Disorders"); other (or unknown) substance–induced sexual dysfunction ("Sexual Dysfunctions"); and other (or unknown) substance/medication–induced major or mild neurocognitive disorder ("Neurocognitive Disorders"). For other (or unknown) substance–induced intoxication delirium and other (or unknown) substance–induced withdrawal delirium, see the criteria and discussion of delirium in the chapter "Neurocognitive Disorders." These other (or unknown) substance–induced disorders are diagnosed instead of other (or unknown) substance intoxication or other (or unknown) substance withdrawal only when the symptoms are sufficiently severe to warrant independent clinical attention.

Unspecified Other (or Unknown) Substance–Related Disorder

292.9 (F19.99)

This category applies to presentations in which symptoms characteristic of an other (or unknown) substance–related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any specific other (or unknown) substance–related disorder or any of the disorders in the substance-related disorders diagnostic class.

Non-Substance-Related Disorders

Gambling Disorder

Diagnostic Criteria   **312.31 (F63.0)**

A. Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period:

1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
2. Is restless or irritable when attempting to cut down or stop gambling.
3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
6. After losing money gambling, often returns another day to get even ("chasing" one's losses).
7. Lies to conceal the extent of involvement with gambling.
8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
9. Relies on others to provide money to relieve desperate financial situations caused by gambling.

B. The gambling behavior is not better explained by a manic episode.

Specify if:

Episodic: Meeting diagnostic criteria at more than one time point, with symptoms subsiding between periods of gambling disorder for at least several months.

Persistent: Experiencing continuous symptoms, to meet diagnostic criteria for multiple years.

Specify if:

In early remission: After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder have been met for at least 3 months but for less than 12 months.

In sustained remission: After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder have been met during a period of 12 months or longer.

Specify current severity:

Mild: 4–5 criteria met.

Moderate: 6–7 criteria met.

Severe: 8–9 criteria met.

Note: Although some behavioral conditions that do not involve ingestion of substances have similarities to substance-related disorders, only one disorder—gambling disorder—has sufficient data to be included in this section.

Specifiers

Severity is based on the number of criteria endorsed. Individuals with mild gambling disorder may exhibit only 4–5 of the criteria, with the most frequently endorsed criteria usually related to preoccupation with gambling and "chasing" losses. Individuals with moderately severe gambling disorder exhibit more of the criteria (i.e., 6–7). Individuals with the most severe form will exhibit all or most of the nine criteria (i.e., 8–9). Jeopardizing relationships or career opportunities due to gambling and relying on others to provide money for gambling losses are typically the least often endorsed criteria and most often occur among those with more gambling disorder. Furthermore, individuals presenting for treatment of gambling disorder typically have moderate to severe forms of the disorder.

Diagnostic Features

Gambling involves risking something of value in the hopes of obtaining something of greater value. In many cultures, individuals gamble on games and events, and most do so without experiencing problems. However, some individuals develop substantial impairment related to their gambling behaviors. The essential feature of gambling disorder is persistent and recurrent maladaptive gambling behavior that disrupts personal, family, and/or vocational pursuits (Criterion A). Gambling disorder is defined as a cluster of four or more of the symptoms listed in Criterion A occurring at any time in the same 12-month period.

A pattern of "chasing one's losses" may develop, with an urgent need to keep gambling (often with the placing of larger bets or the taking of greater risks) to undo a loss or series of losses. The individual may abandon his or her gambling strategy and try to win back losses all at once. Although many gamblers may "chase" for short periods of time, it is the frequent, and often long-term, "chase" that is characteristic of gambling disorder (Criterion A6). Individuals may lie to family members, therapists, or others to conceal the extent of involvement with gambling; these instances of deceit may also include, but are not limited to, covering up illegal behaviors such as forgery, fraud, theft, or embezzlement to obtain money with which to gamble (Criterion A7). Individuals may also en-

gage in "bailout" behavior, turning to family or others for help with a desperate financial situation that was caused by gambling (Criterion A9).

Associated Features Supporting Diagnosis

Distortions in thinking (e.g., denial, superstitions, a sense of power and control over the outcome of chance events, overconfidence) may be present in individuals with gambling disorder. Many individuals with gambling disorder believe that money is both the cause of and the solution to their problems. Some individuals with gambling disorder are impulsive, competitive, energetic, restless, and easily bored; they may be overly concerned with the approval of others and may be generous to the point of extravagance when winning. Other individuals with gambling disorder are depressed and lonely, and they may gamble when feeling helpless, guilty, or depressed. Up to half of individuals in treatment for gambling disorder have suicidal ideation, and about 17% have attempted suicide.

Prevalence

The past-year prevalence rate of gambling disorder is about 0.2%–0.3% in the general population. In the general population, the lifetime prevalence rate is about 0.4%–1.0%. For females, the lifetime prevalence rate of gambling disorder is about 0.2%, and for males it is about 0.6%. The lifetime prevalence of pathological gambling among African Americans is about 0.9%, among whites about 0.4%, and among Hispanics about 0.3%.

Development and Course

The onset of gambling disorder can occur during adolescence or young adulthood, but in other individuals it manifests during middle or even older adulthood. Generally, gambling disorder develops over the course of years, although the progression appears to be more rapid in females than in males. Most individuals who develop a gambling disorder evidence a pattern of gambling that gradually increases in both frequency and amount of wagering. Certainly, milder forms can develop into more severe cases. Most individuals with gambling disorder report that one or two types of gambling are most problematic for them, although some individuals participate in many forms of gambling. Individuals are likely to engage in certain types of gambling (e.g., buying scratch tickets daily) more frequently than others (e.g., playing slot machines or blackjack at the casino weekly). Frequency of gambling can be related more to the type of gambling than to the severity of the overall gambling disorder. For example, purchasing a single scratch ticket each day may not be problematic, while less frequent casino, sports, or card gambling may be part of a gambling disorder. Similarly, amounts of money spent wagering are not in themselves indicative of gambling disorder. Some individuals can wager thousands of dollars per month and not have a problem with gambling, while others may wager much smaller amounts but experience substantial gambling-related difficulties.

Gambling patterns may be regular or episodic, and gambling disorder can be persistent or in remission. Gambling can increase during periods of stress or depression and during periods of substance use or abstinence. There may be periods of heavy gambling and severe problems, times of total abstinence, and periods of nonproblematic gambling. Gambling disorder is sometimes associated with spontaneous, long-term remissions. Nevertheless, some individuals underestimate their vulnerability to develop gambling disorder or to return to gambling disorder following remission. When in a period of remission, they may incorrectly assume that they will have no problem regulating gambling and that they may gamble on some forms nonproblematically, only to experience a return to gambling disorder.

Early expression of gambling disorder is more common among males than among females. Individuals who begin gambling in youth often do so with family members or

friends. Development of early-life gambling disorder appears to be associated with impulsivity and substance abuse. Many high school and college students who develop gambling disorder grow out of the disorder over time, although it remains a lifelong problem for some. Mid- and later-life onset of gambling disorder is more common among females than among males.

There are age and gender variations in the type of gambling activities and the prevalence rates of gambling disorder. Gambling disorder is more common among younger and middle-age persons than among older adults. Among adolescents and young adults, the disorder is more prevalent in males than in females. Younger individuals prefer different forms of gambling (e.g., sports betting), while older adults are more likely to develop problems with slot machine and bingo gambling. Although the proportions of individuals who seek treatment for gambling disorder are low across all age groups, younger individuals are especially unlikely to present for treatment.

Males are more likely to begin gambling earlier in life and to have a younger age at onset of gambling disorder than females, who are more likely to begin gambling later in life and to develop gambling disorder in a shorter time frame. Females with gambling disorder are more likely than males with gambling disorder to have depressive, bipolar, and anxiety disorders. Females also have a later age at onset of the disorder and seek treatment sooner, although rates of treatment seeking are low (<10%) among individuals with gambling disorder regardless of gender.

Risk and Prognostic Factors

Temperamental.   Gambling that begins in childhood or early adolescence is associated with increased rates of gambling disorder. Gambling disorder also appears to aggregate with antisocial personality disorder, depressive and bipolar disorders, and other substance use disorders, particularly with alcohol disorders.

Genetic and physiological.   Gambling disorder can aggregate in families, and this effect appears to relate to both environmental and genetic factors. Gambling problems are more frequent in monozygotic than in dizygotic twins. Gambling disorder is also more prevalent among first-degree relatives of individuals with moderate to severe alcohol use disorder than among the general population.

Course modifiers.   Many individuals, including adolescents and young adults, are likely to resolve their problems with gambling disorder over time, although a strong predictor of future gambling problems is prior gambling problems.

Culture-Related Diagnostic Issues

Individuals from specific cultures and races/ethnicities are more likely to participate in some types of gambling activities than others (e.g., pai gow, cockfights, blackjack, horse racing). Prevalence rates of gambling disorder are higher among African Americans than among European Americans, with rates for Hispanic Americans similar to those of European Americans. Indigenous populations have high prevalence rates of gambling disorder.

Gender-Related Diagnostic Issues

Males develop gambling disorder at higher rates than females, although this gender gap may be narrowing. Males tend to wager on different forms of gambling than females, with cards, sports, and horse race gambling more prevalent among males, and slot machine and bingo gambling more common among females.

Functional Consequences of Gambling Disorder

Areas of psychosocial, health, and mental health functioning may be adversely affected by gambling disorder. Specifically, individuals with gambling disorder may, because of their involvement with gambling, jeopardize or lose important relationships with family members or friends. Such problems may occur from repeatedly lying to others to cover up the extent of gambling or from requesting money that is used for gambling or to pay off gambling debts. Employment or educational activities may likewise be adversely impacted by gambling disorder; absenteeism or poor work or school performance can occur with gambling disorder, as individuals may gamble during work or school hours or be preoccupied with gambling or its adverse consequence when they should be working or studying. Individuals with gambling disorder have poor general health and utilize medical services at high rates.

Differential Diagnosis

Nondisordered gambling.   Gambling disorder must be distinguished from professional and social gambling. In professional gambling, risks are limited and discipline is central. Social gambling typically occurs with friends or colleagues and lasts for a limited period of time, with acceptable losses. Some individuals can experience problems associated with gambling (e.g., short-term chasing behavior and loss of control) that do not meet the full criteria for gambling disorder.

Manic episode.   Loss of judgment and excessive gambling may occur during a manic episode. An additional diagnosis of gambling disorder should be given only if the gambling behavior is not better explained by manic episodes (e.g., a history of maladaptive gambling behavior at times other than during a manic episode). Alternatively, an individual with gambling disorder may, during a period of gambling, exhibit behavior that resembles a manic episode, but once the individual is away from the gambling, these manic-like features dissipate.

Personality disorders.   Problems with gambling may occur in individuals with antisocial personality disorder and other personality disorders. If the criteria are met for both disorders, both can be diagnosed.

Other medical conditions.   Some patients taking dopaminergic medications (e.g., for Parkinson's disease) may experience urges to gamble. If such symptoms dissipate when dopaminergic medications are reduced in dosage or ceased, then a diagnosis of gambling disorder would not be indicated.

Comorbidity

Gambling disorder is associated with poor general health. In addition, some specific medical diagnoses, such as tachycardia and angina, are more common among individuals with gambling disorder than in the general population, even when other substance use disorders, including tobacco use disorder, are controlled for. Individuals with gambling disorder have high rates of comorbidity with other mental disorders, such as substance use disorders, depressive disorders, anxiety disorders, and personality disorders. In some individuals, other mental disorders may precede gambling disorder and be either absent or present during the manifestation of gambling disorder. Gambling disorder may also occur prior to the onset of other mental disorders, especially anxiety disorders and substance use disorders.

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Neurocognitive Disorders

The neurocognitive disorders (NCDs) (referred to in DSM-IV as "Dementia, Delirium, Amnestic, and Other Cognitive Disorders") begin with delirium, followed by the syndromes of major NCD, mild NCD, and their etiological subtypes. The major or mild NCD subtypes are NCD due to Alzheimer's disease; vascular NCD; NCD with Lewy bodies; NCD due to Parkinson's disease; frontotemporal NCD; NCD due to traumatic brain injury; NCD due to HIV infection; substance/medication-induced NCD; NCD due to Huntington's disease; NCD due to prion disease; NCD due to another medical condition; NCD due to multiple etiologies; and unspecified NCD. The NCD category encompasses the group of disorders in which the primary clinical deficit is in cognitive function, and that are acquired rather than developmental. Although cognitive deficits are present in many if not all mental disorders (e.g., schizophrenia, bipolar disorders), only disorders whose core features are cognitive are included in the NCD category. The NCDs are those in which impaired cognition has not been present since birth or very early life, and thus represents a decline from a previously attained level of functioning.

The NCDs are unique among DSM-5 categories in that these are syndromes for which the underlying pathology, and frequently the etiology as well, can potentially be determined. The various underlying disease entities have all been the subject of extensive research, clinical experience, and expert consensus on diagnostic criteria. The DSM-5 criteria for these disorders have been developed in close consultation with the expert groups for each of the disease entities and align as closely as possible with the current consensus criteria for each of them. The potential utility of biomarkers is also discussed in relation to diagnosis. Dementia is subsumed under the newly named entity *major neurocognitive disorder*, although the term *dementia* is not precluded from use in the etiological subtypes in which that term is standard. Furthermore, DSM-5 recognizes a less severe level of cognitive impairment, *mild neurocognitive disorder,* which can also be a focus of care, and which in DSM-IV was subsumed under "Cognitive Disorder Not Otherwise Specified." Diagnostic criteria are provided for both these syndromic entities, followed by diagnostic criteria for the different etiological subtypes. Several of the NCDs frequently coexist with one another, and their relationships may be multiply characterized under different chapter subheadings, including "Differential Diagnosis" (e.g., NCD due to Alzheimer's disease vs. vascular NCD), "Risk and Prognostic Factors" (e.g., vascular pathology increasing the clinical expression of Alzheimer's disease), and/or "Comorbidity" (e.g., mixed Alzheimer's disease–vascular pathology).

The term *dementia* is retained in DSM-5 for continuity and may be used in settings where physicians and patients are accustomed to this term. Although dementia is the customary term for disorders like the degenerative dementias that usually affect older adults, the term *neurocognitive disorder* is widely used and often preferred for conditions affecting younger individuals, such as impairment secondary to traumatic brain injury or HIV infection. Furthermore, the major NCD definition is somewhat broader than the term *dementia,* in that individuals with substantial decline in a single domain can receive this diagnosis, most notably the DSM-IV category of "Amnestic Disorder," which would now be diagnosed as major NCD due to another medical condition and for which the term *dementia* would not be used.

Neurocognitive Domains

The criteria for the various NCDs are all based on defined cognitive domains. Table 1 provides for each of the key domains a working definition, examples of symptoms or observations regarding impairments in everyday activities, and examples of assessments. The domains thus defined, along with guidelines for clinical thresholds, form the basis on which the NCDs, their levels, and their subtypes may be diagnosed.

TABLE 1 Neurocognitive domains

Cognitive domain	Examples of symptoms or observations	Examples of assessments
Complex attention (sustained attention, divided attention, selective attention, processing speed)	*Major:* Has increased difficulty in environments with multiple stimuli (TV, radio, conversation); is easily distracted by competing events in the environment. Is unable to attend unless input is restricted and simplified. Has difficulty holding new information in mind, such as recalling phone numbers or addresses just given, or reporting what was just said. Is unable to perform mental calculations. All thinking takes longer than usual, and components to be processed must be simplified to one or a few. *Mild:* Normal tasks take longer than previously. Begins to find errors in routine tasks; finds work needs more double-checking than previously. Thinking is easier when not competing with other things (radio, TV, other conversations, cell phone, driving).	*Sustained attention:* Maintenance of attention over time (e.g., pressing a button every time a tone is heard, and over a period of time). *Selective attention:* Maintenance of attention despite competing stimuli and/or distractors: hearing numbers and letters read and asked to count only letters. *Divided attention:* Attending to two tasks within the same time period: rapidly tapping while learning a story being read. Processing speed can be quantified on any task by timing it (e.g., time to put together a design of blocks; time to match symbols with numbers; speed in responding, such as counting speed or serial 3 speed).
Executive function (planning, decision making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility)	*Major:* Abandons complex projects. Needs to focus on one task at a time. Needs to rely on others to plan instrumental activities of daily living or make decisions. *Mild:* Increased effort required to complete multistage projects. Has increased difficulty multitasking or difficulty resuming a task interrupted by a visitor or phone call. May complain of increased fatigue from the extra effort required to organize, plan, and make decisions. May report that large social gatherings are more taxing or less enjoyable because of increased effort required to follow shifting conversations.	*Planning:* Ability to find the exit to a maze; interpret a sequential picture or object arrangement. *Decision making:* Performance of tasks that assess process of deciding in the face of competing alternatives (e.g., simulated gambling). *Working memory:* Ability to hold information for a brief period and to manipulate it (e.g., adding up a list of numbers or repeating a series of numbers or words backward). *Feedback/error utilization:* Ability to benefit from feedback to infer the rules for solving a problem. *Overriding habits/inhibition:* Ability to choose a more complex and effortful solution to be correct (e.g., looking away from the direction indicated by an arrow; naming the color of a word's font rather than naming the word). *Mental/cognitive flexibility:* Ability to shift between two concepts, tasks, or response rules (e.g., from number to letter, from verbal to key-press response, from adding numbers to ordering numbers, from ordering objects by size to ordering by color).

