

Alzheimer Disease

Pathogenesis • Morphology • Clinicopathologic correlation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraisakhri.com

Learning outcomes

- Explain amyloid- β and tau accumulation in Alzheimer disease
- Interpret the genetic evidence implicating APP processing
- Recognize the defining gross and microscopic lesions
- Connect neuropathology to cognitive impairment and biomarkers

Clinical focus

Link the lesion, vulnerable brain region, and resulting functional deficit.

Alzheimer disease: Defining context

A progressive neurodegenerative disorder and the leading cause of dementia in older adults

Core presentation

Insidious deterioration of higher cognitive functions, typically beginning with memory disturbance.

Core pathology

Neuritic amyloid plaques, tau-containing tangles, neuronal loss and gliosis.

Age is the dominant epidemiologic determinant

- Symptoms are uncommon before age 50
- Incidence rises markedly with advancing age
- Increasing longevity magnifies population-level disease burden

Interpretation

Risk increases with age, but dementia is not an inevitable consequence of normal aging.

Sporadic and familial disease

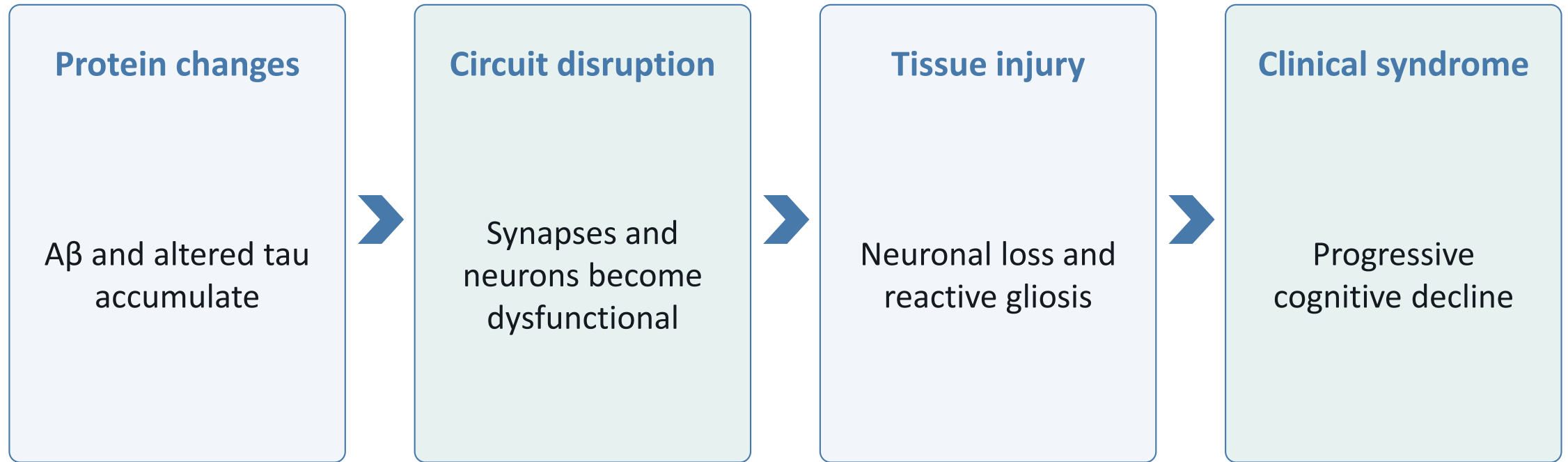
Sporadic presentation

Most Alzheimer disease is not explained by a recognized single-gene pathogenic variant; Age and susceptibility factors matter.

Familial presentation

A minority of cases occur in families; Inherited variants have illuminated APP cleavage, A β 42 generation and aggregation.

From protein pathology to cognitive dysfunction



A disease model: The precise causal interplay between amyloid and tau remains incompletely resolved.

Two defining protein lesions

Neuritic plaques

Extracellular aggregates of amyloid- β in neuropil, often surrounded by dystrophic neuronal processes.

Neurofibrillary tangles

Abnormal intracellular tau filaments; Residual extracellular tangles persist after neuronal loss.

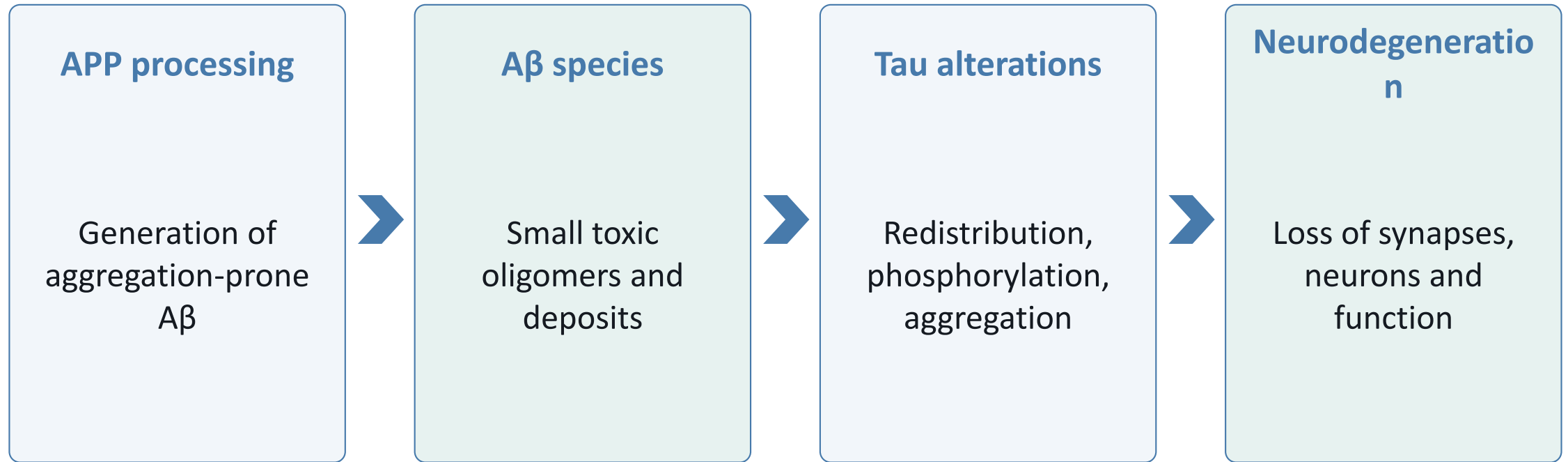
Neurodegeneration is not just aggregation

- Loss of neurons is a major component of advanced disease
- Synaptic dysfunction contributes to impaired cognition
- Reactive glial responses accompany vulnerable regions
- Lesions are regionally selective rather than uniform

**Read pathology
functionally**

Connect the cellular lesion
with network failure and
regional vulnerability.

An amyloid-initiated working model



This is a model supported by genetics and therapy, not a fully settled sequence for every patient.

Why amyloid generation is placed upstream

- Familial AD genes change APP biology or presenilin function
- Variants reducing A β generation can protect against disease
- Tau-only neurodegenerative disorders do not reproduce the full AD process
- Anti-amyloid treatment can modestly slow early cognitive decline

Evidence hierarchy

Convergent genetic and therapeutic data support A β as a major initiating driver.

Tau pathology alone does not define AD

Tau-only disorders

Several neurodegenerative diseases show abundant tau aggregates without the characteristic amyloid deposition of AD.

