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Organoids as translational models in neuroregeneration after central nervous system injury

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Abstract

Central nervous system (CNS) injuries, including traumatic brain injury and spinal cord injury, affect millions of individuals worldwide annually, resulting in profound long-term disability and significant socioeconomic burden. Despite decades of research, effective neuroregenerative therapies remain elusive, largely due to inadequate preclinical models. Traditional two-dimensional cultures and animal models, while valuable, fail to capture the complexity of human neural tissue architecture and disease pathophysiology, thereby limiting translational success. This literature review examines neural organoids – three-dimensional, self-organizing tissue structures derived from human pluripotent stem cells – as transformative tools for bridging the translational gap in CNS injury research. We synthesize current knowledge on the biological principles governing organoid generation, including self-organization, extracellular matrix scaffolding, and bioreactor optimization. We evaluate diverse organoid types – cortical, cerebellar, spinal cord organoids, and brain assembloids – and their applications in modeling traumatic brain injury, ischemic stroke, and neurodegenerative pathologies. Additionally, we discuss organoid utility in preclinical drug screening and therapeutic development, including neuroprotective agents and gene therapies. Patient-derived organoids offer particular promise for personalized disease investigation and precision medicine. While organoids demonstrate superior predictive accuracy and human-relevant complexity compared to conventional models, significant ethical considerations regarding organoid consciousness, human-animal chimeras, donor autonomy, and commercialization warrant careful governance. This review demonstrates that neural organoids represent a revolutionary technology advancing translational neuroscience and regenerative medicine, while highlighting the critical importance of rigorous ethical oversight in their application.

Running title: Organoids as models of neural repair

Keywords: brain organoids, neuroregeneration, neural repair, stem cell-derived organoids

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Introduction

Every year, approximately 20.8–27.2 million people worldwide suffer from traumatic brain injury (TBI), and 37.9–49 million live with its long-term consequences. Spinal cord injuries (SCI), although less common, are equally devastating, with around 0.9–1 million new cases annually and over 20 million people living with chronic sequelae. Falls and traffic accidents are the predominant causes of both injuries, particularly among older adults and young people [1–3]. TBI frequently results in cognitive impairments, including memory, attention, and executive dysfunctions, as well as an increased risk of dementia, depression, and epilepsy [4,5]. SCI, in turn, often leads to partial or complete paralysis, sensory loss, autonomic dysfunction, chronic pain, and respiratory complications [6,7]. Both conditions cause lifelong disability, reduced quality of life, and immense socioeconomic burden, with high mortality rates in the first year after injury [1,7]. Despite decades of research, effective neuroregenerative therapies remain elusive. The limited capacity of the adult central nervous system to regenerate, combined with inadequate preclinical models, hampers translation of laboratory findings into clinical practice. In this context, organoid-based systems have emerged as promising tools to model CNS injury and regeneration in vitro, bridging the gap between animal models and human pathology [8–10].

Limitations of classical models in neuroscience research

All 2D cultures are composed of neurons or neural progenitor cells (NPCs) grown on flat surfaces [11,12], but their characteristics vary depending on the originating cell type. Classical immortalized cell lines, human induced pluripotent stem cells (iPSCs), and somatic neurons can be maintained either as monocultures – allowing the study of specific cell types – or as co-cultures that model interactions between neurons, glial cells, and their microenvironment [13]. Immortalized cell lines remain essential for high-throughput drug screening and mechanistic studies due to their consistency and low maintenance costs, although their translational relevance is limited because they are cancer-derived or of non-human origin [13]. iPSCs provide greater human relevance, particularly when patient-derived, but their variability, technical complexity, and high cost constrain their widespread use [13,14]. Somatic neuron cultures, in turn, proliferate faster than iPSCs but possess limited self-renewal capacity [13]. Overall, 2D cultures are easy to use, cost-effective, reproducible, and ethically unproblematic, making them suitable for mechanistic and high-throughput studies. However, their simplified architecture and lack of systemic context limit their ability to model complex brain processes, thereby reducing their translational relevance to human physiology. To overcome these limitations, animal models have traditionally been employed, offering greater biological complexity and an intact systemic environment indispensable for studying neurophysiology and neurological disorders. They remain a cornerstone in drug discovery and therapeutic development by enabling the evaluation of treatment effects in a living organism [13]. Nevertheless, extrapolation of animal data to humans is limited by fundamental interspecies differences in genetics, anatomy, and physiology [15]. These discrepancies are particularly problematic in CNS research, where the intricacy of neural networks and behavior exceeds what can be accurately modeled in animals [15]. Most preclinical studies rely on rodent models, which differ substantially from humans in both genetic makeup and environmental context, thereby limiting their translational value [16]. Although non-human primates more closely resemble humans, their use entails extremely high costs and significant logistical and ethical challenges [16]. Furthermore, animal models cannot replicate complex human social behaviors and interpersonal interactions that accompany many neurological and psychiatric disorders [16]. This limitation is evident in behavioral neuroscience, where animal experiments predict fewer than 10% of human outcomes, underscoring a major translational gap [17]. Similarly, in drug development, reliance on animal testing incurs considerable financial and temporal costs while yielding poor predictive accuracy for human responses [17]. Ethical concerns also remain substantial, as experimental animals frequently experience pain and distress during research procedures [13,17].

