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Neurocognitive Disorders

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Neurocognitive Disorders

- Neurocognitive Domains
- Delirium
- Major Neurocognitive Disorder
- Mild Neurocognitive Disorder
- Alzheimer's NCD
- Frontotemporal NCD
- Lewy Body NCD
- Vascular NCD
- TBI NCD
- HIV NCD
- Prion Disease NCD
- Parkinson's Disease NCD
- Huntington's Disease NCD
- NCD due to AMC
- NCD due to Mixed Etiologies
- Unspecified NCD

Neurocognitive Domains

Neurocognitive Disorders – Introduction

- Primary clinical feature = **acquired cognitive functional deficit**
  - (vs developmental)

- 6 neurocognitive domains (MAPLES)
  - **Memory**/learning
  - Complex **Attention**
  - **Perceptual-motor**
  - **Language**
  - **Executive function**
  - **Social**

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Neurocognitive Domains – Memory & Learning

Memory & Learning		
Components & Assessment	***Immediate memory***	• Repeating list of words or digits
	Recent memory ***Free recall*** ***Cued recall*** ***Recognition memory***	• Any encoding test (word lists, diagrams) • Recall as many elements of list/diagram • Provide semantic cues • Ask whether it was on the list
	Semantic memory ***Autobiographical*** ***Implicit learning***	• Facts • Personal events, people • Unconscious learning of skills (procedural)
Major Sx	• Repeats self in convo, often within same convo • Can't keep track of short lists (shopping, plans) • Needs freq reminders to orient task at hand	
Mild Sx	• Difficulty recalling recent events • Relies on list making • Needs occasional reminders or re-reading in movies/books • May occasionally repeat self over few weeks to same person • Loses track of whether bills have already been paid	

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Neurocognitive Domains – Complex Attention

Complex Attention		
Components & Assessment	***Sustained attention***	• Maintenance of attention over time • Pressing button every time tone is heard
	Selective attention	• Despite competing stimuli/distractors • Hearing numbers + letters, only count letters
	Divided attention	• Attending to two tasks at same time • Tapping while story being read
	Processing speed	• Time to complete task
Major Sx	• More difficulty if multiple stimuli, easily distracted by competing events • Unable to attend, unless input is restricted/simplified • Difficulty holding new info in mind (new phone numbers, repeating) • Unable to do mental calculations • All thinking takes longer, only able to process a few components	
Mild Sx	• Normal tasks take longer than previously • Beings finding errors in routine tasks, more double-checking • Easier to think if no competing stimuli	

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Neurocognitive Domains – Perceptual-Motor

Perceptual-Motor		
Components & Assessment	***Visual perception***	• Line bisection (visual defect, attentional neglect) • Motor-free tasks (facial recognition, matching) • Whether figure can be "real" from dimensionality
	Visuo-constructional	• Assembling items, requiring hand-eye coordination • Drawing, copying, block assembly
	Perceptual-motor	• Integrating perception with purposeful movement • Pegs into slotted board
	Praxis	• Integrity of learned movements, imitation • Pantomime use of objects (show me how…)
	Gnosis	• Integrity of awareness, recognition (faces, colors)
Major Sx	• Sig difficulty with previously familiar activities (tools, driving) • Sig difficulty navigating in familiar environments • Often more confused at dusk, more shadows, less light	
Mild Sx	• May rely more on maps or others for directions, uses notes, follows others • If not concentrating, may find self lost or turned around • Greater effort for spatial tasks (carpentry, assembly, knitting, parking)	

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Neurocognitive Domains – Language

Language		
Components & Assessment	***Expressive Language***	• Confrontational naming (objects, pictures) • Fluency (name as many words of a group)
	Grammar & syntax	• Omission/incorrect use of articles, prepositions, etc.
	Receptive Language	• Comprehension (word definitions, pointing tasks) • Performance according to verbal command
Major Sx	• Sig difficulty with previously familiar activities (tools, driving) • Sig difficulty navigating in familiar environments • Often more confused at dusk, more shadows, less light	
Mild Sx	• May rely more on maps/others for directions, uses notes, follows others • If not concentrating, may find self lost or turned around • Greater effort for spatial tasks (carpentry, assembly, knitting, parking)	

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Neurocognitive Domains – Executive Function

Executive Function		
Components & Assessment	***Planning***	• Interpreting sequential picture, object arrangement
	Decision making	• Deciding between competing alternatives • Simulated gambling
	Working memory	• Ability hold info for brief period + manipulate it • Adding list of numbers, repeating series backwards
	Feedback/error utilization	• Ability to benefit from feedback to infer rules for solving a problem
	Overriding habits & inhibition	• Ability to choose a more complex/effortful solution • Naming color of word than reading out word
Major Sx	• Abandons complex projects, needs to focus on task at a time • Relies on others to plan IADLs, or to make decisions	
Mild Sx	• More effort to complete multistage projects • More difficulty multitasking, or resuming interrupted tasks • More fatigue from extra effort of organizing, planning, making decisions • Large social gatherings more taxing, less enjoyable due to increased effort needed to follow shifting conversations	

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Neurocognitive Domains – Social Cognition

Social Cognition		
Components & Assessment	***Recognition of emotions***	• Identification of faces with variety of positive & negative emotions
	Theory of mind	• Ability to consider another's mental state
Major Sx	• Behavior clearly out of acceptable social range • Insensitivity to social standards, modesty in dress, topics of conversation • Excessive focus on a topic, despite group's disinterest/direct feedback • Behavioral intention without regard to family or friends • Makes decisions without regard to safety (weather, social setting) • Typically, little insight	
Mild Sx	• "Change in personality" → subtle changes in behavior or attitude • Less ability to recognize social cues, read facial expressions • Less empathy, more extraversion/introversion, less inhibition • Subtle/episodic apathy or restlessness	

Delirium

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Delirium – Diagnostic Criteria

A. **Disturbance in attention & awareness**

B. **Develops over short period of time** (hours to days)
   1. Represents **change from baseline** attention/awareness
   2. Tends to **fluctuate in severity** (over course of a day)

C. **Another disturbance in cognition** (in addition to attention)
   1. Memory, disorientation, language, visuospatial, perception

D. Not better explained by NCD or coma

E. **Pathophysiological consequence of AMC, substance, toxin**
   1. History, physical exam, lab findings
   2. May be due to multiple etiologies

Delirium – Diagnostic Specifiers

- *Specify whether:*
  - **Substance intoxication delirium**
  - **Substance withdrawal delirium**
  - **Medication-induced delirium**
  - **Delirium due to AMC**
  - **Delirium due to multiple etiologies**

- *Specify if:*
  - **Acute:** hours-days
  - **Persistent:** weeks-months

- *Specify if:*
  - **Hyperactive:** psychomotor activity, mood lability, agitation, uncooperative
  - **Hypoactive:** sluggish, lethargy, approaching stupor
  - **Mixed level of activity:** normal or rapidly fluctuating level

Delirium – Diagnostic Features (1)

- Disturbance of attention or awareness = **ESSENTIAL FEATURE**
  - Change in baseline cognition
  - Not better explained by pre-existing or evolving NCD
- Decr ability to **direct, focus, sustain, shift attention**
  - Need to repeat questions, may perseverate with answers to prev questions
  - Easily distracted by irrelevant stimuli
  - May have decr orientation to environment, oneself
- Develops over short time + fluctuates during day
  - Often **worsening in evening** (less external orienting stimuli)
- Evidence of underlying cause
  - AMC, substance intox/withdrawal, medications, toxins, combination

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Delirium – Diagnostic Features (2)

- More VULNERABLE if **mild or major NCD** (impaired brain fxn)

- Accompanying change in at least one other cognitive area
  - Memory/learning → esp recent memory
  - Disorientation → time, place
  - Language
  - Perceptual distortion → typically **visual**, may be simple to complex
  - Perceptual-motor disturbance

- Continuum of normal attention/arousal, delirium, coma
  - Coma = lack of any response to verbal stimuli (do NOT dx delirium)
  - Severe inattention → minimal responses, low arousal (delirium)

Delirium – Associated Features

- **Sleep-wake cycle disturbance** = very common
  - Daytime sleepiness
  - Nighttime agitation, initial insomnia, wakefulness throughout night
  - May have complete **day-night reversal** of sleep-wave cycle

- Emotional disturbances
  - Anxiety, fear, depression, irritability, anger, euphoria, apathy
    - May have rapid shifts
  - Calling out, screaming, muttering, moaning, etc.
    - Esp during night, low stim environments

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Delirium – Prevalence

- Prevalence
  - Highest among **hospitalized older adults**
    - Varies with individual characteristics, care setting, detection methods
  - **Low in community (1-2%)**
    - Increases with AGE (14% if age >85)
    - Nursing homes, post-acute care → 60%
    - End of life → 83%

- In hospital
  - Prevalence → 14-24%
  - Incidence → 6-56%
  - Older adults presenting to ER → 10-30%
  - Older adults post-operatively → 15-53%
  - **ICU → 70-87%**

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Delirium – Development & Course

- MAJORITY have **full recovery** (with or without treatment)
  - Early recognition + intervention → usually shortens duration
- Delirium may progress → stupor, coma, seizures, death
  - Esp if underlying cause remains untreated
- Mortality is HIGH
  - Esp if malignancies or sig underlying medical illness
  - **Up to 40%** die within 1 year of dx

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Delirium – Risk & Prognostic Factors

- Environmental
  - **Functional impairment, low activity levels**
  - **Immobility, falls hx**
  - Psychoactive medications/drugs (alcohol, anticholinergics)

- Genetic & Physiological
  - Major or mild NCD → incr risk + complicate course
  - **Older adults, infants, children** (vs early/middle adulthood)
  - Children → may be related to febrile illness, anticholinergic meds

Delirium – Diagnostic Markers

- Lab findings of underlying medical condition

- EEG → insufficient sensitivity/specificity for diagnostic use
  - **Generalized slowing**
  - Occ fast activity (alcohol withdrawal delirium)

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Delirium – Functional Consequences

- Incr **functional decline**
- Incr **risk of institutional placement**

- Hospitalized pts age >65 with delirium (vs without delirium)
  - **3x risk of nursing home placement**
  - **3x risk of functional decline**
  - (at discharge, 3 months post-discharge)

Delirium – Differential Diagnosis

- Psychotic disorder, mood disorder with psychotic features
- Acute stress disorder
- Malingering, factitious disorder
  - Atypical presentation, no etiological AMC, substance

- Other neurocognitive disorders
  - Delirium vs NCD + delirium, vs NCD only
  - Acuteness of onset, temporal course
  - Difficult if prior NCD not recognize, or persistent cog imp after delirium