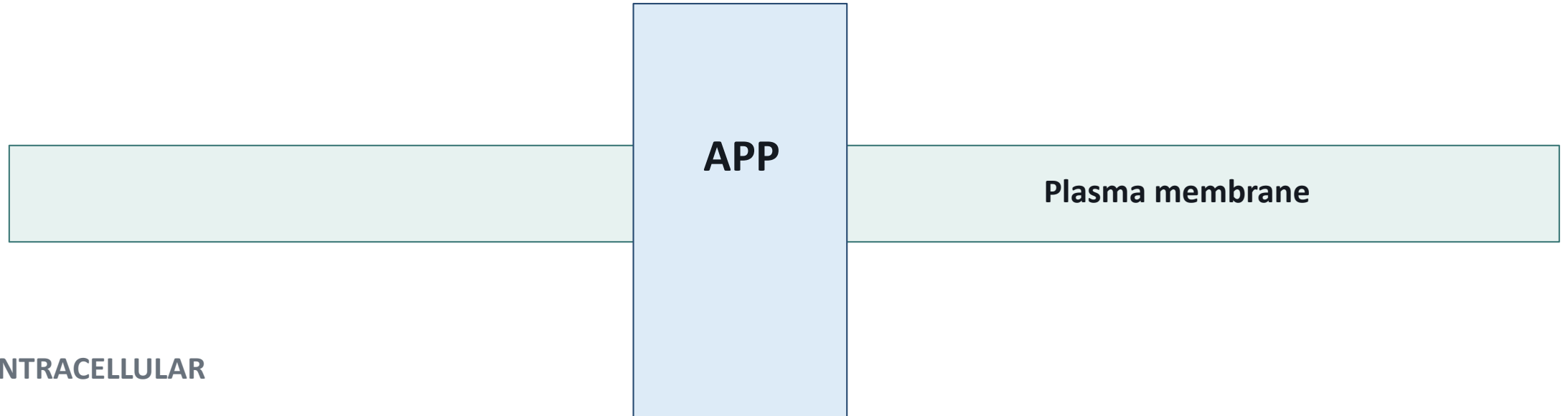
Alzheimer disease

The characteristic pathologic combination is A β deposition plus tau aggregation in a vulnerable distribution.

Amyloid precursor protein topology

EXTRACELLULAR

N-terminus



INTRACELLULAR

C-terminus

Single-pass membrane protein; The A β region spans the extracellular segment and membrane.

APP has two processing routes

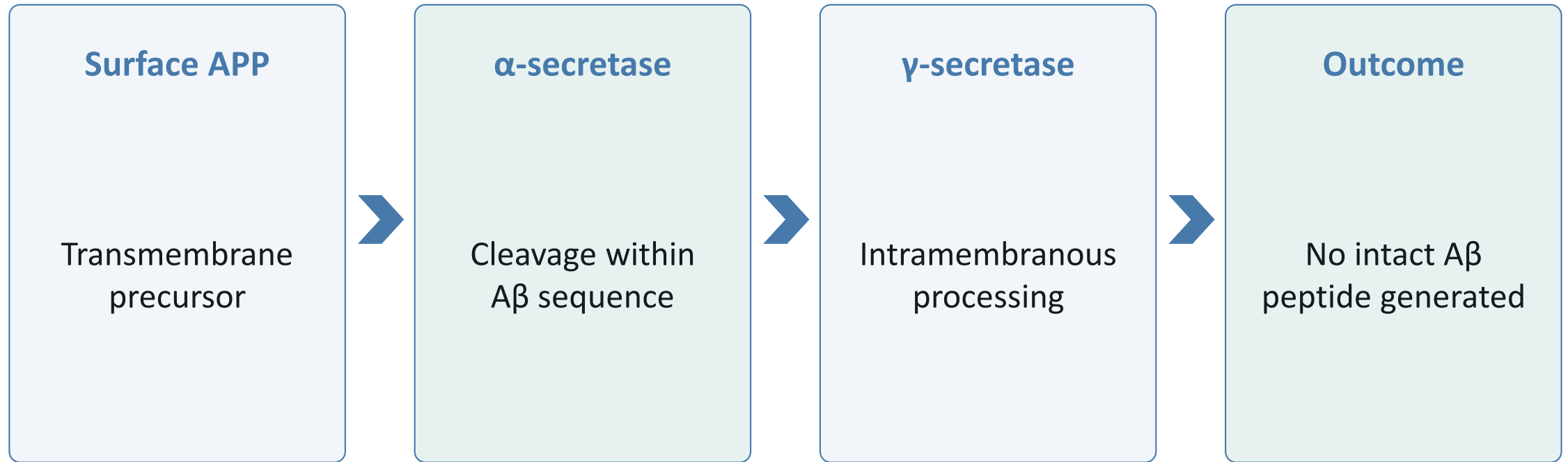
Nonamyloidogenic pathway

α -secretase cleavage prevents formation of the intact A β peptide; γ -secretase processes the remnant.

Amyloidogenic pathway

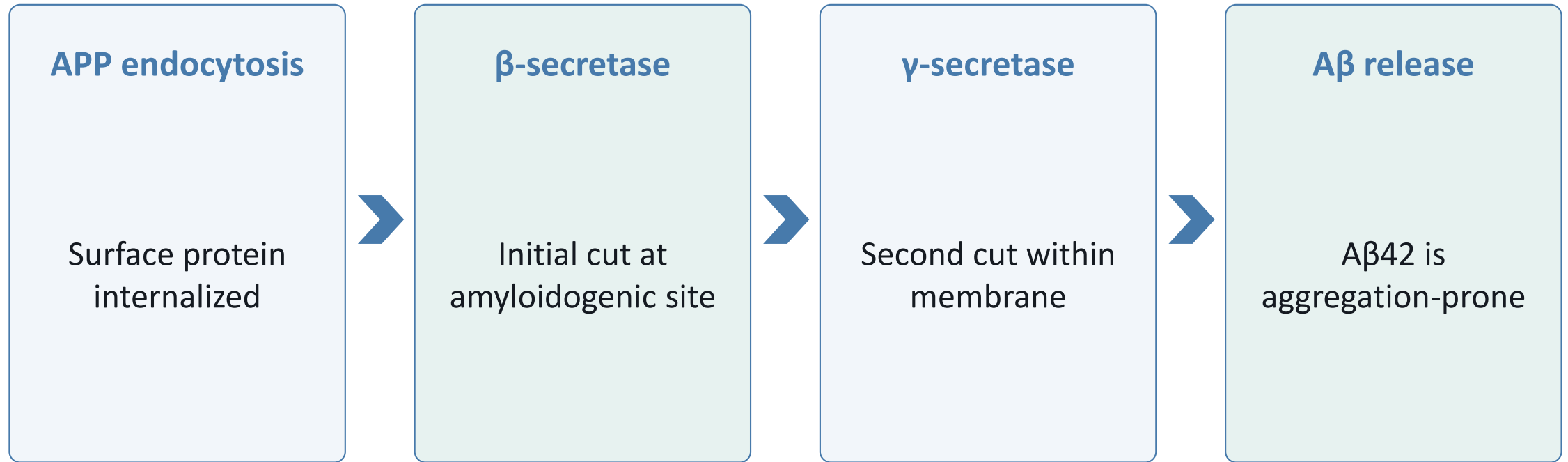
β -secretase cleavage followed by γ -secretase produces amyloid- β peptides, including aggregation-prone A β 42.

Nonamyloidogenic processing



α-secretase cleavage is predominantly associated with the cell surface.

Amyloidogenic processing



Endosomal processing is important; Accumulation reflects generation as well as clearance.

