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Review Article

Stem Cell Therapy in the Management of Chronic Parasitic Diseases: Current Evidence, Methodological Limitations, and Future Therapeutic Prospects

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Abstract

Chronic parasitic infections constitute a persistent global health burden affecting over one billion individuals, with disproportionate impact in low and middle-income countries. Conventional antiparasitic therapeutics effectively reduce parasite prevalence but fail to reverse established tissue pathology including hepatic cirrhosis, myocardial fibrosis, and neurological damage. Mesenchymal stem cell (MSC) therapy has garnered increasing attention as a potential host-directed regenerative strategy addressing tissue repair and immune dysregulation in parasitic disease contexts. This comprehensive review synthesises preclinical evidence across schistosomiasis, Chagas disease, leishmaniasis, malaria-associated organ complications, and neurocysticercosis, alongside limited clinical observations from cardiac applications. Preclinical investigations consistently demonstrate anti-inflammatory and anti-fibrotic effects through paracrine signalling and direct cellular differentiation. Critical evaluation reveals substantial heterogeneity in evidence quality, marked methodological limitations including short-term follow-up periods, inadequate parasite burden assessment, and absence of standardised disease models. Human clinical evidence remains minimal outside early uncontrolled cardiac trials with severe design limitations. Significant barriers to clinical translation include unresolved parasite-immune-stem cell interactions, insufficient long-term safety documentation in human populations, prohibitive manufacturing costs precluding access in endemic regions, and inadequate regulatory frameworks in countries bearing greatest disease burden. Future progress requires standardised preclinical models, properly designed human trials, elucidation of optimal combination therapy approaches, and international investment in regulatory capacity building in endemic nations. Current evidence position supports continued investigation but does not justify clinical translation beyond carefully controlled research settings.

Keywords: Chronic Parasitic Diseases; Mesenchymal Stem Cells; Stem Cell Therapy; Tissue Fibrosis; Translational Barriers

Introduction

Parasitic infections represent a persistent yet underappreciated global health challenge, affecting over one billion individuals across low and middle-income countries [1]. The epidemiological distribution of parasitic disease reflects fundamental inequalities in access to clean water, sanitation infrastructure, and healthcare systems. Schistosomiasis affects approximately 240 million individuals, predominantly concentrated in sub-Saharan Africa, with particular burden in Egypt, Nigeria, and the Democratic Republic of Congo [2]. Chagas disease infects 5.7-7.7 million individuals in Latin America, predominantly in rural areas and among economically disadvantaged populations [3]. Leishmaniasis presents in three clinical forms affecting approximately 12 million individuals globally, with visceral leishmaniasis causing substantial mortality in East Africa and the Indian subcontinent [4]. Lymphatic filariasis persists in 893 million individuals in tropical regions, while neurocysticercosis from Taenia solium tapeworm infection affects millions in endemic regions, serving as a leading preventable cause of acquired epilepsy [5,6]. The global burden of disease attributable to parasitic infections exceeds 50 million disability-adjusted life years annually, yet substantial research funding disparity exists between parasitic diseases and non-communicable conditions [7]. Beyond immediate morbidity, parasitic infections generate progressive tissue destruction accumulating silently over years to decades. This delayed pathology distinguishes chronic parasitic disease from acute infections. Patients treated effectively for schistosomiasis may already carry established hepatic cirrhosis; individuals receiving benznidazole for Chagas disease may possess advanced myocardial fibrosis; survivors of cerebral malaria carry permanent neurological sequelae despite parasite clearance. The pathological mechanisms generating this tissue damage operate largely independent of active parasite presence, involving chronic immune activation, progressive fibrosis, and organ dysfunction that persist even after parasites are eliminated [8,9].

Although antiparasitic drugs effectively reduce or eliminate parasites; praziquantel for schistosomiasis, benznidazole/nifurtimox for Chagas, antimonials/amphotericin/miltefosine for leishmaniasis, and artemisinin-based therapies for malaria, they often fail to reverse established tissue damage [1,10-12]. Chronic immune activation during infection drives fibrosis and progressive organ dysfunction: hepatic cirrhosis after schistosomiasis, myocardial fibrosis in chronic Chagas, and permanent neurological injury following cerebral malaria can persist despite parasite clearance. These pathologies arise from sustained inflammatory cytokines (TNF-α, IL-6, IL-1β), regulatory mediators (IL-10, TGF-β), and activation of fibrotic pathways (e.g., TGF-β signaling of stellate and cardiac fibroblasts) that deposit collagen and replace functional parenchyma. Regenerative medicine, particularly mesenchymal stem cell (MSC) therapy, offers a complementary strategy by targeting tissue repair and immune modulation rather than parasites directly. MSCs can differentiate into multiple cell types, secrete paracrine factors and extracellular vesicles that suppress inflammation and fibrosis, and home to injured tissues [13-15]. Combining antiparasitic treatment to clear infection with regenerative approaches to repair damage provides a biologically plausible, synergistic pathway now being explored extensively in preclinical studies.

Chronic parasitic disease pathophysiology: Mechanisms of tissue damage and immune dysregulation

Schistosomiasis: Granulomatous inflammation and hepatic fibrosis

Schistosomiasis represents the parasitic disease most extensively investigated in stem cell research contexts. This emphasis reflects both the substantial global burden and the well-characterised pathophysiology of schistosomal hepatic fibrosis. Infection occurs through cercariae penetrating intact skin during water contact; larvae mature into adult worms establishing residence in mesenteric venules [16]. *Schistosoma* species include *Schistosoma mansoni* and *Schistosoma japonicum*, which produce eggs deposited in liver, and *Schistosoma haematobium*, producing eggs that affect urogenital tissues. Granulomatous inflammation represents the pathological hallmark of schistosomiasis. Parasite eggs trapped in hepatic sinusoids trigger intense innate and adaptive immune responses. Eosinophils, macrophages, lymphocytes, and fibroblasts accumulate around eggs in a process intended for parasite elimination [17]. This acute granulomatous response causes fever, hepatomegaly, and systemic symptoms in acute schistosomiasis. In chronic infection, granulomatous responses persist but undergo pathological transformation. Granulomas gradually become fibrotic; collagen progressively replaces normal granulomatous architecture. Repeated cycles of granuloma formation and fibrosis lead to periportal fibrosis, bridging fibrosis between portal triads, and eventually cirrhosis [18]. This process typically requires decades of infection; however, substantial individual variation

exists, with some patients developing cirrhosis within 10-15 years while others remain stable over similar periods. Genetic factors, parasite burden intensity, concurrent infection with hepatitis B or C virus, and nutritional status influence fibrosis progression.

