

Creutzfeldt–Jakob Disease

Prion pathogenesis · clinicopathologic progression · diagnosis

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Learning objectives

- Explain how misfolded PrP propagates and causes prion disease.
- Distinguish sporadic, genetic, and iatrogenic CJD.
- Recognize the clinical course and characteristic neuropathology.
- Apply current clinical criteria while identifying diagnostic limitations.
- Integrate infection-control and patient-care implications.

Disease concept: An accelerated proteinopathy

CJD is a rapidly progressive, fatal neurodegenerative prion disease.

- It is the most common human prion disease.
- Misfolded prion protein is central to pathogenesis.
- Spongiform gray-matter change characterizes neuropathology.

CJD within the neurodegenerative diseases

Shared framework

- Selective neuronal injury
- Abnormal protein aggregation
- Clinical pattern reflects the affected neural systems

Prion disease distinction

- Misfolded PrP can template further PrP conversion
- Intercellular propagation is a defining pathogenic feature
- CJD typically progresses over months

Human prion disease spectrum

Human disorder	Context in this lecture
Classic CJD	Principal focus: sporadic, familial, iatrogenic
Variant CJD	Distinct exposure-linked disease; short comparison
Gerstmann–Sträussler–Scheinker syndrome	Inherited prion disease; differential context
Fatal familial insomnia	Inherited prion disease; differential context
Kuru	Acquired prion disease; transmission example

Classic versus variant CJD: Maintain the distinction

Classic CJD

- Typically occurs in older adults
- Usually sporadic
- Rapid dementia prominent early

Variant CJD

- Associated with BSE exposure
- Often affects younger individuals
- Psychiatric / sensory symptoms may precede dementia

Rarity of sporadic CJD

Textbook estimate: Approximately 1 case per million people annually.

- Sporadic CJD as more than 90% of CJD cases.
- Current CDC estimates: Approximately 1–2 CJD cases per million annually.
- These figures reflect different sources; Do not treat them as identical estimates.

Disease-form proportions differ across references

Robbins (11th edition)

- Sporadic form: More than 90% of CJD cases
- Familial forms less common
- Iatrogenic CJD documented

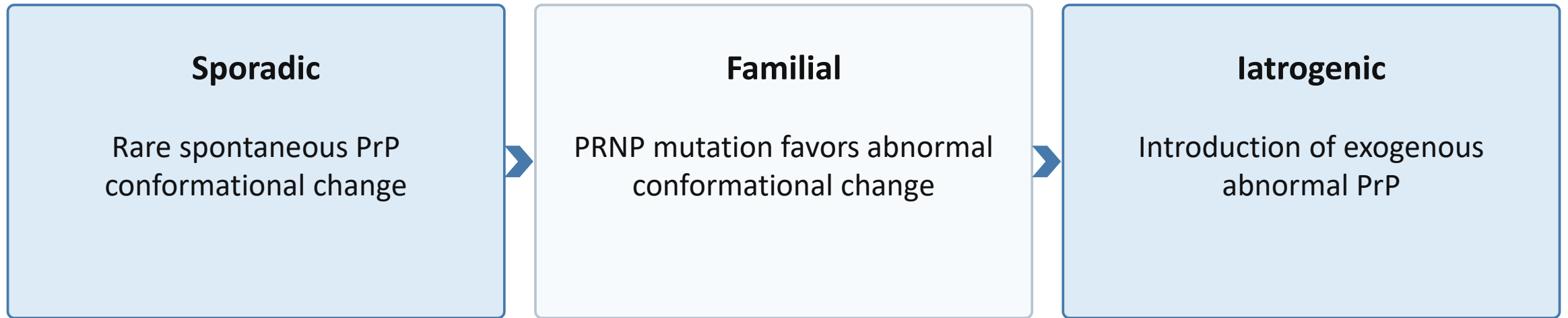
CDC clinical overview (2026)

- Sporadic: About 85%
- Familial: About 5–15%
- Iatrogenic: Less than 1%

Age distribution of classic CJD

- Peak incidence in the seventh decade.
- CDC notes that CJD typically affects adults aged 55 years and older.
- Age modifies pretest suspicion; It does not establish the diagnosis.
- Younger onset requires attention to genetic and variant phenotypes.

Three pathways to the same misfolded protein



Distinct initiating circumstances converge on amplification of abnormal PrP in neural tissue.

What PRNP contributes to disease

- PRNP encodes the host prion protein, PrP.
- Inherited PRNP mutations can increase the tendency toward pathogenic misfolding.
- Familial CJD is one of several inherited human prion disorders.
- Mutation-associated disease is conceptually distinct from acquired exposure.

Documented iatrogenic exposures

Exposure route	Clinical significance
Corneal transplantation	Transmitted CJD has been documented
Dural transplantation	Transmitted CJD has been documented
Intracerebral depth electrodes	Historical transmission via contaminated equipment
Cadaveric growth-hormone preparations	Historically transmitted disease

Transmission is not ordinary interpersonal contagion

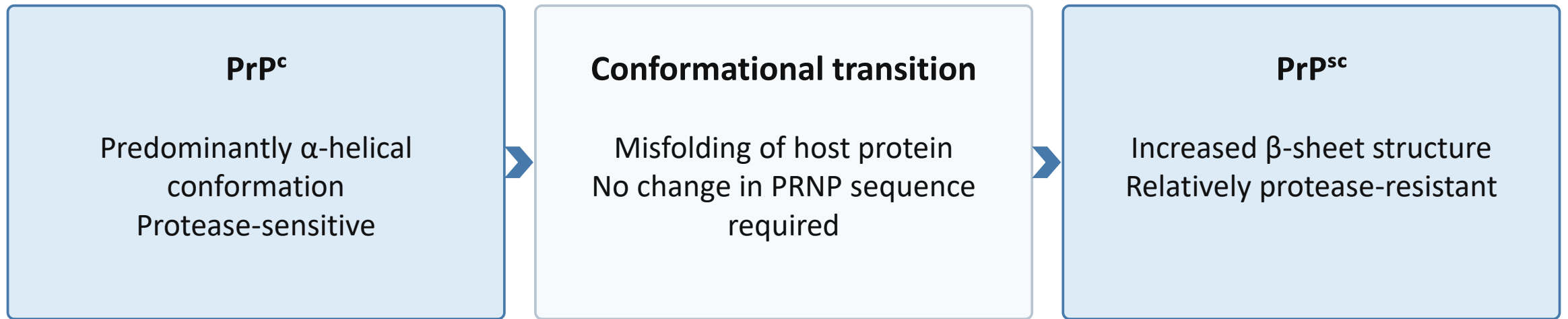
Potentially hazardous exposure

- Contaminated neural tissue / instruments
- Certain transplanted biological products
- Specialized reprocessing for neurosurgery

Routine contact

- CJD does not spread through normal personal contact
- No airborne-droplet transmission
- Standard interpersonal interaction is not the iatrogenic route

Normal PrP versus disease-associated PrP



The central event is a change in protein conformation, not replication of nucleic acid.

