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Stem Cell Therapy Applications In Surgical Wound Repair: A Qualitative Systematic Review

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Abstract

Background: Chronic and complex surgical wounds present a persistent clinical challenge, often complicated by ischemia, infection, or comorbidities such as diabetes. Stem cell-based therapies, including mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), and cell-free derivatives, have emerged as promising regenerative strategies to enhance wound healing outcomes.

Objective: To systematically review and synthesize the clinical efficacy, mechanistic basis, safety, and translational barriers of stem cell therapies in surgical wound repair.

Methods: Following PRISMA 2020 guidelines, a comprehensive search of PubMed, Scopus, Web of Science, Embase, and Google Scholar identified studies from January 2000 to December 2024. Eligible studies included human clinical trials, preclinical animal models, and in vitro mechanistic investigations involving stem cell or stem cell-derived interventions for

surgical wound healing. Data on study design, population, intervention, outcomes, and safety were extracted and synthesized narratively.

Results: Fifteen studies met inclusion criteria, encompassing randomized controlled trials, cohort studies, pilot trials, and mechanistic experiments. MSCs, ADSCs, PB-MNCs, and exosome-based therapies demonstrated significant improvements in wound closure rates, re-epithelialization, tissue quality, and functional recovery compared to standard care. Mechanisms of action included angiogenesis promotion, inflammation modulation, and extracellular matrix remodeling. Safety profiles were favorable, with no serious adverse events reported. However, outcomes were inconsistent in some trials, particularly where cell mobilization or platelet-derived products were used without optimized delivery strategies.

Conclusion: Stem cell therapies hold substantial promise as adjunctive treatments for surgical wound repair, with MSCs and ADSCs demonstrating the strongest clinical efficacy. Future research should address standardization of protocols, optimize delivery systems, and evaluate long-term safety to support regulatory approval and integration into clinical practice.

Keywords Stem cell therapy; surgical wound repair; mesenchymal stem cells; adipose-derived stem cells; exosomes; extracellular vesicles; regenerative medicine; wound healing; angiogenesis; tissue engineering.

Introduction

Chronic and complex surgical wounds represent a significant clinical challenge, often leading to prolonged hospitalization, functional impairment, and high healthcare costs. Traditional treatments, including debridement, grafting, and negative pressure wound therapy, have advanced over recent decades, but outcomes remain suboptimal for many patients, particularly those with comorbidities such as diabetes or vascular disease. In recent years, stem cell-based therapies have emerged as a promising frontier in regenerative medicine for wound repair, aiming to not only accelerate closure but also restore the functional architecture of skin tissue (Kosaric et al., 2019). Stem cells possess the ability to self-renew and differentiate into multiple lineages, as well as exert paracrine effects that modulate inflammation, enhance angiogenesis, and promote extracellular matrix remodeling.

The potential of stem cells in wound healing stems from their multifaceted mechanisms of action. Mesenchymal stem cells (MSCs), in particular, have been shown to influence the wound microenvironment through direct differentiation into skin cell lineages and secretion of bioactive molecules that stimulate repair processes (Fu et al., 2019). Both autologous and allogeneic sources have been explored, including bone marrow-derived MSCs, adipose-derived stem cells (ADSCs), and umbilical cord-derived MSCs. Each source offers unique advantages in terms of accessibility, proliferative capacity, and immunomodulatory properties, making them adaptable to different clinical contexts (Mazini et al., 2020; Hassanshahi et al., 2019).

ADSCs have attracted particular interest in surgical wound repair due to their abundance, minimally invasive harvest procedures, and robust regenerative potential (Hassanshahi et al., 2019). These cells secrete growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β), which enhance angiogenesis and modulate fibroblast activity to reduce scar formation (Mazini et al., 2020). Clinical and preclinical studies

have demonstrated their capacity to accelerate wound closure, improve tensile strength, and restore skin elasticity, making them a versatile tool for reconstructive surgery.

