Plasma phospholipids identify antecedent memory impairment in older adults


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WHAT DOES THIS BLOOD TEST REALLY PREDICT?

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Biomarkers and evaluations?

what are biomarkers?

why are they critical for drug development?

what are the current biomarkers for AD?

what are the limitations of the current biomarkers we have for AD?

define:

metabolomic

lipidomic

What is the composite measure of memory performance?
Think about the following:

(Converter\textsubscript{pre}). The average time for phenoconversion to either aMCI or AD was 2.1 years (range 1–5 years). We defined three main participant groups in this paper: aMCI/AD, Converter and Normal Control (NC). The participants with aMCI and mild AD were combined into a single group (aMCI/AD) because this group was defined by a primary memory impairment, and aMCI is generally thought to reflect the earliest clinically detectable stage of AD. The

_is this really true?_
what are the other measures of memory performance?

The aMCI/AD, Converter and NC groups were defined primarily using a composite measure of memory performance (the decline in $Z_{mem}$ for the Converters ($C_{pre}$ versus $C_{post}$) is shown Fig. 1a). In addition,
Questions to think about:

• What role did APOEε4 play in the “converters” vs. the non-converters?
• How accurate is AD diagnosis?
• What does it mean that the test is 90% accurate?
• Are there any ethical considerations?
consider the differences in dementias:

**Alzheimer's disease**

Most common type of dementia; accounts for an estimated 60 to 80 percent of cases.

**Symptoms:** Difficulty remembering names and recent events is often an early clinical symptom; apathy and depression are also often early symptoms. Later symptoms include impaired judgment, disorientation, confusion, behavior changes and difficulty speaking, swallowing and walking.

New criteria and guidelines for diagnosing Alzheimer's were published in 2011 recommending that Alzheimer's disease be considered a disease with three stages, beginning well before the development of symptoms.

**Brain changes:** Hallmark abnormalities are deposits of the protein fragment beta-amyloid (plaques) and twisted strands of the protein tau (tangles) as well as evidence of nerve cell damage and death in the brain.

The most common early symptom of Alzheimer's is difficulty remembering newly learned information.
Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease causes a type of dementia that gets worse unusually fast.

CJD is the most common human form of a group of rare, fatal brain disorders affecting people and certain other mammals. Variant CJD ("mad cow disease") occurs in cattle, and has been transmitted to people under certain circumstances.

**Symptoms:** Rapidly fatal disorder that impairs memory and coordination and causes behavior changes.

**Brain changes:** Results from misfolded prion protein that causes a "domino effect" in which prion protein throughout the brain misfolds and thus malfunctions.

Infectious CJD is an especially rare form of CJD and results from exposure to an external source of abnormal prion protein. These sources are estimated to account for about 1 percent of CJD cases. The two most common outside sources are:

**Medical procedures** involving instruments used in neurosurgery, growth hormone from human sources or certain transplanted human tissues.

Meat or other products from cattle infected with bovine spongiform encephalopathy ("mad cow disease"), recognized in the mid-1990s as the cause of variant CJD (vCJD).

This slide shows sponge-like lesions in the brain tissue of a CJD patient. (Image courtesy Ermias Belay)
Brain imaging to detect enlargement of the ventricles, often with magnetic resonance imaging (MRI), plays a key role in diagnosing NPH. Several brain disorders, including Alzheimer's disease, can cause overall brain tissue shrinkage that makes the ventricles look larger than normal. In NPH, although the ventricles are enlarged, brain tissue may not appear shrunken.

### Normal pressure hydrocephalus

**Symptoms:** Symptoms include difficulty walking, memory loss and inability to control urination.

**Brain changes:** Caused by the buildup of fluid in the brain. Can sometimes be corrected with surgical installation of a shunt in the brain to drain excess fluid.

The following symptoms are considered hallmarks of normal pressure hydrocephalus:

- **Difficulty walking** that's sometimes compared to the way a person walks "on a boat," with the body bent forward, legs held wide apart and feet moving as if they're "glued to the deck."

