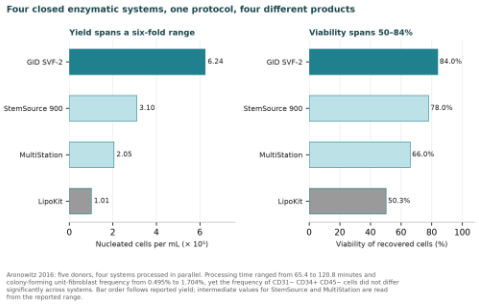

Figure 8: Device architecture imposes an unreported dose. Closed handling may standardise transfers, but filtration, wash volume, enzyme exposure and output assay remain product-defining variables [105,123,132].

Storage requires its own manufacturing record. A systematic review found slow cooling at approximately 1 C/min, storage at -196 C and rapid 37 C warming common, with a 90% FBS plus 4% DMSO plus 6% trehalose formulation recovering more than 80% viability at 1, 6 and 12 months in one included study [133]. Isolated SVF frozen with 10% DMSO retained post-thaw viability of 61.9-65.3%, compared with 67.3% in unfrozen controls, whereas unprotected tissue frozen at -20, -80 or -196 C had temperature-dependent oil release and morphology changes [134,135]. Microfragmented fat cryopreserved at -80 C with 10% DMSO yielded hADSCs after at least 12 months, but frozen lipoaspirate in the same study did not; a recent systematic review similarly concludes that nanofat may need tailored cryopreservation protocols [126,136]. In a murine nanofat study, gradual cooling to -80 C did not outperform fresh or -20 C material on the reported vascular endpoints, while shock freezing had the highest apoptosis; this does not validate clinical storage without cryoprotectant [137]. A 43-patient SVF study also observed a fall from

42.65% to 20.62% viability at 4 C by one month, underscoring that time, temperature, cryoprotectant and thaw method must be reported [138].

Classification and Nomenclature

One word, several materially different products

The same word denotes different products because authors classify by harvest cannula, particle size, intended injection route, processing action, retained adipocyte content, matrix content or isolated-cell phenotype. A review of mechanically obtained products identified 46-47 different terms and definitions; 'nanofat' occurred 93 times and was newly defined 30 times [104]. Consequently, a paper can call a 400-600-micrometre emulsified tissue, a filtered cell- and matrix-rich suspension, or a post-digestion cellular pellet 'nanofat' despite these materials having different tissue architecture and regulatory implications [3,101,117]. Size taxonomies are useful but insufficient: macrofat is often >2.4 mm, microfat uses 1.2-2.4-mm cannula holes, and nanofat is described as 400-600 micrometres and injectable through 27-gauge needles, while SEFFI retains viable adipocyte-containing clusters below 1 mm [73,101,139].

The IFATS/ISCT nomenclature statement anchors 'SVF' to the heterogeneous cell population obtained after enzymatic dissociation of adipose tissue, and recommends describing stromal cells within it by CD45-negative/CD235a-negative/CD31-negative/CD34-positive phenotype rather than labelling the whole mixture as MSCs [3]. That consensus explicitly states that the impact of different enzymatic and mechanical procedures on antigen expression was insufficiently known, which prevents its enzymatic SVF definition from validating every mechanical product called 'SVF' [3]. Copcu's taxonomy instead separates direct adinising and enzymatic digestion from indirect emulsification and microfragmentation, proposing total stromal cells (TOST) for mechanically recovered cell-containing material [104,140]. Broader taxonomies organise products by harvest and processing technique, from millifat and microfat to emulsified fat, centrifuged fat, SVF, cultured cells and cryopreserved fat, or from cell-containing grafts to matrix-enriched and decellularised derivatives [118,141].

System	Basis of classification	Categories	Adoption	Limitation
IFATS/ISCT	Enzymatic tissue dissociation and cell phenotype	SVF; stromal subset defined by CD45-/CD235a-/CD31-/CD34+	International society statement	Does not define mechanically processed tissue products [3]
Copcu / TOST	Direct versus indirect processing and fat preservation	Adinising, enzymatic digestion, emulsification, microfragmentation	Proposed terminology	Terms are not universally adopted [104,140]
Process hierarchy	Harvest, processing and derivative architecture	Milli/microfat, emulsified fat, SVF, cells, matrix and decellularised products	Review frameworks	No common cut-offs or release assays [118,141]
Clinical fat-grafting matrix	Volume demand and recipient-site condition	Small/large volume x healthy/pathologic site	Surgical planning framework	Classifies indication more than manufactured product [142,143]
AD-MPT proposal	Mechanical harvesting and processing descriptors	Structured nomenclature proposed	Recent orthopaedic proposal	Accessible record lacks category cut-offs [144]

Table 7: Classification and nomenclature systems side by side. No single system simultaneously specifies tissue architecture, cell composition, manufacture and clinical indication.

AD-MPT, adipose-derived mechanically processed tissue; IFATS, International Federation for Adipose Therapeutics and Science; ISCT, International Society for Cell and Gene Therapy.

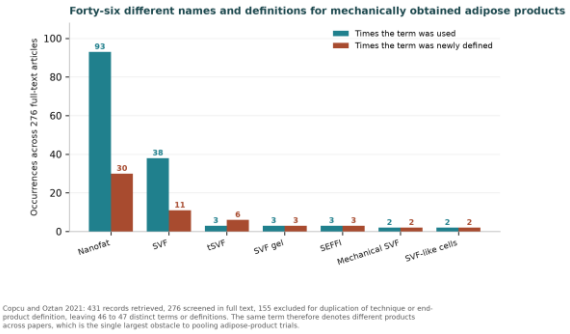

Figure 9: Terminology is a map, not a specification. A product name should be accompanied by harvest, processing, tissue architecture and cell-characterisation descriptors [104,117,144].

Clinical volume classifications add useful context but do not resolve biological nomenclature. Del Vecchio and Rohrich used volume demand and recipient-site health to create four grafting situations, whereas a 62-surgeon ISPRES survey used small-volume less than 100 mL, large-volume 100-200 mL and mega-volume above 300 mL categories [142,145]. The survey also documented different cannulas, aspiration modes and preparation choices for small and large-volume practice, confirming that an indication-based label cannot be used as a proxy for a product composition [145]. A breast-grafting expert panel reached consensus on nine of ten statements but could not reach consensus on storage or cryopreservation, another indication that technical names still outpace harmonised manufacturing standards [65].

Characterisation, Quality Control and Minimum Reporting

Measure the product that was actually injected

A minimum analytical dataset should begin with total nucleated cells per input volume or mass and per final injectable volume, viability with method and timepoint, and the frequency of CD45-negative/CD31-negative/CD34-positive stromal cells. The IFATS/ISCT statement proposes release thresholds for enzymatically derived SVF of viability above 70%, CD34 above 20%, CD31 below 20%, CD45 below 50% and CFU-F above 1%, but these are reference criteria for a defined enzymatic cell population rather than universal pass-fail limits for tissue fragments [3]. Reports should add CFU-F frequency, particle-size distribution or microscopy, residual oil and aqueous fraction, and, where relevant, endothelial, pericytic and immune-cell proportions [71,146]. The importance of this distinction is illustrated by microfragmented adipose tissue: it had a viable-cell ratio of 0.44 +/- 0.12 relative to lipoaspirate and viability fell from 67 +/- 6% to 49 +/- 8%, yet the proportion of ASCs within the CD45-negative compartment did not significantly change [146]. A relative enrichment can therefore coexist with loss of total dose [105,146].

Assays measure different analytes and must not be substituted for one another. Enzymatic digestion counts cells liberated from tissue, direct outgrowth measures cells that migrate and proliferate under culture conditions, flow cytometry measures marker-defined events among analysed cells, and CFU-F measures clonogenic growth under laboratory conditions [3,105]. In the AutoPose-Lipogems comparison, seven-day direct outgrowth was approximately an order of magnitude lower than initial enzymatically liberated counts, so an outgrowth value cannot be presented as the native cell dose [105]. Viability

measured by dye exclusion, metabolic assay, glycerol release or post-thaw adherence also answers different questions; reporting a single percentage without assay, denominator and sampling time creates a false appearance of comparability [90,100,134].

Potency and a usable reporting minimum

No single surface marker is a potency assay. Functional testing should be linked to the proposed mechanism and may include CFU-F, endothelial network support, paracrine-factor release, adipogenic differentiation, immunomodulatory response or a justified disease-relevant assay, with pre-specified acceptance ranges and matched controls [78,86,147]. Current evidence is not sufficient to claim a universal potency correlate: a recent mechanical-SVF synthesis noted that no study statistically analysed image-based differentiation metrics with n of at least 10, and commercial systems have differed in yield, viability, CFU-F and residual enzyme despite similar phenotype frequencies [114,122]. The 2026 comparison of eight commercial nanofat devices found median viability above 85% for all but different technical and biological scores, a practical demonstration that viability alone cannot certify equivalence [132].

MIBO and DOSES offer the appropriate principle: describe the starting material, production process, final product and recipient context so that a reader can identify what was delivered. MIBO supplies reporting checklists for biologic and MSC studies, while the DOSES consensus reached agreement on 27 descriptive items and strongly supported a descriptive framework [147,148]. Adherence cannot be assumed from publication date: audits of PRP studies found 72% overall MIBO adherence with 71% of studies below 80%, and a separate lumbar-disc review also found poor adherence; these are cautionary analogues rather than adipose-specific estimates [149,150]. For adipose derivatives, the minimum dataset should be presented before outcomes rather than reconstructed from a methods paragraph after a clinical claim [72,85].

At a minimum, authors should report donor characteristics and site; full infiltrate composition, volume, temperature and dwell; cannula dimensions and port geometry; aspiration pressure and harvest mode; all separation, wash, filtration, shear, centrifugation and storage parameters; final injectable volume and particle-size distribution; total nucleated and viable-cell dose; CD34-positive/CD31-negative/CD45-negative frequency with gating strategy; CFU-F or a justified potency assay; and residual enzyme testing where digestion was used [3,72,80,147]. The final label should be descriptive - for example, 'mechanically emulsified, 500-micrometre filtered adipose tissue' or 'collagenase-isolated SVF' - rather than relying on nanofat, SVF or stem-cell terminology alone [117,140]. This specification-centric approach makes negative studies interpretable and permits future comparison of products that currently share a name but not a material identity [72,104].

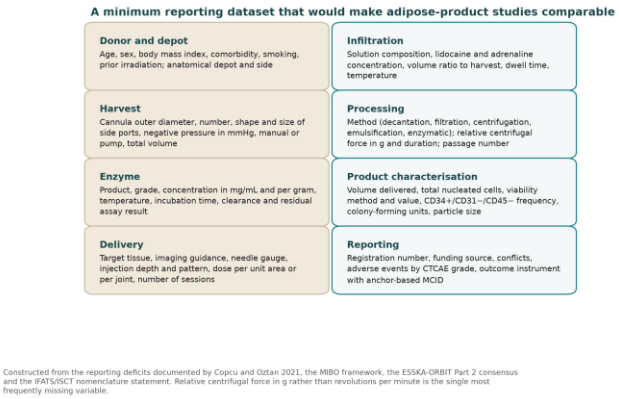

Figure 10: Minimum reporting dataset for adipose derivatives. Report the harvest, process, final material, cellular dose, assay method and clinical delivery as linked parts of a single manufacturing record [3,147,148].

Musculoskeletal Applications: Knee Osteoarthritis and Beyond

Randomised evidence in knee osteoarthritis

Knee osteoarthritis is the only musculoskeletal indication in which adipose-derived products have been tested in several randomised designs, but the interventions span mechanically processed stromal vascular fraction (SVF), micro-fragmented adipose tissue (MFAT), and culture-expanded adipose stromal cells (ASCs), so they should not be treated as a single dose-defined medicine [151–153]. The most informative studies are those with a credible placebo or active comparator, pre-specified patient-reported outcomes and sufficient follow-up, because uncontrolled within-group change is large after an injection procedure [151,153]. Across this evidence base, apparent efficacy diminishes as the comparator becomes more stringent: symptomatic separation is more often reported versus saline or hyaluronic acid (HA) than versus corticosteroid or platelet-rich plasma (PRP) [151,154,155]. Product characterisation is uneven, with several trials reporting injectate volume but not a viable stromal-cell dose, which makes cross-trial biological inference provisional [156–158]. Table 8 therefore presents the randomised evidence by product class and comparator rather than implying interchangeability.

The MILES phase 2/3 trial is the pivotal active-comparator experiment. It randomly assigned 480 adults across five US sites to autologous bone-marrow aspirate concentrate (BMAC), adipose SVF, umbilical cord tissue product or corticosteroid, with 440 participants in the primary analysis and 12-month VAS pain and KOOS pain co-primary outcomes [151]. Mean VAS change was -19.4 with SVF and -20.9 with corticosteroid, a between-group difference of +1.5 points (P=0.56), while KOOS pain improved 17.2 and 17.7 points, respectively, a -0.50-point difference (P=0.82) [151]. BMAC and umbilical cord tissue were similarly non-superior to corticosteroid, and no arm showed a significant MRI osteoarthritis score change, despite all four arms exceeding the investigators' MCID criteria [151]. The trial does not show that SVF is ineffective; rather, it shows that a one-time SVF procedure did not provide a clinically discernible incremental benefit over corticosteroid at 12 months in this population [151]. Procedure burden also differed: post-procedural contusion occurred in 38.6% after SVF versus 0% after corticosteroid, and four SVF products failed release criteria for endotoxin [151].

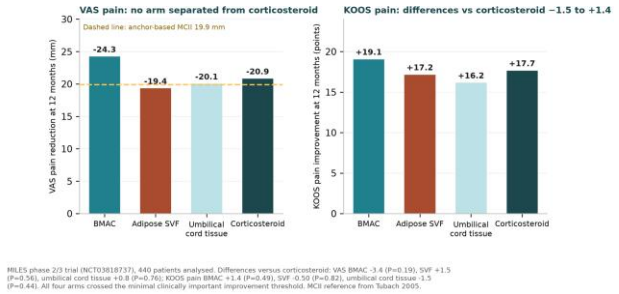

Figure 11: MILES four-arm trial: all groups improved, but SVF did not outperform corticosteroid at 12 months. Mean VAS and KOOS pain changes demonstrate the importance of an active comparator; MRI change was non-significant in every group [151].

The largest blinded saline-controlled MFAT trial is correspondingly sobering. In 120 participants, a single MFAT injection produced a 6-month KOOS4 of 55.5 (95% CI 51.4 to 59.6) versus 51.5 (95% CI 47.4 to 55.6) after isotonic saline, without a significant between-group difference at 6 months or through 24 months [153]. This negative result contrasts with Tantuway's 116-patient SVF-versus-saline trial, in which final KOOS was 78.49 +/- 6.54 versus 59.19 +/- 5.14 and VAS 3.17 +/- 0.94 versus 3.89 +/- 1.04, both P<0.001 [159]. Garza's small three-arm double-blind study (n=39) also favoured high- and low-dose SVF over placebo for median percentage WOMAC improvement at 6 and 12 months, but did not report a numeric cell dose in the abstract and found no cartilage-thickness change on MRI [156]. A three-arm rehabilitation study further reported benefit in both SVF-containing arms over rehabilitation alone at 12 months, but without score means or confidence intervals in the abstract, which limits effect-size interpretation [160]. The discordance between larger blinded MFAT placebo evidence and positive smaller SVF studies is more informative than a pooled direction of effect: blinding, product class, site-specific practice and outcome reporting all remain plausible effect modifiers [153,156,159].