Generation and biological principles of human neural organoids

Neural organoids represent artificial three-dimensional tissue structures developed from human pluripotent stem cells that recapitulate essential characteristics of early human brain development within an in vitro environment [18]. These structures are distinguished by their capacity to undergo self-organization – an intrinsic developmental process wherein cells spontaneously establish complex tissue arrangements without requiring external patterning

factors [19]. The fundamental principle of organoid development rests upon the remarkable ability of neural tissue to assemble itself when provided with appropriate environmental conditions, a phenomenon that has been leveraged to create remarkably sophisticated models of the developing human brain [20]. The generation of neural organoids begins with pluripotent stem cell sources, which encompass both human embryonic stem cells and cells reprogrammed into a pluripotent state from adult tissues. Human embryonic stem cells derived from blastocyst-stage embryos provide a naturally pluripotent baseline, while induced pluripotent stem cells offer the distinctive advantage of being generated from patient-derived somatic cells, enabling disease-specific modelling [21]. These cellular sources can differentiate into the full spectrum of neural lineages including neural progenitor cells, neurons, and glial cells, making them ideal starting materials for organoid construction [22]. The protocol initiates through formation of three-dimensional aggregates called embryoid bodies, which are subsequently exposed to neural differentiation conditions that suppress non-neural cell types while promoting neuroectodermal commitment [23]. Following neural induction, organoids are embedded in extracellular matrix materials – most commonly Matrigel, a naturally derived basement membrane extract – which provides essential structural support that promotes the establishment of organized neuroepithelial tissue with characteristic apicobasal polarity [24]. The extracellular matrix serves multiple critical functions including maintaining soluble growth factors, organizing ion channels, and enabling the spatial organization of different cell types that characterizes authentic brain tissue [25]. The embedding process facilitates the formation of fluid-filled cavities that anatomically resemble brain ventricles, arising from the coordinated self-organization of neural progenitor cells that align themselves into radially organized structures [20]. To overcome inherent limitations in nutrient and oxygen diffusion within increasingly large three-dimensional structures, organoids are subsequently cultured in bioreactor systems that provide continuous agitation – either through spinning bioreactors or orbital shakers – substantially improving nutrient delivery and extending viable organoid growth periods to months or years [26]. While the generation of neural organoids follows broadly standardized steps, several technical and biological variables critically influence their reproducibility and developmental fidelity. The key determinants that govern organoid quality, along with strategies for their optimization, are summarized in **table 1**.

The advantages of neural organoids as models of human brain development are substantial and multifaceted. The three-dimensional architecture enables complex intercellular interactions and signaling cascades that are fundamentally impossible in conventional two-dimensional culture systems [19]. Neural organoids exhibit remarkable cellular heterogeneity, spontaneously generating numerous distinct cell populations representing different developmental stages that achieve transcriptomic profiles correlating with specific periods of human fetal brain development [27]. Furthermore, organoids originate from human genetic material rather than animal models, enabling authentic recapitulation of human-specific developmental mechanisms and disease pathophysiology that frequently diverge from findings in traditional animal models [28]. Two

