

FACULTY GUIDE

Core Module 1:

Overview of Mild Cognitive Impairment and Dementia for an Interprofessional Team

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Slide 1:

- This first module is an introduction to information about mild cognitive impairment (MCI) and the four most common types of dementia—notably: (1) Alzheimer’s disease (AD), (2) vascular dementia (VaD), (3) Lewy body dementia (LBD)—which encompasses dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD), and (4) frontotemporal degeneration (FTD), also known as frontotemporal disorder, frontotemporal dementia, and frontotemporal lobar degeneration (FTLD). Together, these are known as Alzheimer’s Disease and Related Dementias, or ADRD.
- In the ensuing 15 modules, we will cover a wide range of topics about dementia in greater detail, from the perspective of an interprofessional team approach. In this module, we begin by identifying dementia-related changes, as distinguished from those of mild cognitive impairment and normal aging, and potentially modifiable risk factors that may influence expression and progression of dementia-related impairments.

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- These are the topics we will address in this initial module. We begin with a brief review of “normal” aging to better understand and recognize signs and symptoms suggestive of mild cognitive impairment or dementia. We then examine the range of symptoms associated with mild cognitive impairment and dementia, in general, before discussing each of the most common types of Alzheimer’s disease and related dementias, or ADRD.

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- Our goal, by the time we finish with this module, is for you to learn four sets of items. You will be able to:
 - Recognize cognitive, functional, and behavioral changes that distinguish normal aging from mild cognitive impairment and dementia.
 - List the most common types of dementia.
 - Identify the incidence and prevalence of Alzheimer’s disease (AD), along with common risk factors, signs and symptoms, and rate of progression. We will also cover these topics for the other forms of dementia.
 - Identify the three stages of dementia.

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- Most forms of dementia comes on slowly and may be preceded by mild cognitive impairment, or MCI. MCI does not include functional losses.
- While Alzheimer’s disease is the most common type of dementia, it is not the only type. Other types of dementia may manifest with different behaviors, but the non-pharmacological management is basically the same.
- Diagnosis of dementia requires impairment in two or more core cognitive functions.
- Dementia of Alzheimer’s disease has been described as progressing through three stages: early or mild stage, middle or moderate stage, and late-stage or severe dementia.

- Diagnosis is predominantly made by a primary care provider (PCP), neuropsychologist, geriatrician, or neurologist.
- Not all memory issues are indicative of Alzheimer's disease or another type of dementia.

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- We begin with an examination of the factors that are considered when comparing normal aging with dementia.

Slide 8:

- Normal aging brings about changes in the way we function across many domains— physical, cognitive, sensory, language, behavioral and psychological, to name a few.
- Sometimes changes in these domains fall outside what would be considered age-appropriate or normal. Dementia is one of the many possible causes for these changes to occur.
- We are going to start by briefly reviewing each of these domains. Then we will examine how they change with “normal” aging—followed by how they manifest in persons living with dementia.

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- In general, cognitive abilities encompass memory, perception, and executive function—including intellectual thinking, judgment, and reasoning.
- Numerous factors can interfere with cognitive functioning or can lead to a decline of cognitive abilities—including both age and dementia. Typically, fluidity and speed show a slight and gradual decrease over time, whereas crystallized knowledge and wisdom remain stable or improve with age.
- However, cognitive decline can also be attributed to medical and psychological concerns. Heart disease, hypertension, diabetes, and various psychological conditions, such as depression and stress, may be risk factors for cognitive decline. Some medical conditions, including substance use and abuse, delirium, hypothyroidism, dehydration, human immunodeficiency virus (HIV) and autoimmune deficiency syndrome (AIDS), and poor nutrition and vitamin deficiencies (especially vitamin B12), can be associated with cognitive or memory impairment. Medications and medication side effects can also interfere with memory and cognitive functioning.

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- “Executive functions” refer to a group of higher-level cognitive skills that are required to control and coordinate other cognitive abilities and behaviors. Impairments in executive function have been linked to damage to the frontal lobe, as well as to cortical and subcortical structures linking to the frontal lobes—such as the prefrontal cortex, basal ganglia, and thalamus.
- Executive function has been generally separated into organization and regulation:
 - Organization involves the ability to plan and organize, manage time appropriately, be able to sequence a task, and pay attention. It requires cognitive flexibility and working memory.
 - Regulation refers to self-control, emotional regulation, moral reasoning, and decision-making.

- Impairments to executive functioning can result in socially inappropriate behavior, an inability to multitask, and difficulty planning and organizing tasks. The person with impaired executive functions may not be able to understand abstract concepts and cannot process, store or retrieve information. They lose fine motor skills—grasping, writing with a pen, as compared with gross motor skills such as running or kicking a ball. The person may be described as “moody” or emotional, disinhibited, and often apathetic. However, the person with executive function impairments may not be aware that his or her behavior or emotions are problematic.

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- There are many different types of memory, and different models attempt to explain how human memory works.
- Our focus is not on those various models but instead on two general types of memory:
 - Short-term, or working, memory, lasts less than 1 minute. Working memory involves remembering a person’s name after being introduced for the first time, or remembering someone’s address or phone number when they give it to you.
 - In contrast, memories can be stored for the long term—to be recalled throughout one’s lifetime.
 - Often, persons have an easier time recalling an event from childhood (long-term memory) but not why they walked into the kitchen (short-term memory).
- As we will discuss throughout these modules, aging, dementia, and other conditions differentially affect memory retention and loss.

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- Activities of daily living (ADL) refer to functional self-care activities we perform every day.
- ADL are separated into basic ADL and instrumental ADL (IADL).
 - Basic activities of daily living include bathing, eating, dressing, grooming, toileting, and transferring. An inability to perform basic ADL is typically associated with physical disabilities or more severe cognitive impairments.
 - Instrumental activities of daily living require greater executive functioning than ADL. Examples of IADL include being able to manage one’s finances, handle transportation (driving or navigating public transit), shop, prepare meals, use the telephone and other communication devices, manage medications, and do housework and basic home maintenance. Persons retain the ability to perform IADL, although, as a result of aging, it may take them longer than when they were younger.

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- An important consequence of the aging of the American population is the significant increase in the number of older persons with some form of dementia. Perhaps two of the greatest challenges are (1) to distinguish normal aging from mild cognitive impairment and/or a neurodegenerative disorder and (2) to provide appropriate care and guidance to the persons diagnosed with dementia and their care partner or partners.

