Please cite this article in press as: Murray et al., Accelerating biomedical discoveries in brain health through transformative neuropathology of aging and neurodegeneration, Neuron (2025), https://doi.org/10.1016/j.neuron.2025.06.014

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Perspective

Accelerating biomedical discoveries in brain health through transformative neuropathology of aging and neurodegeneration

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SUMMARY

Transformative neuropathology is redefining human brain research by integrating foundational descriptive pathology with advanced methodologies. These approaches, spanning multi-omics studies and machine learning applications, will drive discovery for the identification of biomarkers, therapeutic targets, and complex disease patterns through comprehensive analyses of postmortem human brain tissue. Yet critical challenges remain, including the sustainability of brain banks, expanding donor participation, strengthening training pipelines, enabling rapid autopsies, supporting collaborative platforms, and integrating data across modalities. Innovations in digital pathology, tissue quality enhancement, harmonization of data standards, and machine learning integration offer opportunities to accelerate tissue-level "pathomics" research in brain health through cross-disciplinary collaborations. Lessons from neuroimaging, particularly in establishing common data frameworks and multi-site collaborations, offer a valuable roadmap for streamlining innovations. In this perspective, we outline actionable solutions for leveraging existing resources and strengthening collaboration -where we envision future opportunities to drive translational discoveries stemming from transformative neuropathology.

INTRODUCTION

The integration of advanced multi-omics, digital pathology, and machine learning with traditional neuropathology is transforming our understanding of brain diseases with profound implications for diagnostics, therapeutics, and prevention. What was once the domain of science fiction is now our practical reality, with large-scale molecular-level 'omics studies of human brain tissue

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https://doi.org/10.1016/j.neuron.2025.06.014

uncovering novel biomarkers and therapeutic targets, high-throughput digital whole-slide imaging of microscope slides enabling computerized quantitative analysis of morphology and structural patterns of disease ("pathomics"), and greater availability of neuroimaging and fluid biomarkers to unveil diagnostic and prognostic neuropathologic alterations. Moreover, the high computational capacity provided by machine learning is driving unprecedented insights by enabling prediction, discovery, and characterization of subtle patterns across expansive transcriptomics, proteomics, and whole-slide image pathomics datasets. To explore the transition from theoretical potential to practical application in postmortem brain research, experts convened at a Banbury Center workshop hosted by Cold Spring Harbor Laboratory. A convergence of expertise in brain banking, neuropathology, high-dimensional molecular-level and tissue-level data ('omics), digital pathology, neuroimaging, computational methods, and machine learning was gathered to discuss approaches to optimize and enhance existing workflows and infrastructure in a rapidly evolving biomedical landscape. We report workshop outcomes to promote new biomedical discoveries and introduce the concept of "transformative neuropathology" (Figure 1), a term we use to describe the integration of foundational descriptive pathology with advanced technologies and methodologies. By defining this paradigm shift, we aim to inspire a reimagining of neuropathology's role in driving innovation and addressing critical challenges in brain disease research. For clarity, we use the term neuropathology to refer specifically to tissue-based studies, distinguishing it from biofluid biomarker changes that serve as peripheral indicators of underlying disease. This collaborative effort, driven by the principles of team science, acknowledges that our collective strength lies in the integration of complementary expertise to drive innovation and discovery. We structure this perspective by identifying key challenges facing the realm of research-based biorepositories of human brain tissue that can be utilized as a springboard to inspire future investigations and funding.

PROSPECTIVE BRAIN COLLECTIONS AND INCREASING REPRESENTATION FOR BROADER INSIGHTS

Brain banks, collections, or libraries can serve many functions, such as providing closure to donors' families through diagnostic evaluation, supporting transformative research, providing educational opportunities, and offering cross-disciplinary training opportunities in neuropathology (Figure 2).[2,3] The careful preservation and archiving of brains from individuals who consented to donation by skilled brain bank staff ensure the availability of high-quality tissue, critical to unraveling the complexities of the human brain.[4,5] This essential work not only provides the foundation for promoting scientific discovery but also strengthens the collaborative framework needed to tackle critical questions in aging and neurodegenerative research.[2,6] As the biomedical field continues to move from passive recruitment to active recruitment, expanding brain donor participation

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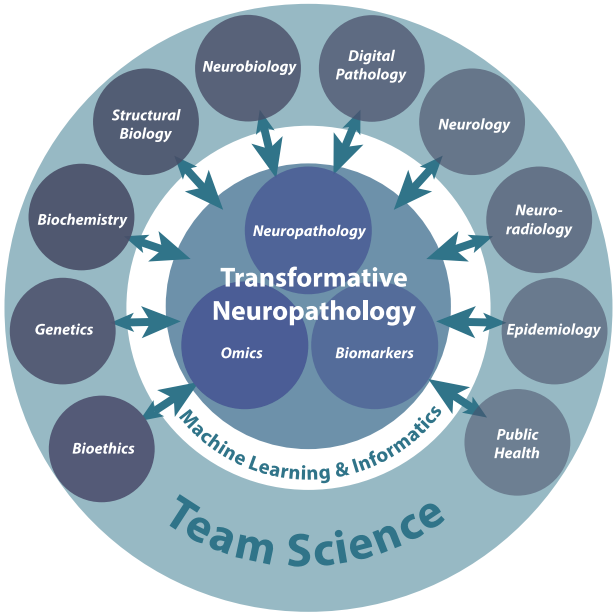

Figure 1. Transformative neuropathology

Through a convergence of team science collaborations, human tissue-based studies have the unprecedented ability to uncover molecular clues that advance our diagnostic and prognostic understanding of brain health and complex brain diseases. The integration of these complementary fields fosters innovative approaches that bridge descriptive pathology with cutting-edge technologies, enabling precise identification of disease mechanisms, predictive diagnostics, and targeted therapeutic strategies. This holistic framework exemplifies the potential of transformative neuropathology in the modern era of advanced biomedical research. Figure concept adapted from Gutt et al.[1]

across different backgrounds (i.e., economic status, aging across the lifespan, cognitive and motor health, geographic ancestry, and industrial and agricultural workers) becomes even more critical. Of particular importance for broader public health messaging and prioritization is the engagement of community advisory boards while enacting participant advisory boards for discussions on existing study protocols and study expansion. Knowledge sharing through audience-tailored informational material to increase global awareness of the role of research, particularly brain donation in populations at higher risk,[7–9] will greatly contribute to the reach of transformative neuropathology by strengthening trust and confidence in research participation (see Box 1 with reference to subsection in line with text).

