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Review

Vascular Aging and Multi-Omic Regulation in Ischemic Stroke: Toward Precision Neurorepair

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ABSTRACT: Ischemic stroke (IS) remains a leading cause of disability and mortality in aging populations. Recovery trajectories are shaped not only by the acute vascular insult but also by pre-existing comorbidities, genetic predisposition, and age-dependent molecular remodeling. Common vascular risk factors, such as diabetes mellitus, atrial fibrillation, hypertension, and dyslipidemia, sustain systemic and cerebral inflammation, promote endothelial dysfunction, disrupt blood–brain barrier integrity, and impair neuroplasticity, collectively limiting neurovascular repair and recovery potential. Recent advances in genomic, epigenomic, and transcriptomic profiling have identified dynamic molecular networks that regulate neuronal survival, angiogenesis, and synaptic plasticity after stroke. However, most discoveries remain correlative. Establishing causality will require perturbation-based approaches, including genome and epigenome editing, patient-derived stem cell and organoid models, and longitudinal multi-omics analyses across diverse ancestries and comorbidity profiles. Such integration will clarify how metabolic and inflammatory states imprint the epigenetic and transcriptional landscape of the aging brain. Emerging evidence implicates DNA methylation, histone modifications, and noncoding RNAs, including circular RNAs, as pivotal regulators of ischemic resilience and neurovascular recovery. Translational studies combining genomic insights with epigenetic pharmacology have demonstrated proof-of-concept efficacy for genotype-guided therapies, RNA-based interventions, and histone deacetylase inhibition. Collectively, these strategies support a systems-level framework that unites vascular biology, multi-omics, and neurorestoration. Within this paradigm, aging is reframed not as a static risk factor but as a modifiable molecular trait, guiding the timing and intensity of interventions to enhance neurorepair, restore vascular integrity, and preserve cognitive resilience.

Keywords: ischemic stroke, comorbidities, vascular aging, epigenetic signatures, epigenetic regulation, precision medicine, neural repair, rehabilitation

INTRODUCTION

Stroke is a prototypical disorder of vascular aging, in which systemic metabolic, inflammatory, and genetic factors converge to drive atherosclerotic plaque formation and, ultimately, cerebral vascular occlusion. Among older adults, ischemic stroke (IS) constitutes the predominant form of cerebrovascular disease and remains a leading cause of long-term disability worldwide [1,2]. Its consequences extend far beyond the acute infarct,

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encompassing chronic cascades of neuroinflammation, oxidative stress, and impaired regeneration that are profoundly shaped by age and comorbid conditions.

The aging process is characterized by cumulative vascular injury, mitochondrial dysfunction, and genomic instability that collectively impair neurovascular plasticity [3]. Comorbidities highly prevalent in the elderly, such as diabetes mellitus, hypertension, atrial fibrillation, and dyslipidemia, act as accelerators of this decline. These conditions amplify endothelial stress, compromise blood–brain barrier (BBB) integrity and sustain low-grade inflammation through mechanisms that intersect with both genetic predisposition and epigenetic remodeling [4–7].

Over the past decade, genome-wide association studies (GWAS) and epigenomic analyses have begun to delineate the heritable and regulatory landscapes that underlie ischemic vulnerability and recovery [8–10]. Variants in genes such as *HDAC9, PTCH1*, and *ABO* influence coagulation, vascular integrity, and inflammatory signaling, while epigenetic modifications, including DNA methylation, histone acetylation, and noncoding RNA regulation, translate metabolic and environmental cues into dynamic transcriptional programs [11,12].

Despite these advances, integrating genetic, epigenetic, and clinical datasets remains a major challenge. Most studies assess molecular signatures at single time points, overlooking the temporal evolution of gene regulation and cellular adaptation during recovery. Moreover, the predominance of genomic datasets derived from individuals of European ancestry limits generalizability and obscures ancestry-specific risk mechanisms [13].

In aging populations, these gaps are particularly consequential. Age not only modifies vascular and metabolic physiology but also reshapes the epigenetic landscape through methylation drift, histone imbalance, and altered noncoding RNA expression, which collectively impair plasticity and neurogenesis [11,14–16]. Elucidating how these age-dependent processes interact to shape recovery trajectories represents both a mechanistic challenge and a therapeutic opportunity.

This review integrates current evidence linking comorbidity-driven vascular stress, genetic variation, and epigenetic remodeling in ischemic stroke, emphasizing molecular mechanisms relevant to aging. By highlighting functional validation, longitudinal study designs, and translational applications, we propose that multi-omic, comorbidity-aware frameworks can shift stroke management from reactive treatment toward predictive and personalized neurorestoration.

METHODS

This review followed PRISMA recommendations adapted for narrative reviews. Literature searches were conducted in PubMed, Scopus, and Web of Science through August 2025 using combinations of the terms *ischemic stroke, aging, comorbidity, epigenetic regulation, circular RNA, multi-omics, precision medicine, and neurovascular recovery.* Both experimental and clinical studies were considered, with emphasis on publications from the past decade. Earlier foundational works were included when necessary to maintain mechanistic and conceptual continuity. Eligible studies comprised peer-reviewed original research, meta-analyses, and reviews addressing genetic, epigenetic, or molecular determinants of stroke risk and recovery, particularly within aging or comorbidity contexts. Articles focusing exclusively on hemorrhagic stroke or non-mammalian models were excluded.

Information extracted from the literature was organized across five thematic domains: (1) comorbidity-associated vascular aging and oxidative stress; (2) genetic determinants of ischemic susceptibility and outcome; (3) epigenetic and noncoding RNA regulation of repair; (4) longitudinal molecular remodeling; and (5) translational integration of multi-omic and precision medicine frameworks. The synthesis prioritized mechanistic convergence, causal inference, and clinical applicability rather than isolated molecular associations, aiming to construct an integrative framework linking molecular regulation with age-dependent stroke recovery potential.