Other Specified Delirium

Other Specified Delirium

- Does not meet full criteria
- Clinical chooses to specify specific reason

- Attenuated delirium syndrome
  - Severity of cognitive impairment falls short

Unspecified Delirium

Unspecified Delirium

- Does not meet full criteria
- Clinical chooses NOT to specify specific reason

Major and Mild Neurocognitive Disorders

Major Neurocognitive Disorder – Diagnostic Criteria

A. **Significant** cog decline, in **1+ cognitive domain**, with both:
   1. **Concern** by individual, clinician or knowledgeable informant, about significant decline
   2. **Quantified clinical assessment**, preferably neuropsychological testing, showing significant impairment

B. **Impairs independence** in everyday activities
   1. (at minimum, complex IADLs)

C. Not due to delirium

D. Not due to another mental disorder

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Mild Neurocognitive Disorder – Diagnostic Criteria

A. **Modest** cog decline, in **1+ cognitive domain**, with both:
   1. **Concern** by individual, clinician or knowledgeable informant, about modest decline
   2. **Quantified clinical assessment**, preferably neuropsychological testing, showing modest impairment

B. **Does NOT impair independence** in everyday activities
   1. But **greater effort or strategies** required (for complex IADLs)

C. Not due to delirium

D. Not due to another mental disorder

Major/Mild NCD – Diagnostic Specifiers

- *Specify whether due to:*
  1. **Alzheimer's disease**
  2. **Frontotemporal lobar degeneration**
  3. **Lewy body disease**
  4. **Vascular disease**
  5. **Traumatic brain injury**
  6. **Substance/mediation use**
  7. **HIV infection**
  8. **Prion disease**
  9. **Parkinson's disease**
  10. **Huntington's disease**
  11. **Another medical condition**
  12. **Multiple etiologies**
  13. **Unspecified**

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Major/Mild NCD – Diagnostic Specifiers

- *Specify (behavioral disturbance):*
  - **Without behavioral disturbance**
  - **With behavioral disturbance** (specify disturbance)

- *Specify (severity):*
  - **Mild** → difficulties with **IADLs**
  - **Moderate** → difficulties with **basic ADLs**
  - **Severe** → **fully dependent**

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Major/Mild NCD – Subtypes

- Subtyped by known or presumed etiology
  - Time course, characteristic domains, associated symptoms
  - **Potentially causative entity** (Parkinson's, Huntington's)
  - **Time frame** (TBI, stroke)
  - **Symptoms** (Alzheimer's, FTD, LBD)

- Clearer when major NCD (vs mild NCD)

Major/Mild NCD – Specifiers (1)

- "With behavioral symptoms"
  - **Psychotic features common** → esp in **mild-mod AD, LBD, FTD**
    - Paranoia, delusions, persecutory themes
    - Not usually disorganized speech/behavior
    - VH more common in NCD (vs depressive, bipolar, psychotic)
  - **Mood disturbances** → depression, anxiety, elation
    - *Depression* → common early in **AD, PD**
    - *Elation* → more common in **FTD**
    - May be seen in earliest stages of mild NCD
    - If full criteria met → make diagnosis of mood disorder too
  - **Agitation common** → esp in mod-severe major NCD
    - Disruptive motor/vocal activity → often due to confusion/frustration

Major/Mild NCD – Specifiers (2)

- "With behavioral symptoms"
  - **Sleep disturbance** → common
    - Insomnia, hypersomnia
    - Circadian rhythm disturbances
  - **Apathy common** → mild NCD or mild major NCD (**esp AD**, FTD)
    - Decr motivation, goal-directed behavior
    - Decr emotional responsiveness
    - May manifest EARLY in course
  - **Other:** wandering, disinhibition, hyperphagia, hoarding

Major/Mild NCD – Diagnostic Features (1)

- A) Acquired cognitive decline, in 1+ cognitive domains
  - **Both concern + objective evidence required** → complementary
    - *Just objective testing* may miss high-functioning
      - Or over-diagnose low-functioning
    - *Just concern* may miss individuals with poor insight
      - Or miss informants who deny/miss symptoms
      - Or over-diagnose "worried well"
  - Concerns
    - Mild NCD → tasks more difficult, more time/effort, compensatory strategies
    - Major NCD → tasks require assistance, abandoned altogether
    - **Must distinguish cognitive loss (vs motor/sensory limitations)**

Major/Mild NCD – Diagnostic Features (2)

- A) Acquired cognitive decline, in 1+ cognitive domains
  - Neuropsychological testing → may have limited availability
    - **Mild NCD → 1-2 standard deviations** (3rd – 16th percentile)
    - **Major NCD → 2+ standard deviations** (3rd percentile or below)
  - Bedside testing → compare to prior performance
    - Adjust for education level, language, culture

- B) Level of independence in everyday functioning
  - Mild NCD → **preserved independence,** may have subtle interference
  - Major NCD → **impaired independence**
    - Others need to take over tasks (individual previously able to do)
  - Continuum, no precise thresholds

Major/Mild NCD – Associated Features

- Varies by etiological subtype

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Major/Mild NCD – Prevalence

- Varies by age, etiological subtype

- Prevalence **increases steeply with age >60 yrs**
  - 70s → 5-10%
  - After → at least 25%

	Mild NCD (MCI)	Major NCD (Dementia)
Age 65	2–10%	1–2%
Age 85	5–25%	Up to 30%

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Major/Mild NCD – Development & Course

- Varies across by age of onset, etiological subtypes

- NCD onset in childhood/adolescence
  - Social, intellectual development repercussions
  - May diagnosis intellectual disability, neurodevelopmental disorder

- NCD onset in youth/midlife
  - Individual/family likely to seek care
  - Easier to identify at younger ages (r/o malingering, factitious disorders)

- NCD onset in older individuals
  - Setting of medical illness, frailty, sensory loss
  - Distinguish from mild NCD vs “normal aging”

Major/Mild NCD – Risk and Prognostic Factors

- Genetic & Physiological
  - **AGE** = strongest risk factor
    - Incr risk of neurodegenerative, cerebrovascular disease
  - **Female gender HIGHER** prevalence of dementia overall
    - Esp Alzheimer's (but mostly due to **greater longevity in females**)

Major/Mild NCD – Culture-Related Diagnostic Issues

- Level or awareness + concern may vary
  - Across ethnic groups, occupational groups
- Deficits more likely to be noticed in **complex activities**
- Neuropsychological testing norms
  - Usually only available for broad populations
  - May not be applicable to some individuals
    - Less than high school **education**
    - Outside **primary language or culture**

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Major/Mild NCD – Gender-Related Diagnostic Issues

- Females with late-life NCD
  - More likely to be **older**
  - More likely to have **more medical comorbidities**
  - More likely to **live alone**

- Gender **differences in frequency** of some etiological subtypes

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Major/Mild NCD – Diagnostic Markers

- Neuropsychological Assessments
  - Key measures → esp at mild level
  - Quantitative assessment of **all relevant domains**
  - **Benchmark** for further decline or response to therapies

- Global brief mental status tests may be helpful
  - May be insensitive (single domain changes)
  - May be overly sensitive (low premorbid abilities)

- Differentiating etiological subtypes
  - Neuroimaging (MRI, PET)
  - Specific markers

Major/Mild NCD – Functional Consequences

- Affect functioning by definition
  - Broad range of functional impairments
  - Can help identify affected cognitive domains
    - Especially if no neuropsychological testing available

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Major/Mild NCD – Differential Diagnosis

- Normal Cognition
  - Inherently arbitrary boundaries (vs mild CD)
  - **Longitudinal evaluation**, quantified assessments
- Delirium
  - Assess **attention + arousal**
  - Persistent delirium may be difficult to distinguish (may also co-occur)
- Major Depressive Disorder
  - **Nonspecific/variable performance** seen in MDD (vs specific patterns)
    - Monitor treatment of MDD over time, may co-occur
- Specific Learning Disorder, Neurodevelopmental Disorders
  - Clarify **baseline status**

Major/Mild NCD – Comorbidity

- Often co-occur with variety of age-related diseases
  - NCD → **incr risk of delirium**
  - In older individuals → **mixed NCD** common
    - Many etiological entities increase in prevalence with age
  - In younger pts → often co-occur with **neurodevelopmental disorders**

- Additional comorbidity related to **etiological subtype**

Alzheimer’s Disease NCD

Alzheimer's Disease NCD – Diagnostic Criteria

A. **Major or mild NCD**

B. **Insidious onset + gradual progression** of impairment
   1. Mild → 1+ cognitive domain
   2. Major → 2+ cognitive domains

C. Probable or possible Alzheimer's disease (see next slides)

D. Not better explained
   1. By cerebrovascular disease, another neurodegenerative disease, effect of substances, another mental/neurological/systemic disorder

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Alzheimer's Disease NCD – Diagnostic Criteria

C. Probable or possible Alzheimer's disease

1. Major NCD
   - ***Probable if either:***
     - Causative genetic mutation (from family history or genetic testing)
     - All 3 of following:
       - Decline in memory/learning + 1 other domain
       - Steady gradual decline, without extended plateaus
       - Not mixed etiology
   - ***Probable otherwise***

2. Mild NCD
   - ***Probable if:***
     - Causative genetic mutation (from family history or genetic testing)
   - ***Probable otherwise***
     - No causative genetic mutation (from family history or genetic testing)
     - All 3 of following:
       - Decline in memory/learning + 1 other domain
       - Steady gradual decline, without extended plateaus
       - Not mixed etiology