TABLE 1 Neurocognitive domains *(continued)*

Cognitive domain	Examples of symptoms or observations	Examples of assessments
Learning and memory (immediate memory, recent memory [including free recall, cued recall, and recognition memory], very-long-term memory [semantic; autobiographical], implicit learning)	*Major:* Repeats self in conversation, often within the same conversation. Cannot keep track of short list of items when shopping or of plans for the day. Requires frequent reminders to orient to task at hand. *Mild:* Has difficulty recalling recent events, and relies increasingly on list making or calendar. Needs occasional reminders or re-reading to keep track of characters in a movie or novel. Occasionally may repeat self over a few weeks to the same person. Loses track of whether bills have already been paid. **Note:** Except in severe forms of major neurocognitive disorder, semantic, autobiographical, and implicit memory are relatively preserved, compared with recent memory.	*Immediate memory span:* Ability to repeat a list of words or digits. **Note:** Immediate memory sometimes subsumed under "working memory" (see "Executive Function"). *Recent memory:* Assesses the process of encoding new information (e.g., word lists, a short story, or diagrams). The aspects of recent memory that can be tested include 1) free recall (the person is asked to recall as many words, diagrams, or elements of a story as possible); 2) cued recall (examiner aids recall by providing semantic cues such as "List all the food items on the list" or "Name all of the children from the story"); and 3) recognition memory (examiner asks about specific items—e.g., "Was 'apple' on the list?" or "Did you see this diagram or figure?"). Other aspects of memory that can be assessed include semantic memory (memory for facts), autobiographical memory (memory for personal events or people), and implicit (procedural) learning (unconscious learning of skills).
Language (expressive language [including naming, word finding, fluency, and grammar, and syntax] and receptive language)	*Major:* Has significant difficulties with expressive or receptive language. Often uses general-use phrases such as "that thing" and "you know what I mean," and prefers general pronouns rather than names. With severe impairment, may not even recall names of closer friends and family. Idiosyncratic word usage, grammatical errors, and spontaneity of output and economy of utterances occur. Stereotypy of speech occurs; echolalia and automatic speech typically precede mutism. *Mild:* Has noticeable word-finding difficulty. May substitute general for specific terms. May avoid use of specific names of acquaintances. Grammatical errors involve subtle omission or incorrect use of articles, prepositions, auxiliary verbs, etc.	*Expressive language:* Confrontational naming (identification of objects or pictures); fluency (e.g., name as many items as possible in a semantic [e.g., animals] or phonemic [e.g., words starting with "f"] category in 1 minute). *Grammar and syntax* (e.g., omission or incorrect use of articles, prepositions, auxiliary verbs): Errors observed during naming and fluency tests are compared with norms to assess frequency of errors and compare with normal slips of the tongue. *Receptive language:* Comprehension (word definition and object-pointing tasks involving animate and inanimate stimuli): performance of actions/activities according to verbal command.

TABLE 1 Neurocognitive domains *(continued)*

Cognitive domain	Examples of symptoms or observations	Examples of assessments
Perceptual-motor (includes abilities subsumed under the terms *visual perception, visuo-constructional, perceptual-motor, praxis,* and *gnosis*)	*Major:* Has significant difficulties with previously familiar activities (using tools, driving motor vehicle), navigating in familiar environments; is often more confused at dusk, when shadows and lowering levels of light change perceptions. *Mild:* May need to rely more on maps or others for directions. Uses notes and follows others to get to a new place. May find self lost or turned around when not concentrating on task. Is less precise in parking. Needs to expend greater effort for spatial tasks such as carpentry, assembly, sewing, or knitting.	*Visual perception:* Line bisection tasks can be used to detect basic visual defect or attentional neglect. Motor-free perceptual tasks (including facial recognition) require the identification and/or matching of figures—best when tasks cannot be verbally mediated (e.g., figures are not objects); some require the decision of whether a figure can be "real" or not based on dimensionality. *Visuoconstructional:* Assembly of items requiring hand-eye coordination, such as drawing, copying, and block assembly. *Perceptual-motor:* Integrating perception with purposeful movement (e.g., inserting blocks into a form board without visual cues; rapidly inserting pegs into a slotted board). *Praxis:* Integrity of learned movements, such as ability to imitate gestures (wave goodbye) or pantomime use of objects to command ("Show me how you would use a hammer"). *Gnosis:* Perceptual integrity of awareness and recognition, such as recognition of faces and colors.
Social cognition (recognition of emotions, theory of mind)	*Major:* Behavior clearly out of acceptable social range; shows insensitivity to social standards of modesty in dress or of political, religious, or sexual topics of conversation. Focuses excessively on a topic despite group's disinterest or direct feedback. Behavioral intention without regard to family or friends. Makes decisions without regard to safety (e.g., inappropriate clothing for weather or social setting). Typically, has little insight into these changes. *Mild:* Has subtle changes in behavior or attitude, often described as a change in personality, such as less ability to recognize social cues or read facial expressions, decreased empathy, increased extraversion or introversion, decreased inhibition, or subtle or episodic apathy or restlessness.	*Recognition of emotions:* Identification of emotion in images of faces representing a variety of both positive and negative emotions. *Theory of mind:* Ability to consider another person's mental state (thoughts, desires, intentions) or experience—story cards with questions to elicit information about the mental state of the individuals portrayed, such as "Where will the girl look for the lost bag?" or "Why is the boy sad?"

Delirium

Diagnostic Criteria

A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).

B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.

C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).

D. The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.

E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Specify whether:

Substance intoxication delirium: This diagnosis should be made instead of substance intoxication when the symptoms in Criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Coding note: The ICD-9-CM and ICD-10-CM codes for the [specific substance] intoxication delirium are indicated in the table below. Note that the ICD-10-CM code depends on whether or not there is a comorbid substance use disorder present for the same class of substance. If a mild substance use disorder is comorbid with the substance intoxication delirium, the 4th position character is "1," and the clinician should record "mild [substance] use disorder" before the substance intoxication delirium (e.g., "mild cocaine use disorder with cocaine intoxication delirium"). If a moderate or severe substance use disorder is comorbid with the substance intoxication delirium, the 4th position character is "2," and the clinician should record "moderate [substance] use disorder" or "severe [substance] use disorder," depending on the severity of the comorbid substance use disorder. If there is no comorbid substance use disorder (e.g., after a one-time heavy use of the substance), then the 4th position character is "9," and the clinician should record only the substance intoxication delirium.

	ICD-9-CM	ICD-10-CM		
		With use disorder, mild	With use disorder, moderate or severe	Without use disorder
Alcohol	291.0	F10.121	F10.221	F10.921
Cannabis	292.81	F12.121	F12.221	F12.921
Phencyclidine	292.81	F16.121	F16.221	F16.921
Other hallucinogen	292.81	F16.121	F16.221	F16.921
Inhalant	292.81	F18.121	F18.221	F18.921
Opioid	292.81	F11.121	F11.221	F11.921

		ICD-10-CM		
	ICD-9-CM	With use disorder, mild	With use disorder, moderate or severe	Without use disorder
Sedative, hypnotic, or anxiolytic	292.81	F13.121	F13.221	F13.921
Amphetamine (or other stimulant)	292.81	F15.121	F15.221	F15.921
Cocaine	292.81	F14.121	F14.221	F14.921
Other (or unknown) substance	292.81	F19.121	F19.221	F19.921

Substance withdrawal delirium: This diagnosis should be made instead of substance withdrawal when the symptoms in Criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Code [specific substance] withdrawal delirium: **291.0 (F10.231)** alcohol; **292.0 (F11.23)** opioid; **292.0 (F13.231)** sedative, hypnotic, or anxiolytic; **292.0 (F19.231)** other (or unknown) substance/medication.

Medication-induced delirium: This diagnosis applies when the symptoms in Criteria A and C arise as a side effect of a medication taken as prescribed.

Coding note: The ICD-9-CM code for [specific medication]-induced delirium is **292.81.** The ICD-10-CM code depends on the type of medication. If the medication is an opioid taken as prescribed, the code is **F11.921.** If the medication is a sedative, hypnotic, or anxiolytic taken as prescribed, the code is **F13.921.** If the medication is an amphetamine-type or other stimulant taken as prescribed, the code is **F15.921.** For medications that do not fit into any of the classes (e.g., dexamethasone) and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the code is **F19.921.**

293.0 (F05) Delirium due to another medical condition: There is evidence from the history, physical examination, or laboratory findings that the disturbance is attributable to the physiological consequences of another medical condition.

Coding note: Include the name of the other medical condition in the name of the delirium (e.g., 293.0 [F05] delirium due to hepatic encephalopathy). The other medical condition should also be coded and listed separately immediately before the delirium due to another medical condition (e.g., 572.2 [K72.90] hepatic encephalopathy; 293.0 [F05] delirium due to hepatic encephalopathy).

293.0 (F05) Delirium due to multiple etiologies: There is evidence from the history, physical examination, or laboratory findings that the delirium has more than one etiology (e.g., more than one etiological medical condition; another medical condition plus substance intoxication or medication side effect).

Coding note: Use multiple separate codes reflecting specific delirium etiologies (e.g., 572.2 [K72.90] hepatic encephalopathy, 293.0 [F05] delirium due to hepatic failure; 291.0 [F10.231] alcohol withdrawal delirium). Note that the etiological medical condition both appears as a separate code that precedes the delirium code and is substituted into the delirium due to another medical condition rubric.

Specify if:

Acute: Lasting a few hours or days.

Persistent: Lasting weeks or months.

Specify if:

    Hyperactive: The individual has a hyperactive level of psychomotor activity that may be accompanied by mood lability, agitation, and/or refusal to cooperate with medical care.

    Hypoactive: The individual has a hypoactive level of psychomotor activity that may be accompanied by sluggishness and lethargy that approaches stupor.

    Mixed level of activity: The individual has a normal level of psychomotor activity even though attention and awareness are disturbed. Also includes individuals whose activity level rapidly fluctuates.

Recording Procedures

Substance intoxication delirium

ICD-9-CM.   The name of the substance/medication intoxication delirium begins with the specific substance (e.g., cocaine, dexamethasone) that is presumed to be causing the delirium. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class. For substances that do not fit into any of the classes (e.g., dexamethasone), the code for "other substance" should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category "unknown substance" should be used.

    The name of the disorder is followed by the course (i.e., acute, persistent), followed by the specifier indicating level of psychomotor activity (i.e., hyperactive, hypoactive, mixed level of activity). Unlike the recording procedures for ICD-10-CM, which combine the substance/medication intoxication delirium and substance use disorder into a single code, for ICD-9-CM a separate diagnostic code is given for the substance use disorder. For example, in the case of acute hyperactive intoxication delirium occurring in a man with a severe cocaine use disorder, the diagnosis is 292.81 cocaine intoxication delirium, acute, hyperactive. An additional diagnosis of 304.20 severe cocaine use disorder is also given. If the intoxication delirium occurs without a comorbid substance use disorder (e.g., after a one-time heavy use of the substance), no accompanying substance use disorder is noted (e.g., 292.81 phencyclidine intoxication delirium, acute, hypoactive).

ICD-10-CM.   The name of the substance/medication intoxication delirium begins with the specific substance (e.g., cocaine, dexamethasone) that is presumed to be causing the delirium. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class and presence or absence of a comorbid substance use disorder. For substances that do not fit into any of the classes (e.g., dexamethasone), the code for "other substance" should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category "unknown substance" should be used.

    When recording the name of the disorder, the comorbid substance use disorder (if any) is listed first, followed by the word "with," followed by the name of the substance intoxication delirium, followed by the course (i.e., acute, persistent), followed by the specifier indicating level of psychomotor activity (i.e., hyperactive, hypoactive, mixed level of activity). For example, in the case of acute hyperactive intoxication delirium occurring in a man with a severe cocaine use disorder, the diagnosis is F14.221 severe cocaine use disorder with cocaine intoxication delirium, acute, hyperactive. A separate diagnosis of the comorbid severe cocaine use disorder is not given. If the intoxication delirium occurs without a comorbid substance use disorder (e.g., after a one-time heavy use of the substance), no accompanying substance use disorder is noted (e.g., F16.921 phencyclidine intoxication delirium, acute, hypoactive).

Substance withdrawal delirium

ICD-9-CM.   The name of the substance/medication withdrawal delirium begins with the specific substance (e.g., alcohol) that is presumed to be causing the withdrawal delirium. The diagnostic code is selected from substance-specific codes included in the coding note included

in the criteria set. The name of the disorder is followed by the course (i.e., acute, persistent), followed by the specifier indicating level of psychomotor activity (i.e., hyperactive, hypoactive, mixed level of activity). Unlike the recording procedures for ICD-10-CM, which combine the substance/medication withdrawal delirium and substance use disorder into a single code, for ICD-9-CM a separate diagnostic code is given for the substance use disorder. For example, in the case of acute hyperactive withdrawal delirium occurring in a man with a severe alcohol use disorder, the diagnosis is 291.0 alcohol withdrawal delirium, acute, hyperactive. An additional diagnosis of 303.90 severe alcohol use disorder is also given.

ICD-10-CM. The name of the substance/medication withdrawal delirium begins with the specific substance (e.g., alcohol) that is presumed to be causing the withdrawal delirium. The diagnostic code is selected from substance-specific codes included in the coding note included in the criteria set. When recording the name of the disorder, the comorbid moderate or severe substance use disorder (if any) is listed first, followed by the word "with," followed by the substance withdrawal delirium, followed by the course (i.e., acute, persistent), followed by the specifier indicating level of psychomotor activity (i.e., hyperactive, hypoactive, mixed level of activity). For example, in the case of acute hyperactive withdrawal delirium occurring in a man with a severe alcohol use disorder, the diagnosis is F10.231 severe alcohol use disorder with alcohol withdrawal delirium, acute, hyperactive. A separate diagnosis of the comorbid severe alcohol use disorder is not given.

Medication-induced delirium. The name of the medication-induced delirium begins with the specific substance (e.g., dexamethasone) that is presumed to be causing the delirium. The name of the disorder is followed by the course (i.e., acute, persistent), followed by the specifier indicating level of psychomotor activity (i.e., hyperactive, hypoactive, mixed level of activity). For example, in the case of acute hyperactive medication-induced delirium occurring in a man using dexamethasone as prescribed, the diagnosis is 292.81 (F19.921) dexamethasone-induced delirium, acute, hyperactive.

Specifiers

Regarding course, in hospital settings, delirium usually lasts about 1 week, but some symptoms often persist even after individuals are discharged from the hospital.

Individuals with delirium may rapidly switch between hyperactive and hypoactive states. The hyperactive state may be more common or more frequently recognized and often is associated with medication side effects and drug withdrawal. The hypoactive state may be more frequent in older adults.

Diagnostic Features

The essential feature of delirium is a disturbance of attention or awareness that is accompanied by a change in baseline cognition that cannot be better explained by a preexisting or evolving neurocognitive disorder (NCD). The disturbance in attention (Criterion A) is manifested by reduced ability to direct, focus, sustain, and shift attention. Questions must be repeated because the individual's attention wanders, or the individual may perseverate with an answer to a previous question rather than appropriately shift attention. The individual is easily distracted by irrelevant stimuli. The disturbance in awareness is manifested by a reduced orientation to the environment or at times even to oneself.

The disturbance develops over a short period of time, usually hours to a few days, and tends to fluctuate during the course of the day, often with worsening in the evening and night when external orienting stimuli decrease (Criterion B). There is evidence from the history, physical examination, or laboratory findings that the disturbance is a physiological consequence of an underlying medical condition, substance intoxication or withdrawal, use of a medication, or a toxin exposure, or a combination of these factors (Criterion E). The etiology should be coded according to the etiologically appropriate subtype (i.e., substance or medication intoxication, substance withdrawal, another medical

condition, or multiple etiologies). Delirium often occurs in the context of an underlying NCD. The impaired brain function of individuals with mild and major NCD renders them more vulnerable to delirium.

There is an accompanying change in at least one other area that may include memory and learning (particularly recent memory), disorientation (particularly to time and place), alteration in language, or perceptual distortion or a perceptual-motor disturbance (Criterion C). The perceptual disturbances accompanying delirium include misinterpretations, illusions, or hallucinations; these disturbances are typically visual, but may occur in other modalities as well, and range from simple and uniform to highly complex. Normal attention/arousal, delirium, and coma lie on a continuum, with coma defined as the lack of any response to verbal stimuli. The ability to evaluate cognition to diagnose delirium depends on there being a level of arousal sufficient for response to verbal stimulation; hence, delirium should not be diagnosed in the context of coma (Criterion D). Many noncomatose patients have a reduced level of arousal. Those patients who show only minimal responses to verbal stimulation are incapable of engaging with attempts at standardized testing or even interview. This inability to engage should be classified as severe inattention. Low-arousal states (of acute onset) should be recognized as indicating severe inattention and cognitive change, and hence delirium. They are clinically indistinguishable from delirium diagnosed on the basis of inattention or cognitive change elicited through cognitive testing and interview.

Associated Features Supporting Diagnosis

Delirium is often associated with a disturbance in the sleep-wake cycle. This disturbance can include daytime sleepiness, nighttime agitation, difficulty falling asleep, excessive sleepiness throughout the day, or wakefulness throughout the night. In some cases, complete reversal of the night-day sleep-wake cycle can occur. Sleep-wake cycle disturbances are very common in delirium and have been proposed as a core criterion for the diagnosis.