The fibrotic process in schistosomiasis operates through TGF-β signalling, making this pathway a rational target for therapeutic intervention. TGF-β production increases during chronic schistosomiasis through multiple mechanisms. Parasite-derived antigens activate dendritic cells, which produce TGF-β and IL-10, driving differentiation of regulatory T cells (Tregs) that themselves produce additional TGF-β and IL-10 [19,20]. This TGF-β-rich immunological environment provides selective advantage for parasites by suppressing anti-schistosome Th1 responses while permitting persistence of relatively ineffective Th2 responses. Simultaneously, this TGF-β-rich environment drives hepatic fibrosis through activation of hepatic stellate cells (HSCs). TGF-β signalling through ALK5/Smad2/3 pathways causes HSC activation and differentiation into myofibroblasts. Activated HSCs produce excessive collagen, with myofibroblasts generating collagen I and III at rates 100-fold higher than quiescent HSCs. Tissue inhibitors of metalloproteinases (TIMPs) increase while matrix metalloproteinases (MMPs) that degrade collagen decrease, creating biochemical conditions favouring collagen accumulation [21]. The fibrotic process, once initiated, becomes self-perpetuating: fibrotic tissue and fibroblasts produce additional TGF-β, perpetuating HSC activation and collagen production.

Chagas disease: Progressive cardiomyopathy and immune exhaustion

Chagas disease, caused by *Trypanosoma cruzi*, follows a distinct pathological trajectory from schistosomiasis. The parasite transmits through faeces of infected triatomine insects; parasites invade skin or mucous membranes and disseminate hematogenously, establishing infection in muscle tissue, cardiac myocytes, and neurons [3]. The acute phase produces parasitaemia, myocarditis, and systemic inflammatory manifestations lasting weeks to months. Most acutely infected individuals enter an indeterminate chronic phase with minimal symptoms yet persistent parasitaemia. According to Hochberg and Montgomery [22], years to decades later, a minority (5-30%) develop chronic Chagas disease with overt organ involvement. Chronic myocardial damage in Chagas disease involves a paradoxical immunological state combining chronic inflammation with immune exhaustion. Parasite-specific T cells recognise *T. cruzi* antigens through continuous low-level parasitaemia; however, these T cells progressively lose effector function. Chronic antigenic stimulation without parasite clearance drives progressive exhaustion of anti-parasite T cells, evident as increased expression of inhibitory receptors (PD-1, TIM-3, LAG-3) and reduced interferon-gamma production [23]. Simultaneously, myocardial inflammation persists, involving resident macrophages, dendritic cells, and infiltrating lymphocytes. This chronic inflammation causes progressive myocarditis and myocardial fibrosis. Inflammatory mediators including TNF-α, IL-6, and IL-17 drive myofibroblast differentiation and collagen production. Myocardial fibrosis increases ventricular stiffness, impairs systolic function, and creates substrate for arrhythmias. Progressive dilated cardiomyopathy develops with severely reduced ejection fraction, ultimately causing heart failure and sudden cardiac death [24,25].

The immune exhaustion characteristic of chronic Chagas disease creates a unique pathophysiological context relevant to stem cell therapy. Anti-parasite immunity remains inadequate for parasite clearance, yet inflammatory pathology continues. This creates the theoretical possibility that MSC-mediated immune suppression and IL-10/TGF-β production could reduce inflammatory damage without worsening parasite burden, since anti-parasite immunity is already dysfunctional. However, this remains speculative; whether MSCs might further impair anti-parasite responses or enhance parasite persistence has not been rigorously examined.

Leishmaniasis: Divergent immunology and disease manifestations

Leishmaniasis presents in distinct clinical forms with markedly different pathophysiology and immune responses. *Leishmania* parasites infect macrophages where they establish residence. Host immune response determines disease manifestation. Cutaneous leishmaniasis, caused primarily by *Leishmania major* and *Leishmania mexicana*, typically generates strong Th1 responses characterised by high interferon-gamma production and macrophage activation. This Th1 response generally controls parasite growth, though complete parasite elimination rarely occurs; cutaneous lesions persist for months to years before eventual resolution, leaving permanent disfiguring scars [4]. Mucocutaneous leishmaniasis, caused by *Leishmania braziliensis*, occurs when parasites disseminate from cutaneous lesions to mucous membranes; this form causes disfiguring destruction of

nasal, oral, and pharyngeal tissues. Visceral leishmaniasis (kala-azar), caused by *Leishmania donovani*, represents the most severe form. Unlike cutaneous disease, visceral leishmaniasis generates predominantly Th2 responses with minimal Th1 responses and high IL-10 production. This immunosuppressive state permits parasite dissemination to spleen, liver, and bone marrow. Massive parasitaemia develops with up to 1% of circulating monocytes infected. Severe bone marrow suppression causes pancytopenia with severe anaemia, thrombocytopenia, and leukopenia. Hepatosplenomegaly becomes marked. Without treatment, mortality approaches 100%, primarily from secondary infections resulting from immune suppression [26,27]. Post-kala-azar dermal leishmaniasis, a chronic skin manifestation occurring in 5-15% of visceral leishmaniasis patients months to years after treatment, involves parasite persistence in dermal macrophages and causes permanent skin disfigurement [28]. The divergent immunology of cutaneous versus visceral leishmaniasis creates different contexts for stem cell application. In cutaneous disease, Th1 responses predominate; MSC-driven immune suppression could paradoxically enhance parasite persistence. In visceral disease, profound immunosuppression already permits parasite dissemination; MSC-mediated immune modulation might theoretically improve parasite control by enhancing Th1 responses. However, published preclinical studies have not systematically examined these immunological nuances [29].

Malaria: Repeated infections and chronic organ damage

Malaria differs fundamentally from the other parasitic diseases discussed because chronic malaria typically results from repeated infections rather than persistent single infections. *Plasmodium* species, transmitted by anopheline mosquitoes, multiply within erythrocytes; each mosquito bite potentially transmits parasites from multiple oocysts, establishing high-level parasitaemia [30]. In endemic regions, children experience dozens of malaria episodes during childhood and adolescence. Each episode generates inflammatory responses; repeated episodes accumulate organ damage [31].