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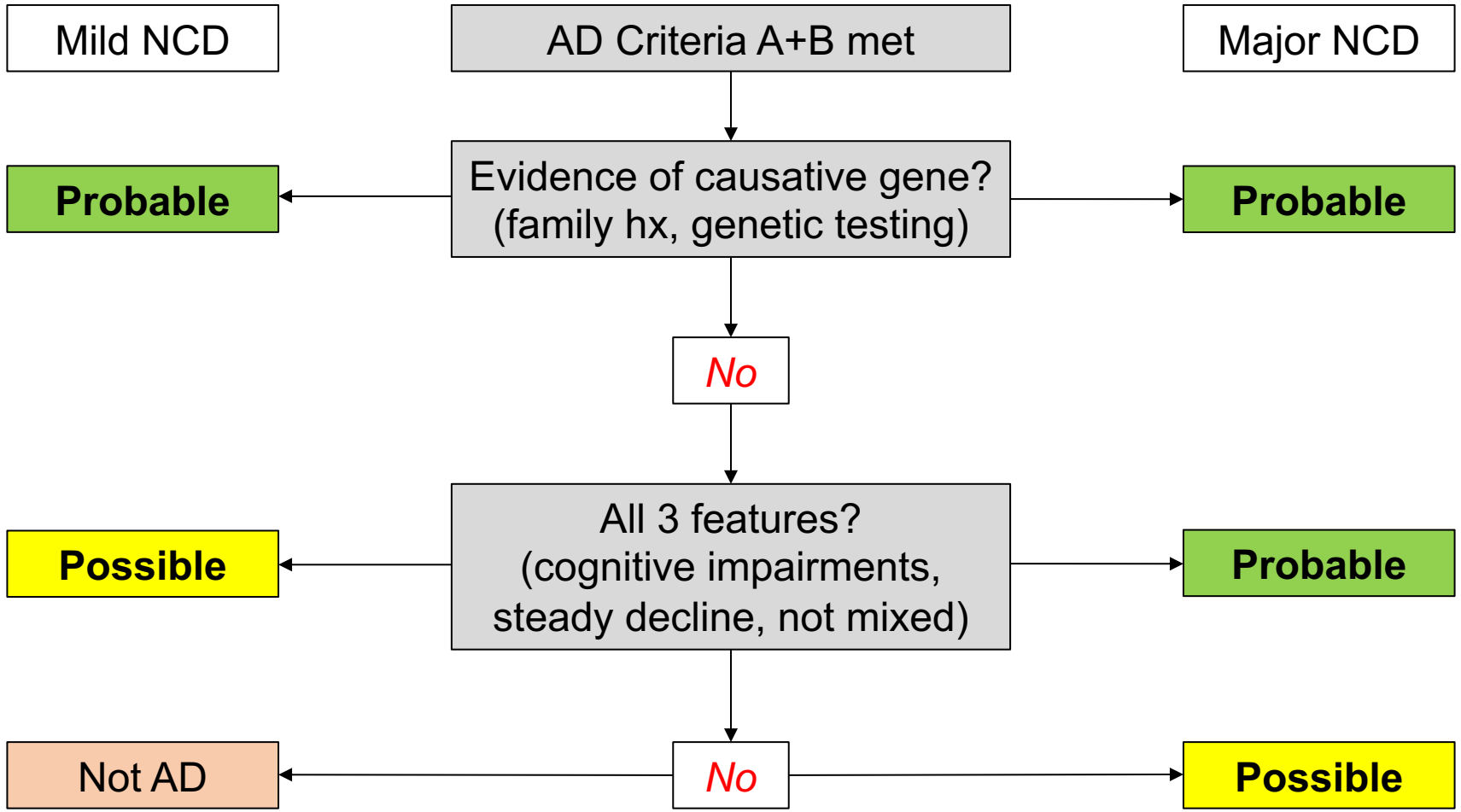
Alzheimer's Disease NCD – Diagnostic Criteria



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Alzheimer's Disease NCD – Diagnostic Features

- B) Insidious onset + gradual progression
  - Cognitive + behavioral symptoms
  - Typical pattern = **amnestic** (impaired memory/learning)
    - Less common → visuospatial, logopenic aphasic variants
  - Mild NCD → deficits in memory/learning, sometimes executive function
  - Major NCD → also visuospatial, perceptual motor, language deficits
  - Social cognition preserved until late in course

- C) Probably or possible etiology
  - Evidence of causative AD gene
    - Genetic testing of **individual**
    - Genetic testing in **affected family member**
    - **Autosomal dominant family hx + autopsy confirmation**

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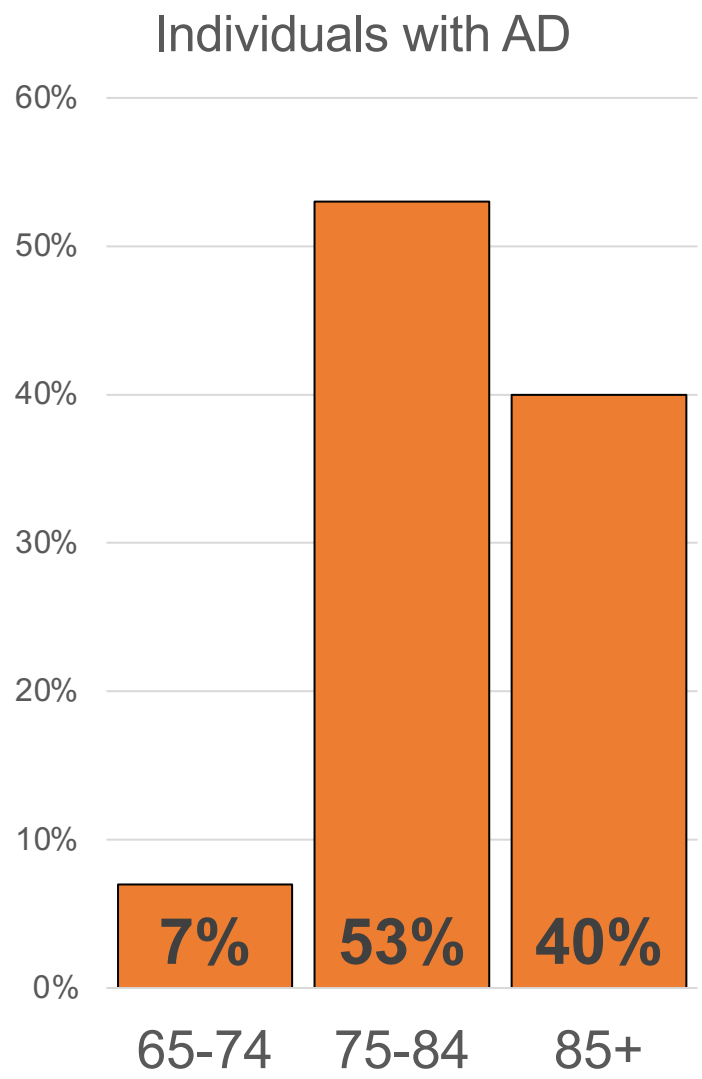
Alzheimer's Disease NCD – Associated Features

- Behavioral + psychological features common
  - Often more distressing than cognitive features
  - Frequent in mild NCD
  - **80% of major NCD due to AD**

Mild NCD *Major NCD (mild severity)*	• **Depression, apathy** common
Major NCD (mod-severe severity)	• Irritability, agitation, combativeness • Wandering • Psychotic features
Late in illness	• **Dysphagia, incontinence** • Gait disturbance • Myoclonus, seizures

Alzheimer's Disease NCD – Prevalence

- Of individuals with AD
  - 7% = age 65-74
  - 53% = age 75-84
  - 40% = age 85+
- Of individuals with any dementia
  - Alzheimer's = 60-90%
- Of individuals with MCI
  - Mild AD NCD = substantial fraction



Alzheimer's Disease NCD – Development & Course

- **Gradual progression**, can have brief plateaus

- Mean survival after dx = **10 years** (up to 20 yrs)
  - Reflects **advance age** of diagnosed patients (not course of disease)

- Late-stages → mute, bedbound
  - Death usually from **aspiration** (if survived full course)

- Symptom onset = **age 80-90 usually**
- Early-onset = age 50-60 → related to causative mutations

- Younger pts more likely to survive full course (less comorbidities)

Alzheimer's Disease NCD – Risk and Prognostic Factors

- Environmental
  - Traumatic brain injury

- Genetic & Physiological
  - **AGE** = strongest risk factor for AD
  - **Apolipoprotein E4 polymorphism** = incr risk, younger onset
    - Esp in homozygous pts
  - Other rare causative genes
  - **Down's syndrome (trisomy 21)** → develop AD if survive to midlife
  - **Vascular risk factors** → indirect vs direct

Alzheimer's Disease NCD – Culture-Related Dx Issues

- Detection may be more difficult
  - If memory loss considered normal
  - If older adults face fewer cognitive demands
  - Very low educational levels

Alzheimer's Disease NCD – Diagnostic Markers

- Pathological diagnosis (post-mortem histopathological exam)
  - **Cortical atrophy**
  - **Amyloid-predominant neuritic plaques**
  - **Tau-predominant neurofibrillary tangles**

- Early-onset, autosomal dominant inheritance, causative genes
  - **Amyloid precursor protein (APP)**
  - **Presenilin 1/2 (PSEN1/2)**

- **Amyloid beta-42 deposition** → early in pathophysiological cascade
  - PET amyloid imaging
  - CSF amyloid beta-42 (low levels)

- Less specific tests for neuronal damage
  - MRI → hippocampal, temporoparietal cortical **atrophy**
  - Fluorodeoxyglucose (FDG) PET → temporoparietal **hypometabolism**
  - CSF → **incr total tau** + phospho-tau levels

- Apo E4 → NOT a diagnostic marker (not necessary or sufficient for dx)

Alzheimer's Disease NCD – Functional Consequences

- Memory loss → can cause sig difficulties early in course

- <u>Social cognition, procedural memory</u>
  - May be **relatively preserved** for extended periods

Alzheimer's Disease NCD – Differential Diagnosis

- Other Neurocognitive Disorders
  - Other neurodegenerative (LBD, FTD) also insidious + gradual
    - But distinctive core features
  - Vascular NCD → hx of stroke, infarcts, white matter hyperintensities
    - If no clear hx or stepwise decline → may look similar

- Other concurrent, active neurological or system illness
  - Consider if temporal relationship/severity
  - May be difficult to distinguish mild NCD from AMC (thyroid, B12 def)

- Major Depressive Disorder
  - Decr daily function, poor concentration → may resemble mild NCD
  - Can distinguish by improvements with treatment

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Alzheimer's Disease NCD – Comorbidity

- **Cerebrovascular disease** → commonly co-occurs

- If comorbid condition contributes to NCD → **mixed etiology**

Frontotemporal NCD

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Frontotemporal NCD – Diagnostic Criteria

A. **Major or mild NCD**

B. **Insidious onset + gradual progression** of impairment

C. Either: **Behavioral Variant** or **Language Variant** (see next slide)

D. Relative sparing of learning, memory, perceptual-motor function

E. Not better explained

1. By cerebrovascular disease, another neurodegenerative disease, effect of substances, another mental/neurological/systemic disorder

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Frontotemporal NCD – Diagnostic Criteria

A. Either: Behavioral or Language Variant

1. **Behavioral Variant** (both) HADES-S
   - ***Behavioral symptoms*** (3+)
     - **Hyperorality** + diet changes
     - **Apathy** or inertia
     - **Disinhibition** of behavior
     - **Empathy** or sympathy loss
     - **Stereotyped,** perseverative or compulsive/ritualistic behavior
   - ***Social or executive functional decline***

2. **Language Variant**
   - ***Language functional decline*** (any)
     - Speech production
     - Word finding
     - Object naming
     - Grammar
     - Word comprehension

Frontotemporal NCD – Diagnostic Criteria

- "Probable" vs "Possible" → genetic factors or imaging present
  - ***Probable FTD NCD***
    - Causative FTD NCD **genetic mutation** (family hx or genetic testing)
    - Disproportionate frontal and/or temporal lobe involvement on **imaging**
  - ***Possible FTD NCD***
    - NO evidence of genetic mutation
    - NO neuroimaging evidence
    - Or not available