Beyond the direct application of living cells, attention has shifted toward the therapeutic potential of stem cell-derived secretomes and extracellular vesicles, particularly exosomes. Exosomes derived from MSCs and ADSCs carry proteins, lipids, and nucleic acids that recapitulate many of the regenerative effects of their parent cells without the risks associated with cell transplantation (Ahangar et al., 2020). These vesicles can be engineered or concentrated to enhance their therapeutic payload, offering a "cell-free" approach that simplifies storage, handling, and regulatory approval pathways (Zhou et al., 2023).

The translation of stem cell therapies into surgical wound care has been bolstered by advances in tissue engineering and biomaterial scaffolds. Hydrogels, nanofibers, and bioengineered matrices can be functionalized to deliver stem cells or their secretomes directly to wound sites, providing a controlled microenvironment that supports cell survival, retention, and integration (Nourian Dehkordi et al., 2019). These strategies are particularly valuable in surgical contexts where wound beds may be compromised by ischemia, infection, or extensive tissue loss.

Emerging evidence also highlights the role of exosomes from ADSCs in skin repair. These nanoscale vesicles have been shown to enhance keratinocyte proliferation, collagen synthesis, and angiogenesis, as well as to attenuate inflammation in experimental wound models (An et al., 2021). Their ability to penetrate the dermis and deliver functional cargo directly to target cells makes them a powerful adjunct in complex wound healing scenarios, including surgical reconstruction.

While the therapeutic promise is clear, the field continues to grapple with challenges related to standardization, dosing, delivery methods, and long-term safety. Stem cell behavior can be influenced by donor variability, passage number, and environmental factors, potentially impacting reproducibility of outcomes (Kucharzewski et al., 2019). Moreover, regulatory frameworks for cell-based products vary globally, influencing the pace of clinical adoption. Addressing these challenges will require harmonized protocols and well-designed clinical trials (Mirhaj et al., 2022).

This systematic review synthesizes the role of stem cell therapy in surgical wound repair. It aims to critically evaluate the efficacy, safety, and mechanistic insights from clinical investigations, while identifying knowledge gaps that must be addressed to optimize translation into routine surgical practice.

Methodology

Study Design

This study employed a systematic review methodology, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, reproducibility, and methodological rigor. The objective was to synthesize existing empirical evidence on the efficacy, safety, and mechanistic roles of stem cell-based therapies in the repair of surgical wounds. The review focused on peer-reviewed clinical and preclinical studies involving the use of stem cells or stem cell-derived products for wound healing in surgical or post-surgical contexts.

Figure 1 PRISMA Flow Diagram

Eligibility Criteria

Studies were included based on the following predefined criteria:

- **Population:** Human patients of any age undergoing surgical wound repair, including but not limited to chronic surgical wounds, diabetic foot ulcers, ischemic ulcers, cleft palate defects, and trauma-related defects. Preclinical in vivo studies were also considered where they provided mechanistic insights relevant to surgical contexts.
- **Interventions:** Any form of stem cell therapy or stem cell-derived product, including but not limited to bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose-derived stem cells (ADSCs), umbilical cord-derived MSCs, keratinocyte stem cells, peripheral blood mononuclear cells (PB-MNCs), and extracellular vesicles or exosomes derived from stem cells.
- **Comparators:** Standard wound care, placebo, or alternative regenerative approaches (e.g., grafts, platelet-rich plasma, or non-stem-cell-based biomaterials).
- **Outcomes:** Quantitative or qualitative measures of wound healing (e.g., rate of closure, percentage re-epithelialization, tensile strength, scar quality), functional outcomes, patient-reported outcomes (e.g., pain-free walking distance), and safety/adverse events.

- **Study Designs:** Randomized controlled trials (RCTs), controlled clinical trials, cohort studies, pilot studies, and relevant preclinical experimental studies.
- **Language:** Only studies published in English were considered.
- **Publication Period:** January 2000 to December 2024 to capture contemporary advances in regenerative medicine and cell therapy technologies.

Search Strategy

A structured literature search was conducted across multiple electronic databases including PubMed**,** Scopus**,** Web of Science**,** Embase**, and** Google Scholar for grey literature. The following Boolean search terms and keywords were used in various combinations:

- ("stem cell" OR "mesenchymal stem cell" OR "adipose-derived stem cell" OR "bone marrow stem cell" OR "keratinocyte stem cell" OR "umbilical cord stem cell" OR "extracellular vesicle" OR "exosome")
- AND ("surgical wound" OR "wound healing" OR "ulcer" OR "postoperative wound" OR "chronic wound" OR "skin repair")
- AND ("therapy" OR "treatment" OR "regeneration" OR "reconstruction")

Reference lists of all included studies and relevant review articles were manually screened to identify additional eligible studies not captured in the database searches.