- **Decline in thinking skills** that includes overall slowing of thought processes, apathy, impaired planning and decision-making, reduced concentration and changes in personality and behavior.

- **Loss of bladder control,** which tends to appear somewhat later in the disease than difficulty walking and cognitive decline.
Previously known as multi-infarct or post-stroke dementia, vascular dementia is the second most common cause of dementia after Alzheimer's disease.

**Symptoms:** Impaired judgment or ability to plan steps needed to complete a task is more likely to be the initial symptom, as opposed to the memory loss often associated with the initial symptoms of Alzheimer's. Occurs because of brain injuries such as microscopic bleeding and blood vessel blockage. The location of the brain injury determines how the individual's thinking and physical functioning are affected.

**Brain changes:** Brain imaging can often detect blood vessel problems implicated in vascular dementia. In the past, evidence for vascular dementia was used to exclude a diagnosis of Alzheimer's disease (and vice versa). That practice is no longer considered consistent with pathologic evidence, which shows that the brain changes of several types of dementia can be present simultaneously. When any two or more types of dementia are present at the same time, the individual is considered to have "mixed dementia" (see entry below).
Most experts estimate that dementia with Lewy bodies is the third most common cause of dementia after Alzheimer's disease and vascular dementia, accounting for 10 to 25 percent of cases.

Symptoms: People with dementia with Lewy bodies often have memory loss and thinking problems common in Alzheimer's, but are more likely than people with Alzheimer's to have initial or early symptoms such as sleep disturbances, well-formed visual hallucinations, and muscle rigidity or other parkinsonian movement features.

Brain changes: Lewy bodies are abnormal aggregations (or clumps) of the protein alpha-synuclein. When they develop in a part of the brain called the cortex, dementia can result. Alpha-synuclein also aggregates in the brains of people with Parkinson's disease, but the aggregates may appear in a pattern that is different from dementia with Lewy bodies.

The brain changes of dementia with Lewy bodies alone can cause dementia, or they can be present at the same time as the brain changes of Alzheimer's disease and/or vascular dementia, with each abnormality contributing to the development of dementia. When this happens, the individual is said to have "mixed dementia."

The hallmark brain abnormalities linked to DLB are named after Frederick H. Lewy, M.D., the neurologist who discovered them while working in Dr. Alois Alzheimer's laboratory during the early 1900s.
Key differences between Alzheimer's and DLB

- **Memory loss** tends to be a more prominent symptom in early Alzheimer's than in early DLB, although advanced DLB may cause memory problems in addition to its more typical effects on judgment, planning and visual perception.

- **Movement symptoms** are more likely to be an important cause of disability early in DLB than in Alzheimer's, although Alzheimer's can cause problems with walking, balance and getting around as it progresses to moderate and severe stages.

- **Hallucinations**, delusions, and misidentification of familiar people are significantly more frequent in early-stage DLB than in Alzheimer's.

- **REM sleep disorder** is more common in early DLB than in Alzheimer's.

- **Disruption of the autonomic nervous system**, causing a blood pressure drop on standing, dizziness, falls and urinary incontinence, is much more common in early DLB than in Alzheimer's.
Mixed dementia

In mixed dementia abnormalities linked to more than one type of dementia occur simultaneously in the brain. Recent studies suggest that mixed dementia is more common than previously thought.

Brain changes: Characterized by the hallmark abnormalities of more than one type of dementia —most commonly, Alzheimer's and vascular dementia, but also other types, such as dementia with Lewy bodies.

NIA-Funded Memory & Aging Project Reveals Mixed Dementia Common

Data from the first 141 volunteers in this research study show that more than 50 percent of those whose brains met pathological criteria for Alzheimer's had pathologic evidence of one or more coexisting dementias.

This study is conducted by the Rush Alzheimer's Disease Center and the Rush Institute for Healthy Aging in Chicago and funded by the National Institute on Aging (NIA).
The key brain changes linked to Parkinson's disease and Parkinson's disease dementia are abnormal microscopic deposits composed chiefly of alpha-synuclein, a protein that's found widely in the brain but whose normal function isn't yet known.