RESULTS AND DISCUSSION

In aging populations, chronic comorbidities critically shape both the onset and outcome of ischemic stroke by promoting systemic inflammation, endothelial dysfunction, and oxidative stress. Persistent hyperglycemia in diabetes drives mitochondrial overproduction of reactive oxygen species (ROS), activates NF-κB signaling, and disrupts nitric oxide bioavailability, resulting in sustained vascular stress [17–20]. Similarly, hypertension induces oxidative injury through angiotensin II–dependent activation of NADPH oxidase, leading to endothelial barrier disruption and microvascular rarefaction. These processes amplify blood–brain barrier (BBB) permeability and promote leukocyte infiltration, effectively linking peripheral inflammation with central neuroinflammatory cascades [21–26]. Within the aging cerebrovasculature, chronic oxidative and metabolic stress impair angiogenesis and neurogenesis, while microglia adopt a pro-inflammatory phenotype that undermines synaptic remodeling [25,27–29].

The convergence of diabetes-, hypertension-, and atrial fibrillation–related mechanisms establishes an inflammatory and hypoxic milieu that restricts neuroplasticity after ischemia. Chronic hyperglycemia promotes the accumulation of advanced glycation end-products, pericyte loss, and sustained microvascular inflammation, culminating in impaired endothelial nitric oxide signaling and diminished cerebrovascular reactivity [6,18,30,31].

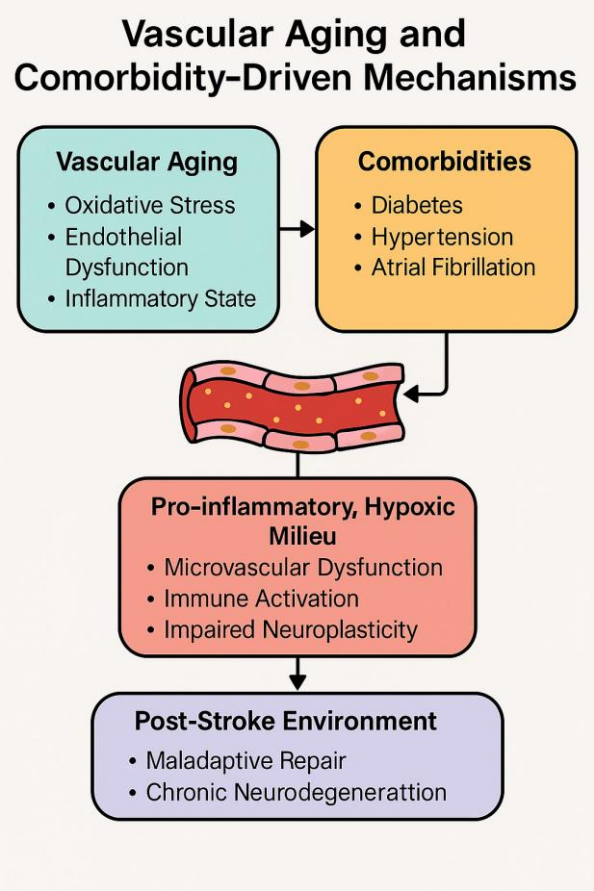

Figure 1. Vascular Aging and Comorbidity-Driven Mechanisms in Post-Stroke Pathophysiology. This diagram illustrates how vascular aging and systemic comorbidities converge to create a maladaptive environment that impairs recovery after stroke. Chronic oxidative stress, endothelial dysfunction, and low-grade inflammation interact with comorbid conditions such as diabetes, hypertension, and atrial fibrillation, promoting a pro-inflammatory, hypoxic milieu characterized by microvascular dysfunction, immune activation, and reduced neuroplasticity. These cumulative effects establish a post-stroke environment dominated by maladaptive repair and progressive neurodegeneration, defining the molecular landscape of recovery failure in the aging brain.

Hypertensive vascular remodeling further exacerbates oxidative stress and disrupts neurovascular coupling via NADPH oxidase–mediated endothelial injury [25,32]. In atrial fibrillation, systemic inflammation and endothelial senescence synergistically promote microthromboembolism and chronic hypoperfusion, accelerating white matter degeneration and constraining synaptic recovery [6,33,34].

Collectively, these comorbidity-driven perturbations sustain a pro-inflammatory, hypoxic, and metabolically inflexible state within the neurovascular unit, disrupting astrocyte–neuron communication and impairing axonal sprouting. Such interrelated processes exemplify comorbidity-driven vascular aging—a cumulative molecular trajectory that primes the aging brain for maladaptive repair and heterogeneous recovery outcomes following ischemia. The interplay between metabolic inflammation, endothelial dysfunction, and immune dysregulation not only governs infarct evolution but also determines long-term circuit reorganization and cognitive resilience [34–39]. Thus, vascular aging should be viewed as a dynamic, progressive process that dictates whether the post-stroke environment fosters neurorepair or perpetuates chronic neurodegeneration (Fig. 1).

Genomic Architecture and Heritable Modifiers of Stroke Outcome

Genetic variation exerts a substantial influence on both susceptibility to and recovery from ischemic injury. Large-scale genome-wide association studies (GWAS) have identified numerous loci associated with ischemic stroke risk and outcome, implicating pathways that regulate vascular tone, endothelial integrity, coagulation, and inflammation [40–42]. Polymorphisms in *HDAC9* have been consistently replicated in large-vessel ischemic stroke and are thought to modulate vascular remodeling and atherosclerotic progression [43]. Additional loci linked to vascular integrity, lipid metabolism, and inflammatory signaling, including 9p21 (*ANRIL*), *SORT1*, and *PITX2*, highlight the polygenic nature of ischemic stroke susceptibility [41].

The GISCOME consortium meta-analysis of post-stroke functional outcomes identified genome-wide and suggestive loci near *TEK*, *NTN4*, and *PTCH1*, connecting vascular development and angiogenic signaling to recovery trajectories [44]. More recently, multi-ancestry GWAS demonstrated that early neurological instability after ischemic stroke is partially heritable, with eight loci reaching genome-wide significance and common variants explaining approximately 9% of the variance in early functional change [45]. Variants influencing coagulation, platelet function, and vascular signaling, such as those at the ABO locus and within Hedgehog pathway, associated regions, may further modulate infarct size, recurrence risk, and microvascular repair capacity [41,43]. Beyond risk, recovery-specific loci implicated in synaptic plasticity, angiogenesis, and neurovascular remodeling

suggest that heritable regulation also governs post-ischemic repair processes [46].

Complementary transcriptomic studies reveal that early peripheral blood gene-expression profiles, particularly those linked to inflammatory and metabolic pathways, correlate strongly with 90-day functional outcomes, underscoring the significance of gene, environment interactions in recovery [46]. Systematic analyses have identified more than 70 polymorphisms across vascular, inflammatory, and metabolic pathways associated with post-stroke disability and recurrence risk, emphasizing the importance of heritable modulation in neurovascular repair and plasticity [47] (Fig. 2).