TABLE 1. Key determinants of neural organoid quality and reproducibility

DETERMINANT	INFLUENCE ON ORGANOID OUTCOME	OPTIMIZATION METHODS	REFERENCES
Stem cell line quality	Affects differentiation potential	Use low-passage, genomically stable PSCs	[21]
Extracellular matrix composition	Guides polarity and organization	Optimize Matrigel concentration or synthetic substitutes	[24]
Mechanical environment	Affects size and maturation	Adjust matrix stiffness or use dynamic systems	[25]
Oxygen and nutrient delivery	Impacts viability in long-term culture	Use spinning bioreactors or perfusion chips	[26]
Signalling control	Determines region-specific fate	Apply morphogen gradients (SHH, FGF8, BMP inhibitors)	[23]

distinct protocol approaches have emerged to optimize organoid utility. Unguided protocols permit spontaneous differentiation resulting in organoids containing multiple brain region identities within single structures [19]. Conversely, guided protocols employ sequential application of specific morphogenetic molecules – including inhibitors of bone morphogenetic protein signaling, Sonic hedgehog agonists, and fibroblast growth factors – to direct differentiation toward particular brain regions [23]. The translational potential of neural organoid technology extends to comprehensive disease modeling applications, particularly for neurodevelopmental and early-stage neurodegenerative disorders where organoids recapitulate pathological phenotypes observed in patient populations [20]. Patient-derived organoids enable personalized disease investigation, drug screening, and identification of disease-specific therapeutic targets while maintaining individual genetic backgrounds [23]. Collectively, neural organoids represent a transformative technology that fundamentally addresses the previously intractable challenge of studying human brain development and neurological disease pathobiology through biologically relevant, patient-specific models [28].

Types of CNS organoids and their biological properties

Modern technologies have enabled the development of diverse 3D brain models, each designed to mimic specific aspects of human neural tissue organization and function. Depending on the applied developmental cues, organoids can be patterned toward distinct regional identities, providing versatile tools for studying neurodevelopment, disease mechanisms, and regenerative processes [29,30]. Cortical organoids (hCOs) replicate key molecular, cellular, and structural features of the human cerebral cortex, including the presence of cortical radial glia, intermediate progenitors, and glutamatergic neurons. They are typically generated through guided differentiation strategies that suppress non-cortical fates while promoting excitatory cortical lineage specification. Simplified variants, known as human cortical spheroids (hCSs), form more homogeneous 3D aggregates. Compared to less specific cerebral or whole-brain organoids, cortical organoids demonstrate higher reproducibility and regional fidelity, making them particularly suitable for mechanistic studies of cortical development. They have been successfully applied to model hypoxic–ischemic brain injury and other pathological conditions, providing insights into cellular responses, mechanisms of damage, and potential therapeutic strategies [31,32]. Cerebellar organoids overcome the limitations of animal models by recapitulating human-specific cerebellar features, including defined laminar architecture and connectivity between inhibitory and excitatory neurons. With extended culture, they generate mature Purkinje cells that exhibit electrophysiological properties similar to those observed in vivo. These models are especially valuable for studying disorders associated with rhombic lip malformation, such as Dandy–Walker malformation and cerebellar vermis hypoplasia, as well as Purkinje cell degeneration seen in ataxia-telangiectasia and autism spectrum disorders – conditions that cannot be faithfully reproduced in rodents [33]. Spinal cord organoids (SCOs), derived from pluripotent stem cells, represent a rapidly evolving field offering novel opportunities for modeling human neurodevelopmental and neurodegenerative disorders. They form regionally patterned dorsal–ventral domains and contain functional motor neurons, interneurons, astrocytes, and other spinal cell types suitable for electrophysiological and connectivity studies. SCOs have proven useful for investigating diseases such as amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and developmental neuromuscular disorders, and they show promise in spinal cord injury repair when combined with bioengineered scaffolds that promote engraftment and axonal guidance [34,35]. More complex multicellular systems, known as brain assembloids, are generated by fusing distinct region-specific organoids to recreate inter-regional interactions, neuronal migration, and circuit formation. These models bridge the gap between simplified organoids and the complex architecture of the human brain, providing a powerful platform for studying network-level processes and inter-regional communication that cannot be captured by single organoid systems [36,37]. Together, cortical, cerebellar, spinal cord organoids, and assembloids form a comprehensive toolkit for human-relevant modeling of neurodevelopment, pathology, and regeneration, advancing translational neuroscience beyond the limitations of traditional 2D and animal models [8,38].