Trial	Design	n	Product and dose	Comparator	Primary outcome and result	Follow-up
MILES	Phase 2/3, single-blind, four-arm	480 randomised; 440 analysed	Autologous SVF; dose not reported here	CSI; BMAC; UCT	VAS: SVF -19.4 vs CSI -20.9; KOOS pain +17.2 vs +17.7; no SVF superiority	12 mo [151]
Barfod	Double-blind RCT	120	Single IA MFAT	Isotonic saline	KOOS4 55.5 vs 51.5 at 6 mo; no significant difference through 24 mo	24 mo [153]
Garza	Double-blind, three-arm RCT	39	High- or low-dose SVF; numeric dose n.r.	Placebo	Median WOMAC improvement at 12 mo: 89.5% high, 68.2% low, 0% placebo	12 mo [156]
Tantuway	RCT	116	IA adipose SVF	Saline	Final KOOS 78.49 vs 59.19; VAS 3.17 vs 3.89; both P<0.001	Final visit [159]
Hong	Double-blind, bilateral self-controlled RCT	16 patients / 32 knees	4 mL autologous SVF	4 mL HA in contralateral knee	Better VAS, WOMAC, ROM and reported WORMS/MOCART cartilage repair; exact values n.r.	12 mo [157]
JointStem	Phase III, double-blind placebo RCT	261 randomised; 252 analysed	Autologous AD-MSC	Placebo	VAS improvement 25.2 vs 15.5 mm; WOMAC 21.7 vs 14.3	6 mo [152]
ADIPOA-2	Phase 2b placebo RCT	135 randomised; 97 analysed	ADSC 2 x 10^6 or 10 x 10^6	Saline	OARSI/OMERACT responders 47.3% vs 54.8%; RR 0.86 (0.58 to 1.28)	Primary endpoint [161]
Lee	Phase IIb placebo RCT	24	Autologous AD-MSC	Saline	WOMAC improved only in cell arm; MRI defect stable versus increased in controls	6 mo [162]
Kuah	Double-blind ascending-dose RCT	20	Allogeneic ASC + supernatant: 3.9 or 6.7 x 10^6	Placebo	VAS improved at 3-12 mo; lateral tibial volume difference 106.47 mm3	12 mo [163]

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Trial	Design	n	Product and dose	Comparator	Primary outcome and result	Follow-up
Jo	Dose-escalation trial	18	AD-MSC 1 x 10^7, 5 x 10^7 or 1 x 10^8	Dose groups	WOMAC and cartilage change principally in 1 x 10^8 group	24 mo [164,165]
Freitag	Three-arm RCT	30	One or two 100 x 10^6 AD-MSC injections	Conservative management	Both cell schedules improved pain/function; MRI score suggested slower progression	12 mo [166]
Richter	Three-arm RCT	75	MFAT	CSI; saline	KOOS pain change +27.8 at 1 y with MFAT vs +13.9 with CSI; saline +6 to +11	12 mo [167]

Table 8: Randomised controlled trials of adipose products in knee osteoarthritis. The strongest inferences arise from blinded placebo-controlled and active-comparator trials; n.r., not reported in the retrieved abstract.

IA, intra-articular; AD-MSC/ADSC, adipose-derived mesenchymal/stromal cell; CSI, corticosteroid injection; UCT, umbilical cord tissue.

Against HA, the signal remains heterogeneous. Hong's within-person bilateral trial gave 4 mL SVF to one knee and 4 mL HA to the other in only 16 participants and reported better symptoms and cartilage imaging with SVF, but supplied neither a cell dose nor extractable effect estimates in the abstract [157]. A 126-patient five-year randomised study reported longer symptom responsiveness with SVF than HA (61.52 versus 30.37 months) and approximately 60% of SVF recipients remaining in an acceptable symptom state, but its positive result must be set beside the null saline-controlled MFAT trial rather than interpreted in isolation [153,168]. In a smaller 2:1 MFAT-versus-HA trial, only KOOS Symptoms differed at six months (+25.0 versus +12.7, P=0.008), while other KOOS domains did not [169]. Thus, HA may be a weaker benchmark for selected symptom scales than saline in a rigorous double-blind study, but the available data do not demonstrate a reliable structural advantage [153,157,169].

Expanded-cell trials provide a second, not necessarily more consistent, evidence stream. The 261-patient JointStem phase III study found greater six-month improvement with autologous AD-MSCs than placebo in 100-mm VAS (25.2 versus 15.5 mm, P=0.004) and total WOMAC (21.7 versus 14.3, P=0.002), but no MRI cartilage difference [152]. In direct contrast, ADIPOA-2 randomised 135 patients to 2 x 10^6 or 10 x 10^6 ASCs or saline and found fewer strict OARSI/OMERACT responders after cells than saline (47.3% versus 54.8%; RR 0.86, 95% CI 0.58 to 1.28; P=0.46) [161]. Lee's 24-person phase IIb trial suggested symptom preservation and stable cartilage defects with cells, but its sample is too small to reconcile this contradiction [162]. Kuah's 20-person allogeneic ASC-plus-supernatant dose-ascending study was principally a safety study, although VAS improved and lateral tibial cartilage volume differed from placebo by 106.47 mm3 (95% CI 13.56 to 199.37) [163]. Jo's 18-patient escalation and two-year extension concentrate apparent benefit in the 1 x 10^8-cell cohort, while Freitag's 30-participant trial reported improvement after one or two 100 x 10^6-cell injections versus conservative management; neither resolves the larger negative ADIPOA-2 endpoint [161,164-166].

Comparisons against platelet-rich plasma and against corticosteroid

Head-to-head studies place adipose products closer to PRP and corticosteroid than placebo-controlled narratives suggest. In Zaffagnini's 118-patient RCT, MFAT and PRP improved IKDC subjective score and KOOS pain to a similar extent, with no overall between-group difference; a post-hoc moderate/severe subgroup achieved the IKDC MCID more often after MFAT (75.0% versus 34.6%, P=0.005) [170]. The Baria trial reported virtually identical six-month KOOS-Pain scores after PRP and MFAT (80.38 versus 81.61; P=0.67), and its 12-month extension again found 78.0 versus 77.8 (P=0.69) with no secondary-outcome

difference [155,158]. An exploratory analysis found BMI inversely associated with MFAT, but not PRP, improvement in KOOS quality-of-life and activities-of-daily-living domains, a plausible but unconfirmed interaction rather than a selection rule [171]. In early OA, a single AMAT injection was not consistently preferable to three LP-PRP plus HA injections: AMAT had worse VAS at one time point and lower KOOS-Sports at another, although fewer adverse events were recorded [172].

Pooled PRP comparisons are not uniformly neutral but their differences are small and domain-specific. A four-RCT meta-analysis (266 patients, 326 knees) favoured PRP for 12-month VAS by 0.99 points (95% CI 0.31 to 1.67), whereas the 0.65 Tegner difference at six months favoured MFAT; no other time point differed [173]. A subsequent six-RCT review concluded that both treatments exceeded MCID and were comparable from one to 24 months, with only a small statistically significant MFAT advantage at six months [174]. The common conclusion is not biological equivalence, because PRP and MFAT preparations differ substantially, but absence of reproducible clinical superiority with present sample sizes and product descriptions [158,173,174]. A prior BMAC-versus-SVF meta-analysis reported greater pain standardised mean difference with SVF but equivalent WOMAC effects across non-uniform studies, and MILES supplied the more decisive randomised evidence by finding neither BMAC nor SVF superior to corticosteroid [151,175].

Corticosteroid is both a clinically relevant benchmark and a test of time course. In MILES, SVF did not beat corticosteroid at 12 months for either pain co-primary endpoint, notwithstanding clinically meaningful within-arm change [151]. Richter's 75-patient three-arm trial suggests a different temporal pattern: MFAT KOOS-Pain improvement rose from 18.1 (95% CI 11.1 to 26.4) at two weeks to 27.8 (19.4 to 37.5) at one year, whereas corticosteroid peaked at 22.2 (15.3 to 30.6) at two weeks and was 13.9 (-2.8 to 29.2) at one year [167]. That finding is compatible with a durable MFAT signal, but it is one trial and does not negate the larger MILES null comparison; pre-specified replication against contemporary corticosteroid protocols is required [151,167]. It nevertheless explains why comparator choice can make a product appear more or less favourable at a particular time point rather than demonstrating disease modification [154,167].

Meta-analyses and network meta-analyses including the direct contradiction between the two network meta-analyses

Conventional meta-analyses generally support a short-to-medium-term symptomatic signal, but their conclusions are constrained by mixing product classes and comparators. Kim's five-RCT SVF review reported statistically significant pain and function improvement at six and 12 months, while the median modified Coleman score was only 70 (range 55 to 75) [176]. A culture-expanded MSC meta-analysis of six RCTs (203 patients) estimated VAS mean difference -13.55 (95% CI -22.19 to -4.90) and cumulative pain SMD -0.54 (95% CI -0.85 to -0.23), without significant pooled structural benefit [177]. The broader 15-study AD-MSC review reported a 12-month WOMAC pain mean difference of -1.85 (95% CI -3.55 to -0.15), an effect whose clinical interpretation depends entirely on scale and anchor [178]. Han's nine-RCT synthesis explicitly found SVF better than saline or HA but inferior to corticosteroid at three months, while culture-expanded ASC was better than saline or conservative care but not HA; this comparator dependence is the central rather than incidental result [154].

Review	Studies and patients included	Pooled estimate with confidence interval	Comparator	Conclusion
Kim 2020	6 RCTs; 203	VAS MD -13.55 (95% CI -22.19 to -4.90); MRI repair SMD 0.11 (-0.51 to 0.73)	No surgery controls	Symptom benefit; no pooled structural benefit [177]
Gadelkarim 2022	15 studies; 463	WOMAC pain MD -1.85 (95% CI -3.55 to -0.15)	Mixed	Small 12-mo pain difference; scale-dependent meaning [178]
Kim 2023	5 RCTs; n.r.	Pain/function significant at 6 and 12 mo; CIs n.r.	Mixed	SVF signal but moderate methodological quality [176]
Han 2025	9 RCTs; 671	Numeric MDs/CIs n.r. in abstract	Saline, HA, CSI, conservative care	SVF favourable to saline/HA, not CSI at 3 mo [154]
Zhao 2021 NMA	43 studies; total n.r.	AD-MSC vs saline VAS WMD -20.93 (-41.71 to -0.78); WOMAC pain -34.85 (-68.03 to -4.86)	Network of 43 studies	AD-MSC ranked first at 6 mo for VAS and WOMAC pain [179]
Han 2020/2021 NMA	43 RCTs; 5,554	Numeric CIs n.r. in abstract	Six interventions	Steroid/HA ranked better; adipose MSC among least likely effective [180]
Anil 2021 NMA	79 RCTs; 8,761	SVF VAS P-score 0.8631-0.9927; WOMAC 12-mo P-score 0.9044	Eight-intervention network	Highest SVF ranking, based on few small studies [181]
Liao 2023 NMA	80 RCTs; 6,934	MSC + physiotherapy walking SMD 2.54	Injection plus physical therapy	Co-interventions drive rankings [182]

Table 9: Systematic reviews, meta-analyses and network meta-analyses. Estimates should be read by comparator, product class and co-intervention rather than as a class-wide effect.

MD, mean difference; SMD, standardised mean difference; WMD, weighted mean difference; n.r., not reported in the retrieved abstract.

The direct contradiction between the two 43-study network meta-analyses must not be concealed. Zhao and colleagues ranked AD-MSC first at six months for VAS (SUCRA 96.7%) and WOMAC pain (85.3%), and estimated 12-month benefit versus saline for VAS of -20.93 (95% credible interval -41.71 to -0.78) [179]. Han, Seo and Shin, working with 43 RCTs and 5,554 patients, instead ranked steroids most likely to improve pain and function and judged adipose MSCs among the least likely effective, with no relevant reduction versus placebo [180]. These are not subtly divergent estimates but opposing clinical messages from superficially similar evidence networks, likely reflecting eligibility, node construction, outcome timing and indirectness rather than a settled biological truth [179,180]. Anil's 79-RCT network, in turn, placed SVF highest by P-score across VAS time points, yet acknowledged that this ranking rested on few small SVF trials; Liao's network found that MSC plus physiotherapy ranked best for walking, illustrating how co-intervention changes the estimand [181,182]. Network ranks should therefore generate hypotheses, not overrule direct saline- and corticosteroid-controlled trials [151,153,179,180].

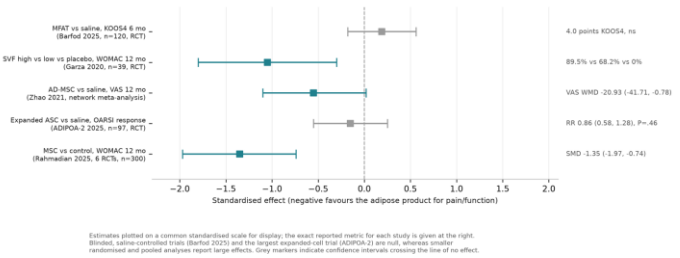


Figure 12: Comparator strength determines the apparent knee osteoarthritis effect. Direct and pooled estimates are more favourable against saline or HA than against corticosteroid and generally similar to PRP [151,154,155,174].

Dose and dose-response including the contradiction between the dose-band pooling and the meta-regression

Dose cannot be inferred from the label SVF or MFAT, because studies variably report lipoaspirate volume,

total nucleated cells, viable stromal cells or expanded cells. Huang's dose-band meta-analysis of 16 studies classified 0-25 x 10^6 cells as low, 25-50 x 10^6 as moderate and >50 x 10^6 as high, and found high-dose injection associated with better pain and function outcomes at three, six and 12 months, accompanied by more adverse events [183]. Rahmadian's later meta-analysis with meta-regression reached the opposite conclusion: across eight arms from six RCTs (300 patients), the 12-month WOMAC SMD was -1.35 (95% CI -1.97 to -0.74; I2=49.8%), doses <=25 million were effective, and dose showed no significant meta-regression relationship [184]. This is a genuine methodological contradiction between categorised dose pooling and continuous cross-study regression, not evidence for a clinical threshold at either 25 or 50 million cells [183,184].

Prospective dose experiments are too small to settle the issue. Garza reported larger percentage WOMAC improvements with high- than low-dose SVF, but did not supply the numeric dose in the retrieved abstract [156]. Jo's stepwise expanded-ASC study and extension placed its symptomatic and structural signal mainly in the 1 x 10^8-cell cohort, while lower groups deteriorated after one year, but this involved only 18 participants [164,165]. In retrospective SVF series, higher injected cell counts correlated with pain improvement in 217 treated knees and lower cell count, higher BMI and worse radiographic grade predicted worse pain outcome in 357 knees; such associations cannot establish an allocation-independent threshold [185,186]. ESSKA-ORBIT accordingly concluded that no optimal expanded-MSC dose can be defined and noted that most dose-response studies used fewer than 100 x 10^6 cells [187]. Future trials should report viable cell dose, total nucleated cells, viability, processing method and potency attributes alongside a pre-specified dose-response model, rather than treating a harvested volume as a dose surrogate [158,163,187].

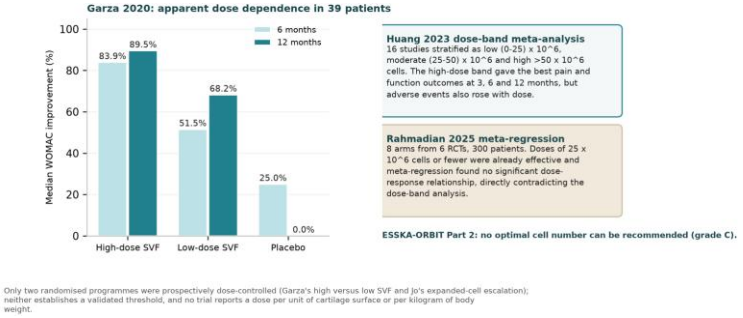


Figure 13: Dose-response evidence is internally inconsistent. Dose-band pooling favours >50 x 10^6 cells, whereas meta-regression finds no significant relationship and efficacy at <=25 x 10^6 cells [183,184].

Structural and imaging outcomes and why they are weak

Claims of cartilage regeneration are not supported by the strongest controlled evidence. MILES found no significant MRI osteoarthritis-score change in any arm, including SVF, while the JointStem phase III study found no MRI cartilage difference despite symptomatic benefit [151,152]. Garza found no cartilage-thickness change, and the MFAT-versus-PRP RCT found no radiographic or MRI structural change in either arm [156,170]. The culture-expanded MSC meta-analysis similarly found no significant MRI cartilage repair, WORMS or odds of cartilage improvement, with broad confidence intervals that are incompatible with a precise structural claim [177]. Structural measures are particularly vulnerable to small samples,

short imaging intervals, multiplicity across regions and discordance from symptoms, so a statistically selected imaging measure should not be presented as disease modification [177,188].

Positive imaging observations are hypothesis-generating rather than confirmatory. Hong reported better WORMS and MOCART cartilage-repair scores with SVF than HA in a 16-patient contralateral-knee trial, and Molnar reported dGEMRIC responders after MFAT, while non-symptom KOOS subscales did not separate from HA [157,169]. Kuah reported a placebo-adjusted lateral tibial cartilage-volume difference in a 20-person safety-oriented study, and Jo described cartilage-volume, arthroscopic and histological changes in the high-dose group without a conventional placebo comparator [163,164]. The durability of symptom response in Zhang's SVF-versus-HA trial is clinically interesting but does not itself document restoration of articular cartilage [168]. Imaging should be treated as corroborative only when blinded, protocolised, adequately powered and concordant with a patient-important responder outcome [152,177].