The individual with delirium may exhibit emotional disturbances, such as anxiety, fear, depression, irritability, anger, euphoria, and apathy. There may be rapid and unpredictable shifts from one emotional state to another. The disturbed emotional state may also be evident in calling out, screaming, cursing, muttering, moaning, or making other sounds. These behaviors are especially prevalent at night and under conditions in which stimulation and environmental cues are lacking.

Prevalence

The prevalence of delirium is highest among hospitalized older individuals and varies depending on the individuals' characteristics, setting of care, and sensitivity of the detection method. The prevalence of delirium in the community overall is low (1%–2%) but increases with age, rising to 14% among individuals older than 85 years. The prevalence is 10%–30% in older individuals presenting to emergency departments, where the delirium often indicates a medical illness.

The prevalence of delirium when individuals are admitted to the hospital ranges from 14% to 24%, and estimates of the incidence of delirium arising during hospitalization range from 6% to 56% in general hospital populations. Delirium occurs in 15%–53% of older individuals postoperatively and in 70%–87% of those in intensive care. Delirium occurs in up to 60% of individuals in nursing homes or post–acute care settings and in up to 83% of all individuals at the end of life.

Development and Course

While the majority of individuals with delirium have a full recovery with or without treatment, early recognition and intervention usually shortens the duration of the delir-

ium. Delirium may progress to stupor, coma, seizures, or death, particularly if the underlying cause remains untreated. Mortality among hospitalized individuals with delirium is high, and as many as 40% of individuals with delirium, particularly those with malignancies and other significant underlying medical illness, die within a year after diagnosis.

Risk and Prognostic Factors

Environmental. Delirium may be increased in the context of functional impairment, immobility, a history of falls, low levels of activity, and use of drugs and medications with psychoactive properties (particularly alcohol and anticholinergics).

Genetic and physiological. Both major and mild NCDs can increase the risk for delirium and complicate the course. Older individuals are especially susceptible to delirium compared with younger adults. Susceptibility to delirium in infancy and through childhood may be greater than in early and middle adulthood. In childhood, delirium may be related to febrile illnesses and certain medications (e.g., anticholinergics).

Diagnostic Markers

In addition to laboratory findings characteristic of underlying medical conditions (or intoxication or withdrawal states), there is often generalized slowing on electroencephalography, and fast activity is occasionally found (e.g., in some cases of alcohol withdrawal delirium). However, electroencephalography is insufficiently sensitive and specific for diagnostic use.

Functional Consequences of Delirium

Delirium itself is associated with increased functional decline and risk of institutional placement. Hospitalized individuals 65 years or older with delirium have three times the risk of nursing home placement and about three times the functional decline as hospitalized patients without delirium at both discharge and 3 months postdischarge.

Differential Diagnosis

Psychotic disorders and bipolar and depressive disorders with psychotic features. Delirium that is characterized by vivid hallucinations, delusions, language disturbances, and agitation must be distinguished from brief psychotic disorder, schizophrenia, schizophreniform disorder, and other psychotic disorders, as well as from bipolar and depressive disorders with psychotic features.

Acute stress disorder. Delirium associated with fear, anxiety, and dissociative symptoms, such as depersonalization, must be distinguished from acute stress disorder, which is precipitated by exposure to a severely traumatic event.

Malingering and factitious disorder. Delirium can be distinguished from these disorders on the basis of the often atypical presentation in malingering and factitious disorder and the absence of another medical condition or substance that is etiologically related to the apparent cognitive disturbance.

Other neurocognitive disorders. The most common differential diagnostic issue when evaluating confusion in older adults is disentangling symptoms of delirium and dementia. The clinician must determine whether the individual has delirium; a delirium superimposed on a preexisting NCD, such as that due to Alzheimer's disease; or an NCD without delirium. The traditional distinction between delirium and dementia according to acuteness of onset and temporal course is particularly difficult in those elderly individuals who had a prior NCD that may not have been recognized, or who develop persistent cognitive impairment following an episode of delirium.

Other Specified Delirium

780.09 (R41.0)

This category applies to presentations in which symptoms characteristic of delirium that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for delirium or any of the disorders in the neurocognitive disorders diagnostic class. The other specified delirium category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for delirium or any specific neurocognitive disorder. This is done by recording "other specified delirium" followed by the specific reason (e.g., "attenuated delirium syndrome").

An example of a presentation that can be specified using the "other specified" designation is the following:

Attenuated delirium syndrome: This syndrome applies in cases of delirium in which the severity of cognitive impairment falls short of that required for the diagnosis, or in which some, but not all, diagnostic criteria for delirium are met.

Unspecified Delirium

780.09 (R41.0)

This category applies to presentations in which symptoms characteristic of delirium that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for delirium or any of the disorders in the neurocognitive disorders diagnostic class. The unspecified delirium category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for delirium, and includes presentations for which there is insufficient information to make a more specific diagnosis (e.g., in emergency room settings).

Major and Mild Neurocognitive Disorders

Major Neurocognitive Disorder

Diagnostic Criteria

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Specify whether due to:

Alzheimer's disease (pp. 611–614)
Frontotemporal lobar degeneration (pp. 614–618)
Lewy body disease (pp. 618–621)
Vascular disease (pp. 621–624)
Traumatic brain injury (pp. 624–627)
Substance/medication use (pp. 627–632)
HIV infection (pp. 632–634)
Prion disease (pp. 634–636)
Parkinson's disease (pp. 636–638)
Huntington's disease (pp. 638–641)
Another medical condition (pp. 641–642)
Multiple etiologies (pp. 642–643)
Unspecified (p. 643)

Coding note: Code based on medical or substance etiology. In some cases, there is need for an additional code for the etiological medical condition, which must immediately precede the diagnostic code for major neurocognitive disorder, as follows:

Etiological subtype	Associated etiological medical code for major neurocognitive disorder[a]	Major neurocognitive disorder code[b]	Mild neurocognitive disorder code[c]
Alzheimer's disease	Probable: 331.0 (G30.9) Possible: no additional medical code	Probable: 294.1x (F02.8x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for Alzheimer's disease.)
Frontotemporal lobar degeneration	Probable: 331.19 (G31.09) Possible: no additional medical code	Probable: 294.1x (F02.8x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for frontotemporal disease.)
Lewy body disease	Probable: 331.82 (G31.83) Possible: no additional medical code	Probable: 294.1x (F02.8x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for Lewy body disease.)
Vascular disease	No additional medical code	Probable: 290.40 (F01.5x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for the vascular disease.)
Traumatic brain injury	907.0 (S06.2X9S)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional code for the traumatic brain injury.)
Substance/ medication-induced	No additional medical code	Code based on the type of substance causing the major neurocognitive disorder[c, d]	Code based on the type of substance causing the mild neurocognitive disorder[d]

Etiological subtype	Associated etiological medical code for major neurocognitive disorder[a]	Major neurocognitive disorder code[b]	Mild neurocognitive disorder code[c]
HIV infection	042 (B20)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional code for HIV infection.)
Prion disease	046.79 (A81.9)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional code for prion disease.)
Parkinson's disease	Probable: 332.0 (G20) Possible: No additional medical code	Probable: 294.1x (F02.8x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for Parkinson's disease.)
Huntington's disease	333.4 (G10)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional code for Huntington's disease.)
Due to another medical condition	Code the other medical condition first (e.g., 340 [G35] multiple sclerosis)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional codes for the presumed etiological medical conditions.)
Due to multiple etiologies	Code all of the etiological medical conditions first (with the exception of vascular disease)	294.1x (F02.8x) (Plus the code for the relevant substance/medication-induced major neurocognitive disorders if substances or medications play a role in the etiology.)	331.83 (G31.84) (Plus the code for the relevant substance/medication-induced mild neurocognitive disorders if substances or medications play a role in the etiology. Do not use additional codes for the presumed etiological medical conditions.)
Unspecified neurocognitive disorder	No additional medical code	799.59 (R41.9)	799.59 (R41.9)

[a]Code first, before code for major neurocognitive disorder.
[b]Code fifth character based on symptom specifier: .x0 without behavioral disturbance; .x1 with behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms).
[c]**Note:** Behavioral disturbance specifier cannot be coded but should still be indicated in writing.
[d]See "Substance/Medication-Induced Major or Mild Neurocognitive Disorder."

Specify:
Without behavioral disturbance: If the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.
With behavioral disturbance *(specify disturbance):* If the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms).

Specify current severity:
Mild: Difficulties with instrumental activities of daily living (e.g., housework, managing money).
Moderate: Difficulties with basic activities of daily living (e.g., feeding, dressing).
Severe: Fully dependent.

Mild Neurocognitive Disorder

Diagnostic Criteria

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Specify whether due to:
Alzheimer's disease (pp. 611–614)
Frontotemporal lobar degeneration (pp. 614–618)
Lewy body disease (pp. 618–621)
Vascular disease (pp. 621–624)
Traumatic brain injury (pp. 624–627)
Substance/medication use (pp. 627–632)
HIV infection (pp. 632–634)
Prion disease (pp. 634–636)
Parkinson's disease (pp. 636–638)
Huntington's disease (pp. 638–641)
Another medical condition (pp. 641–642)
Multiple etiologies (pp. 642–643)
Unspecified (p. 643)

Coding note: For mild neurocognitive disorder due to any of the medical etiologies listed above, code **331.83 (G31.84).** Do *not* use additional codes for the presumed etiological medical conditions. For substance/medication-induced mild neurocognitive disorder, code based on type of substance; see "Substance/Medication-Induced Major or Mild Neurocognitive Disorder." For unspecified mild neurocognitive disorder, code **799.59 (R41.9).**

Specify:

> **Without behavioral disturbance:** If the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.
>
> **With behavioral disturbance** *(specify disturbance):* If the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms).

Subtypes

Major and mild neurocognitive disorders (NCDs) are primarily subtyped according to the known or presumed etiological/pathological entity or entities underlying the cognitive decline. These subtypes are distinguished on the basis of a combination of time course, characteristic domains affected, and associated symptoms. For certain etiological subtypes, the diagnosis depends substantially on the presence of a potentially causative entity, such as Parkinson's or Huntington's disease, or a traumatic brain injury or stroke in the appropriate time period. For other etiological subtypes (generally the neurodegenerative diseases like Alzheimer's disease, frontotemporal lobar degeneration, and Lewy body disease), the diagnosis is based primarily on the cognitive, behavioral, and functional symptoms. Typically, the differentiation among these syndromes that lack an independently recognized etiological entity is clearer at the level of major NCD than at the level of mild NCD, but sometimes characteristic symptoms and associated features are present at the mild level as well.

NCDs are frequently managed by clinicians in multiple disciplines. For many subtypes, multidisciplinary international expert groups have developed specialized consensus criteria based on clinicopathological correlation with underlying brain pathology. The subtype criteria here have been harmonized with those expert criteria.

Specifiers

Evidence for distinct behavioral features in NCDs has been recognized, particularly in the areas of psychotic symptoms and depression. Psychotic features are common in many NCDs, particularly at the mild-to-moderate stage of major NCDs due to Alzheimer's disease, Lewy body disease, and frontotemporal lobar degeneration. Paranoia and other delusions are common features, and often a persecutory theme may be a prominent aspect of delusional ideation. In contrast to psychotic disorders with onset in earlier life (e.g., schizophrenia), disorganized speech and disorganized behavior are not characteristic of psychosis in NCDs. Hallucinations may occur in any modality, although visual hallucinations are more common in NCDs than in depressive, bipolar, or psychotic disorders.

Mood disturbances, including depression, anxiety, and elation, may occur. Depression is common early in the course (including at the mild NCD level) of NCD due to Alzheimer's disease and Parkinson's disease, while elation may occur more commonly in frontotemporal lobar degeneration. When a full affective syndrome meeting diagnostic criteria for a depressive or bipolar disorder is present, that diagnosis should be coded as well. Mood symptoms are increasingly recognized to be a significant feature in the earliest stages of mild NCDs such that clinical recognition and intervention may be important.

Agitation is common in a wide variety of NCDs, particularly in major NCD of moderate to severe severity, and often occurs in the setting of confusion or frustration. It may arise as combative behaviors, particularly in the context of resisting caregiving duties such as bathing and dressing. Agitation is characterized as disruptive motor or vocal activity and tends to occur with advanced stages of cognitive impairment across all of the NCDs.

Individuals with NCD can present with a wide variety of behavioral symptoms that are the focus of treatment. Sleep disturbance is a common symptom that can create a need for clinical attention and may include symptoms of insomnia, hypersomnia, and circadian rhythm disturbances.

Apathy is common in mild and mild major NCD. It is observed particularly in NCD due to Alzheimer's disease and may be a prominent feature of NCD due to frontotemporal lobar degeneration. Apathy is typically characterized by diminished motivation and reduced goal-directed behavior accompanied by decreased emotional responsiveness. Symptoms of apathy may manifest early in the course of NCDs when a loss of motivation to pursue daily activities or hobbies may be observed.

Other important behavioral symptoms include wandering, disinhibition, hyperphagia, and hoarding. Some of these symptoms are characteristic of specific disorders, as discussed in the relevant sections. When more than one behavioral disturbance is observed, each type should be noted in writing with the specifier "with behavioral symptoms."

Diagnostic Features

Major and mild NCDs exist on a spectrum of cognitive and functional impairment. Major NCD corresponds to the condition referred to in DSM-IV as *dementia,* retained as an alternative in this volume. The core feature of NCDs is acquired cognitive decline in one or more cognitive domains (Criterion A) based on both 1) a concern about cognition on the part of the individual, a knowledgeable informant, or the clinician, and 2) performance on an objective assessment that falls below the expected level or that has been observed to decline over time. Both a concern and objective evidence are required because they are complementary. When there is an exclusive focus on objective testing, a disorder may go undiagnosed in high-functioning individuals whose currently "normal" performance actually represents a substantial decline in abilities, or an illness may be incorrectly diagnosed in individuals whose currently "low" performance does not represent a change from their own baseline or is a result of extraneous factors like test conditions or a passing illness. Alternatively, excessive focus on subjective symptoms may fail to diagnose illness in individuals with poor insight, or whose informants deny or fail to notice their symptoms, or it may be overly sensitive in the so-called worried well.

A cognitive concern differs from a complaint in that it may or may not be voiced spontaneously. Rather, it may need to be elicited by careful questioning about specific symptoms that commonly occur in individuals with cognitive deficits (see Table 1 in the introduction to this chapter). For example, memory concerns include difficulty remembering a short grocery list or keeping track of the plot of a television program; executive concerns include difficulty resuming a task when interrupted, organizing tax records, or planning a holiday meal. At the mild NCD level, the individual is likely to describe these tasks as being more difficult or as requiring extra time or effort or compensatory strategies. At the major NCD level, such tasks may only be completed with assistance or may be abandoned altogether. At the mild NCD level, individuals and their families may not notice such symptoms or may view them as normal, particularly in the elderly; thus, careful history taking is of paramount importance. The difficulties must represent changes rather than lifelong patterns: the individual or informant may clarify this issue, or the clinician can infer change from prior experience with the patient or from occupational or other clues. It is also critical to determine that the difficulties are related to cognitive loss rather than to motor or sensory limitations.

Neuropsychological testing, with performance compared with norms appropriate to the patient's age, educational attainment, and cultural background, is part of the standard evaluation of NCDs and is particularly critical in the evaluation of mild NCD. For major NCD, performance is typically 2 or more standard deviations below appropriate norms (3rd percentile or below). For mild NCD, performance typically lies in the 1–2 standard deviation range (between the 3rd and 16th percentiles). However, neuropsychological testing is not available in all settings, and neuropsychological thresholds are sensitive to the specific test(s) and norms employed, as well as to test conditions, sensory limitations, and intercurrent illness. A variety of brief office-based or "bedside" assessments, as described

in Table 1, can also supply objective data in settings where such testing is unavailable or infeasible. In any case, as with cognitive concerns, objective performance must be interpreted in light of the individual's prior performance. Optimally, this information would be available from a prior administration of the same test, but often it must be inferred based on appropriate norms, along with the individual's educational history, occupation, and other factors. Norms are more challenging to interpret in individuals with very high or very low levels of education and in individuals being tested outside their own language or cultural background.

Criterion B relates to the individual's level of independence in everyday functioning. Individuals with major NCD will have impairment of sufficient severity so as to interfere with independence, such that others will have to take over tasks that the individuals were previously able to complete on their own. Individuals with mild NCD will have preserved independence, although there may be subtle interference with function or a report that tasks require more effort or take more time than previously.

The distinction between major and mild NCD is inherently arbitrary, and the disorders exist along a continuum. Precise thresholds are therefore difficult to determine. Careful history taking, observation, and integration with other findings are required, and the implications of diagnosis should be considered when an individual's clinical manifestations lie at a boundary.

Associated Features Supporting Diagnosis

Typically the associated features that support a diagnosis of major or mild NCD will be specific to the etiological subtype (e.g., neuroleptic sensitivity and visual hallucinations in NCD due to Lewy body disease). Diagnostic features specific to each of the subtypes are found in the relevant sections.

Prevalence

The prevalence of NCD varies widely by age and by etiological subtype. Overall prevalence estimates are generally only available for older populations. Among individuals older than 60 years, prevalence increases steeply with age, so prevalence estimates are more accurate for narrow age bands than for broad categories such as "over 65" (where the mean age can vary greatly with the life expectancy of the given population). For those etiological subtypes occurring across the lifespan, prevalence estimates for NCD are likely to be available, if at all, only as the fraction of individuals who develop NCD among those with the relevant condition (e.g., traumatic brain injury, HIV infection).