Long-term research partnerships exemplified by the Oxford Project to Investigate Memory and Ageing,[10] Lothian Birth Cohort 1936,[11] Mayo Clinic Study of Aging,[12] Einstein Aging Study,[13] Minority Aging Research Study,[14] and Brain & Body Donation Program[15] emphasize engagement well before brain donation. Recruiting individuals across the aging spectrum may require intentional outreach strategies, such as including care partners of study participants already enrolled in longitudinal studies, to ensure a minimum set of consistent antemortem measures. In addition to cognitive and motor tests of functional impairment, expanded recruitment strategies open opportunities to optimize healthcare and financial decision-making tools[16,17] that can be compared with neuropathologic accumulation of lesion distribution and severity. Partnerships with ambassadors from the general public and with clinicians through multi-component cooperative program grants further provide mutual opportunities to receive and share knowledge to enhance healthy brain aging (Box 1.1).[18,19] Healthy aging brains provide a baseline understanding of age and sex differences in neuroanatomic structures that are key to the development of tissue-based atlases. Partnerships with internal medicine colleagues, as exemplified by collaboration with cardiovascular colleagues, may initiate a pipeline of well-characterized donors and strengthen communication of the relationship between heart and brain, especially from middle to older age.[20,21] Recruitment of family members and broader engagement with non-dyad support networks of potential brain donors hold great potential for enhancing communication and coordination. Partnerships with places of interment could further expand donor recruitment across populations with limited research participation,[2,22–24] especially helping to define the age range of histologic changes and their relevance as a control for young-onset disorders (e.g., frontotemporal dementia, Alzheimer's in individuals <65 years[25,26]) (Box 1.2). To identify biomarkers predicting brain health, a holistic perspective of cellular fitness and functional decline may be considered.[27–31] Recruitment of healthy aging brain donors remains critical to support predictive models of homeostasis, adaptation, and decline, enabling identification of biomarkers indicating changes in brain vitality (Figure 3).

BUILDING CAPACITY FOR EXPERTISE IN NEUROPATHOLOGY AND INFORMATICS

Historically, the qualifications for brain bank directorship included holding a medical degree with formal medical training. However, with fewer neuropathologists entering the field, there is an immediate need to engage junior neuropathology experts in aging and neurodegenerative research and expand the range of trained professionals who can develop and manage a brain bank (Box 2).[32] The operations required to facilitate brain donation and tissue provision are complex and involve unique expertise that may take years to acquire/master.[3] Neuropathology expertise requires extensive training as an MD or PhD to enable systematic evaluation of age-related histologic changes and a full range of neurologic conditions, including neurodegenerative diseases, cerebrovascular lesions, demyelinating and other neuroinflammatory conditions, central nervous system infections, and neoplastic, metabolic, and neurodevelopmental disorders, depending upon the brain bank's focus. As diagnosis may be a small fraction of the variety of tasks involved in operations, it is imperative to have knowledge of research methodologies and the scientific process when leading a brain bank. Emphasis on training pipelines provided across brain bank networks geared toward neuropathology clinical fellows and neuroscience research trainees is recommended. Brain bank operations training should include didactic workshops and experiential learning on leadership, management, accounting, histology, neuroanatomy, and microscopy to fortify the pipeline of neuropathology faculty (Box 2.1). To further strengthen the future of brain banks with informatics support, data science training with formal training through coursework and hands-on

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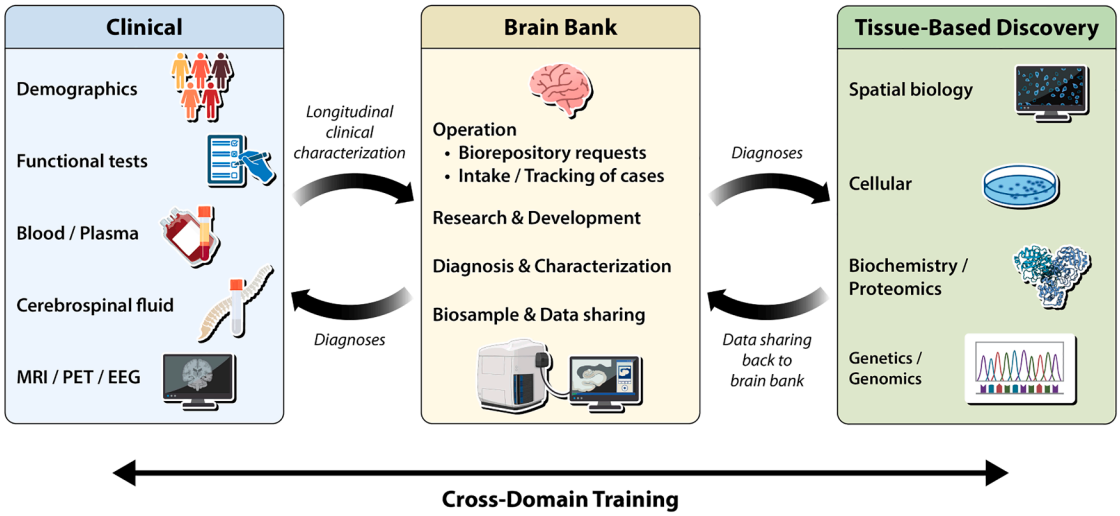

Figure 2. Overview of a brain bank ecosystem

Three boxes depict the ideal brain bank ecosystem with bidirectional flow of information and cross-domain training toward accelerating biomedical discoveries. Blue box: in the clinical domain, when a person is alive, measures such as their demographics (e.g., economic status, age, geographic ancestry, and occupation), functional tests (cognitive/motor health and financial/healthcare decision-making), fluid biomarkers (e.g., blood, plasma, and cerebrospinal fluid), and/or neuroimaging (e.g., MRI, PET, and EEG) data may be collected through prospective cohort studies, providing an antemortem foundation for correlative studies involving other domains (yellow and green boxes). Yellow box: the main functions of a brain bank include tracking/intake of decedents, processing/characterizing of the brain, as well as storing and sharing tissue and associated data. Green box: the tissue-based discovery domain, biosamples/data from the brain bank can be utilized across many methodologies for hypothesis/data-driven discoveries. Data can be shared across all domains, demonstrated by bidirectional arrows, thus enriching multimodal data linkage to biosamples. Training should span across all three domains to aid in a convergence of team science, as this is needed to optimize the transformative potential of the resources (see Figure 1). Note: figure created in BioRender. Acronyms: EEG, electroencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography.

experience is additionally recommended (Box 2.2). Ease of access to human brain tissue for qualified investigators is crucial for supporting translational research. The United Kingdom Brain Bank Network,[33] Netherlands Brain Bank,[34] Parkinson's Progression Markers Initiative (PPMI),[35] Rush Alzheimer Disease Center,[36] National Alzheimer's Coordinating Center,[37] and National Institute of Health's NeuroBioBank,[38] provide an accessible portal for qualified researchers to identify and request human brain tissue. These portals required significant investment in infrastructure and integration of informaticians, showcasing the benefit of dedicated funding for data scientists, bioinformaticians, and biostatisticians to work continually with neuropathology experts with the goal of sustained improvements based on user feedback.