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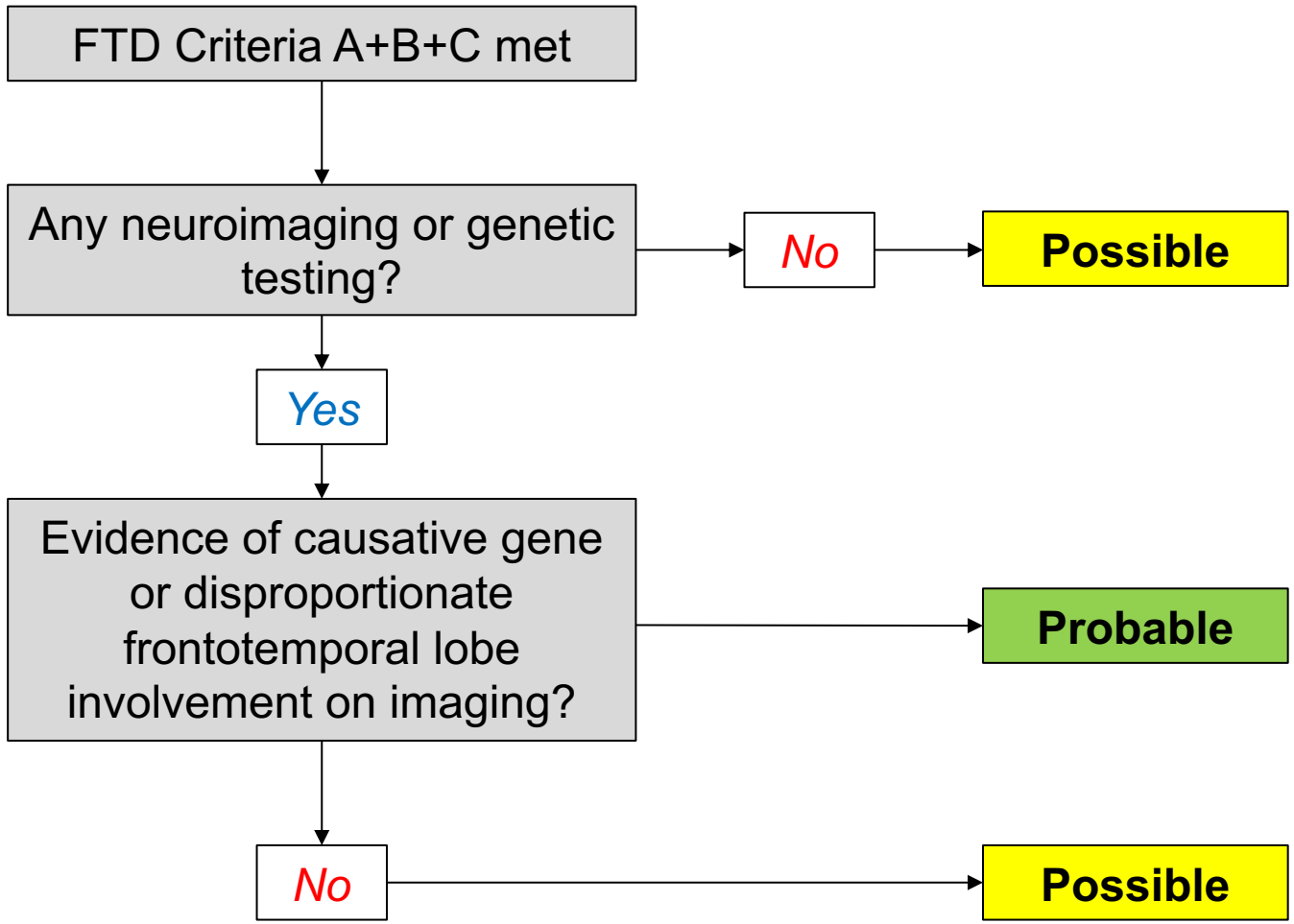
Frontotemporal NCD – Diagnostic Criteria



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Frontotemporal NCD – Diagnostic Features

- **Behavioral variant**
  - **Impaired insight** (can delay medical consultation)
    - Apathy, disinhibition, socially inappropriate behaviors
    - Changes in social style, religious/political beliefs
    - Repetitive movements, hoarding, changes in eating, hyperorality
  - **Cognitive decline less prominent**, few deficits in early stages
    - **Executive function deficits**
      - Mental flexibility, abstraction, response inhibition
      - Lack of planning, disorganization, distractibility, poor judgement
    - **Learning/memory relatively spared**
    - Perceptual-motor preserved early
  - Later stages → **loss of sphincter control**

- **Language variant** → "Primary Progressive Aphasia"
  - 3 subtypes (SNL) = **Semantic, Nonfluent** (agrammatic), **Logopenic**

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Frontotemporal NCD – Associated Features

- Extrapyramidal features may be prominent
  - Can overlap with PSP, CBD
- Motor neuron disease features may be present
  - **Muscle atrophy, weakness**
- Visual hallucinations in subset of pts

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Frontotemporal NCD – Prevalence

- Common cause of **early-onset NCD** (age <65 yrs)
  - 20-25% of FTD NCD occurs in pts >65s yrs
- Population prevalence = 2-10 per 100,000 (0.002-0.01%)
  - Accounts for **5% of all cases of dementia**
- **MALES** → behavioral variant, semantic language variant
- **FEMALES** → nonfluent language variant

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Frontotemporal NCD – Development & Course

- Common age of presentation = **age 60s**
  - Age of onset varies → age 30-90s
- Gradually progressive, median survival:
  - **After symptom onset → 6-11 yrs**
  - **After diagnosis → 3-4 years**
- FTD vs Alzheimer's
  - **FTD = MORE RAPID decline, SHORTER survival**

Frontotemporal NCD – Risk & Prognostic Factors

- Genetic & Physiological
  - **40% have family history of early-onset NCD**
  - **10% show autosomal dominant** inheritance pattern

  - Genetic factors
    - **MAPT** (microtubule associated protein tau gene)
    - **GRN** (granulin gene)
    - **C9ORF72** gene

  - Many with known familial transmission do NOT have known mutation

  - Presence of **motor neuron disease** → more RAPID deterioration

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Frontotemporal NCD – Diagnostic Markers

Variant	Atrophy on CT/MRI
Behavioral (HADES-S)	• **Frontal lobe** (esp medial) • Anterior temporal lobe
Semantic	• Middle, inferior, anterior **temporal lobe** • (bilateral, more left sided)
Nonfluent	• **Left posterior** frontal-insular
Logopenic	• **Left posterior** perisylvian or parietal

- Functional Imaging
  - **Hypoperfusion/hypometabolism** in corresponding regions
  - May be present in early stages (without structure abnormalities)

- Genetic Mutations
  - Can help confirm in familial cases
  - MAPT, GRN, **C9ORF72**, TARDBP, VCP, CHMP2B, FUS

Frontotemporal NCD – Functional Consequences

- Often severe impairment early in course
  - Early onset, involvement of language + behavior
    - → Hyperorality, impulsive wandering, disinhibited behavior
  - May exceed the functional impair due to cognitive deficits

- May lead to nursing home placement or institutionalization
  - Can still be **severely disruptive**
  - Even if otherwise **healthy, non-frail**, no medical comorbidities

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Frontotemporal NCD – Differential Diagnosis

- Alzheimer's NCD → decline in learning + memory
  - **10-30% of FTD** found to have Alzheimer's disease pathology autopsy
    - Esp if **progressive executive dysfunctions syndromes**
      - (without behavior/movement changes)
    - Esp if **logopenic variant**
- Lewy body NCD → core + suggestive features
- Parkinson's NCD → spontaneous established parkinsonism
- Vascular NCD → temporally related cerebrovascular event
  - Can have loss of executive function + behavioral changes
  - Infarctions, white matter lesions on imaging

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Frontotemporal NCD – Differential Diagnosis

- *Other Neurological Conditions*
  - Progressive Supranuclear Palsy (PSP)
    - **Supranuclear gaze palsies**, axial-predominant parkinsonism
    - Pseudobulbar signs, retropulsion
    - Psychomotor slowing, poor working memory, poor executive function
  - Corticobasal Degeneration (CBD)
    - Asymmetric rigidity, myoclonus, limb apraxia, **alien limb** phenomenon
    - Postural instability, cortical sensory loss
  - Motor neuron disease
    - Often features in **behavior variant** (mixed upper, predominantly lower)
- *Other mental disorders and medical conditions*
  - Behavioral variant may be mistaken for primary mental disorder
  - Exclude treatable causes of NCDs

Lewy Body NCD

Lewy Body NCD – Diagnostic Criteria

A. Major or mild NCD

B. **Insidious onset + gradual progression** of impairment

C. Core + suggestive diagnostic features (see next slide)

1. **Core diagnostic features**
   - Fluctuating cognition
   - Recurrent VH
   - Spontaneous parkinsonism
2. **Suggestive diagnostic features**
   - REM sleep behavior disorder
   - Severe neuroleptic sensitivity