Secretase cleavage is biologically consequential

Component	Principal role	Significance
α -secretase	Nonamyloidogenic first cleavage	Precludes intact A β generation
β -secretase	Amyloidogenic first cleavage	Permits A β peptide formation
γ -secretase complex	Intramembranous cleavage	Contains presenilin and processes several substrates

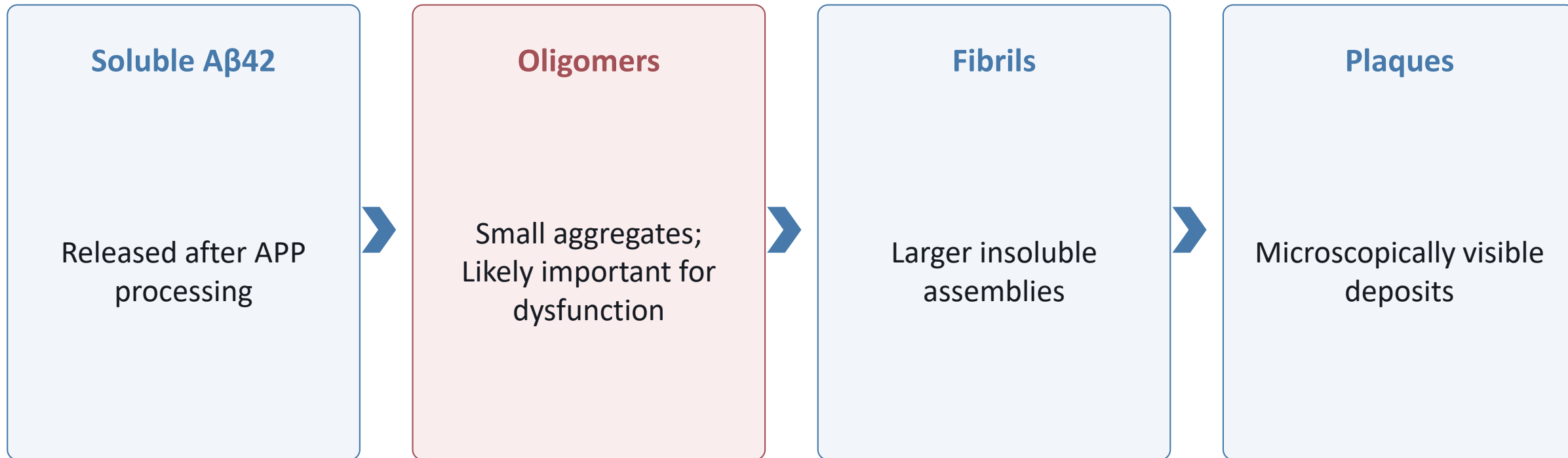
The γ -secretase complex

- Presenilin-1 or presenilin-2 is part of the catalytic complex
- Other components include nicastrin, PEN2 and APO1
- Processes APP and additional membrane proteins, including Notch

Mechanistic implication

Secretase-targeting interventions can affect substrates other than APP.

A β 42: An aggregation-prone peptide



Aggregation state matters: Plaque visibility is not equivalent to direct toxicity

Oligomers and plaques are not interchangeable

Small A β oligomers

Appear especially important for neuronal and synaptic dysfunction; May precede overt plaque accumulation.

Large A β deposits

Aggregates and fibrils form microscopically identifiable extracellular plaques, a defining morphologic lesion.

Where could A β aggregates originate?

- APP reaches intracellular vesicular compartments after endocytosis
- Some A β may aggregate in abnormally alkalinized lysosomes
- Release into extracellular tissue can follow neuronal death

Degree of certainty

Lysosomal aggregation is presented as a developing observation, not the only established origin of plaques.

Excess generation versus impaired removal

Net A β burden depends on production and clearance

Production

APP processing determines the amount and molecular species of A β released.

Removal

Defective degradation and clearance pathways can increase the tissue burden of aggregated peptide.

Familial Alzheimer disease: Key genes

Gene / locus	Mechanistic connection	Pathologic meaning
PSEN1 · chr 14	Presenilin-1 in γ -secretase	Altered amyloidogenic processing
PSEN2 · chr 1	Presenilin-2 in γ -secretase	Altered A β generation
APP · chr 21	Substrate for secretase cleavage	Altered generation or aggregation of A β

PSEN1 and PSEN2 pathogenic variants

- Encode presenilin components of γ -secretase
- Pathogenic variants can change γ -secretase processing outcomes
- Increased production of $A\beta$, especially $A\beta_{42}$
- Provide causal evidence connecting APP cleavage to familial AD

Teaching distinction

Inherited pathogenic variants differ from common APOE susceptibility alleles.

Pathogenic APP variants

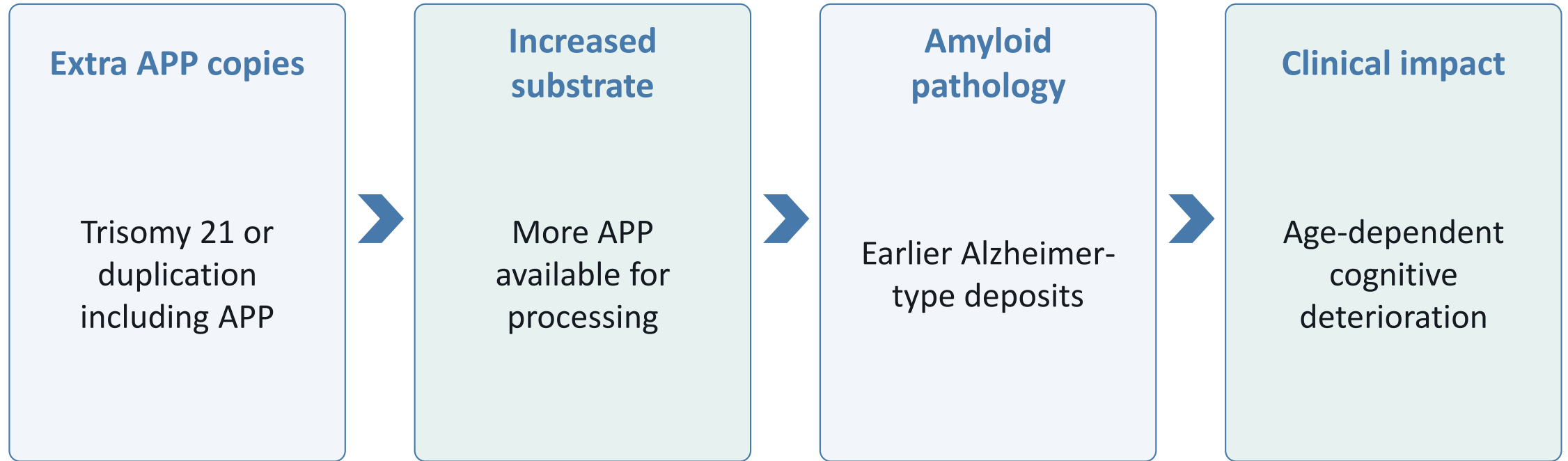
Cleavage-site variants

Some substitutions occur near β - or γ -secretase sites and modify the generation of amyloid- β peptides.

A β -sequence variants

Other substitutions occur within the peptide sequence and increase its intrinsic propensity to aggregate.

Chromosome 21 gene dosage and AD



Chromosome 21 dosage implicates APP abundance in amyloid pathology.

Protective APP A673T variant

Reduced A β generation can confer protection

Molecular observation

The APP A673T variant decreases generation of amyloid- β .

Population phenotype

Carriers have lower amyloid burden and reduced likelihood of age-associated cognitive decline.

Genetic proof and genetic susceptibility

Causal Mendelian variants

Rare familial variants in APP, PSEN1 and PSEN2 directly alter the disease-driving amyloid pathway.

Susceptibility alleles

APOE genotype modifies probability and age of onset; It is not sufficient to diagnose AD.

APOE alleles: $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$

- The APOE gene maps to chromosome 19
- Common variants encode $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ isoforms
- Greater $\epsilon 4$ allele dosage increases susceptibility to AD
- $\epsilon 4$ is associated with an earlier typical age of onset

Critical distinction

Risk alleles alter probability; An APOE $\epsilon 4$ carrier is not necessarily affected.

How APOE ϵ 4 may promote pathology

Amyloid biology

May augment A β generation and deposition.

Tau-mediated injury

May enhance tau-related neurodegeneration through A β -dependent and other mechanisms.

Brain resilience

May impair lysosomal handling and astrocytic maintenance of synapses.

APOE ϵ 4 and neuronal networks

APOE ϵ 4 effects

Altered glial and neuronal biology



GABAergic vulnerability

Reported selective harm to inhibitory neurons



Network imbalance

Early neuronal hyperexcitability

The source frames GABAergic toxicity and hyperexcitability as emerging mechanistic findings.

