Cureus
Part of SPRINGER NATURE

Open Access Review Article

Bypassing the Blood-Brain Barrier: A Dual-Axis Framework for Huntington's Disease Utilizing Glymphatic-Lymphatic Clearance and In Situ Chaperone Synthesis

Review began 10/24/2026
Review ended 11/08/2026
Published 11/20/2026

© **Copyright** 2026
Chen. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.120006

Huan-Wei Chen [1]

1. Chiropractic, Private Chiropractic Practice, Vancouver, CAN

Corresponding author: Huan-Wei Chen, chen.huanwei.dc@gmail.com

Abstract

Huntington's disease (HD) is caused by a cytosine-adenine-guanine (CAG) repeat expansion in the *huntingtin* (HTT) gene, fully penetrant at 40 or more repeats and present in every cell from birth, with mutant huntingtin (mHTT) pathology concentrated earliest in striatal medium spiny neurons (MSNs). Huntingtin-lowering approaches now include invasive intrathecal and intrastriatal delivery and orally bioavailable splicing modifiers, and none has established clinical benefit in a confirmatory randomized comparison. This review proposes active craniospinal tensioning (ACT), a mechanical, non-pharmacological route that acts on cerebrospinal fluid (CSF) and cerebral venous pressure dynamics rather than requiring any molecule to cross the blood-brain barrier. ACT combines two concurrent mechanisms converging on a single venous-side target within Monro-Kellie/Queckenstedt pressure continuity: suboccipital venous occlusion-rebound, proposed to raise and release intracranial CSF pressure and accelerate venous-side glymphatic efflux, and dural pull-recoil, a reverse Queckenstedt effect in which spinal elongation is proposed to generate a CSF-side pressure gradient that agitates perivascular and interstitial fluid, mobilizing stagnant protein, while its coupled venous component joins occlusion-rebound in accelerating venous-side efflux. Because every MSN will eventually express mHTT regardless of intervention, the proposed route is disease-timeline modulation rather than propagation blocking: in cell and animal models, extracellular seeding-competent mHTT accelerates the stochastic nucleation step by which each MSN transitions to aggregation, so clearing that pool is proposed to reduce seed burden and delay nucleation in MSNs that have not yet crossed their threshold. The magnitude of any delay is unknown, and whether exogenous seeding meaningfully contributes to disease timing in humans, where somatic CAG expansion appears to set the pace, remains to be established.

A secondary, hypothesis-generating axis, cerebral venous preconditioning (CVPC), proposes that the same cycle activates heat shock factor 1 (HSF-1) across the neurovascular unit through vessel-wall strain, with a possible contribution from hypoxia-inducible factor 1-alpha (HIF-1α) left open. In HD, this axis faces a disease-specific obstacle, since mHTT drives proteasomal degradation of HSF-1 itself, and the primary claim does not depend on this axis. Because HD is identifiable by genetic testing decades before onset, benefit is predicted to concentrate in premanifest and early-manifest carriers, a stage-dependent gradient that the Huntington's Disease Integrated Staging System (HD-ISS) makes directly testable. Validation is staged, using operator-driven ACT at fixed parameters in carriers at HD-ISS Stages 1-2, with diffusion tensor image analysis along the perivascular space (DTI-ALPS) and plasma neurofilament light chain (NfL) as dual falsification endpoints over at least two years, and any disease-modification claim deferred to a randomized, delayed-start trial before extension to Stage 0 carriers as a preventive application. This framework is entirely theoretical, requires clinical validation, and extends a dual-axis template already proposed for Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS).

Categories: Neurology, Genetics, Preventive Medicine
Keywords: active craniospinal tensioning (act), cerebral venous preconditioning (cvpc), diffusion tensor image analysis along the perivascular space (dti-alps), dural pull-recoil, glymphatic-lymphatic clearance, heat shock factor 1 (hsf-1), huntington's disease (hd), mutant huntingtin (mhtt), plasma neurofilament light chain (nfl), suboccipital venous occlusion-rebound

Introduction And Background

Huntington's disease (HD) is a rare, autosomal dominant neurodegenerative disorder with a pooled global prevalence of 4.88 per 100,000; its incidence is significantly higher in Europe and North America than in Asia [1]. HD is caused by an expanded cytosine-adenine-guanine (CAG) trinucleotide repeat in exon 1 of the *huntingtin* (HTT) gene, first identified in 1993 [2], which produces an abnormally long polyglutamine tract in the huntingtin protein and results in progressive misfolding and aggregation. Alleles with 40 or more repeats are fully penetrant, whereas alleles with 36-39 repeats show reduced penetrance [3,4]. Clinically, HD manifests as a triad of progressive motor dysfunction (classically chorea), cognitive decline, and psychiatric disturbance, with the striatum, and specifically its medium spiny neurons (MSNs), affected earliest and most

severely, though cortical involvement is also observed as disease progresses [4]. At the time of writing, no therapy has received regulatory approval to slow or halt the underlying disease process; symptomatic treatments such as tetrabenazine address chorea but do not modify neurodegeneration [4].

This review has three aims. First, it summarizes current understanding of how HD progresses and the status of disease-modifying therapy. Second, it evaluates whether active craniospinal tensioning (ACT), a non-pharmacological maneuver described in the author's prior work, in which the seated individual is briefly lifted by the suboccipital contact so that body weight tensions the spinal dura and compresses the suboccipital venous plexus for a few seconds, could plausibly act on any part of that progression, distinguishing the established physiology on which it draws from its proposed and untested application to HD. Third, it outlines a preliminary research pathway by which that proposal could be tested and falsified. ACT has not been studied in HD, and every claim about its effect in this disease is hypothetical.

HD's causative mutation is a single expansion, identifiable through genetic testing decades before clinical onset. This is a defining structural feature of the disease, not an incidental one, and it has reshaped how the field approaches clinical research: the Huntington's Disease Integrated Staging System (HD-ISS), a consensus biological and clinical staging framework published in 2022, formally defines a premanifest stage extending from birth in gene-positive individuals through progressive biological, then clinical, then functional decline, explicitly enabling research and intervention trials before the classical motor-onset diagnosis that has historically anchored HD research [3]. Stage 1 is defined by measurable atrophy of the caudate and putamen on volumetric magnetic resonance imaging (MRI), the assessment that determines whether an individual has crossed into detectable neurodegeneration [3]; the same landmark is adopted as the progression endpoint for Tier 3 in the "Methodological framework" section. Biological change within this premanifest window can be detected long before symptoms: in young adult gene carriers, an estimated two decades or more from predicted onset, subtle elevations in cerebrospinal fluid (CSF) and plasma neurofilament light chain (NfL) have been reported in the absence of detectable clinical or cognitive impairment [5].

The pathogenesis of HD is contested across a wider range of proposed mechanisms than its single-gene cause might suggest, and this framework's claim should be read within that landscape, not as a stand-alone account. Transcriptional dysregulation, mitochondrial dysfunction, excitotoxicity, and impaired axonal transport are each independently supported as contributing mechanisms [4]. Most consequentially for this framework, genetic modifier studies indicate that the timing of onset is determined by the length of the uninterrupted CAG repeat rather than by polyglutamine length as such, implicating DNA repair-driven somatic expansion [6], and long somatic expansion of the repeat within individual striatal projection neurons has been shown to precede their degeneration [7]. None of these mechanisms is addressed here. Transcriptional dysregulation, mitochondrial dysfunction, and impaired axonal transport are intracellular or nuclear processes with no extracellular or perivascular transit step for a CSF-directed intervention to act upon. Excitotoxicity does involve the extracellular space, but it is a matter of synaptic and perisynaptic glutamate handling on a timescale of seconds, governed by astrocytic transporter capacity rather than by bulk perivascular fluid movement, and no effect on it is claimed here. This bears directly on the scope of the claim: if the disease clock in each MSN is set predominantly by intracellular somatic expansion, extracellular mechanisms can at most modify the pace of events within that clock, not determine it. The mechanism this framework does engage is the remaining thread, exogenous seeding of mutant huntingtin (mHTT) aggregation through the extracellular and perivascular space, and it is to this thread alone that the following sections apply.

At the center of this seeding thread is a kinetic rather than a propagating process. Aggregation of polyglutamine-expanded huntingtin proceeds through nucleated polymerization, a stochastic process in which each cell's transition from soluble to aggregated protein depends on a probabilistic nucleation event, the slow, chance-dependent formation of a stable aggregate core after which aggregation proceeds rapidly, with timing that varies across genetically identical cells expressing the same mutant protein, as characterized in a cell model [8]. If that nucleation step is rate-limiting, any factor that raises the local concentration of seeding-competent species would be expected to shorten the time to nucleation, since preformed aggregates, or seeds, can supply the core and bypass the slow step. Evidence from model systems indicates that such acceleration can occur from outside the cell: CSF from HD patients seeds mHTT aggregation in a reporter cell model [9], seeding-competent mHTT species have been detected in HD mouse brain with activity tracking disease progression [10], and mHTT propagates transneuronally across three model systems, including human neurons integrated into organotypic brain slices from an HD mouse model and the corticostriatal pathway in vivo, in a manner blocked by botulinum neurotoxins that inactivate the synaptic vesicle fusion machinery [11]. The one human in vivo observation in this group is the recovery of mHTT from genetically unrelated fetal striatal allografts in three patients who died roughly a decade after transplantation, where aggregates were found in the extracellular matrix of the grafted tissue; in the host brain, aggregates were present in neurons, neuropil, extracellular matrix, and blood vessels, placing seeding-competent material in the perivascular compartment this framework proposes to act on [12]. If extracellular seeds shorten the time to nucleation, faster removal of that extracellular pool through glymphatic clearance would be expected to lengthen it. This distinguishes HD from the propagating proteinopathies previously addressed in this series, such as Alzheimer's disease (AD) [13] and amyotrophic lateral sclerosis (ALS) [14], in which templated spread carries pathology into otherwise unaffected tissue. In

HD, every MSN carries the mutation and will eventually express mHTT regardless of what arrives from neighboring cells, so the relevant question is whether extracellular seed burden modifies the timing of each cell's transition to aggregation, not whether it determines that the transition occurs. Whether it does so to a degree that matters for disease timing in humans is not established, and is addressed in the "Limitations" section.