Probable = 2 core *or*
1 core + 1 suggestive

Possible = 1 core *or*
1+ suggestive

D. Not attributable to AMC or better explained by AMD

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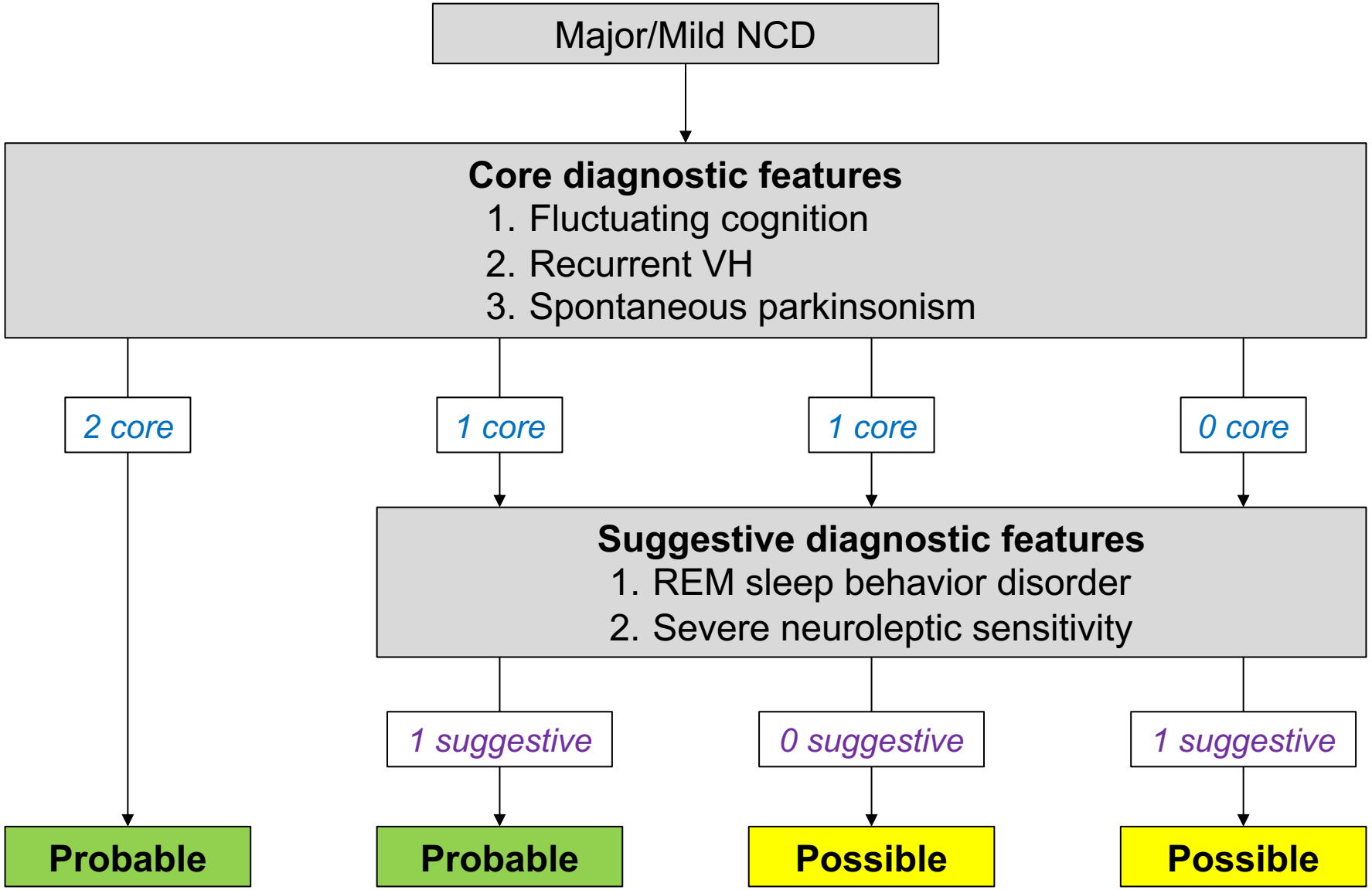
Lewy Body NCD – Diagnostic Criteria



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Lewy Body NCD – Diagnostic Features

- Progressive cognitive impairment
  - Early changes in complex attention, executive function
  - (vs learning/memory in Alzheimer's)

- Core features
  - **Fluctuating symptoms** → can resemble delirium
  - **Complex visual hallucinations**
    - Can also be in other sensory modalities
  - **Spontaneous parkinsonism**
    - Must begin **after onset** of cognitive decline
    - Distinguish from neuroleptic-induced EPS

- Suggestive features
  - **REM sleep behavior disorder** → can be early
  - **Severe neuroleptic sensitivity** → up to 50%

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Lewy Body NCD – Associated Features

- Transient unexplained loss of consciousness
  - **Falls, syncope**
- Autonomic dysfunction
  - **Orthostatic hypotension**
  - **Urinary incontinence**
- Psychiatric
  - **Hallucinations** (visual, auditory, other)
  - **Delusions** (systematized, misidentification)
  - **Depression**

Lewy Body NCD – Prevalence

- General ELDERLY population **= 0.1 – 5%**
  - Dementia cases = **1.7 – 30.5%**
  - Autopsy series → Lewy bodies present in **20 – 35% of dementia**

- **MALES** 1.5x HIGHER

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Lewy Body NCD – Development & Course

- Gradually progressive + insidious onset
  - Often **prodromal delirium**, precipitated by illness or surgery
  - May have occasional plateaus
  - Progresses through severe dementia to death

- Onset = age 60-90s → most cases present in **mid 70s**

- Average survival = **5-7 years**

- Cognitive decline early (>1 year before onset of motor sx)
  - Lewy Body NCD → lewy bodies primarily **cortical**
  - Parkinson's Disease NCD → lewy bodies primarily in **basal ganglia**

Lewy Body NCD – Risk & Prognostic Factors

- Genetic & Physiological
  - Most cases → **NO family history**
  - Familial aggregation may occur
  - Several risk genes identified

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Lewy Body NCD – Diagnostic Markers

Underlying Synucleinopathy	Due to α-synuclein misfolding + aggregation
REM Sleep Behavior Disorder	• **Formal sleep study**
Neuroleptic sensitivity	• **Challenge NOT recommended**
SPECT/CT Perfusion scan	• Low striatal dopamine transporter uptake • Generalized low uptake, **reduced occipital activity**
CT/MRI	• Relative preservation of medial temporal structures
MIBG myocardial scintigraphy	• Low uptake (suggests sympathetic denervation)
EEG	• **Prominent slow-wave activity** • Temporal lobe transient waves

Lewy Body NCD – Functional Consequences

- More functionally impaired for their cognitive deficits
  - Combination of motor, autonomic, psychiatric, sleep symptoms
  - **Worse function + quality of life** (vs other neurodegenerative diseases)

Lewy Body NCD – Differential Diagnosis

- Parkinson's Disease NCD
  - Cognitive decline in established PD (>1 year after PD diagnosis)
  - **If less than 1 year since onset of motor sx** → Lewy Body NCD

Lewy Body NCD – Comorbidity

- Freq coexists with **Alzheimer's** or **cerebrovascular disease**
  - Esp among older age groups
- In Alzheimer's NCD → **60% also have synuclein pathology**
- Higher rates of Lewy body pathology if dementia present

Parkinson’s Disease NCD

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Parkinson's Disease NCD – Diagnostic Criteria

A. Major or mild NCD

B. Established Parkinson's disease

C. **Insidious onset + gradual progression** of impairment

D. Not attributable to AMC or better explained by AMD

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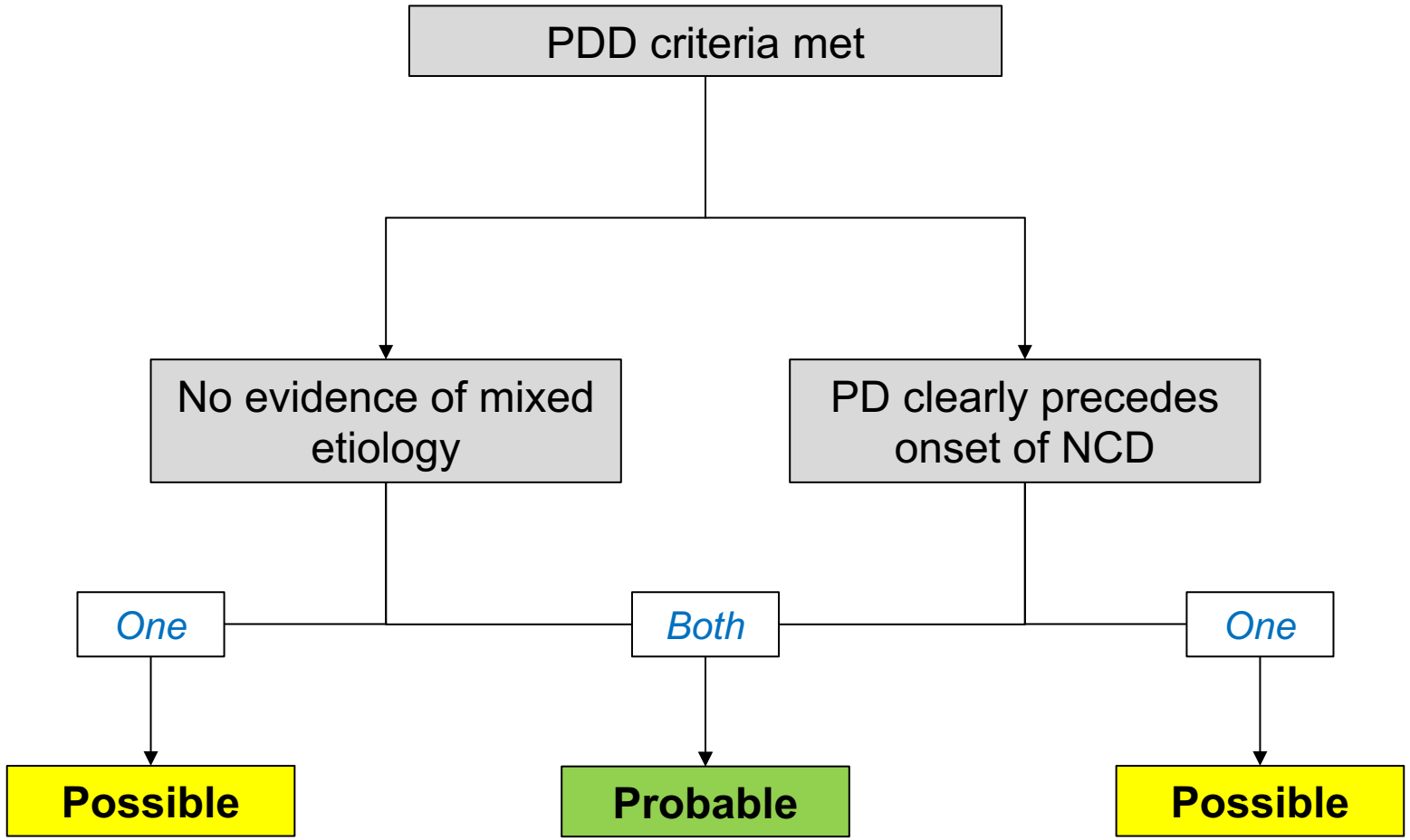
Parkinson's Disease NCD – Diagnostic Criteria



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Parkinson's Disease NCD – Associated Features

Personality	• Apathy • Personality changes
Mood	• Depression • Anxiety
Psychosis	• Hallucinations • Delusions
Sleep	• REM Sleep Behavior Disorder • Excessive daytime sleepiness

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Parkinson's Disease NCD – Prevalence

- Parkinson's disease prevalence INCREASES with age
  - Age 65-69 = 0.5%
  - Age 85+ = 3%
- **More common in MALES**
- Among those with Parkinson's disease
  - **75% develop major NCD**
  - 27% develop mild NCD

Parkinson's Disease NCD – Development & Course

- Onset = between age 60-90 → most present in **early 60s**
  - Mild NCD common early in PD
  - Major NCD typically later

Parkinson's Disease NCD – Risk & Prognostic Factors

- Environmental
  - Parkinson's disease → ?exposure to **herbicides, pesticides**

- Genetic & Physiological
  - NCD in PD → **older age** at disease onset, **incr duration** of disease