Inflammation has opposing roles

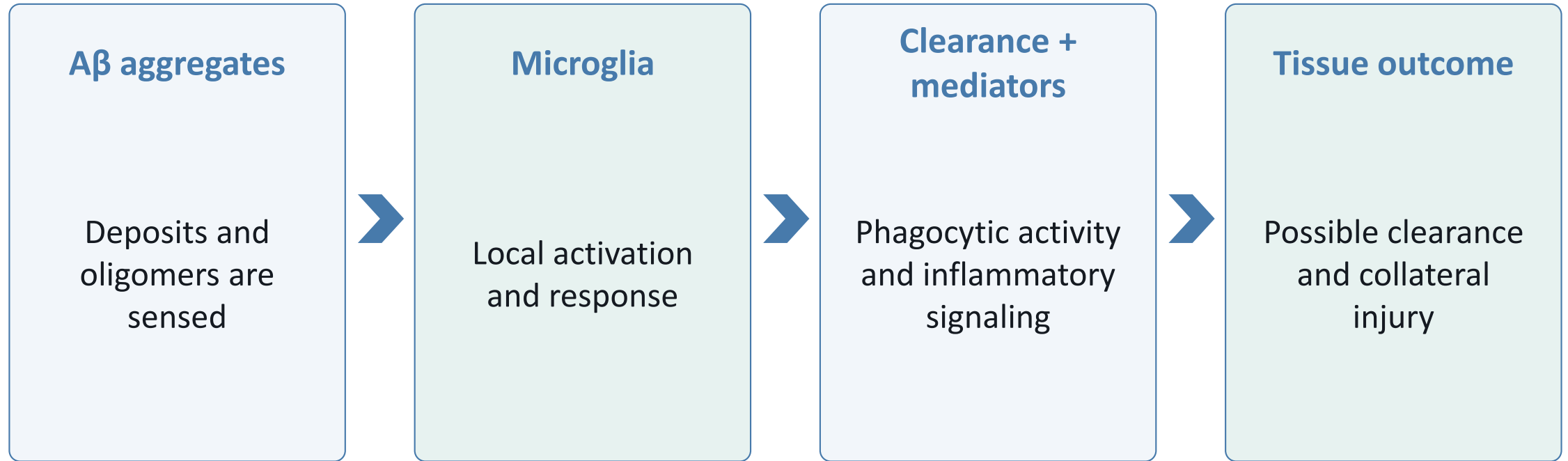
Potentially protective

Microglial and astrocytic responses may facilitate clearance of misfolded or aggregated A β .

Potentially damaging

Activated glia may release injurious mediators, amplify oxidative stress, and alter synaptic connections.

Microglial activation around amyloid



Inflammation is not a single uniformly protective or harmful pathway.

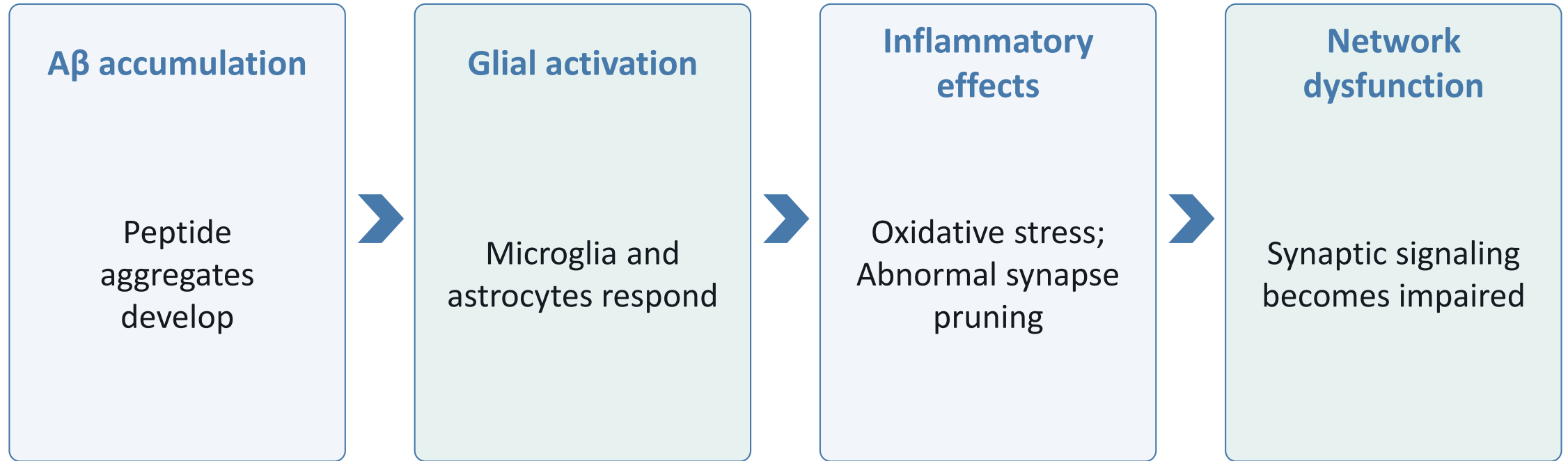
Astrocytes: Support and injury

- Astrocytes react in brain regions burdened by deposits
- Normal astrocyte-dependent synapse maintenance may be impaired
- Inflammatory signaling can interact with tau pathology
- Glial changes influence both clearance and neural resilience

Clinicopathologic link

Synaptic maintenance deficits help explain dysfunction beyond visible plaque counts.

Inflammation, oxidative damage, synapse loss



The cascade is a plausible contributory mechanism; Causality and magnitude remain unresolved.

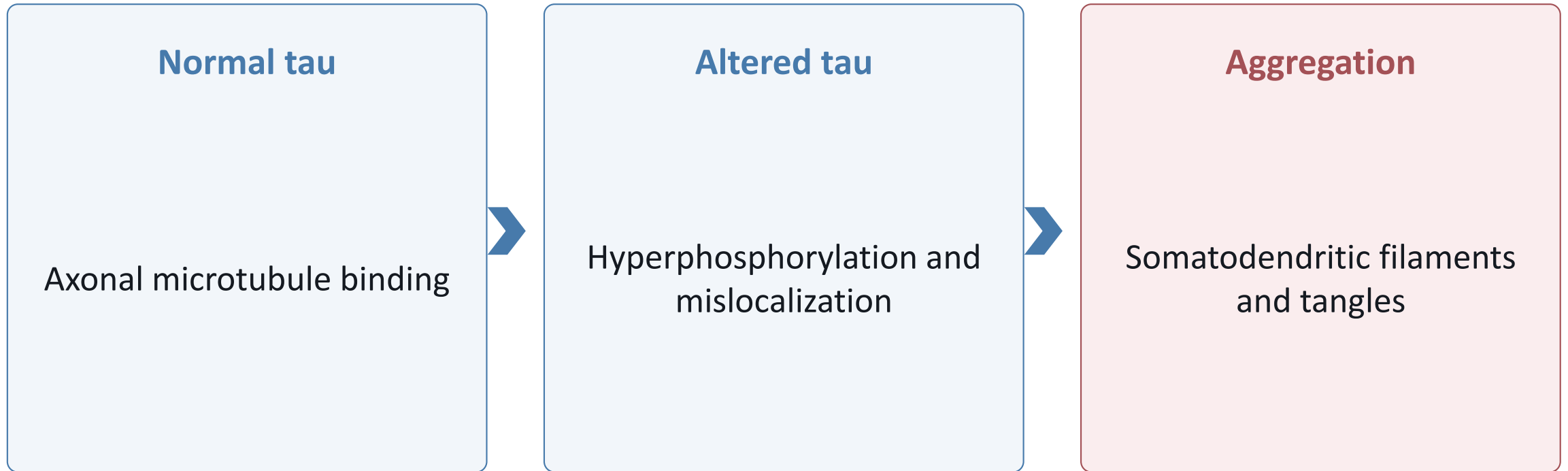
Tau in the healthy neuron

- Tau associates with microtubules in axons
- Microtubules provide essential internal structural support
- Tau–microtubule binding is altered by phosphorylation
- Normal tau distribution is predominantly axonal

Functional meaning

Dysfunctional tau can affect axonal support as well as aggregate within neurons.