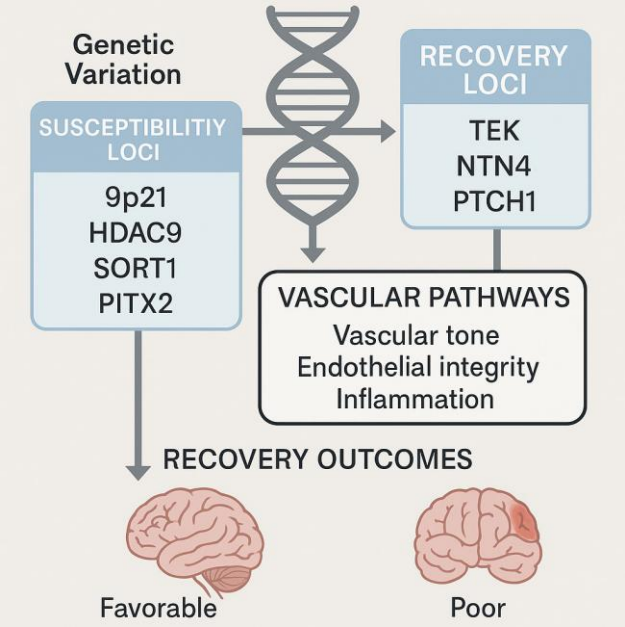

Figure 2. Genetic determinants of stroke susceptibility and recovery outcomes. Schematic representation of how distinct genetic loci influence stroke pathophysiology and recovery trajectories. Susceptibility loci (*e.g., 9p21, HDAC9, SORT1, PITX2)* are associated with increased stroke risk, whereas recovery loci (e.g., *TEK, NTN4, PTCH1*) modulate post-stroke repair processes. These genetic variants converge on vascular pathways regulating vascular tone, endothelial integrity, and inflammation, ultimately shaping recovery outcomes ranging from favorable to poor.

Neuroimaging biomarkers, including white matter hyperintensity (WMH) load, cortical thickness, and infarct topology, contribute to outcome prediction and may reflect underlying genetic influences [48]. Recent studies show that polygenic risk scores (PRS) for ischemic stroke and cerebral small-vessel disease correlate with cognitive decline and WMH burden even in individuals without overt stroke [49]. A 2024 GWAS examining WMH-associated cortical atrophy identified 20 genome-wide significant loci enriched for vascular and glial gene expression and demonstrated that a WMH-based PRS predicts dementia risk [50]. Similarly, the STRONG cohort identified genetic associations with cognitive and mood outcomes one year after stroke, supporting the heritable modulation of recovery trajectories [51].

Recent multi-ancestry meta-analyses integrating genomic, transcriptomic, and epigenomic data have advanced understanding of the molecular mechanisms underlying stroke susceptibility and resilience [52]. These analyses have identified pleiotropic loci associated with vascular tone, coagulation, and immune regulation across diverse ancestries and have linked these loci to transcriptional and proteomic networks involved in vascular remodeling and inflammation [53]. Integrating such genomic insights with dynamic neuroimaging metrics, for example, collateral flow efficiency or perfusion recovery, offers the potential to refine prognostic classification beyond conventional vascular risk factors.

Together, these findings indicate that genetic variation shapes not only stroke susceptibility but also the trajectory of network reorganization and long-term cognitive resilience after ischemia. Integrating genetic and neuroimaging data provides complementary insights into stroke vulnerability and recovery potential. Despite these advances, the predictive accuracy of current integrative models remains limited. A recent meta-analysis found that polygenic scores for recurrent stroke performed inconsistently across cohorts, emphasizing the need for improved phenotypic resolution and greater cohort diversity [54]. Moreover, most genetic studies remain dominated by populations of European ancestry, and functional validation linking variants to biological pathways, such as neurovascular repair or astrocyte–neuron coupling, remains scarce. To achieve true clinical translatability, predictive frameworks must move beyond static genotype associations toward mechanistically informed models that incorporate gene, environment interactions, comorbidity profiles, and aging-dependent molecular drift [55]. Future progress will depend on longitudinal, multi-omics–enhanced imaging cohorts that connect genetic architecture to temporal dynamics in neurovascular remodeling and treatment response, paving the way for biologically grounded precision medicine in stroke [55–57].

Epigenetic Remodeling in the Ischemic and Aging Brain

Epigenetic mechanisms form a dynamic interface between environmental exposures, comorbid metabolic stress, and gene-expression responses to ischemic injury, influencing both stroke susceptibility and recovery

potential. These molecular modifications, including DNA methylation, histone remodeling, and noncoding RNA regulation, mediate the translation of metabolic and inflammatory cues into long-lasting transcriptional changes (Fig. 3).