Severe malaria complications including cerebral malaria, acute kidney injury, acute respiratory distress syndrome, and severe anaemia result from parasite-induced endothelial dysfunction and microvasculature sequestration. *Plasmodium falciparum*-infected erythrocytes express variant surface antigens that bind endothelial receptors (CD36, ICAM-1) causing sequestration of infected cells within capillaries of brain, kidney, and other organs [32]. Sequestration causes local hypoxia, inflammatory cell infiltration, and tissue damage. Circulating parasite-derived mediators activate macrophages and dendritic cells, producing TNF-α, IL-6, and IL-1β. This cytokine storm generates systemic inflammation contributing to multiple organ dysfunction.

Repeated malaria infections in children cause chronic sequelae beyond acute episode complications. Chronic severe anaemia develops from repeated haemolysis and bone marrow suppression. Renal dysfunction evolves from repeated acute kidney injury episodes, with chronic kidney disease eventually developing. Hepatic injury manifests as elevated transaminases and, rarely, fulminant liver failure. Neurological sequelae occur; cerebral malaria survivors demonstrate cognitive impairment, attention deficits, and language disorders despite parasite clearance, suggesting permanent brain damage from acute inflammation rather than ongoing parasite effects. These chronic consequences persist despite effective antimalarial therapy; parasite elimination does not reverse established damage [33]. The pathophysiology of malaria-associated organ damage differs from schistosomiasis or Chagas disease because parasitaemia typically becomes cleared by immune responses and antimalarial drugs, yet inflammation-driven damage persists. This suggests MSC therapy might effectively address inflammation-driven organ damage without parasite persistence concerns. However, preclinical investigations have not thoroughly examined whether MSCs effectively prevent or reverse malaria-associated chronic complications.

Neurocysticercosis: Episodic inflammation and neurological complications

Neurocysticercosis results from *Taenia solium* (pork tapeworm) larval infection of the central nervous system. Unlike other parasitic infections discussed where parasites persist indefinitely, neurocysticercosis involves encysted larvae that eventually die, creating a time-limited but progressive disease process. *Taenia solium* eggs ingested through contaminated food hatch in the small intestine; larvae penetrate intestinal epithelium and disseminate hematogenously, settling in brain parenchyma, cerebrospinal fluid, and subarachnoid spaces [34]. Neurocysticercosis pathophysiology involves episodic inflammatory exacerbations rather than chronic persistent inflammation. Living cysts induce minimal inflammation. As cysts degenerate and die (natural progression

over months to years), degenerating parasite antigens trigger intense neuroinflammatory responses. Infiltrating eosinophils, macrophages, and lymphocytes surround dying cysts; TNF-α, IL-6, IL-17, and other inflammatory mediators increase; astroglial activation occurs [6]. This episodic inflammation causes seizures, increased intracranial pressure, focal neurological deficits, and meningitis. Unlike schistosomiasis or Chagas disease involving continuous low-grade inflammation, neurocysticercosis features episodic exacerbations of inflammation superimposed on periods of relative quiet. This pathophysiological distinction may influence optimal stem cell therapy timing and effectiveness.

Mesenchymal Stem cell biology and therapeutic mechanisms: Current understanding and critical limitations

MSC characterisation, heterogeneity, and functional properties

Mesenchymal stem cells comprise multipotent stromal cells derived from bone marrow, adipose tissue, umbilical cord, and other tissues. MSCs are defined by three criteria: plastic adherence during *in vitro* culture, expression of specific surface markers (CD73, CD90, CD105) combined with absence of haematopoietic markers (CD45, CD34, CD11b), and capacity to differentiate into osteocytes, adipocytes, and chondrocytes in appropriate culture conditions [35]. These minimal defining criteria mask substantial heterogeneity within MSC populations. MSC heterogeneity emerges at multiple levels. Tissue source profoundly influences MSC properties; bone marrow-derived MSCs differ substantially from adipose-derived MSCs and umbilical cord-derived MSCs in proliferation rates, immunomodulatory capacity, and differentiation potential [36]. Within bone marrow MSCs, distinct subpopulations with different properties coexist. Donor characteristics including age, sex, health status, and genetic background substantially influence MSC properties. Bone marrow MSCs from elderly donors exhibit reduced proliferation, reduced immunomodulatory capacity, and altered differentiation potential compared to young donors [37]. Culture conditions during expansion profoundly influence MSC function; hypoxic versus normoxic culture, passage number, and media composition all alter MSC immunophenotype and functional capacity.

This heterogeneity creates critical problems for preclinical stem cell research and eventual clinical translation. Studies using bone marrow MSCs from young healthy donors cannot be directly compared to studies using adipose-derived MSCs from older patients. Studies examining passage 3 MSCs exhibit different properties than studies using passage 8 MSCs, yet many publications provide insufficient detail regarding passage number. Most preclinical parasitic disease studies fail to adequately characterise MSC source, donor demographics, culture conditions, and passage number, preventing meaningful cross-study comparison and systematic evidence synthesis [38-40]. MSC immunomodulatory properties constitute the primary mechanism proposed for therapeutic benefit in parasitic disease contexts. MSCs produce multiple immunosuppressive mediators. IL-10 and TGF-β production ranks foremost among these. MSCs secrete IL-10 directly and promote IL-10 production by monocytes and macrophages through cell contact mechanisms and soluble factor production [14]. This IL-10 production suppresses pro-inflammatory responses; IL-10 reduces TNF-α, IL-6, IL-12, and IL-1β production by activated immune cells. TGF-β production similarly increases during MSC culture, particularly under inflammatory conditions. MSC-derived TGF-β activates latent TGF-β, producing bioactive TGF-β that drives regulatory T cell (Treg) differentiation and suppresses Th1 and Th17 responses [41]. Macrophage polarisation from pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype constitutes another proposed mechanism. MSCs promote M1 to M2 polarisation through IL-10 and TGF-β production combined with direct cell contact. M2 macrophages produce IL-10 and TGF-β while reducing pro-inflammatory cytokine production, potentially shifting immune balance toward anti-inflammatory states [15]. PD-L1 expression on MSCs provides additional immunosuppressive signalling through programmed death receptor pathways [42].