- Major factors that help distinguish normal aging from a neurodegenerative disorder include the type and extent of cognitive impairments, memory loss, impairments in executive functioning (particularly in the ability to focus and pay attention and in the ability to reason and solve problems), and sensory impairments of one or more of the five senses.
- In normal aging, the body and brain gradually slow down, but intelligence remains stable. Our bodies have less physical flexibility and less mental flexibility, and it takes longer for us to process information.
- As we will be discussing shortly, mild cognitive impairment (or MCI) represents a condition in between normal aging and dementia in which persons have notable problems with memory or other core brain functions, but these impairments are not sufficient to interfere with daily life. MCI is not always a precursor to dementia.
- Dementia encompasses a range of neurodegenerative brain disorders. Persons living with dementia have severe enough mental decline so as to interfere with daily life.
- Finally, these changes can lead to functional impairments in basic or instrumental activities of daily living.
- It is important to note that an aging individual who self-reports memory loss does not necessarily have dementia. Instead, the person may be experiencing slower processing capabilities associated with normal aging or impairments caused by any of a variety of treatable conditions. Similarly, although visual impairments may also be associated with a neurodegenerative disorder, they are common among older individuals.
- As we review these aspects, it is important to remember that a diagnosis of dementia involves impairment in core mental functions that result in a loss of function.

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- Typically, normal aging is characterized by:
 - A general slowing of cognitive performance (Older adults typically perform worse than younger adults on tasks of attention and episodic and working memory, but better on tests of general knowledge than younger persons.)
 - A decrease in mental flexibility
 - Some difficulties finding the right word
- Aging does not appear to negatively influence verbal fluency.
- Older people retain their verbal abilities, including vocabulary, but may take longer to remember a name or word. There may be difficulties retrieving the word, but the information is not lost.
 - A mild decrease in short-term or working memory
 - However, recall of past events or long-term memory remains intact.
- Memory is intact for current events. Older persons can name our current president or discuss a recent major current event. They might express more concern to their family physician about forgetting names or words than to their family or friends—but if they were to undergo formal

neurocognitive testing, they would demonstrate performance within normal ranges. There do not appear to be substantial differences in long-term memory between persons with normal aging versus pathological aging, at least during the early stages of dementia.

- Changes in perceptual systems or speed of processing associated with normal aging can influence cognitive processes such as attention and memory. This has been associated with changes in the areas of the brain that are activated for these tasks in older versus younger persons.

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- In addition, people retain independence in both basic and instrumental activities of daily living as they age. Excluding physical limitations (such as osteoarthritis or other comorbidities that limit physical capacity), they don't require assistance bathing and toileting; they can continue managing their finances and preparing meals, although it might take a little longer. In comparison to normal aging, persons living with dementia demonstrate challenges with performing instrumental activities of daily living; in fact, an inability to manage finances may be one of the earlier IADL changes suggestive of dementia.

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- As we age, it becomes more difficult to see and hear with the same clarity we had in our younger years. Impairments in vision, speech, and hearing are common in normal aging. Conditions such as cataracts, glaucoma, and age-related macular degeneration are all more common as we age.
- Age-related declines in both auditory processes and cognitive abilities may influence processing abilities to facilitate comprehension and memory for spoken language. Impaired speech may result from loss of peripheral hearing, as well as central deficits of auditory processing.
- Aging also leads to substantial changes in visual perception. As with auditory changes, the mechanisms underlying the gradual deterioration of visual perception remain unclear.
- Normal aging also leads to impaired sensitivity to taste and smells. Olfactory impairments are common in Alzheimer's disease and may precede onset of cognitive and memory deficits.

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- Dementia is not part of the normal aging process.
- Dementia is a general term; it encompasses a variety of neurodegenerative diseases and conditions that cause progressive cognitive and behavioral impairments affecting activities of daily living.
- Some conditions that cause symptoms of dementia—such as vitamin deficiencies, thyroid problems, or medication side effects—are treatable and reversible.
- It is caused by damage to brain cells. The type of dementia and symptoms depend on which regions of the brain are damaged.
- People can have mixed dementia, which involves symptoms of two or more types of dementia at the same time. Mixed dementia can be very difficult to diagnose without autopsy.

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- Estimates of dementia prevalence in the United States vary by age group, and year.
 - Recent research indicates a global prevalence of all-cause dementia at between 5 and 7 percent among adults ages 60 and older.
 - Estimates from the Aging, Demographics, and Memory Study, or ADAMS, estimated the prevalence of dementia at 13.9 percent in people ages 71 and older, increasing from 5 percent, at ages 71 to 79, to 37.4 percent, among those ages 90 and older.

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- Emerging evidence indicates a possible decline in dementia prevalence worldwide, likely attributed to improvements in the primary prevention of causes such as stroke.
- Survival after a diagnosis of dementia also depends on age at diagnosis. Data from the Health Improvement Network in the United Kingdom found median survival of persons living with dementia diagnosed between ages 60 and 69 was 6.7 years, but only 1.9 years for persons diagnosed at ages 90 and older. Mortality rates were highest in the first year after diagnosis for all.

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- We will discuss the current diagnostic criteria of specific Alzheimer's disease and related dementias in detail in Module 2.
- Let us first define dementia as a “significant deterioration in two or more areas of cognitive function that is severe enough to interfere with a person’s ability to perform everyday activities”.
- According to the National Institute of Neurological Disorders and Stroke, or NINDS, and the National Institute on Aging, or NIA, for a person to be considered to have dementia, the person must meet the following criteria:
 - Two or more core mental functions must be impaired.
 - Memory
 - Language skills
 - Visual perception
 - Ability to focus and pay attention
 - Ability to reason and solve problems
 - The loss of brain function is severe enough that a person has difficulty performing normal everyday tasks, including basic and instrumental activities of daily living.

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- Not all memory issues are indicative of Alzheimer's disease or another type of dementia. We might not be able to recall information as quickly due to changes associated with natural aging—for example, we might not recall a person’s name when we see them, but the name may pop into our heads later that day.

- Not every type of dementia manifests initially with memory impairment, and the type and severity of memory impairment can differ by type of dementia. For some types, memory impairment may not manifest until middle-stage disease.
- The type of memory affected depends on the location of the brain cell damage.
- Initial memory impairment occurs in short-term/working memory and semantic memory.
- Long-term memory is often retained until late-stage dementia.

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- Visuoperceptual and other sensory impairments may result from normal aging and/or from progressive damage to the brain.
- Normal aging typically leads to mild problems with depth perception, visual acuity, loss of peripheral vision, and difficulty adapting to changes in light levels.
- Specific dementias can damage the visual system. Each type of dementia can affect visuoperceptual abilities differently, depending on how the type of dementia damages the brain.
- There can be:
 - Visuoperceptual difficulties (including visual hallucinations)
- As we will discuss, this may be one of the initial symptoms of dementia with Lewy bodies.
 - Auditory problems (and hallucinations)
 - Changes in taste (seen in frontotemporal degeneration)
 - Changes in smell

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- At some point during the course of their dementia, persons living with dementia lose their ability to perform activities of daily living, or ADLs. Typically, during the early stage, the cognitive impairments and impairments in executive functioning lead to difficulties performing instrumental ADLs (among other problems), and the person with dementia requires assistance balancing a checkbook, preparing a meal, making a shopping list. As the dementia progresses, there are increasing functional impairments until (often) late-stage dementia, when the person requires full-time assistance to perform basic ADL.
- Impairments in functional abilities are key components of a diagnosis of dementia.