A protein without a conventional genome

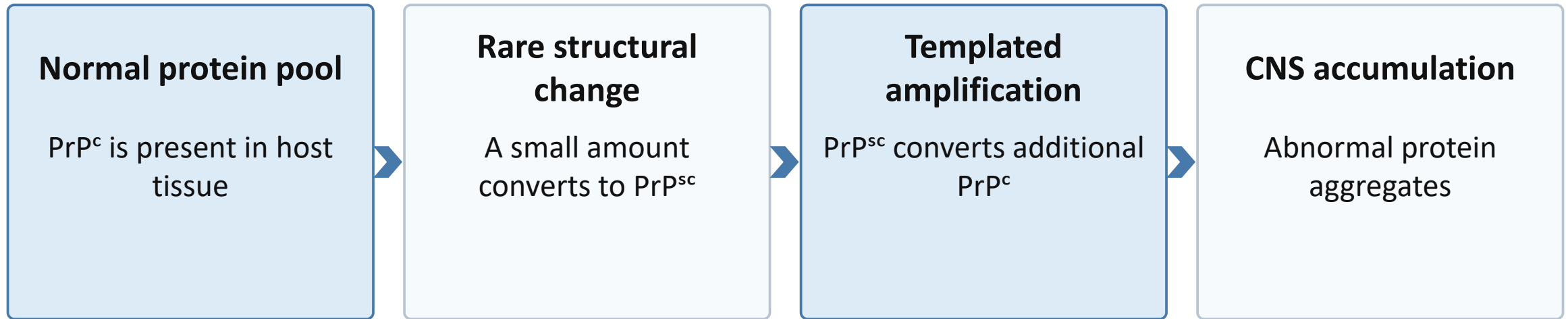
PrP^{sc} can induce PrP^c to assume its abnormal conformation.

- Host PrP provides the substrate for amplification.
- The pathogenic template is the misfolded protein itself.
- Propagation can proceed after the initiating event.

Proteinase K resistance: Diagnostic meaning

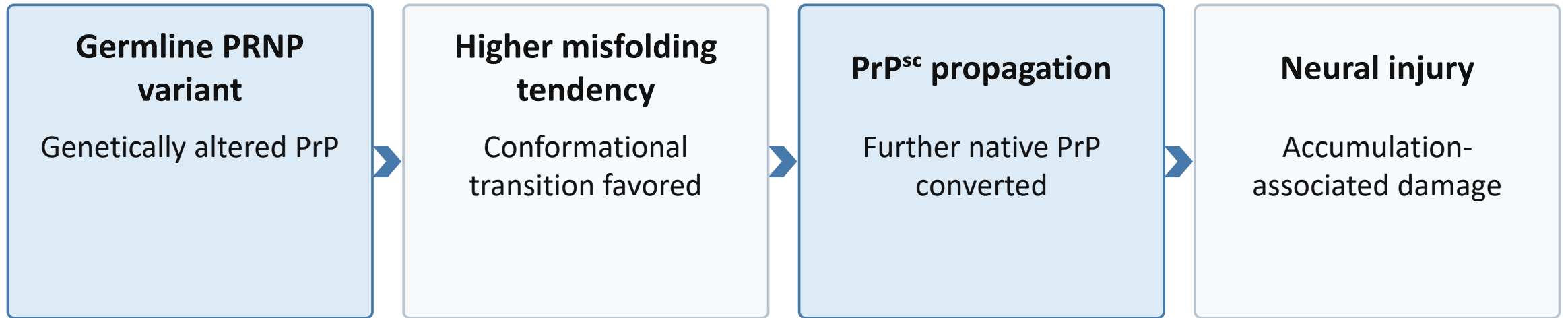
- The abnormal conformer is more resistant to proteolysis than PrP^c.
- Protease treatment enriches detection of disease-associated PrP.
- Tissue immunostaining after partial proteolysis demonstrates PrP^{sc}.
- Protease resistance is a biochemical property, not a clinical symptom.

Sporadic initiation: The low-probability event



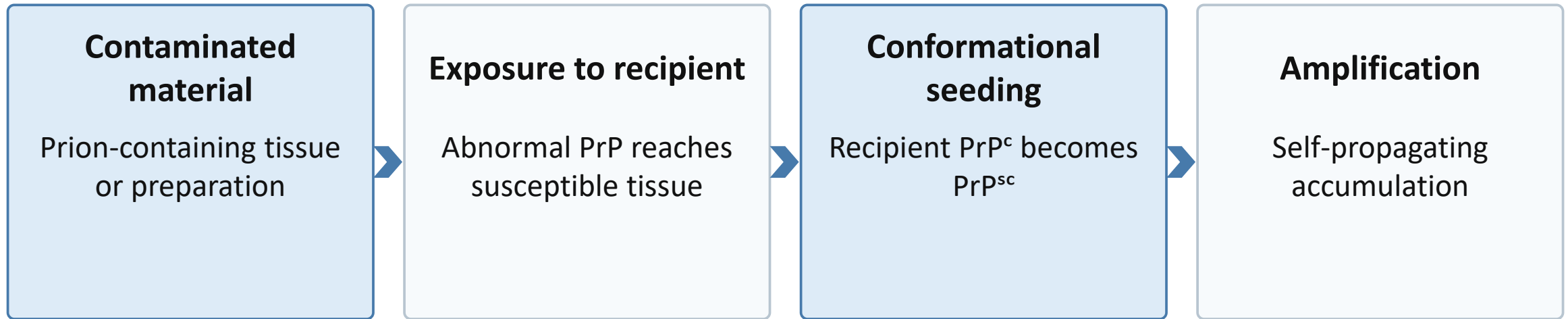
A rare initiation step can be magnified through self-propagating conversion.

Inherited initiation: Altered conversion propensity



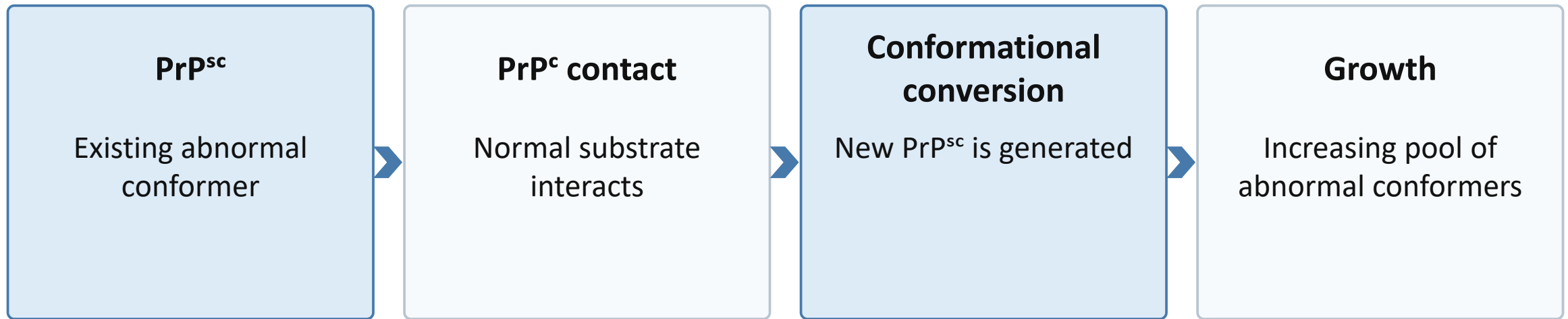
Genetic risk changes the propensity for conversion; The propagation principle is shared.