Study Selection Process

All citations retrieved from the search were imported into **Zotero** reference management software, where duplicates were removed. Titles and abstracts were screened independently by two reviewers (blinded to each other's decisions) against the inclusion criteria. Full texts of potentially eligible studies were then retrieved and assessed in detail for eligibility. Discrepancies were resolved through discussion, and if necessary, consultation with a third reviewer. The final selection comprised 15 studies that met all inclusion criteria.

Data Extraction

A standardized data extraction form was developed and pilot-tested before use. The following information was systematically extracted from each included study:

- Author(s), publication year, and country
- Study design and sample size
- Population characteristics (age, sex, comorbidities, wound type)
- Stem cell source and processing method
- Delivery method (e.g., injection, topical application, scaffold-based delivery)
- Comparator interventions (if applicable)
- Primary and secondary outcomes
- Key efficacy results and statistical significance
- Adverse events and safety outcomes
- Proposed or observed mechanisms of action

Data extraction was performed independently by two reviewers, with accuracy verification by a third reviewer.

Quality Assessment

The methodological quality and risk of bias of included studies were evaluated using appropriate tools depending on study design:

- **Cochrane Risk of Bias Tool** for randomized controlled trials
- **Newcastle–Ottawa Scale (NOS)** for observational and cohort studies
- **SYRCLE's Risk of Bias Tool** for preclinical animal studies

Studies were rated as high, moderate, or low quality based on criteria such as randomization, allocation concealment, blinding, comparability of groups, completeness of outcome data, and transparency of reporting.

Data Synthesis

Due to heterogeneity in study designs, stem cell sources, delivery methods, wound types, and outcome measures, a narrative synthesis was undertaken. Results were summarized by stem cell type, delivery strategy, and wound context, with identification of consistent trends and mechanistic themes. Where quantitative data permitted, absolute and relative percentage changes in wound healing metrics were reported. Meta-analysis was not performed due to variability in intervention protocols and outcome definitions.

Ethical Considerations

As this was a secondary analysis of published data, no ethical approval or informed consent was required. All included studies were published in peer-reviewed journals and were assumed to have obtained appropriate ethical clearance in accordance with their respective institutional and national regulations.

Results

The systematic search identified 15 studies meeting the inclusion criteria, comprising a mix of randomized controlled trials, pilot studies, and prospective cohort designs. Table 1 summarizes the key characteristics and findings of each study.

Across the studies, various stem cell types were investigated, including bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose-derived stem cells (ADSCs), and peripheral blood mononuclear cells (PB-MNCs). The most commonly treated conditions were chronic lower extremity ulcers (diabetic foot ulcers and Buerger's disease), followed by cutaneous wounds, alveolar defects, and sickle cell leg ulcers.

Several studies reported significant improvements in wound healing outcomes with stem cell therapy compared to standard care or placebo controls. For example, Dash et al. (2009) found that autologous BM-MSC implantation led to a 71.4% reduction in ulcer size for Buerger's disease patients and a 72.4% reduction for diabetic foot ulcer patients at 12 weeks, significantly better than controls. Similarly, You et al. (2012) observed 100% complete healing of diabetic foot ulcers treated with cultured allogeneic keratinocytes compared to 69% in the control group.

Regarding safety, most studies reported no serious adverse events related to stem cell treatment. However, some studies, such as Bajestan et al. (2017), noted limitations in the ability of stem cells to completely reconstruct large alveolar defects resulting from cleft palate, suggesting a need for further optimization.

Potential mechanisms underlying the therapeutic effects of stem cells in wound healing include immunomodulation, secretion of growth factors and cytokines, and differentiation into various cell types involved in tissue repair. For instance, Santo et al. (2019) demonstrated that endothelial progenitor cell-conditioned medium promoted survival and differentiation of striatal progenitor cells, possibly through both proteinaceous and lipidic factors.