Broader access to neuropathology training for a more novice audience through conference workshops and publicly available neuropathology-based encyclopedias[39] is also recommended to enhance communication between tissue requestors and tissue providers (Box 2.3). Given the importance of paired phenotypic data with tissue selection (Figure 2), strengthening collaborations with clinicians to enhance translational potential of tissue-based discoveries and consideration of structured clinical training of brain bank support staff to enhance retrospective abstraction of clinical progression are recommended (Box 2.4). Initiatives to enhance the sustainability of brain banks amidst ever-increasing demand for tissue provision may be fostered through infrastructure built into research project grants and cooperative program grants led by brain bank directors, working with home institutions to create cost recovery mechanisms, partnering with development for philanthropic sponsorship, engaging with leadership for institutional support, collaborating with intramural researchers in field-adjacent domains (e.g., cancer research), or applying to government-led opportunities (e.g., the National Institute of Health's NeuroBioBank[38]). The Netherlands Brain Bank[40] and Banner Sun Health's Brain & Body Program instituted partial support through a cost recovery model to facilitate staffing for tissue provision.[15,41] The United Kingdom Brain Bank Network adopted a similar cost recovery model, along with the development of harmonized protocols, legal guidance, and administrative guidance for a comprehensive approach to sustainable brain banking.[33] Sustained support could also enable centralized portals to streamline tissue requests and dissemination while providing access to practical guidance, tutorials, and consultation opportunities. These platforms would promote consistent implementation of best practices and broaden engagement across institutions and experience levels.

INNOVATING TISSUE QUALITY STRATEGIES TO UNLOCK MOLECULAR INSIGHTS

Maximizing the potential of molecular discoveries in aging and neurodegenerative research requires innovative strategies to overcome the limitations posed by the use of archival human brain tissue (Box 3). Advances in molecular-level and tissue-level 'omics (Figure 4), including bulk, single-cell, and spatially resolved methods, enable precise identification of disease signatures.[42–52] High-throughput analysis of frozen or formalin- (or

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Box 1. Low autopsy rate for healthy aging and groups with limited representation in scientific research

Actionable solutions	Timing	Funding
1.1 Enhanced education on brain donation through outreach		
Engaging through science writing for the layperson (e.g., newspapers and social media)	short	institutional
Audience-tailored educational material to increase knowledge of brain donation	short	pilot
Workshops for brain bank coordinators and outreach specialists	short	pilot
Engaging community advisory boards (e.g., respected elders and religious leaders)	short	cooperative
Engaging participant advisory boards on existing study protocols and expansion	short	cooperative
Involving donor families and support networks in outreach efforts for brain donation	short	cooperative
Specialized brain bank coordinator dedicated to public engagement and education	long	cooperative
Centralized web portal to share autopsy technician lists and protocols globally	long	visionary
1.2 Enhanced efforts to recruit healthy aging and broaden the age spectrum of brain donors		
Database entry of recruitment sources for study consideration	short	institutional
Training staff in sensitive etiquette when obtaining consent and medical history	short	institutional
Recruitment from the same recruitment areas as neurodegenerative brain donors	long	cooperative
Partnering with places of interment (e.g., medical examiners and funeral homes)	long	cooperative
Partnering with internal medicine (e.g., gut-brain, heart-brain, and kidney-brain axis)	long	visionary
Impact: broadening education and outreach around brain donation will equip the general public with practical knowledge, build confidence, and increase donor participation, providing researchers with higher-quality, more representative tissue to fuel discovery. Expanding recruitment of healthy aging individuals will transform neuropathology by enabling the creation of generalizable, predictive models of brain health (i.e., homeostasis and vitality), adaptation (i.e., protection and maintenance), and functional decline (i.e., impairment and loss of vitality). These efforts will help researchers and clinicians uncover protective factors, construct personalized aging trajectories, and proactively sustain cognitive resilience through the identification of brain health biomarkers. For the general public, these efforts will contribute to discoveries that extend quality of life, ease caregiving burdens, and strengthen families and economies by elevating brain donation into a celebrated societal contribution.		
Note: actionable solutions were ranked by feasibility, with a tiered funding model considered. Timing: short, immediately actionable; long, long-term aspirations. Funding: institutional: intramural funding opportunities enhancing local impact; pilot: intramural or foundation funding with tangible outcomes; cooperative: foundation or government-sponsored awards enabling program project support of outreach and neuropathology cores; visionary: collaborative funding through partnerships across foundations, government, and/or industry to enable pathways to breakthroughs.		

otherwise) fixed paraffin-embedded (FFPE) brain tissue offers unbiased, multimodal insights into brain physiology and disease, supporting breakthroughs like whole-brain mapping,[43,46,50,53,54] network modeling to uncover druggable targets,[52,55] and identification of key post-translational modifications.[56,57] Omics-based research has emerged as a guiding force in the study of both neuronal and glial biology of aging, highlighting pathway dynamics to discern biologic perturbations as exemplified in human brain development,[58] aging,[59] Alzheimer's disease,[43,60,61] amyotrophic lateral sclerosis,[62] Huntington disease,[47] Lewy body disease,[63] and progressive supranuclear palsy.[64] Deep, quantitative neuropathologic characterization combined with molecular-level 'omics data further enables the reconstruction of cellular trajectories in brain aging and pseudoprogression of disease phases.[43,65] These types of work, made possible by broad collaboration and integration of various data modalities, delineate a clear path toward identifying critical phenotypic markers of cellular states for broader consideration of molecular

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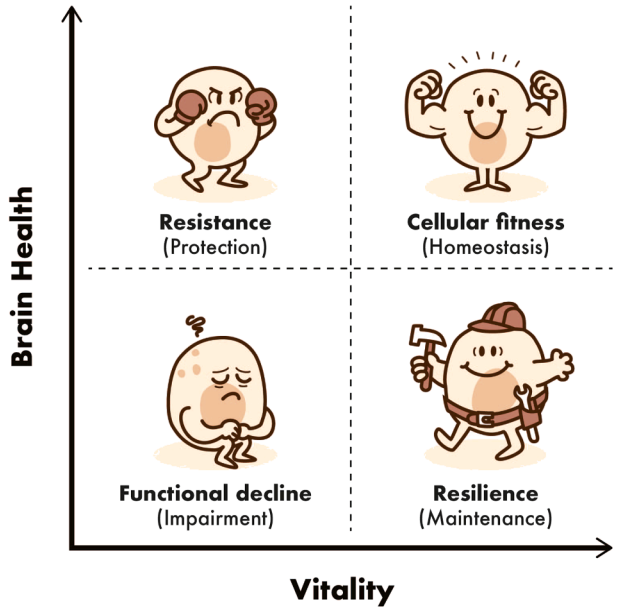