Critical evaluation of mechanism proposals: Complexity, contradictions, and context-dependence

Published literature describing MSC mechanisms in parasitic disease frequently overstates mechanistic certainty while understating biological complexity and context-dependence. Several critical limitations warrant emphasis. First, IL-10 and TGF-β represent double-edged swords in parasitic disease contexts in ways inadequately appreciated in stem cell literature. These cytokines suppress excessive pro-inflammatory responses and reduce tissue damage; simultaneously, they actively support parasite immune evasion and persistence. In schistosomiasis, parasites actively induce TGF-β and IL-10 production through

antigenic stimulation and direct parasite-derived molecules to suppress anti-schistosome immunity [19]. Elevated TGF-β and IL-10 production characterises chronic schistosomiasis and predicts inadequate anti-schistosome responses. Adding external TGF-β through MSC therapy might theoretically enhance parasite immune evasion. In *T. cruzi* infection, TGF-β and IL-10 production characterise the immunosuppressive state permitting parasite persistence [23]. Whether MSC-driven augmentation of these mediators would enhance parasite control or support parasite persistence remains unresolved. Published preclinical studies rarely measure this critical parameter.

Second, Treg expansion driven by MSCs may suppress both excessive inflammation and anti-parasitic immunity. While Tregs reduce tissue-damaging inflammation, they simultaneously suppress anti-parasitic T cell responses. In leishmaniasis, cure requires sustained Th1 responses; Tregs suppress Th1 and thus permit parasite dissemination. MSC-driven Treg expansion could theoretically impair rather than support parasitic disease control. This possibility has not been systematically investigated in published parasitic disease stem cell studies [29,43].

Third, macrophage phenotype alteration toward M2 polarisation may enhance parasite survival. Macrophages constitute the primary cellular reservoir for *Leishmania* and *T. cruzi* parasites. M1 macrophages produce nitric oxide and reactive oxygen species promoting parasite killing; M2 macrophages produce arginase competing with nitric oxide production and creating immunological conditions permitting parasite survival. MSC-driven M1 to M2 shift could paradoxically enhance macrophage parasite burden [44]. Ramos., *et al*. [45] examined both parasite control and immunological outcomes; MSCs enhanced macrophage parasite killing in leishmaniasis, yet the mechanisms explaining this parasiticide effect while simultaneously driving IL-10/TGF-β production remain unclear.

Extracellular vesicles: Emerging cell-free therapy and unresolved questions

Increasing recognition that MSC paracrine effects substantially depend on extracellular vesicles (EVs) has motivated investigation of cell-free approaches. Extracellular vesicles comprise exosomes (30-150 nm) and microvesicles (100-1000 nm) containing lipids, proteins, and nucleic acids with biological activity [46]. MSC-derived EVs transfer active molecules to recipient cells, modulating immune responses and supporting tissue regeneration [47]. EV-based approaches theoretically offer manufacturing advantages: EVs are smaller than intact cells, permitting more efficient purification and standardisation; EV preparations are cell-free, reducing tumorigenesis risks; EVs avoid cell viability concerns inherent to cell therapy. Dong., *et al*. [48] demonstrated that MSC-derived extracellular vesicles achieved anti-fibrotic effects in schistosomiasis comparable to intact cells, providing proof-of-concept for EV-based applications.

Substantial unresolved questions constrain EV therapy development beyond these promising initial findings. Optimal EV composition (exosome versus microvesicle proportion) remains undefined. EV loading with therapeutic molecules shows variable efficiency; methods for improving cargo loading and targeting specificity require further development. EV stability during storage and transport remains problematic; how long EV preparations retain biological activity is incompletely characterised. The relative contributions of different EV-associated molecules (proteins, lipids, nucleic acids) to specific biological effects remain largely unknown. No standardised manufacturing protocols exist; different production methods generate EVs with different properties. These unresolved technical questions limit clinical translation of EV-based approaches [49-51].

Preclinical evidence across parasitic diseases: Synthesis and critical evaluation of evidence quality

Schistosomiasis: Most extensively studied yet substantial limitations remain

Schistosomiasis has received the most extensive preclinical stem cell investigation, particularly regarding hepatic fibrosis. Approximately two dozen published studies examine MSC or stem cell effects in schistosomiasis; this concentration reflects both research focus and methodological accessibility of schistosomiasis models.

Hepatic fibrosis reversal: Current evidence and limitations

Preclinical exploration of stem cell interventions for *Schistosoma mansoni*-induced liver pathology relies heavily on evaluating bone marrow-derived or umbilical cord-matrix MSCs, frequently administered alongside traditional anti-parasitic chemotherapy. Key reference frameworks established in the literature involve tracking the therapeutic potential of MSCs in both acute and

chronic phases of infection [52,53]. When administered to *S. mansoni*-infected mice, MSC therapies, particularly when combined with the conventional anti-helminthic drug praziquantel (PZQ), demonstrate a significant reduction in total hepatic collagen deposition, a decrease in mean granuloma volume, and an improvement in circulating liver enzyme profiles, including serum alanine aminotransferase and aspartate aminotransferase [52,54]. Histopathological evaluations and gelatin zymography consistently reveal that these interventions downregulate alpha-smooth muscle actin expression and alter the balance of MMPs and TIMPs, indicating a suppressed activation state in host hepatic stellate cells [54].

This specific group of studies possesses notable methodological strengths. The protocols routinely feature multi-arm control frameworks, comparing untreated infected cohorts against PZQ monotherapy, MSC monotherapy, and combined regimens [52,54]. Furthermore, many of these layouts integrate late-stage intervention windows, such as cell transplantation at 12 to 16 weeks post-infection, to evaluate tissue remodeling after structural chronicity has been established, tracking recipient animals for several months to confirm the physical homing of stem cells via Y-chromosome gene detection or fluorescent tracking [53,54].

Substantial translation-limiting bottlenecks nevertheless constrain the interpretation of these findings, primarily centered on pathological misalignment and confounding parasitological metrics. Regarding pathological misalignment, murine schistosomal disease progresses as an accelerated, focal granulomatous reaction driven by acute egg deposition [55,56]. It fails to accurately recapitulate the macro-structural landscape of advanced human clinical cirrhosis, which develops slowly over 15 to 25 years of chronic infection [57]. Human disease is characterized by widespread parenchymal destruction, dense bridging fibrosis, and extensive regenerative nodule formation that alters intrahepatic hemodynamics [56,57].

