Biomarkers for Dementia
— Get the Facts

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Biomarkers are measures of what is happening inside the living body, shown by the results of laboratory and imaging tests. Biomarkers can help doctors and scientists diagnose diseases and health conditions, find health risks in a person, monitor responses to treatment, and see how a person’s disease or health condition changes over time. For example, an increased level of cholesterol in the blood is a biomarker for heart-attack risk.

Many types of biomarker tests are used for research on Alzheimer’s disease and related dementias. Changes in the brains of people with these disorders may begin many years before memory loss or other symptoms appear. Researchers use biomarkers to help detect these brain changes in people, who may or may not have obvious changes in memory or thinking. Finding these changes early in the disease process helps identify people who are at the greatest risk of Alzheimer’s or another dementia and may help determine which people might benefit most from a particular treatment.

Use of biomarkers in clinical settings, such as a doctor’s office, is limited at present. Some biomarkers may be used to identify or rule out causes of symptoms for some people. Researchers are studying many types of biomarkers that may one day be used more widely in doctors’ offices and other clinical settings.

Types of Biomarkers and Tests

In Alzheimer’s disease and related dementias, the most widely used biomarkers measure changes in the size and function of the brain and
its parts, as well as levels of certain proteins seen on brain scans and in cerebrospinal fluid and blood.

Brain Imaging

Brain imaging, also called brain scans, can measure changes in the size of the brain, identify and measure specific brain regions, and detect biochemical changes and vascular damage (damage related to blood vessels). In clinical settings, doctors can use brain scans to find evidence of brain disorders, such as tumors or stroke, that may aid in diagnosis. In research settings, brain imaging is used to study structural and biochemical changes in the brain in Alzheimer’s disease and related dementias. There are several types of brain scans.

Computerized Tomography

What is it?
A computerized tomography (CT) scan is a type of X-ray that uses radiation to produce images of the brain. A CT can show the size of the brain and identify a tumor, stroke, head injury, or other potential cause of dementia symptoms. CT scans provide greater detail than traditional X-rays, but a less detailed picture than magnetic resonance imaging (MRI) and cannot easily measure changes over time. Sometimes a CT scan is used when a person can’t get an MRI due to metal in their body, such as a pacemaker.

What’s the procedure like?
During a CT scan, a person lies in a scanner for 10 to 20 minutes. A donut-shaped device moves around the head to produce the image.

What does it show?
A head CT can show shrinkage of brain regions that may occur in dementia, as well as signs of a stroke or tumor.

When is it used?
A CT is sometimes used to help a doctor diagnose dementia based on changes in the size of particular brain regions, compared either to an earlier scan or to what would be expected for a person of the same age and size. It is rarely used in the research arena to study Alzheimer’s disease and related dementias.

Magnetic Resonance Imaging

What is it?
Magnetic resonance imaging (MRI) uses magnetic fields and radio waves to produce detailed images of body structures, including the size and shape of the brain and brain regions. MRI may be able to identify some causes of dementia symptoms, such as a tumor, stroke, or head injury. MRI may also show whether areas of the brain have atrophied, or shrunk.

What’s the procedure like?
During an MRI, a person lies still in a tunnel-shaped scanner for about 30 minutes for diagnostic purposes and up to 2 hours for research purposes. MRI is a safe, painless procedure that does not involve radioactivity. The procedure is noisy, so people are often given earplugs or headphones to wear. Some people become claustrophobic and anxious inside an MRI machine, which can be addressed with anxiety-relieving medication taken shortly before the scan.
Because MRI uses strong magnetic fields to obtain images, people with certain types of metal in their bodies, such as a pacemaker, surgical clips, or shrapnel, cannot undergo the procedure.

**What does it show?**
MRI scans provide pictures of brain structures and whether abnormal changes, such as shrinkage of areas of the brain, are present. Evidence of shrinkage may support a diagnosis of Alzheimer’s or another neurodegenerative dementia but cannot indicate a specific diagnosis. Researchers use different types of MRI scans to obtain pictures of brain structure, chemistry, blood flow, and function, as well as the size of brain regions. MRI also provides a detailed picture of any vascular damage in the brain — such as damage due to a stroke or small areas of bleeding — that may contribute to changes in cognition. Repeat scans can show how a person’s brain changes over time.