Tau redistribution and aggregation



Both microtubule destabilization and aggregate-induced stress are proposed injury mechanisms

Hyperphosphorylated tau

- Tau loses normal microtubule-binding capacity
- Abnormal tau shifts toward somatodendritic compartments
- Insoluble filaments accumulate as neurofibrillary tangles
- Tangles can remain visible after the parent neuron dies

Morphologic consequence

The lesion outlasts the neuron that originally produced it.

What makes aggregated tau injurious?

Aggregate-associated stress

Accumulation of abnormal tau filaments may provoke cellular stress responses.

Loss of normal function

Reduced microtubule stabilization may compromise neuronal structure and function.

The amyloid–tau relationship remains incomplete

- A β oligomers may promote abnormal tau phosphorylation
- The molecular steps connecting A β to tau are not fully established
- Later tangle accumulation may become less dependent on ongoing A β burden
- Both processes are implicated in neuronal dysfunction

Do not overstate

Correlation and experimental mechanistic support do not establish one universal linear pathway.

MAPT mutations are an important differential clue

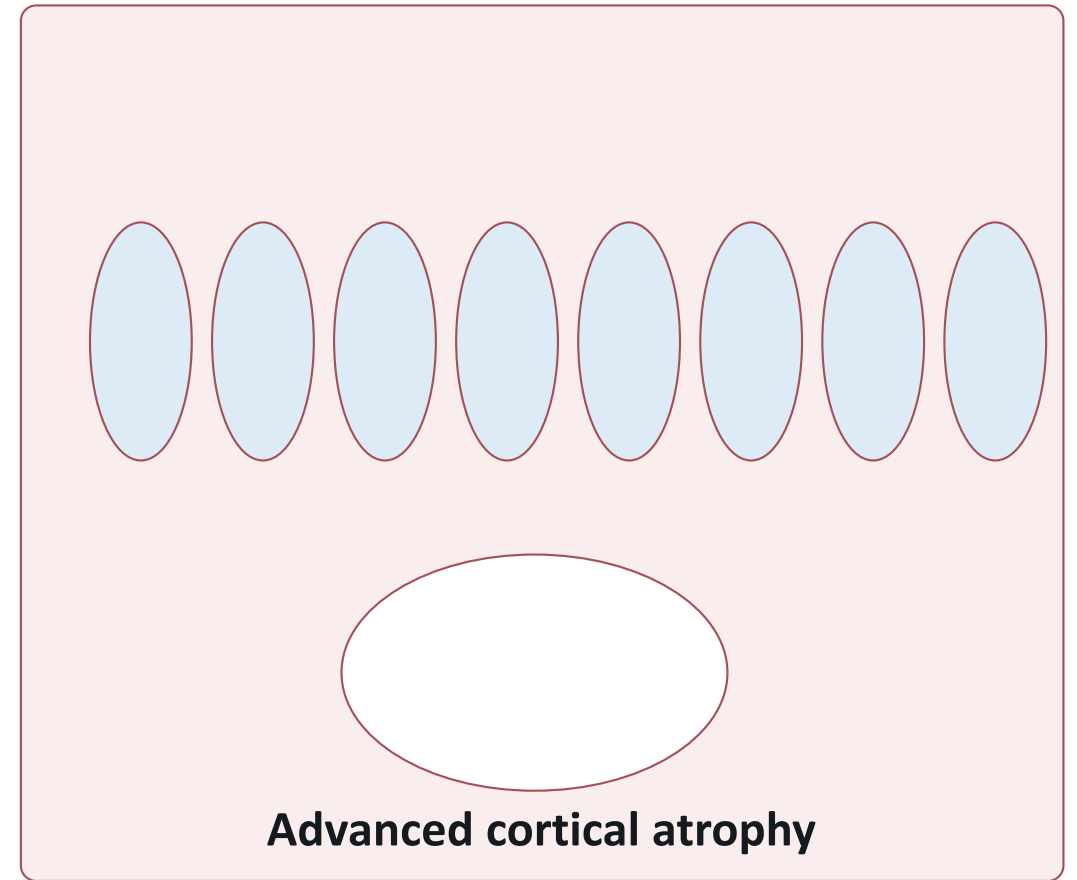
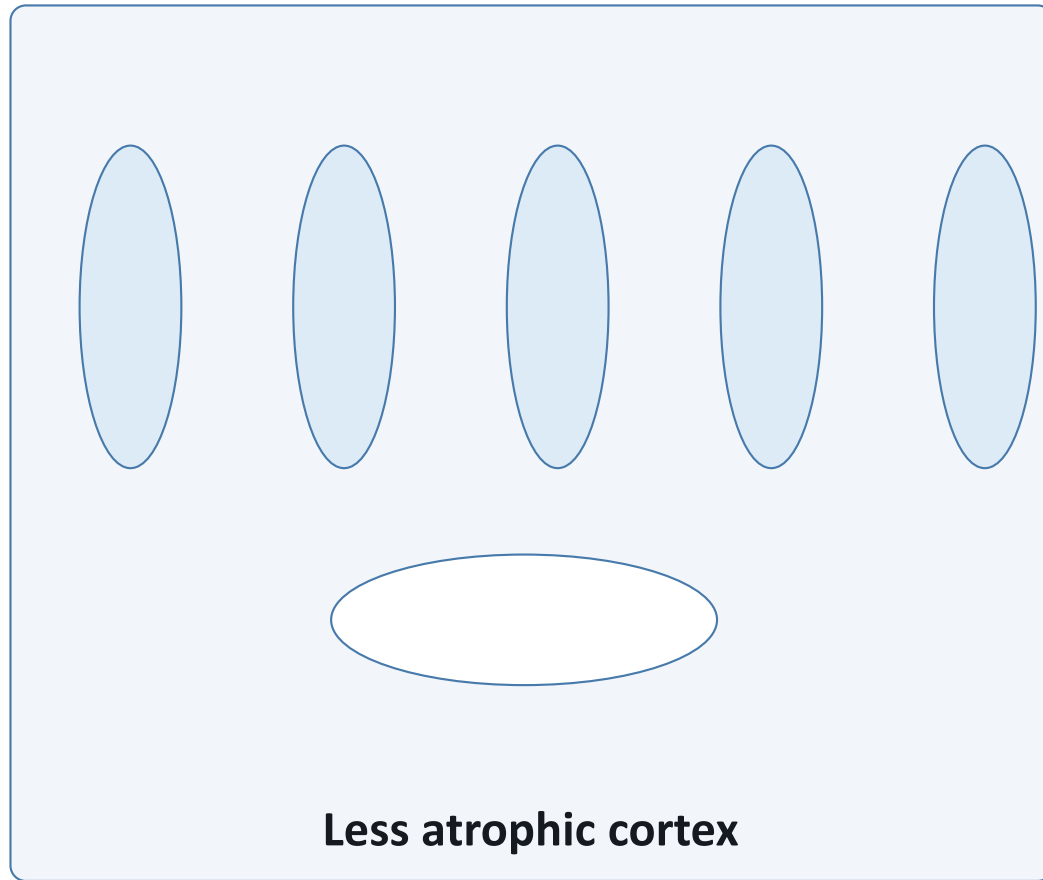
MAPT pathogenic variants

Cause selected frontotemporal lobar degenerations with tau pathology.

Alzheimer disease

Defined by a combined amyloid- β and tau pathologic phenotype; MAPT variants are not a recognized canonical cause.