Adjuvant use with osteotomy, cartilage procedures and arthroscopy where the surgical confound dominates

Adjuvant surgical studies cannot isolate an adipose-product effect unless surgery, rehabilitation and co-interventions are balanced and the randomised contrast directly tests the product. In 78 participants with KL 3-4 OA, arthroscopic debridement plus MFAT improved KOOS-PS by 24.4 +/- 22.5 versus 11.7 +/- 20.2 after debridement alone (P=0.024), but the debridement itself is a major therapeutic and contextual exposure [189]. A 50-person study comparing debridement plus SVF with debridement plus microfracture plus SVF found better 24-month symptoms and WORMS cartilage scores in the microfracture group, which tests the addition of microfracture, not SVF against no SVF [190]. Similarly, a matched-pair high tibial osteotomy cohort reported better IKDC, Lysholm and second-look ICRS grades with ADMSC injection, but osteotomy correction dominates joint loading and precludes attribution to the cells [191].

The earlier arthroscopy literature has the same attribution problem. Koh's 25-patient series combined infrapatellar-fat-pad MSCs, PRP and arthroscopy, improved within-group scores but found final outcomes similar to controls [192]. A later lavage-plus-SVF case series reported maintained or improved cartilage in 14 of 16 second-look examinations, yet included no control group and delivered a mean 4.04 x 10^6 stem cells within a far larger SVF cell population [193]. An early comparative lavage-plus-MSC versus PRP series may be cited historically, but the retrievable record does not support numerical efficacy claims [194]. In rotator cuff repair, MFAT augmentation improved Constant-Murley score at the six-month endpoint (82.78 +/- 7.00 versus 76.66 +/- 10.77; P=0.005) but not at other time points or on rerupture at MRI, so the repair operation and its rehabilitation remain the dominant explanation of recovery [195]. Surgical adjuvant protocols should therefore be evaluated as composite procedures, not cited as proof that injection alone regenerates cartilage or tendon [189,195].

Other joints and tendon indications (hip, ankle, shoulder, rotator cuff, hand and thumb base, plantar fasciitis, gluteal tendinopathy as reported)

Outside the knee, the evidence is sparse and primarily uncontrolled. In early hip OA, 55 of 71 consecutively treated patients were analysed 29-41 months after a 4-mL ultrasound-guided MFAT injection: mean Oxford Hip Score rose 6.9 points, 28 required no further treatment, but 17 proceeded to arthroplasty at

a mean 495 days [196]. A 30-person hip pilot reported transient total WOMAC improvement at one and three months, with 56.7% meeting the study's WOMAC MCID at six and 12 months; it had no control arm [197]. The registry landscape contains small ongoing or active randomised programmes in hip, shoulder, wrist OA and facet OA, but these are not yet a basis for routine care; their relevance is that they may replace uncontrolled signals with active comparator data [196,198]. Published data specific to hand or thumb-base OA are absent from this evidence set, despite an active wrist OA ADRC-versus-corticosteroid registry programme, so efficacy should not be extrapolated across joints [199].

The most developed ankle/tendon comparison is Achilles tendinopathy. In a 44-patient RCT, intratendinous SVF produced better VAS, AOFAS and VISA-A than PRP at 15 and 30 days, but not at later assessments through 180 days [200]. MRI and ultrasound changes in the companion imaging study did not track clinical outcome, reinforcing the separation between morphological change and perceived recovery [188]. For partial-thickness rotator cuff tears, a first-in-human randomised pilot compared a mean 11.4 x 10^6 fresh uncultured adipose-derived regenerative cells with methylprednisolone plus bupivacaine in only 16 modified intention-to-treat participants and reported higher ASES scores after cells at 24 and 52 weeks, without severe injection-related adverse events [198]. An uncontrolled lateral-elbow pilot in 18 tennis players combined culture-expanded ASCs with physiotherapy and reported large symptom and MRI changes, but absence of a comparator prevents separating treatment, rehabilitation and regression to the mean [201].

Tendon evidence overall is too heterogeneous for a class indication. A systematic review of 22 studies and 658 patients found only minor adverse events across rotator cuff, elbow, patellar, Achilles and gluteal tendon indications, but comparative rotator-cuff results were mixed, no controlled elbow study existed, and the single Achilles RCT had no enduring between-group difference at six months [202]. For plantar fasciitis, a randomised crossover pilot of perforating fat injection used a mean 2.6 +/- 1.6 mL per foot and reported reduced fascia thickness and pain in the initial injection group, but involved only 14 participants and had incomplete cross-over symmetry for pain [203]. A four-patient mechanically processed SVF case series in recalcitrant plantar heel pain reported rapid VAS improvement maintained to 360 days, an observation that is appropriately a first-in-indication report rather than efficacy evidence [204]. Evidence for gluteal tendinopathy is represented within broad tendon reviews rather than a definitive adipose-specific randomised dataset, and intradiscal MSC literature remains non-adipose-specific with fair, limited-certainty evidence; large, indication-specific trials remain necessary [202,205,206]. No randomised nanofat comparison appears among the knee trials summarised here, so nanofat should not inherit efficacy claims from mechanically processed SVF or MFAT.

Clinical practice guidelines and consensus statements (ACR, AAOS, OARSI, ESSKA-ORBIT Parts 1 and 2) with their exact grades

Guideline positions are intentionally more conservative than selected positive trials. The American College of Rheumatology/Arthritis Foundation strongly recommends against stem-cell injections in knee and hip OA because preparations and techniques are heterogeneous and insufficiently standardised; it makes no such hand-OA statement because the treatment was not evaluated [199]. The AAOS 2021 non-arthroplasty knee guideline does not address stem-cell, cell-based or adipose therapy with a

recommendation, an absence that should not be reported as endorsement; it gives PRP a Limited (downgraded) recommendation, HA a Moderate (downgraded) recommendation against routine use, and corticosteroid a Moderate (downgraded) statement for short-term relief [207]. OARSI 2019 conditionally recommended HA and corticosteroid for specified OA contexts and strongly recommended against PRP on extremely low-quality evidence, as summarised in the 27-guideline review; its primary PubMed record does not itself provide extractable recommendation text in the available evidence record [208,209].

Body	Year	Statement	Grade or strength
ACR/Arthritis Foundation	2019	Stem-cell injections for knee and/or hip OA are recommended against because of heterogeneous, non-standardised preparations and techniques.	Strongly against [199]
AAOS	2021	No recommendation statement on stem-cell/cell-based/adipose therapy. PRP may reduce pain/function; HA not for routine use; CSI can give short-term relief.	Cells: not addressed; PRP Limited (downgraded); HA Moderate (downgraded) against routine use; CSI Moderate (downgraded) [207]
OARSI	2019	HA and CSI conditionally recommended in guideline review; PRP strongly recommended against for extremely low-quality evidence.	HA conditional; CSI conditional; PRP strongly against [208,209]
ESSKA-ORBIT Part 1, PRP	2024	PRP supported in mild-to-moderate OA (KL <=3) and has a longer effect than corticosteroid with safer profile.	Three Grade A statements; 6 B, 7 C, 12 D [210]
ESSKA-ORBIT Part 2, cell-based	2025	Cell-based therapy is second-line; CBT better than HA to 12 mo but no demonstrated superiority to CSI or advantage over PRP. MFAT and mechanical SVF neither preferred.	CBT vs HA B; no CSI superiority D; no PRP advantage C; MFAT/mechanical SVF D; no harvest/dose recommendation D/C [187]

Table 10: Guideline and consensus positions. Grades are quoted as published and apply to the specific intervention and comparator, not to a generic orthobiologic class.

CBT, cell-based therapy; CSI, corticosteroid injection; KL, Kellgren-Lawrence; MFAT, micro-fragmented adipose tissue.

ESSKA-ORBIT makes the comparator hierarchy explicit. In Part 1, three of 28 PRP statements were grade A and the consensus judged PRP effective in mild-to-moderate OA (KL <=3) and longer acting than corticosteroid with a safer profile [210]. In Part 2, only five of 27 cell-based statements were grade A or B; cell-based therapy was designated second-line, mainly for KL 1-3 disease, while PRP was designated the first-line orthobiologic [187]. The exact cell-therapy grades matter: superiority to HA was grade B, lack of demonstrated superiority over corticosteroid grade D, no acknowledged advantage over PRP grade C, and MFAT versus mechanical SVF equivalence and lack of a preferred harvest technique were grade D [187]. The consensus also advised against combining PRP with cell-based therapy (grade C) and could not identify an optimal expanded-cell dose (grade C), positions consistent with the uncertain direct evidence [184,187]. A separate 2025 Delphi consensus emphasised ethics, transparency, off-label communication and the misuse of the term stem cells, with 85% of its statements reaching unanimous or strong consensus; these process standards are particularly important where product nomenclature outpaces comparative evidence [211].

Interpreting effect sizes against minimal clinically important differences

Statistical significance is not a substitute for patient-important benefit. Tubach and colleagues estimated knee-OA minimal clinically important improvement (MCII) as -19.9 mm for pain VAS and -9.1 points for WOMAC function in a prospective cohort, anchors that make MILES' within-arm pain changes clinically plausible but do not establish SVF superiority over corticosteroid [151,212]. In JointStem, a 25.2-mm VAS

improvement with cells exceeds that VAS MCII whereas the 15.5-mm placebo improvement does not, but the between-group difference is only 9.7 mm and is smaller than the same individual-level MCII anchor [152,212]. Conversely, ADIPOA-2 used a strict OARSI/OMERACT responder definition and was negative despite cell doses of 2 x 10^6 and 10 x 10^6, illustrating how responder-based and mean-change outcomes can generate different impressions of clinical utility [161]. The appropriate question is therefore not whether a treated arm crosses an MCID, but whether the incremental effect versus a credible comparator materially changes the proportion of patients who improve [151,161].

Instrument	Anchor	Threshold	Source
Knee OA pain VAS	Prospective MCII, 4-week cohort	-19.9 mm; -40.8% relative	Tubach [212]
Knee OA WOMAC function	Prospective MCII, 4-week cohort	-9.1 points; -26.0% relative	Tubach [212]
WOMAC after TKR/THR	Systematic review, 0-100 scale (0 best)	TKR pain 13.3-36.0, function 1.8-33.0; THR pain 8.3-41.0, function 9.7-34.0	MacKay [213]
WOMAC after medial open-wedge HTO	Anchor-based MCID	Pain 4.2; stiffness 1.9; function 10.1; total 16.1	Kim [214]
IKDC subjective	MCID/PASS after intra-articular PRP	MCID 8.6 at 6 mo, 8.5 at 12 mo; PASS 59.7, 62.1	Boffa [215]
KOOS subscales	Distribution-based 0.5 SD after triamcinolone	7.98-12.35 across subscales	Galina [216]
VAS MCID achievement	PRP versus HA RCT	Higher PRP MCID-achiever proportion at 6 mo; numeric threshold n.r.	Park [217]
PRP VAS/WOMAC/IKDC	Systematic review	Both LP- and LR-PRP exceeded MCID; no efficacy difference	Kim [218]

Table 11: Minimal clinically important difference and responder thresholds for the instruments used. Thresholds are population-, scale-, direction- and anchor-specific and should not be transferred uncritically between injection and surgical cohorts.

MCII, minimal clinically important improvement; PASS, patient-acceptable symptom state; TKR/THR, total knee/hip replacement; n.r., not reported.

Threshold transfer is a major source of overstatement. In post-arthroplasty cohorts, published WOMAC MCIDs range from 1.8 to 41.0 depending on joint, domain, direction and method, while PASS thresholds likewise vary widely; these values cannot simply validate an OA injection result [213]. HTO-specific thresholds are different again, including WOMAC total MCID 16.1 and substantial clinical benefit 25.3, underscoring that surgery-related anchors should not be imported into a non-operative injection trial [214]. The IKDC MCID of 8.6 at six months and 8.5 at 12 months provides context for the Zaffagnini subgroup result, but it comes from an intra-articular PRP cohort and should be described as an external anchor rather than a universal truth [170,215]. KOOS MCID values of 7.98 to 12.35 after triamcinolone provide a corticosteroid-relevant distribution-based reference, but they do not convert the non-significant MFAT-versus-saline difference in the Barfod trial into evidence of benefit [153,216]. PRP data also show why mean changes alone are inadequate: both leukocyte-poor and leukocyte-rich PRP exceeded VAS, WOMAC and IKDC MCID without between-formulation efficacy differences, although

leukocyte-rich PRP had more pain and swelling reactions [218].

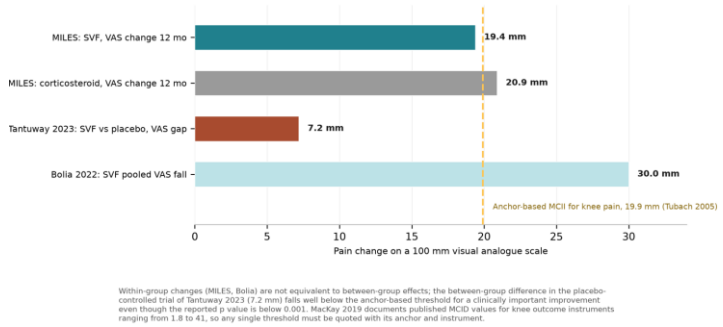


Figure 14: Patient-important interpretation requires an incremental, not within-arm, comparison. MCID thresholds vary by instrument and anchor, so a group crossing a threshold does not demonstrate superiority over saline, corticosteroid or PRP [151,153,212,213].

Taken together, the musculoskeletal evidence supports a narrow conclusion. Adipose-derived products can be associated with symptom improvement in knee OA and selected tendon indications, particularly in smaller studies against saline or HA, but robust trials do not establish consistent superiority over corticosteroid or PRP and do not establish structural regeneration [151,153,154,174,200]. Current guidance consequently favours standardised care and, where an orthobiologic is considered, positions cell-based therapy behind PRP rather than as routine first-line treatment [187,199,207,210]. The next generation of trials should use placebo and active comparators, product-release and potency data, prospectively specified dose-response analysis, blinded imaging, and responder outcomes anchored to validated patient-important thresholds [161,187,212].

Aesthetic, Dermatologic and Reconstructive Applications

Facial rejuvenation and periorbital or infraorbital use

Clinical claims for facial nanofat and SVF span dermal quality, rhytides, pigmentation and contour, but the investigated preparations range from intradermal emulsified fat to cell-enriched structural grafts. A comparative study of structural fat supplemented with nanofat-derived cells and platelet-rich fibrin (n=62) versus structural fat alone (n=77) reported a fall in the test-group VISIA wrinkle score from 57.32+/-12.78 to 32.13+/-9.42 at 12 months and an elasticity increase from 11.05+/-4.74 to 13.87+/-5.42, whereas control values reportedly returned towards baseline; the composite intervention prevents attribution of benefit to nanofat alone [219]. In a 16-person, uncontrolled nasolabial-fold study, injection of 2.0x10^7 nucleated SVF cells increased Cutometer R2 from 0.678+/-0.129 to 0.859+/-0.121 and dermal thickness from 799.31+/-140.40 to 976.50+/-169.90 micrometres at six months, while melanin, erythema and colourimetry were unchanged [220]. These pre-post physiological changes are encouraging but do not establish a patient-important advantage over needling, saline, fat alone or an active rejuvenation treatment.

The most internally controlled facial evidence is a 12-patient split-face study in which intradermal nanofat outperformed contralateral saline on wrinkle severity, GAIS, Antera 3D and FACE-Q, although numerical effects and p values were not reported [221]. A three-product comparison of microfat, nanofat and

extracellular-matrix/SVF gel likewise lacks extractable sample size and effect estimates, which precludes a credible hierarchy between product classes [222]. A face-focused review identified mostly small case series, with reported clinical effect peaking at four to six months in a 67-patient cohort and lower-eyelid discoloration improvement in a 19-patient series; these uncontrolled signals should be interpreted as hypothesis-generating [223]. Animal photoageing data, in which nanofat improved dermal thickness and capillary density versus phosphate-buffered saline, support biological plausibility rather than human efficacy [224]. Narrative dermatology reviews have catalogued these uses but cannot resolve the absence of standardised product definition, blinded outcomes or durable comparative effects [225].

One randomised four-arm infraorbital dark-circle article has been retracted; its reported dermal-thickness differences must not be used as evidence of efficacy or comparative performance [226]. Accordingly, neither nanofat nor SVF can presently be considered proven for infraorbital pigmentation or lower-eyelid dark circles, and future split-face studies should separate colour from shadowing and volume, prespecify patient-reported thresholds, and use photographic acquisition that is masked and reproducible.

Scars: hypertrophic, atrophic, acne, burn and post-surgical

Scar studies illustrate the recurrent distinction between early maturation and final scar quality. In the multicentre double-blind intrapatient tSVF trial in 40 mammoplasty patients, scar appearance improved on the treated side at six months, but not at 12 months; photographic and histological analyses were negative throughout [227]. At 12 months, extracted Patient and Observer Scar Assessment Scale (POSAS) patient scores were 14.4+/-7.6 with tSVF versus 15.3+/-9.0 with placebo and observer scores were 14.5+/-6.4 versus 14.6+/-8.8, with no difference in collagen alignment, depth or width [228]. The other low-risk-of-bias trial, a 12-person randomised split-scar abdominoplasty study, found less erythema and better patient colour scores at three to six months but attenuation by 12 months, with no histological difference at eight months [229]. A systematic review of 12 studies found that these were the only two low-risk-of-bias trials and that both showed the same six-month POSAS advantage lost by 12 months; the most defensible interpretation is accelerated early maturation rather than a durable change in final scar appearance [230].