Overall prevalence estimates for dementia (which is largely congruent with major NCD) are approximately 1%–2% at age 65 years and as high as 30% by age 85 years. The prevalence of mild NCD is very sensitive to the definition of the disorder, particularly in community settings, where evaluations are less detailed. In addition, in contrast with clinical settings, where cognitive concern must be high to seek and locate care, there may be a less clear decline from baseline functioning. Estimates of the prevalence of mild cognitive impairment (which is substantially congruent with mild NCD) among older individuals are fairly variable, ranging from 2% to 10% at age 65 and 5% to 25% by age 85.

Development and Course

The course of NCD varies across etiological subtypes, and this variation can be useful in differential diagnosis. Some subtypes (e.g., those related to traumatic brain injury or stroke) typically begin at a specific time and (at least after initial symptoms related to inflammation or swelling subside) remain static. Others may fluctuate over time (although if this occurs, the possibility of delirium superimposed on NCD should be considered). NCDs due to neurodegenerative diseases like Alzheimer's disease or frontotemporal lobar degeneration typically are marked by insidious onset and gradual progression, and

the pattern of onset of cognitive deficits and associated features helps to distinguish among them.

NCDs with onset in childhood and adolescence may have broad repercussions for social and intellectual development, and in this setting intellectual disability (intellectual developmental disorder) and/or other neurodevelopmental disorders may also be diagnosed to capture the full diagnostic picture and ensure the provision of a broad range of services. In older individuals, NCDs often occur in the setting of medical illnesses, frailty, and sensory loss, which complicate the clinical picture for diagnosis and treatment.

When cognitive loss occurs in youth to midlife, individuals and families are likely to seek care. NCDs are typically easiest to identify at younger ages, although in some settings malingering or other factitious disorders may be a concern. Very late in life, cognitive symptoms may not cause concern or may go unnoticed. In late life, mild NCD must also be distinguished from the more modest deficits associated with "normal aging," although a substantial fraction of what has been ascribed to normal aging likely represents prodromal phases of various NCDs. In addition, it becomes harder to recognize mild NCD with age because of the increasing prevalence of medical illness and sensory deficits. It becomes harder to differentiate among subtypes with age because there are multiple potential sources of neurocognitive decline.

Risk and Prognostic Factors

Risk factors vary not only by etiological subtype but also by age at onset within etiological subtypes. Some subtypes are distributed throughout the lifespan, whereas others occur exclusively or primarily in late life. Even within the NCDs of aging, the relative prevalence varies with age: Alzheimer's disease is uncommon before age 60 years, and the prevalence increases steeply thereafter, while the overall less common frontotemporal lobar degeneration has earlier onset and represents a progressively smaller fraction of NCDs with age.

Genetic and physiological.   The strongest risk factor for major and mild NCDs is age, primarily because age increases the risk of neurodegenerative and cerebrovascular disease. Female gender is associated with higher prevalence of dementia overall, and especially Alzheimer's disease, but this difference is largely, if not wholly, attributable to greater longevity in females.

Culture-Related Diagnostic Issues

Individuals' and families' level of awareness and concern about neurocognitive symptoms may vary across ethnic and occupational groups. Neurocognitive symptoms are more likely to be noticed, particularly at the mild level, in individuals who engage in complex occupational, domestic, or recreational activities. In addition, norms for neuropsychological testing tend to be available only for broad populations, and thus they may not be easily applicable to individuals with less than high school education or those being evaluated outside their primary language or culture.

Gender-Related Diagnostic Issues

Like age, culture, and occupation, gender issues may affect the level of concern and awareness of cognitive symptoms. In addition, for late-life NCDs, females are likely to be older, to have more medical comorbidity, and to live alone, which can complicate evaluation and treatment. In addition, there are gender differences in the frequency of some of the etiological subtypes.

Diagnostic Markers

In addition to a careful history, neuropsychological assessments are the key measures for diagnosis of NCDs, particularly at the mild level, where functional changes are minimal

and symptoms more subtle. Ideally, individuals will be referred for formal neuropsychological testing, which will provide a quantitative assessment of all relevant domains and thus help with diagnosis; provide guidance to the family on areas where the individual may require more support; and serve as a benchmark for further decline or response to therapies. When such testing is unavailable or not feasible, the brief assessments in Table 1 can provide insight into each domain. More global brief mental status tests may be helpful but may be insensitive, particularly to modest changes in a single domain or in those with high premorbid abilities, and may be overly sensitive in those with low premorbid abilities.

In distinguishing among etiological subtypes, additional diagnostic markers may come into play, particularly neuroimaging studies such as magnetic resonance imaging scans and positron emission tomography scans. In addition, specific markers may be involved in the assessment of specific subtypes and may become more important as additional research findings accumulate over time, as discussed in the relevant sections.

Functional Consequences of Major and Mild Neurocognitive Disorders

By definition, major and mild NCDs affect functioning, given the central role of cognition in human life. Thus, the criteria for the disorders, and the threshold for differentiating mild from major NCD, are based in part on functional assessment. Within major NCD there is a broad range of functional impairment, as implemented in the severity specifiers. In addition, the specific functions that are compromised can help identify the cognitive domains affected, particularly when neuropsychological testing is not available or is difficult to interpret.

Differential Diagnosis

Normal cognition.   The differential diagnosis between normal cognition and mild NCD, as between mild and major NCD, is challenging because the boundaries are inherently arbitrary. Careful history taking and objective assessment are critical to these distinctions. A longitudinal evaluation using quantified assessments may be key in detecting mild NCD.

Delirium.   Both mild and major NCD may be difficult to distinguish from a persistent delirium, which can co-occur. Careful assessment of attention and arousal will help to make the distinction.

Major depressive disorder.   The distinction between mild NCD and major depressive disorder, which may co-occur with NCD, can also be challenging. Specific patterns of cognitive deficits may be helpful. For example, consistent memory and executive function deficits are typical of Alzheimer's disease, whereas nonspecific or more variable performance is seen in major depression. Alternatively, treatment of the depressive disorder with repeated observation over time may be required to make the diagnosis.

Specific learning disorder and other neurodevelopmental disorders.   A careful clarification of the individual's baseline status will help distinguish an NCD from a specific learning disorder or other neurodevelopmental disorders. Additional issues may enter the differential for specific etiological subtypes, as described in the relevant sections.

Comorbidity

NCDs are common in older individuals and thus often co-occur with a wide variety of age-related diseases that may complicate diagnosis or treatment. Most notable of these is delirium, for which NCD increases the risk. In older individuals, a delirium during hospitalization is, in many cases, the first time that an NCD is noticed, although a careful history will often reveal evidence of earlier decline. Mixed NCDs are also common in older individuals, as many etiological entities increase in prevalence with age. In younger individuals, NCD often co-occurs with neurodevelopmental disorders; for example, a head in-

jury in a preschool child may also lead to significant developmental and learning issues. Additional comorbidity of NCD is often related to the etiological subtype, as discussed in the relevant sections.

Major or Mild Neurocognitive Disorder Due to Alzheimer's Disease

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).

C. Criteria are met for either probable or possible Alzheimer's disease as follows:

For major neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if either of the following is present; otherwise, **possible Alzheimer's disease** should be diagnosed.

1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.

2. All three of the following are present:

    a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).

    b. Steadily progressive, gradual decline in cognition, without extended plateaus.

    c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

For mild neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history.

Possible Alzheimer's disease is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present:

1. Clear evidence of decline in memory and learning.

2. Steadily progressive, gradual decline in cognition, without extended plateaus.

3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).

D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Coding note: For probable major neurocognitive disorder due to Alzheimer's disease, with behavioral disturbance, code first **331.0 (G30.9)** Alzheimer's disease, followed by **294.11 (F02.81)** major neurocognitive disorder due to Alzheimer's disease. For probable neurocognitive disorder due to Alzheimer's disease, without behavioral disturbance, code first **331.0 (G30.9)** Alzheimer's disease, followed by **294.10 (F02.80)** major neurocognitive disorder due to Alzheimer's disease, without behavioral disturbance.

For possible major neurocognitive disorder due to Alzheimer's disease, code **331.9 (G31.9)** possible major neurocognitive disorder due to Alzheimer's disease. (**Note:** Do *not* use the additional code for Alzheimer's disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

For mild neurocognitive disorder due to Alzheimer's disease, code **331.83 (G31.84).** (**Note:** Do *not* use the additional code for Alzheimer's disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Diagnostic Features

Beyond the neurocognitive disorder (NCD) syndrome (Criterion A), the core features of major or mild NCD due to Alzheimer's disease include an insidious onset and gradual progression of cognitive and behavioral symptoms (Criterion B). The typical presentation is amnestic (i.e., with impairment in memory and learning). Unusual nonamnestic presentations, particularly visuospatial and logopenic aphasic variants, also exist. At the mild NCD phase, Alzheimer's disease manifests typically with impairment in memory and learning, sometimes accompanied by deficits in executive function. At the major NCD phase, visuoconstructional/perceptual-motor ability and language will also be impaired, particularly when the NCD is moderate to severe. Social cognition tends to be preserved until late in the course of the disease.

A level of diagnostic certainty must be specified denoting Alzheimer's disease as the "probable" or "possible" etiology (Criterion C). *Probable Alzheimer's disease* is diagnosed in both major and mild NCD if there is evidence of a causative Alzheimer's disease gene, either from genetic testing or from an autosomal dominant family history coupled with autopsy confirmation or a genetic test in an affected family member. For major NCD, a typical clinical picture, without extended plateaus or evidence of mixed etiology, can also be diagnosed as due to probable Alzheimer's disease. For mild NCD, given the lesser degree of certainty that the deficits will progress, these features are only sufficient for a *possible* Alzheimer's etiology. If the etiology appears mixed, mild NCD due to multiple etiologies should be diagnosed. In any case, for both mild and major NCD due to Alzheimer's disease, the clinical features must not suggest another primary etiology for the NCD (Criterion D).

Associated Features Supporting Diagnosis

In specialty clinical settings, approximately 80% of individuals with major NCD due to Alzheimer's disease have behavioral and psychological manifestations; these features are also frequent at the mild NCD stage of impairment. These symptoms are as or more distressing than cognitive manifestations and are frequently the reason that health care is sought. At the mild NCD stage or the mildest level of major NCD, depression and/or apathy are often seen. With moderately severe major NCD, psychotic features, irritability, agitation, combativeness, and wandering are common. Late in the illness, gait disturbance, dysphagia, incontinence, myoclonus, and seizures are observed.

Prevalence

The prevalence of overall dementia (major NCD) rises steeply with age. In high-income countries, it ranges from 5% to 10% in the seventh decade to at least 25% thereafter. U.S. census data estimates suggest that approximately 7% of individuals diagnosed with Alzheimer's disease are between ages 65 and 74 years, 53% are between ages 75 and 84 years, and 40% are 85 years and older. The percentage of dementias attributable to Alzheimer's disease ranges from about 60% to over 90%, depending on the setting and diagnostic criteria. Mild NCD due to Alzheimer's disease is likely to represent a substantial fraction of mild cognitive impairment (MCI) as well.

Development and Course

Major or mild NCD due to Alzheimer's disease progresses gradually, sometimes with brief plateaus, through severe dementia to death. The mean duration of survival after di-

agnosis is approximately 10 years, reflecting the advanced age of the majority of individuals rather than the course of the disease; some individuals can live with the disease for as long as 20 years. Late-stage individuals are eventually mute and bedbound. Death most commonly results from aspiration in those who survive through the full course. In mild NCD due to Alzheimer's disease, impairments increase over time, and functional status gradually declines until symptoms reach the threshold for the diagnosis of major NCD.

The onset of symptoms is usually in the eighth and ninth decades; early-onset forms seen in the fifth and sixth decades are often related to known causative mutations. Symptoms and pathology do not differ markedly at different onset ages. However, younger individuals are more likely to survive the full course of the disease, while older individuals are more likely to have numerous medical comorbidities that affect the course and management of the illness. Diagnostic complexity is higher in older adults because of the increased likelihood of comorbid medical illness and mixed pathology.

Risk and Prognostic Factors

Environmental.   Traumatic brain injury increases risk for major or mild NCD due to Alzheimer's disease.

Genetic and physiological.   Age is the strongest risk factor for Alzheimer's disease. The genetic susceptibility polymorphism apolipoprotein E4 increases risk and decreases age at onset, particularly in homozygous individuals. There are also extremely rare causative Alzheimer's disease genes. Individuals with Down's syndrome (trisomy 21) develop Alzheimer's disease if they survive to midlife. Multiple vascular risk factors influence risk for Alzheimer's disease and may act by increasing cerebrovascular pathology or also through direct effects on Alzheimer pathology.

Culture-Related Diagnostic Issues

Detection of an NCD may be more difficult in cultural and socioeconomic settings where memory loss is considered normal in old age, where older adults face fewer cognitive demands in everyday life, or where very low educational levels pose greater challenges to objective cognitive assessment.

Diagnostic Markers

Cortical atrophy, amyloid-predominant neuritic plaques, and tau-predominant neurofibrillary tangles are hallmarks of the pathological diagnosis of Alzheimer's disease and may be confirmed via postmortem histopathological examination. For early-onset cases with autosomal dominant inheritance, a mutation in one of the known causative Alzheimer's disease genes—amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2)—may be involved, and genetic testing for such mutations is commercially available, at least for PSEN1. Apolipoprotein E4 cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence.

Since amyloid beta-42 deposition in the brain occurs early in the pathophysiological cascade, amyloid-based diagnostic tests such as amyloid imaging on brain positron emission tomography (PET) scans and reduced levels of amyloid beta-42 in the cerebrospinal fluid (CSF) may have diagnostic value. Signs of neuronal injury, such as hippocampal and temporoparietal cortical atrophy on a magnetic resonance image scan, temporoparietal hypometabolism on a fluorodeoxyglucose PET scan, and evidence for elevated total tau and phospho-tau levels in CSF, provide evidence of neuronal damage but are less specific for Alzheimer's disease. At present, these biomarkers are not fully validated, and many are available only in tertiary care settings. However, some of them, along with novel biomarkers, will likely move into wider clinical practice in the coming years.

Functional Consequences of Major or Mild Neurocognitive Disorder Due to Alzheimer's Disease

The prominence of memory loss can cause significant difficulties relatively early in the course. Social cognition (and thus social functioning) and procedural memory (e.g., dancing, playing musical instruments) may be relatively preserved for extended periods.

Differential Diagnosis

Other neurocognitive disorders.   Major and mild NCDs due to other neurodegenerative processes (e.g., Lewy body disease, frontotemporal lobar degeneration) share the insidious onset and gradual decline caused by Alzheimer's disease but have distinctive core features of their own. In major or mild vascular NCD, there is typically history of stroke temporally related to the onset of cognitive impairment, and infarcts or white matter hyperintensities are judged sufficient to account for the clinical picture. However, particularly when there is no clear history of stepwise decline, major or mild vascular NCD can share many clinical features with Alzheimer's disease.

Other concurrent, active neurological or systemic illness.   Other neurological or systemic illness should be considered if there is an appropriate temporal relationship and severity to account for the clinical picture. At the mild NCD level, it may be difficult to distinguish an Alzheimer's disease etiology from that of another medical condition (e.g., thyroid disorders, vitamin B_{12} deficiency).

Major depressive disorder.   Particularly at the mild NCD level, the differential diagnosis also includes major depression. The presence of depression may be associated with reduced daily functioning and poor concentration that may resemble an NCD, but improvement with treatment of depression may be useful in making the distinction.

Comorbidity

Most individuals with Alzheimer's disease are elderly and have multiple medical conditions that can complicate diagnosis and influence the clinical course. Major or mild NCD due to Alzheimer's disease commonly co-occurs with cerebrovascular disease, which contributes to the clinical picture. When a comorbid condition contributes to the NCD in an individual with Alzheimer's disease, then NCD due to multiple etiologies should be diagnosed.

Major or Mild Frontotemporal Neurocognitive Disorder

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.
B. The disturbance has insidious onset and gradual progression.
C. Either (1) or (2):
   1. Behavioral variant:
      a. Three or more of the following behavioral symptoms:
          i. Behavioral disinhibition.
          ii. Apathy or inertia.
          iii. Loss of sympathy or empathy.
          iv. Perseverative, stereotyped or compulsive/ritualistic behavior.
          v. Hyperorality and dietary changes.
      b. Prominent decline in social cognition and/or executive abilities.

2. Language variant:

   a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension.

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

E. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Probable frontotemporal neurocognitive disorder is diagnosed if either of the following is present; otherwise, **possible frontotemporal neurocognitive disorder** should be diagnosed:

1. Evidence of a causative frontotemporal neurocognitive disorder genetic mutation, from either family history or genetic testing.

2. Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging.

Possible frontotemporal neurocognitive disorder is diagnosed if there is no evidence of a genetic mutation, and neuroimaging has not been performed.

Coding note: For probable major neurocognitive disorder due to frontotemporal lobar degeneration, with behavioral disturbance, code first **331.19 (G31.09)** frontotemporal disease, followed by **294.11 (F02.81)** probable major neurocognitive disorder due to frontotemporal lobar degeneration, with behavioral disturbance. For probable major neurocognitive disorder due to frontotemporal lobar degeneration, without behavioral disturbance, code first **331.19 (G31.09)** frontotemporal disease, followed by **294.10 (F02.80)** probable major neurocognitive disorder due to frontotemporal lobar degeneration, without behavioral disturbance.