Iatrogenic initiation: Introduction of a seed



The infectious property follows from seeded protein misfolding.

Self-propagation: A molecular cascade



Templating links a molecular event to exponential-looking propagation; No growth curve is implied.

Propagation versus accumulation

Propagation

- Cell-associated conversion of PrP^c into PrP^{sc}
- Can account for transmission between tissues / hosts
- Requires native protein substrate

Accumulation

- PrP^{sc} persists and aggregates in nervous tissue
- Correlates with neuropathologic injury
- Specific downstream toxicity mechanisms remain incompletely understood

What is established—and what remains uncertain

PrP^{sc} accumulation is strongly linked to neural injury.

- Spongiform change and neuronal loss as outcomes.
- The precise route from PrP aggregation to cytoplasmic vacuoles is unresolved.
- Avoid assigning a single unverified molecular toxicity pathway.

Histopathologic signature

Spongiform transformation of gray matter is the hallmark.

- Microscopic vacuoles are variably sized and multifocally distributed.
- The cerebral cortex and deep gray nuclei are important sites.
- In advanced disease: Neuronal loss, gliosis, and status spongiosus.

Anatomic distribution of spongiform change

Cerebral cortex

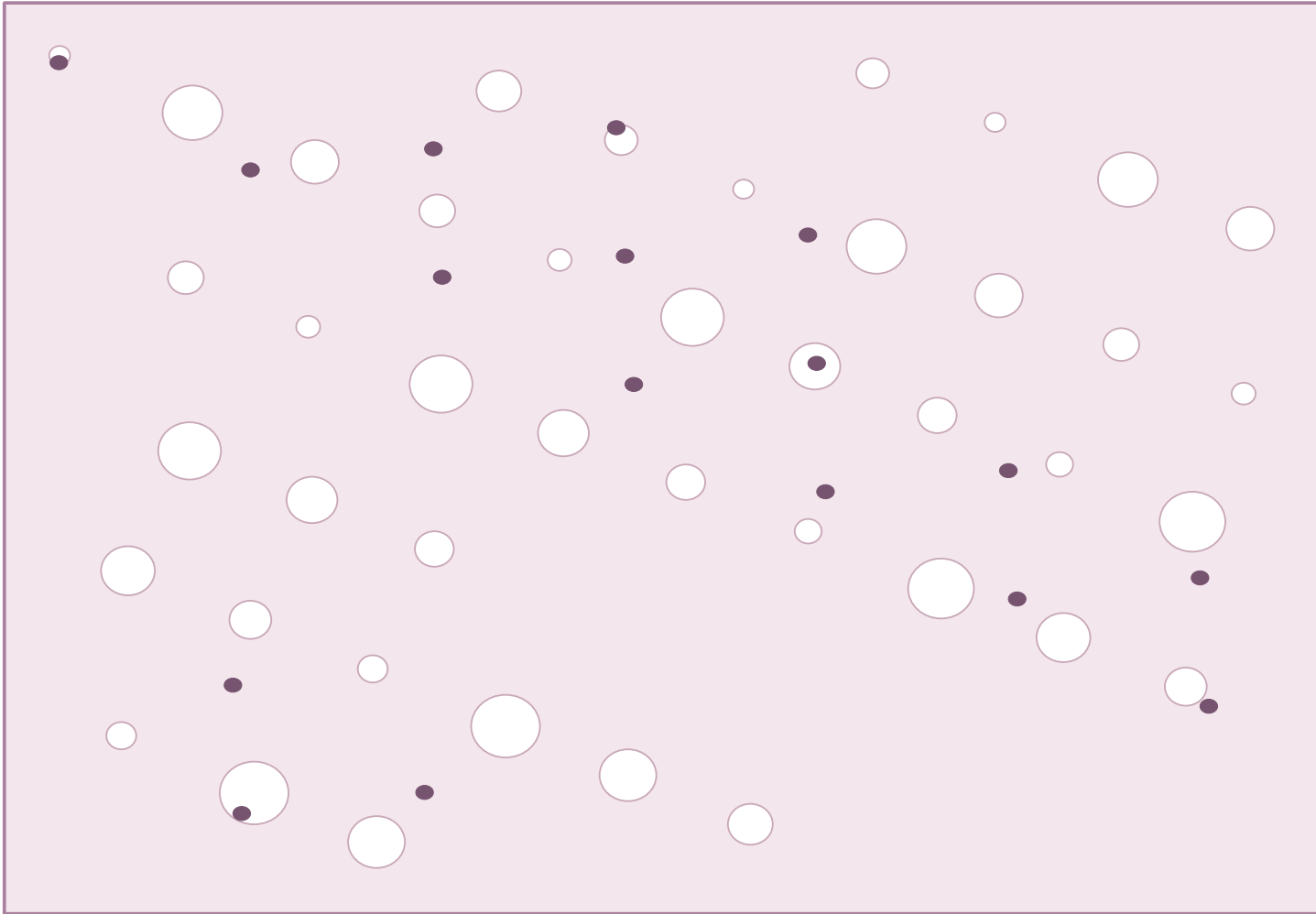
Caudate

Putamen

- Cerebral cortex is prominently involved.
- The caudate and putamen are named deep-gray targets.
- The lesion is multifocal and unevenly distributed.
- A conceptual region map does not depict specimen anatomy.