Parkinson's Disease NCD – Diagnostic Markers

- Neuropsychological testing

- Structural imaging, DAT (dopamine transporter) scans
  - Differentiate lewy body-related dementias (PDD, LBD) vs non-lewy body-related dementias (AD, FTD)

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Parkinson's Disease NCD – Differential Diagnosis

- Lewy Body NCD
  - 1 year rule, more difficult to distinguish mild NCD
- Alzheimer's Disease NCD
  - Motor features of PD, but **both can co-occur**
- Vascular NCD
  - May have **parkinsonian features** due to subcortical small vessel disease
  - But not sufficient for diagnosis of PD
  - Clear associated with cerebrovascular changes
- NCD due to AMC (neurodegenerative disorders)
  - PSP, CBD, MSA, NPH, tumors
- Neuroleptic-induced parkinsonism
  - Can occur in other NCD when dopamine-blocking drugs are used
- Other medical conditions
  - Delirium, medication side effects, sedation, severe hypothyroidism, B12 deficiency

Parkinson's Disease NCD – Comorbidity

- May coexist with **Alzheimer's or cerebrovascular disease**
  - Esp in older individuals

- Co-occurrence of depression/apathy
  - Can worsen **functional** impairment

Vascular NCD

Vascular NCD – Diagnostic Criteria

A. Major or mild NCD

B. Vascular etiology
   A. Deficit onset **temporally related** to cerebrovascular events
   B. Prominent decline in **complex attention** and **frontal-executive function**

C. Presence of **cerebrovascular disease sufficient** to account for neurocognitive deficits (history, physical, neuroimaging)

D. Not attributable to AMC or better explained by AMD

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Vascular NCD – Diagnostic Criteria

- Probable Vascular NCD (1+)
  - **Neuroimaging evidence** of sufficient parenchymal injury due to cerebrovascular disease
  - Deficits **temporally related** to cerebrovascular events
  - **Clinical + genetic evidence** present (eg. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy - CADASIL)

- Possible Vascular NCD
  - Otherwise

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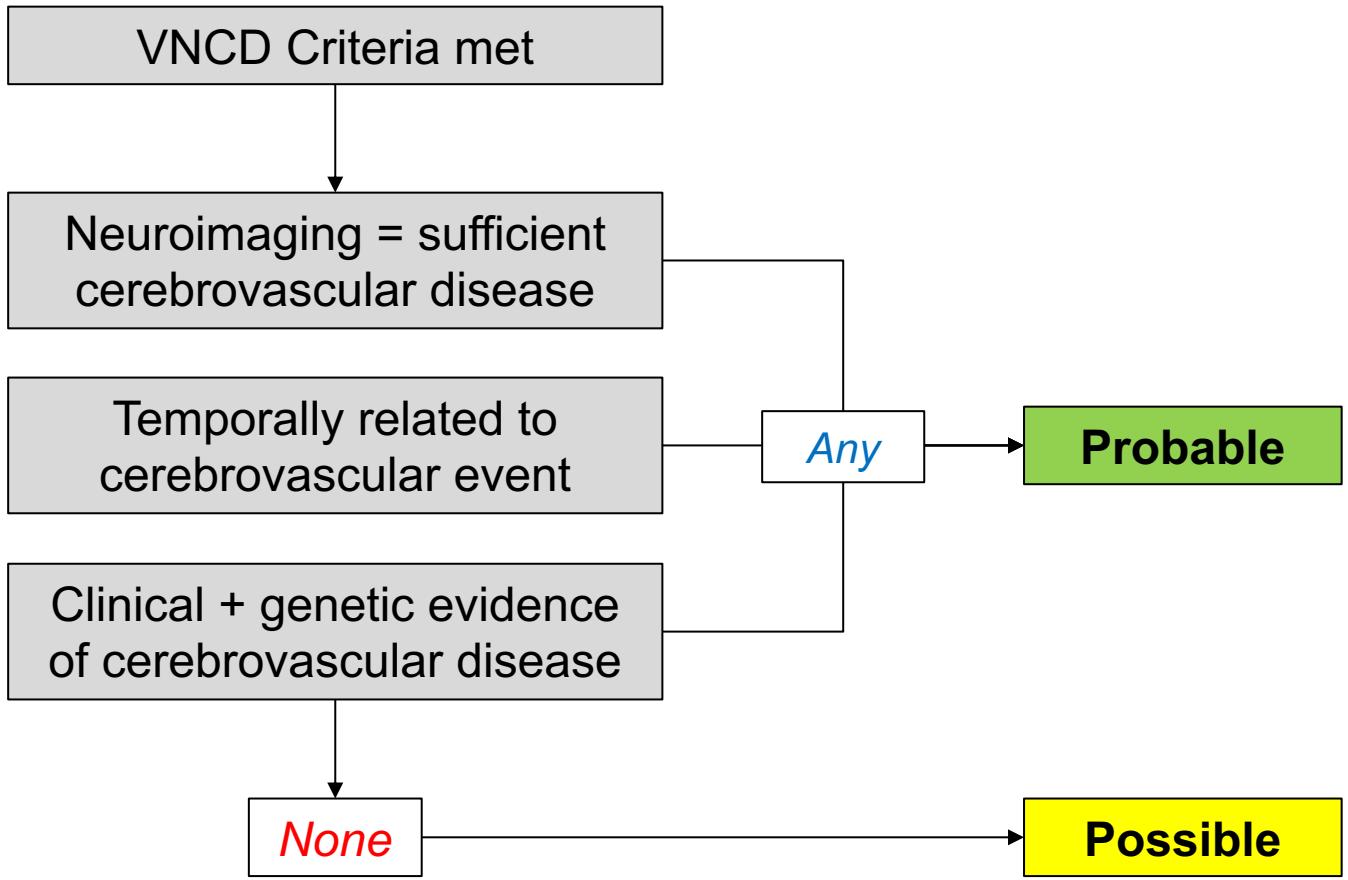
Vascular NCD – Diagnostic Criteria



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Vascular NCD – Diagnostic Features

- Vascular etiology can be very heterogenous
  - Different types of vascular lesions, extent, location, combinations
  - Large vessel strokes, microvascular disease
  - Focal, multifocal, diffuse

- Patterns of decline = varied
  - **Large vessel strokes, subcortical strokes, multiple lacunar infarcts**
    - Acute stepwise or fluctuating decline
    - May have intervening periods of stability or even improvement
  - **Small vessel disease** in white matter, BG, thalamus (subcortical changes)
    - Gradual onset, slow progression, punctuated by acute events
    - Disruption of **cortical-subcortical circuits**
    - Deficits in complex attention, processing speed
    - Executive function likely affected

Vascular NCD – Associated Features

- History and signs of **stroke or TIAs**

- Psychiatric symptoms
  - **Personality changes**
  - **Abulia** (lack of motivation, more severe than apathy)
  - Mood changes, depression, emotional lability

- "Vascular Depression"
  - **Late-onset** depressive symptoms
  - Psychomotor **slowing**
  - **Executive** dysfunction
  - Progressive small vessel ischemic disease

Vascular NCD – Prevalence

- US population
  - Age 65-70 = 0.2%
  - **Age 80+ = 16%**

- 3 months post-stroke → **20-30%** diagnosed with dementia

Neuropathology Series	Age 70	Age 90+
Vascular NCD	13%	45%
Alzheimer's NCD	24%	51%
Mixed Vascular + Alzheimer's	2%	46%

Vascular NCD – Development & Course

- Can occur at any age → **increases exponential after age 65**

- Course may vary
  - Acute onset with partial improvement
  - Stepwise decline, progressive decline
  - Fluctuations, plateaus of vary duration

- Pure subcortical vascular NCD → slowly progressive
  - Simulates Alzheimer's NCD

Vascular NCD – Risk & Prognostic Factors

- Environmental
  - Neuroplasticity factors → education, exercise, mental activity

- Genetic & Physiological
  - **Cerebrovascular disease risk factors = risk factors for vascular NCD**
    - Hypertension, diabetes, smoking, obesity
    - High cholesterol, high homocysteine
    - Risk factors for atherosclerosis, atrial fibrillation, cerebral emboli
  - **Cerebral amyloid angiopathy** → amyloid deposits within arterial vessels
  - **CADASIL** = hereditary condition
    - Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Vascular NCD – Diagnostic Markers

- Structural Imaging → CT or MRI

- No other established biomarkers

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Vascular NCD – Functional Consequences

- Commonly associated with **physical deficits**

Vascular NCD – Differential Diagnosis

- Other neurocognitive disorders
  - Alzheimer's NCD → **memory deficit early**, **without focal lesions**
    - Worsening of memory, language, executive function, perceptual-motor
    - CSF markers (beta-amyloid, phosphorylated tau), amyloid imaging
  - Lewy body NCD → **core features** (fluctuating cog, VH, parkinsonism)
  - Frontotemporal NCD → **behavioral features or language impairment**
    - Insidious onset, gradual progression

- Other medical conditions
  - **Present + sufficient severity** to account for cognitive impairment

- Other mental disorders
  - Delirium (but may be superimposed on pre-existing vascular NCD)
  - MDD (but degree of cognitive impairment may be out of proportion)
  - Can diagnose both

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Vascular NCD – Comorbidity

- Commonly co-occurs with **Alzheimer's Disease NCD**
- Commonly co-occurs with **depression**

Traumatic Brain Injury NCD

Traumatic NCD – Diagnostic Criteria

A. Major or mild NCD

- *Impact to head*
- *Rapid movement of brain within skull*

B. Evidence of traumatic brain injury, and 1+

1. Loss of **consciousness**
2. Posttraumatic **amnesia**
3. **Disorientation** and confusion
4. **Neurological signs**
   - Neuroimaging evidence, new seizures, worsening pre-existing seizure disorder, visual field cuts, anosmia, hemiparesis

C. NCD presents immediately after either:

1. Occurrence of TBI or recovery of consciousness
2. Persists past acute post-injury period

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Traumatic NCD – Diagnostic Features

- Variable cognitive presentation
  - Common deficits
    - **Complex attention, executive ability**
    - **Learning, memory**
    - **Slowed processing, social cognition**
  - In more severe TBI (brain contusion, ICH, penetrating injury)
    - Additional deficits → **aphasia, neglect, constructional dyspraxia**

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Traumatic NCD – Associated Features

Emotional	• Irritability, easy frustration • Anxiety, tension • Affective lability
Personality	• Disinhibition, aggression • Apathy, suspiciousness
Physical	• Headache, vertigo, dizziness, anosmia • Tinnitus, hyperacusis, photosensitivity • Fatigue, sleep disorders • **Sensitivity to psychotropic medications**
Neurological *(more severe TBI)*	• Seizures, visual disturbance • Hemiparesis, cranial nerve deficits
Orthopedic injuries	