For possible major neurocognitive disorder due to frontotemporal lobar degeneration, code **331.9 (G31.9)** possible major neurocognitive disorder due to frontotemporal lobar degeneration. (**Note:** Do *not* use the additional code for frontotemporal disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

For mild neurocognitive disorder due to frontotemporal lobar degeneration, code **331.83 (G31.84)**. (**Note:** Do *not* use the additional code for frontotemporal disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Diagnostic Features

Major or mild frontotemporal neurocognitive disorder (NCD) comprises a number of syndromic variants characterized by the progressive development of behavioral and personality change and/or language impairment. The behavioral variant and three language variants (semantic, agrammatic/nonfluent, and logopenic) exhibit distinct patterns of brain atrophy and some distinctive neuropathology. The criteria must be met for either the behavioral or the language variant to make the diagnosis, but many individuals present with features of both.

Individuals with behavioral-variant major or mild frontotemporal NCD present with varying degrees of apathy or disinhibition. They may lose interest in socialization, self-care, and personal responsibilities, or display socially inappropriate behaviors. Insight is usually impaired, and this often delays medical consultation. The first referral is often to a psychiatrist. Individuals may develop changes in social style, and in religious and political beliefs, with repetitive movements, hoarding, changes in eating behavior, and hyperorality. In later stages, loss of sphincter control may occur. Cognitive decline is less prominent, and formal testing may show relatively few deficits in the early stages. Common neurocognitive symptoms are lack of planning and organization, distractibility, and poor judgment. Deficits in executive function, such as poor performance on tests of mental

flexibility, abstract reasoning, and response inhibition, are present, but learning and memory are relatively spared, and perceptual-motor abilities are almost always preserved in the early stages.

Individuals with language-variant major or mild frontotemporal NCD present with primary progressive aphasia with gradual onset, with three subtypes commonly described: semantic variant, agrammatic/nonfluent variant, and logopenic variant, and each variant has distinctive features and corresponding neuropathology.

"Probable" is distinguished from "possible" frontotemporal NCD by the presence of causative genetic factors (e.g., mutations in the gene coding for microtubule-associated protein tau) or by the presence of distinctive atrophy or reduced activity in frontotemporal regions on structural or functional imaging.

Associated Features Supporting Diagnosis

Extrapyramidal features may be prominent in some cases, with an overlap with syndromes such as progressive supranuclear palsy and corticobasal degeneration. Features of motor neuron disease may be present in some cases (e.g., muscle atrophy, weakness). A subset of individuals develop visual hallucinations.

Prevalence

Major or mild frontotemporal NCD is a common cause of early-onset NCD in individuals younger than 65 years. Population prevalence estimates are in the range of 2–10 per 100,000. Approximately 20%–25% of cases of frontotemporal NCD occur in individuals older than 65 years. Frontotemporal NCD accounts for about 5% of all cases of dementia in unselected autopsy series. Prevalence estimates of behavioral variant and semantic language variant are higher among males, and prevalence estimates of nonfluent language variant are higher among females.

Development and Course

Individuals with major or mild frontotemporal NCD commonly present in the sixth decade of life, although the age at onset varies from the third to the ninth decades. The disease is gradually progressive, with median survival being 6–11 years after symptom onset and 3–4 years after diagnosis. Survival is shorter and decline is faster in major or mild frontotemporal NCD than in typical Alzheimer's disease.

Risk and Prognostic Factors

Genetic and physiological.   Approximately 40% of individuals with major or mild frontotemporal NCD have a family history of early-onset NCD, and approximately 10% show an autosomal dominant inheritance pattern. A number of genetic factors have been identified, such as mutations in the gene encoding the microtubule associated protein tau (MAPT), the granulin gene (GRN), and the C9ORF72 gene. A number of families with causative mutations have been identified (see the section "Diagnostic Markers" for this disorder), but many individuals with known familial transmission do not have a known mutation. The presence of motor neuron disease is associated with a more rapid deterioration.

Diagnostic Markers

Computed tomography (CT) or structural magnetic resonance imaging (MRI) may show distinct patterns of atrophy. In behavioral-variant major or mild frontotemporal NCD, both frontal lobes (especially the medial frontal lobes) and the anterior temporal lobes are atrophic. In semantic language–variant major or mild frontotemporal NCD, the middle, inferior, and anterior temporal lobes are atrophic bilaterally but asymmetrically, with the

left side usually being more affected. Nonfluent language–variant major or mild fronto-temporal NCD is associated with predominantly left posterior frontal-insular atrophy. The logopenic variant of major or mild frontotemporal NCD is associated with predomi-nantly left posterior perisylvian or parietal atrophy. Functional imaging demonstrates hy-poperfusion and/or cortical hypometabolism in the corresponding brain regions, which may be present in the early stages in the absence of structural abnormality. Emerging bio-markers for Alzheimer's disease (e.g., cerebrospinal fluid amyloid-beta and tau levels, and amyloid imaging) may help in the differential diagnosis, but the distinction from Alzhei-mer's disease can remain difficult (the logopenic variant is in fact often a manifestation of Alzheimer's disease).

In familial cases of frontotemporal NCD, the identification of genetic mutations may help confirm the diagnosis. Mutations associated with frontotemporal NCD include the genes encoding microtubule-associated protein tau (MAPT) and granulin (GRN), C9ORF72, transactive response DNA-binding protein of 43 kDa (TDP-43, or TARDBP), valosin-containing protein (VCP), chromatin modifying protein 2B (CHMP2B), and fused in sarcoma protein (FUS).

Functional Consequences of Major or Mild Frontotemporal Neurocognitive Disorder

Because of the relative early age at onset of the disorder, the disorder oftens affects work-place and family life. Because of the involvement of language and/or behavior, function is often more severely impaired relatively early in the course. For individuals with the be-havioral variant, prior to diagnostic clarification there may be significant family disrup-tion, legal involvement, and problems in the workplace because of socially inappropriate behaviors. The functional impairment due to behavioral change and language dysfunc-tion, which can include hyperorality, impulsive wandering, and other dishinhibited be-haviors, may far exceed that due to the cognitive disturbance and may lead to nursing home placement or institutionalization. These behaviors can be severely disruptive, even in structured care settings, particularly when the individuals are otherwise healthy, non-frail, and free of other medical comorbidities.

Differential Diagnosis

Other neurocognitive disorders.   Other neurodegenerative diseases may be distinguished from major or mild frontotemporal NCD by their characteristic features. In major or mild NCD due to Alzheimer's disease, decline in learning and memory is an early feature. However, 10%–30% of patients presenting with a syndrome suggestive of major or mild frontotemporal NCD are found at autopsy to have Alzheimer's disease pathology. This oc-curs more frequently in individuals who present with progressive dysexecutive syn-dromes in the absence of behavioral changes or movement disorder or in those with the logopenic variant.

In major or mild NCD with Lewy bodies, core and suggestive features of Lewy bodies must be present. In major or mild NCD due to Parkinson's disease, spontaneous parkin-sonism emerges well before the cognitive decline. In major or mild vascular NCD, depend-ing on affected brain regions, there may also be loss of executive ability and behavioral changes such as apathy, and this disorder should be considered in the differential diagno-sis. However, history of a cerebrovascular event is temporally related to the onset of cog-nitive impairment in major or mild vascular NCD, and neuroimaging reveals infarctions or white matter lesions sufficient to account for the clinical picture.

Other neurological conditions.   Major or mild frontotemporal NCD overlaps with pro-gressive supranuclear palsy, corticobasal degeneration, and motor neuron disease clinically as well as pathologically. Progressive supranuclear palsy is characterized by

supranuclear gaze palsies and axial-predominant parkinsonism. Pseudobulbar signs may be present, and retropulsion is often prominent. Neurocognitive assessment shows psychomotor slowing, poor working memory, and executive dysfunction. Corticobasal degeneration presents with asymmetric rigidity, limb apraxia, postural instability, myoclonus, alien limb phenomenon, and cortical sensory loss. Many individuals with behavioral-variant major or mild frontotemporal NCD show features of motor neuron disease, which tend to be mixed upper and predominantly lower motor neuron disease.

Other mental disorders and medical conditions.   Behavioral-variant major or mild frontotemporal NCD may be mistaken for a primary mental disorder, such as major depression, bipolar disorders, or schizophrenia, and individuals with this variant often present initially to psychiatry. Over time, the development of progressive neurocognitive difficulties will help to make the distinction. A careful medical evaluation will help to exclude treatable causes of NCDs, such as metabolic disturbances, nutritional deficiencies, and infections.

Major or Mild Neurocognitive Disorder With Lewy Bodies

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. The disorder has an insidious onset and gradual progression.

C. The disorder meets a combination of core diagnostic features and suggestive diagnostic features for either probable or possible neurocognitive disorder with Lewy bodies.
    For probable major or mild neurocognitive disorder with Lewy bodies, the individual has two core features, or one suggestive feature with one or more core features. For **possible major or mild neurocognitive disorder with Lewy bodies,** the individual has only one core feature, or one or more suggestive features.

    1. Core diagnostic features:

        a. Fluctuating cognition with pronounced variations in attention and alertness.
        b. Recurrent visual hallucinations that are well formed and detailed.
        c. Spontaneous features of parkinsonism, with onset subsequent to the development of cognitive decline.

    2. Suggestive diagnostic features:

        a. Meets criteria for rapid eye movement sleep behavior disorder.
        b. Severe neuroleptic sensitivity.

D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Coding note: For probable major neurocognitive disorder with Lewy bodies, with behavioral disturbance, code first **331.82 (G31.83)** Lewy body disease, followed by **294.11 (F02.81)** probable major neurocognitive disorder with Lewy bodies, with behavioral disturbance. For probable major neurocognitive disorder with Lewy bodies, without behavioral disturbance, code first **331.82 (G31.83)** Lewy body disease, followed by **294.10 (F02.80)** probable major neurocognitive disorder with Lewy bodies, without behavioral disturbance.

For possible major neurocognitive disorder with Lewy bodies, code **331.9 (G31.9)** possible major neurocognitive disorder with Lewy bodies. (**Note:** Do *not* use the additional code for Lewy body disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

For mild neurocognitive disorder with Lewy bodies, code **331.83 (G31.84).** (**Note:** Do *not* use the additional code for Lewy body disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Diagnostic Features

Major or mild neurocognitive disorder with Lewy bodies (NCDLB), in the case of major neurocognitive disorder (NCD), corresponds to the condition known as dementia with Lewy bodies (DLB). The disorder includes not only progressive cognitive impairment (with early changes in complex attention and executive function rather than learning and memory) but also recurrent complex visual hallucinations; and concurrent symptoms of rapid eye movement (REM) sleep behavior disorder (which can be a very early manifestation); as well as hallucinations in other sensory modalities, depression, and delusions. The symptoms fluctuate in a pattern that can resemble a delirium, but no adequate underlying cause can be found. The variable presentation of NCDLB symptoms reduces the likelihood of all symptoms being observed in a brief clinic visit and necessitates a thorough assessment of caregiver observations. The use of assessment scales specifically designed to assess fluctuation may aid in diagnosis. Another core feature is spontaneous parkinsonism, which must begin after the onset of cognitive decline; by convention, major cognitive deficits are observed at least 1 year before the motor symptoms. The parkinsonism must also be distinguished from neuroleptic-induced extrapyramidal signs. Accurate diagnosis is essential to safe treatment planning, as up to 50% of individuals with NCDLB have severe sensitivity to neuroleptic drugs, and these medications should be used with extreme caution in managing the psychotic manifestations.

The diagnosis of mild NCDLB is appropriate for individuals who present with the core or suggestive features at a stage when cognitive or functional impairments are not of sufficient severity to fulfill criteria for major NCD. However, as for all mild NCDs, there will often be insufficient evidence to justify any single etiology, and use of the unspecified diagnosis is most appropriate.

Associated Features Supporting Diagnosis

Individuals with NCDLB frequently experience repeated falls and syncope and transient episodes of unexplained loss of consciousness. Autonomic dysfunction, such as orthostatic hypotension and urinary incontinence, may be observed. Auditory and other nonvisual hallucinations are common, as are systematized delusions, delusional misidentification, and depression.

Prevalence

The few population-based prevalence estimates for NCDLB available range from 0.1% to 5% of the general elderly population, and from 1.7% to 30.5% of all dementia cases. In brain bank (autopsy) series, the pathological lesions known as Lewy bodies are present in 20%–35% of cases of dementia. The male-to-female ratio is approximately 1.5:1.

Development and Course

NCDLB is a gradually progressive disorder with insidious onset. However, there is often a prodromal history of confusional episodes (delirium) of acute onset, often precipitated by illness or surgery. The distinction between NCDLB, in which Lewy bodies are primarily cortical in location, and major or mild NCD due to Parkinson's disease, in which the pathology is primarily in the basal ganglia, is the order in which the cognitive and motor symptoms emerge. In NCDLB, the cognitive decline is manifested early in the course of illness, at least a year before the onset of motor symptoms (see the section "Differential Di-

agnosis" for this disorder). Disease course may be characterized by occasional plateaus but eventually progresses through severe dementia to death. Average duration of survival is 5–7 years in clinical series. Onset of symptoms is typically observed from the sixth through the ninth decades of life, with most cases having their onset when affected individuals are in their mid-70s.

Risk and Prognostic Factors

Genetic and physiological.   Familial aggregation may occur, and several risk genes have been identified, but in most cases of NCDLB, there is no family history.

Diagnostic Markers

The underlying neurodegenerative disease is primarily a synucleinopathy due to alpha-synuclein misfolding and aggregation. Cognitive testing beyond the use of a brief screening instrument may be necessary to define deficits clearly. Assessment scales developed to measure fluctuation can be useful. The associated condition REM sleep behavior disorder may be diagnosed through a formal sleep study or identified by questioning the patient or informant about relevant symptoms. Neuroleptic sensitivity (challenge) is not recommended as a diagnostic marker but raises suspicion of NCDLB if it occurs. A diagnostically suggestive feature is low striatal dopamine transporter uptake on single photon emission computed tomography (SPECT) or positron emission tomography (PET) scan. Other clinically useful markers potentially include relative preservation of medial temporal structures on computed tomography (CT)/magnetic resonance imaging (MRI) brain scan; reduced striatal dopamine transporter uptake on SPECT/PET scan; generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity; abnormal (low uptake) MIBG myocardial scintigraphy suggesting sympathetic denervation; and prominent slow-wave activity on the electroencephalogram with temporal lobe transient waves.

Functional Consequences of Major or Mild Neurocognitive Disorder With Lewy Bodies

Individuals with NCDLB are more functionally impaired than would be expected for their cognitive deficits when contrasted to individuals with other neurodegenerative diseases, such as Alzheimer's disease. This is largely a result of motor and autonomic impairments, which cause problems with toileting, transferring, and eating. Sleep disorders and prominent psychiatric symptoms may also add to functional difficulties. Consequently, the quality of life of individuals with NCDLB is often significantly worse than that of individuals with Alzheimer's disease.

Differential Diagnosis

Major or mild neurocognitive disorder due to Parkinson's disease.   A key differentiating feature in clinical diagnosis is the temporal sequence in which the parkinsonism and the NCD appear. For NCD due to Parkinson's disease, the individual must develop cognitive decline in the context of established Parkinson's disease; by convention, the decline should not reach the stage of major NCD until at least 1 year after Parkinson's is diagnosed. If less than a year has passed since the onset of motor symptoms, the diagnosis is NCDLB. This distinction is clearer at the major NCD level than at the mild NCD level.

The timing and sequence of parkinsonism and mild NCD may be more difficult to determine because the onset and clinical presentation can be ambiguous, and unspecified mild NCD should be diagnosed if the other core and suggestive features are absent.

Comorbidity

Lewy body pathology frequently coexists with Alzheimer's disease and cerebrovascular disease pathology, particularly among the oldest age groups. In Alzheimer's disease, there is concomitant synuclein pathology in 60% of cases (if amygdala-restricted cases are included). In general, there is a higher rate of Lewy body pathology in individuals with dementia than in older individuals without dementia.

Major or Mild Vascular Neurocognitive Disorder

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. The clinical features are consistent with a vascular etiology, as suggested by either of the following:

1. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.

2. Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function.

C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.

D. The symptoms are not better explained by another brain disease or systemic disorder.

Probable vascular neurocognitive disorder is diagnosed if one of the following is present; otherwise **possible vascular neurocognitive disorder** should be diagnosed:

1. Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimaging-supported).

2. The neurocognitive syndrome is temporally related to one or more documented cerebrovascular events.

3. Both clinical and genetic (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease is present.

Possible vascular neurocognitive disorder is diagnosed if the clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.

Coding note: For probable major vascular neurocognitive disorder, with behavioral disturbance, code **290.40 (F01.51).** For probable major vascular neurocognitive disorder, without behavioral disturbance, code **290.40 (F01.50).** For possible major vascular neurocognitive disorder, with or without behavioral disturbance, code **331.9 (G31.9).** An additional medical code for the cerebrovascular disease is not needed.