Conceptual region map; Not anatomical proportions

Spongiform change in the neuropil: Schematic



01

Unevenly distributed clear vacuoles

02

Microscopic neuropil involvement

03

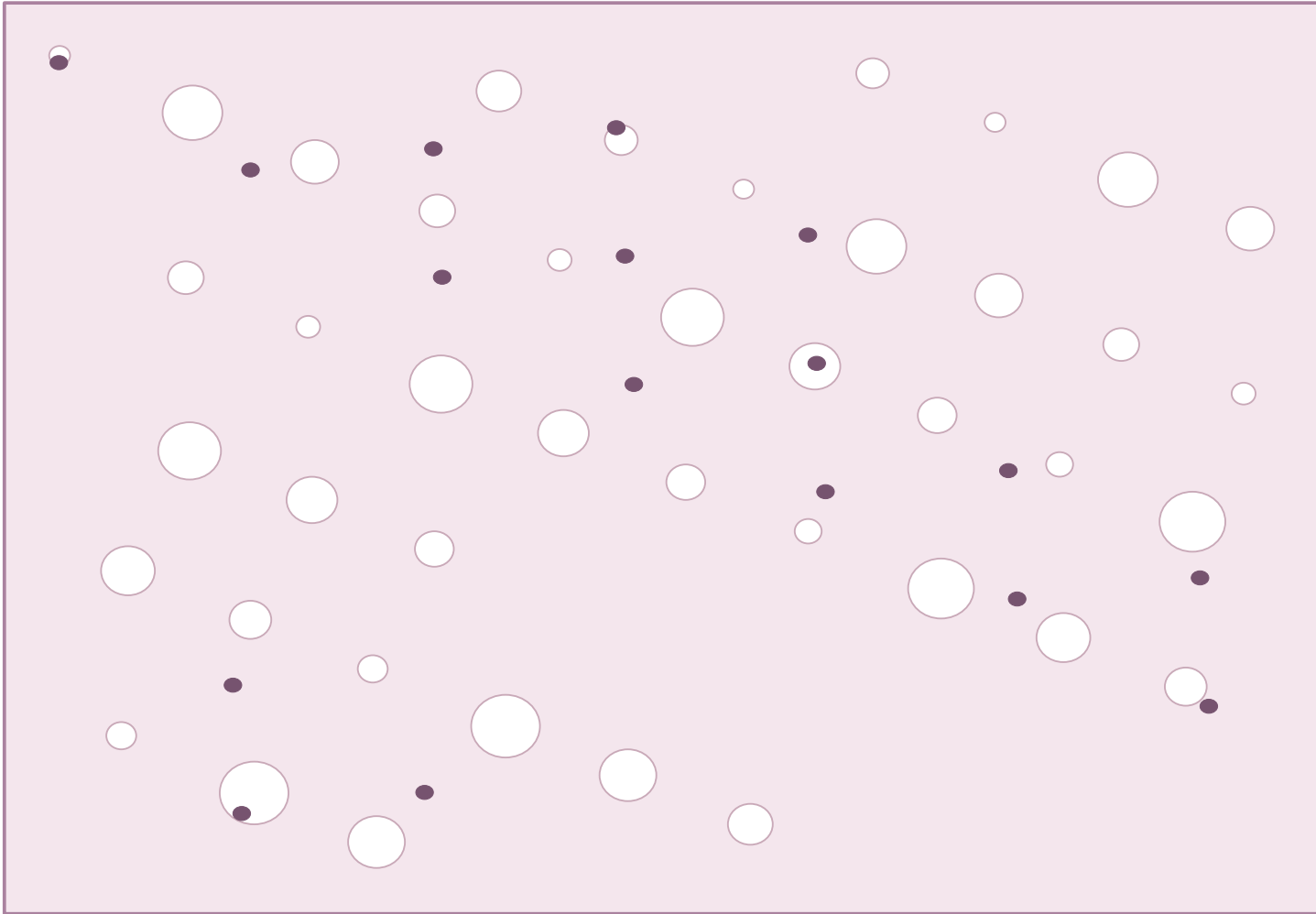
Neuron perikarya may also contain vacuoles

Schematic illustration — not a clinical/histologic specimen

The neuropil is a major compartment of injury

- Small clear spaces interrupt the background of neuronal processes.
- Vacuoles vary in diameter rather than forming identical, regular pores.
- The distribution can be patchy within involved gray matter.
- Histologic vacuolation requires clinicopathologic interpretation.

Vacuoles can extend into neuronal perikarya



01

Unevenly distributed clear vacuoles

02

Microscopic neuropil involvement

03

Neuron perikarya may also contain vacuoles

Schematic illustration — not a clinical/histologic specimen

Histologic progression within gray matter

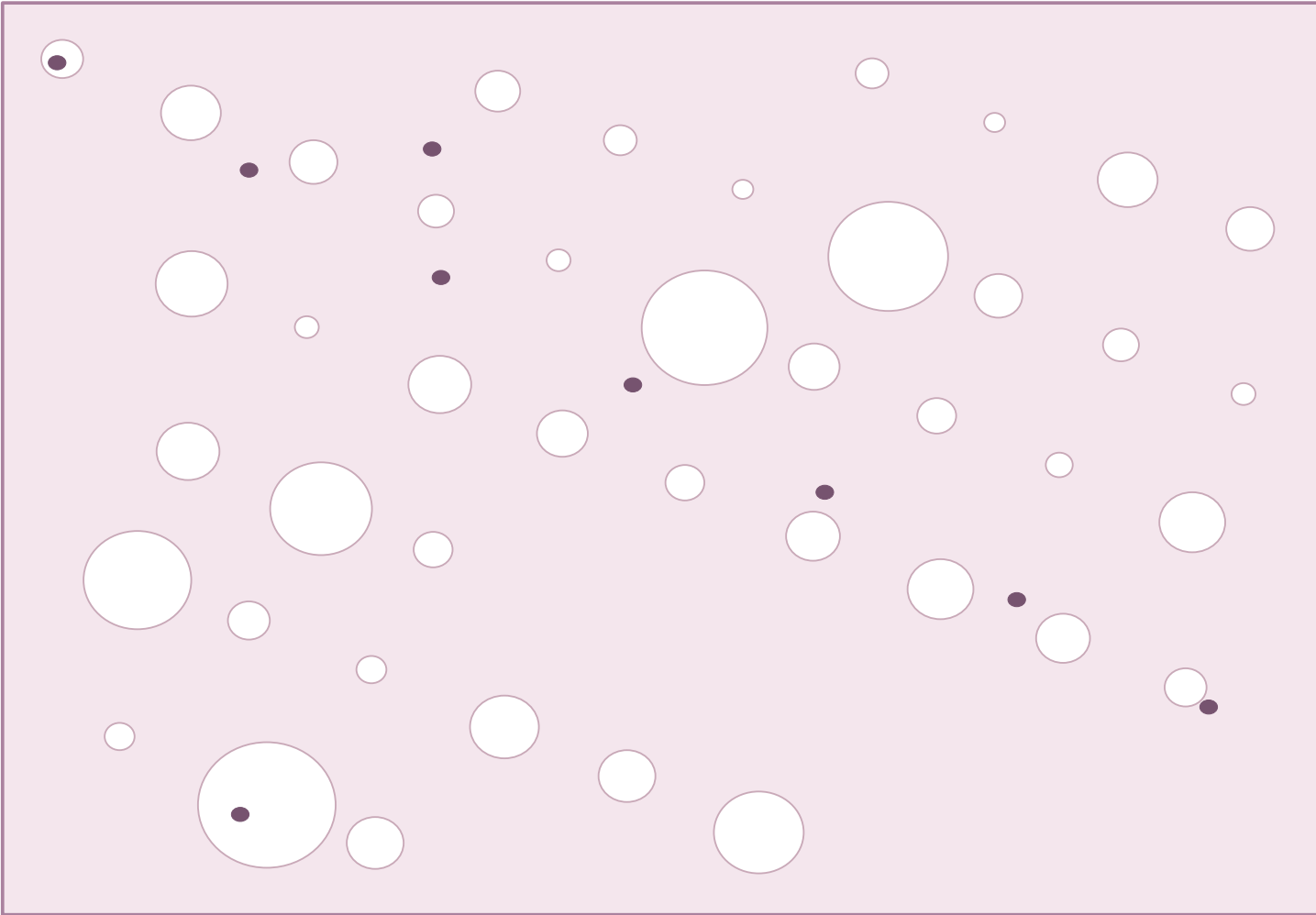
Early / less advanced

- Scattered variably sized vacuoles
- Neuropil remains largely identifiable
- Gross atrophy may be minimal