This same kinetic model sets an explicit boundary for a mechanical, CSF/perivascular intervention. No mechanism on the primary macro-fluidic axis acts on mHTT expression, on somatic repeat expansion, or on intracellular aggregation once nucleation has occurred within a given MSN; the secondary micro-biochemical axis is the only component proposed to act intracellularly, and it is addressed separately below. The claim is confined to the extracellular, seeding-competent mHTT pool and is meaningful only for MSNs that have not yet crossed their nucleation threshold at the time seed burden is reduced. Because the mutation is present from birth and fully penetrant, no intervention acting on the extracellular space can prevent the disease from occurring; the framework is scoped to modulating the disease timeline, and references below to preventive applications denote intervention before symptom onset rather than prevention of the disease itself. It predicts that any benefit should concentrate in premanifest and early-manifest carriers, in whom the proportion of MSNs still short of that threshold is greatest, although the validation pathway proposed below begins in carriers at HD-ISS Stages 1-2 rather than Stage 0, for reasons of endpoint sensitivity set out in the "Methodological framework" section.

Efforts to deliver disease-modifying agents illustrate the barrier constraint facing central nervous system-targeted therapeutics in HD. Huntingtin-lowering antisense oligonucleotides (ASOs) cannot cross the blood-brain barrier (BBB) and have required repeated intrathecal injection, bypassing rather than crossing the barrier [15]. An adeno-associated viral gene therapy, ifezuntirgene inilparvovec (AMT-130), is delivered by stereotactic neurosurgical infusion directly into the striatum. In ongoing Phase 1/2 studies, slower progression on a composite clinical rating scale has been reported at three years in high-dose participants relative to a propensity score-matched external natural-history comparison; at four years, in the smaller subset of participants reaching that timepoint, the prespecified comparison on the same scale did not reach statistical significance, while a measure of functional capacity continued to favor treatment [16]. A biologics license application seeking accelerated approval, supported by the three-year analysis and submitted before the four-year results were announced, was accepted by the US Food and Drug Administration for priority review in November 2026, with a decision pending [16,17].

Huntingtin lowering is also no longer confined to invasive delivery. Votoplam (formerly PTC518) is an orally bioavailable small-molecule splicing modifier that promotes degradation of HTT messenger RNA and reaches the central nervous system without intrathecal or intraparenchymal administration. It met its primary endpoint of blood HTT lowering in Phase 2 PIVOT-HD study, and in a 24-month interim analysis of an extension in which all participants received active drug, the sponsor reported dose-dependent slowing on the composite Unified Huntington's Disease Rating Scale relative to a propensity-weighted external natural-history cohort; a randomized Phase 3 trial is ongoing [18]. These are topline results that have not been peer-reviewed, and the comparison carries the external-control limitation addressed in the "Limitations" section.

Current HD-specific disease-modification efforts also illustrate a gap between engaging a molecular target and changing clinical progression, and they define the biomarker context in which any new intervention would be evaluated. The ASO tominersen, delivered by repeated intrathecal injection, lowered CSF mHTT in a dose-dependent manner, yet dosing in the Phase 3 GENERATION HD1 trial (NCT03761849) was halted, with the more frequently dosed arm faring worse than placebo on clinical outcomes [19]. A follow-up Phase 2 trial in younger, earlier-stage participants (GENERATION HD2, NCT05686551) enrolled 301 participants over a minimum 16-month treatment period and was discontinued in July 2026; according to the sponsor, it significantly lowered both mHTT and NfL relative to placebo without meaningful clinical benefit [20]. NfL is therefore a biomarker already used in HD disease-modification trials, but this result also shows that a favorable change in NfL indicates biological activity rather than clinical benefit, a distinction that the validation design proposed here adopts. No HD disease-modifying therapy has yet proven effective in a Phase 3 trial. This lack of precedent, rather than barrier access alone, which an orally bioavailable agent now partly addresses, motivates examining a non-pharmacological mechanism that acts on a different step: huntingtin lowering reduces mHTT production within cells, whereas the mechanism proposed here acts on clearance of mHTT already released into the extracellular space. The two are therefore not alternatives, and if both proved active, they could, in principle, be combined.

Evidence of glymphatic involvement in HD is limited but emerging. In a cohort of 49 mHTT carriers, 35 manifest and 14 premanifest, compared with 35 healthy controls, diffusion tensor image analysis along the perivascular space (DTI-ALPS) indices were reduced in carriers relative to controls and lower in manifest than in premanifest carriers, correlating with clinical manifestations and disease burden and corroborated by basal ganglia perivascular space analysis [21]. In a mouse model, CSF clearance efficiency measured by dynamic glucose-enhanced MRI was diminished before phenotypic onset and deteriorated with disease progression, corroborated by fluorescence CSF tracer influx imaging, and perivascular expression of the astroglial water channel aquaporin-4 (AQP4), a key mediator of glymphatic exchange, was reduced in both HD mouse brain and human HD brain [22]. Together, these findings are consistent with glymphatic dysfunction as a premanifest feature that worsens with progression rather than a late epiphenomenon,

though the human imaging evidence derives from a single cross-sectional cohort, with 14 premanifest carriers, in which a stage gradient cannot be distinguished from a cohort effect; the longitudinal evidence is from an animal model, and DTI-ALPS remains an indirect proxy whose interpretation as a glymphatic readout has been questioned [23]. No human study has yet shown that improving glymphatic function reduces mHTT seed burden or alters clinical outcomes in HD, and this remains a central untested premise of the present framework.

The paragraphs above summarize HD pathophysiology and the status of disease-modifying therapy as currently understood in the field; the remainder of this Introduction turns from established disease biology to the hypothesis this framework proposes, and readers should treat this as the point where established findings give way to this paper's own proposal.

The proposed mechanisms of ACT are developed in full in the companion AD and ALS frameworks [13,14] and are summarized only briefly here. Its primary hypothesis is the macro-fluidic axis, suboccipital venous occlusion-rebound and dural pull-recoil, proposed to act on Monro-Kellie/Queckenstedt pressure continuity to accelerate the passive venous-side efflux of the glymphatic system [14]. This continuity is the principle that, within the rigid skull, a change in venous blood volume is transmitted to CSF pressure, as shown by jugular compression, which raises CSF pressure and is the basis of the Queckenstedt test. Dural pull-recoil is proposed to act in the reverse direction, a reverse Queckenstedt effect in which spinal elongation generates a CSF-side pressure gradient. Its secondary, more speculative micro-biochemical axis, cerebral venous preconditioning (CVPC), proposes heat shock factor 1 (HSF-1) activation across the neurovascular unit, beginning at the vessel wall, with the contribution of hypoxia-inducible factor 1-alpha (HIF-1α) left open. ACT refers to the maneuver whether self-administered (ACT-SA) or operator-driven (ACT-OD), two forms proposed to be mechanically equivalent and described in prior technical reports [24-26]. This review extends that template to HD with three disease-specific considerations: the cell-autonomous etiology that narrows the macro-fluidic claim to timeline modulation, developed in “The macro-fluidic axis” below; the mHTT-driven degradation of HSF-1 itself [27] that gates the micro-biochemical axis, developed in “the micro-biochemical axis”; and the HD-ISS staging infrastructure that makes the predicted stage-dependent gradient directly testable, developed across both.

Review

Literature search methodology

This is a narrative, hypothesis-generating review rather than a systematic review, and no Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was generated. Because the physical and biochemical basis for ACT and CVPC was searched and developed in the companion AD and ALS frameworks [13,14], searches here targeted HD-specific literature. PubMed/MEDLINE was searched on November 8, 2026, without a lower date bound, using six search strings covering glymphatic and perivascular clearance and DTI-ALPS, mHTT seeding and propagation, somatic expansion and genetic modifiers of onset, huntingtin-lowering and gene therapies, HSF-1 and heat shock protein 70 (HSP70), and cancer incidence; the exact strings and the number of records retrieved by each are given in Table *1*. These were supplemented by reference-list snowballing and by targeted searches for individual claims, including HD-ISS staging, huntingtin-lowering trial status, and CSF mHTT and NfL biomarkers. Studies were eligible if they addressed one of these topics directly and were published in peer-reviewed journals. No language filter was applied, and all sources cited are published in English. Human trials, imaging and biomarker cohorts, epidemiological studies, animal models, and cell-based studies were all eligible, since each supports a different kind of claim. Conference abstracts, preprints, and other non-peer-reviewed sources were excluded, except trial status and topline results not yet published, which were taken from registry entries and sponsor communications and are cited as such rather than as evidence of efficacy. Priority was given to recent reviews, cohort studies, and trial reports. Source selection was conducted by a single reviewer (the author), without a second screener or formal risk-of-bias assessment, which carries a risk of selection bias. In place of formal appraisal, the type and level of evidence for each claim are identified as that claim is developed, distinguishing human from animal and cell-based evidence and HD-specific from extrapolated evidence, and summarized in the tables that accompany those sections. The literature is synthesized narratively, without meta-analysis, because the included studies differ too widely in design, population, model system, and outcome measure to permit quantitative pooling.