For mild vascular neurocognitive disorder, code **331.83 (G31.84).** (**Note:** Do *not* use an additional code for the vascular disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Diagnostic Features

The diagnosis of major or mild vascular neurocognitive disorder (NCD) requires the establishment of an NCD (Criterion A) and the determination that cerebrovascular disease is the dominant if not exclusive pathology that accounts for the cognitive deficits (Criteria B and C). Vascular etiology may range from large vessel stroke to microvascular disease; the

presentation is therefore very heterogeneous, stemming from the types of vascular lesions and their extent and location. The lesions may be focal, multifocal, or diffuse and occur in various combinations.

Many individuals with major or mild vascular NCD present with multiple infarctions, with an acute stepwise or fluctuating decline in cognition, and intervening periods of stability and even some improvement. Others may have gradual onset with slow progression, a rapid development of deficits followed by relative stability, or another complex presentation. Major or mild vascular NCD with a gradual onset and slow progression is generally due to small vessel disease leading to lesions in the white matter, basal ganglia, and/or thalamus. The gradual progression in these cases is often punctuated by acute events that leave subtle neurological deficits. The cognitive deficits in these cases can be attributed to disruption of cortical-subcortical circuits, and complex attention, particularly speed of information processing, and executive ability are likely to be affected.

Assessing for the presence of sufficient cerebrovascular disease relies on history, physical examination, and neuroimaging (Criterion C). Etiological certainty requires the demonstration of abnormalities on neuroimaging. The lack of neuroimaging can result in significant diagnostic inaccuracy by overlooking "silent" brain infarction and white matter lesions. However, if the neurocognitive impairment is temporally associated with one or more well-documented strokes, a probable diagnosis can be made in the absence of neuroimaging. Clinical evidence of cerebrovascular disease includes documented history of stroke, with cognitive decline temporally associated with the event, or physical signs consistent with stroke (e.g., hemiparesis; pseudobulbar syndrome, visual field defect). Neuroimaging (magnetic resonance imaging [MRI] or computed tomography [CT]) evidence of cerebrovascular disease comprises one or more of the following: one or more large vessel infarcts or hemorrhages, a strategically placed single infarct or hemorrhage (e.g., in angular gyrus, thalamus, basal forebrain), two or more lacunar infarcts outside the brain stem, or extensive and confluent white matter lesions. The latter is often termed *small vessel disease* or *subcortical ischemic changes* on clinical neuroimaging evaluations.

For mild vascular NCD, history of a single stroke or extensive white matter disease is generally sufficient. For major vascular NCD, two or more strokes, a strategically placed stroke, or a combination of white matter disease and one or more lacunes is generally necessary.

The disorder must not be better explained by another disorder. For example, prominent memory deficit early in the course might suggest Alzheimer's disease, early and prominent parkinsonian features would suggest Parkinson's disease, and a close association between onset and depression would suggest depression.

Associated Features Supporting Diagnosis

A neurological assessment often reveals history of stroke and/or transient ischemic episodes, and signs indicative of brain infarctions. Also commonly associated are personality and mood changes, abulia, depression, and emotional lability. The development of late-onset depressive symptoms accompanied by psychomotor slowing and executive dysfunction is a common presentation among older adults with progressive small vessel ischemic disease ("vascular depression").

Prevalence

Major or mild vascular NCD is the second most common cause of NCD after Alzheimer's disease. In the United States, population prevalence estimates for vascular dementia range from 0.2% in the 65–70 years age group to 16% in individuals 80 years and older. Within 3 months following stroke, 20%–30% of individuals are diagnosed with dementia. In neuropathology series, the prevalence of vascular dementia increases from 13% at age 70 years to 44.6% at age 90 years or older, in comparison with Alzheimer's disease (23.6%–51%) and combined vascular dementia and Alzheimer's disease (2%–46.4%). Higher prevalence has

been reported in African Americans compared with Caucasians, and in East Asian countries (e.g., Japan, China). Prevalence is higher in males than in females.

Development and Course

Major or mild vascular NCD can occur at any age, although the prevalence increases exponentially after age 65 years. In older individuals, additional pathologies may partly account for the neurocognitive deficits. The course may vary from acute onset with partial improvement to stepwise decline to progressive decline, with fluctuations and plateaus of varying durations. Pure subcortical major or mild vascular NCD can have a slowly progressive course that simulates major or mild NCD due to Alzheimer's disease.

Risk and Prognostic Factors

Environmental.   The neurocognitive outcomes of vascular brain injury are influenced by neuroplasticity factors such as education, physical exercise, and mental activity.

Genetic and physiological.   The major risk factors for major or mild vascular NCD are the same as those for cerebrovascular disease, including hypertension, diabetes, smoking, obesity, high cholesterol levels, high homocysteine levels, other risk factors for atherosclerosis and arteriolosclerosis, atrial fibrillation, and other conditions increasing the risk of cerebral emboli. Cerebral amyloid angiopathy is an important risk factor in which amyloid deposits occur within arterial vessels. Another key risk factor is the hereditary condition cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, or CADASIL.

Diagnostic Markers

Structural neuroimaging, using MRI or CT, has an important role in the diagnostic process. There are no other established biomarkers of major or mild vascular NCD.

Functional Consequences of Major or Mild Vascular Neurocognitive Disorder

Major or mild vascular NCD is commonly associated with physical deficits that cause additional disability.

Differential Diagnosis

Other neurocognitive disorders.   Since incidental brain infarctions and white matter lesions are common in older individuals, it is important to consider other possible etiologies when an NCD is present. A history of memory deficit early in the course, and progressive worsening of memory, language, executive function, and perceptual-motor abilities in the absence of corresponding focal lesions on brain imaging, are suggestive of Alzheimer's disease as the primary diagnosis. Potential biomarkers currently being validated for Alzheimer's disease, such as cerebrospinal fluid levels of beta-amyloid and phosphorylated tau, and amyloid imaging, may prove to be helpful in the differential diagnosis. NCD with Lewy bodies is distinguished from major or mild vascular NCD by its core features of fluctuating cognition, visual hallucinations, and spontaneous parkinsonism. While deficits in executive function and language occur in major or mild vascular NCD, the insidious onset and gradual progression of behavioral features or language impairment are characteristic of frontotemporal NCD and are not typical of vascular etiology.

Other medical conditions.   A diagnosis of major or mild vascular NCD is not made if other diseases (e.g., brain tumor, multiple sclerosis, encephalitis, toxic or metabolic disorders) are present and are of sufficient severity to account for the cognitive impairment.

Other mental disorders.   A diagnosis of major or mild vascular NCD is inappropriate if the symptoms can be entirely attributed to delirium, although delirium may sometimes be superimposed on a preexisting major or mild vascular NCD, in which case both diagnoses can be made. If the criteria for major depressive disorder are met and the cognitive impairment is temporally related to the likely onset of the depression, major or mild vascular NCD should not be diagnosed. However, if the NCD preceded the development of the depression, or the severity of the cognitive impairment is out of proportion to the severity of the depression, both should be diagnosed.

Comorbidity

Major or mild NCD due to Alzheimer's disease commonly co-occurs with major or mild vascular NCD, in which case both diagnoses should be made. Major or mild vascular NCD and depression frequently co-occur.

Major or Mild Neurocognitive Disorder Due to Traumatic Brain Injury

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. There is evidence of a traumatic brain injury—that is, an impact to the head or other mechanisms of rapid movement or displacement of the brain within the skull, with one or more of the following:

   1. Loss of consciousness.
   2. Posttraumatic amnesia.
   3. Disorientation and confusion.
   4. Neurological signs (e.g., neuroimaging demonstrating injury; a new onset of seizures; a marked worsening of a preexisting seizure disorder; visual field cuts; anosmia; hemiparesis).

C. The neurocognitive disorder presents immediately after the occurrence of the traumatic brain injury or immediately after recovery of consciousness and persists past the acute post-injury period.

Coding note: For major neurocognitive disorder due to traumatic brain injury, with behavioral disturbance: For ICD-9-CM, first code **907.0** late effect of intracranial injury without skull fracture, followed by **294.11** major neurocognitive disorder due to traumatic brain injury, with behavioral disturbance. For ICD-10-CM, first code **S06.2X9S** diffuse traumatic brain injury with loss of consciousness of unspecified duration, sequela; followed by **F02.81** major neurocognitive disorder due to traumatic brain injury, with behavioral disturbance.

For major neurocognitive disorder due to traumatic brain injury, without behavioral disturbance: For ICD-9-CM, first code **907.0** late effect of intracranial injury without skull fracture, followed by **294.10** major neurocognitive disorder due to traumatic brain injury, without behavioral disturbance. For ICD-10-CM, first code **S06.2X9S** diffuse traumatic brain injury with loss of consciousness of unspecified duration, sequela; followed by **F02.80** major neurocognitive disorder due to traumatic brain injury, without behavioral disturbance.

For mild neurocognitive disorder due to traumatic brain injury, code **331.83 (G31.84).** (**Note:** Do *not* use the additional code for traumatic brain injury. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Specifiers

Rate the severity of the neurocognitive disorder (NCD), not the underlying traumatic brain injury (see the section "Development and Course" for this disorder).

Diagnostic Features

Major or mild NCD due to traumatic brain injury (TBI) is caused by an impact to the head, or other mechanisms of rapid movement or displacement of the brain within the skull, as can happen with blast injuries. *Traumatic brain injury* is defined as brain trauma with specific characteristics that include at least one of the following: loss of consciousness, posttraumatic amnesia, disorientation and confusion, or, in more severe cases, neurological signs (e.g., positive neuroimaging, a new onset of seizures or a marked worsening of a pre-existing seizure disorder, visual field cuts, anosmia, hemiparesis) (Criterion B). To be attributable to TBI, the NCD must present either immediately after the brain injury occurs or immediately after the individual recovers consciousness after the injury and persist past the acute post-injury period (Criterion C).

The cognitive presentation is variable. Difficulties in the domains of complex attention, executive ability, learning, and memory are common as well as slowing in speed of information processing and disturbances in social cognition. In more severe TBI in which there is brain contusion, intracranial hemorrhage, or penetrating injury, there may be additional neurocognitive deficits, such as aphasia, neglect, and constructional dyspraxia.

Associated Features Supporting Diagnosis

Major or mild NCD due to TBI may be accompanied by disturbances in emotional function (e.g., irritability, easy frustration, tension and anxiety, affective lability); personality changes (e.g., disinhibition, apathy, suspiciousness, aggression); physical disturbances (e.g., headache, fatigue, sleep disorders, vertigo or dizziness, tinnitus or hyperacusis, photosensitivity, anosmia, reduced tolerance to psychotropic medications); and, particularly in more severe TBI, neurological symptoms and signs (e.g., seizures, hemiparesis, visual disturbances, cranial nerve deficits) and evidence of orthopedic injuries.

Prevalence

In the United States, 1.7 million TBIs occur annually, resulting in 1.4 million emergency department visits, 275,000 hospitalizations, and 52,000 deaths. About 2% of the population lives with TBI-associated disability. Males account for 59% of TBIs in the United States. The most common etiologies of TBI in the United States are falls, vehicular accidents, and being struck on the head. Collisions and blows to the head that occur in the course of contact sports are increasingly recognized as sources of mild TBI, with a concern that repeated mild TBI may have cumulatively persisting sequelae.

Development and Course

The severity of a TBI is rated at the time of injury/initial assessment as mild, moderate, or severe according to the thresholds in Table 2.

The severity rating of the TBI itself does not necessarily correspond to the severity of the resulting NCD. The course of recovery from TBI is variable, depending not only on the specifics of the injury but also on cofactors, such as age, prior history of brain damage, or substance abuse, that may favor or impede recovery.

TABLE 2   Severity ratings for traumatic brain injury

Injury characteristic	Mild TBI	Moderate TBI	Severe TBI
Loss of consciousness	<30 min	30 minutes–24 hours	>24 hours
Posttraumatic amnesia	<24 hours	24 hours–7 days	>7 days
Disorientation and confusion at initial assessment (Glasgow Coma Scale Score)	13–15 (not below 13 at 30 minutes)	9–12	3–8

Neurobehavioral symptoms tend to be most severe in the immediate aftermath of the TBI. Except in the case of severe TBI, the typical course is that of complete or substantial improvement in associated neurocognitive, neurological, and psychiatric symptoms and signs. Neurocognitive symptoms associated with mild TBI tend to resolve within days to weeks after the injury with complete resolution typical by 3 months. Other symptoms that may potentially co-occur with the neurological symptoms (e.g., depression, irritability, fatigue, headache, photosensitivity, sleep disturbance) also tend to resolve in the weeks following mild TBI. Substantial subsequent deterioration in these areas should trigger consideration of additional diagnoses. However, repeated mild TBI may be associated with persisting neurocognitive disturbance.

With moderate and severe TBI, in addition to persistence of neurocognitive deficits, there may be associated neurophysiological, emotional, and behavioral complications. These include seizures (particularly in the first year), photosensitivity, hyperacusis, irritability, aggression, depression, sleep disturbance, fatigue, apathy, inability to resume occupational and social functioning at pre-injury level, and deterioration in interpersonal relationships. Moderate and severe TBI have been associated with increased risk of depression, aggression, and possibly neurodegenerative diseases such as Alzheimer's disease.

The features of persisting major or mild NCD due to TBI will vary by age, specifics of the injury, and cofactors. Persisting TBI-related impairment in an infant or child may be reflected in delays in reaching developmental milestones (e.g., language acquisition), worse academic performance, and possibly impaired social development. Among older teenagers and adults, persisting symptoms may include various neurocognitive deficits, irritability, hypersensitivity to light and sound, easy fatigability, and mood changes, including depression, anxiety, hostility, or apathy. In older individuals with depleted cognitive reserve, mild TBI is more likely to result in incomplete recoveries.

Risk and Prognostic Factors

Risk factors for traumatic brain injury.   Traumatic brain injury rates vary by age, with the highest prevalence among individuals younger than 4 years, older adolescents, and individuals older than 65 years. Falls are the most common cause of TBI, with motor vehicle accidents being second. Sports concussions are frequent causes of TBI in older children, teenagers, and young adults.

Risk factors for neurocognitive disorder after traumatic brain injury.   Repeated concussions can lead to persistent NCD and neuropathological evidence of traumatic encephalopathy. Co-occurring intoxication with a substance may increase the severity of a TBI from a motor vehicle accident, but whether intoxication at the time of injury worsens neurocognitive outcome is unknown.

Course modifiers.   Mild TBI generally resolves within a few weeks to months, although resolution may be delayed or incomplete in the context of repeated TBI. Worse outcome from

moderate to severe TBI is associated with older age (older than 40 years) and initial clinical parameters, such as low Glasgow Coma Scale score; worse motor function; pupillary nonreactivity; and computed tomography (CT) evidence of brain injury (e.g., petechial hemorrhages, subarachnoid hemorrhage, midline shift, obliteration of third ventricle).

Diagnostic Markers

Beyond neuropsychological testing, CT scanning may reveal petechial hemorrhages, subarachnoid hemorrhage, or evidence of contusion. Magnetic resonance image scanning may also reveal hyperintensities suggestive of microhemorrhages.

Functional Consequences of Major or Mild Neurocognitive Disorder Due to Traumatic Brain Injury

With mild NCD due to TBI, individuals may report reduced cognitive efficiency, difficulty concentrating, and lessened ability to perform usual activities. With major NCD due to TBI, an individual may have difficulty in independent living and self-care. Prominent neuromotor features, such as severe incoordination, ataxia, and motor slowing, may be present in major NCD due to TBI and may add to functional difficulties. Individuals with TBI histories report more depressive symptoms, and these can amplify cognitive complaints and worsen functional outcome. Additionally, loss of emotional control, including aggressive or inappropriate affect and apathy, may be present after more severe TBI with greater neurocognitive impairment. These features may compound difficulties with independent living and self-care.

Differential Diagnosis

In some instances, severity of neurocognitive symptoms may appear to be inconsistent with the severity of the TBI. After previously undetected neurological complications (e.g., chronic hematoma) are excluded, the possibility of diagnoses such as somatic symptom disorder or factitious disorder need to be considered. Posttraumatic stress disorder (PTSD) can co-occur with the NCD and have overlapping symptoms (e.g., difficulty concentrating, depressed mood, aggressive behavioral disinhibition).

Comorbidity

Among individuals with substance use disorders, the neurocognitive effects of the substance contribute to or compound the TBI-associated neurocognitive change. Some symptoms associated with TBI may overlap with symptoms found in cases of PTSD, and the two disorders may co-occur, especially in military populations.

Substance/Medication-Induced Major or Mild Neurocognitive Disorder

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. The neurocognitive impairments do not occur exclusively during the course of a delirium and persist beyond the usual duration of intoxication and acute withdrawal.

C. The involved substance or medication and duration and extent of use are capable of producing the neurocognitive impairment.

D. The temporal course of the neurocognitive deficits is consistent with the timing of substance or medication use and abstinence (e.g., the deficits remain stable or improve after a period of abstinence).

E. The neurocognitive disorder is not attributable to another medical condition or is not better explained by another mental disorder.