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- We will cover behavioral and psychological symptoms of dementia, or BPSD, in detail in Modules 5, 6, and 7, but for now, let's introduce the topic.
- A serious consequence of dementia involves behavioral and psychological symptoms of dementia. While care partners and potential patients are initially concerned with memory impairment and impairments with instrumental activities of daily living, as the dementia progresses it is often BPSD that become particularly concerning.

- These symptoms appear at different stages in different types of dementia. In addition, not all persons manifest them.
 - Mood disorders, particularly apathy, depression, and dysphoria
 - Sleep disorders, such as insomnia (e.g., hypersomnia, circadian rhythm disorders) and obstructive sleep apnea
 - Psychiatric symptoms, particularly delusions and hallucinations
 - Agitation, along with aggression and anxiety

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- Mild cognitive impairment is becoming one of the most common clinical manifestations of the elderly, although we do not yet understand the underlying pathology.
- MCI is an umbrella term for conditions usually marked by problems with memory, language, judgment, and thinking that are greater than those expected for the age of the person, but less than those required to meet the criteria for a diagnosis of dementia. It is believed to represent an intermediate stage between the normal decline of aging and the more serious decline associated with dementia. The person with MCI can still carry out everyday activities

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- Not all mild cognitive impairment progresses to dementia; some people will revert to normal cognition. In addition, not all MCI that progresses to dementia leads to Alzheimer's disease. In some cases, it progresses to a different type of dementia.
 - For example, evidence suggests a different cognitive profile of MCI associated with progression to Alzheimer's disease versus MCI progressing to Lewy body dementia.
- MCI is characterized by mild but measurable changes in thinking abilities as shown on cognitive screening or formal neuropsychiatric testing, and symptoms may be noticeable to the person's family and friends.
- However, a Cochrane review concluded that evidence demonstrates that the Mini Mental State Examination, or MMSE, which is a 30-question assessment frequently used to measure cognitive impairment, cannot identify those MCI patients who are most likely to progress to dementia (Arevalo-Rodriguez et al., 2016). We will discuss the MMSE in detail in Module 2.
- The most common form of mild cognitive impairment is amnestic MCI, or aMCI, in which memory is the primary problem; about 50 percent of persons with aMCI will progress to dementia within 5 years. MCI can also occur in other non-memory cognitive domains—language, visuospatial, or frontal executive functions such as organizing, planning, and multitasking.
- From a clinical perspective, MCI is most likely to be first detected in primary care among primary care providers and clinicians with adequate training to notice the symptoms. However, the symptoms may be overlooked or minimized. There is no treatment for MCI.
- Often, the care partner might note functional deficits—such as those involving instrumental activities of daily living, (Brown et al., 2011), or the person might complain of memory impairments.

- Having fewer chronic medical conditions and younger age predict reversion from MCI back to normal cognition. This is considered rare.
- It is believed that MCI progresses to dementia at a rate of approximately 10 to 20 percent a year among people ages 65 and older.

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- Data from the Mayo Clinic Study of Aging identified a number of variables that may be predictive of progression from cognitively normal to mild cognitive impairment in men and women. Lower education, self-reported memory concerns, diabetes, and a history of stroke, atrial fibrillation, and/or alcohol problems increases the risk for both men and women; being a current smoker, and having midlife dyslipidemia or hypertension increases the risk in women, whereas having a maximum adult body mass index of 30 kg/m² or more and being either never married or widowed appears predictive for men. Clinicians may be able to use this information to identify persons with these risk factors who might benefit from more extensive diagnostic testing.
- There are some modifiable predictors, or risk or prognostic factors, associated with MCI—including diabetes, prediabetes, metabolic syndrome, hypertension, hyperlipidemia, low dietary folate, chronic alcohol abuse, and possibly chronic renal failure.
- Treating some of these factors—such as low dietary folate—could potentially decrease the incidence of MCI conversion to dementia, although treating the others does not appear to prevent MCI.
- Data from the Mayo Clinic Study of Aging reported that 50 percent of persons with mild cognitive impairment had non-psychotic symptoms, compared with 25 percent of cognitively normal adults. In particular, persons with MCI were more likely to have apathy, agitation, anxiety, irritability, and depression than were cognitively normal persons.
- Neuropsychiatric symptoms—including depression, anxiety, apathy, sleep disorders, and agitation—may increase the risk of conversion from MCI to dementia. However, many untrained primary care professionals overlook these symptoms, as they are common and not specific to dementia. Because of this, we will discuss these behaviors and psychological symptoms of dementia in ensuing Modules 5, 6, and 7.
- Psychosis in MCI is more likely associated with severe frontal lobe symptoms than with AD, although it can occur in both. However, MCI patients usually only display agitated behavior that is not physically aggressive.

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- Depressive symptoms are common in persons with mild cognitive impairment, affecting up to two-thirds of persons with MCI.
- Depressive symptoms may hasten conversion from MCI to Alzheimer's disease.
- A history of depression—and even of early-onset depression (which in this case was defined as depression that began before age 60)—increases the risk of developing Alzheimer's disease.

- Depression with MCI appears to double the risk of development of Alzheimer's disease. Even subsyndromal depressive symptoms (or symptoms that are not sufficient to meet the clinical diagnosis of depression) are significantly associated with subsequent cognitive decline.
- Recent study findings suggest that effective management of depression may be a possible intervention target for MCI and possibly dementia.

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- While Alzheimer's disease is the most common type of dementia, it is not the only type.
- Other forms of dementia may have similar manifestations as those associated with Alzheimer's disease—cognitive impairment, memory loss, behavioral manifestations. There might be other manifestations, such as delusions or hallucinations that are not typically associated with Alzheimer's disease.
- We are going to examine the types of dementia that fall under the category of Alzheimer's disease and related dementias: Alzheimer's disease; vascular dementia; the Lewy body dementias, which include both Parkinson's disease dementia and dementia with Lewy bodies; and frontotemporal degeneration.

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- Alzheimer's disease is the most common cause of dementia in people over age 65 and accounts for 60 to 80 percent of cases.
- Estimates indicate that approximately 5 million Americans are affected by Alzheimer's disease, with approximately 200,000 to 250,000 people affected who are under the age of 65. The aging of the population is likely to cause a doubling of the number of people with Alzheimer's disease by the year 2050
- Starting at age 65, a person's risk of developing Alzheimer's disease doubles every 5 years
- By 85+ years and older, will have signs of AD.

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- The typical age of Alzheimer's disease onset is 65 and older; people diagnosed at a younger age are considered to have early-onset Alzheimer's disease.
- Early-onset dementia, or EOD, is considered when dementia onset occurs in people aged 30 to 65. (We discuss this in more detail in Module 2.)
- However, there is disagreement regarding the upper age limit for early-onset cases. It remains a gray area because more and more people are being correctly diagnosed at earlier ages due to education and awareness efforts. These differences have important consequences when considering prevalence and incidence of EOD, or for the individual who is facing an earlier retirement and higher costs of care for a longer duration. This distinction is less relevant for our purposes, as the management and issues will be the same with using either age limit.
- Up to 5 percent of cases of Alzheimer's disease are early-onset. Some cases of early-onset dementia have no known cause, and many cases are inherited, called familial Alzheimer's disease, or FAD.