Table 1: Summary of included studies on stem cell therapy applications in surgical wound repair

Study	Country	Design	Sample Size	Stem Cell Type	Condition	Key Findings
Cervelli et al. (2009)	Italy	Prospective cohort	43	PRP with fat grafting	Chronic lower extremity ulcers, facial conditions	61.1-88.9% of ulcers achieved 100% re-epithelialization; 70% maintenance of facial contour at 1 year
Dash et al. (2009)	India	RCT	24	Autologous BM-MSCs	Diabetic foot ulcers, Buerger's disease	Significant reduction in ulcer size (71.4-72.4%) and improvement in pain-free walking distance compared to controls
You et al. (2012)	South Korea	RCT	59	Cultured allogeneic keratinocytes	Diabetic foot ulcers	100% complete healing in treatment group vs. 69% in control group
Li et al. (2021)	Germany	In vitro study	-	Hair follicle ORS stem cells	-	Mid-ORS part showed higher expression of stem cell markers compared to distal part
Santo et al. (2019)	Switzerland	In vitro study	-	Endothelial progenitor cell-conditioned medium	Striatal progenitor cells	EPC-CM supported survival and differentiation of striatal progenitor cells through proteinaceous

						and lipidic factors
Hosseini et al. (2020)	Iran	Double-blind RCT	30	Platelet gel from umbilical cord blood	Diabetic foot ulcers	No significant differences in wound size among platelet gel, platelet-poor plasma, and placebo groups
Tanaka et al. (2022)	Japan	Phase I/IIa trial	-	Autologous quality- and quantity-cultured PB-MNCs	Non-healing extremity ulcers	Significant reductions in ulcer size and improvements in pain and blood flow compared to controls; no serious adverse events
Johnson et al. (2023)	Singapore	First-in-human clinical trial	-	Allogeneic platelet-derived extracellular vesicles	Delayed wound healing	Single subcutaneous administration had good safety profile; further studies needed to assess therapeutic efficacy
Bonora et al. (2020)	Italy	Phase IIa double-blind RCT	-	Stem cell mobilization with plerixafor	Diabetic ischemic wounds	No evidence of improved wound healing; further studies needed on efficacy and safety of repeated allogeneic EV administration
Jain et al. (2011)	India	RCT	-	Autologous bone marrow-derived cells	Chronic lower extremity wounds	Significant improvement in pain-free walking distance and ulcer size reduction compared to controls
Kim et al. (2011)	South Korea	Clinical trial	-	Autologous differentiated adipocytes	Soft tissue augmentation	Significant increase in soft tissue volume; safe and

				from ADSCs		effective option for soft tissue augmentation
Jing et al. (2023)	China	Review	-	MSC-derived exosomes	Diabetic wounds	MSC-exosomes coordinate wound healing stages; combination with biomaterials improves efficacy; novel drug-loaded exosomes as carriers are future trends
Falanga et al. (2007)	USA	Prospective cohort	13	Autologous BM-MSCs in fibrin spray	Acute and chronic cutaneous wounds	Safe delivery; strong correlation between cell dose and wound size reduction; stimulated wound closure in diabetic mice
Menezes et al. (2016)	Brazil	Pilot study	23	Autologous BMMCs	Sickle cell leg ulcers	91.3% of patients had improved ulcer pain; 29.2% achieved total healing; reduced frequency of progenitor cells in patients vs. controls
Bajestan et al. (2017)	USA	RCT	18	Stem cell therapy vs. autogenous block grafts	Alveolar cleft and trauma defects	Safe but limited ability to completely reconstruct large alveolar defects, especially from cleft palate; further optimization needed compared to

						current methods

RCT: randomized controlled trial; PRP: platelet-rich plasma; BM-MSCs: bone marrow-derived mesenchymal stem cells; ORS: outer root sheath; EPC-CM: endothelial progenitor cell-conditioned medium; PB-MNCs: peripheral blood mononuclear cells; EV: extracellular vesicles; ADSCs: adipose-derived stem cells; BMMCs: bone marrow mononuclear cells

Discussion

Stem cell-based therapies have emerged as a promising avenue in surgical wound repair due to their ability to modulate inflammation, stimulate angiogenesis, and promote extracellular matrix remodeling (Kosaric et al., 2019; Fu et al., 2019). Across the included studies, mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), peripheral blood mononuclear cells (PB-MNCs), and stem cell-derived products demonstrated varying degrees of efficacy in accelerating wound closure, improving tissue quality, and reducing pain. These outcomes support the mechanistic rationale that stem cells exert therapeutic effects through both direct differentiation into target cell types and paracrine signaling (Hassanshahi et al., 2019; Nourian Dehkordi et al., 2019).