Traumatic NCD – Prevalence

- US → 1.7 million TBI annually → 52,000 deaths
  - 2% of population with TBI-associated disability
  - **MALES = 59% of TBIs**
- Most common etiology
  - **Falls**
  - **MVAs**
  - **Struck on head**
- Collisions + blows to head during contact sports
  - **Repeated mild TBI** → cumulative persisting sequelae

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Traumatic NCD – Development & Course

Injury Characteristic	Mild TBI	Moderate TBI	Severe TBI
Loss of Consciousness	<30 min	30 min – 1 day	>1 day
Posttraumatic Amnesia	<1 day	1 day – 1 week	>1 week
Initial GCS	15 – 13 (13+ at 30 mins)	12 – 9	8 – 3

- TBI severity NOT necessarily correlated with NCD severity
  - Recovery is variable (age, prior brain damage, substance abuse)
  - Neurobehavioral symptoms → most severe **immediately after** TBI

- Mild-moderate TBI → usually complete/substantial improvement
  - If depleted cognitive reserve, mild TBI more likely to incompletely recovery

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Traumatic NCD – Development & Course

Mild TBI	Moderate–Severe TBI
• Depression, irritability • Headache, photosensitivity • Fatigue, sleep disturbance	*Additional features* • Apathy, aggression • Seizures (esp first year)
• If **substantial deterioration** after, consider **additional diagnosis**	• Inability to resume prior **occupational + social function** • Deterioration in **interpersonal relationships**
• Resolves within **days to weeks** • **Complete resolution by 3 mos**	• **Persistent deficits**
• **Repeated mild TBI**, may be associated with persistent disturbance	• Increased risk of **depression, aggression, neurodegenerative** disease (Alzheimer's)

Traumatic NCD – Development & Course

Features of persisting TBI NCD → vary with age, injury, cofactors	
Infant, Child	**Older Teens, Adults**
• Delayed **dev milestones** • Worse **academic performance** • Impaired **social** development	• Neurocognitive deficits • Irritability, hostility • Depression, anxiety, apathy • Hypersensitivity to light/sound • Easily fatigued

Traumatic NCD – Risk & Prognostic Factors

- Risk factors for TBI
  - Highest prevalence: **age <4, older adolescents, age >65**
  - Most common causes = **1) Falls, 2) MVA**
  - **Sport concussions** = frequent in older children, teens, young adults

- Risk factors for NCD after TBI
  - **Repeated concussions** → persistent NCD, traumatic encephalopathy
  - **Co-occurring intoxication** → may increases severity of TBI

- Course modifiers
  - Mild TBI → usually resolves within few weeks to months
  - Moderate-severe TBI → factors associated with worse outcomes
    - **Age >40, initial GCS, worse motor function, pupillary nonreactivity**
    - **CT evidence of brain injury** (petechial hemorrhages, subarachnoid hemorrhage, midline shift, obliteration of third ventricle)

Traumatic NCD – Diagnostic Markers

- Neuropsychological testing

- CT → petechial hemorrhages, SAH, contusion

- MRI → hyperintensities (suggest microhemorrhages)

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Traumatic NCD – Functional Consequences

- Mild NCD due to TBI
  - Decr cognitive efficiency, difficulty concentrating
  - Decr ability to perform usual activities
- Major NCD due to TBI
  - Difficulty with **independent living + self-care**
- Neuromotor features → may add to functional difficulties
  - Incoordination, ataxia, motor slowing
- Depressive symptoms → can worse function
  - Loss of **emotional control** (aggression, inappropriate affect, apathy)
    - May present with greater neurocognitive impairment

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Traumatic NCD – Differential Diagnosis

- If neurocognitive symptoms inconsistent with TBI severity
  - Need to **exclude undetected** neurological complications
  - Possibility of **somatic symptom disorder or factitious disorder**

- PTSD can co-occur
  - **Overlapping symptoms**
  - Concentration, low mood, aggressive behavioral disinhibition

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Traumatic NCD – Comorbidity

- Substance use → contribute/compound neurocognitive changes

- PTSD can co-occur (esp in military populations)

Substance/Medication-Induced NCD

Sub/Med-Induced NCD – Diagnostic Criteria

A. Major or mild NCD

B. Presentation of neurocognitive impairments:
   1. **Not exclusively during delirium**
   2. **Persist beyond** usual duration of intoxication + acute withdrawal

C. Substance/medication is **capable** of producing impairment

D. Temporal course consistent with:
   1. **Timing** of substance/medication use
   2. Deficits stable/improve after **period of abstinence**

E. Not attributable to AMC or another mental disorder

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Sub/Med-Induced NCD – Diagnostic Specifiers

- Potential Substances
  - **Alcohol** → non-amnestic, amnestic types
  - **Inhalants**
  - **Sedative, hypnotic or anxiolytics**
  - **Other (or unknown)**

- *Specify if:*
  - **Persistent** → continued significant impairment after extended abstinence

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Sub/Med-Induced NCD – Diagnostic Features

- Beyond usual duration of intoxication + acute withdrawal
  - Can initially reflect slow recovery of brain function (due to prolonged use)
  - Symptom and imaging improvements may be seen over many months
  - May continue for extended period → **persistent specifier**

- Sedative, hypnotic or anxiolytics → greater **memory deficits**

- Alcohol → executive function, memory/learning
  - **Korsakoff's NCD** = prominent amnesia + confabulation
    - Impaired learning, rapid forgetting
  - **Wernicke's encephalopathy** = nystagmus, lateral gaze palsy, ataxia

- Methamphetamines → executive function, memory/learning
  - Assoc with evidence **vascular injury** (similar profile to vascular NCD)
  - Focal weakness, unilateral incoordination, asymmetrical reflexes

Sub/Med-Induced NCD – Associated Features

Intermediate-Duration Drug-Induced NCD		Severe Drug-Induced NCD
CNS Depressants	**Stimulant Drugs**	**Long-term Alcohol Use**
• Irritability • Anxiety • Dysphoria • Sleep disturbance	• Rebound depression • Apathy • Hypersomnia	*Neuromotor features* • Incoordination • Ataxia • Motor slowing *Loss of emotional control* • Aggression • Inappropriate affect • Apathy

Sub/Med-Induced NCD – Prevalence

- Prevalence unknown
  - More likely if → **older, longer use, nutritional deficits**
- Alcohol abuse
  - Mild NCD, intermediate duration → **30-40% within 2 mos** of abstinence
    - May persist, esp if not stable abstinent after age 50
  - **Major NCD rare** → may result from nutritional deficits (Korsakoff's)
- Quitting cocaine, methamphetamine, opioids, PCP, sedatives
  - Mild NCD, intermediate duration → **may occur in one-third, can persist**
  - **Major NCD rare** → methamphetamine-related cerebrovascular disease
- Solvents → linked to **major/mild NCD**, intermediate/persistent
- Limited evidence for NCD due to cannabis, hallucinogens

Sub/Med-Induced NCD – Development & Course

- Longer, severe SUD → greater likelihood of NCD
  - Most likely persistent if **not abstinence after age 50**
    - Decr neural plasticity, other age-related brain changes
  - But can have complete recovery if **stable abstinence before age 50**

- Early abuse → may lead to defects in neural development
  - Maturation of **frontal circuitries, social cognition**
  - Especially **alcohol** (aging + alcohol-induced brain injury)

Sub/Med-Induced NCD – Risk & Prognostic Factors

- **Older age**
- **Longer use**
- **Persistent use past age 50**

- Alcohol-induced NCD
  - Long-term nutritional deficiencies
  - Liver disease
  - Vascular risk factors
  - Cardiovascular/cerebrovascular disease

Sub/Med-Induced NCD – Diagnostic Markers

- Chronic Alcohol Abuse
  - MRI → can be normal/abnormal
    - **Cortical thinning, white matter loss**
    - **Enlargement of sulci/ventricles**
  - Diffusion tensor imaging → white matter tract damage
  - MR spectroscopy
    - Decr N-acetylaspartate, incr markers of inflammation/white matter injury
  - Can reverse after successful abstinence

- Methamphetamine MRI
  - Hyperintensities suggestive of **microhemorrhages**
  - Can see **large infarctions**

Sub/Med-Induced NCD – Functional Consequences

- Reduced cognitive efficiency, difficulty concentrating
  - Beyond that seen in many other NCDs
- May have associated motor syndromes

Sub/Med-Induced NCD – Differential Diagnosis

- Intox/withdrawal → **risk of other causative conditions**
  - TBI, infections (HIV, HCV, syphilis)

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Sub/Med-Induced NCD – Comorbidity

- Many mental disorders can contribute to cognitive impairment
  - SUD, intoxication, withdrawal highly comorbid
- **TBI more common** with substance use
- Severe, long-term AUD → **major organ diseases**
  - Cerebrovascular disease, cirrhosis
- Amphetamine-induced NCD → **vascular NCD**

HIV NCD

HIV NCD – Diagnostic Criteria

A. Major or mild NCD

B. Documented HIV infection

C. Not better explained by non-HIV conditions
   1. Including **secondary HIV brain disease**
   2. (progressive multifocal leukoencephalopathy, cryptococcal meningitis)

D. Not attributable to AMC or another mental disorder

HIV NCD – Diagnostic Features

- HIV-1 infection
  - Infection several types of cells → particularly **immune cells**
    - Depletion of T-helped CD4 lymphocytes → immunocompromised
    - Opportunistic infections, neoplasms
  - Acquired Immune Deficiency Syndrome (AIDS)
  - Dx: ELISA → confirm with Western blot or PCR

- HIV NCD → generally **"subcortical pattern"**
  - **Impaired executive function, slowed processing speed**
  - **Impaired attention, difficulty learning new information**
  - Fewer problems with recall
  - Language difficulties (aphasia) uncommon → may have decr fluency
  - HIV can affect any part of brain → other possible patterns

HIV NCD – Associated Features

- More prevalent if
  - Prior episode of **severe immunosuppression**
  - **High CSF viral loads**
  - **Advanced HIV disease** (anemia, hypoalbuminemia)

- Advanced HIV NCD
  - **Neuromotor features** → incoordination, ataxia, motor slowing
  - **Loss of emotional control** → aggression, inappropriate affect, apathy

HIV NCD – Prevalence

- Depends on stage of HIV disease
  - 33-50% → at least mild neurocognitive disturbance (not full criteria)
  - **25% → mild NCD**
  - **<5% → major NCD**

HIV NCD – Development & Course

- Variable course → resolve, improve, slowly worsen, fluctuating
  - With current antiviral treatment, **rapid progression uncommon**
  - Abrupt mental state Δ → r/o other medical sources, secondary infections

- Affect many brain regions → different trajectories
  - Preferentially **"subcortical pattern"**
  - May interact with age-related conditions → motor/gait slowing