A newer double-blind split-wound trial in 50 analysed abdominoplasty patients found all six observer POSAS domains and overall opinion better with nanofat at six months, with median vascularity 2 versus 4 and relief 3 versus 5, all $p<0.001$; its longer-term trajectory will be decisive [231]. In breast reduction, a 45-patient three-arm randomised study found both fat and nanofat-enriched fat superior to no injection at six months on Vancouver Scar Scale (VSS) items and pain, while nanofat exceeded fat only for pigmentation in the review-level extraction [232]. A later 45-person multicentre split-incision SVF trial likewise reported a six-month VSS benefit that was no longer maintained at nine months, reinforcing the temporal pattern across preparations [233]. This pattern matters more than a nominal p value because no scar trial has demonstrated a sustained advantage against a stated minimal clinically important difference.

Uncontrolled and high-risk studies have reported larger apparent effects. In 48 post-burn facial scars, nanofat improved POSAS pigmentation and pliability but not thickness, relief or ImageJ photographic analysis at six months [234]. In a 34-patient observational series, 26 patients (76.5%) achieved a good

outcome, but the contrast between scars younger than five years (92.6% good outcomes) and older scars (14.3%) indicates substantial prognosis-related confounding [235]. A 20-patient atrophic-scar case series reported patient POSAS total score reduction from 28.80 to 12.20 and improved melanin optical density, but no change in elastic-fibre fraction; there was no control group [236]. Preparation comparisons are additionally difficult because studies label different mechanically processed fractions as nanofat or SVF without reporting a common viable-cell or matrix release criterion [237].

For acne scars, all participants in a 30-person comparative study received nanofat plus platelet-rich plasma (PRP), with 15 also receiving fractional CO2 laser; subcutaneous thickness increased similarly in both groups (+0.668 versus +0.630 cm; p=0.7289), and FACE-Q did not differ between groups [238]. In a seven-person randomised split-face trial, adding intradermal SVF to subcutaneous nanofat improved apparent scars and yielded between-side differences in dermal and total thickness at one month, but the sample and three-month follow-up are insufficient for clinical inference [239]. Small controlled data also favour SVF versus saline for traumatic or surgical scars at six months (16 analysed of 20 enrolled), with only transient mild pain reported [240], and favour subcision plus SVF over subcision alone for acne-scar area and volume, but not depth, in ten participants [241]. For hypertrophic scars, a six-study meta-analysis found SVF plus fractional CO2 laser superior to other treatments for VSS (SMD -1.3573, 95% CI -2.2475 to -0.4672; I2=23%), while transepidermal water loss was not significantly different; this supports a combination signal but mixes pre-post and comparative evidence [242]. An Egyptian burn trial of fat grafting plus nanofat dressing favoured the intervention for healing time, contracture, texture and pain, but had high risk of bias and no extractable absolute effects; a small post-laser trial of adipose-derived conditioned medium reported lower erythema and melanin indices without histological differences [243,244].

An independent systematic review of 12 nanofat-only studies did not pool scar outcomes because of clinical heterogeneity and judged the evidence generally low level despite mostly favourable reported POSAS, FACE-Q and VSS findings [245]. A scoping review of mechanically fractionated products likewise graded the van Dongen tSVF and PRP+tSVF trials as equivocal because final blinded quality and satisfaction outcomes were not superior to their controls [246].

Study	Design	n	Intervention	Comparator	Outcome instrument	Result	Follow-up
Vestita 2018 [221]	Split-face controlled	12	Intradermal nanofat	Contralateral saline	WSRS, GAIS, Antera 3D, FACE-Q	All reported measures favoured nanofat; no numerical effect reported	n.r.
van Dongen 2022 [227,228]	Double-blind intrapatient RCT	40; 34 at 1 y	tSVF in breast scar	Contralateral placebo	POSAS; photographs; histology	Six-month POSAS benefit; no 12-month difference. Patient 14.4 vs 15.3; observer 14.5 vs 14.6	12 mo
Ramaut 2024 [229]	Randomised double-blind split-scar RCT	12	Intradermal nanofat	Untreated contralateral half	POSAS, Mexameter, histology	Less erythema and better early scores; attenuation by 12 mo; histology negative	12 mo
Kemaloglu 2021 [232]	Three-arm prospective RCT	45	Nanofat-enriched fat	Fat alone; no injection	VSS, VAS	Both graft arms better than no injection; nanofat better than fat only for pigmentation	6 mo
Tenna 2017 [238]	Comparative study	30	Nanofat+PRP+fractional CO2 laser	Nanofat+PRP	Ultrasound, FACE-Q	Thickness gain +0.630 vs +0.668 cm; between-group p=0.7289	n.r.
Behrangi 2022 [239]	Single-blind split-face RCT	7	Nanofat+SVF	Nanofat	Visioface, ultrasound	At 1 mo, greater dermal and total thickness with SVF (p=0.042; p=0.040)	3 mo

Table 12: Randomised and controlled aesthetic and scar studies. Split-site designs reduce interparticipant confounding, but short follow-up and heterogeneous products limit comparative inference.

n.r., not reported; mo, months; y, year; WSRS, Wrinkle Severity Rating Scale; VSS, Vancouver Scar Scale.

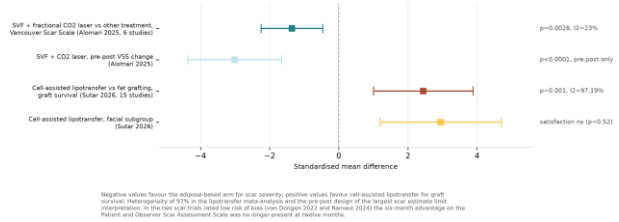


Figure 15: Aesthetic and scar effect sizes are large but rest on heterogeneous evidence. The early scar signal is not sustained at 12 months, and the cell-assisted lipotransfer estimate has very high heterogeneity [227,229,242,247].

Androgenetic alopecia

The alopecia literature is small and product-heterogeneous: a systematic review identified nine studies and 236 patients, while another found six studies and 188 patients, including three randomised trials, without a pooled effect estimate or an established patient-important hair-density threshold [248,249]. In one comparative study, PRP increased hair count by 11.28 hairs whereas SVF-augmented PRP increased it by 19.45 hairs, with pull-test reduction of 80.78% versus 34.01%; the record does not state arm sizes [250]. This direction of effect was not replicated in a randomised trial of 18 participants: hair count improved within both PRP (+11.44+/-4.69) and SVF-PRP (+7.78+/-3.03) arms, but the between-group difference was null (p=0.917), as was the diameter comparison [251]. Thus, Figure 16 should be read as a summary of reported within-study signals, not proof that adding SVF improves on PRP.

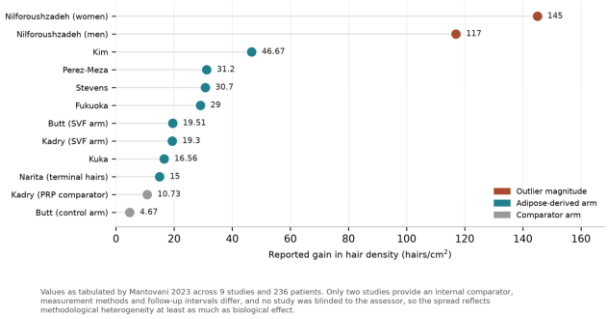


Figure 16: Androgenetic alopecia evidence is discordant. A comparative study favoured SVF-PRP, whereas the small randomised comparison found no incremental benefit over PRP [250,251].

Vitiligo and pigmentary disorders

No confirmed clinical nanofat or adipose-derived SVF repigmentation dataset was identified for vitiligo. A systematic review of 48 regenerative-medicine studies involving 2,186 patients explicitly concluded that trials of SVF remain necessary, despite reporting activity for non-adipose interventions such as melanocyte-keratinocyte transplantation and PRP [252]. These other cell therapies provide a benchmark rather than indirect proof: in a 25-person within-subject trial of epidermal autologous skin-cell suspension, 36% of treated lesions achieved at least 80% repigmentation at week 24 versus 0% of control

lesions, with durability to week 52 [253], and a melanocyte-keratinocyte transplantation cohort reported mean VASI improvement of 80.5+/-20.9% at one year, sustained at 80-90% to 84 months [254]. The only adipose-specific pigmentation signal located was a guinea-pig experiment in which SVF inhibited UVB-associated pigmentation and shortened fading time; it cannot justify clinical use for vitiligo [255].

Striae and skin quality

A prospective single-blind study randomised 50 women with abdominal striae albae to PRP, nanofat, or a PRP-nanofat mixture before abdominoplasty. Both single treatments increased type I collagen relative to untreated striae, while the combination produced the highest collagen signal ($p<0.0001$) and superior clinical improvement ($p=0.001$) [256]. The biopsy endpoint is mechanistically informative, but absence of a reported follow-up interval, patient-important effect magnitude and long-term blinded assessment means that collagen production should not be conflated with durable improvement in striae appearance. Across skin-quality indications, the appropriate next comparison is not untreated skin alone but an active standard such as microneedling, laser or PRP delivered with equal attention to co-interventions.

Cell-assisted lipotransfer and graft retention

Cell-assisted lipotransfer (CAL) is conceptually distinct from intradermal nanofat: it attempts to enrich a volume graft with SVF or expanded adipose stromal cells, and therefore requires volumetric outcomes, dose reporting and a conventional-fat comparator. Earlier systematic review evidence reported disparate retention results, from 64.8+/-10.2% versus 46.4+/-9.3% in one comparison to 74% versus 79% in another, illustrating that enrichment cannot be treated as a uniform intervention [257]. In a six-versus-six randomised breast-augmentation trial using at least 20x10^6 expanded ASC/mL, retention was 80.2% with enrichment versus 45.1% with untreated fat ($p=0.0022$) [258]. By contrast, a within-patient 10-person trial at 10x10^6 ASC/mL found no difference at either four months (54.3% versus 56.2%) or 12 months (54.0% versus 55.9%), suggesting that dose, culture expansion and graft context may all modify effect [259].

In breast reconstruction, a 20-patient comparative study reported CAL-SVF retention of 73.8% versus 62.2% at six months and 65.4% versus 48.4% at 12 months, with one fat-necrosis event in each arm [260]. A 23-person multicentre facial RCT similarly found MRI survival of 71.27+/-10.43% with SVF enrichment versus 61.98+/-13.46% at 24 weeks, yet a five-patient CAL breast-augmentation series found only 47% of initial postoperative volume at one year and no relation between SVF-cell ratio and survival [261,262]. A recent 15-study meta-analysis favoured CAL for graft survival (SMD 2.44, 95% CI 1.00-3.88; $p=0.001$), but the very high heterogeneity ($I2=97.19\%$) and null satisfaction result ($p=0.52$) mean that the pooled estimate is not transportable as a single expected retention gain [247].

Study	Design	n	Comparison	Effect estimate	Conclusion
Kolle 2020 [258]	RCT	12	>=20x10^6 ASC/mL CAL vs fat	Retention 80.2% vs 45.1%; p=0.0022	Large difference, but six participants per arm
Vester-Glowinski 2019 [259]	Within-patient RCT	10	10x10^6 ASC/mL CAL vs fat	12-mo retention 54.0% vs 55.9%; p=0.566	No benefit at lower dose
Jeon 2021 [260]	Comparative	20	CAL-SVF vs conventional fat, breast reconstruction	65.4% vs 48.4% retention at 12 mo; p=0.03	Suggestive, small non-randomised sample
Wufuer 2024 [261]	Multicentre RCT	23	SVF-enriched vs conventional facial fat	71.27% vs 61.98% survival at 24 wk; p<0.012	Short-term MRI benefit

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-130

Study	Design	n	Comparison	Effect estimate	Conclusion
Sutar 2026 [247]	Systematic review/meta-analysis	15 studies	CAL vs conventional fat	SMD 2.44 (95% CI 1.00-3.88); I2=97.19%	Pooled benefit is extremely heterogeneous
Krastev 2019 [263]	Matched cohort	587	AFT vs conventional/no reconstruction	Locoregional-recurrence HR 0.63 (95% CI 0.25-1.60)	No observed recurrence increase
Tukiama 2022 [264]	Matched-cohort meta-analysis	4,247	Lipofilling vs controls	IRR 0.92 (95% CI 0.68-1.26); p=0.620	No increased oncologic risk

Table 13: Cell-assisted lipotransfer and oncologic safety evidence. Retention and recurrence evidence answer different questions and should not be interpreted as a shared efficacy or safety endpoint.

ASC, adipose-derived stromal cell; CAL, cell-assisted lipotransfer; AFT, autologous fat transfer; IRR, incidence-rate ratio.

Breast reconstruction and the oncologic safety literature

The clinical case for fat grafting in irradiated reconstruction is primarily reconstructive and symptom-oriented, rather than evidence that an SVF-containing product reverses radiation injury. In a retrospective case-control series of 61 patients with 62 irradiated reconstructed breasts, serial lipofilling improved LENT-SOMA scores and resolved flap thinning in four treated breasts; exact scores were not reported and follow-up averaged 17.6 months [265]. A blinded placebo-controlled tissue-expansion trial of intradermal SVF in 20 treated patients reported skin-thickness advantages at eight and 12 weeks and no severe adverse events over two years, but its small size and apparently counterintuitive signed mean differences require cautious interpretation [266]. A randomised prospective pilot in post-mastectomy radiation injury remains ongoing, so a direct high-quality efficacy answer is still unavailable [267].

Oncologic safety data are reassuring but almost entirely retrospective and susceptible to selection, survivorship and surveillance biases. In a matched cohort of 587 women, locoregional recurrence occurred in 8 of 287 AFT recipients versus 11 of 300 controls (HR 0.63, 95% CI 0.25-1.60; p=0.33); mean post-AFT follow-up was five years compared with 8.6 years in controls [263]. A 59-study meta-analysis found an incidence-rate difference of -0.15% per year (95% CI -0.36 to 0.07), yet mean follow-up after transfer was only 2.7 years [268]. The meta-analysis limited to nine matched cohorts (4,247 subjects) reported a locoregional-recurrence incidence-rate ratio of 0.92 (95% CI 0.68-1.26), which excludes a large excess but does not prove biological neutrality [264].

Other comparative data point in the same direction: a 42 versus 126 matched cohort found locoregional recurrence of 7.1% versus 6.3% (p=0.856) [269]; a 125 versus 125 matched cohort found 2.4% versus 4.0% locoregional recurrence and HR 0.30 (95% CI 0.09-1.01) [270]; and a 919-breast cohort reported HR 0.337 (95% CI 0.173-0.658) in favour of AFT [271]. The latter apparent protection is not a plausible indication to use fat transfer as anticancer therapy and more likely reflects residual selection and timing biases. Similarly, the multicentre CRAFT case-cohort study found no association with recurrence after adjustment (HR 0.97, 95% CI 0.54-1.8), but only 64 participants had received fat transfer [272]. These data support no observed signal of excess recurrence in selected treated survivors; they do not replace prospective long-term oncologic surveillance, especially for cell-enriched or culture-expanded products.

Chronic wounds, diabetic foot ulcers and venous leg ulcers

The most persuasive wound evidence uses a standard-care comparator rather than pre-post closure alone. In the MiFrAADiF single-centre trial, complete healing after diabetic-foot minor amputation was 44/55 (80%) with microfragmented adipose tissue versus 23/50 (46%) with standard care at six months (p=0.0064), although mean healing time was 2.8 months in both groups and two abdominal haematomas occurred [273]. A phase-I series injecting 30x10^6 SVF cells into 63 diabetic foot ulcers reported 51 complete closures at six months and 50 healed at 12 months, but lacks a comparator and cannot disentangle natural healing, offloading and selection [274]. In a 100-person chronic-ulcer RCT, ADSVF every three weeks reportedly achieved nine-week complete healing in 46/47 versus 30/48 with conventional dressings, with fewer post-intervention infections (3 versus 14), but the numerical results are available through a systematic-review extraction rather than the primary abstract [275,276].

For recalcitrant venous leg ulcers, a phase-II trial of eight versus eight patients found shorter mean healing time with centrifuged adipose tissue containing progenitor cells (17.5+/-7.0 versus 24.5+/-4.9 weeks) and lower pain (2.7+/-2.0 versus 6.6+/-3.0), with an inverse correlation between CD34+/CD45- cell content and healing time [277]. In a 16-person uncontrolled pilot, all seven venous ulcers epithelialised after a single 9-15x10^6-cell SVF application, but the wide 71-174-day range and absence of control preclude a comparative estimate [278]. An SVF-plus-PRP case series healed four of five chronic ulcers in a mean 71.75+/-29.57 days; combining biologically active interventions makes the independent contribution of either component unknowable [279]. The 16-RCT wound and scar review could not pool results because products, indications and endpoints were too heterogeneous, and rated five studies at high risk of bias; this is a strong rationale for indication-specific, adequately powered trials rather than a generic wound-healing claim [276].