Figure 3. Framework for identifying predictive markers of brain health

Vitality and brain health are mapped along orthogonal axes to illustrate hypothesized transitions in cellular states and biomarkers relevant to aging and neurodegeneration. The top right quadrant represents cellular fitness (homeostasis), depicted as high vitality and health. The top left quadrant reflects resistance (protection) or avoidance of neuropathology. The bottom right quadrant illustrates resilience (maintenance) or coping with neuropathology. Finally, the bottom left quadrant portrays functional decline (impairment), visualized as a loss of vitality with a broken circuit. This model framework personifies cellular responses, emphasizing the potential to identify vitality biomarkers that predict preserved or declining brain health.

diagnostics. Perhaps paving the way to investigating the frequent observation of mixed pathologies in neurodegeneration by challenging the notion that concurrent proteinopathies are merely coincidental or secondary. Instead, concurrent pathologies may reflect a broader systems-level vulnerability in which perturbations in one molecular pathway destabilize others, fostering the emergence of codeposition of neuropathologic features as composite phenotypes (e.g., TAR DNA-binding protein 43 [TDP-43] immunoreactivity in tau-positive tangles or astrocytic plaques[66–69]). This alternative hypothesis considers a shift from viewing mixed pathologies as independent, coexisting diseases to the consideration that codeposition itself represents a distinct, biologically meaningful disease state. Molecular diagnostics beyond immunohistochemistry have the potential to transform neurodegenerative disease management of brain health through a deeper understanding of cellular fitness changes, preclinical detection, and individualized treatment. Evaluation of biopsies from peripheral organs, skin, or biofluids is also expected to gain momentum in this critical area (Box 3.1).[20,31,70]

Scientific advances, like those uncovered by cryo-electron microscopy,[71–75] are the direct result of innovative approaches to investigate archival brain tissue. A coordinated effort to develop methods for utilizing pre-existing materials (e.g., stored fixed or frozen tissue) is essential to unlocking the full potential of archival collections. As technology advances, new approaches (e.g., probe-based technology for FFPE tissue[7]) can be applied to tissue previously considered suboptimal (Box 3.2). New imaging techniques, like array tomography combined with super-resolution microscopy, require non-standard autopsy tissue processing,[76,77] which includes immediate use of fresh tissue upon procurement (Box 3.3). This necessitates additional funding to support brain bank staff to perform rapid-response protocols and ensure timely communication between tissue providers and the research team. Through continued collaborative innovations, we stand at the precipice of further breakthroughs in brain health that are needed to alleviate the burden of these devastating diseases on individuals and their families. To future-proof valuable tissue samples (i.e., biosamples) for multi-scale 'omics methodologies, the continuation of centralized resources is recommended to establish best practices and minimum standards for tissue preparation (e.g., fixation and freezing) and storage (Box 3.4). While it may not be possible to overhaul protocols for the entirety of a brain bank's archival collection, it is crucial to understand the quantitative variables that ensure optimal tissue quality for each modality and to underscore the importance of a flexible and collaborative framework between neuropathology experts and researchers to allow for innovative use of tissue.[2,76–78]

STREAMLINING DIGITAL SLIDE SHARING AND ANALYSIS TO ENHANCE TRANSLATIONAL PATHOMICS

Digital pathology is a versatile technology that continues to advance our understanding of the spatial biology of age-related changes, neurodegenerative lesions, and cerebrovascular insults.[79–81] To maximize the utility of digital pathology, there is a need for efficient slide-sharing capabilities and neuropathology-centric initiatives (Box 4).[3,82] Whole-slide images are scanned at high resolution to enable the neuropathology expert, clinician, and/or researcher to digitally view the entirety of the tissue or specific areas of interest. Digitized slides can be annotated for diagnostic, research, and/or educational purposes. Digitization comes with the added value of integrating pathomics analyses through computational analytic tools for high-throughput image segmentation of neuroanatomic structures to objectively quantify lesions and histologic changes (Box 4.1). Efforts to compare established semi-quantitative scores with digital pathology measures show a strong correlation between the manual scores and digitized measures, offering hope toward automated quantification of disease burden.[83–86] Staging systems of neurodegenerative diseases[87–93] are often inherent to the success of consensus initiatives with clinician and scientific partners.[94–100] With digital pathology already benefiting efforts like the Rainwater criteria for progressive supranuclear palsy[99] and McKee criteria for chronic traumatic encephalopathy,[91] we embrace a present reality with continued opportunities to apply machine learning and neural networks to systematically analyze whole-slide images using pathomics approaches to complement diagnostic procedures in a brain bank.[86,101–105] Toward envisioning a future where integrated pathomics models of neurodegeneration exist for real-time comparison, inspiration may be drawn from lessons learned by computational approaches in neuroimaging to capture heterogeneous tissue and lesion morphology (i.e., radiomics).[106–111]

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Box 2. Dearth of neuropathology experts and informaticians with brain banking knowledge

Actionable solutions	Timing	Funding
2.1 Neuropathology training fellowships for MDs and PhDs		
Training initiatives to enhance collaboration across brain bank networks	short	pilot
Workshops on leadership, management, accounting, histology, and neuroanatomy	short	pilot
Training pipelines for MD- and PhD-trained clinicians and scientists	long	pilot
Pathway to independence support for neuropathology experts	long	visionary
2.2 Data science training and integration		
Postbaccalaureate informatics training through didactic summer coursework	short	pilot
Structured mentorship for informaticians in aging and neurodegeneration research	short	project
Training Without Walls pilot projects across an expansive network of brain banks	long	visionary
2.3 NeuroPathopedia—Neuropathology-based encyclopedia		
Online resource cataloging macroscopic and microscopic histologic features	short	pilot
Digitization of WSI with interactive tools with diagnostic/molecular information	short	pilot
Citizen science approach to labeling structures/cellular architecture/lesions on WSI	long	visionary
2.4 Phenotypic data collection and tissue provision		
Clinician partnerships in the cohort-building process and interpretation of results	short	institutional
Clinical progression, lifestyle, and cardiovascular risk factors databased	short	pilot
Perimortem events (e.g., details on the agonal period, cause of death, and tissue quality)	short	pilot
Brain bank-specific LIS with a relational database for metadata and tissue provision	long	cooperative
Specialized database management professional dedicated to brain bank	long	cooperative
Clinical abstraction in real-time as brains are being accessioned	short	visionary
Disease-agnostic web portal of tutorials, best practices, and challenges/strategies	long	visionary

Impact: working to address the shortage of neuropathology experts and informaticians will promote a new era of discovery by cultivating a scientific workforce skilled in innovative data integration, digital pathology, and collaborative brain banking. For clinicians, these initiatives will deepen connections between clinical care and research, leading to richer diagnostic insights, dynamic data interpretation, and a more nuanced understanding of brain health across the lifespan. For the general public, the development of publicly accessible resources like NeuroPathopedia and a transparent data ecosystem will honor donor contributions, accelerate discovery, and inspire a societal movement toward achieving breakthroughs in neurodegenerative disease.