- HIV primarily in adults (via risky behaviors)
- Infants/children → neurodevelopmental delay
- Older age → additive/interactive effects with aging/other NCDs

HIV NCD – Risk & Prognostic Factors

- HIV Infection
  - IVDU, unprotected sex, unprotected blood supply

- HIV NCD (mild/major)
  - **HIV NCD overall** has **NOT declined significantly** with combined ARV
    - Inadequate CNS HIV control
    - Drug-resistant viral strains
    - Chronic systemic + rain inflammation
    - Comorbid factors (aging, drug abuse, prev CNS trauma, co-infxn, HCV)
    - ?neurotoxicity from chronic exposure to ARV
  - **Major HIV NCD** has **decreased sharply**

HIV NCD – Functional Consequences

- Variable

- Interference with **disease management, ARV adherence**
  - Impaired executive function, slowed processing

- Likelihood of comorbid disease → more challenges

HIV NCD – Differential Diagnosis

- If pre-existing **NCD worsened by HIV** → diagnose HIV NCD
  - Infections (HCV, syphilis), drug abuse, prev TBI, neurodevelopmental

- <u>Differentiate from other NCDs</u>
  - Steady or stepwise deterioration → neurodegen or vascular
  - **Stable, fluctuating (without progression), improving** → HIV

- <u>Abrupt onset or worsening of cognitive impairment</u>
  - Active investigation of **non-HIV etiology**
  - Opportunistic infections **(toxoplasmosis, cryptococcus)**
  - Neoplasias **(CNS lymphomas)**

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HIV NCD – Comorbidity

- **Cerebrovascular disease, metabolic syndrome**
  - Associated with chronic systemic + brain inflammation
- **Substance used disorders**
- **Other STDs**

Prion NCD

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Prion Disease NCD – Diagnostic Criteria

A. Major or mild NCD

B. **Insidious onset + rapid progression (common)**

C. Evidence of prion disease
   1. Motor features → **myoclonus, ataxia**
   2. **Biomarker** evidence

D. Not attributable to AMC or another mental disorder

Prion Disease NCD – Diagnostic Features

- Subacute spongiform encephalopathies (transmissible prions)
  - **Sporadic Creutzfeldt-Jakob disease = MOST COMMON**
    - **Rapid progression** to major NCD → as quick as 6 months
  - Variant Creutzfeldt-Jakob disease = rarer
    - (Bovine spongiform encephalopathy, "mad cow" disease)
  - Kuru
  - Gerstmann-Straussler-Scheinker syndrome
  - Fatal insomnia

Sporadic CJD	Variant CJD	Biomarkers
More movement sx • Ataxia • Startle reflex • Myoclonus • Chorea • Dystonia	*More psychiatric sx* • Depression • Anxiety • Withdrawal	• MRI DWI/FLAIR lesions • CSF → tau, 14-3-3 protein • EEG → triphasic waves • Family hx or genetic testing for rare familial forms • **Confirm with biopsy/autopsy**

Prion Disease NCD – Prevalence

- Sporadic CJD
  - Annual incidence = **1-2 cases per million people**
  - **Prevalence = unknown** (very low due to short survival)

Prion Disease NCD – Development & Course

- Onset
  - Can occur at any age → teens to late life
  - **Peak age = age 67** (sporadic CJD)
- Prodromal symptoms
  - Fatigue, anxiety, concentration, sleep, appetite
- After several weeks
  - Incoordination, abnormal vision + gait
  - Abnormal movements → myoclonus, choreoathetoid, ballistic
  - Rapidly progressive dementia
- Several months → rapid progression to major impairment
  - Rarely → progress over 2 years, similar to other NCDs

Prion Disease NCD – Risk Factors & Prognosis

- Environmental
  - **Cross-species transmission** of prion infections (BSE → variant CJD)
  - Transmission by **corneal transplant, human growth factor injection**

- Genetic & Physiological
  - Genetic component in **15% of cases → autosomal dominant** mutation

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Prion Disease NCD – Diagnostic Markers

- **Confirmed only by biopsy or autopsy**
  - No distinctive findings on CSF, developing biomarkers
- CSF → tau protein, 14-3-3 protein (sporadic CJD)
- MRI DWI
  - Multifocal gray matter hyperintensities in subcortical + cortical regions
- EEG → periodic **sharp, triphasic, synchronous discharges**

Prion Disease NCD – Differential Diagnosis

- Other major NCDs
  - May have similar course
  - Typically distinguished by rapid progression, cerebellar + motor symptoms

Huntington’s NCD

Huntington's Disease NCD – Diagnostic Criteria

A. Major or mild NCD

B. **Insidious onset + gradual progression**

C. **Huntington's disease established, or risk**
   A. Family history or genetic testing

D. Not attributable to AMC or another mental disorder

Huntington's Disease NCD – Diagnostic Criteria

- Progressive cognitive impairment
  - Early changes in **executive function**
    - Processing speed, organization, planning
  - Less so learning/memory

- Motor abnormalities → after cognitive + behavioral changes
  - **Bradykinesia** → slowing of voluntary movement
  - **Chorea** → involuntary jerking movements

- Definite HD diagnosis
  - **Unequivocal, extrapyramidal motor abnormalities**
  - **Family history of HD or genetic testing**
    - Genetic testing → CAG trinucleotide repeat expansion
      - (HTT gene, chromosome 4)

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Huntington's Disease NCD – Associated Features

- Psychiatric symptoms → often precede motor symptoms
  - Depression, apathy
  - Irritability, anxiety
  - Obsessive-compulsive symptoms
  - Psychosis more rare

Huntington's Disease NCD – Prevalence

- Prevalence
  - Worldwide → 2.7 per 100,000
  - NA, EU, AUS → 5.7 per 100,000
  - Asia → 0.40 per 100,000

Huntington's Disease NCD – Development & Course (1)

- Average age at diagnosis = **40 years** (varies widely)
  - Age at onset → **inversely correlated with CAG expansion length**
  - Median survival = 15 years after motor symptom diagnosis

- Juvenile HD → onset before age 20
  - **Bradykinesia, dystonia, rigidity** (rather than chorea of adult-onset)

Huntington's Disease NCD – Development & Course (2)

- Gradually progressive
  - **Psychiatric + cognitive sx predate** motor sx **by >15 years**
    - Initial sx → depressed mood, anxiety, irritability
    - Behavioral sx → apathy, disinhibition, impulsivity, impaired insight
  - Early movement sx → **fidgeting, mild apraxia** (esp fine motor)
    - Develops ataxia, postural instability
    - Eventually dysarthria → communication barrier
  - Advanced motor disease → progressive **ataxia, non-ambulatory**
  - End-stage → **impaired eating/swallowing**
  - Death → **aspiration pneumonia**

Huntington's Disease NCD – Risk & Prognostic Factors

- Genetic & Physiological
  - Genetic basis = **fully penetrant autosomal dominant**
  - Expansion of **CAG trinucleotide repeat**
    - **In huntingtin gene (chromosome 4)**
    - Repeat length **>36 → HD**
    - Longer repeat lengths → early age of onset

Huntington's Disease NCD – Diagnostic Markers

- Genetic testing = main test to determine HD
  - If positive family history, pt may request testing when presympomatic
  - **HD diagnosis not made until symptoms manifest**

- Neuroimaging changes
  - Volume loss in **basal ganglia** (esp **caudate nucleus, putamen**)
  - Progresses over course of illness

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Huntington's Disease NCD – Functional Consequences

- Prodromal phase + early disease
  - Occupational decline = most common
- Emotional, behavioral, cognitive aspects → functional decline
  - Processing speed, imitation, attention (rather than memory impairment)
  - Affects social + family life
- Later disease → ataxia, dysarthria, impulsivity, irritability
  - Affects **impairment + daily care needs**
  - More than attributable to cognitive decline
- Severe choreic movements
  - Can interfere with **care provision** → bathing, dressing, toileting

Huntington's Disease NCD – Differential Diagnosis

- Other mental disorders
  - Mood instability, irritability, compulsive behaviors
  - Distinguish by motor symptoms, genetic testing
- Other NCD
  - Early HD symptoms (executive dysfunction, impaired psychomotor speed)
  - May resemble other NCDs (e.g. vascular NCD)
- Other movement disorders (associated with chorea)
  - **Wilson's disease, drug-induced tardive dyskinesia, senile chorea**
  - **Sydenham's chorea, systemic lupus erythematous**
  - Can present with similar course to HD without positive genetic testing
    - Considered HD phenocopy

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NCD due to AMC

NCD due to AMC – Diagnostic Criteria

A. Major or mild NCD

B. **Pathophysiological consequence of AMC**
   1. History, physical exam, lab findings

C. Not better explained by another mental disorder or another specific neurocognitive disorder

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NCD due to AMC – Diagnostic Features

Structural lesions • Primary/secondary brain tumors • Subdural hematoma • Slowly progressive hydrocephalus • Normal-pressure hydrocephalus	**Metabolic conditions** • Kuf's disease • Adrenoleukodystrophy • Metachromatic leukodystrophy • Other storage diseases (adult/child)
Hypoxia • Hypoperfusion from heart failure	**Hepatic failure** **Renal failure**
Endocrine conditions • Hypothyroidism • Hypercalcemia • Hypoglycemia	**Immune disorders** • Temporal arteritis • Systemic lupus erythematosus
Nutritional conditions • Thiamine deficiency • Niacin deficiency	**Other neurological conditions** • Epilepsy • Multiple sclerosis
Infectious conditions • Neurosyphilis • Cryptococcus	**External CNS injury** • Electrical shock • Intracranial radiation

NCD due to AMC – Development & Course

- Follows underlying medical disorder
  - If treatable → may improve or stabilize
  - If deteriorative course → progression of neurocognitive deficits

NCD due to AMC – Diagnostic Markers

- Associated with nature/severity of medical condition
  - **Physical exam**
  - **Lab findings**
  - **Clinical features**

NCD due to AMC – Differential Diagnosis

- Other major/mild NCD
  - Presence of attributable medical condition **DOES NOT exclude** possibility of another major/mild NCD
  - **If deficits persist after successful tx** → consider another etiology

NCD due to Mixed Etiologies

NCD due to Mixed Etiologies – Diagnostic Criteria

A. Major or mild NCD

B. **Pathophysiological consequence of multiple etiologies**
   1. History, physical exam, lab findings
   2. **Excluding substances**

C. Not better explained by another mental disorder or delirium

NCD due to Mixed Etiologies – Development & Course

- **Probable role of multiple medical conditions** in NCD dev

Unspecified NCD

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Unspecified NCD

- Clinically significant distress or functional impairment
- **Does not meet full criteria** for any NCD disorders
- **Precise etiology cannot be determined** with sufficient certainty