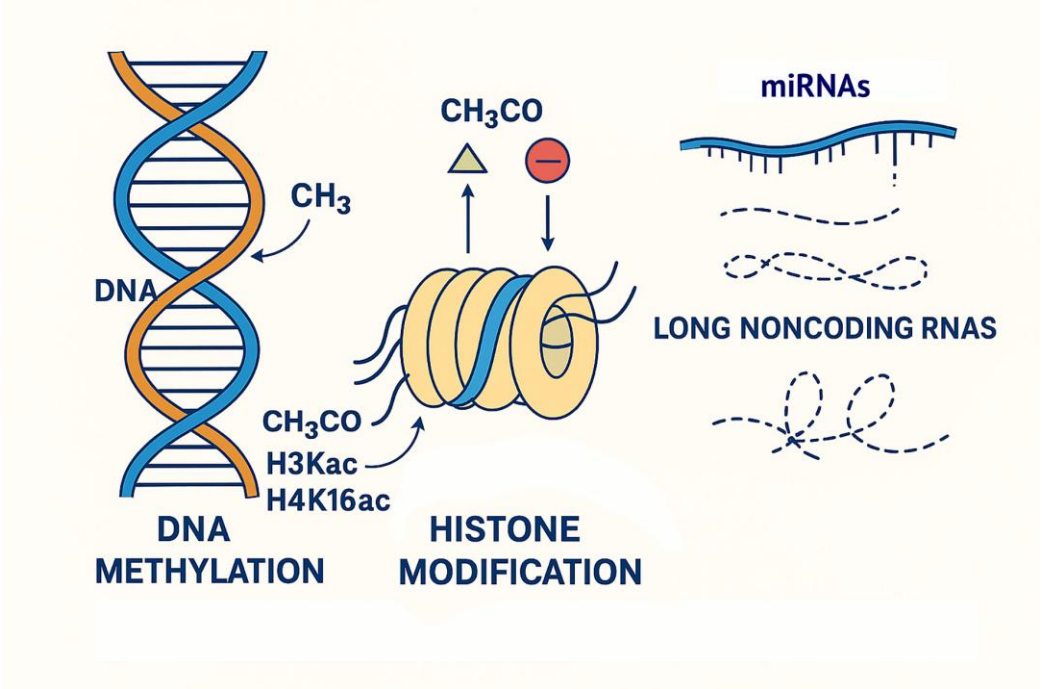

Figure 3. Epigenetic and noncoding RNA mechanisms of gene regulation. Illustration of key epigenetic processes that modulate gene expression without altering DNA sequence. DNA methylation involves the addition of methyl groups (CH_3) to cytosine residues, typically leading to transcriptional repression. Histone modifications, such as acetylation (CH_3CO) at histone residues (H3Kac, H4K16ac), alter chromatin accessibility and influence gene activation or silencing. In parallel, noncoding RNAs—including microRNAs and long noncoding RNAs—regulate gene expression post-transcriptionally or through chromatin remodeling, forming an integrated layer of epigenetic control.

DNA Methylation and Vascular Pathophysiology

Epigenome-wide association studies (EWAS) have identified differential DNA methylation patterns that contribute to vascular pathology and recurrence risk after ischemic stroke. In patients treated with clopidogrel, hypomethylation of *TRAF3* (cg03548645) was associated with increased vascular recurrence and enhanced platelet aggregation, while hypermethylation of *PPM1A* (cg04985020) predicted recurrent vascular events among aspirin-treated patients [58,59]. These findings indicate that DNA methylation modulates drug response and vascular risk in the post-stroke setting.

Epigenetic regulation of vascular remodeling genes also influences structural vessel pathology. In two independent ischemic stroke cohorts (n ≈ 320), elevated promoter methylation of *CDKN2B* correlated with increased carotid and aortic arch calcification, independent of traditional cardiovascular risk factors [60,61]. This connects the 9p21 locus, long implicated in atherogenesis, to an epigenetic mechanism impairing vascular repair. Similarly, global and *LINE-1* hypomethylation correlate with elevated *VCAM1* expression and ischemic risk, supporting the existence of a methylation, inflammation axis linking metabolic stress to vascular dysfunction [62]. Collectively, these observations demonstrate that methylation dynamics in inflammatory and repair-related pathways form a mechanistic bridge between environmental stressors and recurrent vascular injury.

Histone Remodeling and Chromatin Adaptability

Histone acetylation states critically influence neuronal survival after ischemia. Reduced acetylation of histones H3 and H4 is consistently observed in ischemic brain tissue and correlates with neuronal death, whereas inhibition of histone deacetylases (HDACs) restores pro-survival transcriptional programs, promotes angiogenesis, and limits apoptosis [12, 63]. Evidence from ischemia–reperfusion models implicates *HDAC4* in endothelial injury, suggesting that isoform-specific *HDAC* inhibition may help preserve blood–brain barrier integrity and support neurogenesis [64].

Aging, Epigenetic Drift, and Ischemic Vulnerability

In the aging brain, cumulative epigenetic drift interacts with ischemic stress to sustain pro-inflammatory signaling, impair mitochondrial bioenergetics, and reduce chromatin flexibility [3]. Age-related erosion of DNA methylation fidelity, quantified through "epigenetic clocks," tracks biological aging and predicts adverse cerebrovascular outcomes [65–68]. Concurrently, cerebral ischemia induces global hypoacetylation of histones H3 and H4, which can be reversed by *HDAC* inhibition to restore neuronal resilience through activation of trophic and plasticity-related loci such as *BDNF* [68–71].

Microglial priming further amplifies this maladaptive epigenetic landscape. Prior exposure to inflammatory or metabolic stress imprints persistent histone and methylation signatures that bias microglia toward exaggerated pro-inflammatory responses during subsequent ischemic insults [72,73]. This process contributes to a chronic, self-sustaining inflammatory tone within the aged neurovascular unit (Fig. 4).

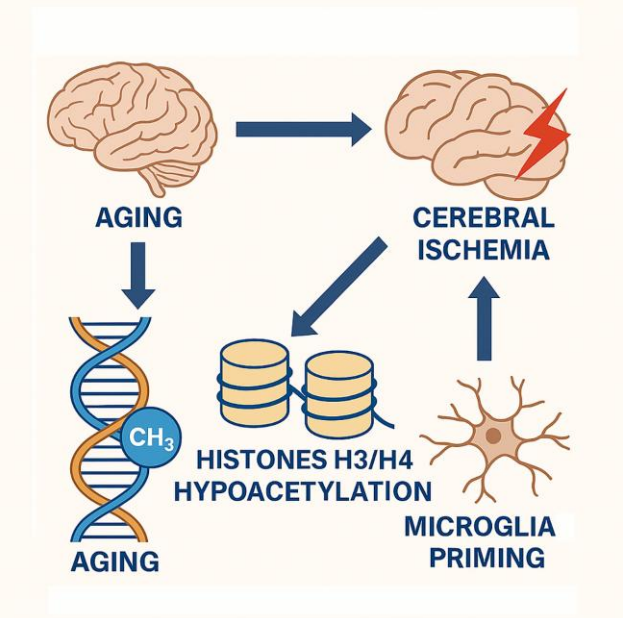

Figure 4. Aging-related epigenetic drift and ischemic vulnerability. Schematic representation of how aging-associated epigenetic alterations increase susceptibility to ischemic injury. Progressive epigenetic drift, illustrated by altered DNA methylation (CH_3), leads to chromatin instability and impaired gene regulation. Concurrently, ischemic stress promotes global hypoacetylation of histones H3/H4, further restricting transcription of neuroprotective and plasticity-related genes. Microglial priming—shaped by prior inflammatory or metabolic challenges—enhances pro-inflammatory reactivity during ischemia, reinforcing a maladaptive cycle of neurovascular dysfunction and poor recovery in the aging brain.

