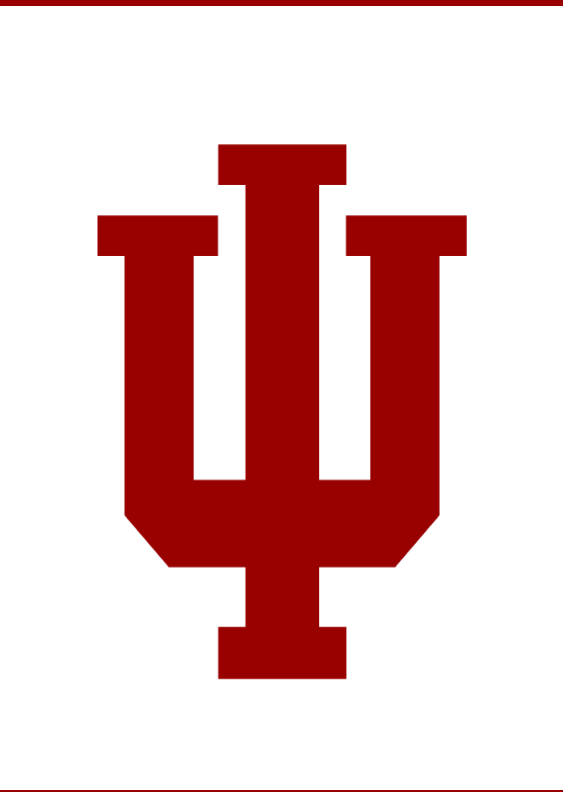




Systems Biology, Pathways, and Precision Medicine of ADRD:

Infrastructure, Big Data, and Collaboration are Shaping the Future

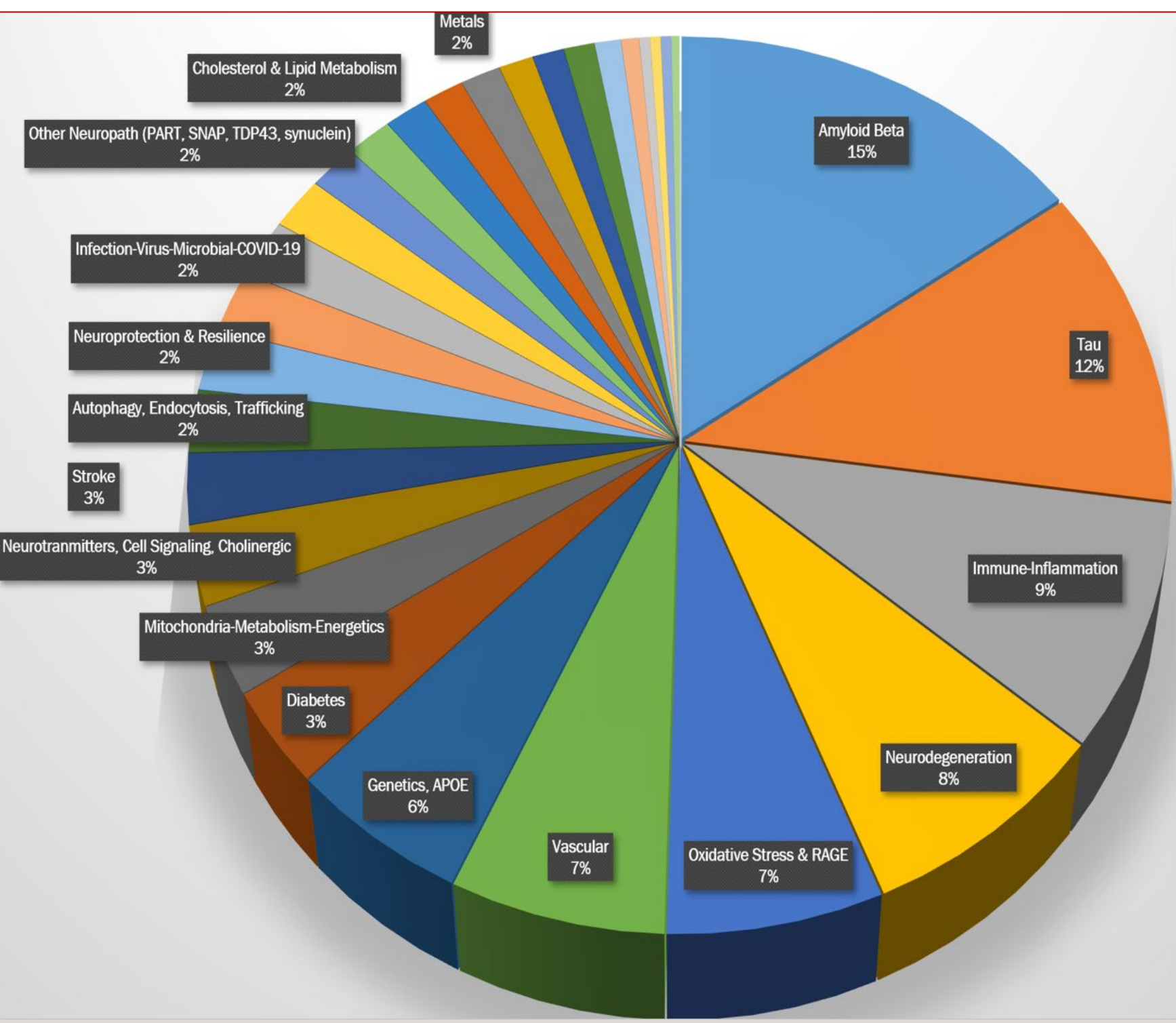