Topic	Search string	Records
Glymphatic clearance and DTI-ALPS	(“Huntington’s disease” OR huntingtin) AND (“glymphatic” OR “perivascular clearance” OR “DTI-ALPS”)	17
mHTT seeding and propagation	(“mutant huntingtin” OR mHTT) AND (“seeding” OR “prion-like” OR propagation OR “transneuronal”)	64
Somatic expansion and genetic modifiers	(“Huntington’s disease”) AND (“somatic expansion” OR “genetic modifier” OR “CAG repeat”) AND onset	572
Huntingtin-lowering and gene therapies	(“Huntington’s disease”) AND (“antisense oligonucleotide” OR “gene therapy” OR “huntingtin lowering” OR “blood-brain barrier”)	793
HSF-1 and HSP70	(“heat shock factor 1” OR HSF1 OR “heat shock protein 70”) AND (Huntington OR huntingtin)	112
Cancer incidence	(“Huntington’s disease”) AND (cancer OR neoplasm OR malignancy)	1055

TABLE 1: PubMed/MEDLINE search strings and number of records retrieved (searched November 8, 2026, no lower date bound)

CAG, cytosine-adenine-guanine; DTI-ALPS, diffusion tensor image analysis along the perivascular space; HSF-1, heat shock factor 1; HSP70, heat shock protein 70; mHTT, mutant huntingtin.

The macro-fluidic axis

Mechanical Clearance as a Route to Modulating Nucleation Timing

The physical basis for mechanical clearance via suboccipital venous occlusion-rebound and dural pull-recoil, grounded in the Monro-Kellie doctrine and the Queckenstedt test, is developed in full in the companion ALS framework [14] and is not re-derived here. The mechanism is proposed to be threshold-dependent: the applied force must be sufficient both to occlude the suboccipital venous plexus and to bring the dural sac to full tension [14]. The load specified in the ACT-OD technical report, 60%-70% of body weight [24], is the value for which the maneuver has been described and was proposed in the companion ALS framework as sufficient for both [14]. Neither threshold has an established value, and the relation between an applied axial load and transmural pressure at the plexus depends on contact area and intervening tissue, neither of which has been characterized [14]. The load is therefore specified for reproducibility rather than because it has been shown to exceed a known threshold.

The target of this clearance in HD is the extracellular, seeding-competent mHTT pool described in the "Introduction" [8-12]. Unlike ALS, where clearance is proposed to interrupt templating into otherwise unaffected cells [14], clearance in HD can act only on the rate at which MSNs cross their nucleation threshold, not on whether they cross it, and its magnitude in any individual depends on the proportion of MSNs that have not yet done so.

The safety consideration raised by deliberately provoking transient venous congestion, developed in the ALS framework [14], applies with added weight in HD, where involuntary movements, gait and balance impairment, dysphagia, and, in some patients, reduced awareness of their own symptoms are common [4]. The last point bears directly on the protocol, since the presyncopal endpoint depends on the participant perceiving and signaling symptom onset; the supervised delivery this implies is specified in the "Methodological framework" section below.

Anatomical Reach in HD

The anatomical reach of both mechanisms, whole-brain for occlusion-rebound via the shared craniocervical venous outflow bottleneck and craniospinal for dural pull-recoil via the continuity of CSF-filled perivascular space, is unchanged from the companion ALS framework [14]. What is HD-specific is how this reach relates to the disease's primary site of pathology.

HD's earliest and most severe pathology lies in the striatum [4], a deep supratentorial structure distant from the craniocervical junction. Unlike ALS, where the bulbar motor neuron pools occupy the medullary region immediately adjacent to ACT's craniocervical site of action [14], HD offers no anatomical proximity rationale, and the framework's claim rests entirely on the proposed whole-brain reach of both mechanisms. The basis for that reach is that the craniocervical venous outflow forms a common bottleneck for the entire intracranial compartment, so a pressure perturbation applied there is not regional in effect; in the upright seated position in which ACT is performed, cerebral venous drainage shifts substantially from the internal

jugular veins to the suboccipital venous plexus, so the suboccipital target lies on the dominant outflow route in that posture [14].

The whole-brain clearance proposed for occlusion-rebound through Monro-Kellie pressure continuity [14] depends on more than just pressure transmission. A uniform rise in intracranial pressure during the occlusion phase generates little gradient within the parenchyma, and convective movement of interstitial fluid depends on pressure gradients rather than on absolute pressure. The occlusion phase is therefore proposed to accumulate potential, and the rebound phase, when venous outflow resumes and pressure falls, to perform most of the clearance work, through differences in compliance between the venous, CSF, and interstitial compartments that could produce transient gradients along perivascular pathways during that transition. Whether such gradients arise in deep parenchyma, and whether they are large or sustained enough to move interstitial fluid at the level of the striatum, has not been characterized; this, rather than anatomical distance as such, is the principal uncertainty in the reach claim for HD.

Dural pull-recoil contributes to this reach in a complementary role developed in the companion ALS framework [14]. Its direct CSF-side pathway depends solely on the CSF-filled perivascular and interstitial spaces throughout the brain, and its coupled venous pathway is proposed to reach the intracranial compartment nearly uniformly via the rigid cranial vault. Cranially, its CSF-side role is proposed to be primarily agitatory, dislodging adherent protein throughout the perivascular and interstitial space and placing it in suspension for removal by its coupled venous component and the rebound phase of occlusion-rebound. Because HD's pathology lies predominantly in the brain, this cranial division of roles is the relevant one here, and the spinal role, in which pull-recoil performs both agitation and removal and which is load-bearing in ALS [14], is not required. Whether this agitation reaches the striatal interstitium has likewise not been characterized.

HD does, however, carry one measurement advantage. DTI-ALPS samples periventricular white matter at the level of the lateral ventricle bodies by fixed methodological necessity [23], and the caudate nucleus lines the wall of the lateral ventricle, so the proposed primary imaging endpoint samples tissue adjacent to HD's primary site of pathology. Consistent with this, glymphatic impairment in mHTT carriers has been reported specifically in periventricular white matter and in basal ganglia perivascular space [21]. This proximity remains a sampling advantage, not evidence of effect: DTI-ALPS is an indirect diffusivity measure and cannot itself confirm clearance activity within the striatum [23]. The same proximity also carries a liability specific to HD. Caudate atrophy and ventricular enlargement progress over the measurement intervals proposed here, altering the geometry of the region from which the index is derived, and the DTI-ALPS index is known to be sensitive to white matter geometry independent of perivascular diffusion [23]. Whether and in which direction this biases serial measurement in HD carriers has not been characterized, and it bears on the interpretation of a declining index, addressed in the "Limitations" section.

Because the relevant anatomy is broadly uniform across patients while the proportion of MSNs still short of their nucleation threshold is not, the heterogeneity that matters in HD is disease stage rather than anatomical site. HD-ISS defines this progression in four stages, from the presence of the expanded allele without detectable biological change through measurable striatal atrophy, the emergence of clinical signs, and functional decline [3]. An evidence-tiering approach across these stages offers a more defensible framing than a single, undifferentiated claim (Table *2*), reflecting the expected size of the pre-nucleation MSN pool rather than independently confirming efficacy at any tier.

HD-ISS stage	Evidence tier	Rationale
Stage 0 (expanded allele, no detectable biological change)	Suggestive	Largest proposed pool of MSNs not yet past their nucleation threshold; rests on nucleation-dependent aggregation kinetics and exogenous seeding evidence [8-12]; no clearance effect has been measured, and no biomarker change is yet detectable, which is why this stage is addressed in Tier 3, and in a parallel feasibility cohort, rather than in Tier 2
Stage 1 (measurable caudate and putamen atrophy)	Suggestive	Same kinetic rationale applied to a pool proposed to be slightly smaller; reduced DTI-ALPS indices reported in premanifest carriers [21]; no anatomical proximity to ACT's site of action, and no clearance effect has been measured
Stage 2 (clinical signs)	Suggestive-to-Extrapolated	Same kinetic rationale applied to a pre-nucleation pool proposed to be smaller as striatal pathology advances; further reduced DTI-ALPS indices in manifest disease [21] indicate greater glymphatic impairment, though the contribution of concurrent atrophy to the index is uncharacterized, and whether greater impairment makes clearance more or less tractable is unknown
Stage 3 (functional decline)	Extrapolated	Substantial MSN loss [4] leaves a proposed residual pre-nucleation pool of uncertain size; any effect is expected to be smallest here and least distinguishable from natural-history decline
Intracellular processes (mHTT expression, somatic CAG expansion, post-nucleation aggregation)	Excluded	Intracellular or intranuclear processes with no extracellular or perivascular transit step; addressed neither by suboccipital compression nor by dural elongation [6,7]

TABLE 2: Evidence tiering for the proposed relevance of ACT-mediated mechanical clearance across HD-ISS stages

HD-ISS stages as defined in [3].

ACT, active craniospinal tensioning; CAG, cytosine-adenine-guanine; DTI-ALPS, diffusion tensor image analysis along the perivascular space; HD, Huntington's disease; HD-ISS, Huntington's Disease Integrated Staging System; mHTT, mutant huntingtin; MSN, medium spiny neuron.

The micro-biochemical axis

A Secondary, Mechanotransductive and Hypoxic Route to In Situ Chaperone Synthesis

CVPC proposes that the same occlusion-rebound cycle activates HSF-1 across the neurovascular unit, beginning at the vessel wall, through mechanical wall strain, independent of oxygen tension, with a HIF-1α contribution left open rather than excluded. Its trigger, its candidate site of action, and the untested extension from arterial smooth muscle to the cerebral venous neurovascular unit are developed in full in the companion AD and ALS frameworks [13,14] and are not re-derived here. As in those frameworks, no specific molecular transducer for this response is proposed or assumed. What differs in HD is not the trigger or the target cell population but the availability of the transcription factor on which the response depends.