Systemic sclerosis, Parry-Romberg disease, radiation-induced fibrosis and HIV-associated facial lipoatrophy

In systemic sclerosis, placebo-controlled trials have not shown a broad, reproducible functional benefit. In SCLERADEC-II (n=40), three-month Cochin Hand Function Scale change was -9.2+/-12.2 with SVF and -7.6+/-13.2 with lactated Ringer placebo, without demonstrated superiority [280]. In the 88-person STAR trial, the 48-week treatment difference was 2.62 points (95% CI -2.4 to 7.6; p=0.299), failing the primary endpoint; the diffuse cutaneous subgroup had a possible but imprecise signal and more patients exceeded the stated MCID [281]. Local digital-ulcer data are more positive: ADSVF mixed with micrografts improved ulcer number, Raynaud symptoms, quality of life and pain in 19 analysed participants, while fat grafting plus medical treatment improved complete healing, capillary counts and pain versus sham in a 38-person RCT [282,283].

For facial systemic sclerosis, a prospective 93-person cohort undergoing 275 fat-grafting procedures reported 53.1% mean retention at approximately three years and Mouth Handicap score improvement from 28 to 23, but repeated treatment was associated with higher retention and patient selection cannot be excluded [284]. A very small retrospective series combining microfat and nanofat in progressive hemifacial atrophy or localised scleroderma reported non-significant improvements in symmetry, volume and texture among eight operated patients [285]. A broader facial-reconstruction meta-analysis found

pooled satisfaction of 91.1% and pooled retention of 59.0% for congenital deformities, but this aggregates heterogeneous diagnoses and techniques rather than proving benefit in Parry-Romberg disease [286].

In HIV-associated facial lipoatrophy, fat transfer has a reconstructive role but its durability and adverse-event profile vary. A 59-person comparative study found no thickness-gain difference among autologous fat (3.3+/-4.1 mm), polylactic acid (3.5+/-4.0 mm) and polyacrylamide hydrogel (2.1+/-3.0 mm; p=0.687), while all serious adverse events occurred in the fat-transfer arm [287]. A 23-person referral-centre series reported 25% complications, principally reabsorption, hypertrophy and haematoma, despite mean satisfaction of 7.7/10 [288]. The largest identified retrospective series (n=317) reported a good one-year aesthetic result in 63% with no recorded adverse events, a discrepancy that emphasises differences in ascertainment and outcome definition [289].

Study	Design	n	Product	Outcome	Result
Lonardi 2019 [273]	Single-centre RCT	114	Microfragmented adipose tissue	Diabetic-foot minor-amputation healing	6-mo complete healing 80% vs 46%; p=0.0064
Tanios 2021 [275,276]	RCT	100	ADSVF every 3 wk	Mixed chronic-ulcer closure	9-wk healing 46/47 vs 30/48; p<0.001
Zollino 2019 [277]	Phase-II RCT	16	Centrifuged adipose/SVF	Venous-ulcer healing time, pain	17.5 vs 24.5 wk; p<0.036; lower pain
Daumas 2022 [280]	Multicentre RCT	40	AD-SVF into fingers	Cochin Hand Function Scale	-9.2 vs -7.6 at 3 mo; no superiority
Khanna 2022 [281]	RCT	88	Adipose-derived regenerative cells	Cochin Hand Function Scale	Difference 2.62 (95% CI -2.4 to 7.6); p=0.299
Del Papa 2019 [283]	RCT	38	Fat graft+medical treatment	Systemic-sclerosis digital-ulcer healing	Higher complete healing and pain improvement; p<0.0001
Panettiere 2009 [265]	Retrospective case-control	61	Serial lipofilling	Irradiated breast LENT-SOMA	Scores improved; exact effects not reported

Table 14: Wounds, ulcers and fibrotic disease studies. Positive closure and symptom signals are not yet supported by a harmonised product specification or a poolable evidence base.

AD-SVF/ADSVF, adipose-derived stromal vascular fraction; mo, months; wk, weeks.

Complications of fat transfer and facial injection

Routine complication estimates should be interpreted separately from catastrophic facial embolic events. A 42-study meta-analysis of 6,268 recipients estimated an overall fat-transfer complication incidence of 4.2%, with infection 1.0%, fat necrosis 0.7% and face-specific complications 4.0%; most included non-randomised studies were not high quality [290]. The prospective GRAFT registry captured 7,052 procedures and reported 5.01% overall complications, including 1.94% for facial procedures and 7.29% for breast procedures [291]. These figures reflect common, reportable events such as cysts, infection and palpable masses, but cannot quantify very rare intravascular events reliably.

Facial injection deserves a separate consent discussion because visual loss, cerebral embolism and skin necrosis are low-frequency but potentially permanent. A systematic review of 103 facial-fat-grafting studies found 354 adverse events among 4,579 patients, with intravascular injection/embolism accounting for 87 events; importantly, it was completely unreported in prospective studies and RCTs, demonstrating profound reporting bias [292]. A case-based review identified 58 complications in 38 reported patients, including 11 hemiplegias, seven visual losses and three skin-necrosis events; more than half of severe events followed forehead-temporal injection [293]. The absence of an event in a small aesthetic trial therefore cannot be presented as evidence that the injection plane, cannula or product is

safe.

The fat-versus-hyaluronic-acid comparison in filler-associated visual loss is particularly concerning. Among reported cases, autologous fat was associated with diffuse vascular occlusion in 61/64 (95.3%) versus 44/68 (64.7%) for hyaluronic acid, ophthalmic-artery occlusion in 42/64 (65.6%) versus 21/68 (30.9%), brain infarction in 29/65 (44.6%) versus 11/105 (10.5%), and worse final acuity (2.83+/-0.64 versus 2.16+/-1.17 logMAR), all p<0.001 [294]. A review of ocular complications after fat injection found that 38 of 47 historical cases resulted in complete vision loss, with only five retaining any acuity; retinal ischaemia is thought to become permanent after roughly 90 minutes, even though exceptional recovery after immediate treatment has been reported [295]. Accordingly, procedural governance should prioritise anatomy-based avoidance of high-risk sites, conservative aliquots and pressure, immediate recognition of vascular compromise, and explicit consent that distinguishes common local sequelae from irreversible visual and neurological harm.

Non-Orthopaedic and Systemic Applications

The most developed non-orthopaedic programme is darvadstrocel (Cx601), an expanded allogeneic adipose-derived mesenchymal stromal cell product for complex perianal fistulas in Crohn disease. In ADMIRE-CD, 212 patients were randomised to a single 120-million-cell intralesional dose or 24 mL saline; combined remission at week 24 was 50% (53/107) versus 34% (36/105), an ITT difference of 15.2 percentage points (97.5% CI 0.2 to 30.3; p=0.024) [296]. At week 52, combined remission was 56.3% versus 38.6%, but the 104-week extension retained only 40 patients and therefore cannot establish durable comparative effectiveness [297].

ADMIRE-CD II did not reproduce the earlier effect: 568 participants had week-24 combined remission of 48.8% with darvadstrocel and 46.3% with placebo (difference 2.4%; 95% CI -5.8 to 10.6; p=0.571) [298]. INSPECT was retrospective and small, with 104-week remission of 53.5% versus 43.5% [299]. Meta-analysis found an approximately one-year healing advantage but no convincing early or more-than-two-year estimate [300]. EU withdrawal in December 2024 was commercial, not a safety action [301].

Trial	Indication	Design; n	Product and dose	Result
ADMIRE-CD	Complex Crohn fistula	Phase 3 RCT; 212	Allogeneic expanded ASC; 120 million	Week-24 combined remission 50% vs 34%; difference 15.2 points [296]
ADMIRE-CD II	Complex Crohn fistula	Phase 3 RCT; 568	Darvadstrocel; single local dose	Week-24 combined remission 48.8% vs 46.3%; p=0.571 [298]
SCIENCE	Ischaemic HFrEF	Phase 2 RCT; 133	Allogeneic AD-MSC; intramyocardial	LVESV change 0.3 mL at 6 months; p=0.945 [302]
APOLLO	Anterior STEMI	RCT; 14	Autologous ADRC; mean 17.4 million, intracoronary	Between-group infarct-size p=0.48 [303]
ADRC-ED	Post-prostatectomy erectile dysfunction	RCT; 70	Autologous ADRC; single intracavernous bolus	No IIEF-5 difference at 12 months; p>0.99 [304]
cGvHD phase I/II	Chronic graft-versus-host disease	Single-arm; 14	AD-MSC; 1 or 3 x 10^6 cells/kg	8/10 completers in complete remission; no SUSARs [305]

Table 15: Non-orthopaedic trials. Designs, products and outcomes should not be pooled as a single SVF evidence base.

Cardiac studies have been small and clinically neutral. ATHENA ended early and found no ventricular-function or volume difference; PRECISE randomised 27 patients without a definitive clinical endpoint [306,307]. APOLLO had no between-group infarct-size effect, and SCIENCE found no six-month ventricular,

symptom, biomarker or quality-of-life benefit [302,303].

Small vascular reports remain hypothesis-generating rather than practice changing. Ten amputation-candidate patients with non-reconstructable critical limb ischaemia received SVF, but only five had six-year follow-up and the report supplied no comparative analysis [308]. In a Japanese five-patient pilot of intramuscular ADRCs for Fontaine stage IV critical limb ischaemia, ulcer area decreased and all patients were amputation-free at six months, whereas ankle-brachial index and skin perfusion pressure were not significantly changed [309].

Urological evidence is weak and mixed. Stress-incontinence meta-analysis estimated ADSC continence recovery at 0.40 with high heterogeneity and no source advantage; a five-patient ADSC-collagen pilot had three later surgeries, and a ten-patient phase I study did not quantify adverse events [310–312].

Genital studies are uncontrolled. In menopause, 80% of 50 treated women had normalised scores at six months; 18 lichen-sclerosus participants improved after nanofat plus SVF; and a 59-man Peyronie cohort reported greater median curvature reduction with microfat than nanofat [313–315].

The erectile-dysfunction literature demonstrates the value of a placebo comparator: 70 men after radical prostatectomy randomised to autologous intracavernous ADRCs or placebo showed no difference at 12 months in IIEF-5, erection-hardness score or RigiScan measures, and no severe treatment-related event [304]. That null result should carry greater inferential weight than uncontrolled restoration claims in other sexual-medicine indications.

Ophthalmic delivery changes the risk calculus. Three commercial-clinic patients developed severe bilateral visual loss after intravitreal adipose-derived cells for macular degeneration, with retinal detachment and one-year acuity down to no light perception; a further report described vision loss in retinitis pigmentosa [316,317]. An eight-eye suprachoroidal study reported no complication at six months but no extractable effect size [318].

Systemic and central-neural administration should be distinguished from same-day joint injection. Ten people with chronic spinal cord injury received 100 million intrathecal autologous AD-MSCs; 44 adverse events occurred, 17 judged possibly related, headache affected eight patients and MRI showed cauda-equina root clumping in eight without clinical correlation [319]. A phase II report in 24 people with relapsing-remitting multiple sclerosis described favourable quality-of-life and disability estimates at 52 weeks, but remains a small, externally reported trial [320].

Controlled intravascular-MSC data are more reassuring than efficacy claims but do not represent advertised systemic SVF: 55 RCTs found more fever but no excess infection, thrombosis or malignancy/ectopic tissue [321]. A 13-patient COVID study recorded one death after dosing, and an ARDS meta-analysis suggested only short-term mortality benefit [322,323].

Marketed intravenous, intrathecal, inhaled and other systemic uses extend well beyond this evidence base. Documented unproven-intervention case series include infections, cardiovascular events, tumours,

neurological injury, blindness and deaths [324]. Glioproliferative spinal lesions after intrathecal stem-cell tourism, including paraplegia in one report and glioneuronal lumbosacral-root growth in another, show why route-specific surveillance cannot be replaced by generic claims of autologous safety [325,326].

Safety

Safety attribution begins with procedure. Historical surveys found 95 deaths in 496,245 lipoplasties (19.1 per 100,000) and 45 serious events in 66,570 procedures (0.68 per 1,000); a later mortality review found thromboembolic origin in 38.1% of 42 deaths [327–329].

Gluteal fat grafting is the clearest demonstration that delivery plane can dominate risk. The ASERF Task Force recorded 32 fatal and 103 non-fatal pulmonary fat emboli among 198,857 reported career cases, a combined rate of 1:1,473 and fatal rate of 1:6,214 [330]. Deep intramuscular injection was associated with fatal pulmonary-fat-embolism incidence-rate ratio 4.03 (95% CI 2.44 to 6.66) and non-fatal ratio 6.15 (3.37 to 11.24); cannulas at least 4.1 mm and subcutaneous delivery were protective [330]. After practice changes, reported pulmonary-fat-embolism risk fell from 1:1,030 to 1:2,492, while the reported 2017-2019 mortality was 1:14,921 [331].

Autopsy and case reviews support a mechanical vascular-injury mechanism. Mexican and Colombian deaths occurred during injection or within 24 hours, and all 16 reviewed fatal cases had microembolism [332,333]. In a CDC review, 92% of 2019-2020 cases involved gluteal transfer and 90% of autopsied deaths were embolic [334].

Case compilations describe severity, not incidence. Among 137 reported patients, mortality was 34.3%; pulmonary fat embolism alone had 86.1% mortality, while isolated ocular embolism commonly caused permanent visual loss [335]. Another review found 12 deaths among 36-37 patients with outcome data [336].

Event	Incidence	Denominator	Source
Liposuction mortality	19.1 per 100,000	95 deaths / interpolated 496,245 lipoplasties	[327]
Liposuction serious adverse event	0.68 per 1,000	45 events / 66,570 procedures	[328]
Gluteal fat-grafting fatal PFE	1:6,214	32 fatalities / 198,857 career cases	[330]
Gluteal fat-grafting combined PFE	1:1,473	135 PFE / 198,857 career cases	[330]
Facial fat-grafting complications	2.27%	104 events / 4,577 patients	[337]
Breast fat-grafting complications	17.2%	3,565 patients across 22 articles	[338]
Knee SVF transient swelling	7%	6 / 84 patients	[339]

Table 16: Procedure-related complications and their denominators. Denominators generally describe harvesting or grafting procedures, not the isolated cellular fraction.

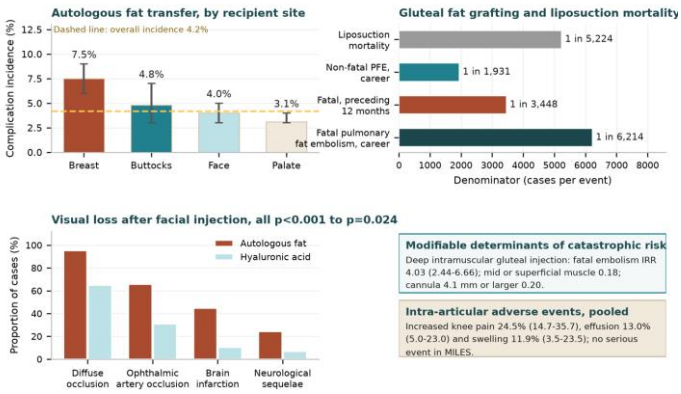


Figure 17: Safety depends on harvest, processing, route and anatomical delivery plane, rather than on a generic designation of adipose-derived cells.

Local events matter for consent. Facial fat grafting had a 2.27% pooled complication rate, while breast reviews reported 17.2% and 27.8% overall complication rates; fat necrosis, calcification and imaging confounding were prominent [337,338,340].

These breast data should not be misrepresented as oncologic proof for cell-enriched grafts. In 8,541 patients with breast cancer, observational evidence found no statistically significant difference in overall survival, disease-free survival or local recurrence after autologous fat grafting, but the confidence intervals and non-randomised design leave a different question from the safety of enzymatically isolated SVF or expanded cells [341].

Infection risk arises from liposuction, aspiration, injection and manufacturing. A multistate outbreak after unapproved umbilical-cord products caused culture-confirmed bacterial infections in 20 patients, 19 of whom required hospitalisation; 54% of 160 tested product vials were contaminated, with genomic linkage between product and patient isolates [342]. The outbreak was not an adipose-SVF study, but it is directly relevant to claims that a biologic preparation is safe because it is marketed as a cell product: sterility assurance and traceable processing are independent safety requirements.