Epigenetic Memory and Functional Consequences

The cumulative outcome of these changes is the establishment of an "epigenetic memory" of vascular injury, a rigid chromatin configuration that perpetuates inflammatory gene expression, limits synaptic and vascular regeneration, and diminishes responsiveness to rehabilitative stimuli [74–76]. Even under optimal management of vascular risk factors, this retained rigidity constrains the brain's regenerative capacity and may drive the progressive neurodegenerative trajectory often observed after stroke in older individuals [3,75] (Fig. 5).

Restoring Epigenetic Plasticity

Preclinical studies indicate that re-establishing epigenetic plasticity can enhance recovery in the aging brain. Broad and selective *HDAC* inhibitors restore histone acetylation at promoters of neurotrophic and metabolic genes, suppress microglial activation, and promote angiogenesis and synaptic recovery after ischemic injury [68,71,77]. Metabolic interventions that increase acetyl-CoA availability or improve mitochondrial function can similarly reverse histone hypoacetylation and rejuvenate transcriptional flexibility, improving post-ischemic plasticity and functional outcomes [78,79]. Collectively, these findings support the concept that targeting epigenetic rigidity, particularly in aged neural tissue, represents a promising strategy to promote neurorepair and resilience following stroke.

Epigenetic and Post-Transcriptional Remodeling in Stroke and Aging: Circular RNAs as Regulatory Hubs

In parallel with canonical ischemic injury cascades, epigenetic and post-transcriptional mechanisms recalibrate gene expression after stroke. Human and experimental studies reveal dynamic DNA methylation changes at stroke-relevant loci associated with both outcome (e.g., *EXOC4*) and vascular pathology (e.g., *CDKN2B*), while global histone acetylation declines after ischemia and can be counteracted by *HDAC* inhibition to support pro-survival and pro-angiogenic programs [60,80,81].

At the post-transcriptional level, circRNA–miRNA interactions fine-tune astroglial activation and autophagy, adding a regulatory layer that integrates with chromatin and transcriptional control. For example, circHECTD1 modulates astrocyte activation and inflammatory signaling, demonstrating the dual epigenetic and post-transcriptional regulation of neurovascular recovery [82,83].

These mechanisms are strongly age-modulated. Epigenetic clock studies show that stroke patients

frequently exhibit accelerated biological aging, while aging-related DNA methylation drift and blood–brain barrier (BBB) repair deficits reduce the transcriptional flexibility of neurons and endothelial cells. This shift biases the post-stroke environment toward persistent inflammation and diminished plasticity [66,76]. Collectively, these observations support a phased transition from early inflammatory and apoptotic bias to later metabolic and neuroplasticity-associated programs, with aging determining both the magnitude and timing of these molecular transitions [76,80].

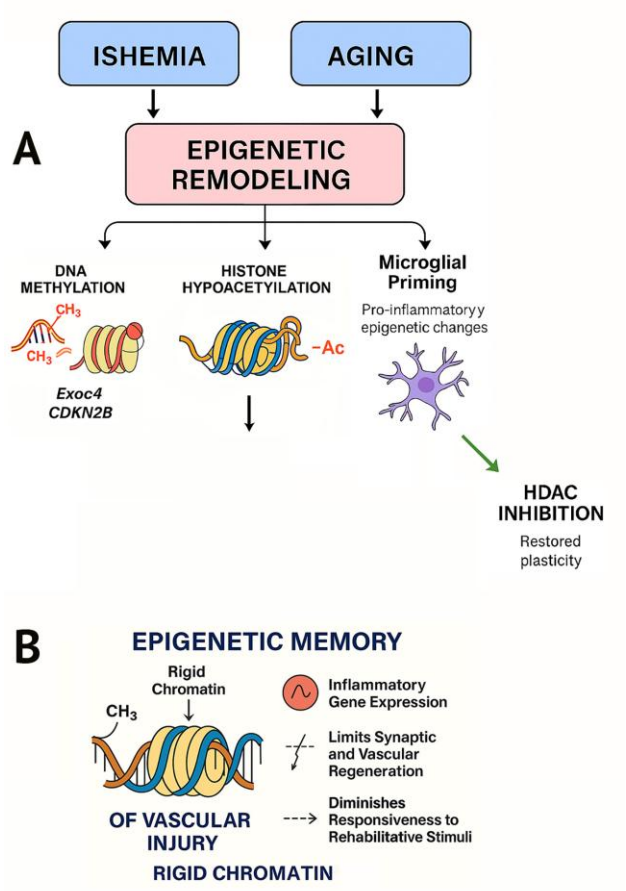

Figure 5. Epigenetic remodeling and memory in ischemia and aging. (A) Schematic overview of ischemia- and aging-induced epigenetic remodeling. Both stressors trigger DNA methylation changes at stroke-relevant loci (e.g., *EXOC4*, *CDKN2B*) and global histone hypoacetylation, leading to reduced chromatin accessibility and transcriptional repression. In parallel, microglial priming establishes a pro-inflammatory epigenetic phenotype that amplifies neuroinflammatory responses upon secondary insults. Pharmacological HDAC inhibition counteracts hypoacetylation, restoring chromatin plasticity and neurovascular resilience. **(B)** Concept of epigenetic memory of vascular injury. Persistent chromatin rigidity maintains inflammatory gene expression and limits both synaptic and vascular regeneration. This maladaptive "memory" diminishes the brain's responsiveness to rehabilitative stimuli, contributing to chronic inflammation and impaired recovery after stroke.

Circular RNAs as Integrative Regulators

Within this multilayered regulatory landscape, circular RNAs (circRNAs) have emerged as central post-transcriptional hubs linking epigenetic control, cellular signaling, and intercellular communication. CircRNAs function as microRNA sponges, decoys for RNA-binding proteins, and scaffolds for transcriptional and translational complexes [84,85]. Their closed-loop structure provides exceptional stability, making them both reliable biomarkers and mechanistic effectors in ischemic pathology.

Several circRNAs, including circHECTD1 and circDLGAP4, modulate inflammatory signaling and endothelial barrier function, influencing astrocyte activation and BBB integrity [82,86]. Others, such as circFUNDC1 and circPDS5B, regulate mitochondrial autophagy, vascular remodeling, and cell survival, thereby linking energy metabolism to neurovascular homeostasis [87]. Through these functions, circRNAs integrate metabolic, inflammatory, and reparative signals across cellular compartments following ischemia.