- As we will discuss shortly, three known genetic mutations are associated with EOD: amyloid precursor protein, presenilin 1, and presenilin 2 (Nicolas et al., 2015).

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- The etiology of Alzheimer's disease is not yet known. Different hypotheses have been proposed for inherited forms associated with specific genetic mutations.
- Many "risk" factors have been associated with non-inherited forms of Alzheimer's disease:
 - Advancing age: The prevalence of AD increases from 1 to 2 percent at age 65 to 15 percent at age 75 and 25–50 percent by age 85.
 - Cardiovascular and metabolic syndrome risk factors include many modifiable factors, such as physical inactivity, hyperlipidemia (particularly during midlife), hypertension, diabetes, smoking, and obesity.
 - Diabetes has been identified as a risk factor for mild cognitive impairment and an accelerated progression to AD, but it may slow functional decline in patients who already have mild AD.
 - Heart failure may contribute to the development of AD as a result of reduced cerebral blood flow and dysfunction of the neurovascular unit, but it is likely that several other mechanisms are also involved.
 - Head trauma—particularly a traumatic brain injury, or TBI, within 10 years—is another risk factor. TBI also predicts a faster rate of progression of functional decline.

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- Having a family history with a first-degree relative affected increases the risk of late-onset Alzheimer's disease, which is further increased with each additional first-degree relative.
- Having specific apolipoprotein E (APOE) gene mutations increases the risk of Alzheimer's disease.
- A number of specific genetic mutations have been identified and linked with early-onset Alzheimer's disease.
- Approximately 5 percent of cases of Alzheimer's disease are caused by three known genetic mutations involving the gene for amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) proteins

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- People who inherit any of these genetic mutations are at high risk of developing Alzheimer's disease, usually with an earlier onset.
- There is a significant association between general fluid cognitive function and four genes associated with AD: TOMM40 (translocase of outer mitochondrial membrane 40 homolog), APOE, ABCG1 (ATP-binding cassette sub-family G member 1), and MEF2C (myocyte-specific enhancer factor 2C, also known as MADS box transcription enhance factor 2, polypeptide C).

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- Major hypotheses linking changes in the brains of Alzheimer's disease patients with disease symptoms include these:
 - The cholinergic hypothesis stems from autopsy findings of degeneration of cholinergic neurons of the basal forebrain and a decline in cholinergic markers in the cerebral cortex of brains from AD patients.
 - In the amyloid hypothesis, abnormal processing of amyloid precursor protein is believed to trigger neurodegeneration in AD, and inflammation in the vicinity of beta-amyloid (or AB)-plaques leads to the death of nearby neurons.
 - Finally, the tau hypothesis is predicated on an accumulation of hyperphosphorylated tau along with, or interacting with, neurofibrillary tangles leading to neuronal dysfunction and death.
- Although AB plaques have a key role in the pathogenesis of Alzheimer's disease, the severity of cognitive impairment is associated more with the burden of neocortical neurofibrillary tangles.

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- As we will discuss later in Modules 2 and 4, genetic testing is not generally recommended outside of clinical trials or unless there is a specific indication for it.
- There are three common forms of apolipoprotein, or APOE: ε2, ε3, and ε4.
- APOE ε3 is the most common allele and apparently has a neutral role; it neither decreases nor increases the risk of Alzheimer's disease.

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- APOE ε4 is primarily responsible for transporting cholesterol and lipids in the blood, and it may play a role in amyloid clearance.
- The APOE ε4 allele has been shown to increase the risk for late-onset Alzheimer's disease and age-related cognitive decline, and Lewy body dementia, or LBD.
 - According to the National Human Genome Research Institute (2013), a person who inherits the *APOE4* allele from only one parent has a threefold increase in load risk, whereas a person that inherits *APOE4* from both parents is 10 times more likely to develop Alzheimer's disease.
 - A recent study of nearly 350 healthy adults found that having a parental family history of AD along with the APOE4 allele was associated with microstructural white matter differences believed to be precursors to AD.
 - People with mixed Alzheimer's disease and Lewy body dementia—and we will discuss LBD in upcoming slides—have a different clinical phenotype versus persons with only AD.
 - APOE status also appears to influence the effect of depression on Alzheimer's disease. Specifically, a recent study found that recent depression (within 10 years of the onset of dementia) was strongly associated with a dementia diagnosis regardless of APOE status,

whereas depression from more than 10 years earlier was only a risk factor for persons who were APOE ε4 carriers.

- Data from the Baltimore Longitudinal Study on Aging found that having only one ε4 allele increases all-cause mortality by about 77 percent compared with non-carriers.

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- In contrast, one of the largest studies on this topic determined the APOE ε2 genotype is associated with delaying the onset of Alzheimer's disease and Lewy body dementia—and potentially delaying LBD by up to 4 years. The ε2 allele also protects against functional decline in amnestic mild cognitive impairment and Alzheimer's disease.

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- A diagnosis of Alzheimer's disease is predominantly made by the primary care provider, neuropsychologist, a geriatrician, or a neurologist and is based on the person's physical and neurological examinations, medical and family history, psychiatric history, and history of cognitive and behavioral changes.
- In some cases, the person may need to be referred to a neuropsychologist for more specific cognitive testing or to a neurologist for a brain MRI or head CT scan.
- Often a diagnosis requires input—or substantiation and additional information—from the person's family or a close friend, also often referred to as an "informant."
- Although clinical research criteria include cerebrospinal fluid biomarkers for a diagnosis, they are not usually included in clinical practice and used primarily in the research setting. In addition, current biomarkers can only differentiate between persons with AD and healthy people; they cannot distinguish between the different types of dementias.
- We will discuss in detail the diagnostic criteria revised in 2011 by NIA and the Alzheimer's Association, as well as changes to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), in Module 2.

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- After 27 years, in 2011, the National Institute on Aging published new clinical diagnostic criteria for Alzheimer's disease, including research guidelines for earlier stages of the disease. The hypothetical model proposed by Jack and colleagues divides Alzheimer's disease into three phases, beginning with a preclinical, presymptomatic phase in which individuals are cognitively normal but some have AD pathological changes. They note an emerging body of evidence that indicates the pathophysiological process underlying Alzheimer's disease begins years before any diagnostic symptoms—such as cognitive impairment—first appear, possibly up to 20 years earlier.
 - There is also some evidence that cognitive performance begins to decline before the onset of clinical symptoms that are suggestive of mild cognitive impairment. These changes may be apparent as early as 6½ years before MCI. Currently, the conceptual framework of a "preclinical phase" is purely for research purposes and has no practical clinical use.