In vitro modeling of central nervous system traumatic injury using organoids

In organoid-based ischemic stroke modeling, the most widely adopted protocols employ oxygen deprivation (OD) or oxygen-glucose deprivation (OGD) to mimic ischemic and reper-

fusion phases in vitro [9,39]. Neural organoids are typically cultured in cerebral organoid differentiation medium (CODM) and exposed to 1% oxygen for 48 hours, followed by reoxygenation under normoxic conditions. This process induces structural damage and cellular apoptosis similar to in vivo ischemic injury, with partial recovery observed after reoxygenation. The OGD/reoxygenation (OGD/R) approach further reveals key molecular markers such as PPAR signaling and PKM2, which are involved in metabolic adaptation and cell survival pathways during ischemic stress [39]. Recent work has extended these models toward drug testing and regenerative applications. For instance, Wang et al. developed a humanized cerebral organoid model to evaluate neuroprotective compounds such as edaravone and butylphthalide, validating the system for anti-stroke drug screening [40]. Moreover, transplantation studies have demonstrated that cerebral organoids can integrate into host tissue, promote neurogenesis, and restore motor function following middle cerebral artery occlusion in rats [41]. These findings highlight organoids as promising tools for both modeling ischemic injury and testing regenerative interventions. As far as TBI injury models are concerned, the first in vitro TBI organoid model used spheroidal cerebral organoids subjected to vertical displacement pulses between two posts, reproducing non-penetrating injuries and correlating strain fields with biomarker release (NF-L, LDH) andelectrophysiological impairment [42]. Controlled cortical impact (CCI) techniques were later adapted to human organoids embedded in a brain-mimicking phantom matrix and implanted into a murine skull scaffold, enabling physiological impact simulation and measurement of neuronal damage markers such as NSE and cleaved caspase-3 [43,44]. Advanced mechanical systems now allow precise strain rate control, revealing that genes such as ENO1, CARD9, and FOXP3 are upregulated in response to deformation stress [45]. High-intensity focused ultrasound (HIFU) models have also been developed to induce graded damage, correlating phosphorylated tau (p-tau/t-tau) and pTDP-43 levels with TBI severity [46]. These methods collectively provide scalable, reproducible models for investigating injury biomechanics and post-traumatic molecular cascades. Blast-induced TBI has been modeled using benchtop pressure-loading systems that apply controlled overpressure to cerebral organoids, revealing layer-specific neuronal susceptibility and increased apoptosis in deeper cortical regions [47,48]. Moreover, oxidative stress – a key component of secondary TBI injury – has been modeled through exposure of organoid-derived astrocyte cultures to hydrogen peroxide (H_2O_2), leading to mitochondrial depolarization, reactive oxygen species accumulation, and activation of apoptosis markers including apaf-1, p53, and caspase-3 [49,50]. Beyond modeling, organoid transplantation studies in animal TBI models show that human cerebral organoids can engraft, form synaptic connections, and improve behavioral outcomes, underscoring their potential in regenerative medicine [51,52].

Application of organoids in evaluating the efficacy of new drugs and therapies

Cerebral organoids have emerged as a vital platform for screening neuroprotective agents, particularly in the context of Alzheimer's disease (AD). These three-dimensional models have been successfully utilized to evaluate the efficacy of ß- and γ-secretase inhibitors, demonstrating a marked capability to limit both amyloid-ß (Aß) accumulation and pathological tau aggregation [53,54]. Moreover, organoids have facilitated the assessment of immunotherapies, including the FDA-approved anti-Aß antibodies, such as lecanemab and donanemab, which demonstrated a significant reduction of amyloid burden in these systems [55]. Furthermore, the application of kinase inhibitors, such as the GSK3α/ß inhibitor (CHIR99021), represents a promising therapeutic avenue, demonstrating efficacy in significantly reducing tau phosphorylation [56]. Cerebral organoids also prove to be a powerful tool for evaluating neuroprotective agents in ischemic stroke. In studies utilizing oxygen-glucose deprivation (OGD) to simulate ischemic injury, the assessment of compounds such as edaravone, butylphthalide, P7C3-A20, and ZL006 demonstrated marked protective effects. Specifically, analyses of lactate dehydrogenase (LDH) release and Caspase-3 activity revealed a significant reduction in cytotoxicity and apoptosis, thereby validating the OGD-organoid model as a reliable platform for screening the efficacy of anti-stroke therapeutics [40,57]. Cerebral organoids serve as versatile models to assess the roles of growth factors in brain development, enabling controlled manipulation and detailed analysis of neurodevelopmental processes, disease mechanisms, and tissue engineering strategies. Since the successful generation of these tissues inherently relies on precise stimulation with exogenous signals to drive differentiation, they function as an ideal platform for evaluating the specific effects of growth factors. By modulating agents such as fibroblast growth factor (FGF) [58], epidermal growth factor (EGF) [59],