Candidate Targets Under HSF-1 Depletion

In ALS, the case for a non-neuronal route rests on the documented high threshold for HSF-1 activation in motor neurons [14]. HD presents a more restrictive situation: mHTT does not simply raise the threshold for HSF-1 activation but drives the degradation of HSF-1 itself. mHTT increases levels of casein kinase 2 alpha prime (CK2α′), which phosphorylates HSF-1, and of the E3 ligase F-box and WD repeat domain-containing 7 (Fbxw7), which then targets it for proteasomal breakdown, a pathway demonstrated in HD mouse striatum, patient-derived striatal MSNs, and postmortem HD brain tissue; genetic reduction of CK2α′ in HD mice restored HSF-1 levels and improved disease-related phenotypes [27], indicating that the depletion is reversible in principle rather than fixed. The downstream capacity of the pathway, should HSF-1 be activated, is supported in HD models: chaperone levels decline progressively in an HD mouse model, and induction of stress proteins has been proposed as a therapeutic approach on that basis [28], while a constitutively active form of HSF-1 suppresses polyglutamine aggregate formation in cellular and mouse models [29]. The question in HD is therefore not whether HSF-1 activation would help but whether enough HSF-1 remains to be activated. The magnitude of residual HSF-1 at any given disease stage has not been quantified in a way that would permit prediction of whether a mechanotransductive stimulus could still produce a functional response.

The astrocyte-mediated route emphasized in ALS [14] remains available as a second, non-exclusive pathway, and astrocytes may be the more direct recipients of CVPC's mechanical trigger. Astrocytic endfeet ensheath the capillaries and venules that engorge during occlusion and are proposed to be the first cells deformed, locally around each engorged vessel rather than through the uniform rise in intracranial pressure, which is consistent with a change in parenchymal mechanical state; jugular venous compression increases brain tissue stiffness on magnetic resonance elastography in healthy volunteers [30]. Astrocytic dysfunction is itself implicated in HD: mHTT expressed in glia reduces glutamate transporter expression and contributes to neuronal excitotoxicity [31], and forced astrocytic expression of the chaperone DNAJB6 protects neighboring striatal neurons in a non-cell-autonomous manner [32]. The astrocytic route is not, however, a fallback that escapes the HSF-1 problem. mHTT is expressed in astrocytes as well as neurons; astrocytes have not been shown to be exempt from its HSF-1-degrading effects, and the DNAJB6 precedent bypassed endogenous HSF-1 through forced overexpression rather than testing whether astrocytes' own inducible machinery remains intact under mHTT burden [32]. Both cellular routes are therefore proposed to be governed by the same variable, cumulative mHTT burden. Astrocytic endfoot pathology in HD, including reduced perivascular AQP4 expression in both mouse and human brain [22], bears on this route in an unresolved direction: it indicates that the cell compartment first deformed during occlusion is itself altered by the disease, without establishing whether mechanotransductive capacity is preserved.

The heat shock response in HD also declines with disease progression, independently of the trigger used to evoke it. In HD mouse models, a pharmacological heat shock protein 90 inhibitor initially induced a heat shock response, but the response progressively declined as disease advanced, accompanied by altered chromatin architecture at heat shock protein gene promoters [33]. Together with progressive HSF-1 degradation [27], this yields a stage-dependent prediction in the same direction as the macro-fluidic tiering in Table *2*, though for a different reason: any CVPC contribution should be greatest in premanifest carriers and diminish through manifest disease. The open HIF-1α route does not depend on HSF-1 abundance and is therefore not gated in the same way, but its relevance to mHTT aggregation has not been established, and it is not proposed here to compensate for HSF-1 depletion. Whether CVPC's mechanical trigger activates HSF-1 in MSNs, astrocytes, both, or neither under mHTT burden has not been tested, nor whether the deformation magnitude produced by transient occlusion is sufficient to do so. This axis therefore remains a secondary, hypothesis-generating extension that neither strengthens nor weakens the primary macro-fluidic claim.

Precedent and Contrast: Prior Pharmacological Evidence

Unlike ALS, where arimoclomol, a pharmacological HSF-1 co-inducer, reached a completed Phase 3 trial that did not improve outcomes [34], and unlike Niemann-Pick disease type C, where it showed benefit in a Phase 2/3 trial [35], no HSF-1 co-inducer has been trialed in human HD. The evidence bearing on this pathway in HD is preclinical only and, as above, indicates that pharmacological induction of the heat shock response loses efficacy as disease advances [33]. CVPC's relevance to HD therefore lacks even the negative-trial precedent available to the ALS framework, and the explicit prediction that any contribution diminishes with stage is offered as a testable boundary condition on the axis rather than as support for it.

Convergence and sequence at the neurovascular unit

The two axes are hypothesized to follow the biphasic timeline developed in the companion frameworks [13,14]. In the Synchronous Phase, suboccipital venous occlusion-rebound and dural pull-recoil occur concurrently within the same several-second maneuver. Dural pull-recoil acts on the CSF compartment and is proposed to perturb perivascular and interstitial fluid, while its coupled venous component and occlusion-rebound converge on the same venous-side target, proposed to accelerate efflux throughout the intracranial compartment, although extension of this reach to the striatum has not been verified. This phase requires no biochemical response from the target cell and so does not depend on HSF-1, but its relevance to disease timing depends on the proportion of MSNs not yet past their nucleation threshold and is proposed to decline with HD-ISS stage (Table *2*).

In the Metachronous Phase, hours later, HSF-1 activation in MSNs, astrocytes, or both, if it occurs, would add incremental protection. The companion frameworks treat HSF-1 as present and available [13,14], but HD cannot assume this, since mHTT drives progressive HSF-1 degradation [27] and the heat shock response becomes impaired as disease advances [33], so this phase is also proposed to diminish with stage. Interaction between successive sessions has not been characterized and is not assumed.

Because both phases decline with stage, for different reasons, an observed stage-dependent pattern cannot be attributed to either axis. This is accepted since the primary claim rests solely on the macro-fluidic axis. Plasma neural-derived exosomal HSP70, adopted from the companion AD framework [13], is proposed as an optional exploratory readout of the micro-biochemical axis, outside the falsification rule.

Established evidence versus proposed framework

The evidentiary basis for this framework is uneven and should be read as such (Table *3*). No component, macro-fluidic or micro-biochemical, has been directly measured in the context of ACT or in HD; every claim

connecting established physiology to ACT's proposed effect is therefore inferential rather than demonstrated.

Component	Established evidence	Proposed/unverified application
Applied load and occlusion threshold	The ACT-OD load is specified at 60%-70% of body weight [24]	Whether this load achieves suboccipital venous plexus occlusion or full dural tension in vivo has not been tested, and presyncope is used as an unvalidated proxy
Craniocervical venous anatomy and proposed reach	Anatomical continuity of the craniocervical venous network is established; the whole-brain and craniospinal reach proposed for the two mechanisms is derived in [14] and is theoretical	Whether the proposed whole-brain reach extends to the striatum, a deep structure distant from the craniocervical junction, has not been tested
Glymphatic impairment in HD	Reduced DTI-ALPS indices in mHTT carriers relative to controls, lower in manifest than premanifest carriers, corroborated by basal ganglia perivascular space analysis [21], on an indirect proxy[23]; impaired CSF clearance worsening with progression in an HD mouse model, with reduced perivascular AQP4 expression in both mouse and human HD brain [22]	Whether ACT changes DTI-ALPS indices, whether any change reflects clearance within the striatum, and whether serial change can be distinguished from the effect of progressive caudate atrophy and ventricular enlargement on the sampled region, have not been tested; the human imaging evidence derives from a single cross-sectional cohort of 49 carriers [21]
Nucleation kinetics and exogenous seeding	Aggregation proceeds by stochastic nucleation [8]; HD CSF seeds aggregation in reporter cells [9]; seeding activity tracks progression in HD mice [10]; mHTT transfers between neurons and into grafted tissue, and is present in host-brain extracellular matrix and blood vessels [11,12]	Whether reducing extracellular seed burden meaningfully delays nucleation in vivo, relative to intracellular kinetics driven by somatic CAG expansion [6,7], has not been tested
Extracellular mHTT as a measurable target	CSF mHTT is quantifiable by an analytically validated ultrasensitive assay [36]	Whether ACT alters CSF mHTT, in which direction, given that clearance from the interstitial space into the CSF could transiently raise it, and whether CSF concentration reflects the interstitial seed pool accessible to clearance, have not been tested
Plasma NfL as a progression marker	Plasma NfL rises with disease burden and proximity to predicted onset [5,37]; NfL was lowered alongside mHTT in an HD trial without clinical benefit [20]	Whether ACT attenuates the NfL trajectory, and whether any attenuation reflects seed clearance rather than another effect, have not been tested; a favorable change would indicate biological activity, not clinical benefit
Mechanical strain as an HSF-1 trigger	Mechanical/hemodynamic strain activates HSF-1 in vascular tissue, demonstrated in arterial smooth muscle; reviewed in [13,14]	Whether venous-side wall strain, or the local parenchymal deformation it produces, activates HSF-1 in MSNs or astrocytes, a cross-vessel-type and cross-cell-type extension, has not been tested
HSF-1 availability in HD	mHTT drives proteasomal degradation of HSF-1 [27], and the heat shock response becomes progressively impaired with disease advancement in HD models [33]	Whether sufficient HSF-1 remains at each HD-ISS stage for CVPC to act on has not been tested
HSF-1/chaperone protection once induced	Active HSF-1 suppresses polyglutamine aggregation in cellular and mouse models [29]; chaperone levels decline progressively in HD mice [28]; astrocytic chaperone expression protects striatal neurons non-cell-autonomously [32]	Contingent on the two rows above, the protective consequence is established in models, and the open question is whether CVPC produces the induction under mHTT burden

TABLE 3: Established physiology versus this framework's proposed, unverified application of that physiology to ACT in HD

ACT, active craniospinal tensioning; ACT-OD, operator-driven active craniospinal tensioning; AQP4, aquaporin-4; CAG, cytosine-adenine-guanine; CSF, cerebrospinal fluid; CVPC, cerebral venous preconditioning; DTI-ALPS, diffusion tensor image analysis along the perivascular space; HD, Huntington's disease; HD-ISS, Huntington's Disease Integrated Staging System; HSF-1, heat shock factor 1; mHTT, mutant huntingtin; MSN, medium spiny neuron; NfL, neurofilament light chain.