- A second, prodromal phase of mild cognitive impairment involves early symptoms that do not (yet) meet the criteria for dementia. Not all persons with MCI will develop Alzheimer's disease. Persons with MCI do not necessarily progress to dementia.
- The third and final phase is Alzheimer's disease dementia, defined as impairments in multiple domains that are severe enough to produce loss of function.

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- A person who has met the criteria for a diagnosis of dementia of Alzheimer's disease (also known clinically as Alzheimer's disease)—notably, impairments in multiple domains that are severe enough to produce loss of function—will progress through three stages with increasing degrees of impairment: mild, moderate, and severe (or end-stage) dementia.
- There are no diagnostic tests to indicate progression from one stage to the next.
- People generally progress through the stages at a gradual rate, although each person progresses at his or her own rate based on a wide range of variables.
- The value of understanding the stages is that the person's medical, social, and global needs change based on his or her deteriorating capabilities as he or she progresses through the stages. (We will discuss this further in Modules 5 through 7.)
 - Early-stage or mild Alzheimer's disease is characterized by very mild cognitive decline that is sufficient to cause functional impairments. (We will discuss this in detail in Module 5.)
 - Middle-stage or moderate Alzheimer's disease is characterized by more moderate cognitive decline, along with behavioral and other psychological symptoms. Persons in this stage have noticeable impairments apparent to others outside of their immediate friends and family. (We will describe this in Module 6.)
 - Late-stage, or severe, Alzheimer's disease, is characterized by significant impairments in cognitive and functional abilities. (End-stage dementia is covered in Module 12.)

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- Alzheimer's disease is a progressive dementia, with increasing impairments as the neurodegeneration increases. The rate of progression varies from patient to patient.
 - People in early-stage disease remain independent, although their symptoms are apparent and begin to interfere with their ability to perform instrumental activities of daily living. With advancing dementia, impairments become more challenging to the person and care partners, and the person has increasing functional impairments. Motor skills remain intact until late-stage disease.
 - The specific manifestations are discussed in detail in Modules 5, 6, 7, and 12.
- Alzheimer's disease is the 6th leading cause of all deaths in the United States and the 5th leading cause of death for people ages 65 and older.
 - Studies suggest that persons with Alzheimer's disease who are over age 80 live as few as 3 to 4 years after diagnosis, but younger people may live as long as 10 or more years.

- In 2013, more than 84,000 Americans died from Alzheimer's (the cause of death listed on their death certificate was "Alzheimer's disease"), but another 700,000 are expected to die WITH Alzheimer's. In other words, these people will die of other causes such as consequences of diabetes, other pre-existing medical conditions, or conditions likely associated with Alzheimer's disease (such as pneumonia), but their listed cause of death will not be Alzheimer's disease.

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- Vascular dementia is another common form of dementia, considered by some to be second after Alzheimer's disease.
- Vascular dementia results from a blockage or reduction in blood flow to the brain—usually from a stroke or a series of strokes—that deprives brain cells of oxygen and nutrients, damaging the cortex of brain, which is the area associated with learning, memory, and language.
 - Subcortical vascular dementia is characterized by:
 - Severe stenosis and occlusion of small vessels that lead to white matter ischemia and multiple lacunar infarctions in subcortical structures
 - Relatively slow progression of symptoms
 - Clinical manifestations associated with cholinergic deficits—very similar to Alzheimer's disease
 - Stroke-related vascular dementia is caused by series of small strokes—mini/silent strokes or transient ischemic attacks. As increasing areas are damaged, symptoms of vascular dementia appear. Multi-infarct dementia usually affects men more than women, in ages 60 to 75.
 - Autopsy results show a majority of persons living with dementia (PLwD) over age 80 likely had mixed dementia—with aspects of both Alzheimer's disease and vascular dementia.
 - A recently published article based on more than 30 years of surveillance of participants in the Framingham Heart Study reported that the rates of dementia, and particularly vascular dementia, have steadily decreased over the past 4 decades, apparently attributable to declining rates of heart disease—but only among persons with at least a high school diploma. The study also found a decreasing prevalence of most vascular risk factors—except for diabetes and obesity. The authors noted decreasing rates of the risk of dementia from stroke, atrial fibrillation, and heart failure. In addition, over the course of the study, people were diagnosed with dementia at later ages, increasing from age 80 to age 85. However, the investigators noted that the number of persons living with dementia is anticipated to increase over the next decades as the number of older people increases.

Slide 54:

- Numerous medical factors have been associated with increased risk of vascular dementia.
- Although it isn't technically a "medical" factor, advancing age increases the risk of vascular disease as well as vascular dementia.

- A wide range of cardiovascular diseases have been linked with vascular dementia, including, but not limited to, atherosclerosis, hyperlipidemia, atrial fibrillation, coronary artery disease, peripheral arterial disease, and low cardiac output.
- Diabetes mellitus, hyperglycemia, insulin resistance, and metabolic syndrome have been linked with dementia and cognitive impairments.
 - Recent research notes ethnic differences in the prevalence of diabetes and other geriatric conditions that may influence the risk of vascular disorders and thus vascular dementia.
- Cerebrovascular disease, small vessel disease, systemic lupus erythematosus, temporal arteritis, and brain hemorrhage have also been associated with vascular dementia, as have chronic kidney disease and amyloid angiopathy.
- A prior stroke or heart attack is each independently associated with an increased risk of Alzheimer's disease and vascular cognitive impairment, or VCI, suggesting the need for a cognitive assessment in all post-stroke and post-myocardial infarction patients.

Slide 55:

- Approximately 50 percent of persons with vascular dementia have hypertension.
- Early treatment of hypertension can reduce risk of VaD and slow progression.
- Modifiable risk factors that have been associated with an increased risk of vascular dementia include:
 - Obesity
 - Smoking
 - Lack of physical activity or exercise
 - Lack of social support
 - A “heart-unhealthy” diet, which can be modified by prescribing a beneficial diet: foods with possible protective benefits, including antioxidants, fish oil, vitamin D, B-complex vitamins, Mediterranean diet, and moderate alcohol consumption

Slide 56:

- The manifestations of vascular dementia are diverse and related to the areas of the brain that have been affected.
- It can be very difficult to identify symptoms of vascular dementia versus Alzheimer's disease unless there is evidence that the symptoms were directly and temporally related to vascular brain damage. Consequently, persons with vascular dementia may have similar manifestations as those with Alzheimer's disease.
 - However, on neuropsychological screening, persons with Alzheimer's disease are usually amnestic (can repeat but not learn or encode new information, so they have poor recall and recognition), whereas persons with classic subcortical vascular dementia can learn over repeated trials, with effort, and store encoded information. They have trouble freely recalling, but they can recognize the content they have learned when given options.
- There are cortical and subcortical syndromes:

- Cortical VaD symptoms vary by original stroke location.
- Subcortical VaD manifests with focal motor signs, gait disturbance, personality/mood changes, and cognitive syndrome with mild memory deficits, psychomotor retardation, and abnormal executive function.
- People who have a prolonged period of transient ischemic attacks may see a gradual decline in memory, whereas people who suffer a large cerebrovascular accident will have immediate and profound symptoms.
- In general, symptoms are similar to those of other types of dementia, including increasing difficulty in performing activities of daily living, speech difficulties, trouble walking, impaired coordination/balance, lack of facial expression, urinary incontinence, and depression.
- It is believed that a majority of persons with VaD do not have “pure” vascular dementia; most have a “mixed” dementia, particularly a combination of VaD with Alzheimer’s disease.
- Symptoms of cortical vascular dementia often progress in a stepwise fashion—alternating between lapses in memory and reasoning and periods of stability, with additional lapses apparent with each subsequent stroke or transient ischemic attack.