**When is it used?**
Doctors often use MRI scans to identify or rule out causes of memory loss, such as a stroke or other vascular brain injury, tumors, or hydrocephalus. These scans also can be used to assess brain shrinkage.

In the research arena, various types of MRI scans are used to study the structure and function of the brain in aging and Alzheimer’s disease. In clinical trials, MRI can be used to monitor the safety of novel drugs and to examine how treatment may affect the brain over time.

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**Positron Emission Tomography**

**What is it?**
Positron emission tomography (PET) uses small amounts of a radioactive substance, called a tracer, to measure specific activity — such as glucose (energy) use — in different brain regions. Different PET scans use different tracers. PET is commonly used in dementia research but less frequently in clinical settings.

**What’s the procedure like?**
The person having a PET scan receives an injection of a radioactive tracer into a vein in the arm, then lies on a cushioned table, which is moved into a donut-shaped scanner. The PET scanner takes pictures of the brain, revealing regions of normal and abnormal chemical activity. A PET scan is much quieter than MRI. The entire process, including the injection and scan, takes about 1 hour.

The amount of radiation exposure during a PET scan is relatively low. People who are concerned about radiation exposure or who have had many X-rays or imaging scans should talk with their doctor.

**What does it show?**
Fluorodeoxyglucose (FDG) PET scans measure glucose use in the brain. Glucose, a type of sugar, is the primary source of energy for cells. Studies show that people with dementia often have abnormal patterns of decreased glucose use in specific areas of the brain. An FDG PET scan can show a pattern that may support a diagnosis of a specific cause of dementia.
Amyloid PET scans measure abnormal deposits of a protein called beta-amyloid. Higher levels of beta-amyloid are consistent with the presence of amyloid plaques, a hallmark of Alzheimer’s disease. Several tracers may be used for amyloid PET scans, including florbetapir, flutemetamol, florbetaben, and Pittsburgh compound B.

Tau PET scans detect abnormal accumulation of a protein, tau, which forms tangles in nerve cells in Alzheimer’s disease and many other dementias. AV-1451 is a tau tracer that can help identify the presence of tau tangles in the brain. Several other tau tracers, such as PI-2620 and MK-6240, are also being studied in clinical trials and other research settings.

When is it used?
In clinical care, FDG PET scans may be used if a doctor strongly suspects frontotemporal dementia as opposed to Alzheimer’s dementia based on the person’s symptoms, or when there is an unusual presentation of symptoms.

Amyloid PET imaging is sometimes used by medical specialists to help with a diagnosis when Alzheimer’s disease is suspected but uncertain, even after a thorough evaluation. Amyloid PET imaging may also help with a diagnosis when people with dementia have unusual or very mild symptoms, an early age of onset (under age 65), or any of several different conditions, such as severe depression, that may contribute to dementia symptoms. A negative amyloid PET scan rules out Alzheimer’s disease.

In research, amyloid and tau PET scans are used to determine which individuals may be at greatest risk for developing Alzheimer’s disease, to identify clinical trial participants, and to assess the impact of experimental drugs designed to affect amyloid or tau pathways.

Cerebrospinal Fluid Biomarkers
Cerebrospinal fluid (CSF) is a clear fluid that surrounds the brain and spinal cord, providing protection and insulation. CSF also supplies numerous nutrients and chemicals that help keep brain cells healthy. Proteins and other substances made by cells can be detected in CSF, and their levels may change years before symptoms of Alzheimer’s and other brain disorders appear.

Lumbar Puncture

What is it?
CSF is obtained by a lumbar puncture, also called a spinal tap, an outpatient procedure used to diagnose several types of neurological problems.

What’s the procedure like?
People either sit or lie curled up on their side while the skin over the lower part of the spine is cleaned and injected with
a local anesthetic. A very thin needle is then inserted into the space between the bones of the spine. CSF either drips out through the needle or is gently drawn out through a syringe. The entire procedure typically takes 30 to 60 minutes.

After the procedure, the person lies down for a few minutes and may receive something to eat or drink. People can drive themselves home and resume regular activities, but they should refrain from strenuous exercise for about 24 hours.