Note: actionable solutions were ranked by feasibility, with a tiered funding model considered. Metadata is defined as accompanying information pertaining to file type, tissue preparation, and neuroanatomic structure. Acronym: LIS, laboratory information system; WSI, whole-slide images. Timing: short, immediately actionable; long, long-term aspirations. Funding: institutional: intramural funding opportunities enhancing local impact; pilot: intramural or foundation funding with tangible outcomes; cooperative: foundation or government-sponsored awards facilitating clinical training, cross-disciplinary partnerships, and broader impact through enhanced digital communication; visionary: collaborative funding through partnerships across foundations, government, and/or industry to enable pathways to breakthroughs.

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Box 3. Tissue quality innovations needed to maximize molecular discoveries

Actionable solutions	Timing	Funding
3.1 Molecular and biochemical diagnostics beyond immunohistochemistry		
Utilize pre-existing archival brain bank material for tissue innovations	short	pilot
Partnering with clinicians to evaluate the utility of biopsied antemortem brain tissue	short	pilot
Quantitative comparison of biofluid changes with postmortem brain changes	short	project
Comparison of skin or peripheral organ changes to brain as biomarker readouts	long	visionary
Develop a region-based molecular atlas prioritizing selectively vulnerable regions	long	visionary
Compare systems-level whole-brain spatial molecular atlas across the aging spectrum	long	visionary
3.2 Enhancing procurement areas and autopsy response teams for biosample collection		
Specimen procurement facilities designed for tissue procurement	long	institutional
Rapid-response, on-call 24/7 autopsy teams to enhance postmortem tissue quality	long	visionary
3.3 Harmonization in tissue preparation (fixative, freezing), storage, and inventory		
Dedicated brain bank staff updating minimum needs for fixation and freezing	short	institutional
Working group on basic methods for tissue preparation for emerging technologies	short	pilot
Working group on QC methods for tissue archival metrics for frozen and fixed tissue	short	pilot
Working group on cost-benefit of 'omics approaches to maximizing scientific yield	short	pilot
Mediation analyses of QC metrics with 'omics data to assess disease contribution	long	project
Deployment of brain bank-specific inventory systems with harmonization standards	long	visionary
Impact: advances in tissue procurement, tissue quality, and molecular diagnostics will expand the scientific scope of brain banking, allowing researchers to chart new biological landscapes, refine predictive models, and drive advances across emerging technologies. For clinicians, enhanced access to well-characterized tissue will sharpen clinicopathologic correlations, supporting earlier identification of risk profiles and personalized cognitive health strategies. For the general public, maximizing the scientific value of each donation will accelerate discovery and foster families and communities through breakthroughs that promote brain health across the lifespan.		
Note: actionable solutions were ranked by feasibility, with tiered funding model considered. Acronym: QC, quality control; 24/7, 24 h a day, 7 days a week. Timing: short, immediately actionable; long, long-term aspirations. Funding: institutional: intramural funding opportunities enhancing local impact; pilot: intramural or foundation funding with tangible outcomes; project: foundation or government-sponsored awards facilitating investigator-initiated, hypothesis-driven research; visionary: collaborative funding through partnerships across foundations, government, and/or industry to enable pathways to breakthroughs.		

Centralized neuropathology efforts to host and share digital slides are vital to overcoming local infrastructure limitations and fostering collaboration (Box 4.2).[114] Notably, the Digital Slide Archive,[115] originally designed for cancer research,[116] is being adapted for aging and neurodegenerative disease research, showcasing the potential for global collaboration (Box 4.3).[82] In lieu of a central repository, individual brain banks are drawing upon local resources and philanthropy to make their collections digitally available.[117] The benefits of digital pathology go beyond technical aspects. Integration of digital pathology into clinical practice offers significant potential for improved diagnostics and treatment planning through systematic analyses of autopsied individuals with antemortem clinical data.[118–121] For example, digital pathology can quantitatively measure histologic changes, enhancing the translational value of postmortem studies that investigate neuroimaging and fluid biomarker changes.[122–124] By capturing the heterogeneity of neurodegeneration and aging brains, digital pathology supports research toward developing

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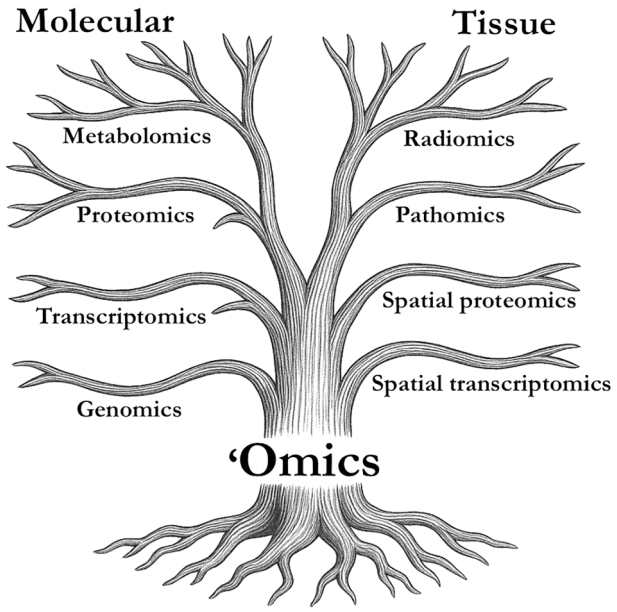

Figure 4. Molecular-level and tissue-level 'omics branches
The illustration depicts two primary branches of the interrogation of high-dimensional data in the 'omics field. Broad molecular-level classification includes bulk or single-cell genomics of DNA (epigenomics, pharmacogenomics), transcriptomics of RNA (epitranscriptomics), proteomics of proteins (interactomics, structural proteomics), and metabolomics of metabolites (lipidomics, glycomics, fluxomics). Broad tissue-level 'omics classification includes spatial transcriptomics and spatial proteomics with molecular profiling of preserved tissue architecture, pathomics of morphologic and structural whole-slide imaging features, and radiomics of extracted features from neuroimaging.

targeted, personalized treatments.[79,93,125,126] As the aging and neurodegeneration fields advance, continued exploration, collaboration, and support for an alliance of worldwide brain banks could be key to unlocking the full potential of digital pathology in biomedical research and clinical applications (Box 4.4).