Intra-articular data are more reassuring about catastrophic events but still incompletely quantified. A review of 844 culture-expanded intra-articular procedures recorded four serious events, of which one infection after marrow aspiration was probably related and one pulmonary embolism possibly related; seven events were considered possibly product-related and were pain or swelling [343]. An SVF review of 914 patients reported no serious adverse event, but most studies were non-randomised and did not calculate a pooled adverse-event rate [344].

Joint symptoms may be underplayed: across 28 knee-OA RCTs, MSC therapy increased injection pain, swelling and other adverse events [345]. Adipose-MSC meta-analysis found no overall event increase, but a network analysis estimated higher odds across several products; sparse events and incomplete ascertainment preclude safety equivalence [339,346,347].

Accordingly, risk should be allocated across three layers: cells and excipients, harvest and processing, and anatomical delivery. Intravenous controlled MSC data may inform infusion reactions but cannot establish safety for clinic-marketed intravenous SVF; liposuction and gluteal-grafting denominators describe real procedural hazards but cannot quantify isolated-cell toxicity; and small joint studies cannot exclude rare infection, neoplasia or thromboembolism [321,327,344].

Regulation

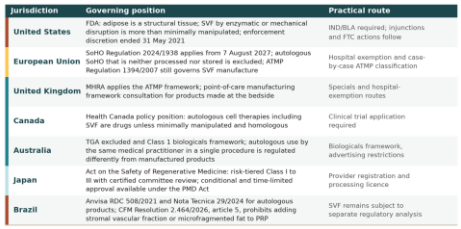
In the United States, the regulatory question is not whether a preparation is autologous but whether it meets all criteria for regulation solely as a section 361 HCT/P. Section 1271.3 distinguishes minimal manipulation of structural tissue from that of cells or nonstructural tissue, defines homologous use as the same basic function, and contains a specific bone-marrow carve-out without an equivalent for adipose tissue [348]. Section 1271.10 requires minimal manipulation, homologous use only, no impermissible combination and an appropriate systemic-effect condition; failure of one criterion triggers drug/biologic regulation, including IND and BLA requirements [349].

The same surgical procedure exception applies only where the same HCT/P is removed and implanted in the same procedure [350]. FDA 2017 Q&A and 2020 guidance treat adipose as structural tissue; disruption that destroys its architecture is generally more than minimally manipulated [351,352]. Rinsed adipose may be homologous for soft-tissue filling, unlike arthritis or neurological regeneration; enforcement discretion ended 31 May 2021 [352].

FDA inspection described at least 256 US Stem Cell Clinic SVF lots, systemic and spinal administration, and sterility-related CGMP deviations [353]. American CryoStem and Mother Stem letters addressed unapproved, more-than-minimally-manipulated adipose products for systemic use; Safari Stem Cell received a comparable veterinary warning [354–356].

The Southern District of Florida held US Stem Cell Clinic SVF adulterated and misbranded, and its injunction barred manufacture/distribution until compliance [357,358]. The Eleventh Circuit and Ninth Circuit held enzymatically processed SVF outside the same-procedure exception; Supreme Court denial of review left both holdings in force [359–361].

FTC actions address unsubstantiated disease claims independently of FDA status. The Regenerative Medical Group order included adipose products, imposed a $3.31-million judgment suspended on $525,000 payment, and supported nearly $515,000 in 270 consumer refunds [362–364]. Final 2024 Stem Cell Institute orders permanently barred marketing and imposed $5,155,146 [365,366].



Jurisdiction	Governing position	Practical route
United States	FDA: adipose is a structural tissue; SVF by enzymatic or mechanical disruption is more than minimally manipulated; enforcement discretion ended 31 May 2021	IND/BLA required; injunctions and FTC actions follow
European Union	SoHO Regulation 2024/1938 applies from 7 August 2027; autologous SoHO that is neither processed nor stored is excluded; ATMP Regulation 1394/2007 still governs SVF manufacture	Hospital exemption and case-by-case ATMP classification
United Kingdom	MHRA applies the ATMP framework; point-of-care manufacturing framework consultation for products made at the bedside	Specials and hospital-exemption routes
Canada	Health Canada policy position: autologous cell therapies including SVF are drugs unless minimally manipulated and homologous	Clinical trial application required
Australia	TGA excluded and Class 1 biologicals framework; autologous use by the same medical practitioner in a single procedure is regulated differently from manufactured products	Biologicals framework, advertising restrictions
Japan	Act on the Safety of Regenerative Medicine: risk-tiered Class I to III with certified committee review; conditional and time-limited approval available under the PMD Act	Provider registration and processing licence
Brazil	Anvisa RDC 508/2021 and Nota Técnica 29/2024 for autologous products; CFM Resolution 2.464/2026, article 5, prohibits adding stromal vascular fraction or microfragmented fat to PRP	SVF remains subject to separate regulatory analysis

Figure 18: Point-of-care adipose preparations occupy different regulatory routes according to manipulation,

intended function, setting and jurisdiction.

Jurisdiction	Instrument	Classification of point-of-care SVF	Practical route	Key date
United States	21 CFR 1271; FDA guidance	Generally drug/biologic if enzymatically isolated or non-homologous	IND/BLA unless all 361 criteria or narrow same-procedure exception	Discretion ended 31 May 2021 [349,352]
European Union	ATMP Regulation 1394/2007; CAT	OA SVF: sCTMP; cosmetic lipofilling SVF: not ATMP	Central ATMP authorisation where classified	SoHO applies 7 Aug 2027 [367–370]
United Kingdom	Human Medicines Regulations; MHRA	ATMP when substantially manipulated or non-homologous	Marketing authorisation; hospital exemption/specials only with licence	Windsor Framework 1 Jan 2025 [371]
Canada	Autologous Cell Therapy Policy	Autologous cell product is a drug; narrow lymphohaematopoietic exception	New-drug authorisation or clinical-trial route	Policy 17 Jan 2020 [372]
Australia	TGA HCT exclusions	Excluded only if same practitioner, hospital and no consumer advertising	Otherwise regulated biological	Guidance 2024-26 [373–375]
Japan	Act on the Safety of Regenerative Medicine	Risk-classified regenerative medicine	Plan review; facility permission/notification	Act 2013; amended 2022 [376]
Brazil	ANVISA RDC 505; CFM 2.464/2026	Advanced therapy if extensively manipulated or different function	Registration or approved research; PRP cannot include SVF	RDC in force 1 Jul 2021; CFM 2026 [377,378]

Table 17: Regulatory position by jurisdiction. Classification does not follow the marketing label 'autologous' alone.

The European Union separates ATMP regulation from the incoming substances-of-human-origin framework. Regulation 1394/2007 defines ATMPs and makes central marketing authorisation compulsory; its list of non-substantial manipulations includes centrifugation, cell separation and filtration but not enzymatic digestion [367]. Regulation 2024/1938 applies from 7 August 2027, excludes autologous material neither processed nor stored before application, and applies alongside ATMP rules where SoHO is starting material for ATMP manufacture [370].

CAT considers enzymatic cell release substantial manipulation and adipose cells placed outside fat tissue ATMPs [379]. It classified OA SVF as sCTMP but cosmetic-lipofilling SVF as non-ATMP; its list also includes tissue-engineered wound, cartilage and bone products and PRP-SVF for perianal fistula [368,369,380,381].

CAT classification is an optional recommendation delivered within 60 days and is not binding on national borderline decisions, leaving scope for Member-State variation despite a common scientific vocabulary [382]. In the United Kingdom, ATMPs require MHRA authorisation; hospital exemption and 'specials' routes remain restricted to non-routine, licensed manufacture rather than a general clinic exemption [371].

Canada treats autologous cell therapies as drugs, and a device licence does not authorise the resulting product [372]. Australia requires same-practitioner hospital manufacture and no consumer advertising for exclusion; Japan uses prospective risk-class review and facility permission [373–376].

Brazilian RDC 505 limits the same-procedure exclusion to minimal manipulation and the same function [377]. CFM Resolution 2.464/2026 Article 5 prohibits SVF, microfragmented fat, stem cells and cell products as PRP additives outside research or specific regulation; earlier CFM opinions and its technical chamber urge research-context caution [378,383–385].

For competitive athletes, this distinction is practical rather than semantic. WADA's 2026 list prohibits normal or genetically modified cells or cell components where there is potential to enhance performance, placing SVF and ASC interventions within M3.2, and it separately constrains large intravenous infusions

and performance-relevant growth factors [386]. PRP and related procedures remain not prohibited, but that permission does not extend to an adipose-cell or cell-component adjunct [387].

Economics, Market and Payer Coverage

Prices and availability show a market that is poorly aligned with evidence maturity. In a US secret-shopper study of 273 contacted centres, the mean quoted price for a unilateral same-day knee 'stem-cell' injection was $5,156 (SD $2,446; n=65), while the mean claimed efficacy was 82% (n=36) [388]. In the Chicago region, mean single-knee 'stem cell' prices were $1,451.75 in orthopaedic practices and $4,593.50 in alternative clinics ($p<0.001$), illustrating both price dispersion and the absence of a standardised product behind the quoted service [389].

As of March 2021, 1,480 US businesses operated 2,754 clinics, including 437 marketing autologous adipose interventions; only 3.78% disclosed prices [390,391]. In a 59-business audit, 71% used testimonials, four mentioned trials and fewer than 2% of cited papers directly supported the sold intervention [392].

Commercial estimates require caution: one report valued the global MSC-therapy market at USD 103.2 million in 2025 and the adipose share at 37.71% in 2024, not a validated direct-to-consumer SVF estimate [393]. In contrast, US 2024 volumes included 349,728 liposuction procedures, and the international survey recorded 947,007 facial fat grafts [394,395].

Item	Value or position	Source
Same-day knee injection, US	$5,156 mean; claimed efficacy 82%	[388]
US clinic market	1,480 businesses; 2,754 clinics; 437 adipose marketers	[390,391]
Price transparency	3.78% of businesses disclosed prices	[391]
Commercial MSC market estimate	USD 103.2m in 2025; adipose share 37.71% in 2024	[393]
Aetna	Experimental, investigational or unproven; includes SVF+PRP for Crohn fistula	[396]
Anthem	Investigational and not medically necessary for all indications	[397]
Cigna and BCBSM/BCN	Not medically necessary or not covered for orthopaedic applications	[398,399]

Table 18: Economics and payer coverage. Direct-to-consumer prices are usually out-of-pocket and not a proxy for validated value.

Payers are uniform: Aetna lists adipose interventions and SVF-PRP for Crohn fistula as unproven; Anthem calls all autologous ADRC therapy investigational; Cigna calls fat-derived stem-cell therapy not medically necessary; and BCBSM/BCN lists related adipose products investigational without CMS coverage [396–399].

That uniformity should not be mistaken for a formal consensus that every biological effect is absent. An audit of five national payer policies found 123 unique references, 56.9% Level IV evidence and 62.6% papers reporting efficacy, leading the authors to argue that payer citations themselves did not consistently substantiate denial [400]. The more defensible conclusion is narrower: no stable product, clinically important benefit and durable safety package has yet supported routine coverage.

Quality of the Evidence Base

Methodological quality reviews caution against treating the number of systematic reviews as independent confirmation. Among 22 systematic reviews and meta-analyses of stem-cell therapy for knee

osteoarthritis, every review was rated critically low by AMSTAR 2 and high risk of bias by ROBIS; protocol registration, excluded-study lists and publication-bias assessment were frequent omissions [401]. An umbrella review of 50 clinical studies and 13 reviews similarly found absent protocol registration in 11 reviews, no reporting of included-study funding in any review and limited discussion of risk of bias or publication bias [402].

Appraisal	Sample of reviews	Tool	Result
Knee-OA stem-cell reviews	22 systematic reviews/meta-analyses	AMSTAR 2; ROBIS	22/22 critically low; 22/22 high ROBIS risk [401]
Knee-OA umbrella review	13 reviews; 50 clinical studies	AMSTAR 2 domains	11 no protocol; 12 no excluded-list; 0 funding report [402]
PRP-OA meta-research	31 systematic reviews; 79 abstracts for spin	AMSTAR 2; spin analysis	26/31 critically low; every abstract had spin, mean 5.5 instances [403]

Table 19: Methodological quality appraisals. Review-level quality failures compound the clinical-trial limitations.

Spin is therefore a reporting problem, not merely an editorial nuisance. In a meta-research appraisal of 31 PRP osteoarthritis reviews, 83.8% were critically low quality and none were moderate or high; in 79 abstracts every one contained at least one form of spin, averaging 5.5 instances [403]. For the present literature, readers should prioritise prespecified, comparator-controlled outcomes; identify product, dose, viability and route; distinguish within-group change from between-group effect; and treat unquantified safety assertions as missing data rather than reassurance.

Discussion

The central finding of this review is not that adipose-derived preparations lack biological activity, but that biological plausibility has outrun clinical demonstration. Adipose tissue provides an accessible source of cellular, extracellular-matrix and paracrine constituents, yet the preparation labelled SVF, nanofat, microfat, ADRC or AD-MSC differs materially by donor, harvest, device, manipulation, cell yield, viability, culture history, adjunct and route. The resulting literature often asks whether a name works rather than whether a defined product, delivered for a defined indication at a defined dose, improves a patient-important outcome. The positive fistula signal in the first ADMIRE-CD trial and its absence in ADMIRE-CD II are a particularly useful warning against extrapolating from mechanistic plausibility or a single successful programme [296,298].

Clinical effects also follow a comparator gradient. Improvements against baseline, or against no intervention, are common across aesthetic, musculoskeletal and genital reports; inference weakens when the comparator is saline, and weaker still when it is an active standard such as hyaluronic acid, corticosteroid, platelet-rich plasma or structured rehabilitation. The absence of a placebo-controlled erectile-dysfunction benefit after radical prostatectomy, despite favourable uncontrolled sexual-medicine reports, demonstrates why expectation, natural history and procedural co-intervention must be modelled rather than ignored [304,313,314]. For knee osteoarthritis, statistically positive pooled scores should be interpreted against prespecified minimal clinically important differences, structural endpoints and active comparators, not only against p values [345].

Product heterogeneity is the dominant confounder. Same-day mechanical fractions retain a different tissue architecture from enzymatically isolated SVF; both differ from culture-expanded, selected,

cryopreserved or allogeneic MSC products. Even within a nominal class, dose may be reported as volume, total nucleated cells, viable cells, colony-forming units or not at all, while processing descriptions may give revolutions per minute rather than relative centrifugal force. This precludes naïve pooling and means that a reassuring safety result for intravascular, trial-manufactured MSCs cannot establish safety for a marketed intravenous SVF preparation [321,355].

The reporting problem is therefore both technical and ethical. Studies frequently omit harvest volume, tissue depot, device, enzyme, centrifugation force, final volume, viability, immunophenotype, sterility testing, concomitant products and adverse-event ascertainment; a label of 'autologous' does not repair these omissions. Review-level synthesis cannot compensate when its inputs are incompletely specified: all 22 assessed knee-OA stem-cell reviews were critically low by AMSTAR 2 and high risk of bias by ROBIS [401]. Claims should be calibrated to the probability of clinically important net benefit, and unquantified statements that no adverse events occurred should be read as an ascertainment limitation rather than proof of absence.

There is an important asymmetry between aesthetic and orthopaedic evidence. Structural fat grafting has an established reconstructive and aesthetic logic, substantial procedure volumes, and outcomes such as contour, retention and imaging sequelae that are specific to the grafting procedure; its main hazards include fat necrosis, calcification, infection, embolism and, in gluteal grafting, a delivery-plane-dependent risk of pulmonary fat embolism [330,331,338]. By contrast, orthopaedic marketing typically claims anti-inflammatory, regenerative or cartilage-restorative action, yet joint trials usually do not demonstrate structural restoration and often pool incompatible cell products. The clinical proposition in the latter setting is therefore more ambitious and requires more stringent evidence than is supplied by a favourable pain trajectory alone [345,402].

Regulatory divergence partly reflects different legal architectures, but the underlying biological distinction is convergent. US courts now agree that enzymatically isolated adipose SVF is not the same HCT/P removed from the patient and is regulated as a drug/biologic when it falls outside the section 361 criteria [359–361]. EU CAT decisions likewise classify enzymatically released SVF for osteoarthritis as an ATMP while recognising an indication-specific non-ATMP lipofilling context, and Australia, Canada, Japan and Brazil each impose conditions that cannot be reduced to 'same-day autologous' [368,369,372,373,376,377].

The evidence-market mismatch has direct consequences for patients. Thousands of US clinics have advertised cell interventions, prices are rarely disclosed, and the mean quoted fee for a same-day knee injection has been in the range of several thousand dollars [388,390,391]. Payers consequently take uniform non-coverage positions for cell-enriched adipose interventions, although the literature they cite is heterogeneous and not always methodologically decisive [396–400]. The appropriate response is not a blanket inference that all autologous approaches are ineffective, but transparent separation of established structural grafting, investigational regulated products and unproven commercial claims.