Coding note: The ICD-9-CM and ICD-10-CM codes for the [specific substance/medication]-induced neurocognitive disorders are indicated in the table below. Note that the ICD-10-CM code depends on whether or not there is a comorbid substance use disorder present for the same class of substance. If a mild substance use disorder is comorbid with the substance-induced neurocognitive disorder, the 4th position character is "1," and the clinician should record "mild [substance] use disorder" before the substance-induced neurocognitive disorder (e.g., "mild inhalant use disorder with inhalant-induced major neurocognitive disorder"). If a moderate or severe substance use disorder is comorbid with the substance-induced neurocognitive disorder, the 4th position character is "2," and the clinician should record "moderate [substance] use disorder" or "severe [substance] use disorder," depending on the severity of the comorbid substance use disorder. If there is no comorbid substance use disorder, then the 4th position character is "9," and the clinician should record only the substance-induced neurocognitive disorder. For some classes of substances (i.e., alcohol; sedatives, hypnotics, anxiolytics), it is not permissible to code a comorbid mild substance use disorder with a substance-induced neurocognitive disorder; only a comorbid moderate or severe substance use disorder, or no substance use disorder, can be diagnosed. Behavioral disturbance cannot be coded but should still be indicated in writing.

		ICD-10-CM		
	ICD-9-CM	With use disorder, mild	With use disorder, moderate or severe	Without use disorder
Alcohol (major neurocognitive disorder), nonamnestic-confabulatory type	291.2	NA	F10.27	F10.97
Alcohol (major neurocognitive disorder), amnestic-confabulatory type	291.1	NA	F10.26	F10.96
Alcohol (mild neurocognitive disorder)	291.89	NA	F10.288	F10.988
Inhalant (major neurocognitive disorder)	292.82	F18.17	F18.27	F18.97
Inhalant (mild neurocognitive disorder)	292.89	F18.188	F18.288	F18.988
Sedative, hypnotic, or anxiolytic (major neurocognitive disorder)	292.82	NA	F13.27	F13.97
Sedative, hypnotic, or anxiolytic (mild neurocognitive disorder)	292.89	NA	F13.288	F13.988
Other (or unknown) substance (major neurocognitive disorder)	292.82	F19.17	F19.27	F19.97
Other (or unknown) substance (mild neurocognitive disorder)	292.89	F19.188	F19.288	F19.988

Specify if:

Persistent: Neurocognitive impairment continues to be significant after an extended period of abstinence.

Recording Procedures

ICD-9-CM.   The name of the substance/medication-induced neurocognitive disorder begins with the specific substance/medication (e.g., alcohol) that is presumed to be causing the neurocognitive symptoms. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class. For substances that do not fit into any of the classes, the code for "other substance" should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category "unknown substance" should be used.

The name of the disorder (i.e., [specific substance]-induced major neurocognitive disorder or [specific substance]-induced mild neurocognitive disorder) is followed by the type in the case of alcohol (i.e., nonamnestic-confabulatory type, amnestic-confabulatory type), followed by specification of duration (i.e., persistent). Unlike the recording procedures for ICD-10-CM, which combine the substance/medication-induced disorder and substance use disorder into a single code, for ICD-9-CM a separate diagnostic code is given for the substance use disorder. For example, in the case of persistent amnestic-confabulatory symptoms in a man with a severe alcohol use disorder, the diagnosis is 291.1 alcohol-induced major neurocognitive disorder, amnestic-confabulatory type, persistent. An additional diagnosis of 303.90 severe alcohol use disorder is also given. If the substance/medication-induced neurocognitive disorder occurs without a comorbid substance use disorder (e.g., after a sporadic heavy use of inhalants), no accompanying substance use disorder is noted (e.g., 292.82 inhalant-induced mild neurocognitive disorder).

ICD-10-CM.   The name of the substance/medication-induced neurocognitive disorder begins with the specific substance (e.g., alcohol) that is presumed to be causing the neurocognitive symptoms. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class and presence or absence of a comorbid substance use disorder. For substances that do not fit into any of the classes, the code for "other substance" should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category "unknown substance" should be used.

When recording the name of the disorder, the comorbid substance use disorder (if any) is listed first, followed by the word "with," followed by the name of the disorder (i.e., [specific substance]-induced major neurocognitive disorder or [specific substance]-induced mild neurocognitive disorder), followed by the type in the case of alcohol (i.e., nonamnestic-confabulatory type, amnestic-confabulatory type), followed by specification of duration (i.e., persistent). For example, in the case of persistent amnestic-confabulatory symptoms in a man with a severe alcohol use disorder, the diagnosis is F10.26 severe alcohol use disorder with alcohol-induced major neurocognitive disorder, amnestic-confabulatory type, persistent. A separate diagnosis of the comorbid severe alcohol use disorder is not given. If the substance-induced neurocognitive disorder occurs without a comorbid substance use disorder (e.g., after a sporadic heavy use of inhalants), no accompanying substance use disorder is noted (e.g., F18.988 inhalant-induced mild neurocognitive disorder).

Diagnostic Features

Substance/medication-induced major or mild NCD is characterized by neurocognitive impairments that persist beyond the usual duration of intoxication and acute withdrawal (Criterion B). Initially, these manifestations can reflect slow recovery of brain functions from a period of prolonged substance use, and improvements in neurocognitive as well as

brain imaging indicators may be seen over many months. If the disorder continues for an extended period, *persistent* should be specified. The given substance and its use must be known to be capable of causing the observed impairments (Criterion C). While nonspecific decrements in a range of cognitive abilities can occur with nearly any substance of abuse and a variety of medications, some patterns occur more frequently with selected drug classes. For example, NCD due to sedative, hypnotic, or anxiolytic drugs (e.g., benzodiaz-epines, barbiturates) may show greater disturbances in memory than in other cognitive functions. NCD induced by alcohol frequently manifests with a combination of impair-ments in executive-function and memory and learning domains. The temporal course of the substance-induced NCD must be consistent with that of use of the given substance (Criterion D). In alcohol-induced amnestic confabulatory (Korsakoff's) NCD, the features include prominent amnesia (severe difficulty learning new information with rapid forget-ting) and a tendency to confabulate. These manifestations may co-occur with signs of thi-amine encephalopathy (Wernicke's encephalopathy) with associated features such as nystagmus and ataxia. Ophthalmoplegia of Wernicke's encephalopathy is typically charac-terized by a lateral gaze paralysis.

In addition to or independent of the more common neurocognitive symptoms related to methamphetamine use (e.g., difficulties with learning and memory; executive func-tion), methamphetamine use can also be associated with evidence of vascular injury (e.g., focal weakness, unilateral incoordination, asymmetrical reflexes). The most common neu-rocognitive profile approximates that seen in vascular NCD.

Associated Features Supporting Diagnosis

Intermediate-duration NCD induced by drugs with central nervous system depressant effects may manifest with added symptoms of increased irritability, anxiety, sleep disturbance, and dysphoria. Intermediate-duration NCD induced by stimulant drugs may manifest with re-bound depression, hypersomnia, and apathy. In severe forms of substance/medication-induced major NCD (e.g., associated with long-term alcohol use), there may be prominent neuromotor features, such as incoordination, ataxia, and motor slowing. There may also be loss of emotional control, including aggressive or inappropriate affect, or apathy.

Prevalence

The prevalence of these conditions is not known. Prevalence figures for substance abuse are available, and substance/medication-induced major or mild NCDs are more likely in those who are older, have longer use, and have other risk factors such as nutritional deficits.

For alcohol abuse, the rate of mild NCD of intermediate duration is approximately 30%–40% in the first 2 months of abstinence. Mild NCD may persist, particularly in those who do not achieve stable abstinence until after age 50 years. Major NCD is rare and may result from concomitant nutritional deficits, as in alcohol-induced amnestic confabulatory NCD.

For individuals quitting cocaine, methamphetamine, opioids, phencyclidine, and sed-ative, hypnotics, or anxiolytics, substance/medication-induced mild NCD of intermediate duration may occur in one-third or more, and there is some evidence that these substances may also be associated with persistent mild NCD. Major NCD associated with these sub-stances is rare, if it occurs at all. In the case of methamphetamine, cerebrovascular disease can also occur, resulting in diffuse or focal brain injury that can be of mild or major neu-rocognitive levels. Solvent exposure has been linked to both major and mild NCD of both intermediate and persistent duration.

The presence of NCD induced by cannabis and various hallucinogens is controversial. With cannabis, intoxication is accompanied by various neurocognitive disturbances, but these tend to clear with abstinence.

Development and Course

Substance use disorders tend to commence during adolescence and peak in the 20s and 30s. Although longer history of severe substance use disorder is associated with greater likelihood of NCD, the relationships are not straightforward, with substantial and even complete recovery of neurocognitive functions being common among individuals who achieve stable abstinence prior to age 50 years. Substance/medication-induced major or mild NCD is most likely to become persistent in individuals who continue abuse of substances past age 50 years, presumably because of a combination of lessened neural plasticity and beginnings of other age-related brain changes. Earlier commencement of abuse, particularly of alcohol, may lead to defects in later neural development (e.g., later stages of maturation of frontal circuitries), which may have effects on social cognition as well as other neurocognitive abilities. For alcohol-induced NCD, there may be an additive effect of aging and alcohol-induced brain injury.

Risk and Prognostic Factors

Risk factors for substance/medication-induced NCDs include older age, longer use, and persistent use past age 50 years. In addition, for alcohol-induced NCD, long-term nutritional deficiencies, liver disease, vascular risk factors, and cardiovascular and cerebrovascular disease may contribute to risk.

Diagnostic Markers

Magnetic resonance imaging (MRI) of individuals with chronic alcohol abuse frequently reveals cortical thinning, white matter loss, and enlargement of sulci and ventricles. While neuroimaging abnormalities are more common in those with NCDs, it is possible to observe NCDs without neuroimaging abnormalities, and vice versa. Specialized techniques (e.g., diffusion tensor imaging) may reveal damage to specific white matter tracts. Magnetic resonance spectroscopy may reveal reduction in *N*-acetylaspartate, and increase in markers of inflammation (e.g., myoinositol) or white matter injury (e.g., choline). Many of these brain imaging changes and neurocognitive manifestations reverse following successful abstinence. In individuals with methamphetamine use disorder, MRI may also reveal hyperintensities suggestive of microhemorrhages or larger areas of infarction.

Functional Consequences of Substance/Medication-Induced Major or Mild Neurocognitive Disorder

The functional consequences of substance/medication-induced mild NCD are sometimes augmented by reduced cognitive efficiency and difficulty concentrating beyond that seen in many other NCDs. In addition, at both major and mild levels, substance/medication-induced NCDs may have associated motor syndromes that increase the level of functional impairment.

Differential Diagnosis

Individuals with substance use disorders, substance intoxication, and substance withdrawal are at increased risk for other conditions that may independently, or through a compounding effect, result in neurocognitive disturbance. These include history of traumatic brain injury and infections that can accompany substance use disorder (e.g., HIV, hepatitis C virus, syphilis). Therefore, presence of substance/medication-induced major or mild NCD should be differentiated from NCDs arising outside the context of substance use, intoxication, and withdrawal, including these accompanying conditions (e.g., traumatic brain injury).

Comorbidity

Substance use disorders, substance intoxication, and substance withdrawal are highly co-morbid with other mental disorders. Comorbid posttraumatic stress disorder, psychotic disorders, depressive and bipolar disorders, and neurodevelopmental disorders can contribute to neurocognitive impairment in substance users. Traumatic brain injury occurs more frequently with substance use, complicating efforts to determine the etiology of NCD in such cases. Severe, long-term alcohol use disorder can be associated with major organ system disease, including cerebrovascular disease and cirrhosis. Amphetamine-induced NCD may be accompanied by major or mild vascular NCD, also secondary to amphetamine use.

Major or Mild Neurocognitive Disorder Due to HIV Infection

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. There is documented infection with human immunodeficiency virus (HIV).

C. The neurocognitive disorder is not better explained by non-HIV conditions, including secondary brain diseases such as progressive multifocal leukoencephalopathy or cryptococcal meningitis.

D. The neurocognitive disorder is not attributable to another medical condition and is not better explained by a mental disorder.

Coding note: For major neurocognitive disorder due to HIV infection, with behavioral disturbance, code first **042 (B20)** HIV infection, followed by **294.11 (F02.81)** major neurocognitive disorder due to HIV infection, with behavioral disturbance. For major neurocognitive disorder due to HIV infection, without behavioral disturbance, code first **042 (B20)** HIV infection, followed by **294.10 (F02.80)** major neurocognitive disorder due to HIV infection, without behavioral disturbance.

For mild neurocognitive disorder due to HIV infection, code **331.83 (G31.84).** (**Note:** Do *not* use the additional code for HIV infection. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Diagnostic Features

HIV disease is caused by infection with human immunodeficiency virus type-1 (HIV-1), which is acquired through exposure to bodily fluids of an infected person through injection drug use, unprotected sexual contact, or accidental or iatrogenic exposure (e.g., contaminated blood supply, needle puncture injury to medical personnel). HIV infects several types of cells, most particularly immune cells. Over time, the infection can cause severe depletion of "T-helper" (CD4) lymphocytes, resulting in severe immunocompromise, often leading to opportunistic infections and neoplasms. This advanced form of HIV infection is termed *acquired immune deficiency syndrome* (AIDS). Diagnosis of HIV is confirmed by established laboratory methods such as enzyme-linked immunosorbent assay for HIV antibody with Western blot confirmation and/or polymerase chain reaction–based assays for HIV.

Some individuals with HIV infection develop an NCD, which generally shows a "sub-cortical pattern" with prominently impaired executive function, slowing of processing speed, problems with more demanding attentional tasks, and difficulty in learning new information, but fewer problems with recall of learned information. In major NCD, slowing may be prominent. Language difficulties, such as aphasia, are uncommon, although reductions in fluency may be observed. HIV pathogenic processes can affect any part of the brain; therefore, other patterns are possible.

Associated Features Supporting Diagnosis

Major or mild NCD due to HIV infection is usually more prevalent in individuals with prior episodes of severe immunosuppression, high viral loads in the cerebrospinal fluid, and indicators of advanced HIV disease such as anemia and hypoalbuminemia. Individuals with advanced NCD may experience prominent neuromotor features such as severe incoordination, ataxia, and motor slowing. There may be loss of emotional control, including aggressive or inappropriate affect or apathy.

Prevalence

Depending on stage of HIV disease, approximately one-third to over one-half of HIV-infected individuals have at least mild neurocognitive disturbance, but some of these disturbances may not meet the full criteria for mild NCD. An estimated 25% of individuals with HIV will have signs and symptoms that meet criteria for mild NCD, and in fewer than 5% would criteria for major NCD be met.

Development and Course

An NCD due to HIV infection can resolve, improve, slowly worsen, or have a fluctuating course. Rapid progression to profound neurocognitive impairment is uncommon in the context of currently available combination antiviral treatment; consequently, an abrupt change in mental status in an individual with HIV may prompt an evaluation of other medical sources for the cognitive change, including secondary infections. Because HIV infection preferentially affects subcortical regions over the course of illness, including deep white matter, the progression of the disorder follows a "subcortical" pattern. Since HIV can affect a variety of brain regions, and the illness can take on many different trajectories depending on associated comorbidities and consequences of HIV, the overall course of an NCD due to HIV infection has considerable heterogeneity. A subcortical neurocognitive profile may interact with age over the life course, when psychomotor slowing and motor impairments such as slowed gait may occur as a consequence of other age-related conditions so that the overall progression may appear more pronounced in later life.

In developed countries, HIV disease is primarily a condition of adults, with acquisition via risky behaviors (e.g., unprotected sex, injection drug use) beginning in late adolescence and peaking during young and middle adulthood. In developing countries, particularly sub-Saharan Africa, where HIV testing and antiretroviral treatments for pregnant women are not readily available, perinatal transmission is common. The NCD in such infants and children may present primarily as neurodevelopmental delay. As individuals treated for HIV survive into older age, additive and interactive neurocognitive effects of HIV and aging, including other NCDs (e.g., due to Alzheimer's disease, due to Parkinson's disease), are possible.

Risk and Prognostic Factors

Risk and prognostic factors for HIV infection. Risk factors for HIV infection include injection drug use, unprotected sex, and unprotected blood supply and other iatrogenic factors.

Risk and prognostic factors for major or mild neurocognitive disorder due to HIV infection. Paradoxically, NCD due to HIV infection has not declined significantly with the advent of combined antiretroviral therapy, although the most severe presentations (consistent with the diagnosis of major NCD) have decreased sharply. Contributory factors may include inadequate control of HIV in the central nervous system (CNS), the evolution of drug-resistant viral strains, the effects of chronic long-term systemic and brain inflammation, and the effects of comorbid factors such as aging, drug abuse, past history of CNS trauma, and co-infections, such as with the hepatitis C virus. Chronic exposure to antiretroviral drugs also raises the possibility of neurotoxicity, although this has not been definitively established.

Diagnostic Markers

Serum HIV testing is required for the diagnosis. In addition, HIV characterization of the cerebrospinal fluid may be helpful if it reveals a disproportionately high viral load in cerebrospinal fluid versus in the plasma. Neuroimaging (i.e., magnetic resonance imaging [MRI]) may reveal reduction in total brain volume, cortical thinning, reduction in white matter volume, and patchy areas of abnormal white matter (hyperintensities). MRI or lumbar puncture may be helpful to exclude a specific medical condition such as cryptococcus infection or herpes encephalitis that may contribute to CNS changes in the context of AIDS. Specialized techniques such as diffusion tensor imaging may reveal damage to specific white matter tracts.

Functional Consequences of Major or Mild Neurocognitive Disorder Due to HIV Infection

Functional consequences of major or mild NCD due to HIV infection are variable across individuals. Thus, impaired executive abilities and slowed information processing may substantially interfere with the complex disease management decisions required for adherence to the combined antiretroviral therapy regimen. The likelihood of comorbid disease may further create functional challenges.