Exosomal circRNAs and Neurovascular Communication

Exosomal circRNAs extend this regulatory role by mediating intercellular communication among neurons, astrocytes, microglia, and endothelial cells [83,88,89]. Distinct exosomal circRNA profiles have been described in large-artery atherosclerotic stroke, supporting their diagnostic and mechanistic potential [90,91]. Acting as vesicle-borne molecular shuttles, circRNAs such as circTLK1 and circHIPK2 deliver regulatory RNAs and proteins across the neurovascular unit, modulating angiogenesis, axonal regeneration, and apoptosis through interactions with miR-335 and miR-124, respectively [92,93].

Aging, circRNA Remodeling, and Epigenetic Convergence

In the aging brain, altered circRNA biogenesis and vesicular cargo composition reflect cumulative oxidative and metabolic stress, which disrupts neuron, glia signaling and diminishes regenerative capacity [94,95]. These changes likely contribute to the reduced neuroplasticity and slower recovery trajectories observed in older stroke survivors. Importantly, multi-omics studies reveal that circRNA, miRNA, mRNA regulatory circuits operate within broader epigenetic frameworks, influencing chromatin accessibility and RNA splicing in an age-dependent manner [96,97] (Fig. 6).

Future Directions

Defining the causal roles of circRNAs in ischemic resilience and aging will require advanced functional genomics. Emerging tools such as CRISPR/Cas13-based circRNA editing, combined with single-cell multi-omics, provide new avenues for dissecting these regulatory networks [98]. Applying such technologies to longitudinal and age-stratified models will be essential to uncover how circRNAs coordinate metabolism, inflammation, and repair across the aging neurovascular system.

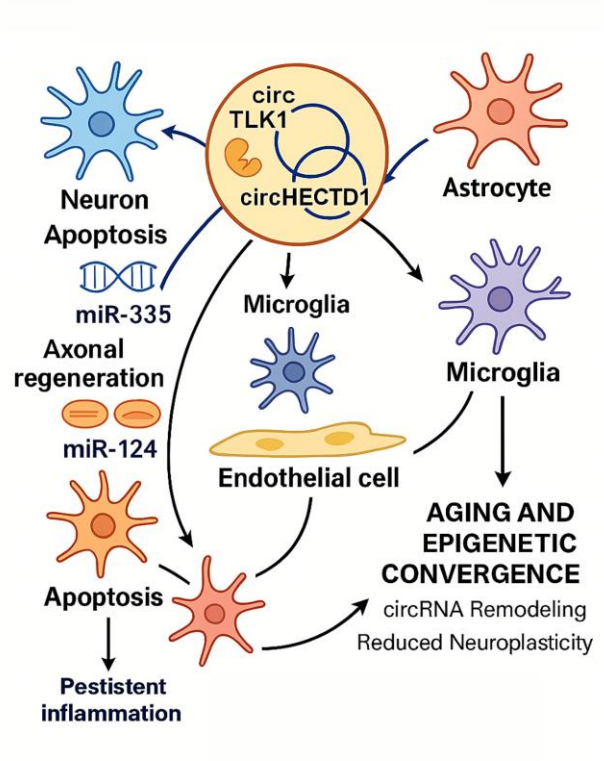

Figure 6. Exosomal circRNAs and neurovascular communication across aging and ischemia. Schematic representation of exosomal circular RNAs (circRNAs) as mediators of intercellular signaling within the neurovascular unit. Exosomes containing circTLK1, circHIPK2, and circHECTD1 shuttle regulatory RNAs and proteins between neurons, astrocytes, microglia, and endothelial cells. These vesicle-borne circRNAs interact with miR-335 and miR-124 to modulate apoptosis, axonal regeneration, angiogenesis, and inflammatory responses. In parallel, aging-related oxidative and metabolic stress alter circRNA biogenesis and vesicular cargo composition, driving circRNA remodeling and reduced neuroplasticity. The convergence of these processes promotes persistent inflammation and impaired recovery, linking exosomal RNA communication with epigenetic dysregulation in the aging brain.

Temporal Molecular Dynamics During Recovery

Recovery after ischemic stroke is a dynamic, multi-phasic process in which molecular priorities evolve from acute injury containment to tissue remodeling and network reorganization. The temporal sequence of these molecular events reflects coordinated transcriptional, epigenetic, and cellular adaptations that determine long-term functional outcomes, particularly in the aging brain.

Acute Phase: Injury Containment and Inflammation

During the acute phase, ischemia rapidly activates inflammatory, apoptotic, and oxidative stress pathways that shape the initial injury environment [11, 83, 99]. Glial cells and infiltrating immune populations release cytokines, reactive oxygen species, and proteolytic enzymes, contributing to secondary damage but also initiating early repair signaling. These responses are tightly regulated by transcriptional bursts and chromatin remodeling that define the early inflammatory landscape.

Subacute Phase: Transition to Repair

As the response progresses into the subacute phase, gene-expression programs shift toward repair and reorganization. Upregulation of angiogenic mediators such as VEGFA and ANGPT2, extracellular matrix remodeling enzymes, and neurotrophic factors including BDNF and NGF supports angiogenesis, synaptic plasticity, and axonal sprouting [100-102]. Small extracellular vesicles (sEVs) derived from mesenchymal stromal cells (MSCs) have been shown to reduce macrophage infiltration and promote angiogenesis in aged rodent models, underscoring the potential of vesicle-mediated interventions to rejuvenate vascular repair [103, 104].

Epigenetic and Post-Transcriptional Remodeling

Concurrently, epigenetic and post-transcriptional mechanisms, including DNA methylation, histone acetylation, and circRNA, miRNA interactions, recalibrate transcriptional activity toward recovery. These modifications reflect adaptive reprogramming of neuronal and glial identity, supporting a shift from pro-inflammatory to pro-regenerative molecular states. Longitudinal transcriptomic and methylomic profiling reveals distinct temporal waves of regulation: early pro-inflammatory and cell-death signatures give way to metabolic, synaptic, and neuroplasticity-associated networks that dominate later phases of repair. In aged individuals, however, this sequence is frequently delayed or blunted. Age-associated methylation drift, histone hypoacetylation, and altered noncoding RNA regulation

attenuate the flexibility of these molecular transitions, biasing the system toward persistent inflammation and incomplete regeneration.