Advanced / destructive

- Marked neuronal loss
- Reactive gliosis
- Larger confluent vacuolated spaces

Advanced spongiform injury



01

Confluent vacuolated areas

02

Few remaining neurons

03

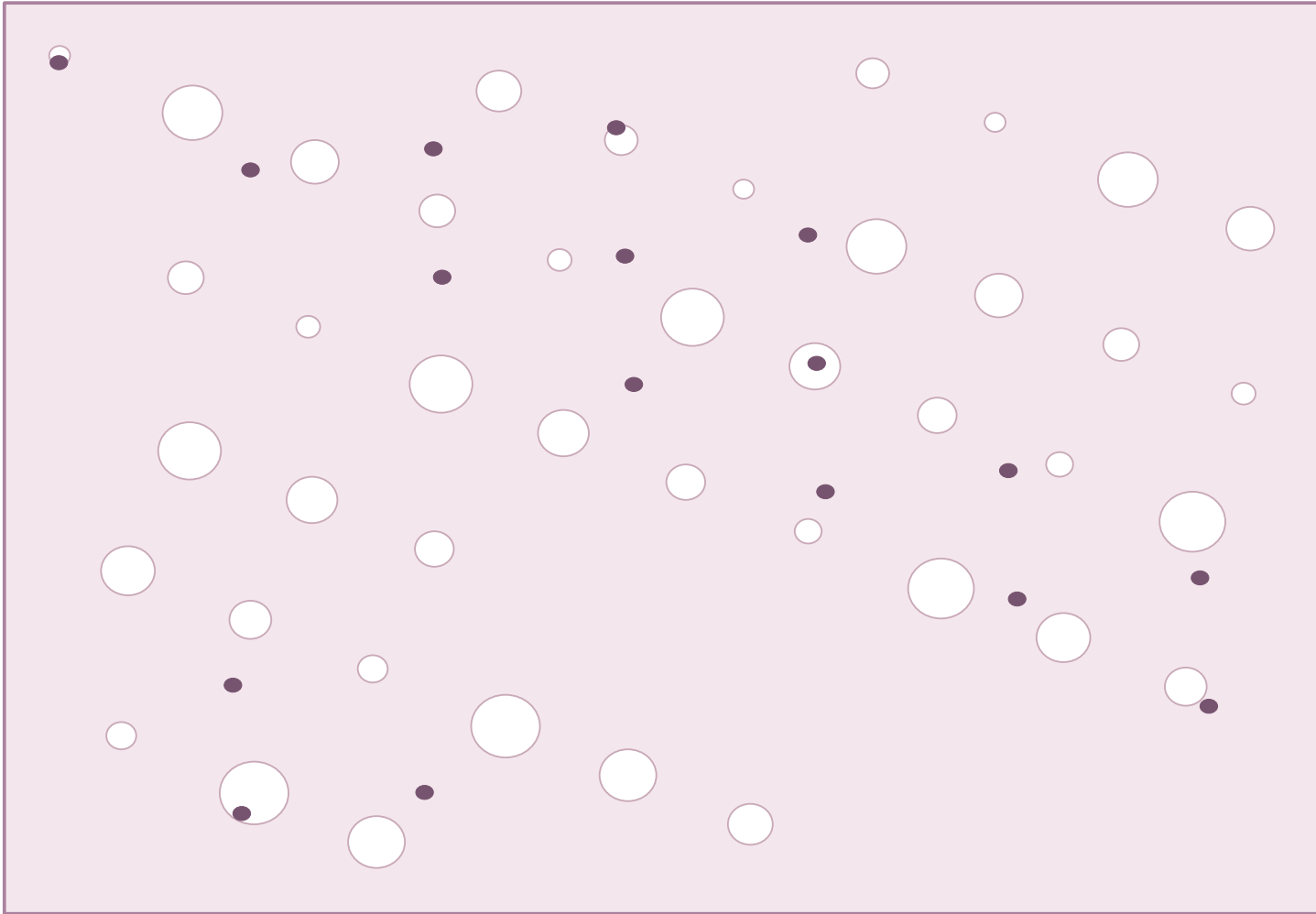
Severe tissue destruction

Schematic illustration — not a clinical/histologic specimen

Neuronal loss links morphology to decline

- Loss of functional neurons compromises neural circuits.
- Neuronal loss can become severe in advanced spongiform lesions.
- Distribution across cortical and subcortical gray matter helps explain global neurologic dysfunction.
- This is a clinicopathologic interpretation, not a quantitative causal model.

Reactive gliosis accompanies advanced injury



01

Vacuolated neuropil

02

Neuronal injury / loss

03

Reactive gliosis in advanced lesions

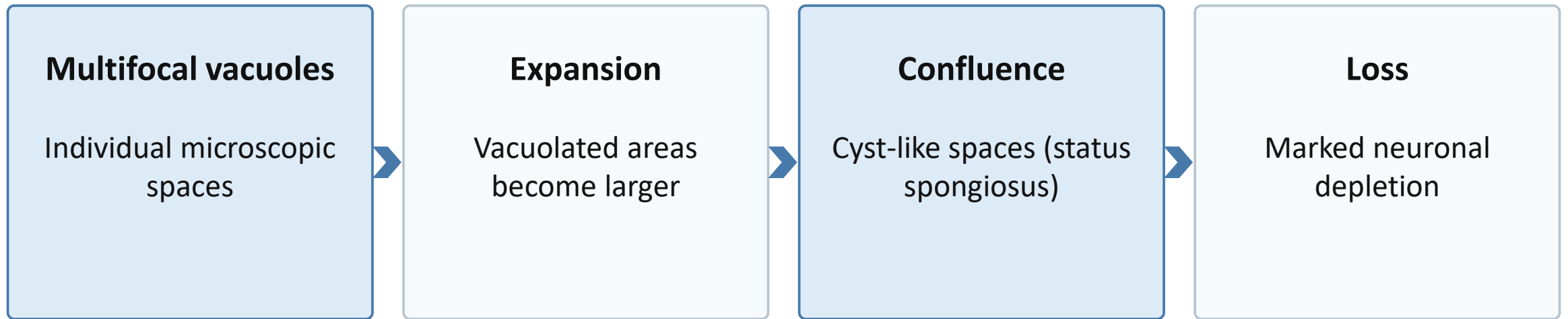
Schematic illustration — not a clinical/histologic specimen

A notable negative finding: Little inflammation

Inflammation is notably absent despite marked tissue damage.

- CJD is not characterized by a conventional inflammatory encephalitis pattern.
- Absence of substantial inflammation helps characterize the lesion.
- A noninflammatory biopsy alone is not sufficient to establish CJD.