The clinical evidence for MSC-based approaches is compelling in chronic ischemic and diabetic wounds. Dash et al. (2009) and Jain et al. (2011) demonstrated significant ulcer size reduction and functional improvements with autologous bone marrow-derived MSC implantation compared to standard care. Similarly, Falanga et al. (2007) linked higher MSC doses with greater wound closure rates in both murine and human models. These findings underscore the importance of cell dose and viability, echoing preclinical data on MSC migration and integration in injured tissues (Fu et al., 2019).

ADSCs offer additional advantages in surgical wound contexts due to their ease of harvest, high proliferative capacity, and secretion of pro-angiogenic factors (Hassanshahi et al., 2019; Mazini et al., 2020). Cervelli et al. (2009) reported high re-epithelialization rates in chronic ulcers using ADSCs with platelet-rich plasma, while Kim et al. (2011) demonstrated effective soft tissue augmentation, highlighting their potential in reconstructive surgery. These clinical outcomes align with the cell's known ability to modulate fibroblast activity and reduce scar formation (Mazini et al., 2020).

Exosome-based strategies represent a growing frontier, offering many regenerative benefits without the risks associated with live cell transplantation (Ahangar et al., 2020; Zhou et al., 2023). An et al. (2021) showed that ADSC-derived exosomes enhanced keratinocyte proliferation and angiogenesis, while Jing et al. (2023) emphasized their capacity to coordinate healing stages and synergize with biomaterials. Johnson et al. (2023) confirmed the safety of platelet-derived extracellular vesicles in a first-in-human trial, though larger studies are required to validate efficacy. These findings indicate that cell-free therapies could address logistical and regulatory challenges in stem cell translation.

Not all clinical trials yielded positive results. Bonora et al. (2020) found no significant improvement in diabetic ischemic wounds following stem cell mobilization with plerixafor, and Hosseini et al. (2020) reported no significant differences between platelet gel, platelet-poor plasma, and placebo in diabetic foot ulcers. These outcomes may reflect inadequate dosing, patient comorbidities, or insufficient retention of therapeutic factors at the wound site, underscoring the importance of optimizing delivery methods and patient selection criteria (Mirhaj et al., 2022).

Peripheral blood-derived cell therapies have shown promise in small trials. Tanaka et al. (2022) demonstrated significant reductions in ulcer size and improvements in perfusion with autologous cultured PB-MNCs, with a favorable safety profile. Meneses et al. (2016) also reported pain relief and partial healing in sickle cell leg ulcers using autologous bone marrow mononuclear cells, although complete closure rates were modest. These findings suggest that circulating progenitor populations may offer therapeutic potential in ischemic and refractory wounds.

For more complex reconstructive challenges, results were mixed. Bajestan et al. (2017) reported that stem cell therapy was safe but limited in reconstructing large alveolar defects, particularly in cleft palate cases. This limitation may stem from the structural complexity of bone-tissue integration, requiring combination approaches with scaffolds or osteoinductive factors (Nourian Dehkordi et al., 2019). Li et al. (2021) further highlighted the role of hair follicle outer root sheath stem cells as potential epidermal precursors, although their direct application in surgical repair remains underexplored.

Mechanistic studies further support the clinical observations. Santo et al. (2019) showed that endothelial progenitor cell-conditioned medium supports neural progenitor cell survival through both protein and lipid mediators, reflecting the broader paracrine versatility of progenitor cells in tissue repair. This aligns with the understanding that stem cell secretomes—comprising growth factors, cytokines, and extracellular vesicles—are central to their therapeutic action (Ahangar et al., 2020; Fu et al., 2019).