Chronic Phase: Remodeling and Plasticity

During the chronic phase, molecular programs stabilize around pathways governing axonal remodeling, synaptic connectivity, and circuit reorganization. Persistent low-grade inflammation, metabolic rigidity, and epigenetic memory of ischemic injury constrain recovery potential, particularly in aged or comorbid brains. Restoration of chromatin plasticity and energy metabolism during this stage may be critical to sustain long-term neurorepair and cognitive resilience.

From Association to Causation: Functional Genomics and Epigenetic Pharmacology in Stroke Recovery

Beyond Cross-Sectional Biomarkers: The Need for Dynamic Multi-Omic Integration

Most biomarker and omics studies in stroke remain cross-sectional, limiting insight into the temporal orchestration of molecular recovery mechanisms. Integrating time-resolved multi-omic datasets, encompassing genomics, transcriptomics, proteomics, and metabolomics, with advanced neuroimaging biomarkers could delineate distinct, phase-specific therapeutic windows. Interventions such as HDAC inhibition, microRNA modulation, or metabolic enhancement may yield maximal benefit when synchronized with the brain's intrinsic molecular rhythms of repair. Such a phase-aligned, multi-omic approach provides a biologically grounded framework for optimizing post-stroke recovery, particularly in the context of vascular aging and interindividual heterogeneity.

From Association to Mechanism: Functional Validation and Modeling Platforms

Despite abundant associative data linking genes, epigenetic regulators, and noncoding RNAs to ischemic outcomes, causal validation remains limited. Translating statistical associations into mechanistic understanding requires direct perturbation under disease-relevant conditions.

For endothelial pathways critical to stroke and vascular risk, *HDAC9* has been functionally linked to endothelial injury and endothelial to mesenchymal transition (EndMT), its upregulation worsens cerebral ischemia–reperfusion injury and apoptosis, whereas silencing mitigates damage. Genetic manipulation of *HDAC9* in endothelial cells induces EndMT and destabilizes plaque phenotype, underscoring a causal barrier-stabilizing role consistent with GWAS findings [105].

Unbiased functional genomics approaches, such as pooled CRISPR–Cas9 screens in 3D endothelial culture, have mapped epigenetic modifiers governing endothelial survival under VEGFA pathway stress, establishing tractable links between omic discovery and biological mechanism [106]. Similarly, CRISPR interference and activation (CRISPRi/a) tools validated in neurons now permit enhancer and promoter perturbation under oxygen–glucose deprivation conditions, extending mechanistic interrogation to neuronal models [107].

To capture the human genetic and cellular context, iPSC-derived stroke models expose patient-specific neurons to ischemia-like stress in real time, while brain and neurovascular organoids recapitulate multicellular crosstalk, angiogenesis, and glial reactivity [108–111]. Together, these human-relevant systems complement rodent models and form the experimental foundation for causal validation of molecular candidates identified through omics.

Epigenetic Pharmacology: From Mechanism to Translation

Epigenetic pharmacology provides a powerful parallel approach for functional validation and therapeutic exploration. Broad-spectrum histone deacetylase inhibitors, such as valproic acid (VPA) and sodium butyrate (NaB), consistently confer neuroprotection and enhance repair in preclinical stroke models. VPA reduces infarct volume and increases histone acetylation following transient focal ischemia, whereas NaB attenuates ischemia–reperfusion injury and dampens neuroinflammation in rodents [111–113].

At the DNA methylation level, inhibition of DNA methyltransferases (DNMTs) with 5-aza-2′-deoxycytidine or decitabine protects against ischemic damage and decreases astrocytic methylation, implicating methylation dynamics in delayed injury [114]. At the "reader" layer, BET bromodomain inhibition suppresses neuroinflammation and limits infarct expansion in ischemia–reperfusion models, demonstrating the tractability of acetyl lysine recognition as a therapeutic target [115,116].

Selectivity and timing remain pivotal for clinical translation. HDAC9, a stroke-relevant isoform with vascular roles, illustrates the importance of isoform-specific targeting and phase aware dosing [104]. Beyond small molecules, RNA-based therapeutics provide precise and reversible modulation. MicroRNA mimics or antagomirs, for example miR-122 and miR-181, improve outcomes in rodent middle cerebral artery occlusion

(MCAO) models, and antisense oligonucleotides targeting epigenetic enzymes such as Hdac2 have proven feasible in the CNS [117,118].

Aging as a Determinant of Epigenetic Therapy Response

Aging profoundly modifies both the necessity for and the efficacy of epigenetic interventions after stroke. Brain endothelial and barrier functions undergo age-associated epigenetic drift, biasing repair toward chronic inflammation, BBB leakiness, and impaired angiogenesis [75]. Consequently, the therapeutic window for chromatin-modifying drugs narrows with age, emphasizing the need for biological age–based stratification in treatment design.

Nonetheless, several epigenetic agents retain efficacy in aged models. Delayed (>6 h) administration of sodium butyrate remains neuroprotective in older female rats, reducing BBB permeability and oxidative stress in early phases while enhancing IGF-1 signaling later in recovery [113]. Similarly, BET inhibition decreases infarct volume and inflammatory mediators in aged mice, confirming the feasibility of targeting acetyl-lysine readers in the senescent brain [119].

Integrative Multi-Omics and Precision Medicine Approaches

Integrative Multi-Omics: From Data to Mechanism

Bringing together genomic, epigenomic, transcriptomic, proteomic, and metabolomic datasets with clinical and imaging phenotypes enables the identification of convergent biological pathways in ischemic stroke. These integrated analyses link inherited risk, vascular pathology, and environmental influences into shared molecular mechanisms that govern injury and recovery.

General-purpose multi-omics frameworks such as MOFA+ and DIABLO decompose complex, multi-layer signals into latent biological factors or discriminative components, allowing investigators to distinguish shared versus modality-specific variation and to derive composite biomarker panels from heterogeneous data [120]. In stroke specifically, multi-omics datasets are now beginning to connect systemic and cerebrovascular responses with clinical outcomes. Integrated proteo-transcriptomic studies have identified candidate causal genes by combining brain and blood signatures, while endothelial multi-omics approaches have mapped reperfusion injury programs, revealing targetable inflammatory and barrier-related pathways [52].