BUILDING COLLABORATIVE PLATFORMS TO ACCELERATE TISSUE-BASED DISCOVERIES

Key considerations regarding increased slide digitization and increasingly linked molecular-level and tissue-level 'omics datasets are data storage and harmonization of common data elements (Box 5). There is a critical need for data to be harmonized, comply with international data protection laws, and use common data models to allow access and analysis between research groups without dependence on proprietary software.[82] Looking to the neuroimaging field for inspiration, notable initiatives demonstrating the aspirational power of unity in scientific exploration, comprise among others PPMI[35] and Alzheimer's Disease Neuroimaging Initiative (ADNI).[127] Recognizing the importance of a central data repository, universal file formats, and the need for collaborative platforms—the Laboratory of NeuroImaging (LONI) was founded.[128] LONI's focus on data sharing enhances transparency and harmonization within the neuroimaging community,[129] benefiting multi-site interpretation of data. LONI houses and manages ADNI data, enabling the infrastructure for ADNI's harmonization efforts that continue to accelerate progress in understanding Alzheimer's disease and related dementias. ADNI data are used to both test[130] and validate novel hypotheses.[109] However, the applicability of ADNI-based findings across economic backgrounds, as well as those having multiple disease etiologies,[131] was recognized as a limitation motivating novel recruitment efforts with focused efforts to strengthen study participation.[132] Qualified researchers seeking to reverse engineer postmortem findings[87,88,133] can request data from initiatives like ADNI,[134] PPMI,[35] and the Longitudinal Early Onset Alzheimer's Disease Study[135] to more broadly examine heterogeneous biomarker patterns through identification of longitudinal trajectories[111] or toward enhanced molecular diagnostics of fluid biomarkers.[136,137] Conversely, open platforms and online repositories for neuroimaging (e.g., OpenNeuro[138] and Neurovault[134]) and high-dimensional molecular data (e.g., Alzheimer's disease knowledge portal[139] and Global Parkinson's Genetics Program[140]) enable data deposition from individual groups to enhance reusability of datasets.

As we usher in the next frontiers of neuropathology, harmonizing methodologies and data across research endeavors to promote interoperability standards for common data elements with enough flexibility for local innovation will be critical.[82,141] Integrating digital pathology and 'omics datasets, ranging from immunohistochemistry to spatial transcriptomics, remains a major challenge due to variability in biosample processing, staining protocols, and analyte stability. To address this, a tiered harmonization framework built out by working groups, where core elements are harmonized while preserving flexibility for site- or study-specific innovations, may offer a practical path toward cross-laboratory reproducibility and interoperability. However, caution should be applied to mandatory adherence to common data elements to avoid penalization of brain banks that lack funding to update protocols (Box 5.1). By implementing a case-level tracking system through a digital object identifier (DOI) (Box 5.2) in collaboration with bioethicists and establishing a codified brain library through an accessible portal, data tracking, sharing, and harmonization will be enhanced, laying a robust foundation for future advancements (Box 5.3). The DOI system would allow brain banks to assess tissue quality through automated feedback from publications and enable researchers to select the highest quality biosamples for new studies while integrating findings from earlier analyses. This system could not only increase the value of existing brain tissue repositories but also accelerate biomedical discoveries. A key feature of tissue preservation is systematic neuroanatomic dissection. Looking ahead, the development of a human common coordinate framework[142] emerges as a visionary approach to further enhance harmonization (Box 5.4), offering a unified language for researchers worldwide and firmly establishing the biomedical science community in an era of transformative neuropathologic research. Similar approaches were developed for antemortem neuroimaging, such as the "neuromaps" initiative working across multiple brain maps.[143] Currently, annotation of Brodmann areas in reference to the Allen Brain Atlas[144,145] is an increasingly used neuroanatomic resource that could be leveraged to create the human common coordinate framework. As spatial biology interrogation of the human brain continues to

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Box 4. Limited capabilities for digital slide sharing to facilitate harmonization of disease staging and capturing phenotypic heterogeneity

Actionable solutions	Timing	Funding
4.1 Neuroanatomic segmentation for digitized slides		
WSI brain segmentation software tools to distinguish gray matter and white matter	short	pilot
WSI masking tools for (sub)cortical structures, lamina, and nuclei subdivisions	long	visionary
4.2 Slide-sharing efforts		
Working groups toward the development of recommended metadata terminology	short	pilot
Brain bank personnel with coding skills and/or computer engineering collaborations	long	project
Open-source WSI software employed locally for FAIR slide-sharing purposes	short	cooperative
WSI file type harmonization to common standard (e.g., DICOM, TIFF, and OME-NGFF)	long	visionary
4.3 Alliance of brain banks		
Workshops for brain banking and digital pathology training	short	pilot
Working group on FFPE tissue preparation and IHC reporting standards	short	pilot
Working group on tissue banking for high-quality fixed and frozen tissue	long	pilot
Operationalize misfolded protein quantification using digital pathology/ML tools	short	cooperative
Operationalize CVD/WM changes quantification using digital pathology/ML tools	short	visionary
Develop open-source tools on heterogeneous datasets across multiple brain banks	long	visionary
Centralized portal to deposit reporting standards, recommendations, and tools	long	visionary
Impact: expanding digital slide sharing, neuroanatomic segmentation tools, and harmonized metadata standards will transform global brain banking into an integrated, data-rich ecosystem that enables researchers to uncover previously inaccessible pathomics dimensions of disease heterogeneity and resilience. For clinicians and researchers alike, more precise digital pathology will accelerate the translation of multimodal neuroimaging and molecular data into individualized insights on brain aging trajectories. For the general public, the creation of a connected, open access digital infrastructure will broaden research opportunities, ensuring every donation fuels impactful and generalizable science. Together, these advances will usher in a new global era of collaborative, precision-driven neuropathology.		
Note: actionable solutions were ranked by feasibility, with a tiered funding model considered. Metadata is defined as accompanying information pertaining to file type, tissue preparation, and neuroanatomic structure. Acronym: CVD, cerebrovascular disease; DICOM, digital imaging and communications in medicine[112]; FAIR, findable, accessible, interoperable, and reusable; IHC, immunohistochemistry; ML, machine learning; TIFF, tag image file format; OME-NGFF, open microscopy environment's next generation file format[113]; WM, white matter; WSI, whole-slide image. Timing: short, immediately actionable; long, long-term aspirations. Funding: pilot: intramural or foundation funding with tangible outcomes; project: foundation or government-sponsored awards facilitating investigator-initiated, hypothesis-driven research; cooperative: foundation or government-sponsored awards facilitating cross-disciplinary partnerships and broader impact through enhanced digital communication; visionary: collaborative funding through partnerships across foundations, government, and/or industry to enable pathways to breakthroughs.		

accelerate, brain banks may consider translating local sampling protocols to publicly available tissue atlases for reporting of regions and Brodmann areas toward wider applicability of tissue-based findings.