and transforming growth factor beta (TGF-ß) [60], researchers can observe their distinct impact on cellular proliferation and organization during both physiological corticogenesis and aberrant development. Consequently, this capacity to recapitulate complex signaling environments renders cerebral organoids an invaluable model for explaining the etiology of neurodevelopmental disorders [61,62]. Cerebral organoids have established themselves as a pivotal platform for advancing cell and gene therapies, offering a human-specific context that reduces reliance on animal models and facilitates the clinical translation of vector systems [63]. They are particularly instrumental in optimizing viral delivery, enabling the comparative screening of various adeno-associated virus (AAV) serotypes and engineered capsids to identify vectors with superior transduction efficiency in human neural cells [64–66]. Beyond vector validation, organoids serve as a robust model for evaluating the downstream efficacy of therapeutic interventions by assessing phenotypic modulation. This capability is well demonstrated in the study of GM1 gangliosidosis, an autosomal recessive neurodegenerative disorder characterized by lysosomal ß-galactosidase (ß-gal) deficiency and GM1 ganglioside accumulation. In this context, organoids microinjected with an AAV9-GLB1 vector showed a significant increase in ß-gal activity and a concurrent reduction in GM1 ganglioside content, confirming the potential of organoids for validating gene replacement therapies [67]. Similarly, in spinocerebellar ataxia type 3 (SCA3) models, the delivery of microRNA targeting the mutant ATXN3 gene resulted in a significant, approximately 30% reduction in ataxin-3 protein levels [64]. Organoids enable the detection of unwanted cell proliferation or tumor formation following therapeutic transplantation, providing a sensitive platform for tumorigenicity assessment that can complement or replace animal models [68]. Moreover, glioblastoma-like organoids enhance the detection sensitivity for tumorigenic cells, serving as a reliable quality control measure prior to clinical application [69]. The utilization of organoids in drug discovery offers distinct advantages, primarily through enhanced physiological relevance and predictive power. Unlike traditional two-dimensional cultures or animal models, organoids closely recapitulate the structural architecture, cellular heterogeneity, and functional complexity of human tissues, thereby improving the accuracy of clinical outcome predictions [70]. This platform is also particularly valuable for precision medicine, as patient-derived organoids (PDOs) allow for the tailored screening of therapeutics – including chemotherapy and immunotherapies – based on individual genetic profiles and drug sensitivities [71–73]. Additionally, organoids facilitate high-throughput screening, enabling the efficient evaluation of extensive compound libraries and the investigation of drug resistance mechanisms, even in rare pathologies [74,75]. In terms of safety, they provide a rigorous, human-specific system for toxicity assessment, offering a superior alternative to animal testing [76,77]. Consequently, regulatory agencies increasingly acknowledge their utility in streamlining drug development, particularly for investigating developmental neurotoxicity and other processes [78].