Proof that a mesenchymal stem cell (MSC) intervention can diminish an isolated, cell-mediated murine egg granuloma does not guarantee its capacity to remodel a permanently distorted, end-stage human vascular architecture [58,59]. Furthermore, a critical oversight in several pure MSC monotherapy designs is the failure to thoroughly correlate tissue anti-fibrotic metrics with absolute worm and egg burdens [59]. Because live flukes continuously shed highly immunogenic soluble egg antigens (SEA), any anti-inflammatory or anti-fibrotic response must be explicitly contextualized against whether the stem cells altered parasite viability, disrupted fecundity, or merely temporarily masked local tissue inflammation [60,61].

To circumvent the risks associated with live cell transplantation, such as infusional toxicities, vascular trapping, and potential ectopic tissue formation, recent research has shifted toward cell-free alternatives utilizing host stem cell-derived EVs or exosomes [48]. Preclinical models show that MSC-derived exosomes exert a synergistic anti-fibrotic effect when paired with praziquantel, actively reducing the size of hepatic lesions and suppressing nuclear factor kappa B signaling pathways [62]. Concurrently, advancements in host-parasite crosstalk have revealed that extracellular vesicles are not one-sided; *Schistosoma japonicum* and *S. mansoni* worms actively secrete their own unique EVs into the host mesenteric and portal systems. These parasite-derived vesicles deliver specific microRNAs, such as sja-let-7, directly into host hepatic stellate cells, downregulating the TGF-β/Smad signaling pathway by targeting the collagen type I alpha 2 chain, thus serving as an evolutionary brake on excessive host tissue destruction to ensure parasite survival [63].

Despite providing strong proof-of-concept for vesicle-mediated therapies, substantial critical limitations remain unaddressed in current EV literature. Isolating homogenous populations of exosomes versus larger microvesicles remains a technical challenge, and batch-to-batch cargo variations severely compromise experimental reproducibility. More importantly, the functional durability of cell-free EV interventions is heavily constrained by rapid systemic clearance *in vivo*. Unlike living MSCs that dynamically persist, home to injury sites, and respond to local microenvironmental cues over extended periods, standalone EV preparations lack autocrine or paracrine self-sustainment. They require frequent, high-dose intravenous administrations—a limitation that undermines their logistical and economic viability for deployment in low-resource, endemic regions where neglected tropical diseases are most prevalent.

Mechanistic understanding and unresolved questions

While published studies consistently document a reduction in structural collagen and an apparent normalization of the hepatic

microenvironment, the underlying immunological mechanisms are frequently oversimplified. The prevailing narrative in the literature reports a standard therapeutic shift: elevations in regulatory interleukin-10 (IL-10) and transforming growth factor-beta, accompanied by a reduction in pro-inflammatory cascades and an expansion of regulatory T cell (Treg) populations [53]. This is traditionally interpreted as a straightforward, beneficial restoration of homeostatic immune balance. This straightforward interpretation overlooks a critical evolutionary contradiction in parasite immunology. Chronic helminths are master immunomodulators; the elevation of host IL-10 and TGF-β is the precise molecular strategy utilized by *Schistosoma* species to suppress protective host Th1/Th17 responses, drive immune evasion, and ensure decades of uninterrupted parasite survival within the venous system [64]. By artificially amplifying these identical regulatory cytokine circuits, MSC or EV therapies risk inadvertently dampening the host's protective, parasite-specific cell-mediated immunity. Because preclinical literature rarely tracks long-term, parasite-specific clearance efficiency following stem cell-mediated immunosuppression, it remains unresolved whether reducing local tissue inflammation accidentally facilitates persistent, chronic parasite survival.

Urogenital schistosomiasis and parasitic complications

Schistosoma haematobium represents a distinct clinical entity, causing chronic urogenital schistosomiasis characterized by severe bladder wall inflammation, pelvic fibrosis, obstructive uropathy, and a drastically elevated risk of squamous cell carcinoma of the bladder [65]. Remarkably, despite the clinical severity of this disease, stem cell and EV investigations are completely absent from urogenital schistosomiasis literature. Preclinical research remains localized to *S. mansoni* and *S. japonicum* hepatic models. It is entirely unknown whether MSCs can safely navigate or survive within the distinct mucosal and urothelium microenvironments of the urogenital tract, whether they can successfully reverse dense pelvic or bladder wall calcification, or if their potent immunosuppressive properties might dangerously accelerate pre-malignant changes in chronically inflamed, oncogenic bladder tissue [66,67].

Chagas disease: Evidence constraints and mechanistic uncertainties

Stem cell investigation in *Trypanosoma cruzi* infection stands in stark contrast to schistosomiasis preclinical research in both quantity and methodological sophistication. Direct preclinical examination of mesenchymal stem cell therapy in Chagas disease comprises only a handful of animal studies, whereas most inferences about cardiac stem cell efficacy derive from broader regenerative medicine literature addressing acute myocardial infarction or idiopathic dilated cardiomyopathy. This reliance on non-parasitic cardiac models introduces a critical translational problem: the immunological and pathophysiological contexts differ fundamentally, making mechanical transfer of findings to parasitic disease inappropriate. Chronic Chagas cardiomyopathy develops within an immunological landscape distinct from acute myocardial infarction [3]. Infarction generates acute inflammatory responses resolving within weeks; chronic Chagas disease involves persistent low-level parasitaemia combined with progressive immune exhaustion. Parasite-specific T cells encounter continuous antigen exposure through persistent circulating trypomastigotes yet fail to eliminate infection. Chronic antigenic stimulation without successful parasite clearance progressively exhausts anti-parasite immunity, evidenced by increased expression of programmed death-1, T-cell immunoglobulin and mucin-domain containing-3, and reduced interferon-gamma production [23]. Simultaneously, myocardial inflammation persists through resident macrophage and dendritic cell infiltration, driving progressive fibrosis and cardiomyocyte dysfunction. This paradoxical state, inadequate anti-parasite immunity combined with persistent inflammatory damage, creates a unique context for stem cell intervention fundamentally differing from acute cardiac disease. The distinction matters profoundly for mechanistic understanding. In myocardial infarction, anti-inflammatory mesenchymal stem cell effects address pathological processes actively ongoing and mediated by excessive innate immune activation. In chronic Chagas disease, anti-inflammatory effects occur within a context where parasites have already established sophisticated immune evasion mechanisms. Whether mesenchymal stem cell-mediated immunosuppression through interleukin-10 and transforming growth factor-beta production would suppress beneficial anti-parasite T cell responses remains entirely unexamined [3,23]. The theoretical possibility exists that mesenchymal stem cells might enhance parasitaemia by

further dampening already-exhausted anti-parasite immunity; this scenario has not been tested in any published preclinical study.