Oncologic safety

The oncologic safety considerations developed in the companion ALS framework [14] apply here without

modification. HD adds one disease-specific epidemiological signal bearing on the chaperone-related consideration. Reduced cancer incidence has been reported in HD in French, Swedish, and European REGISTRY cohorts [38-40], although an Enroll-HD analysis of 2,608 participants found an age-sex standardized rate slightly above general-population rates [41], and a larger Enroll-HD analysis of 18,892 gene expansion carriers found no overall difference from controls, with lower prevalence in premanifest carriers that may partly reflect their younger age [42]. The mechanism is unknown: CAG repeat length showed no association with cancer in two cohorts [38,40], but an inverse association in the larger Enroll-HD analysis [42], and huntingtin overexpression did not alter survival in cancer-prone mouse models [43]. If the mechanism involves a reduced capacity of affected cells to withstand malignant transformation, a locally induced pro-survival chaperone response could, in principle, work against it; this is a plausible, unresolved concern rather than an established contraindication, further constrained by mHTT-driven HSF-1 degradation [27]. ACT should therefore be contraindicated or used with caution in patients with any known or suspected malignancy and is intended for practitioner-supervised application. In the validation pathway below, the baseline MRI acquired for DTI-ALPS is also reviewed for intracranial and craniocervical mass lesions before enrollment.

Methodological framework and priorities for clinical validation

Design Principles, Scope, and Tier 1

The pathway below is a preliminary research proposal intended to make this hypothesis testable, not an established intervention protocol; its parameters are specified in advance only so that a first study can be interpreted against them. An animal model is not proposed as a preliminary step, for the same reasons detailed in the companion ALS framework [14]. This framework adopts the Tier 1/Tier 2 staged design and dual-endpoint falsification standard established there, with the parameters of each tier fixed in advance rather than revised in response to an initial result.

The validation pathway is restricted to gene-positive adults at HD-ISS Stages 0-2, with Stage 0 addressed in Tier 3. Because ACT is proposed to slow the nucleation of MSNs that have not yet crossed their threshold, rather than reverse neuronal loss already sustained, the tissue it could protect is greatest early on. The secondary endpoint adopted below is characterized by natural-history trajectories across premanifest and manifest carriers [37], and the GENERATION HD2 trial of tominersen likewise enrolled younger participants with early HD [20]. ACT at HD-ISS Stage 3 is therefore not proposed for formal validation here. Its application in individual patients rests with the supervising practitioner on a case-by-case basis, and no inference of efficacy is drawn from such use. Throughout the pathway, ACT is proposed as a supplementary adjunct to standard care, not as an alternative to symptomatic therapy, and participants continue their existing treatment.

Tier 1 is disease-nonspecific and follows the companion ALS framework [14]. It consists of a single supervised ACT cycle per session with continuous vital-sign monitoring, intended to establish whether the maneuver is tolerated rather than to characterize its proposed mechanism. A result showing no clinically significant adverse vital-sign perturbation, obtained in any population, supports proceeding to HD-specific testing. The acute Tier 1a feasibility sub-study specified there, a small, fixed number of ACT-OD-delivered cycles with pre- and post-maneuver DTI-ALPS comparison, applies here without modification, since DTI-ALPS's sensitivity to a brief mechanical perturbation is a property of the imaging method and the maneuver, not of any single disease's pathology. As in the companion ALS framework [14], a null Tier 1a result is treated as uninformative as to mechanism rather than as evidence against the macro-fluidic axis.

Disease-Specific Tier 1 and Delivery Mode

Disease-specific Tier 1 reconfirmation is nonetheless proposed before Tier 2, given the possibility of HD-related alterations in perivascular architecture or CSF dynamics that a healthy volunteer cohort would not capture. It is performed on participants who meet the Tier 2 eligibility criteria below. Premanifest participants are enrolled only if they have already learned their gene status through established predictive testing and genetic counseling; no genetic testing is performed for the purpose of the study. ACT-OD is specified as the delivery mode throughout this framework's HD validation pathway, for safety rather than mechanism. Because each hold is maintained until presyncopal onset, an operator-driven device builds supervision into every cycle, allowing the operator to release the load independently of the participant's response. All sessions are logged for hold duration and presyncopal onset.

The practitioner screening specified in the companion ALS framework [14] for autonomic dysfunction, arrhythmia, and uncontrolled hypertension applies unchanged, including its provision that a screened condition requires supervising-practitioner assessment before enrollment rather than serving as grounds for exclusion. Known or suspected craniocervical instability, as in rheumatoid arthritis, is treated as an exclusion criterion, since longitudinal distraction may stress compromised craniocervical ligaments. Four further considerations are specific to HD. Psychiatric status, including depression and suicidality, which are common in HD [4,44], is screened as in standard HD trial practice. Symptomatic medications used in HD, including antipsychotics and vesicular monoamine transporter 2 inhibitors, can cause orthostatic hypotension and sedation [4], so their use and dose are recorded at enrollment, since they may lower the

threshold for presyncope or blunt its perception. Capacity to give informed consent is assessed directly, given the disease's cognitive involvement. The participant's ability to reliably perceive and signal the onset of presyncope, maintain a stable position despite involuntary movements, and remain safely seated throughout the recovery period is verified during the first supervised exposure. Participants whom the practitioner judges unable to meet these requirements or to tolerate the fixed parameters are not enrolled, rather than enrolled under modified parameters, so that practitioner judgment governs eligibility while the tested protocol remains fixed.

Proposed Study Parameters

Because ACT as applied to HD has never been directly tested, the parameters below are fixed rather than left open to iterative adjustment, for the same reasons of falsifiability established in the companion ALS framework [14]. The applied load for ACT-OD is fixed at full lift-off of the participant from the seated surface, with the feet remaining in contact with the floor, which places approximately 60%-70% of body weight on the cervical spine [24]. Hold duration is defined by a physiological endpoint rather than by time: each session consists of a single hold maintained until presyncopal onset, typically reached at approximately five seconds, with 10 seconds as the absolute maximum permitted in the ALS framework [14], a ceiling the endpoint-defined hold is not expected to reach. Presyncopal onset is defined as the participant’s first perception of lightheadedness, tinnitus, visual dimming, or impending faintness [24,25], which is signaled to the operator, who immediately releases the load, with the participant remaining seated and supported until symptoms have fully resolved; no attempt is made to intensify these symptoms. Presyncopal onset serves as a practical, tolerability-based endpoint rather than a validated marker of suboccipital occlusion [14]. Because reduced awareness of one's own symptoms is common in HD [4], the operator does not rely on the participant's signal alone and releases the load on observing signs of presyncope irrespective of whether onset has been reported. Involuntary movements may also affect stability during the recovery period, so the participant is not left unsupported until seated stability and symptom resolution are both confirmed. The absence of presyncopal onset within 10 seconds is treated as a signal to pause and reassess rather than as grounds to increase load. The hold duration reached in each session is recorded, both to document protocol fidelity and as a potential dose variable.

Session frequency is fixed at three times daily, at the upper end of the range specified in prior technical reports [24-26], rather than the three- to five-times-daily frequency adopted for ALS, on the grounds that ALS's short, fatal prognosis justified a less conservative baseline [14]. HD's course, extending over more than a decade after onset and preceded by a long premanifest phase, warrants no departure from the original range. Investigators may adopt different parameters if they are specified before enrollment and reported, in which case results test a modified protocol. These parameters are informed by the author's own sustained personal practice since 2017 without adverse effect, in which holds of approximately five seconds reliably produced presyncope, whereas holds approaching 10 seconds produced poorly tolerated presyncope; that evidence is anecdotal, single-subject, and non-HD-specific, and does not establish safety or efficacy at a population level.

Tier 2: Endpoints, Duration, and Falsification

Only following a positive HD-specific Tier 1 result is Tier 2 proposed: sustained ACT-OD practice at the fixed parameters above, with repeat measurement against baseline, in gene-positive adults at HD-ISS Stages 1-2, stratified by stage, with CAG-Age Product, a measure combining CAG repeat length and age that indexes cumulative mutant huntingtin exposure, recorded for each participant. This population overlaps that of the GENERATION HD2 trial, which enrolled adults aged 25-50 years with early HD [20]. Changes to symptomatic therapy during the study are recorded.