Gross morphology: Cortical atrophy



Schematic: Thinner cortical gyri, wider sulci, and enlarged ventricular spaces with tissue loss

Anatomic distribution of neurodegeneration

Early vulnerable

Entorhinal cortex,
hippocampus, medial
temporal network

Wider involvement

Association neocortex;
Frontal, temporal and
parietal lobes

Relative sparing

Primary motor and sensory
cortices until later phases

Medial temporal vulnerability

- Entorhinal cortex and hippocampus are involved early
- Amygdala and related medial temporal structures become affected
- These structures are typically severely atrophic in later disease
- The regional pattern helps explain the prominence of early memory deficits

Anatomy to symptom

Medial temporal circuit disruption maps to impaired memory formation and retrieval.

Hydrocephalus ex vacuo is volume loss

Primary event

Neuronal and cortical tissue are progressively lost, producing narrowed gyri and widened sulci.

Secondary appearance

Ventricles enlarge to occupy space lost from surrounding parenchyma; This is not primary CSF outflow obstruction.

Microscopic disease is not only plaques

Neuritic plaques

Focal neuropil deposits containing amyloid and damaged axodendritic processes.

Neurofibrillary tangles

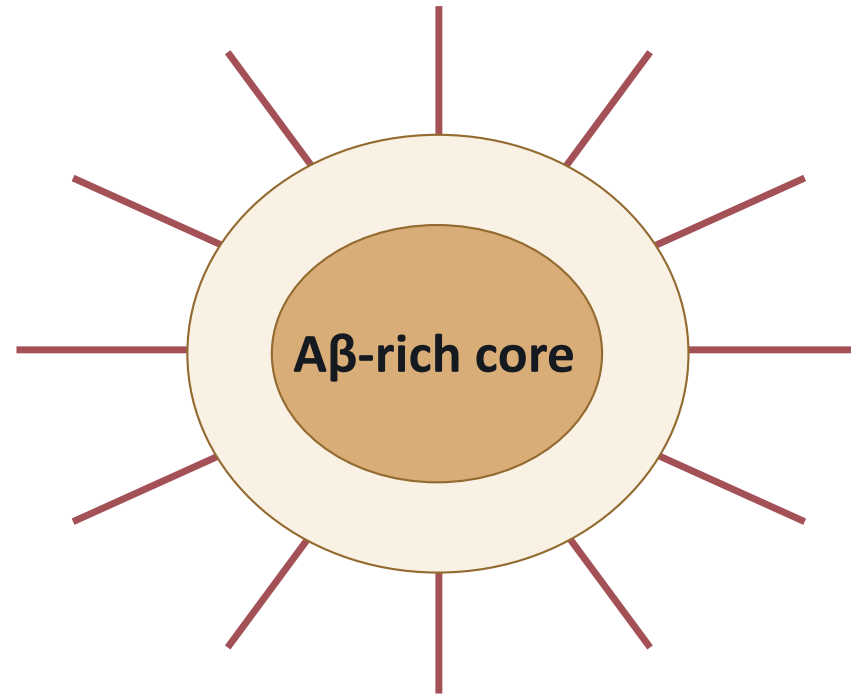
Intraneuronal abnormal tau aggregates; Ghosts persist extracellularly.

Neuronal loss / gliosis

Progressive tissue injury with reactive glial cells in affected brain regions.

Neuritic plaque: Essential architecture

Dystrophic neuritic processes



Resident microglia and reactive astrocytes at the periphery

Schematic representation of a neuritic plaque — not a photomicrograph

The neuritic plaque core

- Central amyloid-rich core surrounded by abnormal neurites
- A β is the dominant amyloid component
- Other associated proteins may include complement and apolipoproteins
- Microglia and reactive astrocytes may lie at the periphery

Staining principle

A β immunostaining or Congo red can identify amyloid in a plaque core.

Diffuse plaques differ from neuritic plaques

Diffuse amyloid plaques

A β deposition without a prominent collar of dystrophic neurites; Can involve superficial cortex, basal ganglia and cerebellum.

Neuritic plaques

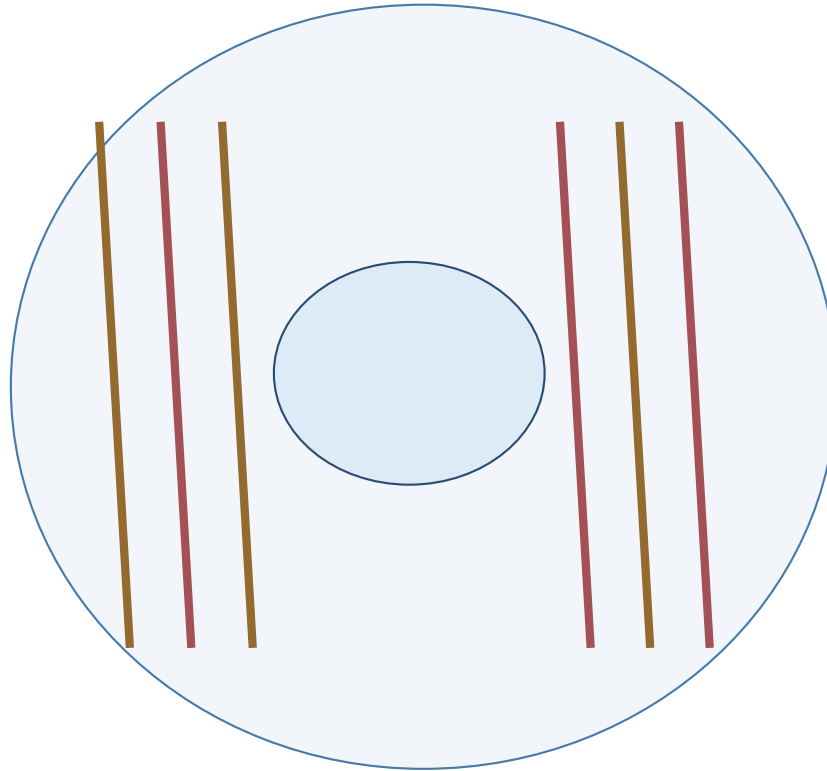
A β -rich core with adjacent damaged neuritic profiles; One of the classic pathologic hallmarks of AD.

Recognizing plaques in tissue

Method	What it highlights	Interpretive point
H&E	Some plaque-associated neuropil abnormalities	Not optimally sensitive for amyloid typing
Congo red	Amyloid-containing core	Demonstrates amyloid chemistry
A β immunohistochemistry	Amyloid- β peptide deposits	Connects visible deposit to A β biology

Neurofibrillary tangles: Cellular morphology

**Tau-containing
intracellular filaments**



Nucleus displaced or
encircled by tangle

Schematic neuron; Not histologic evidence

Tangle shape depends on neuronal form

Flame-shaped tangles

In pyramidal neurons, filament bundles often form an elongated profile.

Globose tangles

Rounder neuronal profiles can show filaments distributed around the nucleus.

Tangles in H&E, silver and tau stains

Technique	Typical appearance	Purpose
H&E	Basophilic fibrillar neuronal structures	Initial morphology
Bielschowsky silver	Strong highlighting of neuronal fibrils	Increased morphologic conspicuity
Tau immunohistochemistry	Tau-positive tangles, neurites and threads	Protein identity / distribution