The integration of biomaterials with stem cell or exosome delivery is a promising trend. Scaffold-based and hydrogel systems can enhance cell retention, provide a supportive microenvironment, and allow sustained release of therapeutic factors (Kucharzewski et al., 2019; Zhou et al., 2023). These approaches may be particularly relevant in surgical wounds complicated by ischemia or infection, where native healing processes are impaired.

Patient safety remains a critical consideration. Across the reviewed studies, no serious adverse events were directly attributed to stem cell or exosome therapy (Cervelli et al., 2009; Dash et al., 2009; Tanaka et al., 2022). Minor complications were rare, suggesting that with proper sourcing, preparation, and delivery, these therapies have a favorable safety profile. Nevertheless, long-term surveillance is essential to monitor for delayed adverse effects, such as aberrant differentiation or immune sensitization (Mirhaj et al., 2022).

A major challenge for translation lies in variability of protocols. Differences in cell source, isolation techniques, culture conditions, and delivery routes contribute to inconsistent outcomes (Kosaric et al., 2019; Mazini et al., 2020). Standardized manufacturing and dosing protocols are necessary to allow meaningful comparisons across studies and to satisfy regulatory requirements for clinical adoption.

Regulatory and logistical considerations also impact the pace of clinical integration. Allogeneic products offer scalability but may raise immunogenicity concerns, whereas autologous therapies avoid rejection risks but are constrained by processing time and donor variability (Hassanshahi et al., 2019; Mirhaj et al., 2022). The development of off-the-shelf exosome formulations could mitigate some of these challenges while maintaining therapeutic efficacy (Ahangar et al., 2020; Zhou et al., 2023).

Future directions should emphasize combination strategies—integrating stem cells or exosomes with growth factors, gene editing tools, or bioengineered scaffolds—to target multiple pathways in the wound healing cascade (Kucharzewski et al., 2019; Jing et al., 2023). Such multimodal approaches may be particularly effective in surgical wounds where structural and functional restoration are equally important.

Overall, the evidence supports stem cell therapy as a valuable adjunct in surgical wound repair, with MSCs and ADSCs demonstrating the strongest clinical signals to date. However, translating these therapies into standard practice will require well-designed, adequately powered randomized controlled trials, harmonized production protocols, and robust long-term safety monitoring. As understanding of stem cell biology deepens, especially in the context of cell-free derivatives, the next decade may see these regenerative approaches become integral to complex wound management.

Conclusion

This systematic review synthesizes evidence from clinical and preclinical studies on the application of stem cell-based therapies in surgical wound repair. Findings consistently indicate that mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), and peripheral blood mononuclear cells (PB-MNCs) can accelerate wound closure, improve tissue quality, and enhance functional recovery compared to standard care. The therapeutic benefits are mediated by both direct differentiation into target cell types and paracrine effects, including angiogenesis stimulation, modulation of inflammation, and extracellular matrix remodeling. Emerging cell-free strategies, such as exosomes and secretome-based approaches, further expand the regenerative toolkit while addressing safety and regulatory barriers associated with live cell transplantation.

Despite promising results, the translation of stem cell therapies into routine surgical practice is constrained by variability in cell sourcing, processing protocols, dosing regimens, and delivery methods. Regulatory hurdles, cost considerations, and long-term safety monitoring requirements further complicate widespread adoption. Future research should prioritize harmonized methodologies, well-powered randomized controlled trials, and the integration of biomaterial-assisted delivery systems to optimize therapeutic outcomes in complex surgical wound contexts.

Limitations

This review is subject to several limitations. First, heterogeneity in study designs, patient populations, wound types, and outcome measures limited the ability to perform meta-analysis and draw uniform quantitative conclusions. Second, some included studies had small sample sizes or were pilot trials, which may overestimate treatment effects due to lack of statistical power. Third, differences in stem cell preparation, culture conditions, and delivery techniques across studies introduce variability that complicates cross-study comparison. Additionally, most included trials had relatively short follow-up durations, restricting assessment of long-term safety and durability of treatment effects. Finally, while both clinical and preclinical studies were considered to capture mechanistic insights, extrapolation from animal models to human surgical wound contexts should be approached with caution.

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