Status spongiosus: Late tissue destruction



“Status spongiosus” describes advanced morphologic change, not a disease subtype.

Electron-microscopic correlate

- Membrane-bound vacuoles on electron microscopy.
- These vacuoles occur within the cytoplasm of neuronal processes.
- The ultrastructural finding complements—but does not replace—routine histology.
- It is distinct from extracellular amyloid plaque material.

Why gross cerebral atrophy may be limited

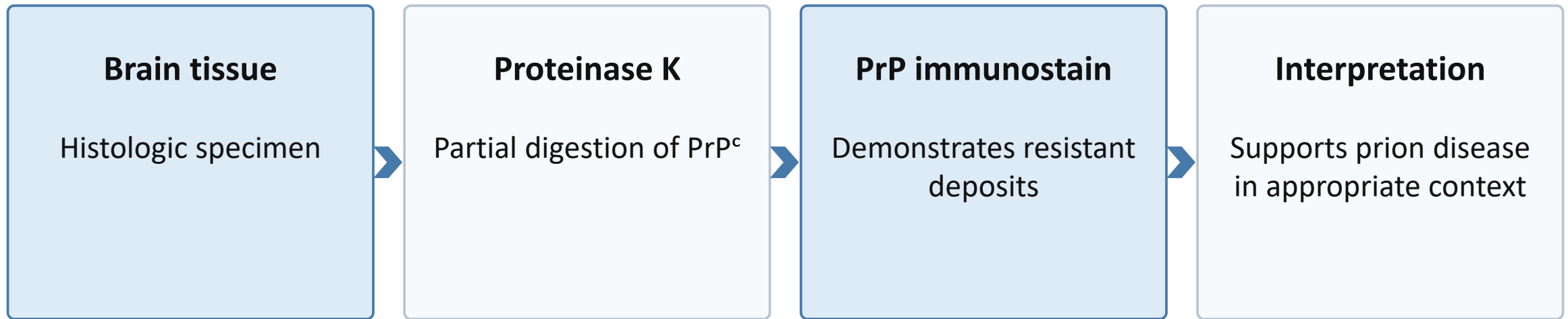
Typical rapid course

- Functional deterioration is fast.
- There is often little grossly visible cerebral atrophy.
- Microscopic damage can be marked despite a subtle gross examination.

Long-surviving cases

- A minority survive for years.
- Extensive gray-matter atrophy may develop.
- Long duration allows cumulative tissue loss to become grossly apparent.

Demonstrating the disease-associated protein



The target is disease-associated PrP^{sc}; Staining is not a generic marker of dementia.

Kuru plaques: Deposited PrP amyloid

- Kuru plaques contain extracellular aggregates of abnormal PrP.
- They can stain with Congo red and periodic acid–Schiff (PAS).
- Their usual occurrence in the cerebellum.
- Abundant cortical plaques are particularly associated with variant CJD.

Spongiosis versus PrP plaques

Spongiform change

- Clear microscopic vacuoles
- Involves neuropil and sometimes neuronal cell bodies
- The central architectural lesion

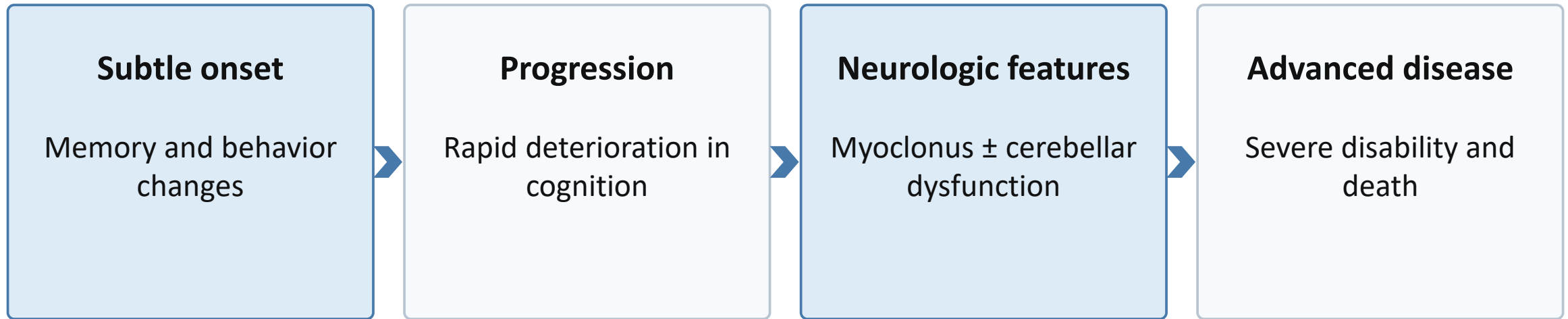
Kuru plaques

- Extracellular deposits of aggregated abnormal PrP
- Amyloid-type histochemical staining
- Distribution differs among prion disease forms

Integrating the key neuropathology findings

Observation	Interpretation / limitation
Vacuolated gray-matter neuropil	Classic spongiform pattern
Neuronal depletion	Advanced neurodegenerative injury
Reactive gliosis	Reaction to ongoing tissue damage
Little inflammation	Characteristic negative clue
Protease-resistant PrP	Disease-associated protein evidence

Clinical evolution of classic CJD



Sequence is schematic: Not every patient has every manifestation or the same interval.

Initial cognitive and behavioral disturbance

- Early memory changes may be subtle.
- Behavioral disturbance can precede overt dementia.
- The time course is often more discriminating than an isolated symptom.
- Serial clinical history is essential to recognize rapid progression.

Rapidly progressive dementia is central

A steep cognitive decline over months is the characteristic presentation.

- CJD can move rapidly from mild cognitive changes to profound impairment.
- Early course may overlap with other causes of cognitive decline.
- The disease's tempo is a major clinicopathologic clue.

Startle myoclonus

Sudden sensory stimulation may trigger prominent involuntary muscle jerks.

- Startle myoclonus is a characteristic feature.
- A single sign does not independently establish CJD.
- Movement phenomena occur alongside progressive cognitive dysfunction.

Cerebellar involvement: Clinical expression

- Cerebellar dysfunction can manifest as ataxia.
- Ataxia in a minority of affected patients.
- The absence of ataxia does not exclude classic CJD.
- Visual or cerebellar signs are also used in current clinical criteria.

Clinical features and plausible anatomic context

Clinical observation	Clinicopathologic context
Progressive dementia	Widespread cerebral cortical dysfunction
Ataxia	Cerebellar system dysfunction
Startle myoclonus	Abnormal motor-system excitability
Behavioral change	Disruption of distributed cognitive networks

Anatomic correlations are explanatory; They are not a one-to-one lesion map.

Prognosis is severe

Mean survival of about 7 months after symptom onset.

- The textbook characterizes CJD as uniformly fatal.
- CDC reports a median of approximately 4–5 months in its clinical overview.
- Mean and median are different summary statistics; Do not equate them.

Diagnostic framing: Suspected to definite

Modern clinical assessment uses graded diagnostic certainty.