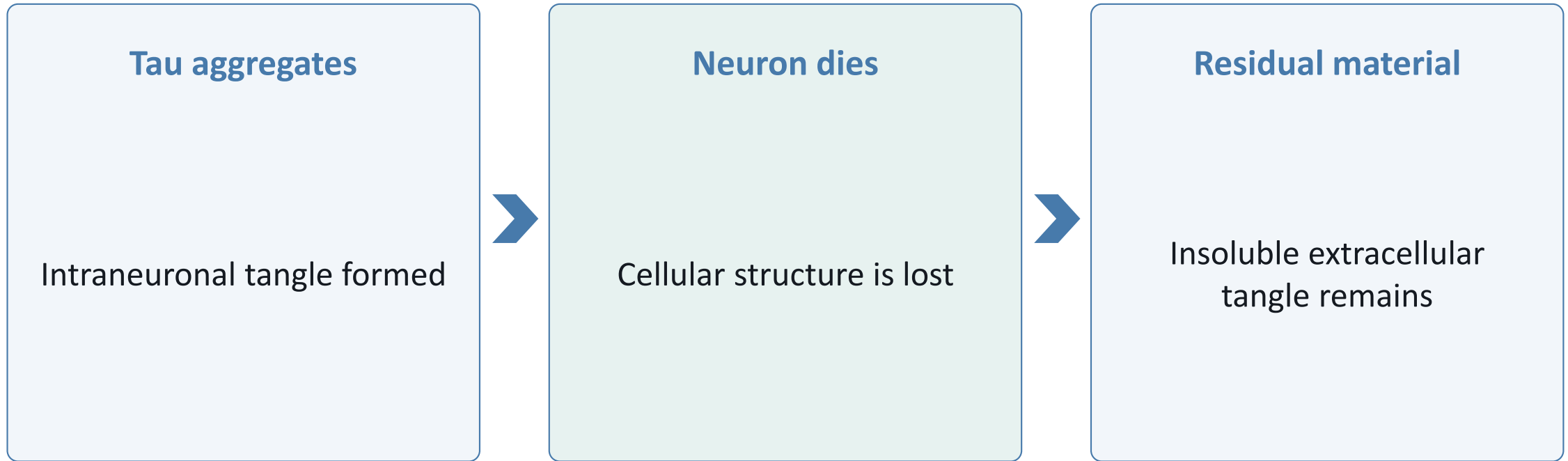
Neuropil threads extend tau pathology

- Aggregated tau is not restricted to neuronal perikarya
- Tau-positive filaments also occur in affected axons
- Dystrophic neurites in neuritic plaques can contain tau
- Neuropil thread burden reflects widespread neuritic pathology

Morphologic synthesis

Amyloid plaques and tau pathology can coexist within the same microscopic region.

Ghost tangles persist after neuronal loss



Ghost or tombstone tangles are tissue footprints of neuronal death.

Tangles are not specific for AD

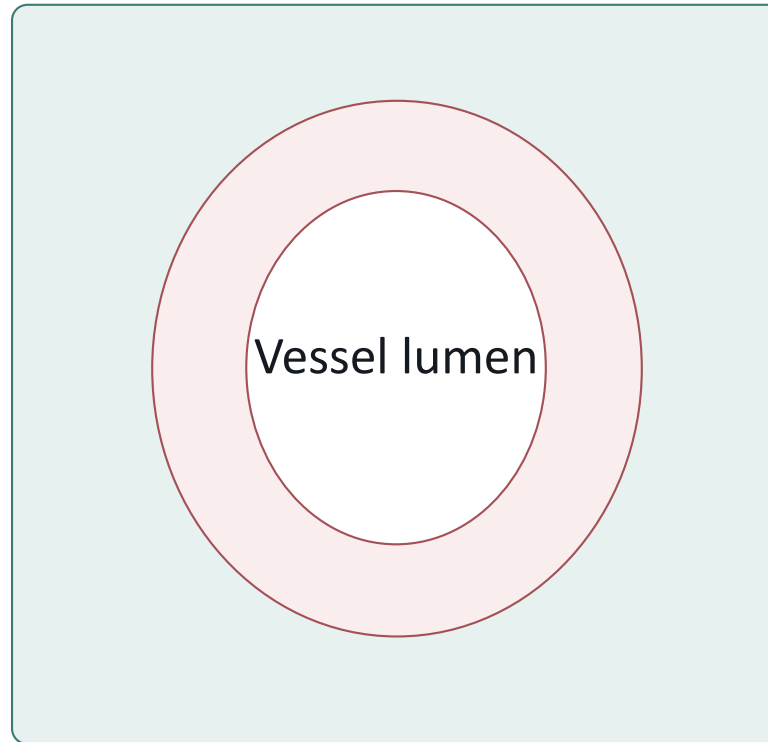
- Several primary tauopathies show neurofibrillary pathology
- Abundant tangles alone cannot define Alzheimer disease
- Lesion combination and distribution inform attribution
- Correlate microscopy with the broader disease context

Diagnostic caution

Tau immunoreactivity is a protein-identification test, not an AD-specific test.

Cerebral amyloid angiopathy

A β deposits in vessel wall



Predominantly A β 40 rather than plaque-enriched A β 42

Schematic cerebral amyloid angiopathy; Not a photomicrograph

Plaque A β 42 versus vascular A β 40

Parenchymal plaque deposits

Neuritic and diffuse plaques are relatively enriched in amyloid- β 42.

Vascular amyloid deposition

Cerebral amyloid angiopathy predominantly contains amyloid- β 40.

Amyloid angiopathy is not unique to AD

- Cerebral amyloid angiopathy commonly accompanies AD
- CAA also occurs in people without Alzheimer dementia
- Tissue location and peptide composition differ from plaque amyloid

Interpretation

Vascular amyloid is a related but non-specific pathologic finding.

Tangle burden and dementia severity

Tau tangle burden

The number of tangles generally correlates more closely with the severity of dementia.

Plaque burden

Large plaque loads are strongly associated with AD, but plaque number alone is less tightly linked with cognitive severity.

Additional correlates of cognitive dysfunction

Choline acetyltransferase loss

Biochemical evidence of impaired cholinergic neuronal function.

Synaptophysin reduction

Reduced immunoreactivity reflects a loss of synaptic markers.

Combined lesion burden

Severe cognitive impairment is associated with extensive plaques and tangles.

The clinical course is progressive

Initial phase

Forgetfulness and memory disturbance predominate;
Subtle higher-cognitive deficits may be present.



Established disease

Language, mathematical abilities and learned motor skills progressively deteriorate.



Advanced disease

Incontinence, mutism and loss of independent ambulation can develop.

Early manifestations reflect memory networks

- Insidious impairment is typical rather than abrupt onset
- Memory disturbance is often the first major manifestation
- Medial temporal neuronal loss is anatomically relevant
- Progressive change over time distinguishes disease from a static deficit

Clinical inference

A typical phenotype is consistent with AD but is not by itself pathognomonic.

Multidomain cognitive decline develops

Language

Progressive difficulty with linguistic functions.

Calculation

Impairment of mathematical skills.

Praxis

Loss of previously learned motor skills.

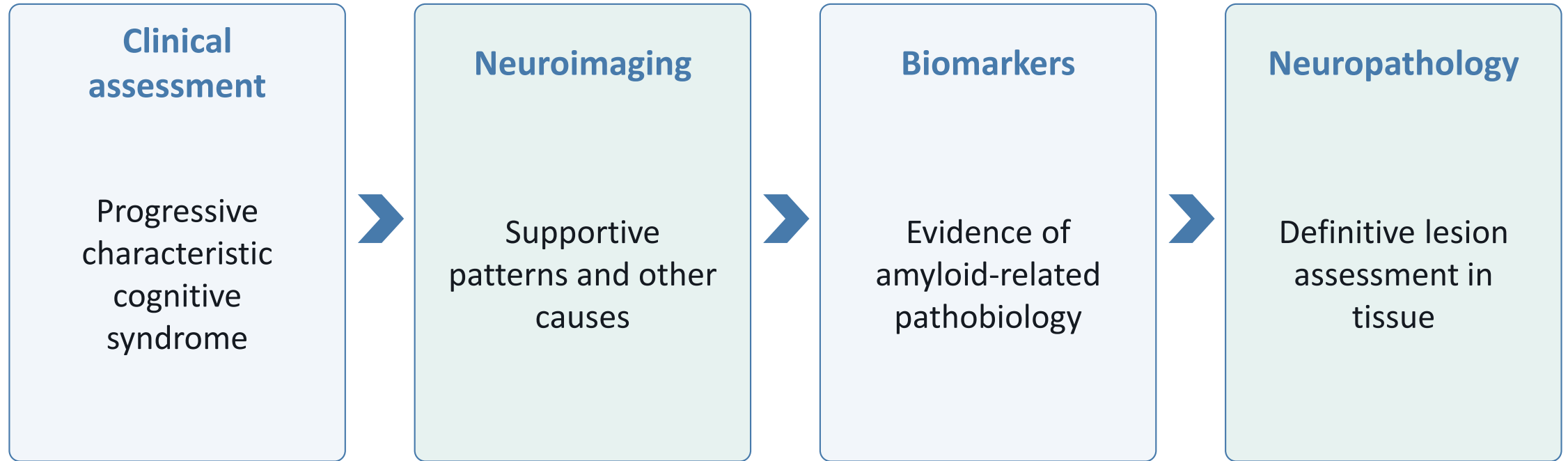
End-stage disease and complications

- Profound loss of independence may occur
- Individuals may become mute or unable to walk
- Incontinence develops in advanced disease
- Intercurrent illness—often pneumonia—commonly precipitates death

Clinical severity

Late-stage dependence reflects extensive network and neuronal injury.