Slide 57:

- Persons with vascular dementia can manifest with a very wide range of symptoms, depending on the location of the neurologic damage.
- Among the cognitive symptoms are:
 - Memory problems, forgetfulness, and confusion (which may worsen at night)
 - Slowed thinking
 - Personality changes and loss of social skills
 - Difficulty planning, organizing, and following instructions
 - Getting lost in familiar areas
- Common emotional symptoms may include:
 - Mood changes—depression and irritability
 - Inappropriate laughter or crying
 - Apathy
- Hallucinations and delusions may be present
- Sensory impairments include slurred speech and language problems, such as difficulties finding words
- Physical difficulties may include:
 - Reduced ability to complete activities of daily living
 - Difficulty doing things that used to come easily
 - Dizziness and balance problems
 - Leg or arm weakness or tremors
 - Rapid shuffling steps
 - Loss of bladder and/or bowel control
 - Trouble walking and gait impairment
 - Impaired coordination and balance
 - Lack of facial expression
 - Urinary incontinence

Slide 58:

- Speed of progression varies by person and vascular risk factors. Specific vascular risk factors, such as low-density lipoprotein (LDL)-cholesterol and possibly hypercholesterolemia, are associated with increased cognitive decline, whereas other factors, including overweight and smoking, do not appear to have a significant effect.
- Impairments worsen with each additional stroke or vascular insult.
- Progress may occur in steps, with plateaus followed by periods of rapid deterioration.
- A recent study using data from 32 U.S. Alzheimer's Disease Centers involving more than 5800 persons aged 60 or older determined that persons with vascular dementia had a slower rate of functional decline compared with persons with Alzheimer's disease.
- There are no valid current rates of survival.
- Early studies found that most persons survived 5 to 9.3 years after a stroke. A subsequent reevaluation suggested that the median survival for persons with vascular dementia was 3.3 years. In contrast, the lifespan after diagnosis of Alzheimer's disease is estimated at 3 to 8 years (or longer) depending on age of onset, sex, ethnicity, and other comorbid conditions.

Slide 60:

- Lewy body dementia (LBD) is an umbrella term for 2 related conditions – dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). The defining features of LBD include motor Parkinsonism and cognitive impairments.
- The predominant difference between these two types regards the timing of the cognitive impairments and Parkinsonian motor symptoms. Dementia with Lewy bodies is diagnosed when dementia onset occurs less than 1 year after Parkinsonian symptoms appear, whereas PDD is diagnosed if the onset of dementia occurs several years after Parkinsonian symptoms appear or Parkinson's disease has been diagnosed. DLB is often associated with a more severe course than PDD.
- Diagnosis of Lewy body dementia is challenging, even among experts. However, it is important to make an early and accurate diagnosis, as there can be a high rate of adverse effects if the person is treated with antipsychotics.
- There are many genetic similarities among Lewy body dementia, Parkinson's disease, and Alzheimer's disease. Consequently, it can be difficult to perform a differential diagnosis. However, it is important to correctly diagnose LBD as some therapeutic agents for other diseases are not appropriate for patients with LBD. DLB and PDD share many clinical and pathological similarities and have generally been considered different points on a spectrum.
- Persons with mixed Alzheimer's disease and Lewy body dementia have a different clinical phenotype from persons with AD only. Those with mixed dementia have an earlier age of onset of dementia symptoms, a lower age of mortality, and a greater frequency of having at least one Apolipoprotein E (APOE) e4 allele.
- Lewy bodies are abnormal aggregations, or clumps, of the protein alpha-synuclein and represent the pathological hallmark of Lewy body dementia. When Lewy bodies develop in the cortex, the

result is dementia with Lewy bodies, or DLB. They can also aggregate in different parts of the brain, leading to Parkinson's disease—and eventually Parkinson's disease dementia—and multiple system atrophy. It is believed that there is greater density of Lewy bodies in DLB than in PDD and that the structural and pathologic changes are more severe in DLB than in PDD.

- Alpha-synuclein (asyn) aggregates are likely to develop in an area deep in the brain—the substantia nigra—and spread to other areas. These clumps are believed to cause degeneration of nerve cells producing dopamine. In addition, diffuse amyloid-beta plaques are commonly seen in both PDD and LBD.

Slide 62:

- It is difficult to estimate the prevalence of dementia with Lewy bodies completely separately from that of PDD. The estimated prevalence of Lewy body dementia, or LBD, is 1.3 million cases in the United States, but it is believed to be highly underdiagnosed and frequently misdiagnosed.
- LBD affects up to 5 percent of older adults and up to 30 percent of all dementia cases.

Slide 63:

- A recent systematic review of relevant literature suggests dementia with Lewy bodies, or DLB, accounted for 4.2 percent of all dementias diagnosed in the community, rising to 7.5 percent of those diagnosed in secondary care, or by specialists such as neurologists or neuropsychiatrists. The incidence was 3.8 percent of new dementia cases. The study noted a significant increase in DLB diagnoses using the revised and updated 2005 International Consensus Criteria (ICC) compared with the original 1996 criteria.
- DLB appears to affect men more than it affects women and increases in incidence with age. However, it appears to affect people at a younger age than does PDD.

Slide 64:

- Parkinson's disease, or PD, affects about 1 million Americans.
- Approximately 23–30 percent of people diagnosed with PD also have Parkinson's disease dementia. That percentage increases to 80 percent of persons with PD after more than 15 years.
- There is a high rate of Parkinson's disease-mild cognitive impairment at the time of diagnosis; up to 15 to 20 percent of patients have MCI with PD, which is associated with a poor quality of life and more severe motor symptoms.
- There is a rising prevalence of Parkinson's disease with increasing age.
- PD rates are also affected by race: PD is substantially more common in Caucasians than African Americans or Asians in the United States.
- There seems to be a higher incidence of PD in specific ethnicities—Asians, Europeans, North Africans, North and South Americans. But it is highest among Ashkenazi Jews.
- PDD appears to increase more slowly with age than dementia with Lewy bodies.