Participants receiving an investigational or approved huntingtin-lowering therapy are not enrolled in Tier 2. This reflects endpoint interpretability, not a judgment against that therapy: huntingtin lowering can reduce NfL independently of any clearance effect [20], so a change in either endpoint could not be attributed to ACT. Outside this study, ACT is proposed as an adjunct that may be used alongside such therapy, acting at a different step. Should a huntingtin-lowering therapy become part of standard care, excluding its users would no longer be practical, and its use would instead be recorded and treated as a stratification variable.

DTI-ALPS is retained as the primary endpoint for consistency across this series, with the proximity of its sampling region to the caudate noted above as a sampling advantage rather than as the basis for its selection. Plasma NfL is adopted as a clearance-independent secondary endpoint, analogous to plasma NfL in the ALS framework's Tier 2 [14], because it is well characterized in HD, rises with disease burden and proximity to predicted onset, and provides published natural-history trajectories against which an attenuated course can be assessed [37]; because it is a biomarker already measured in HD disease-modification trials [20]; and because it keeps the validation pathway free of lumbar puncture. CSF mHTT, measurable by an analytically validated assay [36], is not required, since a clearance mechanism could move mHTT from the interstitial space into the CSF and so shift its concentration in either direction (Table *3*); investigators may add it or other molecular measures, but such measures lie outside the falsification rule specified here. Plasma neural-derived exosomal HSP70, adopted from the companion AD framework [13],

may be included as an optional exploratory readout of the micro-biochemical axis, drawn from the same blood sample and subject to the vesicle-isolation caveats noted there; it neither supports nor falsifies the primary claim. Fluid-attenuated inversion recovery (FLAIR) and susceptibility-weighted sequences can be added to the same MRI sessions used for DTI-ALPS, allowing white matter hyperintensities and cerebral microbleeds to be read as safety measures of small-vessel injury without a separate visit.

Tier 2 extends its observation period to at least two years, rather than the three- to six-month interval used in the ALS framework, a departure justified by HD's long course rather than by a change to the falsification standard. The interval is set by the rate at which the secondary endpoint changes rather than by the interval over which a clinical difference would become detectable: plasma NfL trajectories in HD have been characterized over multi-year follow-up [37], and no longitudinal HD cohort has yet established a DTI-ALPS decline rate. A two-year minimum is accordingly proposed, rather than an optimum, with a longer observation period preferable where feasible.

A positive result requires favorable change on both endpoints: DTI-ALPS stabilization or elevation relative to baseline, since no reliable longitudinal decline rate exists against which a smaller, attenuated decline could be distinguished from measurement noise, and a plasma NfL trajectory attenuated relative to published natural-history rates matched on CAG-Age Product. Consistent with the dual-endpoint standard in the companion ALS framework [14], a decline in DTI-ALPS relative to baseline, or a plasma NfL trajectory at or beyond the matched natural-history rate, either alone, is sufficient to falsify the claim. The stage-dependent gradient predicted by both axes, concentrated benefit in earlier stages, is tested as a secondary prediction rather than a falsification criterion, given the small size of stratified subgroups and the confounding of stage with age, disease duration, and symptomatic medication.

Imaging should follow a harmonized acquisition protocol on the same scanner across visits, and a concurrent control group is preferable even at this stage where feasible. Sample size, the statistical analysis plan, and the thresholds defining favorable and unfavorable change should be prespecified with independent statistical input prior to enrollment, and any efficacy study should include clinically meaningful outcomes alongside imaging and fluid endpoints. Because Tier 2 compares each participant against baseline and published natural-history rates rather than a concurrent control, a positive result would establish biological activity, not disease modification, since favorable change relative to historical data may also arise from regression to the mean, differences in assays, scanners, or protocols between studies, or selection of motivated participants. A positive Tier 2 result would therefore be confirmed in a randomized, delayed-start trial before any disease-modification claim is made: if an early-start group retains its advantage after a later-start group begins ACT, the difference cannot be explained by a symptomatic or placebo effect, and all participants eventually receive the intervention. The composite Unified Huntington's Disease Rating Scale may be included as an exploratory clinical measure but should not substitute for the imaging and fluid endpoints, given the potential for confounding by concurrent symptomatic therapy. Disease stage, CAG-Age Product, symptomatic medication, physical activity level, and any structural spinal condition limiting elongation are recorded as stratification variables.

Tier 3 and the Boundary of the Pathway

A positive Tier 2 result would motivate a third stage not proposed in the ALS framework: extension into HD-ISS Stage 0 carriers, gene-positive adults without detectable biological change, in whom this framework predicts the largest pre-nucleation MSN pool and therefore the greatest potential benefit (Table *2*). This is the preventive application of ACT, in the sense defined in the "Introduction." Because HD is identifiable decades before onset, carriers currently have no intervention between learning their gene status and the emergence of symptoms; should validation succeed, a low-cost, practitioner-supervised maneuver [24] practiced as a regular routine from that point is the use this framework ultimately proposes. Tier 3 retains the hold, frequency, and delivery-mode rules of Tier 2. Endpoint sensitivity, however, cannot be assumed to carry over: plasma NfL rises slowly in carriers far from predicted onset [5,37], so a Tier 3 design would need a progression measure suited to that population rather than inherit Tier 2's. Transition from HD-ISS Stage 0 to Stage 1, defined by measurable caudate and putamen atrophy on volumetric MRI [3], is a natural candidate, since the required sequences can be acquired in the same scan session as DTI-ALPS, with time to clinical onset as the longer-term outcome. Using a staging landmark as the outcome makes the endpoint definition and the staging system the same instrument, which is appropriate where the question is whether transition is delayed, but means the result is interpretable only against the HD-ISS cutoffs as published. Because the clinically meaningful magnitude of any delay is not self-evident, a Tier 3 protocol would prespecify it. Typical motor onset falls in the fourth to sixth decade [4], so a delay large enough to move onset toward the eighth decade would leave most of adult life unaffected, whereas a delay of months would be detectable without being consequential; which of these is achievable, if any, cannot be estimated from existing evidence, and the required sample size and observation period follow from whichever threshold is chosen. This extension addresses the distinct, stronger claim that sustained practice could delay biological progression or clinical onset; as an efficacy study, it should be conducted with a concurrent control group and should not be undertaken before a positive Tier 2 result, though feasibility testing in this population need not wait, as set out below.

Because no disease-modifying therapy has yet received regulatory approval, as noted in the “Introduction,”

HD-ISS Stage 0 carriers have no established preventive option, so that, once Tier 1 safety is established, the balance of risk favors early feasibility testing in this population. A feasibility cohort of Stage 0 carriers may therefore begin in parallel with Tier 2, measuring only tolerability, adherence, and retention, with no efficacy claim, and continue into long-term follow-up, so that retention data and accumulated baseline imaging are available when Tier 2 reads out. Adherence is the specific question this cohort addresses: although each hold lasts only seconds, Tier 3 would ask largely healthy carriers to sustain 3 operator-supervised sessions daily over years, without the symptomatic incentive available to patients with established disease, and whether that is achievable is unknown. This staged pathway does not address, and cannot be extended to address, the intracellular processes outside the reach of mechanical clearance (Table *2*): no tier tests mHTT expression or somatic CAG expansion, and neither is expected to be affected; any intracellular contribution of the micro-biochemical axis lies outside the falsification rule. The full staged pathway is summarized in Table *4*.

Stage	Population	Design	Endpoints	Decision rule
Tier 1 (disease-nonspecific)	Any population	Single supervised ACT cycle per session with continuous vital-sign monitoring; Tier 1a: small, fixed number of ACT-OD cycles with pre- and post-maneuver DTI-ALPS [14]	Vital-sign perturbation; Tier 1a: acute DTI-ALPS change	No clinically significant adverse perturbation supports HD-specific testing; a null Tier 1a result is uninformative as to mechanism
HD-specific Tier 1	Gene-positive adults meeting Tier 2 eligibility criteria	Supervised ACT-OD exposure at fixed parameters	Tolerability; ability to signal presyncopal onset and maintain stable seated position	Positive result required before Tier 2
Tier 2	Gene-positive adults at HD-ISS Stages 1-2, stratified by stage, CAG-Age Product recorded; huntingtin-lowering therapy excluded for endpoint interpretability	Sustained ACT-OD at fixed parameters [24] (full lift-off with feet in contact, single hold to presyncopal onset, 10-second maximum, 3 times daily) for at least 2 years, against baseline and matched natural-history rates [37]	Primary: DTI-ALPS; secondary: plasma NfL	Favorable change on both required; unfavorable change on either falsifies the claim; a positive result establishes biological activity only, to be confirmed in a randomized, delayed-start trial
Stage 0 feasibility cohort	HD-ISS Stage 0 carriers	In parallel with Tier 2, after Tier 1 safety; long-term follow-up	Tolerability, adherence, retention	No efficacy claim
Tier 3	HD-ISS Stage 0 carriers	After a positive Tier 2 result; Tier 2 hold, frequency, and delivery rules; concurrent control group	Transition to HD-ISS Stage 1 on volumetric MRI [3]; time to clinical onset	Clinically meaningful delay prespecified

TABLE 4: Summary of the proposed staged validation pathway for ACT in HD

ACT, active craniospinal tensioning; ACT-OD, operator-driven active craniospinal tensioning; CAG, cytosine-adenine-guanine; DTI-ALPS, diffusion tensor image analysis along the perivascular space; HD, Huntington's disease; HD-ISS, Huntington's Disease Integrated Staging System; MRI, magnetic resonance imaging; NfL, neurofilament light chain.

Long-Term Safety

Because ACT is proposed for sustained practice, including by largely healthy premanifest carriers, its safety over years to decades cannot be established within any single tier. Participants who continue ACT after their study period would remain in structured long-term follow-up with standardized adverse-event reporting, including repeat review of the MRI small-vessel measures, so that multi-year exposure data accumulate beyond the trial periods. The author's sustained personal practice since 2017, noted above, is consistent with long-term tolerability but remains anecdotal and does not substitute for this follow-up.