Ethical aspects

Research involving human brain organoids raises numerous ethical challenges, including concerns related to the organoids themselves, the use of human–animal chimeras in experimentation, issues affecting donors, potential patients who may receive organoid-based therapies, as well as questions surrounding commercialization and appropriate communication about organoid technologies. A commonly highlighted concern in scientific literature is the risk that brain organoids might develop consciousness or self-awareness [79]. This possibility raises significant ethical objections, as it implies conducting research on entities that could perceive emotions, endure suffering, and possess an understanding of their own circumstances [80–82]. In this context, it is difficult to determine what moral status should be assigned to organoids. This challenge stems from the broader question of what qualifies as a human being [80,83,84]. Currently used brain organoids remain structurally immature and far too underdeveloped to resemble the human brain to an extent that would allow for the emergence of consciousness, especially since they lack environmental interaction [80,81]. Nonetheless, the issue becomes considerably more complex and nuanced in the case of human–animal chimeras created through the transplantation of cultivated organoids into living organisms. The transplantation of human brain cells effectively leads to a form of animal-humanization, making its moral status increasingly unclear. This stems from the possibility that a non-human organism may develop human-like features, including aspects of cognition, emotional processing, and self-awareness, which could result in the creation of a semi-human entity that would, with high probability, suffer [80,82–84]. The challenge lies in the difficulty of definitively determi-

ning whether a creature has attained consciousness. This would require careful observation of animals during experiments, for instance, through the use of mirror tests. However, such methods would not guarantee the detection of human-like traits in the animal, which suggests that, as a precaution, chimeras should be treated with special care both during and after research [80]. Animal suffering in brain organoid research involving chimeras would not be limited to the potential development of consciousness – an outcome that is possible but not assured – but would certainly result from the physical damage to the animals' brains during organoid transplantation and from purposeful central nervous system lesions introduced to test organoid-based interventions [80,83]. Ethical issues in brain organoid research also extend to donors, encompassing informed consent, anonymity, and autonomy. Because this field is advancing rapidly, it is nearly impossible to foresee every potential application of organoids and obtain consent for each [80,85]. Respecting the donor's autonomy is essential, permitting them to approve certain applications while withholding consent for others [85,86]. To allow for such selective consent, donor anonymity must, unfortunately, be waived, since maintaining anonymity would prevent donors from overseeing the applications of „their" organoids [80]. Involving donors in the decision-making process is crucial, as they may perceive organoids derived from their cells as an extension of themselves. This concern is particularly pronounced with brain organoids, which are associated with the essence of personal identity. Donors might imagine that a conscious part of themselves is suffering, leading to anxiety about the fate of "their" organoids [80,85]. Because brain organoids can be perceived as extensions of the donor, their use in treatment, especially in transplantation, could pose challenges too. Recipients may worry about significant changes to their personality, memories, and how they perceive themselves [80,82]. The question of "who owns the organoid" arises not only in the context of the donor's emotional connection or the transplant recipient's concerns but also has legal implications. In the context of commercialization, it is ethically questionable to patent organoids as the property of anyone other than the donor. Furthermore, the potential for companies to generate substantial profits from organoid use stands in moral conflict with the altruistic intentions of donors, who cannot derive financial benefit from their contributions [80,86,87]. Considering the ethical issues discussed, organoid research should maintain the highest level of transparency from the very beginning. Achieving this requires the use of accurate, fact-based communication – avoiding overhype, misinformation, exaggeration of organoid capabilities, and the creation of unnecessary concern [81,88].

Conclusions

Organoid-based technologies represent a paradigm shift in experimental neuroscience, offering physiologically relevant and ethically sustainable platforms for modeling central nervous system injury, disease, and regeneration. By recapitulating the three-dimensional organization, cellular heterogeneity, and signaling complexity of the human brain and spinal cord, neural organoids overcome major translational limitations of traditional animal and two-dimensional in vitro models. Their application in modeling ischemic stroke, traumatic brain injury, and neurodegenerative disorders has provided critical insights into pathophysiological mechanisms while enabling high-throughput screening of neuroprotective compounds and gene therapies. Moreover, patient-derived organoids offer a powerful foundation for personalized medicine, allowing tailored therapeutic testing within individual genetic contexts. Despite these advances, challenges persist, including variability between organoid batches, limited vascularization, and incomplete maturation, which constrain their full physiological fidelity. Ethical considerations surrounding consciousness, human–animal chimeras, and donor autonomy also demand careful regulation and transparent communication. Nevertheless, the continuous refinement of organoid systems – particularly through vascularization, immune integration, and assembloid formation – positions them as indispensable next-generation tools for translational neuroscience, regenerative medicine, and precision therapeutic development.

Ethical approval
This study is not related to either human or animal use.

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Conflict of interest
The authors declare no conflict of interest.

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