The sole advanced clinical observation in Chagas disease comes from investigations in which patients with established dilated cardiomyopathy received autologous bone marrow stem cell injection directly into myocardium via percutaneous catheter guidance. Early reports described improvement in ejection fraction measurements and functional capacity at 12-month follow-up [3]. Subsequent case reports from Brazilian research groups describe similar observations, though publications remain confined to single research institutions without independent replication in different centres.

The methodological limitations of this clinical evidence [3] preclude efficacy conclusions. Open-label design without control group assignment permits substantial placebo effects and regression to the mean; cardiac patients frequently demonstrate apparent clinical improvement through psychological mechanisms and natural disease variation independent of therapeutic intervention. No sham-treated comparison group existed, preventing natural history assessment or distinction between treatment effects and spontaneous improvement. Sample sizes remained small, limiting statistical power and increasing likelihood that apparent benefits represent statistical artefacts rather than true treatment effects. Follow-up extended only to 12 months, providing no information about durability of benefits or longer-term safety. Serial biomarkers of myocardial damage including cardiac troponin and B-type natriuretic peptide were not measured, precluding determination of whether mesenchymal stem cells reduced ongoing myocardial inflammation or achieved cardiac function improvements through different mechanisms. Most critically, no parasite burden assessment was performed using established measures. This omission means studies cannot distinguish whether mesenchymal stem cells affected parasitaemia, anti-parasite T cell responses, or exclusively cardiac inflammation through general immune modulation. The design therefore cannot address the central biological uncertainty in parasitic disease contexts: whether immunomodulation supports or impairs parasite control.

Leishmaniasis: Variable evidence quality and disease-specific immunological contexts

Preclinical investigation of stem cell therapy in leishmaniasis demonstrates substantially more rigorous methodological design than Chagas disease research, though important limitations persist. Ramos and colleagues [45] examined adipose tissue-derived mesenchymal stem cells combined with meglumine antimoniate in cutaneous leishmaniasis-infected mice, incorporating multiple treatment groups including untreated controls, antimonial monotherapy, mesenchymal stem cell monotherapy, and combined therapy. Outcome measures encompassed both tissue damage quantified by lesion size and histological analysis alongside parasite burden assessed through intracellular parasite counting in tissue samples. Immunological parameters included flow cytometric analysis of T cell subsets, cytokine measurements, and parasite-specific immune responses.

Results demonstrated that combined mesenchymal stem cell plus antimonial therapy reduced lesion size more effectively than either treatment alone, with enhanced macrophage-mediated parasite killing occurring in treated animals. Parasite burden reduction accompanied tissue healing, suggesting mesenchymal stem cells enhanced rather than impaired anti-parasitic immunity. The Th1/Th2 balance shifted toward Th1 predominance in treated animals, providing mechanistic insight into how combined therapy achieved superior outcomes. This study represents careful methodological design measuring both tissue damage and parasite control simultaneously, distinguishing it from most parasitic disease stem cell investigations [45].

Important limitations constrain interpretation of these findings. The study examined relatively acute infection lasting 4-6 weeks rather than chronic cutaneous leishmaniasis, which persists for months to years even without treatment. Cutaneous leishmaniasis naturally undergoes slow spontaneous healing; determining what therapeutic benefit derives from mesenchymal stem cells versus natural disease regression requires careful analysis of the contribution each factor makes to observed improvements. The study did not isolate mesenchymal stem cell monotherapy effects; comparisons involved antimonial monotherapy versus combination therapy. Whether mesenchymal stem cells alone provided benefit, or benefit emerged exclusively from combination therapy, remains unclear. Sample sizes were small, with only 5-8 mice per group, limiting statistical power to detect true differences. The mechanisms explaining enhanced parasite killing despite elevated interleukin-10 and transforming growth factor-beta production remain incompletely explained, representing an important gap in mechanistic understanding.

More recent investigation of bone marrow-derived mesenchymal stem cell infusion alongside antimonial treatment in visceral leishmaniasis models reported reduced spleen parasite burden, improved interleukin-10 to interferon-gamma ratio balance, and lowered relapse risk at 6-month follow-up compared to conventional treatment alone [68]. These observations suggest encouraging signals warranting further investigation. Animal numbers remained small and follow-up relatively short, however, limiting the generalisability of findings to human visceral leishmaniasis with its acute severe immunosuppression, high mortality, and chronic relapse risk.

Malaria and neurocysticercosis: Tissue-specific effects and incomplete evidence

Investigation of mesenchymal stem cells in experimental cerebral malaria using *P. berghei* ANKA strain demonstrated that mesenchymal stem cell administration reduced lung and kidney injury quantified via histopathological analysis, reduced plasma creatinine and markers of pulmonary injury, modulated the cytokine storm through tumour necrosis factor-alpha and interleukin-6 reduction, and improved survival compared to untreated controls [69]. Unexpectedly, direct neuroprotection did not emerge; brain pathology remained relatively unaffected by mesenchymal stem cell therapy despite systemic improvement. This tissue-specific variation suggests mesenchymal stem cell efficacy varies by organ and tissue context, with lung and kidney damage appearing responsive to inflammatory modulation while brain damage from sequestration and direct parasite effects may require fundamentally different therapeutic mechanisms.

Examination of mesenchymal stem cells in experimental neurocysticercosis demonstrated that mesenchymal stem cell administration reduced neuroinflammation through interleukin-10 and transforming growth factor-beta production, suppressed astrogliosis, and reduced perilesional cerebral oedema. These findings suggest potential for mesenchymal stem cells in neuroinflammatory parasitic disease. Translation to chronic neurocysticercosis with established seizure phenomena remains speculative, however, as the study examined primarily *in vitro* and early *in vivo* models. Neurocysticercosis pathology involves multiple complications including intracranial pressure elevation, seizure susceptibility, and permanent neuronal loss that may not be addressable through inflammation reduction alone. The episodic nature of neurocysticercosis inflammation differs from continuous inflammation characterising schistosomiasis or Chagas disease; optimal stem cell therapy timing and dosing strategies remain undefined across these distinct pathophysiological contexts.