Some people feel brief pain during the procedure, but most have little discomfort. A few may have a mild headache afterward, which usually disappears after taking a pain reliever and lying down. Sometimes, people develop a persistent headache that gets worse when they sit or stand. This type of headache can be treated with a blood patch, which involves injecting a small amount of the person’s blood into his or her lower back to stop a leak of CSF.

Certain people cannot have a lumbar puncture, including people who take medication such as warfarin to thin their blood, have a low platelet count or an infection in the lower back, or have had major back surgery.

**What does it show?**

The most widely used CSF biomarkers for Alzheimer’s disease measure certain proteins: beta-amyloid 42 (the major component of amyloid plaques in the brain), tau, and phospho-tau (major components of tau tangles in the brain). In Alzheimer’s disease, beta-amyloid 42 levels in CSF are low, and tau and phospho-tau levels are high, compared with levels in people without Alzheimer’s or other causes of dementia.

**When is it used?**

In clinical practice, CSF biomarkers may be used to help diagnose Alzheimer’s, for example, in cases involving an unusual presentation of symptoms or course of progression. CSF also can be used to evaluate people with unusual types of dementia or with rapidly progressive dementia.

In research, CSF biomarkers are valuable tools for early detection of a neurodegenerative disease. They are also used in clinical trials to assess the impact of experimental medications.

**Other Types of Biomarkers**

**Blood Tests**

Proteins that originate in the brain, such as tau and beta-amyloid 42, may be measured with sensitive blood tests. Levels of these proteins may change because of Alzheimer’s, a stroke, or other brain disorders. These blood biomarkers are less accurate than CSF biomarkers for identifying Alzheimer’s and related dementias. However, new methods to measure these brain-derived proteins, particularly beta-amyloid 42/beta-amyloid 40 and phospho-tau 181, have improved, suggesting that blood tests may be used in the future for screening and perhaps diagnosis.

Many other proteins, lipids, and other substances can be measured in the blood, but so far none has shown value in diagnosing Alzheimer’s.
Currently, dementia researchers use blood biomarkers to study early detection, prevention, and the effects of potential treatments. They are not used in doctors' offices and other clinical settings.

**Genetic Testing**

Genes are structures in a body’s cells that are passed down from a person’s birth parents. They carry information that determines a person’s traits and keep the body’s cells healthy. Problems with genes can cause diseases like Alzheimer’s.

A genetic test is a type of medical test that analyzes DNA from blood or saliva to determine a person’s genetic makeup. A number of genetic combinations may change the risk of developing a disease that causes dementia.

Genetic tests are not routinely used in clinical settings to diagnose or predict the risk of developing Alzheimer’s or a related dementia. However, a neurologist or other medical specialist may order a genetic test in rare situations, such as when a person has an early age of onset or a strong family history of Alzheimer’s or a related brain disease. A genetic test is typically accompanied by genetic counseling for the person before the test and when results are received. Genetic counseling includes a discussion of the risks, benefits, and limitations of test results.

Genetic testing for APOE e4, the main genetic risk factor for late-onset Alzheimer’s disease, is available as a direct-to-consumer or commercial test. It is important to understand that genetic testing provides only one piece of information about a person’s risk. Other genetic and environmental factors, lifestyle choices, and family medical history also affect a person’s risk of developing Alzheimer’s disease.

In research studies, genetic tests may be used, in addition to other assessments, to predict disease risk, help study early detection, explain disease progression, and study whether a person’s genetic makeup influences the effects of a treatment.


**Biomarkers in Development**

Researchers are studying other biomarker tests for possible use in diagnosing and tracking Alzheimer’s disease and other types of dementia. These biomarkers include reduced ability to smell, the presence of certain proteins in the retina of the eye, and other proteins that indicate the health of neurons. At this point, doctors do not use these biomarkers to diagnose dementia.

**Biomarkers in Dementia Diagnosis**

Some biomarkers may be part of a diagnostic assessment for people with symptoms of Alzheimer’s or a related dementia. Other parts of the assessment typically include a medical history; physical exam; laboratory tests; neurological tests of balance, vision, and other cognitive functions; and neuropsychological tests of memory, problem solving, language skills, and other mental functions.
Different biomarkers provide different types of information about the brain and may be used in combination with each other and with other clinical tests to improve the accuracy of diagnosis — for example, in cases where the age of onset or progression of symptoms is not typical for Alzheimer’s or a related brain disorder.