The deposits are called "Lewy bodies".

Another complicating factor is that many people with both dementia with Lewy bodies and Parkinson's disease dementia also have plaques and tangles — hallmark brain changes linked to Alzheimer's disease.

As Parkinson's disease progresses, it often results in a progressive dementia similar to dementia with Lewy bodies or Alzheimer's.

**Symptoms:** Problems with movement are a common symptom early in the disease. If dementia develops, symptoms are often similar to dementia with Lewy bodies.

**Brain changes:** Alpha-synuclein clumps are likely to begin in an area deep in the brain called the substantia nigra. These clumps are thought to cause degeneration of the nerve cells that produce dopamine.

Parkinson's disease

Parkinson's is estimated to affect nearly 2 percent of those older than age 65. It is estimated that 50 to 80 percent of those with Parkinson's disease eventually experience Parkinson's disease dementia.

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FTD used to be called Pick's disease after Arnold Pick, a physician who in 1892 first described a patient with distinct symptoms affecting language.

Symptoms: Typical symptoms include changes in personality and behavior and difficulty with language. Nerve cells in the front and side regions of the brain are especially affected.

Brain changes: No distinguishing microscopic abnormality is linked to all cases. People with FTD generally develop symptoms at a younger age (at about age 60) and survive for fewer years than those with Alzheimer's.

Diagnosis
There is no single test — or any combination of tests — that can conclusively diagnose frontotemporal dementia. FTD is a "clinical" diagnosis representing a doctor's best professional judgment about the reason for a person's symptoms. Magnetic resonance imaging (MRI) often plays a key role in diagnosis because it can detect shrinkage in the brain's frontal and temporal lobes, which is a hallmark of FTD. In some cases, it may be hard to distinguish FTD from Alzheimer's disease.
Key Differences Between FTD and Alzheimer's

- **Age at diagnosis** may be an important clue. Most people with FTD are diagnosed in their 50s and early 60s. Only about 10 percent are diagnosed after age 70. Alzheimer's, on the other hand, grows more common with increasing age.
- **Memory loss** tends to be a more prominent symptom in early Alzheimer's than in early FTD, although advanced FTD often causes memory loss in addition to its more characteristic effects on behavior and language.
- **Behavior changes** are often the first noticeable symptoms in bvFTD, the most common form of FTD. Behavior changes are also common as Alzheimer's progresses, but they tend to occur later in the disease.
- **Problems with spatial orientation** — for example, getting lost in familiar places — are more common in Alzheimer's than in FTD.
- **Problems with speech.** Although people with Alzheimer's may have trouble thinking of the right word or remembering names, they tend to have less difficulty making sense when they speak, understanding the speech of others, or reading than those with FTD.
- **Hallucinations and delusions** are relatively common as Alzheimer's progresses, but relatively uncommon in FTD.
Huntington’s disease is a progressive brain disorder caused by a single defective gene on chromosome 4.

**Symptoms:** Include abnormal involuntary movements, a severe decline in thinking and reasoning skills, and irritability, depression and other mood changes.

**Brain changes:** The gene defect causes abnormalities in a brain protein that, over time, lead to worsening symptoms.

The defective gene identified in 1993 causes virtually all Huntington’s disease.

The huntingtin gene defect involves extra repeats of one specific chemical code in one small section of chromosome 4. The normal huntingtin gene includes 17 to 20 repetitions of this code among its total of more than 3,100 codes. The defect that causes Huntington's disease includes 40 or more repeats. Genetic tests for Huntington’s disease measure the number of repeats present in an individual’s huntingtin protein gene.
Wernicke-Korsakoff Syndrome

Korsakoff syndrome is a chronic memory disorder caused by severe deficiency of thiamine (vitamin B-1). The most common cause is alcohol misuse.

Symptoms: Memory problems may be strikingly severe while other thinking and social skills seem relatively unaffected.

Brain changes: Thiamine helps brain cells produce energy from sugar. When thiamine levels fall too low, brain cells cannot generate enough energy to function properly.