The groundbreaking partnership of a neuropathologist and neurobiologist's team in the Seattle Alzheimer's Disease Brain Cell Atlas provides a fruitful example of flexibility within a brain bank to enhance background diversity of biosample collection,

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Box 5. Relative lack of common neuropathologic data models and secure storage platforms

Actionable solutions	Timing	Funding
5.1 Data harmonization for common data elements		
Working group on minimum set of common core data elements (e.g., age and location)	short	pilot
Working group on aging- and disease-relevant variables both validated/replicated	short	pilot
Working group on optimal experimental variables aligning with broad pursuits	short	pilot
Data framework to delineate quality control measures and experimental metrics	long	cooperative
Implementation of protocol updates with flexibility to allow for local innovation	long	visionary
5.2 Biosample-level tracking through a universal digital object identifier		
Develop methods to apply PHI-free DOI brain donors and tissue/data derivatives	short	pilot
Integration and backfilling of the PHI-free DOI to existing repositories	short	cooperative
5.3 Codified brain library through an accessible portal		
Centralized, affordable data storage for slide-sharing efforts and publication deposit	long	cooperative
Disease-agnostic systematized entry portal with minimum standards for metadata	long	visionary
5.4 Common coordinate framework		
Working group on CCF agreement/implementation toward a common language	short	pilot
CCF development to establish neuroanatomic reference points at microscale	long	cooperative
Atlas-based warping of local sampling procedures to CCF using postmortem MRI	long	cooperative
CCF multi-site implementation as a unifying framework for spatial representation	long	visionary
Impact: developing and implementing common data models, secure tracking systems, and a unified coordinate framework will establish an integrated foundation for brain banks, enabling researchers to produce scalable, reproducible discoveries that transcend single-site limitations. For clinicians, harmonized data integration will support earlier identification of disease patterns, autopsy-confirmed longitudinal tracking, and more tailored cognitive health strategies. For the general public, these innovations will amplify the scientific impact of brain donation, accelerating interventions that extend healthy lifespan and ease the burdens of cognitive decline. Collectively, these efforts will orchestrate a robust, data-driven infrastructure to drive future discoveries in brain health.		
Note: actionable solutions were ranked by feasibility, with tiered funding model considered. Metadata is defined as accompanying information pertaining to file type, tissue preparation, and neuroanatomic structure. Acronym: CCF, common coordinate framework; DOI, digital object identifier; MRI, magnetic resonance imaging; PHI, protected health information; WSI, whole-slide image. Timing: short, immediately actionable; long, long-term aspirations. Funding: pilot: intramural or foundation funding with tangible outcomes; cooperative: foundation or government-sponsored awards facilitating cross-disciplinary partnerships and broader impact through enhanced digital communication; visionary: collaborative funding through partnerships across foundations, government, and/or industry to enable pathways to breakthroughs.		

interdisciplinary collaboration, adaptability to new research questions, comprehensive metadata, and ethical considerations.[43] The Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD) team has pioneered the development of open access tools to study the human brain at a granular level, allowing for an unprecedented resolution of Alzheimer's disease pathology.[43,46] By categorizing individual cells based on gene activity, the cooperative program team aims to identify selectively vulnerable neuronal and glial cell types, laying the groundwork for targeted therapies. While the protocols developed may not be applicable or even possible to apply to large-scale brain banking efforts, the focused effort to categorize individual cells based on gene activity on even a small number of brains continues to yield big results.[43,46,53,145,146] We embrace a new era where cross-disciplinary collaborations resulting from

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Box 6. Emerging need for machine learning to optimize brain bank workflow

Actionable solutions	Timing	Funding
6.1 Quality control for digitized slides		
Open-source integration of deidentification scripts to scrub PHI from slide label	short	pilot
Working group to develop metadata companion to replace PHI on slide label	short	pilot
QC repository of tissue artifacts (e.g., agonal events, processing, and digitization)	short	pilot
Open-source integration of QC factors evaluating slide staining and scan quality	long	cooperative
6.2 Convergence of multimodal data streams		
Develop efficient data organization models to amalgamate multimodal data streams	long	cooperative
Deploy model to unveil hidden patterns while factoring in potential bias in datasets	long	visionary
Impact: integrating machine learning into brain banking will enhance a precision-driven future by automating quality control, improving data integration, and revealing complex biological patterns. For researchers and clinicians, these advances will streamline tissue validation, facilitate metadata standardization, and unlock personalized risk trajectories of predictive models across the aging continuum. For the general public, applying computer-based approaches to maximize the value of brain donation will accelerate innovation, extend healthy brain span, and reduce the societal and economic impact of neurodegenerative disease. Together, these advances will fuel a dynamic new era where brain banking becomes a catalyst for lasting breakthroughs in healthy brain aging.		
Note: actionable solutions were ranked by feasibility, with tiered funding model considered. Metadata is defined as accompanying information pertaining to file type, tissue preparation, and neuroanatomic structure. Acronym: PHI, protected health information; QC, quality control. Timing: short, immediately actionable; long, long-term aspirations. Funding: pilot: intramural or foundation funding with tangible outcomes; cooperative: foundation or government-sponsored awards facilitating cross-disciplinary partnerships and broader impact through enhanced digital communication; visionary: collaborative funding through partnerships across foundations, government, and/or industry to enable pathways to breakthroughs.		

cooperative program successes will continue to inspire visionary opportunities in molecular connectivity mapping, disease microenvironment analysis, drug target discovery, and intelligent diagnostics.

HARNESSING MACHINE LEARNING TO REVOLUTIONIZE BRAIN BANKING

While attention is primarily focused on applying machine learning for research endeavors seeking to automate time-intensive, repetitive work and diagnostic applications,[147–149] it is imperative to explore the vast spectrum of potential applications beyond these domains (Box 6). The untapped potential of machine learning could revolutionize processes beyond diagnostic prediction to instead focus on "pain points" in data acquisition and processing in a brain bank. Consider the prospect of expediting quality control workflows through quality control mechanisms where machine learning serves as an adept assistant in expediting tasks and enhancing overall efficiency of brain banking and digital pathology workflows (Box 6.1). For instance, the integration of machine learning in decision-making could extend to the realm of selecting suitable cases for specific molecular-level and tissue-level 'omics analyses, streamlining research pathways, and optimizing resource allocation. Moreover, image analysis tools from the private sector[150] are already developed for image sharpening, modulating, and transforming, simply awaiting creative application to histologic images. To mitigate privacy and reduce security concerns over stored genotype-phenotype data, analytic tools could be designed without the ability to decrypt genetic data or to scrub protected health information from digitized microscope slide labels.[151] The journey toward fully harnessing machine learning's potential will entail envisioning and embracing novel use cases that enhance outcomes and foster a more streamlined and effective ecosystem.