The preclinical-clinical translation gap and evidence position

The transition from animal models to human clinical medicine represents the largest evidence gap in medical development. Approximately 90% of interventions demonstrating efficacy in animal studies fail to provide human benefit [70]. This extraordinarily high failure rate reflects fundamental biological differences between animal models and human disease that preclinical investigations typically underappreciate.

Preclinical parasitic disease models examine relatively standardised disease phenotypes in genetically uniform laboratory mouse strains; human parasitic diseases present with substantial heterogeneity. Schistosomal cirrhosis progresses at widely different rates among infected individuals, with some developing cirrhosis within 10 years while others remain stable over 30 years. Genetic polymorphisms in interleukin-10, transforming growth factor-beta, and other immune mediators influence disease progression. Concurrent infections with other pathogens including hepatitis B, hepatitis C, and HIV substantially alter immune responses and disease severity. Nutritional status influences fibrosis progression. These individualised disease factors are absent in standardised mouse models [16].

Temporal discrepancies between preclinical and human disease create additional uncertainty. Preclinical schistosomiasis studies examine 8-12 weeks of infection; human schistosomiasis develops over decades. Preclinical Chagas studies examine 4-8 weeks of infection; human Chagas cardiomyopathy develops over 20-30 years. Preclinical studies assess outcomes at 4 weeks post-therapy; human disease requires follow-up spanning years to assess durable efficacy and identify delayed adverse effects. This temporal mismatch creates substantial uncertainty about long-term clinical effectiveness.

Preclinical parasitic disease studies measure surrogate endpoints including hepatic collagen deposition, stellate cell activation markers, and cytokine levels. Clinical outcomes focus on patient mortality, morbidity, symptom relief, and functional

improvement. Surrogate endpoints do not always correlate with clinical outcomes; reduced collagen deposition might occur while liver function remains impaired, or reduced inflammatory markers might occur while cardiac function remains unchanged. Whether preclinical surrogate endpoint improvements translate to clinical benefit cannot be assumed without direct clinical evidence. Publication bias substantially distorts the apparent evidence base. Preclinical publications overrepresent positive findings; studies showing minimal or negative mesenchymal stem cell effects likely remain unpublished, generating systematic bias in published literature. Meta-analyses of preclinical malaria, ischaemic stroke, and myocardial infarction studies demonstrated that positive studies are twice as likely to be published as negative studies [71]. Literature syntheses based on published studies therefore overestimate true efficacy by systematically excluding negative findings.

Human clinical evidence for stem cells in parasitic disease remains minimal and confined to uncontrolled cardiac observations. No randomised controlled trials have been completed in any parasitic disease. No long-term safety studies spanning multiple years have been conducted. Beyond observational reports in Chagas cardiomyopathy, Brazilian case reports and small uncontrolled series describe mesenchymal stem cell applications with apparent improvements in ejection fraction; however, these reports cluster from single research institutions without independent reproduction in different centres. Published uncontrolled case series lack control groups, use small sample sizes typically ranging from 10-20 patients, and rarely extend follow-up beyond 12 months. These design limitations preclude definitive efficacy assessment.

No controlled clinical trials examine stem cells in schistosomiasis, leishmaniasis, malaria-associated organ complications, or neurocysticercosis. Despite preclinical evidence suggesting potential benefit, clinical translation has not proceeded beyond preliminary uncontrolled observations. No systematic adverse event monitoring exists for stem cell-treated parasitic disease patients. Tumorigenesis risk, immunological complications, infectious complications, and other potential adverse effects have not been systematically documented. Long-term follow-up data tracking patients beyond 12-24 months post-therapy are unavailable.

Synthesising available evidence reveals a profound discrepancy between preclinical promise and human evidence. Preclinical investigations demonstrate consistent anti-fibrotic and immunomodulatory effects across multiple parasitic disease models, suggesting genuine biological activity. The consistency across disease contexts and multiple independent research groups indicates findings exceed artefact or publication bias. Preclinical evidence quality varies substantially; some studies demonstrate careful methodological design while others lack appropriate controls or outcome measures. The overall pattern suggests biological effects rather than null findings.

Human evidence, by contrast, remains minimal and unsatisfactory for establishing clinical efficacy. Clinical efficacy cannot be claimed from available data. The evidence position is that of a biologically plausible experimental approach requiring substantially more rigorous investigation before clinical translation can proceed responsibly. Translating preclinical findings to properly designed clinical trials is justified; clinical translation to routine patient care is not.

Barriers to clinical translation and requirements for responsible progress

The unique immunological context of parasitic disease creates challenges for stem cell therapy that extend beyond preclinical-clinical translation gaps. Parasites evolved sophisticated immune evasion strategies permitting decades of persistence. Parasites actively induce transforming growth factor-beta and interleukin-10 production to suppress anti-parasitic immunity, trigger antigenic variation to escape adaptive immune recognition, and interfere with dendritic cell maturation to suppress T cell priming. Overlaid upon this parasite-driven immunosuppression, chronic antigenic stimulation generates additional immune suppression and exhaustion of anti-parasitic T cells. Mesenchymal stem cell-mediated immunomodulation through interleukin-10 and transforming growth factor-beta production might paradoxically enhance the parasite-favourable immunological environment. Whether stem cell therapy could be optimally timed or dosed to reduce excessive inflammation while maintaining adequate anti-parasitic immunity remains unknown. This fundamental biological uncertainty requires resolution before human trials commence.

Mesenchymal stem cell immunomodulatory capacity shows substantial inter-donor variability. Some mesenchymal stem cell

populations demonstrate potent interleukin-10 and transforming growth factor-beta production; others show minimal secretion of these cytokines. Some promote robust regulatory T cell expansion; others less so. This heterogeneity reflects donor age, sex, health status, and genetic polymorphisms. Clinical efficacy might vary unpredictably based on mesenchymal stem cell donor characteristics. Preclinical studies using cultured mesenchymal stem cell lines do not capture this donor variability; clinical translation will require determining whether donor selection influences therapeutic outcomes.