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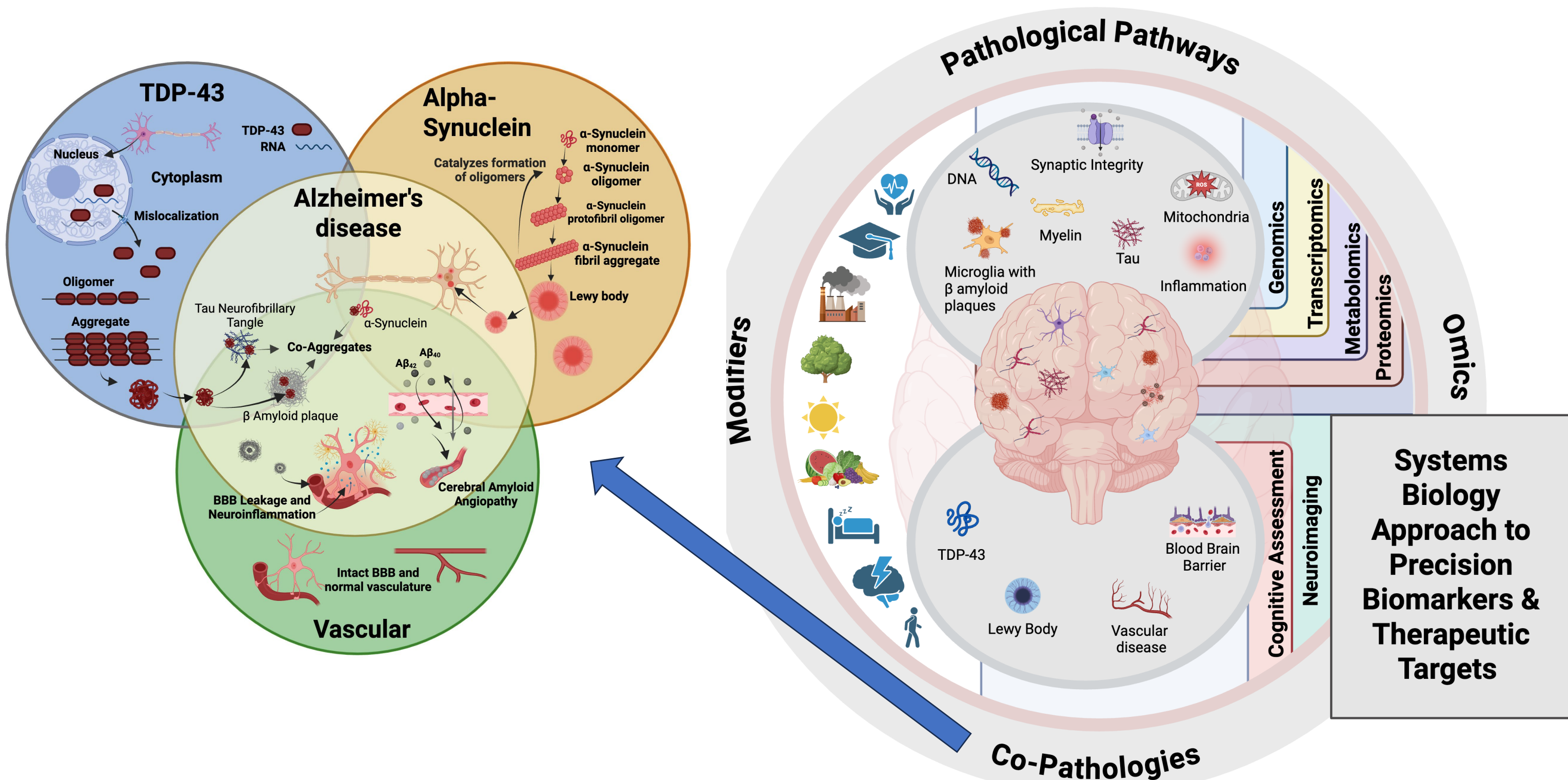