Practice would change with adequately powered, multicentre trials using a locked manufacturing protocol, independent product characterisation, sham or active comparator matched to clinical context,

prespecified minimal clinically important differences, blinded outcome assessment and long-term safety surveillance. Such trials should embed economic evaluation and publish patient-level harms by harvest, processing and delivery stage. Until then, the most defensible clinical posture is indication-specific caution: do not infer efficacy across products, do not transfer safety across routes, and do not allow a regulatory label or payment model to substitute for comparative evidence.

A Three-Tier Framework for Clinical Use

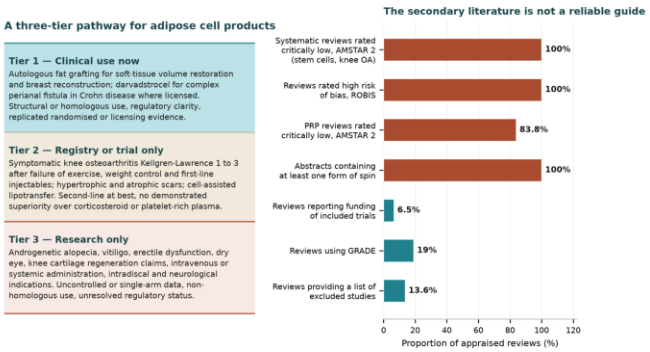


Figure 19: A three-tier framework separates established structural fat grafting from regulated investigation and unproven commercial cell claims.

Tier	Indications	Evidence basis	Regulatory status	Recommended setting
1. Established structural use	Autologous soft-tissue filling, reconstructive contour restoration and selected cosmetic lipofilling	Procedure-specific observational and systematic-review evidence; does not establish cell-enrichment benefit	Use only within applicable tissue, surgical and advertising rules	Credentialled surgical practice with imaging-aware follow-up and complication pathways
2. Regulated investigation	Serious conditions with a biologically coherent target and a defined investigational product	Preclinical rationale plus early clinical signal; no routine-practice proof	IND/CTA/ATMP or equivalent, ethics review and product release controls	Registered, prospective trial or tightly governed hospital programme
3. Unproven commercial use	Systemic, intrathecal, ocular or broad musculoskeletal 'regeneration' claims without a defined product and comparator	Uncontrolled reports, testimonials or indirect evidence	Often outside applicable exemption or marketing rules	Do not offer as routine care; refer to a regulated trial where available

Table 20: Three-tier framework for clinical use. Tier assignment follows indication, product definition, comparative evidence, route and regulatory route together.

Tier 1 is deliberately narrow. It recognises that transferring autologous fat can be a legitimate structural procedure but does not convert every lipoaspirate preparation into a cell therapy or support systemic, joint or regenerative claims. The clinical record supports explicit counselling on retention, imaging findings and delivery-related hazards, particularly the subcutaneous-only safety discipline for gluteal transfer [331,338,340].

Tier 2 is the appropriate home for defined SVF, ADRC and AD-MSC products whose expected benefit remains uncertain. Entry requires a protocol with identity, potency and sterility criteria; a comparator proportionate to the intervention; independent adverse-event adjudication; and public registration. In jurisdictions applying ATMP, drug/biologic or regenerative-medicine controls, regulation should be treated as a framework for evidence generation rather than a badge of efficacy [349,367,376].

Tier 3 includes commercial offerings that conflate harvest with efficacy, describe a heterogeneous fraction

as a proven stem-cell medicine, or use vulnerable patients' unmet need to justify systemic or irreversible delivery. The ophthalmic blindness cases, contamination outbreak and federal enforcement record show that this category raises both evidence and patient-protection concerns [316,342,353,366].

Research Agenda

Priority question	Proposed design	Primary endpoint	Minimum sample or duration	Feasibility
Does a defined point-of-care adipose fraction improve knee-OA pain beyond active care?	Multicentre, blinded, sham-controlled RCT with standardised harvest, device and release criteria	Between-group pain and function change exceeding prespecified MCID	250 per group; 24 months	High, if product protocol is locked and sham is acceptable
Which product attribute predicts response or harm?	Nested mechanistic cohort across a core RCT	Validated association between product attribute and clinical response	All RCT participants; independent laboratory	Moderate; requires central biobanking and assay harmonisation
Can fistula benefit be reproduced in a defined phenotype?	International placebo-controlled phase 3 trial with MRI and clinical endpoints	Composite remission plus sustained remission	400 per group; 104 weeks	Moderate; depends on product access and recruitment
What is the route-specific safety incidence?	Mandatory prospective registry linked to batch, harvest and delivery records	Serious adverse events adjudicated by causal layer	10,000 procedures; 5 years	Moderate; requires regulatory and professional-society participation
Does cell enrichment improve structural fat-grafting outcomes?	Blinded within-patient or randomised controlled reconstructive study	Retention, imaging events and patient-reported outcome	150 per group; 24 months	High for breast/facial indications with imaging follow-up
What is the cost-effectiveness of regulated use?	Trial-based economic evaluation with societal and payer perspectives	Cost per quality-adjusted life-year and budget impact	Embedded in phase 3 trial; 2-5 years	High once a clinically meaningful endpoint is established

Table 21: Research agenda. The first priority is reproducible product definition and a comparator capable of changing practice.

The first studies should not attempt to answer every indication at once. They should choose conditions in which the delivery route is defensible, the outcome is patient-important and measurable, standard care leaves material residual burden, and an active or sham comparator can be implemented ethically. Registry infrastructure should begin in parallel, because uncommon embolic, infectious, oncological and neurological events will not be resolved by conventional efficacy trials alone [335,341,342].

Limitations

This narrative review is limited by the heterogeneity and uneven reporting of the primary literature, by the reliance of some regulatory and market statements on documents that may change, and by the fact that different jurisdictions use non-identical legal tests. It does not perform a de novo meta-analysis, and it cannot correct missing product characterisation, selective publication or comparator imbalance in included studies. The quality appraisals reviewed here indicate that these constraints also affect secondary syntheses [401-403].

Some evidence originates from small single-arm studies, meeting reports, case series or commercial market assessments, which are retained because they illuminate safety, regulation or the gap between marketing and clinical evidence rather than because they establish efficacy. Reported absence of a serious adverse event in small cohorts has limited exclusionary value, and safety observations cannot be transported between liposuction, intralesional injection, intra-articular administration, intravascular infusion and intrathecal delivery [319,321,336].

Conclusions

Nanofat and SVF are not single interventions. Established structural fat grafting should be separated from enzymatically isolated, mechanically fractionated, culture-expanded and systemically delivered cellular products. Across most non-structural indications, clinical evidence remains insufficiently standardised and comparator-controlled to support routine use; the most credible signals require replication with a defined product and clinically important endpoint [296,298,402].

Safety is route- and procedure-dependent, while regulation and payer policy increasingly distinguish structural fat transfer from cell-enriched or non-homologous claims. The field should prioritise transparent manufacturing, controlled trials, route-specific surveillance and honest communication over broad regenerative branding [330,348,367,397].

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Non-financial interests relevant to adipose-derived products, devices, clinics or trials.

Ethics statement

This article is a narrative review of published literature and does not involve new human participants, animals, or identifiable patient data. Ethical approval and informed consent were therefore not required.

Author contributions

All authors approved the final manuscript.

Data Availability

Data sharing is not applicable to this article because no new datasets were generated or analysed. The sources reviewed are cited in the reference list.

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348. 21 CFR section 1271.3 — Definitions (HCT/P regulations; as amended 66 FR 5466, 19 Jan 2001; 81 FR 60223, 31 Aug 2016). section 1271.3(d)(4) exempts from the HCT/P definition "minimally manipulated bone marrow for homologous use and not combined with another article" — there is no parallel carve-out for adipose tissue, which is the structural reason bone marrow aspirate and adipose SVF are treated differently.
349. 21 CFR section 1271.10 — Are my HCT/P's regulated solely under section 361 of the PHS Act and the regulations in this part, and if so what must I do? Sets the four cumulative criteria for an HCT/P to be regulated solely under section 361: (1) minimally manipulated; (2) intended for homologous use only, as reflected by labelling, advertising and other indications of intent; (3) manufacture does not involve combination with another article except water, crystalloids or a sterilizing/preserving/storage agent; (4) either no systemic effect and not dependent on the metabolic.

350. 21 CFR section 1271.15(b) — Are there any exceptions from the requirements of this part? (same surgical procedure exception). Verbatim: the requirements do not apply to an establishment that "removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure." The operative words on which the adipose litigation turned are "such HCT/P's" and "the same surgical procedure"; FDA reads "such HCT/P's" as requiring that the material implanted be the same as the material removed.
351. U.S. FDA, CBER. Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception — Guidance for Industry, November 2017.
352. U.S. FDA, CBER. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use — Guidance for Industry and FDA Staff, July 2020 (supersedes the November 2017 guidance, corrected December 2017).
353. U.S. FDA press announcement. FDA warns US Stem Cell Clinic of significant deviations, August 2017. FDA reported that the Florida clinic processed autologous adipose tissue into SVF and administered it intravenously or directly into the spinal cord for Parkinson's disease, ALS, COPD, heart disease and pulmonary fibrosis. Inspection findings included at least 256 lots of SVF products and significant deviations from CGMP including sterility failures that put patients at risk of infection.
354. U.S. FDA press announcement. FDA warns American CryoStem Corporation of significant deviations related to its unapproved stem cell product, 2018. FDA found that "Atcell," an adipose-derived product, was more than minimally manipulated and was marketed for anoxic brain injury, Parkinson's disease, ALS, stroke and multiple sclerosis, delivered intravenously, intrathecally and by aerosol, without a BLA or IND. The action illustrates FDA's treatment of processed adipose products distributed to third-party physicians rather than used within one practice.
355. U.S. FDA warning letter to Mother Stem Institute Corp. (Alvaro Skupin, MD), Coral Gables, Florida, 20 August 2024, reference CBER-24-680118. The firm produced SVF by enzymatic digestion of autologous adipose tissue and administered it intravenously for Alzheimer's disease, diabetes, lupus and rheumatoid arthritis.
356. U.S. FDA warning letter to Safari Stem Cell LLC, 5 April 2024, WL 24-661023 (veterinary). Following an inspection on 1–4 May 2023, FDA cited culture-expanded adipose-derived cell products combined with platelet-rich plasma for animal use as unapproved new animal drugs, and listed eight CGMP deviations. The letter shows the same analytical framework (culture expansion = more than minimal manipulation) being applied on the veterinary side, where a large share of adipose cell marketing occurs.
357. U.S. FDA press announcement. Federal court issues decision holding US Stem Cell clinics and owner adulterated and misbranded stem cell products, 3 June 2019. Judge Ursula Ungaro of the U.S. District Court for the Southern District of Florida granted the government summary judgment, in an action the Department of Justice filed on FDA's behalf in May 2018. The court held the adipose-derived SVF products were adulterated and misbranded drugs.
358. U.S. FDA. Statement on stem cell clinic permanent injunction and FDA's ongoing efforts to protect patients from risks of unapproved products. The permanent injunction bars US Stem Cell Clinic LLC (Weston, FL), US Stem Cell Inc. (Sunrise, FL) and Kristin Comella, PhD, "from manufacturing or distributing any and all stromal vascular fraction (SVF) products, which are adipose (fat) tissue derived stem cell products, until they come into compliance" with the FD&C Act and PHS Act.
359. United States v. US Stem Cell Clinic, LLC, 998 F.3d 1302 (11th Cir. 2 June 2021), No. 19-13276, D.C. Docket No. 0:18-cv-61047-UU. The Eleventh Circuit (Jordan, Marcus, and Ginsburg by designation, writing) affirmed summary judgment and a permanent injunction against the clinic's five-step isolation of SVF from lipoaspirate, resuspended in saline or PRP. Holding on the same surgical procedure exception: "we hold the same surgical procedure exception unambiguously does not apply," because "By the time the stromal-vascular fraction is reinjected, it is no.
360. United States v. California Stem Cell Treatment Center, Inc., 117 F.4th 1213 (9th Cir. 27 Sept 2024), No. 22-56014, D.C. No. 5:18-cv-01005-JGB-KK. Argued 7 February 2024 before Wardlaw, Friedland and Sung; the panel reversed and remanded the district court's post-bench-trial judgment for the defendants (624 F. Supp. 3d, C.D. Cal., Judge Jesus G. Bernal).
361. California Stem Cell Treatment Center, Inc. v. United States, No. 24-1189 (U.S. Supreme Court docket; petition for certiorari filed 19 May 2025; certiorari denied 14 October 2025). The Supreme Court's denial of review leaves the Ninth Circuit's holding in force and ends the circuit-level challenge to FDA's position that enzymatically isolated adipose SVF is a drug/biologic outside the same surgical procedure exception.
362. Federal Trade Commission. Regenerative Medical Group, Inc., Telehealth Medical Group, Inc., and Bryn Jarald Henderson, D.O., FTC File No. 172 3062, No. 8:18-cv-01838-AG-KES (C.D. Cal.). FTC alleged deceptive claims that "amniotic stem cell therapy" treats autism, cerebral palsy, Parkinson's disease, multiple sclerosis and other serious conditions without competent and reliable scientific evidence. The case is the FTC's principal stem-cell marketing enforcement template and its order language reaches adipose-derived products
363. Stipulated Order for Permanent Injunction and Monetary Judgment, FTC v. Regenerative Medical Group, Inc. et al., entered 25 October 2018. The order's definition of "Stem Cell Therapy" expressly includes cells derived from adipose tissue, so the injunction's evidence-substantiation requirements apply to adipose-derived marketing. It imposes a monetary judgment of $3.31 million, suspended upon payment of $525,000, reflecting revenue of at least $3.31 million earned between 2014 and 2017.
364. Federal Trade Commission press release. FTC returns almost $515,000 to consumers who bought deceptively marketed amniotic stem cell therapy, April 2019. The FTC mailed 270 refund cheques totalling approximately $515,000, an average of about $1,907 per

consumer. The figure is a useful lower bound on typical per-patient out-of-pocket spending in this market segment.

365. Federal Trade Commission press release. Stem Cell Institute co-founders, companies banned from marketing stem cell treatments, ordered to pay more than $5.1 million, 8 January 2025 (FTC and State of Georgia v. Peyroux, Detelich, Regenerative Medicine Institute of America LLC d/b/a Stem Cell Institute of America, No. 1:21-cv-03329-AT (N.D. Ga.); FTC File No. 182 3125). Following a complaint filed in August 2021 and an 82-page summary-judgment opinion issued 11 March 2024, orders were entered on 26 December 2024 permanently banning the defendants from marketing any regenerative medicine treatment. The monetary relief totals $5,155,146: $3,310,146 in consumer redress plus $1,845,000 in civil penalties under Georgia law.
366. Order Granting Injunctive Relief, FTC and State of Georgia v. Peyroux et al., N.D. Ga., December 2024. The injunctive order again defines "Stem Cell Therapy" to include adipose-derived cell products, so the marketing ban and substantiation requirements apply to SVF and related adipose interventions. Together with the 2018 order, this establishes that adipose-derived marketing claims are actionable under section 5 FTC Act independently of FDA premarket status.
367. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products, OJ L 324, 10.12.2007, pp. 121–137. Article 2(1)(a) defines an ATMP as a gene therapy medicinal product, a somatic cell therapy medicinal product (sCTMP) or a tissue engineered product (TEP). https://eur-lex.europa.eu/eli/reg/2007/1394/oj
368. European Medicines Agency / CAT. Scientific recommendation on classification of advanced therapy medicinal products: stromal vascular fraction cells, EMA/534818/2017, 24 August 2017 (procedure finalised 30 June 2017). CAT classified SVF cells intended to relieve the symptoms of osteoarthritis as a somatic cell therapy medicinal product. This is the closest EU analogue to the US position in the SVF litigation: intended non-homologous, symptom-modifying use of enzymatically released adipose cells pulls the product into medicinal product regulation.
369. European Medicines Agency / CAT. Scientific recommendation on classification of advanced therapy medicinal products: autologous cells of the stromal vascular fraction of adipose tissue, EMA/500673/2012, 24 July 2012
370. Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application, OJ L, 2024/1938, 17.7.2024.
371. MHRA / GOV.UK guidance. Advanced therapy medicinal products: regulation and licensing in the UK, last updated 6 March 2025. ATMPs are defined in the Human Medicines Regulations 2012 and MHRA is the competent authority; all ATMPs placed on the market require a UK-wide marketing authorisation, and Great Britain-only authorisations have not been possible since the Windsor Framework took effect on 1 January 2025.
372. Health Canada. Policy Position Paper — Autologous Cell Therapy Products, published 17 January 2020. Five consolidated policy statements: autologous cell therapy products meet the definition of a drug, so sections 8 and 11 of the Food and Drugs Act apply; all such products except minimally manipulated lymphohematopoietic cells for homologous transplantation are new drugs requiring authorization under Division 8 of the Food and Drug Regulations, with investigational use only under Division 5 (clinical trial applications.
373. Therapeutic Goods Administration (Australia). Biological products that are exempt or excluded from TGA regulation (page dated 18 October 2025). An autologous human cell and tissue product escapes TGA regulation only if all of three conditions hold: it is collected from a patient under the clinical care of a medical or dental practitioner registered in a State or Territory; it is manufactured by that practitioner or persons under their professional supervision in a hospital (except for storage and testing) for that same patient, who must be a patient of that hospital.
374. Therapeutic Goods Administration (Australia). Regulation of stem cell treatments: information for practitioners (page dated 7 April 2026). TGA states flatly: "Autologous HCT products, including stem cell treatments, cannot be advertised." Outside the hospital setting, products must be prepared with "minimal manipulation," and TGA adds that "Most stem cell products do not meet this criterion." The commencement date of the advertising prohibition is not stated on this page: n.a.
375. Therapeutic Goods Administration (Australia). Understanding regulation of autologous human cell and tissue (HCT) products, 11 September 2024. The guidance frames autologous HCT regulation under the Therapeutic Goods Act 1989 and Therapeutic Goods Regulations 1990, referencing the Therapeutic Goods (Guidelines for Multi-Site Licences) Instrument 2020 for practices operating across sites. The specific exclusion criteria and advertising prohibition are not restated on this page; they appear in au_tga_excluded and au_tga_stemcell.
376. Act on the Safety of Regenerative Medicine (Japan), Act No. 85 of 27 November 2013, as amended by Act No. 68 of 2022 (Japanese Law Translation, Ministry of Justice). Article 2(7)–(9) sets three risk classes: Class I where the effect on human life and health is unclear or where there is a risk of serious effects even with considerable care; Class II where there is a risk of affecting life or health (excluding Class I); Class III neither.
377. ANVISA. Resolução da Diretoria Colegiada — RDC nº 505, de 27 de maio de 2021 — "Dispõe sobre o registro de produto de terapia avançada"; in force 1 July 2021 (art. 52). Article 3º, II excludes from the registration requirement autologous collection-and-reimplantation procedures that cumulatively satisfy three conditions: (a) performed during the same surgical act or the same therapeutic procedure; (b) with minimal manipulation; and (c) with the objective of performing the same function.
378. Conselho Federal de Medicina (Brazil). Resolução CFM nº 2.464, de 2 de julho de 2026 — "Regulamenta o uso de plasma rico em plaquetas como procedimento médico adjuvante no tratamento de condições osteomusculares específicas e dá outras providências";