- Possible CJD: Compatible syndrome without qualifying supportive evidence.
- Probable CJD: Qualifying clinical features plus RT-QuIC or other supportive testing.
- Definite CJD: Neuropathologic / tissue-based confirmation.
- The CDC criteria here are a contemporary supplement to Robbins, not a quotation from the textbook.

MRI as a supportive diagnostic test

- Current CDC probable-CJD criteria include high signal in the caudate or putamen.
- Alternatively, signal in at least two specified cortical regions may qualify.
- Accepted sequences include DWI or FLAIR.
- Imaging findings must be integrated with syndrome and alternative diagnoses.

EEG: A characteristic supportive pattern

- Typical EEG can show periodic sharp-wave complexes.
- A qualifying EEG can support probable sporadic CJD under the CDC pathway.
- EEG is not the sole criterion for clinical diagnosis.
- A nondiagnostic EEG does not by itself exclude CJD.

CSF neuronal injury marker versus prion assay

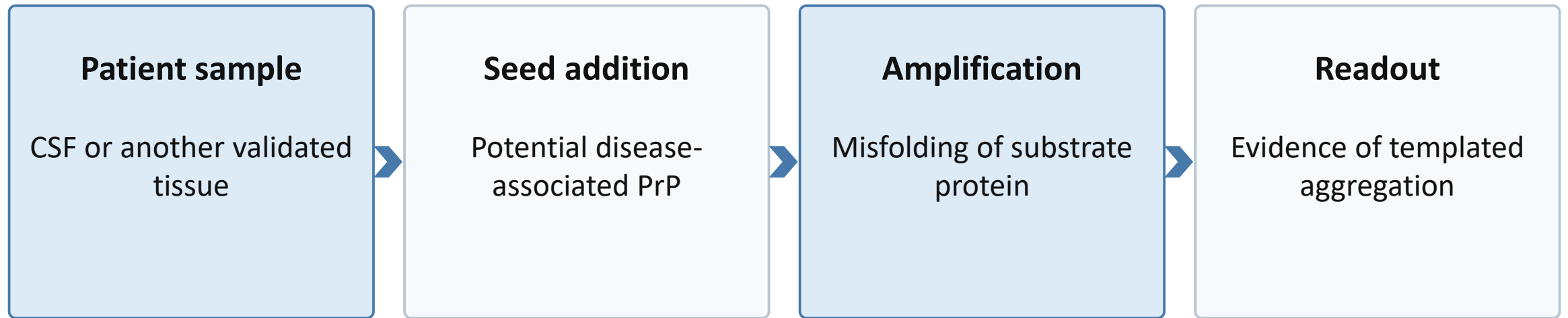
CSF 14-3-3

- Marker used within a specified clinical diagnostic pathway
- CDC criterion applies when illness duration is <2 years
- Not equivalent to direct prion-seeding detection

CSF RT-QuIC

- Amplifies PrP misfolding initiated by disease-associated seed
- Positive test plus neuropsychiatric disorder supports probable CJD
- Assay performance differs by prion disease subtype

RT-QuIC: Assay logic



A positive assay is powerful support but a negative assay cannot exclude every phenotype.

CDC probable sCJD: RT-QuIC pathway

A neuropsychiatric disorder plus a positive RT-QuIC assay.

- RT-QuIC positivity in CSF or other tissues is the laboratory requirement.
- This is one independent route to a probable sporadic CJD classification.
- Laboratory evidence is interpreted alongside the clinical syndrome.

CDC probable sCJD: Multimodal pathway

Rapidly progressive dementia plus at least 2 of 4 clinical features.

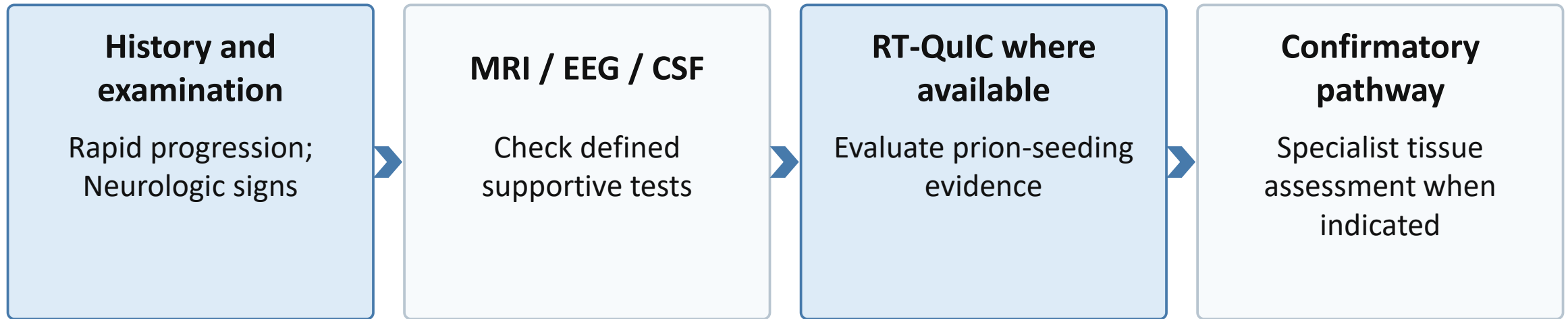
- Clinical features: Myoclonus; Visual/cerebellar signs; Pyramidal/extrapyramidal signs; Akinetic mutism.
- Additionally, ≥ 1 qualifying test: Periodic sharp-wave EEG, appropriate CSF 14-3-3, or defined MRI abnormality.
- Routine investigation must not suggest an alternative diagnosis.

CDC possible sporadic CJD

Progressive dementia with at least 2 of the 4 specified features.

- Features: Myoclonus, visual/cerebellar signs, pyramidal/extrapyramidal signs, akinetic mutism.
- No positive qualifying test that would establish probable CJD.
- Disease duration <2 years, and no alternative diagnosis on routine evaluation.

A disciplined suspected-CJD workup



Throughout the evaluation, consider potentially treatable alternative causes of rapid cognitive decline.

Definite CJD: Tissue-based evidence

- CDC includes neuropathologic examination for confirmation.
- Disease-associated protease-resistant PrP can be demonstrated immunochemically or by Western blot.
- Scrapie-associated fibrils are another recognized confirmatory feature.
- Brain biopsy is not required for every clinically probable case.

Recognizing a diagnostic limitation

No single clinical symptom proves CJD.

- A compatible syndrome and appropriate laboratory evidence establish graded probability.
- RT-QuIC sensitivity varies among prion disease phenotypes.
- Routine evaluation must actively consider alternative explanations.