Full Publication
Bice et al 2026
Molecular Neurodegen

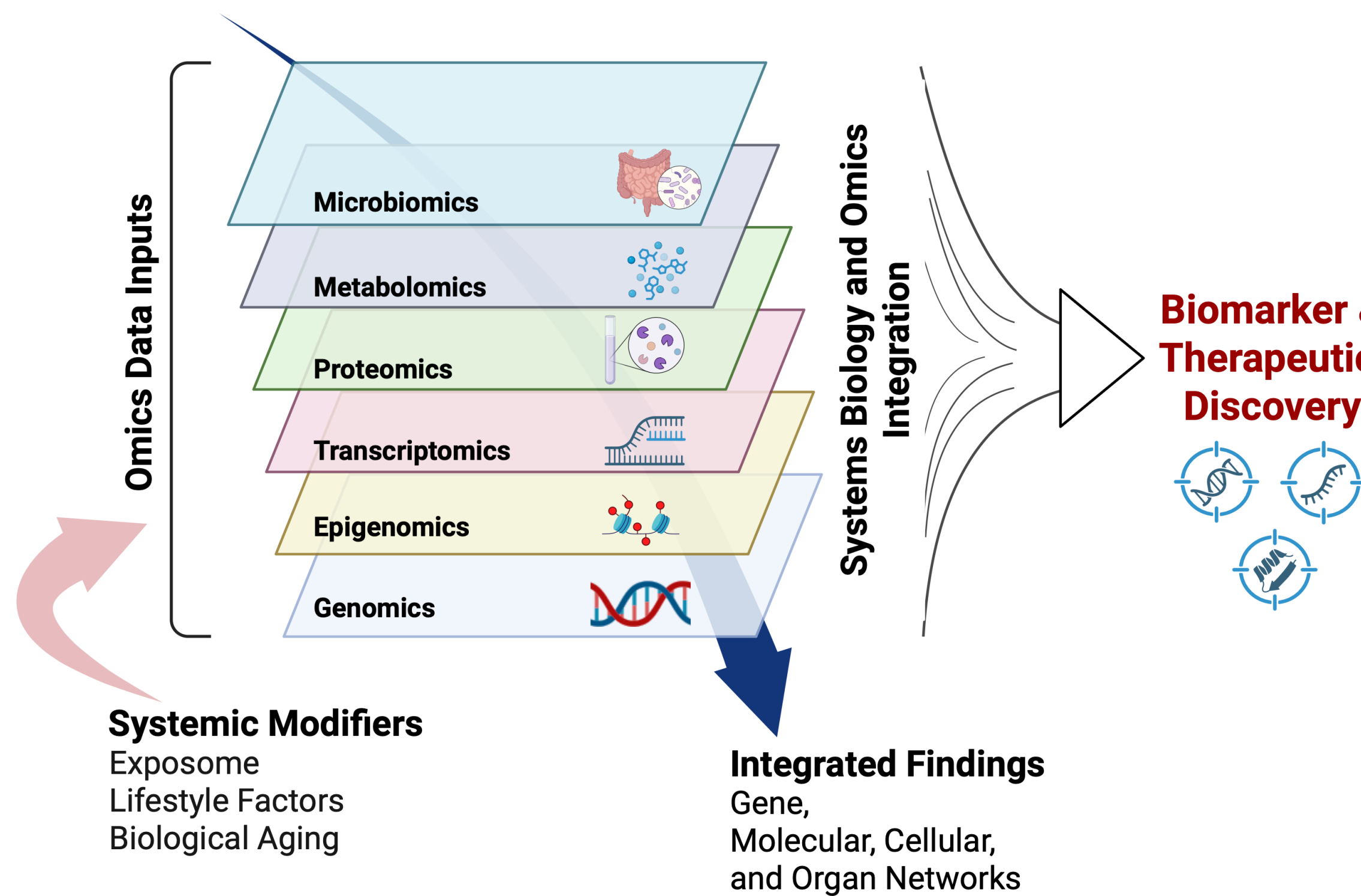
Complexity of ADRD



Systems Biology Landscape of AD



Multiomics in Context



Background

The Evolving Landscape of ADRD Research
AD/ADRD are a complex group of diseases with clinical and biological heterogeneity characterized by an array of molecular and cellular interactions across diverse biological domains. To capture this complexity, systems biology approaches, which integrate multi-omics and pathway-level data, offer a robust framework for understanding disease pathogenesis.

Methods

- Systematic scoping review conducted following PRISMA-ScR guidelines.
- PubMed search (2009–2024) using 48 CADRO-informed biological domain terms combined with “Alzheimer*”.
- 48,940 records identified; 26,606 unique studies retained after deduplication.
- ML–assisted screening (ASReview).
- Studies were categorized across major biological pathways and evaluated for molecular, cellular & systems relevance.

Biological Pathways

- Key Biological Pathways Identified**
- Hallmark pathology:** $A\beta$ and tau remain central but insufficient alone
 - Proteostasis:** Pathological accumulation of misfolded proteins
 - Immune/inflammation:** chronic neuroinflammatory processes
 - Oxidative Stress, Mitochondrial Dysfunction, Metal ions**
 - Synaptic integrity:** Synaptic loss, vesicle trafficking, synaptic plasticity and network dysfunction
 - Neurogenesis:** formation / integration of new neurons into existing neural networks
 - Neurometabolic dysfunction:** insulin, etc.
 - Sex differences and Hormones**
 - Co-Pathologies:** vascular contributions, Alpha Synuclein, TDP-43

Biological Complexity

Overlapping pathological processes in AD/ADRD necessitate integrative systems approaches. At least 22 major pathways were identified as having substantial literature support.

Systems Biology and Data Integration

Systems biology integrates multi-omics data—genomics, transcriptomics, proteomics, epigenomics, metabolomics/lipidomics, microbiomics—across various biological scales to model the complex interactions inherent in disease pathology. By leveraging multi-omics datasets, network-level mechanisms that underlie AD/ADRD heterogeneity are increasingly identified. Integrative approaches have the potential to bridge biological pathways and connect these patterns with syndromic phenotypic features in a manner that can lead to clinically actionable insights. This will facilitate discovery of novel biomarkers and therapeutic targets that extend beyond the limitations of traditional single-target and single-pathway approaches.

Bice PJ, Nho K, Ertekin-Taner N, Saykin AJ. Systems biology of Alzheimer's Disease: a scoping review of key pathways and mechanisms. Mol Neurodegeneration 21, 21 (2026). <https://doi.org/10.1186/s13024-026-00934-4> (see QR code above)

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Conclusions

Large-Scale Data Resources

Initiatives such as the ADSP, ADNI, KBASE, NACC, CLEAR-AD, GNPC, ADDI, and others, augmented by artificial intelligence (AI) and machine learning (ML) as in AI4AD.org, are facilitating systems-level discovery and advancing precision medicine strategies.

Future Directions

- Integration of multi-omics datasets using systems biology frameworks
- Increasing use of AI and machine learning for novel pathway discovery
- Translation of systems-level insights into clinically actionable biomarkers, repurposed therapeutic opportunities, and novel pharmacologic targets
- Development of individualized, stage-specific biomarkers and therapeutic strategies