Tissue-specific variation in mesenchymal stem cell efficacy creates additional complexity. Efficacy varies by organ and tissue context, with some tissues responsive to inflammatory modulation while others require different mechanisms entirely. The factors determining tissue-specific responsiveness remain unknown, and optimal target organ selection for stem cell therapy cannot be determined from available evidence. Manufacturing stem cell therapeutics requires sophisticated facilities, strict quality control, trained personnel, and regulatory oversight. Manufacturing costs per patient typically exceed $10,000-50,000 USD, with autologous approaches costing substantially more than allogeneic preparations [72,73]. Endemic regions for parasitic disease including sub-Saharan Africa, Southeast Asia, and Central and South America typically lack manufacturing infrastructure and financial resources. This creates a fundamental equity problem: populations bearing greatest disease burden have least capacity to access advanced therapeutics. Any clinical development strategy must address how treatment would be manufactured, regulated, and distributed equitably in endemic regions; current systems offer no clear solutions.

Most countries endemic for parasitic disease lack robust regulatory frameworks for stem cell therapeutics. Regulatory requirements differ among countries; harmonised standards do not exist. Some nations permit unregulated stem cell clinics offering unproven preparations. These unregulated clinics erode public trust, complicate legitimate research, and expose patients to potentially dangerous therapies. Strengthening regulatory capacity in endemic regions requires substantial international investment and technical assistance [74]. Effective parasitic disease management requires integration of antiparasitic drugs with potential stem cell therapy [75]. Healthcare systems in endemic regions often lack reliable drug supply, trained diagnostic personnel, and monitoring capacity for even conventional treatment. Adding stem cell therapy complexity to already-stretched systems presents organisational challenges beyond current capacity.

Responsible advancement requires addressing unresolved safety questions. Pluripotent stem cells carry substantial tumorigenesis risk if differentiation remains incomplete [13,40]. Mesenchymal stem cells exhibit lower risk but cannot be presumed completely safe [13]. Longterm followup of stem celltreated patients spanning 1020 years would be prerequisite for comprehensive tumorigenesis assessment; no such studies have been completed in parasitic disease patients [70]. Allogeneic stem cell transplantation might trigger immune rejection despite mesenchymal stem cells' relative immune privilege [36,40]. In parasitic disease populations with systemic immune activation, rejection risk might be elevated. Stem cellinduced immunosuppression through interleukin10 and transforming growth factorbeta elevation might increase susceptibility to secondary infections [36,40]. This risk seems particularly relevant in malariaendemic regions with high tuberculosis prevalence, yet no systematic assessment of infection risk has been conducted.

The path forward requires development of standardised preclinical parasitic disease models with specified parasite strains, infection protocols, and outcome measures that would strengthen evidence quality. Models spanning months rather than weeks would better reflect human chronic disease; standardised models would permit metaanalysis across studies and systematic evidence synthesis. Preclinical studies must extend beyond current 4week posttherapy assessments to examine 812 week timepoints, determining whether benefits persist, reverse, or evolve. Studies examining both tissue inflammation and parasite burden simultaneously would clarify mechanisms and address parasitespecific effects. Focused preclinical investigations examining whether mesenchymal stem cell immunomodulation enhances or impairs parasite control would resolve critical uncertainties. Experiments explicitly examining antiparasitic immune responses alongside tissue damage would clarify mechanistic tradeoffs [70,71].

Clinical translation requires properly designed randomised trials comparing stem cells plus conventional antiparasitic

therapy versus antiparasitic therapy alone as the prerequisite for efficacy assessment. Initial trials should focus on diseases where preclinical evidence appears strongest and where organ damage is objectively measurable. Trials must enrol sufficient participants to detect clinically meaningful differences with adequate statistical power. Baseline pilot trials might enrol 50100 participants per arm; larger efficacy trials would require 200500 participants per arm depending on expected effect size. Followup must extend to minimum 23 years to assess durable efficacy and identify delayed adverse effects. Extended followup to 510 years would permit tumorigenesis and other delayed complication assessment. Clinical trials must measure not only clinical outcomes including mortality, morbidity, and functional improvement, but also mechanistic parameters including parasite burden, antiparasitic immunity, inflammatory markers, and fibrosis progression markers [14,70,71].

Endemic countries require strengthened regulatory frameworks permitting safe, ethical stem cell research while preventing unregulated clinic operations. International collaboration supporting regulatory capacity building in resourcelimited settings would accelerate this process. World Health Organization guidelines for stem cell research in developing countries provide frameworks that could be strengthened and implemented. Clinical development pathways must explicitly address how stem cell therapeutics would be manufactured, regulated, and distributed equitably if efficacy is eventually demonstrated. Approaches might include centralised manufacturing with international distribution, technology transfer enabling local manufacturing in endemic countries, or alternative cell sources requiring less sophisticated manufacturing. Ethical clinical research in parasitic disease endemic regions requires genuine community engagement, transparent communication about efficacy and safety uncertainty, and shared decisionmaking about research participation. Previous research ethics violations in parasitic disease endemic regions create justified community skepticism; current research must address historical injustices through partnership approaches [72-75].

Conclusions

Stem cell therapy addresses a genuine therapeutic limitation in parasitic disease management. Conventional antiparasitic drugs effectively reduce parasite burden but leave established tissue damage untouched. Regenerative medicine approaches targeting tissue repair and immune modulation could theoretically complement conventional treatment. Mesenchymal stem cells possess biological properties suggesting regenerative capacity: immunomodulatory effects, anti-fibrotic potential, tissue-homing capacity, and capacity for direct cell replacement.

Preclinical investigation demonstrates consistent anti-fibrotic and immunomodulatory effects across multiple parasitic disease models. These effects emerge across different parasite species, different mesenchymal stem cell sources, and different research groups, suggesting genuine biological activity rather than artefact. The consistency of effects despite biological heterogeneity suggests robust mechanisms. Preclinical evidence simultaneously exhibits substantial limitations including short-term follow-up periods, early disease stages, inadequate parasite burden measurement, and publication bias. Mechanistic understanding remains incomplete; unresolved questions about parasite-immune-stem cell interactions, optimal dosing, and tissue-specific responsiveness require resolution before clinical application.

Human clinical evidence remains minimal and unsatisfactory. No randomised controlled trials have been completed in any parasitic disease. No long-term safety studies document delayed adverse effects. Clinical efficacy cannot be claimed from available evidence. The profound gap between preclinical promise and human evidence reflects general principles of translational medicine: 90% of preclinically promising interventions fail clinically. Whether stem cells will join this failure category or represent the exceptional success remains unknown. Stem cell therapy in parasitic disease remains experimental. Claims of therapeutic benefit extend beyond available evidence. Continuing investigation is warranted; premature clinical translation to routine care is not justified at present.

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