Physicians with expertise in Alzheimer’s disease and related dementias are the most appropriate clinicians to order biomarker tests and interpret the results. These physicians include neurologists, geriatric psychiatrists, neuropsychologists, and geriatricians.

Currently, Medicare and other health insurance plans cover only certain, limited types of biomarker tests for dementia symptoms, and their use must be justified based on the person’s symptoms and specific criteria.

Read more about diagnosing dementia at www.nia.nih.gov/health/diagnosing-dementia.

**Biomarkers in Dementia Research**

Research on biomarkers for Alzheimer’s disease and other dementias has shown rapid progress. Biomarkers provide detailed measures of abnormal changes in the brain, which can aid in early detection of possible disease in people with very mild or unusual symptoms. People with Alzheimer’s disease and related dementias progress at different rates, and biomarkers may help predict and monitor their progression.

In addition, biomarker measures may help researchers:

- Better understand how risk factors and genetic variants are involved in Alzheimer’s disease
- Identify participants who meet particular requirements, such as having certain genes or amyloid levels, for clinical trials and studies
- Track study participants’ responses to a test drug or other intervention, such as physical exercise

**How You Can Help**

The use of biomarkers is allowing scientists to make great strides in identifying potential new treatments and ways to prevent or delay dementia. These advances are possible because thousands of people have participated in clinical trials and studies. Clinical trials need participants of all different ages, sexes, races, and ethnicities to ensure that study results apply to as many people as possible, and that treatments will be safe and effective for everyone who will use them. Major medical breakthroughs could not happen without the generosity of research participants who become partners in these scientific discoveries.

To learn more about participating in clinical research, visit www.nia.nih.gov/health/clinical-trials.
The Future of Biomarkers

Advances in biomarkers during the past decade have led to exciting new findings. Researchers can now see Alzheimer’s-related changes in the brain while people are alive, track the disease’s onset and progression, and test the effectiveness of promising drugs and other potential treatments. To build on these successes, researchers hope to further biomarker research by:

- Developing and validating a full range of biomarkers, particularly those that are less expensive and/or less invasive, to help test drugs that may prevent, treat, and improve diagnosis of Alzheimer’s and related dementias
- Advancing the use of novel PET imaging, CSF, and blood biomarkers to identify specific changes in the brain related to Alzheimer’s and other neurodegenerative dementias
- Using new MRI methods to measure brain structure, function, and connections
- Developing and refining sensitive clinical and neuropsychological assessments to help detect and track early-stage disease
- Using biomarkers in combination to build a model of Alzheimer’s disease progression over decades, from its earliest, presymptomatic stage through dementia

For More Information

Alzheimer’s and related Dementias Education and Referral (ADEAR) Center
1-800-438-4380 (toll-free)
adear@nia.nih.gov
www.alzheimers.gov

The National Institute on Aging’s ADEAR Center offers information and publications for families, caregivers, and professionals on diagnosis, treatment, patient care, caregiver needs, long-term care, education and training, and research related to Alzheimer’s disease and related dementias. Staff members answer telephone, email, and written requests and make referrals to local and national resources. Visit the ADEAR website to learn more about Alzheimer’s and related dementias, find clinical trials, and sign up for email updates.

To find clinical trials and studies on Alzheimer’s and related dementias, visit:

- ADEAR Center Clinical Trials Finder, www.nia.nih.gov/alzheimers/clinical-trials
- Alzheimer’s Disease Neuroimaging Initiative (ADNI), www.adni3.org

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adear@nia.nih.gov
www.alzheimers.gov

The National Institute on Aging’s ADEAR Center offers information and publications for families, caregivers, and professionals on diagnosis, treatment, patient care, caregiver needs, long-term care, education and training, and research related to Alzheimer’s disease and related dementias. Staff members answer telephone, email, and written requests and make referrals to local and national resources. Visit the ADEAR website to learn more about Alzheimer’s and related dementias, find clinical trials, and sign up for email updates.

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- ADEAR Center Clinical Trials Finder, www.nia.nih.gov/alzheimers/clinical-trials
- Alzheimer’s Disease Neuroimaging Initiative (ADNI), www.adni3.org