Differential Diagnosis

In the presence of comorbidities, such as other infections (e.g., hepatitis C virus, syphilis), drug abuse (e.g., methamphetamine abuse), or prior head injury or neurodevelopmental conditions, major or mild NCD due to HIV infection can be diagnosed provided there is evidence that infection with HIV has worsened any NCDs due to such preexisting or comorbid conditions. Among older adults, onset of neurocognitive decline related to cerebrovascular disease or neurodegeneration (e.g., major or mild NCD due to Alzheimer's disease) may need to be differentiated. In general, stable, fluctuating (without progression) or improving neurocognitive status would favor an HIV etiology, whereas steady or stepwise deterioration would suggest neurodegenerative or vascular etiology. Because more severe immunodeficiency can result in opportunistic infections of the brain (e.g., toxoplasmosis; cryptococcosis) and neoplasia (e.g., CNS lymphoma), sudden onset of an NCD or sudden worsening of that disorder demands active investigation of non-HIV etiologies.

Comorbidity

HIV disease is accompanied by chronic systemic and neuro-inflammation that can be associated with cerebrovascular disease and metabolic syndrome. These complications can be part of the pathogenesis of major or mild NCD due to HIV infection. HIV frequently co-occurs with conditions such as substance use disorders when the substance has been injected and other sexually transmitted disorders.

Major or Mild Neurocognitive Disorder Due to Prion Disease

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.
B. There is insidious onset, and rapid progression of impairment is common.
C. There are motor features of prion disease, such as myoclonus or ataxia, or biomarker evidence.

D. The neurocognitive disorder is not attributable to another medical condition and is not better explained by another mental disorder.

Coding note: For major neurocognitive disorder due to prion disease, with behavioral disturbance, code first **046.79 (A81.9)** prion disease, followed by **294.11 (F02.81)** major neurocognitive disorder due to prion disease, with behavioral disturbance. For major neurocognitive disorder due to prion disease, without behavioral disturbance, code first **046.79 (A81.9)** prion disease, followed by **294.10 (F02.80)** major neurocognitive disorder due to prion disease, without behavioral disturbance.

For mild neurocognitive disorder due to prion disease, code **331.83 (G31.84).** (**Note:** Do *not* use the additional code for prion disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Diagnostic Features

The classification of major or mild neurocognitive disorder (NCD) due to prion disease includes NCDs due to a group of subacute spongiform encephalopathies (including Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, kuru, Gerstmann-Sträussler-Scheinker syndrome, and fatal insomnia) caused by transmissible agents known as *prions.* The most common type is sporadic Creutzfeldt-Jakob disease, typically referred to as Creutzfeldt-Jakob disease (CJD). Variant CJD is much rarer and is associated with transmission of bovine spongiform encephalopathy, also called "mad cow disease." Typically, individuals with CJD present with neurocognitive deficits, ataxia, and abnormal movements such as myoclonus, chorea, or dystonia; a startle reflex is also common. Typically, the history reveals rapid progression to major NCD over as little as 6 months, and thus the disorder is typically seen only at the major level. However, many individuals with the disorder may have atypical presentations, and the disease can be confirmed only by biopsy or at autopsy. Individuals with variant CJD may present with a greater preponderance of psychiatric symptoms, characterized a by low mood, withdrawal, and anxiety. Prion disease is typically not diagnosed without at least one of the characteristic biomarker features: recognized lesions on magnetic resonance imaging with DWI (diffusion-weighted imaging) or FLAIR (fluid-attenuated inversion recovery), tau or 14-3-3 protein in cerebrospinal fluid, characteristic triphasic waves on electroencephalogram, or, for rare familial forms, family history or genetic testing.

Prevalence

The annual incidence of sporadic CJD is approximately one or two cases per million people. Prevalence is unknown but very low given the short survival.

Development and Course

Prion disease may develop at any age in adults—the peak age for the sporadic CJD is approximately 67 years—although it has been reported to occur in individuals spanning the teenage years to late life. Prodromal symptoms of prion disease may include fatigue, anxiety, problems with appetite or sleeping, or difficulties with concentration. After several weeks, these symptoms may be followed by incoordination, altered vision, or abnormal gait or other movements that may be myoclonic, choreoathetoid, or ballistic, along with a rapidly progressive dementia. The disease typically progresses very rapidly to the major level of impairment over several months. More rarely, it can progress over 2 years and appear similar in its course to other NCDs.

Risk Factors and Prognosis

Environmental.   Cross-species transmission of prion infections, with agents that are closely related to the human form, has been demonstrated (e.g., the outbreak of bovine spongiform encephalopathy inducing variant CJD in the United Kingdom during the mid-1990s). Transmission by corneal transplantation and by human growth factor injection has been documented, and anecdotal cases of transmission to health care workers have been reported.

Genetic and physiological.   There is a genetic component in up to 15% of cases, associated with an autosomal dominant mutation.

Diagnostic Markers

Prion disease can be definitively confirmed only by biopsy or at autopsy. Although there are no distinctive findings on cerebrospinal fluid analysis across the prion diseases, reliable biomarkers are being developed and include 14-3-3 protein (particularly for sporadic CJD) as well as tau protein. Magnetic resonance brain imaging is currently considered the most sensitive diagnostic test when DWI is performed, with the most common finding being multifocal gray matter hyperintensities in subcortical and cortical regions. In some individuals, the electroencephalogram reveals periodic sharp, often triphasic and synchronous discharges at a rate of 0.5–2 Hz at some point during the course of the disorder.

Differential Diagnosis

Other major neurocognitive disorders.   Major NCD due to prion disease may appear similar in its course to other NCDs, but prion diseases are typically distinguished by their rapid progression and prominent cerebellar and motor symptoms.

Major or Mild Neurocognitive Disorder Due to Parkinson's Disease

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.
B. The disturbance occurs in the setting of established Parkinson's disease.
C. There is insidious onset and gradual progression of impairment.
D. The neurocognitive disorder is not attributable to another medical condition and is not better explained by another mental disorder.

Major or mild neurocognitive disorder probably due to Parkinson's disease should be diagnosed if 1 and 2 are both met. **Major or mild neurocognitive disorder possibly due to Parkinson's disease** should be diagnosed if 1 or 2 is met:

1. There is no evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).
2. The Parkinson's disease clearly precedes the onset of the neurocognitive disorder.

Coding note: For major neurocognitive disorder probably due to Parkinson's disease, with behavioral disturbance, code first **332.0 (G20)** Parkinson's disease, followed by **294.11 (F02.81)** major neurocognitive disorder probably due to Parkinson's disease, with behavioral disturbance. For major neurocognitive disorder probably due to Parkinson's disease, without behavioral disturbance, code first **332.0 (G20)** Parkinson's disease, fol-

lowed by **294.10 (F02.80)** major neurocognitive disorder probably due to Parkinson's disease, without behavioral disturbance.

For major neurocognitive disorder possibly due to Parkinson's disease, code **331.9 (G31.9)** major neurocognitive disorder possibly due to Parkinson's disease. (**Note:** Do *not* use the additional code for Parkinson's disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

For mild neurocognitive disorder due to Parkinson's disease, code **331.83 (G31.84).** (**Note:** Do *not* use the additional code for Parkinson's disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Diagnostic Features

The essential feature of major or mild neurocognitive disorder (NCD) due to Parkinson's disease is cognitive decline following the onset of Parkinson's disease. The disturbance must occur in the setting of established Parkinson's disease (Criterion B), and deficits must have developed gradually (Criterion C). The NCD is viewed as *probably* due to Parkinson's disease when there is no evidence of another disorder that might be contributing to the cognitive decline *and* when the Parkinson's disease clearly precedes onset of the NCD. The NCD is considered *possibly* due to Parkinson's disease *either* when there is no evidence of another disorder that might be contributing to the cognitive decline *or* when the Parkinson's disease precedes onset of the NCD, but not both.

Associated Features Supporting Diagnosis

Frequently present features include apathy, depressed mood, anxious mood, hallucinations, delusions, personality changes, rapid eye movement sleep behavior disorder, and excessive daytime sleepiness.

Prevalence

The prevalence of Parkinson's disease in the United States steadily increases with age from approximately 0.5% between ages 65 and 69 to 3% at age 85 years and older. Parkinson's disease is more common in males than in females. Among individuals with Parkinson's disease, as many as 75% will develop a major NCD sometime in the course of their disease. The prevalence of mild NCD in Parkinson's disease has been estimated at 27%.

Development and Course

Onset of Parkinson's disease is typically between the sixth and ninth decades of life, with most expression in the early 60s. Mild NCD often develops relatively early in the course of Parkinson's disease, whereas major impairment typically does not occur until late.

Risk and Prognostic Factors

Environmental.   Risk factors for Parkinson's disease include exposure to herbicides and pesticides.

Genetic and physiological.   Potential risk factors for NCD among individuals with Parkinson's disease include older age at disease onset and increasing duration of disease.

Diagnostic Markers

Neuropsychological testing, with a focus on tests that do not rely on motor function, is critical in detecting the core cognitive deficits, particularly at the mild NCD phase. Structural neuroimaging and dopamine transporter scans, such as DaT scans, may differentiate Lewy body–related dementias (Parkinson's and dementia with Lewy bodies) from non–

Lewy body–related dementias (e.g., Alzheimer's disease) and can sometimes be helpful in the evaluation of major or mild NCD due to Parkinson's disease.

Differential Diagnosis

Major or mild neurocognitive disorder with Lewy bodies.   This distinction is based substantially on the timing and sequence of motor and cognitive symptoms. For NCD to be attributed to Parkinson's disease, the motor and other symptoms of Parkinson's disease must be present well before (by convention, at least 1 year prior) cognitive decline has reached the level of major NCD, whereas in major or mild NCD with Lewy bodies, cognitive symptoms begin shortly before, or concurrent with, motor symptoms. For mild NCD, the timing is harder to establish because the diagnosis itself is less clear and the two disorders exist on a continuum. Unless Parkinson's disease has been established for some time prior to the onset of cognitive decline, or typical features of major or mild NCD with Lewy bodies are present, it is preferable to diagnose unspecified mild NCD.

Major or mild neurocognitive disorder due to Alzheimer's disease.   The motor features are the key to distinguishing major or mild NCD due to Parkinson's disease from major or mild NCD due to Alzheimer's disease. However, the two disorders can co-occur.

Major or mild vascular neurocognitive disorder.   Major or mild vascular NCD may present with parkinsonian features such as psychomotor slowing that may occur as a consequence of subcortical small vessel disease. However, the parkinsonian features typically are not sufficient for a diagnosis of Parkinson's disease, and the course of the NCD usually has a clear association with cerebrovascular changes.

Neurocognitive disorder due to another medical condition (e.g., neurodegenerative disorders).   When a diagnosis of major or mild NCD due to Parkinson's disease is being considered, the distinction must also be made from other brain disorders, such as progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, tumors, and hydrocephalus.

Neuroleptic-induced parkinsonism.   Neuroleptic-induced parkinsonism can occur in individuals with other NCDs, particularly when dopamine-blocking drugs are prescribed for the behavioral manifestations of such disorders

Other medical conditions.   Delirium and NCDs due to side effects of dopamine-blocking drugs and other medical conditions (e.g., sedation or impaired cognition, severe hypothyroidism, B_{12} deficiency) must also be ruled out.

Comorbidity

Parkinson's disease may coexist with Alzheimer's disease and cerebrovascular disease, especially in older individuals. The compounding of multiple pathological features may diminish the functional abilities of individuals with Parkinson's disease. Motor symptoms and frequent co-occurrence of depression or apathy can make functional impairment worse.

Major or Mild Neurocognitive Disorder Due to Huntington's Disease

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.
B. There is insidious onset and gradual progression.
C. There is clinically established Huntington's disease, or risk for Huntington's disease based on family history or genetic testing.

D. The neurocognitive disorder is not attributable to another medical condition and is not better explained by another mental disorder.

Coding note: For major neurocognitive disorder due to Huntington's disease, with behavioral disturbance, code first **333.4 (G10)** Huntington's disease, followed by **294.11 (F02.81)** major neurocognitive disorder due to Huntington's disease, with behavioral disturbance. For major neurocognitive disorder due to Huntington's disease, without behavioral disturbance, code first **333.4 (G10)** Huntington's disease, followed by **294.10 (F02.80)** major neurocognitive disorder due to Huntington's disease, without behavioral disturbance.

For mild neurocognitive disorder due to Huntington's disease, code **331.83 (G31.84)**. (**Note:** Do *not* use the additional code for Huntington's disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Diagnostic Features

Progressive cognitive impairment is a core feature of Huntington's disease, with early changes in executive function (i.e., processing speed, organization, and planning) rather than learning and memory. Cognitive and associated behavioral changes often precede the emergence of the typical motor abnormalities of bradykinesia (i.e., slowing of voluntary movement) and chorea (i.e., involuntary jerking movements). A diagnosis of definite Huntington's disease is given in the presence of unequivocal, extrapyramidal motor abnormalities in an individual with either a family history of Huntington's disease or genetic testing showing a CAG trinucleotide repeat expansion in the HTT gene, located on chromosome 4.

Associated Features Supporting Diagnosis

Depression, irritability, anxiety, obsessive-compulsive symptoms, and apathy are frequently, and psychosis more rarely, associated with Huntington's disease and often precede the onset of motor symptoms.

Prevalence

Neurocognitive deficits are an eventual outcome of Huntington's disease; the worldwide prevalence is estimated to be 2.7 per 100,000. The prevalence of Huntington's disease in North America, Europe, and Australia is 5.7 per 100,000, with a much lower prevalence of 0.40 per 100,000 in Asia.

Development and Course

The average age at diagnosis of Huntington's disease is approximately 40 years, although this varies widely. Age at onset is inversely correlated with CAG expansion length. Juvenile Huntington's disease (onset before age 20) may present more commonly with bradykinesia, dystonia, and rigidity than with the choreic movements characteristic of the adult-onset disorder. The disease is gradually progressive, with median survival approximately 15 years after motor symptom diagnosis.

Phenotypic expression of Huntington's disease varies by presence of motor, cognitive, and psychiatric symptoms. Psychiatric and cognitive abnormalities can predate the motor abnormality by at least 15 years. Initial symptoms requiring care often include irritabity, anxiety, or depressed mood. Other behavioral disturbances may include pronounced apathy, disinhibition, impulsivity, and impaired insight, with apathy often becoming more progressive over time. Early movement symptoms may involve the appearance of fidgetiness of the extremities as well as mild *apraxia* (i.e., difficulty with purposeful movements), particularly with fine motor tasks. As the disorder progresses, other motor problems include impaired gait (*ataxia*) and postural instability. Motor impairment eventually affects speech production (*dysarthria*) such that the speech becomes very difficult to understand,

which may result in significant distress resulting from the communication barrier in the context of comparatively intact cognition. Advanced motor disease severely affects gait with progressive ataxia. Eventually individuals become nonambulatory. End-stage motor disease impairs motor control of eating and swallowing, typically a major contributor to the death of the individual from aspiration pneumonia.

Risk and Prognostic Factors

Genetic and physiological.   The genetic basis of Huntington's disease is a fully penetrant autosomal dominant expansion of the CAG trincleotide, often called a *CAG repeat* in the huntingtin gene. A repeat length of 36 or more is invariably associated with Huntington's disease, with longer repeat lengths associated with early age at onset. A CAG repeat length of 36 or more is invariably associated with Huntington's disease.

Diagnostic Markers

Genetic testing is the primary laboratory test for the determination of Huntington's disease, which is an autosomal dominant disorder with complete penetrance. The trinucleotide CAG is observed to have a repeat expansion in the gene that encodes huntingtin protein on chromosome 4. A diagnosis of Huntington's disease is not made in the presence of the gene expansion alone, but the diagnosis is made only after symptoms become manifest. Some individuals with a positive family history request genetic testing in a presymptomatic stage. Associated features may also include neuroimaging changes; volume loss in the basal ganglia, particularly the caudate nucleus and putamen, is well known to occur and progresses over the course of illness. Other structural and functional changes have been observed in brain imaging but remain research measures.

Functional Consequences of Major or Mild Neurocognitive Disorder Due to Huntington's Disease

In the prodromal phase of illness and at early diagnosis, occupational decline is most common, with most individuals reporting some loss of ability to engage in their typical work. The emotional, behavioral, and cognitive aspects of Huntington's disease, such as disinhibition and personality changes, are highly associated with functional decline. Cognitive deficits that contribute most to functional decline may include speed of processing, initiation, and attention rather than memory impairment. Given that Huntington's disease onset occurs in productive years of life, it may have a very disruptive effect on performance in the work setting as well as social and family life. As the disease progresses, disability from problems such as impaired gait, dysarthria, and impulsive or irritable behaviors may substantially add to the level of impairment and daily care needs, over and above the care needs attributable to the cognitive decline. Severe choreic movements may substantially interfere with provision of care such as bathing, dressing, and toileting.

Differential Diagnosis

Other mental disorders.   Early symptoms of Huntington's disease may include instability of mood, irritability, or compulsive behaviors that may suggest another mental disorder. However, genetic testing or the development of motor symptoms will distinguish the presence of Huntington's disease.

Other neurocognitive disorders.   The early symptoms of Huntington's disease, particularly symptoms of executive dysfunction and impaired psychomotor speed, may resemble other neurocognitive disorders (NCDs), such as major or mild vascular NCD.