DOU 15 July 2026, Edição 131, Seção 1, p. 70; in force on publication. The resolution authorises PRP only as an adjuvant for four indications — knee osteoarthritis, lumbar discopathy, lateral epicondylitis of the elbow, and meniscal repair — and requires PRP to be exclusively autologous peripheral blood, minimally manipulated, non-transfusional, with platelet concentration above physiological baseline (normally 150,000–350,000/μL), processed exclusively per Nota Técnica Anvisa nº 29/2024 or its. https://sistemas.cfm.org.br/normas/arquivos/resolucoes/BR/2026/2464_2026.pdf

379. European Medicines Agency, Committee for Advanced Therapies. Reflection paper on classification of advanced therapy medicinal products, EMA/CAT/600280/2010 rev.1, adopted 22 May 2015. Key operative sentence for SVF: "Enzymatic digestion of a tissue to release cells is also considered to be substantial manipulation, when the aim is to dissociate cell-cell contacts and the released cells are administered into patients." The paper defines same essential function as cells "used to maintain the original function(s) in the same anatomical or histological environment," and states that "adipose cells transplanted. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en.pdf-0
380. European Medicines Agency. Scientific recommendations on classification of advanced therapy medicinal products (running list of CAT classification decisions). The list contains roughly 40 adipose-related entries and shows the fine-grained, indication-dependent line-drawing: SVF in Lactated Ringer's for osteoarthritis pain = sCTMP (25/11/2015); the same for non-healing wounds = TEP (25/11/2015); SVF for cartilage/bone defects and ADSCs for the same = TEP (both 16/06/2017); SVF+ADSC for cutis laxa senilis = TEP (16/09/2016); keloid scars = TEP (23/03/2016); adipose MSC for ALS =. https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/advanced-therapies-marketing-authorisation/scientific-recommendations-classification-advanced-therapy-medicinal-products
381. European Medicines Agency. CAT monthly report of application procedures, guidelines and related documents on advanced therapies, October 2019. Among the classifications reported, a combination of platelet-rich plasma with stromal vascular fraction for perianal fistula wound healing was classified as a tissue engineered product, as were adipose MSCs for diabetic foot ulcers and adipose stromal cells for bone and cartilage defects including osteoarthritis. https://www.ema.europa.eu/en/documents/committee-report/cat-monthly-report-application-procedures-guidelines-and-related-documents-advanced-therapies-october-2019_en.pdf
382. European Medicines Agency. Advanced therapy classification (procedural overview under Article 17 of Regulation (EC) No 1394/2007). ATMP classification is an optional scientific procedure: a developer may ask CAT for a recommendation, which is issued within 60 days after consultation with the European Commission. Because it is optional and non-binding on national borderline decisions, EU classification of adipose products is fragmented across Member States even where CAT precedent exists. https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/advanced-therapies-marketing-authorisation/advanced-therapy-classification
383. Conselho Federal de Medicina (Brazil). Parecer CFM nº 32/2019, approved 26 November 2019 (rapporteur Cons. Yáscara Pinheiro Lages Pinto; Protocolo CFM nº 5.609/2018; subject: use of platelet-rich plasma in dermatology). The ementa holds that PRP use in dermatology "deve se dar no contexto da pesquisa clínica e aguardar novas evidências que comprovem segurança e eficácia, segundo os critérios do sistema CEP/Conep." The opinion notes the persistent absence of consensus on regulating PRP and other conventional and advanced cell therapies and that the available publications were of low methodological quality. https://sistemas.cfm.org.br/normas/arquivos/pareceres/BR/2019/32_2019.pdf
384. Conselho Federal de Medicina (Brazil). Parecer CFM nº 43/2016, approved 28 October 2016 — "Uso aspirado de medula óssea para tratamento de lesões ortopédicas". CFM classified bone marrow aspirate for orthopaedic lesions as an experimental procedure, permissible only within research protocols approved by the CEP/CONEP system, applying Resolução CFM nº 2.128/2015 and citing Resolução CFM nº 1.982/2012 on the recognition of new procedures. It is the closest CFM precedent for autologous orthobiologic concentrates other than PRP; it does not mention adipose tissue or SVF (n.a. https://sistemas.cfm.org.br/normas/arquivos/pareceres/BR/2016/43_2016.pdf
385. Conselho Federal de Medicina (Brazil), Câmara Técnica sobre Produtos e Técnicas em Procedimentos Estéticos. Câmara Técnica alerta sobre uso de células tronco em tratamentos (portal news item; the page dates itself only as "quarta-feira (13)", so the year should be treated as uncertain). CFM warns physicians against advertising stem cells in aesthetic procedures, noting that many procedures marketed as "stem cell" treatments are in fact liposuctioned fat grafts supposedly "enriched" with stem cells — described as a variation of a 20-year-old fat grafting technique with no consistent data confirming that stem cells are present. https://portal.cfm.org.br/noticias/camara-tecnica-alerta-sobre-uso-de-celulas-tronco-em-tratamentos/
386. World Anti-Doping Agency. Prohibited List — International Standard, valid 1 January 2026. Section M3 Gene and Cell Doping prohibits, where there is potential to enhance sport performance, M3.1 nucleic acids or nucleic acid analogues that alter genome sequences and/or gene expression (including gene editing, gene silencing and gene transfer), and M3.2 "The use of normal or genetically modified cells or cell components (e.g. https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf
387. World Anti-Doping Agency. Summary of Major Modifications and Explanatory Notes — 2026 Prohibited List, September 2025. WADA states verbatim: "Note that Platelet-Rich Plasma (PRP) and related procedures remain not prohibited." For M3, the notes explain that "Cell components (e.g. nuclei and organelles such as mitochondria and ribosomes) are added to the existing prohibition of using normal or genetically modified cells," extending the cell-doping provision to exosome- and mitochondria-type preparations.

https://www.wada-ama.org/sites/default/files/2025-09/2026_list_explanatory_note_en_final_september_2025.pdf

388. Piuzzi NS, Ng M, Chughtai M, Khlopas A, Ng K, Mont MA, Muschler GF. The Stem-Cell Market for the Treatment of Knee Osteoarthritis: A Patient Perspective. J Knee Surg. 2018;31(6):551–556. doi:10.1055/s-0037-1604443. PMID 28738432. A prospective cross-sectional secret-shopper study queried 317 US centres offering direct-to-consumer stem-cell therapies for musculoskeletal conditions, successfully contacting 273. https://pubmed.ncbi.nlm.nih.gov/28738432/
389. Khan ZA, Kaplan DJ, Hevesi M, Dasari SP, Kerzner B, Fortier LM, Jackson GR, Brusalis CM, Yanke AB, Chahla J, Cole BJ, Verma NN. The Availability and Pricing of Orthobiologic Knee Injections in the Chicago Metropolitan Area: A Market Assessment Study. Orthop J Sports Med. 2025;13(6):23259671241310452. doi:10.1177/23259671241310452. PMID 40485878. Across 25 orthopaedic sports medicine practices and 40 alternative clinics (chiropractic and stand-alone regenerative medicine) in seven Illinois and two Indiana counties, mean single-knee prices were: PRP $686.00 (SD 172.73) at orthopaedic versus $925.16 (462.99) at alternative clinics (P = .011); "stem cell" $1,451.75 (768.68) versus $4,593.50 (2,712.36) (P < .001); BMC $3,500.00 (1,322.88) versus $5,093.00 (2,564.25) (P =. https://pmc.ncbi.nlm.nih.gov/articles/PMC12144338/
390. Turner L. The American stem cell sell in 2021: U.S. businesses selling unlicensed and unproven stem cell interventions. Cell Stem Cell. 2021;28(11):1891–1895. doi:10.1016/j.stem.2021.10.008. As of 31 March 2021 there were 1,480 US businesses operating 2,754 clinics marketing stem cell interventions. By cell source, autologous adipose-derived interventions were marketed by 437 businesses (29.52%), second to autologous bone marrow (671; 45.33%) and far ahead of peripheral blood (42; 2.83%). https://www.cell.com/cell-stem-cell/pdf/S1934-5909(21)00420-3.pdf
391. (see econ_turner2021) Turner L. The American stem cell sell in 2021. Cell Stem Cell. 2021;28(11):1891–1895. The definitive published count for the US direct-to-consumer market: 1,480 businesses, 2,754 clinics as of 31 March 2021, of which 437 businesses (29.52%) marketed autologous adipose-derived interventions. Price opacity is itself a finding: only 3.78% disclosed prices. https://www.cell.com/cell-stem-cell/pdf/S1934-5909(21)00420-3.pdf
392. Cook M, Richey A, Brafman DA, Frow EK. Weighing up the evidence used by direct-to-consumer stem cell businesses. Stem Cell Reports. 2021;16(12):2852–2860. doi:10.1016/j.stemcr.2021.10.007. PMID 34767748. An audit of 59 southwestern US stem cell businesses (27 sole-focus, 32 main-focus) across 13 forms of website evidence found that 58 (98%) gave authoritative "textbook"-style descriptions of stem cells, >80% gave technical procedure descriptions, 42 (71%) used patient testimonials, 12 (20%) invoked celebrities or athletes, and only 4 mentioned registered clinical trials. https://pmc.ncbi.nlm.nih.gov/articles/PMC8693621/
393. Grand View Research. Mesenchymal Stem Cell Therapy Market (2025–2030) Size, Share & Trends Analysis Report By Type (Autologous, Allogenic), By Source (Bone Marrow, Umbilical Cord, Adipose), By Disease Indication, By Region, And Segment Forecasts. The report estimates the global MSC therapy market at USD 80.9 million in 2024, USD 103.2 million in 2025 and USD 296.6 million by 2030, a CAGR of 23.5% (2025–2030), with the adipose source segment holding the largest revenue share at 37.71% in 2024 and Asia Pacific at 71.56% of 2024 revenue. https://www.grandviewresearch.com/industry-analysis/mesenchymal-stem-cell-therapy-market-report
394. American Society of Plastic Surgeons. 2024 Plastic Surgery Statistics: Cosmetic Surgery Procedures. US cosmetic procedure volumes for 2024 (versus 2023): facial fat grafting 34,260 (34,216; 0%), buttock augmentation with fat grafting 29,466 (29,383; 0%), liposuction 349,728 (347,782; +1%), and total cosmetic surgical procedures 1,585,878 (1,575,244; +1%). Breast augmentation with fat grafting is not reported separately (n.a.); implant-based breast augmentation was 306,196. https://www.plasticsurgery.org/documents/news/statistics/2024/cosmetic-procedure-trends-2024.pdf
395. International Society of Aesthetic Plastic Surgery. 2025 ISAPS International Survey on Aesthetic/Cosmetic Procedures Performed in 2024. Worldwide, Fat Grafting – Face reached 947,007 procedures in 2024, up 19.2%, and Hand Rejuvenation with Fat Grafting 100,093, against 17,415,678 total surgical procedures (−6.7%) and 37,951,364 total surgical plus non-surgical procedures (−4.8%). Fat grafting to the face was therefore one of the few growing surgical categories in a contracting global aesthetic surgery market. https://www.isaps.org/media/razfvmsk/isaps-global-survey-2024.pdf
396. Aetna Clinical Policy Bulletin No. 0784, Blood and Adipose Tissue Derived Products for Selected Indications. Aetna lists as "experimental, investigational, or unproven because the effectiveness of these approaches has not been established": adipose tissue-derived stem cell injection (Habeo) for chondromalacia patellae, diabetic wounds, knee osteoarthritis, scleroderma "and all other indications"; autologous adipose-derived regenerative cell therapy (e.g., Lipogems) for partial-thickness rotator cuff tear "and all other indications";.
397. Anthem Medical Policy MED.00132, Autologous Adipose-derived Regenerative Cell Therapy; publish date 01/06/2026; last review 11/06/2025. Position statement: "Autologous adipose-derived regenerative cell therapy is considered investigational and not medically necessary for all indications," applied to ICD-10 "All diagnoses." Codes addressed are 46999, 55899, 0489T, 0490T, 0565T, 0566T, 0717T and 0718T; fat-grafting codes 15771–15774 were moved to a separate clinical guideline (CG-SURG-123), separating structural fat grafting from cell-enriched claims for.
398. Cigna Medical Coverage Policy 0552, Stem Cell Therapy for Orthopaedic Applications; effective 15 December 2025; next review 15 December 2026. The policy defines stem cell therapy as mesenchymal stem cells "taken from bone marrow, fat tissue, amniotic membrane, and blood and membrane in the joints" and finds it not medically necessary for musculoskeletal tissue regeneration or repair, joint disease, osteoarthritis of the knee, hip, ankle or shoulder, fracture repair including long-bone non-union, and osteonecrosis repair.

399. Blue Cross Blue Shield of Michigan / Blue Care Network joint medical policy, Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow) (Turning Point policy OR-1047.25); policy effective 1 July 2026; BCBSM signature 21 April 2026; next review 2nd quarter 2027; literature reviewed through March 2026. Position: "Mesenchymal stem cell therapy for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue is experimental/investigational.
400. Kotlier JL, Fathi A, Ong M-Y, Feingold CL, Lurie BM, Freshman RD, Mayfield CK, Petrigliano FA, Liu JN. Commercial Insurance Payer References Do Not Substantiate Coverage Denial of Stem Cell Therapy for Orthopedic Applications. HSS J. 2025 Aug 5:15563316251357013.
401. Liu A, Yu W, Chen J, Guo T, Niu P, Feng H, Jia Y. Methodological Quality and Risk of Bias of Systematic Reviews and Meta-Analyses on Stem Cells for Knee Osteoarthritis: A Cross-Sectional Survey. Stem Cells Dev. 2022;31(15–16):431–444.
402. Shang Z, Wanyan P, Zhang B, Wang M, Wang X. A systematic review, umbrella review, and quality assessment on clinical translation of stem cell therapy for knee osteoarthritis: are we there yet? Stem Cell Res Ther. 2023;14:91.
403. Andia I, Silvestre A, Del Amo C, Eymard F, Bard H. The Platelet-Rich Plasma research ecosystem. 2025 Nov 4; PMCID PMC12636882 (journal title not shown on the fetched page: n.a.). This review reports a meta-research appraisal (attributed to Onuki MEO et al., Rev Bras Ortop (São Paulo), 2025;60(1):1–14.