Looking to the future, the power of advancements in computational pathomics pipelines could be redirected toward seemingly obsolete techniques. By combining pioneering data processing methods with historic approaches (e.g., Nissl) or routine techniques (e.g., hematoxylin & eosin [H&E]-stained tissue), it may be possible to discover intricate markers and insights through simpler and more widely accessible measures. This transformative approach relies on training complex models with high-level data and then distilling that knowledge for application to routine technologies like H&E staining.[152] Computer-driven visualization and data mining from existing slide archives hold immense potential for identifying previously overlooked cellular and subcellular changes,[153] as well as enabling integration with genomics[154] and other large-scale data sources. Importantly, adapting machine learning models to routine stains, such as H&E staining, carries little risk. Limited data availability, particularly well-annotated whole-slide images, remains a major barrier to machine learning adoption in neuropathology. Addressing this will require harmonization of digital workflows

across brain banks, increased interoperability for slide sharing, and creation of centralized, annotated repositories. Emerging methods such as transformer-based histopathology models and foundation models trained via multiple instance learning offer promise, while scalable solutions like cloud-based computing may enable efficient handling of petabyte-scale image datasets and multimodal integration.[102,155–162] Foundation modeling and weakly supervised modeling are promising areas to ameliorate the pains of limited annotated data by training on what is available (i.e., unlabeled slides or slide-level labels rather than specific in-slide labels).[163–165]

To overcome the relative lack of labeled images to inform classification or segmentation models,[163] recent vision-language foundation models for pathology have introduced promising solutions. For example, leveraging image-text pairs with descriptions available from medically oriented social media, the Large-scale Artificial Intelligence Open Network,[166] educational sources, and images and descriptions from PubMed literature, the OpenPath dataset was developed.[163] These vision-language pathology models enable users to retrieve examples by image-based or natural language searches.[163,164] Moreover, machine learning approaches are already providing an expanded repertoire for 'omics studies through integration with light microscopy for isotropic super-resolution of synapses,[167] decision-making for gene prioritization,[168] and lesion identification.[86,101,102,104,105] Application of machine learning may play a critical role in facilitating a convergence of data streams (Box 6.2), seeking to propel the biomedical science community forward as researchers continue to push the bounds through integration of complex technologies like spatial transcriptomics and electron microscopy to study brain injury.[42] Ultimately, machine learning approaches could be a key additional element in the neuropathology expert's toolbox, serving to speed up and enhance their ability to derive meaningful insights from tissue in health and disease.

While multimodal clinicopathologic and biomarker data integration holds the potential to strengthen computational findings and clinical applications toward machine learning-derived molecular subtypes,[82] it remains critically important to consider the generalizability of the model based on input parameters. Studies largely based on late-onset forms of disease may not generalize to young-onset forms where frequency of males and females, disease duration, lesion distribution, and severity of pathology may differ.[25,26,79,169,170] Biogeographic ancestry computed using genetic markers may influence risk factors (e.g., cardiovascular[171–173]) that may affect molecular mechanisms contributing to avoidance of neuropathology (i.e., resistance) and/or coping with neuropathology (i.e., resilience).[27] Harmonization efforts in brain banking and digital pathology would greatly facilitate the creation of large, more generalizable datasets. This visionary effort would enable machine learning practitioners to better address the issue of model validation, generalizability, and sampling imbalance by more easily replicating real-world issues using whole cohorts and holdout sets during training toward machine learning-derived molecular subtypes. Establishing subtype-specific therapeutic vulnerabilities and testing these in prospective clinical trials will be critical to realizing the promise of personalized interventions. Cross-disciplinary collaboration between neuropathology experts, computational scientists, clinicians, and clinical trialists will be essential to bridging the gap between data-driven discovery and precision medicine.

CONCLUSION

Advancements in brain banking, multi-scale 'omics, digital pathology, and machine learning mark an unprecedented era in neuropathology. By coining the term transformative neuropathology, we hope to provide a unifying framework that highlights the field's evolving role in leveraging advanced technologies to accelerate discovery and translational research while honoring the impact of descriptive and correlative studies. The methods and collaborations discussed here illustrate the vast potential of human brain tissue studies to drive molecular breakthroughs that delay disease progression and emphasize the importance of early disease detection. The rapidly evolving field requires striking a balance between supporting large, comprehensive brain banks and small, more specialized ones. While large brain banks facilitate broad-scale studies and initiatives, smaller brain banks excel in focused, targeted research. Supporting both large and small brain banks ensures that a wide range of research priorities—whether broad or specialized—advance our understanding of the human brain. However, both large and small brain banks often experience understaffing. To ensure their sustainability, tissue requestors and providers must proactively work together. This includes directing funds toward brain banks, fostering partnerships with clinical teams, harmonizing data, and cross-training the next generation of researchers. Such efforts will ensure that brain banks remain at the forefront of biomedical discoveries, advancing our understanding of brain health in aging and neurodegeneration to improve outcomes. By incorporating advanced technologies into human brain tissue research, we can unlock new opportunities for biomedical discovery. This integrated approach will ultimately enhance diagnostic precision, enable personalized therapy, and significantly reduce the global burden of neurodegenerative diseases on patients, families, support networks, and healthcare systems.

ACKNOWLEDGMENTS

Support for the workshop hosted at Cold Spring Harbor Laboratory was provided by Chan Zuckerberg Initiative DAF, an advised fund of Silicon Valley Community Foundation. Preparation for this perspective was supported in part by the National Institute on Aging (R01-AG075802, U54-AG076040, RF1-AG069052, U19-AG060909, and U24-AG072122–03S1) and the National Institute of Neurological Disorders and Stroke (R01-NS127186, U24-NS133945, and U24-NS133949). We thank Dr. Thomas Beach, Dr. Thomas Montine, and Dr. Sara Dunlop for their counsel during the preparation of this article, and we gratefully acknowledge the work of Dr. Derek Caetano-Anolles for the design of Figures 1, 2, and 3 and Hsin-Pei Wang for the initial design of Figure 2. We also extend our gratitude to Dr. Lilian Coie for support in drafting the manuscript.

DECLARATION OF INTERESTS

C.M.K. is a consultant for Eisai, Ltd. W.W.S. serves on the scientific advisory board for Lyterian Therapeutics. L.P. is funded by the Oxford GSK Institute of Molecular and Computational Medicine. D.J.I. holds unpaid professional affiliations with the Scientific Advisory Boards of the Lewy Body Dementia Association (LBDA) and the Association for Frontotemporal Degeneration (AFTD). His institution receives clinical trial funding from Denali, Prevail, Passage Bio, CervoMed, and Transposon. E.B.L. has received consulting fees from

Eli Lilly and Wavebreak Therapeutics. T.L.S.-J. declares no conflicts directly related to this manuscript but has received payments for consulting, scientific talks, or collaborative research over the past 10 years from AbbVie, Sanofi, Merck, Scottish Brain Sciences, Jay Therapeutics, Cognition Therapeutics, Ono, and Eisai. She also serves as a charity trustee for the British Neuroscience Association and the Guarantors of Brain and as a scientific advisor to several charities and non-profit organizations. W.T.K. is supported by U24AG072122.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the author(s) used ChatGPT and Perplexity.AI to parallel challenges described in section headings to reflect actionable solutions, summarize impact statements, guide cellular personification in Figure 3, and guide 'omics branches in Figure 4. After using this tool/service, the authors reviewed the literature, edited the content as needed, and take full responsibility for the content of the publication.

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