Complementing DNA-based analyses, a multi-ancestry genomic meta-analysis demonstrated how genetic variation informs drug discovery and risk prediction across ancestries, emphasizing the importance of aligning downstream omics data to population-specific genetic architecture [51]. Moreover, small-RNA signatures in neuron-enriched extracellular vesicles (EVs) illustrate how circulating post-transcriptional markers can mirror ongoing neuronal injury, supporting the development of minimally invasive, mechanistically anchored biomarkers [121] (Fig. 7).

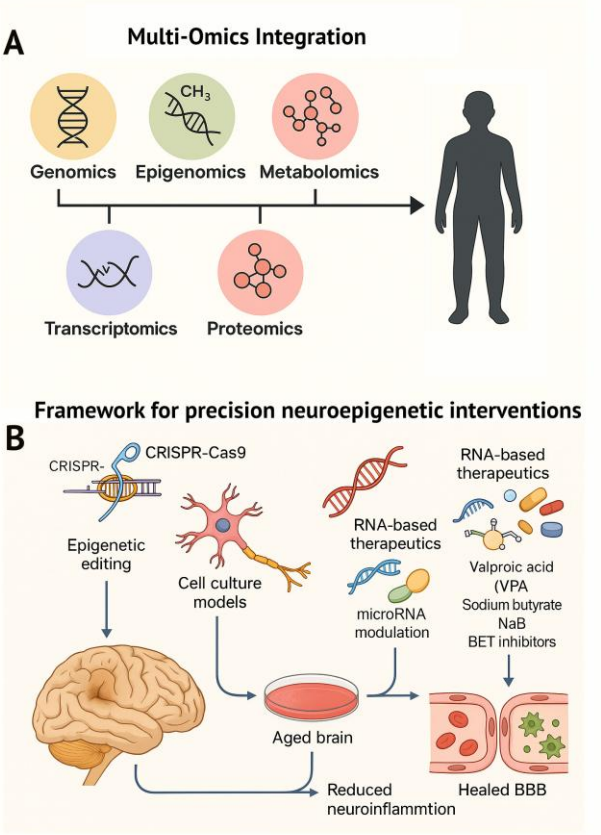

Figure 7. Integrative multi-omics and precision epigenetic therapeutics for neurovascular repair. (A) Schematic representation of multi-omics integration encompassing genomics, epigenomics, transcriptomics, proteomics, and metabolomics. The convergence of these data layers enables a systems-level understanding of molecular pathways driving stroke pathology, aging-related decline, and recovery potential. **(B)** Conceptual framework for precision neuroepigenetic interventions. CRISPR–Cas9-based epigenetic editing and cell culture models derived from the aged brain provide experimental platforms for mechanistic validation. RNA-based therapeutics, including microRNA modulators and histone deacetylase (HDAC)–targeting compounds (e.g., valproic acid, sodium butyrate, BET inhibitors), promote restoration of blood–brain barrier (BBB) integrity and reduction of neuroinflammation. Together, these approaches aim to reprogram maladaptive molecular states and enhance neurovascular repair in the aging brain.

Toward Biological-Age–Aware Stratification

These integrative approaches support biological endotyping, stratifying patients by molecular programs rather than demographic parameters alone. In aging populations, such stratification becomes particularly valuable because epigenetic age and methylome configuration, rather than chronological age, track biological resilience and recovery potential [3].

Epigenetic-clock and brain-specific methylome studies provide the conceptual and methodological foundation for incorporating biological age into stroke-omics models. Longitudinal profiling of methylation drift, histone balance, and non-coding RNA expression may allow for real-time assessment of neurovascular plasticity and recovery potential. In this framework, biological age functions not merely as a correlate of vulnerability but as a quantifiable molecular phenotype guiding therapeutic prioritization.

From Mechanism to Translation: Precision and Timing

To bridge molecular discoveries with actionable interventions, researchers are pairing multi-omic readouts with advanced neuroimaging and machine learning, creating multimodal predictive frameworks for diagnosis and outcome forecasting. Recent reviews underscore both the potential and the pitfalls of such integration, particularly challenges related to cohort size, bias, and harmonization, while advocating for prospective, standardized data pipelines in stroke research [122].

The next frontier involves temporal precision. Integrating multi-omics with phase-specific biological rhythms of recovery may enable dynamic therapeutic timing, where interventions such as HDAC inhibition, microRNA modulation, or metabolic enhancement are delivered at biologically optimal windows. This approach supports the concept of phase aligned, mechanism guided therapy, shifting clinical strategy from fixed treatment windows to molecularly adaptive care.

A Systems-Level Model for Neurorepair

Ischemic stroke represents the intersection of vascular aging, systemic comorbidity, and molecular regulation. Integrating genetic, epigenetic, and transcriptomic evidence reveals that recovery is not a discrete event, but a dynamic continuum of cellular reprogramming shaped by biological age, metabolic context, and environmental exposure. DNA methylation drift, histone remodeling, and noncoding RNA activity jointly modulate neurovascular plasticity, determining whether regenerative mechanisms are preserved or progressively lost with age.

Despite major advances in associative omics, most discoveries remain correlative. Establishing causality will require direct perturbation studies, including genome and epigenome editing, patient-derived stem cell and organoid models, and multi time point molecular profiling, to define how specific pathways drive repair or degeneration. Expanding these analyses to multi ancestry and comorbidity aware frameworks will further elucidate how systemic diseases such as diabetes, hypertension, and dyslipidemia imprint the molecular landscape of the aging brain.

Translationally, the convergence of genomic insight and epigenetic pharmacology is paving the way toward precision neurorepair. Genotype guided pharmacotherapy and targeted epigenetic modulators have already demonstrated proof of concept in preclinical studies. Integrating RNA based therapeutics and real time molecular diagnostics into clinical workflows could enable phase specific, personalized interventions that dynamically adapt to the evolving biology of the ischemic and aging brain.

Looking ahead, a systems level framework that unites vascular biology, multiomics, and neurorestoration offers a path to transform stroke care, from population level risk models to individualized, biology driven recovery. Within this paradigm, age is redefined not as a static risk factor but as a modifiable molecular trait, guiding the timing, selection, and intensity of interventions to maximize neurorepair and preserve cognitive resilience.

Author Contributions

D.F.P., M.A. and L.M. wrote the main manuscript text. T.R.D., D.H., and A.P.-W. reviewed and edited the manuscript. M.A and D.F.P prepared the figures. All authors have read and agreed to the published version of the manuscript.

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Competing interests

None

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