Diagnosis is multimodal



Neuropathologic examination as the definitive diagnostic reference.

Amyloid PET demonstrates cerebral deposits

- ^{18}F -labeled amyloid-binding compounds visualize brain $\text{A}\beta$ deposits
- Positive imaging can precede clinical dementia
- Amyloid positivity indicates pathology, not a complete measurement of impairment
- Interpret alongside the clinical phenotype and other evidence

Use of biomarkers

Biologic evidence and clinical functional severity are distinct concepts.

Plasma A β 42:A β 40 ratio

A reduced plasma A β 42:A β 40 ratio supports amyloid-related pathobiology

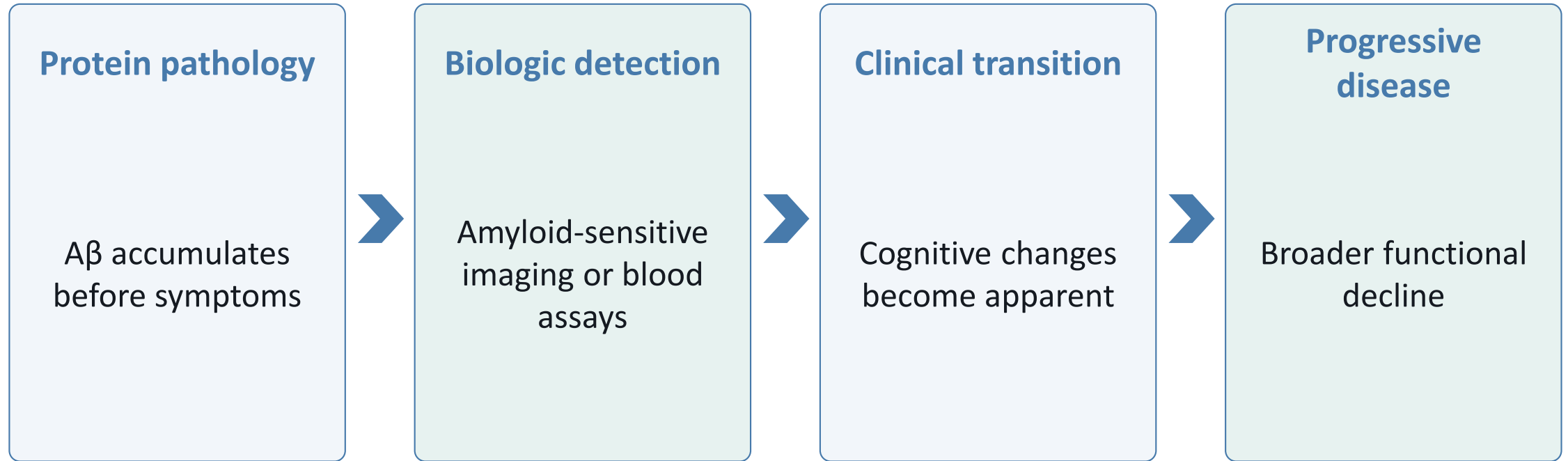
What is measured

Relative concentrations of amyloid- β peptide species in blood.

What it cannot replace

Clinical evaluation, differential diagnosis, or contextual biomarker interpretation.

Biomarkers and the preclinical interval



Biologic abnormalities may be identifiable before a patient meets clinical criteria for dementia.

Clinical and pathologic states are not synonymous

Finding	Can indicate	Does not establish alone
Amyloid PET positivity	Brain amyloid deposition	Current symptomatic dementia
Low plasma A β 42:A β 40	Altered amyloid biology	Full phenotype or severity
Tau-containing tangle	Tau pathology	Alzheimer-specific diagnosis
Insidious memory decline	Compatible clinical syndrome	Unique molecular etiology

Alzheimer disease versus FTLD

Feature	Alzheimer disease	Frontotemporal lobar degeneration
Early emphasis	Memory dysfunction	Behavior / personality or language
Protein profile	A β + tau hallmark lesions	Often tau or TDP-43 proteinopathy
Typical anatomy	Medial temporal and association cortex	Predominantly frontal / temporal lobes

Why plaque–tangle recognition matters

**The integrated diagnosis is anatomical, molecular
and clinical**

Pathology

Which protein? Which cellular
compartment? Which regional
distribution?

Patient

Which cognitive deficits? How
progressive? How much functional
impairment?

Therapeutic strategies arise from mechanisms

Anti-amyloid strategies

Immunologic removal of A β aggregates; Modest slowing of decline reported in early disease.

Secretase-directed approaches

Investigational modulation of APP processing and A β production.

Tau-directed approaches

Investigational approaches to prevent or modify abnormal tau changes.

A β -directed treatment: Benefit and limits

- Reduced amyloid burden under antibody therapy
- Cognitive decline can be slowed in selected early AD populations
- The observed benefit is described as modest
- Amyloid clearance alone does not equate to reversal of established neuronal loss

Therapeutic reasoning

Intervention is most plausible before extensive irreversible circuit injury.

Integrating protein, compartment and lesion

Protein species	Principal compartment	Characteristic lesion
A β 42	Extracellular neuropil	Neuritic or diffuse amyloid plaque
Abnormal tau	Intraneuronal then residual extracellular	Neurofibrillary or ghost tangle
A β 40	Vascular wall	Cerebral amyloid angiopathy

Case: A progressive amnestic syndrome

- Older adult with years of progressive forgetfulness
- Subsequent language and calculation difficulties
- Imaging reports cortical volume loss
- Question: Which two pathologic protein lesions would be expected?

Pause for discussion

Predict the cellular localization of each hallmark lesion before revealing the answer.

Case explanation: Connect clinical and pathology

Predicted amyloid lesion

Extracellular neuritic plaques containing aggregated A β peptides and dystrophic neurites.

Predicted tau lesion

Intraneuronal neurofibrillary tangles, followed by residual extracellular ghost tangles.

Five mechanistic conclusions

- APP cleavage and impaired clearance determine A β burden
- Genetic findings strongly support an initiating role for amyloid
- Abnormal tau disrupts microtubule biology and forms tangles
- Inflammation and synaptic injury contribute to degeneration
- Clinical dysfunction reflects regional loss of viable networks

Conceptual discipline

The mechanistic connections are supported but not exhaustively resolved.

Five diagnostic conclusions

- Cortical atrophy and ex-vacuo ventricular expansion are gross manifestations
- Neuritic plaques and tau tangles are the microscopic hallmarks
- CAA is common but not specific and is enriched for A β 40
- Tangle burden generally tracks cognitive severity better than plaque count
- Biomarkers can detect amyloid biology before dementia develops

Slide-to-practice principle

Never equate a single morphologic, imaging or blood result with the complete diagnosis.

Reference and recommended source figures

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026)
- Chapter 28, The Central Nervous System, pp. 1161–1165
- Figure 28.36: APP cleavage and amyloid processing
- Figures 28.37–28.38: gross atrophy and microscopic lesions

Morphology reading

Review authentic gross and histologic photographs in the original textbook alongside these native schematics.