Slide 65:

- In general, there are few known risk factors for Lewy body dementia. The Mayo Clinic notes male gender, older than age 60, and a family history as possible risk factors.
- An important risk factor for Parkinson's disease dementia is duration of Parkinson's disease—the probability of developing PDD is approximately 80 percent with extended time since Parkinson's disease diagnosis.
- In addition to a diagnosis of Parkinson's disease-mild cognitive impairment, other risk factors and correlates for PDD include increasing age and duration of PD, male sex, "atypical" Parkinsonian features (such as increased symmetry of Parkinsonism, speech and swallowing difficulties, and presence of gastrointestinal and/or urologic problems at baseline), and other non-motor symptoms (such as visual hallucinations, apathy, depression, and rapid eye movement sleep behavior disorder, or RBD).
- RBD is a sleep disorder in which a person physically acts out his or her dreams, which are typically vivid and unpleasant, using vocalizations and sudden, often violent arm and leg movements (Mayo Clinic, 2014). This has been referred to as "dream-enacting behavior." Rapid eye movement sleep behavior disorder is most often seen in persons with LBD. In fact, it is suggestive of Lewy body dementia and predictive for neurodegeneration in persons with Parkinson's disease. RBD may precede dementia and worsen the prognosis. REM sleep is a normal stage of sleep during which people dream; up to 20 percent of sleep is spent in REM sleep.

Slide 66:

- The defining features of Lewy body disease include motor Parkinsonism and cognitive impairments. Depending upon the type of dementia, there may also be visual hallucinations, fluctuating consciousness, loss of smell, sleep difficulties, and other non-motor symptoms even during early stages of the dementia. There may be a period of MCI preceding the motor symptoms.
- The clinical manifestations of dementia with Lewy bodies and Parkinson's disease dementia are initially different, but they become more similar as the disease progresses, such that by middle- and late-stage disease they are essentially the same.
- Dementia with Lewy bodies
- A comparison of persons with early dementia with Lewy bodies versus early Alzheimer's disease in Norway reported some similarities and numerous differences between the two types of dementia. Specifically, while memory impairment was the most common presenting symptom in DLB, it occurred in just over half of the persons with DLB (57 percent) compared with 99 percent of persons with early Alzheimer's disease. Nearly half of persons with DLB (44 percent) had visual hallucinations. In contrast, only 3 percent of persons with Alzheimer's disease had visual hallucinations. Other common initial manifestations of DLB included depression, problem solving difficulties, and gait problems, along with tremor or stiffness.
- Hallucinations are among the most common core features of DLB prior to the initial evaluation, followed by Parkinsonism and cognitive fluctuations
 - Recurrent visual hallucinations may occur in up to 80 percent of persons with DLB.

- DLB is characterized by fluctuations in all symptoms, including cognitive ability, attention, and alertness. Visual and auditory hallucinations are common, as are sleep difficulties—particularly rapid eye movement, or REM sleep behavior disorder, or RBD.
- Parkinson's disease dementia
- Motor symptoms precede psychiatric and other symptoms in persons with PDD. Hallmark symptoms in early-stage PDD are movement related: bradykinesia, rigidity, tremor, and/or postural instability. Cognitive testing shows slowed processing speed, decreased ability to pay attention, and decreased executive dysfunction; however, unlike Alzheimer's disease, memory remains intact throughout most of the stages of PDD. Other manifestations of PDD include RBD and visuoperceptual changes, as well as depression.
- Persons with DLB generally have a poorer cognitive performance, poorer semantic fluency, and lower scores on visual and verbal memory performance and in visuospatial domains, compared with patients with PDD. Generally, the differences are mostly in the expression of Parkinsonism, hallucinations and delirium, and the presence of noncognitive symptoms.

Slide 67:

- Research indicates a prodromal stage of Lewy body dementia/Parkinson's disease dementia that is characterized by dysautonomia, olfactory dysfunction, rapid eye movement (REM) sleep behavior disorder, or RBD, and psychiatric symptoms that are apparent years before the onset of dementia (possibly decades earlier with dementia with Lewy bodies).
 - Dysautonomia refers to a disorder of functioning of the autonomic nervous system, or ANS—predominantly of the sympathetic or parasympathetic components, but excessive ANS activity can also occur. Dysautonomia can be acute or chronic and progressive or reversible.
 - Olfactory dysfunction involves problems with taste or smell. Anosmia is the absence of the sense of smell.
- Far less is known regarding progression of LBD compared with knowledge on Alzheimer's disease. The Lewy Body Disease Association (LBDA) estimates an average duration of 5 to 7 years, with a range from 2 to 20 years. Survival time is shorter in DLB compared with Alzheimer's disease.
- Men with DLB have increased mortality versus men with AD.

Slide 69:

- Frontotemporal degeneration (FTD) is also known as frontotemporal disorder, frontotemporal dementia, or frontotemporal lobar degeneration, or FTLD. FTD is a heterogeneous group of disorders with overlapping clinical symptoms but different causative genes and differing underlying pathologies.
- FTD generally has rapid progression associated with damage to the frontal and/or temporal lobes, which are the areas responsible for behavior, emotion, and language. The disease process affects frontotemporal brain structures but generally spares memory networks.

- Imaging may show tau, or Pick bodies—which is why FTD was originally called Pick’s disease—or TDP43 (TAR DNA-binding protein 43, or transactive response DNA binding protein 43 kDa) or FUS (fused in sarcoma protein) inclusions.

Slide 71:

- Frontotemporal degeneration usually strikes persons at an earlier age (those younger than age 60) and is often considered a rare cause of dementia after age 65, with only about 25 percent of FTD cases in that age group but is the second most common cause of early-onset dementia after Alzheimer’s disease. In fact, about 60 percent of people who are diagnosed with FTD are between ages 45 and 64.
- The estimated prevalence is approximately 15 to 22 per 100,000, with an equal gender distribution. Approximately 50,000 to 60,000 Americans are affected.

Slide 72:

- There are at least three distinctive clinical syndromes, each with heterogeneous neuropathology.
- Progressive behavior/personality decline—Behavioral variant frontotemporal degeneration, or bvFTD, is the most common variant. It is characterized by marked personality changes and changes in social conduct.

Slide 73:

- Progressive language decline—Primary progressive aphasia, or PPA—is subdivided into three different syndromes, all (at least initially) mostly language related.
 - Semantic dementia (sFTD), or loss of general knowledge memory in both verbal and non-verbal domains
 - Progressive non-fluent aphasia, or PNFA, which refers to progressive loss of language skills —Some patients with PNFA develop full-blown corticobasal syndrome as the disease progresses.
 - Progressive logopenic aphasia (PLA), or impairments in repetition and naming difficulties.
- Progressive motor decline, which is rare. This includes corticobasal syndrome, amyotrophic lateral sclerosis, or supranuclear palsy.
- Frontotemporal degeneration is difficult to diagnose because numerous psychiatric conditions are similar to early bvFTD symptoms, including late-onset bipolar disorder, late-onset schizophrenia-like psychosis, late-onset depression, and attention deficit hyperactivity disorder in middle and older age.
- While we are not addressing them in this module, an international consortium recently revised the diagnosis into a hierarchy of possible FTD, probable FTD, and definite FTD. We will cover this in Module 2.