Why each diagnostic modality contributes

Modality	Distinct contribution
Clinical history	Tempo and neurologic phenotype
MRI (DWI / FLAIR)	Pattern of gray-matter signal abnormality
EEG	Characteristic electrophysiologic pattern
CSF 14-3-3	Supportive injury-related biomarker in defined context
RT-QuIC	Disease-associated prion-seeding assay
Neuropathology	Confirmatory tissue assessment

Classic CJD and variant CJD: High-yield contrasts

Feature	Classic CJD	Variant CJD
Age distribution	Predominantly older adults	Typically younger adults
Early symptom pattern	Rapid cognitive decline	Psychiatric / sensory changes
Pathologic emphasis	Spongiosis in gray matter	Prominent cortical florid / kuru-type plaques
Exposure association	Usually sporadic	Linked to BSE exposure
Clinical time course	Generally faster	Relatively slower

BSE-linked disease must not be misclassified

Variant CJD is distinct from classic sporadic CJD.

- Young onset and behavioral symptoms early in variant CJD.
- The BSE exposure link belongs to variant CJD.
- Do not imply that sporadic classic CJD is contracted by eating beef.

Instrument and tissue precautions

- Prion infectivity is unusually resistant to routine decontamination.
- Exposure concern is greatest for brain, spinal cord, and ocular tissues.
- CDC provides dedicated protocols for contaminated surgical instruments.
- Use institutional infection-control procedures; Do not improvise sterilization protocols.

Risk communication in clinical settings

Avoid false reassurance

- Histology and brain-instrument exposure require special handling
- Potential iatrogenic transmission is a documented risk
- Specialist laboratory coordination matters

Avoid unnecessary isolation stigma

- CJD is not spread by ordinary contact
- Standard care and supportive interaction remain appropriate
- Explain the difference between routine contact and high-risk tissue exposure

Management and patient-care implications

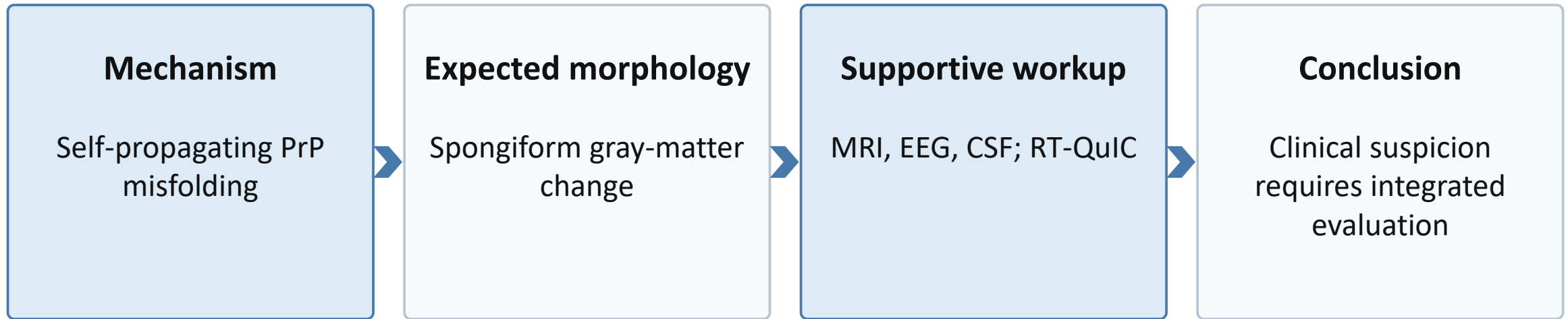
- There is no therapy proven to stop or slow classic CJD progression.
- Care centers on symptom relief, safety, and functional support.
- The rapid clinical course makes early planning and caregiver communication important.
- A diagnosis should be based on an appropriate specialist evaluation.

Case 1: Rapid decline with myoclonus

A 68-year-old develops memory changes, progressive dementia, and stimulus-induced jerks over several months.

- Which disease mechanism best accounts for the clinical tempo?
- Which major microscopic pattern would you expect?
- What additional evidence could support a probable diagnosis?

Case 1: Integrated interpretation



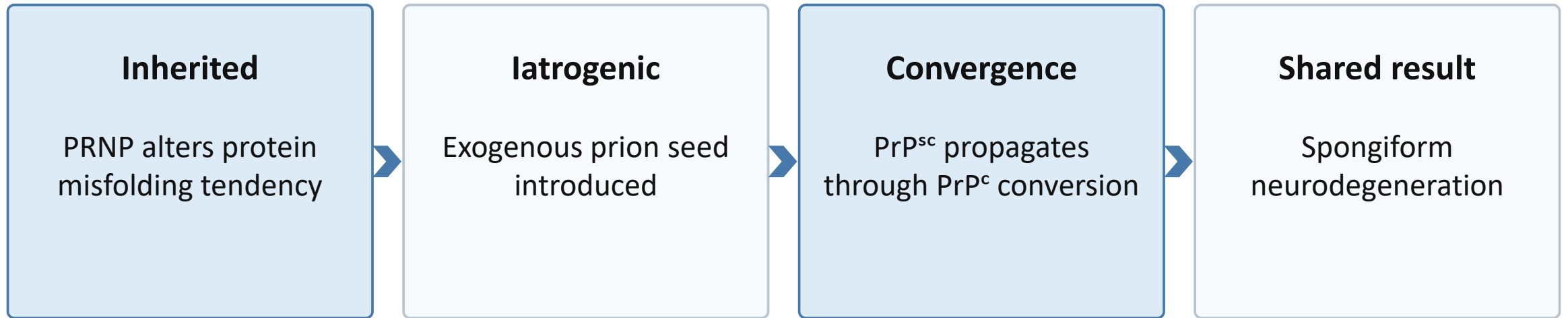
Case is a hypothetical teaching scenario; No individual patient data are represented.

Case 2: Exposed tissue versus family history

Two patients have rapid neurologic deterioration: One has a PRNP-linked family history, the other a remote cadaveric tissue exposure.

- What distinguishes inherited from iatrogenic initiation?
- What step in prion propagation is shared by both?
- Which history prompts specialized risk communication?

Case 2: Contrasting initiators



Different routes of initiation can produce the same propagation mechanism.

Microscopy checkpoint: Interpret the pattern

Gray matter shows multifocal small vacuoles, neuronal loss, gliosis, and no appreciable inflammation.

- Name the defining architectural pattern.
- Which protein assay can demonstrate disease-associated deposition?
- Why does minimal gross atrophy not exclude this diagnosis?

Five teaching conclusions

- CJD is the most common human prion disease and usually progresses rapidly.
- Misfolded PrP propagates by templated conversion of host PrP.
- Spongiform gray-matter change is the central morphologic pattern.
- Probable diagnosis uses clinical features plus defined test evidence.
- Tissue confirmation and specialist infection-control practices remain important.

Selected sources and figure provenance

Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th ed. (2026). Ch. 28, pp. 1159–1161.

CDC. Clinical Overview of Creutzfeldt-Jakob Disease. Updated January 21, 2026.

CDC. Infection Control for CJD. Updated January 21, 2026.

CDC. Clinical Overview of Variant CJD. November 12, 2024.

Rhoads DD et al. Diagnosis of prion diseases by RT-QuIC results in improved surveillance. Neurology. 2020.

All tissue illustrations in this presentation are original, labeled schematics; no diagnostic photographs were reproduced.