Limitations

Several limitations are shared across this series and are addressed in full in the companion AD and ALS frameworks [13,14] rather than restated here. They include the narrative, non-systematic review format, with source selection by a single author without a second screener or formal quality appraisal; the fact that no component of ACT's proposed mechanism has been directly measured in any disease context, including the maneuver's actual intracranial and CSF pressure magnitudes, the timing relationship between occlusion and elongation, and whether either produces detectable glymphatic clearance change; the unresolved debate over the convective model of glymphatic transport on which the macro-fluidic axis draws, with some rodent studies finding parenchymal solute transport consistent with diffusion rather than bulk flow [45]; and the absence of any non-invasive method to confirm suboccipital venous plexus occlusion in vivo, including the inadequacy of jugular or vertebral vein flow as a surrogate and the unvalidated presyncope proxy. What follows addresses the respects in which HD's disease biology modifies, narrows, or adds to these shared limitations.

First, regarding disease biology, the contribution of exogenous seeding to disease timing in human HD is not established, and the strongest current evidence on timing, from genetic modifier and somatic expansion studies [6,7], indicates that the disease clock in each MSN is set predominantly by an intracellular process; this framework does not address it. The evidence that extracellular mHTT accelerates nucleation derives from cell-based seeding assays, animal models, and graft studies [8-12]. Should the exogenous-seeding contribution prove minor relative to intracellular kinetics driven by somatic expansion, the macro-fluidic axis's timeline-modulation potential would be correspondingly reduced, regardless of whether ACT achieves its proposed clearance effect. Nor does any existing evidence permit an estimate of the magnitude of the delay that a given reduction in seed burden would produce.

Second, regarding biomarkers, neither endpoint proposed in the "Methodological framework" section above directly measures the mechanism's proposed target. DTI-ALPS cannot confirm clearance activity within the striatum [23], and the progressive caudate atrophy and ventricular enlargement noted in "Anatomical Reach in HD" mean that a declining index in a progressing carrier may reflect structural change rather than clearance. Plasma NfL measures neuronal injury rather than extracellular mHTT, so a favorable trajectory would indicate altered neurodegeneration without attributing it to seed clearance, and NfL has been lowered in an HD trial without accompanying clinical benefit [20]. Plasma NfL also rises slowly in carriers far from predicted onset [5,37], so its sensitivity is weakest in the earliest HD-ISS stages, precisely where this framework predicts benefit to be greatest; a null result in those strata may reflect endpoint insensitivity rather than absence of effect.

Third, regarding mechanism, as in ALS [14], the macro-fluidic axis acts only on the extracellular fraction of a predominantly intracellular protein, and the proportion of disease-relevant mHTT that transits the extracellular or perivascular space is not established. Transfer between cells may also occur through synaptic, contact-dependent routes: in the model systems above, propagation was blocked by inactivating synaptic vesicle fusion [11], indicating a route less accessible to bulk fluid clearance than freely suspended protein. Should such routes dominate, the macro-fluidic axis's potential would correspondingly be reduced.

Fourth, regarding clinical evidence, the closest existing tests of reducing mHTT have not yet established clinical benefit in a randomized setting, as reviewed in the "Introduction" [19,20], and the reported slowing with AMT-130 derives from small Phase 1/2 studies compared against a propensity score-matched external natural-history control that has not yet been published in full [16]. That comparison illustrates a limitation this framework's own validation design shares: at the later timepoint, attrition in the external control reached approximately half, and, according to the sponsor’s analysis, participants lost to follow-up were progressing faster than those retained, so the comparator's apparent decline rate was itself shaped by who remained in it. A design comparing against published natural-history rates, as proposed here, is exposed to the same bias, which is one reason a positive result is treated as provisional pending randomized confirmation. The tominersen results also bear directly on the premise of this framework, since CSF mHTT was lowered without clinical benefit [19,20]. If CSF mHTT tracks the extracellular seed pool, this argues against that pool as a meaningful driver of disease timing. The result does not settle the question because tominersen reduces mHTT synthesis within cells rather than clearing extracellular seeds; CSF concentration may not reflect the interstitial pool (Table *3*); and the harm observed with frequent dosing may have obscured any benefit. Nevertheless, it is the closest human evidence against the premise.

Fifth, regarding the secondary axis, beyond the untested trigger shared with the companion frameworks, the micro-biochemical axis depends on a transcription factor that mHTT progressively depletes [27,33], as set out in "The micro-biochemical axis," and the exosomal HSP70 measure proposed as an exploratory readout carries the vesicle-isolation uncertainty noted in the companion AD framework [13].

Sixth, regarding methodology, disease stage is correlated with age, disease duration, CAG-Age Product, and symptomatic medication, and natural-history NfL trajectories themselves vary with CAG-Age Product [37], so any stage-stratified comparison must be made against a comparator matched on these variables rather than a single population rate.

Finally, regarding clinical applicability, ACT is not proposed as universally applicable in HD. Dural pull-

recoil depends on achievable spinal elongation, which is not expected to be precluded by normal aging but may be reduced in individual patients by coexisting structural spinal conditions, such as ossification of the posterior longitudinal ligament, ankylosing spondylitis, rheumatoid arthritis, or surgical fusion; suboccipital venous occlusion-rebound targets the suboccipital venous plexus, which is largely independent of spinal flexibility [14], so where elongation is limited, the expectation is that pull-recoil's contribution narrows rather than that the macro-fluidic axis is lost. Other pre-existing conditions, structural or systemic, such as autonomic dysfunction, may limit or preclude application in individual patients, and the decision to apply it rests with the supervising practitioner. ACT's original purpose as a preventive posture-correction and spinal-decompression maneuver [25] also bears on this: sustained practice begun before structural changes develop is proposed to help preserve the spinal mobility on which pull-recoil depends.

Conclusions

HD is caused by a CAG repeat expansion that is fully penetrant at 40 or more repeats and is present in every cell from birth, and no disease-modifying therapy has yet proven effective in a Phase 3 trial or received regulatory approval. This framework proposes ACT, which delivers suboccipital venous occlusion-rebound and dural pull-recoil concurrently, as a mechanical route to disease-timeline modulation that requires no molecule to cross the BBB. Its primary hypothesis is that glymphatic clearance of extracellular, seeding-competent mHTT reduces the seed burden that accelerates nucleation, thereby delaying a step that each MSN will eventually undergo regardless. The claim is deliberately narrow: a disease clock set predominantly by intracellular somatic expansion forecloses propagation blocking, the contribution of exogenous seeding to disease timing in humans is not established, and the magnitude of any delay cannot be estimated from existing evidence. A secondary hypothesis, CVPC-mediated HSF-1 activation, faces the HD-specific obstacle that mHTT degrades HSF-1 itself, and the primary claim does not depend on this axis.

This framework is entirely theoretical and is offered as a falsifiable hypothesis. Tier 2 requires concordant favorable change on DTI-ALPS and plasma NfL over at least two years in carriers at HD-ISS Stages 1-2, and unfavorable change on either is sufficient to falsify the claim; a positive result would establish biological activity only, pending confirmation in a randomized, delayed-start trial. Only then would Tier 3 test whether practice begun in Stage 0 carriers delays biological progression or clinical onset. Because HD is identifiable decades before onset, should validation succeed, ACT, a low-cost posture-correction and spinal-decompression maneuver, could then be practiced from the time gene status is known. The same dual-axis logic is extended to spinocerebellar ataxia and to prion diseases, including fatal familial insomnia, in forthcoming companion papers, each as an independent hypothesis. ACT is proposed as a supplementary, practitioner-supervised adjunct under investigation, not a replacement for standard care.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Huan-Wei Chen

Acquisition, analysis, or interpretation of data: Huan-Wei Chen

Drafting of the manuscript: Huan-Wei Chen

Critical review of the manuscript for important intellectual content: Huan-Wei Chen

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

The author used an AI-assisted writing tool (Claude, Anthropic PBC, San Francisco, CA) to support manuscript drafting and language editing. All scientific content, clinical interpretations, and intellectual contributions remain the author's own.