Slide 74:

- Behavioral variant frontotemporal degeneration is characterized by progressive behavioral and personality decline. Persons with bvFTD manifest with emotional swings and uncharacteristic changes in behavior and judgment. They may lose the ability to show sympathy or empathy, and many have apathy early in the disease. They may appear distracted and rude, with a loss of inhibitions. They may have compulsive and impulsive ritualistic behaviors, with hyperorality and dietary changes. The symptoms often first appear at a younger age, at or before age 60, and survival tends to be of much less duration than that of Alzheimer's disease.
- Primary progressive aphasia variations of FTD are characterized by progressive language decline, including impairments in the ability to speak, understand, read, and write.
 - The person may have aphasia, which is an impaired or inability to use or understand words, although the person retains the physical ability to speak properly. In other words, the person has the physical ability to form words but cannot find the correct word or cannot understand what is being said. With primary progressive aphasia, over time the person slowly loses the ability to talk, read, write, or comprehend language.
 - Dysarthria is an impairment in the physical ability to speak properly (slurring, for example), but the message is normal.
 - Either form of primary progressive aphasia can have behavioral or language symptoms plus motor and extrapyramidal symptoms.
 - Some patients develop full-blown corticobasal syndrome as the disease progresses.
- Persons with FTD with progressive motor decline have various difficulties with physical movement, including the inability to use one or more limbs, shaking, difficulty walking, frequent falls, and poor coordination. However, they can retain the ability to perform activities of daily living.

Slide 75:

- Between 15 and 40 percent of persons with behavioral variant frontotemporal degeneration have a family history of dementia.
- Between 10 and 30 percent of persons with frontotemporal degeneration show an autosomal dominant pattern of inheritance.
- The strength of the family history is highly predictive in that mutations can now be shown in most patients with two or more first-degree relatives with a dementia syndrome compatible with FTD. Consequently, people demonstrating possible symptoms of FTD should be asked about their family history.
- FTD commonly features the accumulation of certain neuronal proteins. Those that have been identified as the most important include microtubule-associated protein tau, or MAPT (also called tau gene); transactive response DNA-binding protein, or TARDBP; and the fused in sarcoma protein, or FUS.
 - A mutation in the MAPT gene causes abnormalities in tau protein. Inheriting a mutation in this gene is almost a guarantee of developing an FTD, and usually bvFTD, but the exact age of onset and symptoms are not predictable.

- A mutation in the progranulin (PGRN) gene can cause different symptoms in different family members, and it is mostly associated with bvFTD.
- Mutations in the valosin-containing protein (VCP), charged multivesicular body protein 2B (CHMP2B), TARDBP, and FUS genes are associated with very rare familial types of frontotemporal degeneration.
- The most common genetic abnormality in familial FTD and familial amyotrophic lateral sclerosis involves an unusual mutation in the chromosome 9 open reading frame 72 (C9orf72) gene.
- In Niemann-Pick Disease type C1, there is a significant association between apolipoprotein E (APOE) polymorphisms and severity, similar to that with Alzheimer's disease, but no effect of tau polymorphisms.
- Some patients with one or more first-degree relatives with a disease on the FTD spectrum might undergo screening for MAPT and GRN gene mutations, in tandem with appropriate genetic counseling; however, this may not be appropriate for all patients.

Slide 76:

- Persons with behavioral variant frontotemporal degeneration (bvFTD) demonstrate disinhibition, apathy, and stereotypic (ritualized) behaviors.
- Characteristic manifestations of FTD include changes in behavior and personality, language problems, and motor problems. Blunting of affect and apathy are common, and persons with bvFTD also show emotional lability, anxiety, irritability, and euphoria. Patients lack motivation and are no longer interested in their hobbies. These changes can lead to increasing social isolation.
- Up to 40 percent of persons with bvFTD have depression, which can lead to an inaccurate initial diagnosis of major depressive disorder.
- Memory is impaired to a much lesser degree than with Alzheimer's disease, although episodic memory disturbances may occur. The changes generally have a gradual onset. However, there is a more marked deterioration in memory and executive function in persons with bvFTD compared with persons with Alzheimer's disease.
- However, persons with FTD lack insight (understanding or acknowledgment) of their unusual behaviors.
- Persons with FTD lack inhibitions, which can lead to inappropriate and impulsive actions. New onset criminality, hypersexuality, or pathological gambling (to name a few) can be indicative of possible FTD. Persons might repeat insensitive or inappropriate jokes, stories, or phrases.
- There can be changes in eating habits, with regard to amounts and preferences, because of damage to the hypothalamus, which is involved in coordinating feeding needs. Persons with FTD appear to lean more toward eating sweet foods, and binge eating is common.
- Psychotic features, such as hallucinations and delusions, are not common, and there is far less cognitive impairment than in Alzheimer's disease.

Slide 77:

- Research using the Frontotemporal Dementia Rating Scale, which is a scale developed to help stage frontotemporal degeneration and determine disease progression, has demonstrated that patients with behavioral variant frontotemporal degeneration have greater disease severity and a faster progression through the clinical stages than do patients with the language variants of FTD, regardless of the length of symptoms.
 - However, the presence of language impairment at diagnosis is associated with shorter survival than no language impairment.
- Study suggests later age of onset associated with faster disease progression versus those with earlier age at onset.
- FTD may progress more rapidly than Alzheimer's disease.
- People generally live 3 to 10 years after diagnosis (with survival being 5 to 8 years after symptoms first appear).

Slide 79:

- We've covered the most common types of dementia, but there are numerous other causes, including autoimmune disorders, infections, trauma, toxicities, and neoplasms.
- Creutzfeldt-Jakob disease is a rapidly progressive fatal disorder, and 85 percent die within 1 year. It impairs cognition and coordination and causes behavioral changes.
- Dementia is a manifestation of Huntington chorea.
- Sporadic cerebral amyloid angiopathy is an important cause of spontaneous intracerebral hemorrhage and cognitive impairment in older people.
- Normal pressure hydrocephalus is another cause of dementia.
- HIV-associated neurocognitive disorders (HAND)—including AIDS-dementia complex (ADC) and HIV-associated dementia (HAD). The most severe form (HAD) has decreased with the introduction of highly active retroviral therapy, or HAART, but milder forms remain common.

Slide 81:

These items are provided to allow faculty to evaluate what students have learned. The items can be used in several ways including given at the end of the lecture to assess knowledge or as a pre/post test to assess knowledge gain. These items have face validity. Psychometric testing was not conducted on these items.

Answers

Question 1: c. Persons living with dementia have severe enough mental decline so as to interfere with daily life.

Slide 82:**Answers**

Question 2: b. Huntington's disease

Question 3: d. Heart-healthy diet

Slide 83:

Questions 4: d. The rate of progression through the stages of dementia depends upon the underlying cause of dementia.