References

1. Medina A, Mahjoub Y, Shaver L, Pringsheim T: Prevalence and incidence of Huntington's disease: an updated systematic review and meta-analysis. Mov Disord. 2022, 37:2327-35. 10.1002/mds.29228

2. The Huntington's Disease Collaborative Research Group: A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993, 72:971-83. 10.1016/0092-8674(93)90585-e
3. Tabrizi SJ, Schobel S, Gantman EC, et al.: A biological classification of Huntington's disease: the integrated staging system. Lancet Neurol. 2022, 21:632-44. 10.1016/S1474-4422(22)00120-X
4. Bates GP, Dorsey R, Gusella JF, et al.: Huntington disease. Nat Rev Dis Primers. 2015, 1:15005. 10.1038/nrdp.2015.5
5. Scahill RI, Zeun P, Osborne-Crowley K, et al.: Biological and clinical characteristics of gene carriers far from predicted onset in the Huntington's disease Young Adult Study (HD-YAS): a cross-sectional analysis. Lancet Neurol. 2020, 19:502-12. 10.1016/S1474-4422(20)30143-5
6. Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium: CAG repeat not polyglutamine length determines timing of Huntington's disease onset. Cell. 2019, 178:887-900.e14. 10.1016/j.cell.2019.06.036
7. Handsaker RE, Kashin S, Reed NM, et al.: Long somatic DNA-repeat expansion drives neurodegeneration in Huntington's disease. Cell. 2025, 188:623-39.e19. 10.1016/j.cell.2024.11.038
8. Colby DW, Cassady JP, Lin GC, Ingram VM, Wittrup KD: Stochastic kinetics of intracellular huntingtin aggregate formation. Nat Chem Biol. 2006, 2:319-23. 10.1038/nchembio792
9. Tan Z, Dai W, van Erp TG, et al.: Huntington's disease cerebrospinal fluid seeds aggregation of mutant huntingtin. Mol Psychiatry. 2015, 20:1286-93. 10.1038/mp.2015.81
10. Ast A, Buntru A, Schindler F, et al.: mHTT seeding activity: a marker of disease progression and neurotoxicity in models of Huntington's disease. Mol Cell. 2018, 71:675-88.e6. 10.1016/j.molcel.2018.07.032
11. Pecho-Vrieseling E, Rieker C, Fuchs S, et al.: Transneuronal propagation of mutant huntingtin contributes to non-cell autonomous pathology in neurons. Nat Neurosci. 2014, 17:1064-72. 10.1038/nn.3761
12. Cicchetti F, Lacroix S, Cisbani G, et al.: Mutant huntingtin is present in neuronal grafts in Huntington disease patients. Ann Neurol. 2014, 76:31-42. 10.1002/ana.24174
13. Chen HW: Bypassing the blood-brain barrier: a dual-axis framework for alzheimer's disease utilizing glymphatic-lymphatic clearance and in situ chaperone synthesis. Cureus. 2026, 18:e113424. 10.7759/cureus.113424
14. Chen HW: Bypassing the blood-central nervous system (CNS) barrier: a dual-axis framework for amyotrophic lateral sclerosis (ALS) utilizing glymphatic-lymphatic clearance and in situ chaperone synthesis. Cureus. 2026, 18:e117043. 10.7759/cureus.117043
15. Saft C: Huntington's disease: disappointments and new beginnings. Lancet Neurol. 2022, 21:582-4. 10.1016/S1474-4422(22)00189-2
16. uniQure: uniQure announces additional data from ongoing Phase I/II studies of ifezuntirgene inilparvovec (AMT-130) in Huntington's disease showing continued slowing of disease progression. (2026). Accessed: November 8, 2026: https://uniqure.gcs-web.com/node/13001/pdf.
17. uniQure: uniQure announces FDA acceptance and priority review of the biologics license application for ifezuntirgene inilparvovec for the treatment of Huntington's disease. (2026). Accessed: November 8, 2026: https://www.biospace.com/press-releases/uniqure-announces-fda-acceptance-and-priority-review-of-the-biologics-license....
18. PTC Therapeutics: PTC Therapeutics reports positive topline results from month 24 interim analysis of PIVOT-HD extension study of votoplam. (2026). Accessed: November 8, 2026: https://ir.ptcbio.com/news-releases/news-release-details/ptc-therapeutics-reports-positive-topline-results-month-24.
19. McColgan P, Thobhani A, Boak L, et al.: Tominersen in adults with manifest Huntington's disease . N Engl J Med. 2023, 389:2203-5. 10.1056/NEJMc2300400
20. Roche: Update on two clinical studies: GENERATION HD2 (tominersen) and POINT-HD (RG6496) . (2026). Accessed: November 8, 2026: https://hdsa.org/wp-content/uploads/2026/07/Roche-GENERATION-HD2-_-POINT-HD-global-patient-community-letter-July2026.pdf.
21. Yin JH, Cao LX, Liu YO, Huang Y: Diffusion along perivascular spaces as a marker for glymphatic system impairment in Huntington's disease. Mov Disord. 2025, 40:1409-19. 10.1002/mds.30194
22. Liu H, Chen L, Zhang C, et al.: Glymphatic influx and clearance are perturbed in Huntington's disease . JCI Insight. 2024, 9:e172286. 10.1172/jci.insight.172286
23. Taoka T, Ito R, Nakamichi R, Nakane T, Kawai H, Naganawa S: Diffusion tensor image analysis ALong the perivascular space (DTI-ALPS): revisiting the meaning and significance of the method. Magn Reson Med Sci. 2024, 23:268-90. 10.2463/mrms.rev.2023-0175
24. Chen HW: Operator-driven active craniospinal tensioning (ACT) device for non-ambulatory application . Cureus. 2026, 18:e114854. 10.7759/cureus.114854
25. Chen HW: Active craniospinal tensioning (ACT) for posture correction and spinal decompression: biomechanical rationale for glymphatic clearance and cerebral venous preconditioning (CVPC). Cureus. 2026, 18:e112433. 10.7759/cureus.112433
26. Chen HW: Active craniospinal tensioning (ACT): axial spinal traction for glymphatic modulation . Cureus. 2026, 18:e101796. 10.7759/cureus.101796
27. Gomez-Pastor R, Burchfiel ET, Neef DW, et al.: Abnormal degradation of the neuronal stress-protective transcription factor HSF1 in Huntington's disease. Nat Commun. 2017, 8:14405. 10.1038/ncomms14405
28. Hay DG, Sathasivam K, Tobaben S, et al.: Progressive decrease in chaperone protein levels in a mouse model of Huntington's disease and induction of stress proteins as a therapeutic approach. Hum Mol Genet. 2004, 13:1389-405. 10.1093/hmg/ddh144
29. Fujimoto M, Takaki E, Hayashi T, Kitaura Y, Tanaka Y, Inouye S, Nakai A: Active HSF1 significantly suppresses polyglutamine aggregate formation in cellular and mouse models. J Biol Chem. 2005, 280:34908-16. 10.1074/jbc.M506288200
30. Hatt A, Cheng S, Tan K, Sinkus R, Bilston LE: MR elastography can be used to measure brain stiffness changes as a result of altered cranial venous drainage during jugular compression. AJNR Am J Neuroradiol. 2015, 36:1971-7. 10.3174/ajnr.A4361
31. Shin JY, Fang ZH, Yu ZX, Wang CE, Li SH, Li XJ: Expression of mutant huntingtin in glial cells contributes to neuronal excitotoxicity. J Cell Biol. 2005, 171:1001-12. 10.1083/jcb.200508072

32. Bason M, Meister-Broekema M, Alberts N, Dijkers P, Bergink S, Sibon OC, Kampinga HH: Astrocytic expression of the chaperone DNAJB6 results in non-cell autonomous protection in Huntington's disease. Neurobiol Dis. 2019, 124:108-17. 10.1016/j.nbd.2018.10.017
33. Labbadia J, Cunliffe H, Weiss A, et al.: Altered chromatin architecture underlies progressive impairment of the heat shock response in mouse models of Huntington disease. J Clin Invest. 2011, 121:3306-19. 10.1172/JCI57413
34. Benatar M, Hansen T, Rom D, et al.: Safety and efficacy of arimoclomol in patients with early amyotrophic lateral sclerosis (ORARIALS-01): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Neurol. 2024, 23:687-99. 10.1016/S1474-4422(24)00134-0
35. Mengel E, Patterson MC, Da Riol RM, et al.: Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment. J Inherit Metab Dis. 2021, 44:1463-80. 10.1002/jimd.12428
36. Fodale V, Boggio R, Daldin M, et al.: Validation of ultrasensitive mutant Huntingtin detection in human cerebrospinal fluid by single molecule counting immunoassay. J Huntingtons Dis. 2017, 6:349-61. 10.3233/JHD-170269
37. Byrne LM, Rodrigues FB, Blennow K, et al.: Neurofilament light protein in blood as a potential biomarker of neurodegeneration in Huntington's disease: a retrospective cohort analysis. Lancet Neurol. 2017, 16:601-9. 10.1016/S1474-4422(17)30124-2
38. Coarelli G, Diallo A, Thion MS, et al.: Low cancer prevalence in polyglutamine expansion diseases. Neurology. 2017, 88:1114-9. 10.1212/WNL.0000000000003725
39. Ji J, Sundquist K, Sundquist J: Cancer incidence in patients with polyglutamine diseases: a population-based study in Sweden. Lancet Oncol. 2012, 13:642-8. 10.1016/S1470-2045(12)70132-8
40. McNulty P, Pilcher R, Ramesh R, et al.: Reduced cancer incidence in Huntington's disease: analysis in the registry study. J Huntingtons Dis. 2018, 7:209-22. 10.3233/JHD-170263
41. Panegyres PK, Chen HY: Alzheimer's disease, Huntington's disease and cancer. J Clin Neurosci. 2021, 93:103-5. 10.1016/j.jocn.2021.09.012
42. Rocha N, Ringold J, Moreira Sassi KL, Lee E, Tharp E, Chandra S, Furr Stimming E: Revisiting the link between Huntington's disease and cancer: evidence from the Enroll-HD dataset. Neuroepidemiology. 2026, 1. 10.1159/ned/adwag003
43. Chan LL, Hill A, Lu G, Van Raamsdonk J, Gascoyne R, Hayden MR, Leavitt BR: Huntingtin overexpression does not alter overall survival in murine cancer models. J Huntingtons Dis. 2022, 11:383-9. 10.3233/JHD-220554
44. van Duijn E, Fernandes AR, Abreu D, Ware JJ, Neacy E, Sampaio C: Incidence of completed suicide and suicide attempts in a global prospective study of Huntington's disease. BJPsych Open. 2021, 7:e158. 10.1192/bjo.2021.969
45. Smith AJ, Yao X, Dix JA, Jin BJ, Verkman AS: Test of the 'glymphatic' hypothesis demonstrates diffusive and aquaporin-4-independent solute transport in rodent brain parenchyma. Elife. 2017, 6:e27679. 10.7554/eLife.27679