Alzheimer’s disease (AD) is an irreversible, progressive brain disease that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks of daily living. Although treatment can help manage the symptoms of AD, there is currently no cure for the disease, although clinical trials for treatments are ongoing.

In 2023, the FDA approved Leqembi (lecanemab), a monoclonal antibody that targets and helps eliminate beta amyloid, a protein that builds up in the brains of individuals with Alzheimer’s disease. Studies showed the drug slowed the rate of cognitive and functional decline by 27%.

According to the Alzheimer’s Association, an estimated 6.7 million Americans age 65 and older are living with Alzheimer’s dementia in 2023. Seventy-three percent are age 75 or older. Of the total US population, about 1 in 9 people (10.8%) age 65 and older has Alzheimer’s dementia.

The percentage of people with Alzheimer’s dementia increases with age:
- 5.3% of people age 65 to 74,
- 13.8% of people age 75 to 84,
- 33.3% of people age 85 and older have Alzheimer’s dementia.

People younger than 65 can also develop Alzheimer’s dementia. Although prevalence studies of younger-onset dementia in the US are limited, researchers believe about 110 of every 100,000 people ages 30-64 years, or about 200,000 Americans in total, have younger-onset dementia.

AD begins deep in the brain where healthy neurons begin to work less efficiently and eventually die. This process gradually spreads to the brain’s learning and memory center—the hippocampus—and other areas of the brain, which also begin to shrink. At the same time, beta-amyloid plaques and neurofibrillary tangles begin to spread throughout the brain. Scientists believe these brain changes begin 10-20 years before the signs or symptoms of the disease appear.

What is molecular imaging?

Molecular imaging is a type of medical imaging that provides detailed pictures of what is happening inside the body at the molecular and cellular level. Where other diagnostic imaging procedures—such as x-rays, computed tomography (CT) and ultrasound—predominantly offer anatomical pictures, molecular imaging allows physicians to see how the body is functioning and to measure its chemical and biological processes.

Molecular imaging offers unique insights into the human body that enable physicians to personalize patient care. In terms of diagnosis, molecular imaging is able to:
- provide information that is unattainable with other imaging technologies or that would require more invasive procedures such as biopsy or surgery
- identify disease in its earliest stages and determine the exact location of a tumor, often before symptoms occur or abnormalities can be detected with other diagnostic tests

As a tool for evaluating and managing the care of patients, molecular imaging studies help physicians:
- assess the function of nerves or brain tissue that use dopamine or other neurotransmitters that have become abnormal in PD
- determine the extent or severity of the disease
• select the most effective therapy based on the unique biologic characteristics of the patient and the molecular properties of a tumor or other disease
• determine a patient's response to specific drugs
• accurately assess the effectiveness of a treatment regimen
• adapt treatment plans quickly in response to changes in cellular activity
• assess disease progression

Molecular imaging procedures are noninvasive, safe and painless.

How does molecular imaging work?
When disease occurs, the biochemical activity of cells begins to change. For example, cancer cells multiply at a much faster rate and are more active than normal cells. Brain cells affected by dementia consume less energy than normal brain cells. Heart cells deprived of adequate blood flow begin to die.

As disease progresses, this abnormal cellular activity begins to affect body tissue and structures, causing anatomical changes that may be seen on CT or MRI scans. For example, cancer cells may form a mass or tumor. With the loss of brain cells, overall brain volume may decrease or affected parts of the brain may appear different in density than the normal areas. Similarly, the heart muscle cells that are affected stop contracting and the overall heart function deteriorates.

Molecular imaging excels at detecting the cellular changes that occur early in the course of disease, often well before structural changes can be seen on CT and MR images.

Most molecular imaging procedures involve an imaging device and an imaging agent, or probe. A variety of imaging agents are used to visualize cellular activity, such as the chemical processes involved in metabolism, oxygen use or blood flow.

In nuclear medicine, which is a branch of molecular imaging, the imaging agent is a radiotracer, a compound that includes a radioactive atom, or isotope. Other molecular imaging modalities, such as optical imaging and molecular ultrasound, use a variety of different agents. Magnetic resonance (MR) spectroscopy is able to measure chemical levels in the body, without the use of an imaging agent.

Once the imaging agent is introduced into the body, it accumulates in a target organ or attaches to specific cells. The imaging device detects the imaging agent and creates pictures that show how it is distributed in the body. This distribution pattern helps physicians discern how well organs and tissues are functioning.

What molecular imaging technologies are used for Alzheimer's disease?
Diagnosis of AD is currently a long process that may include a detailed patient history, physical and neurological exams, laboratory tests and a lengthy process of eliminating other possible causes of mental decline. Although experienced practitioners can diagnose the disease with up to 90 percent accuracy, a definitive diagnosis of AD is still only possible by autopsy following a patient's death.

Researchers are exploring how Positron emission tomography (PET) can help physicians diagnose AD earlier and more accurately and effectively manage patients with the disease.
What is PET?

PET involves the use of an imaging device (PET scanner) and a radiotracer that is injected into the patient's bloodstream. A frequently used PET radiotracer is $^{18}\text{F}$-fluorodeoxyglucose (FDG), a compound derived from a simple sugar and a small amount of radioactive fluorine.

Once the radiotracer accumulates in the body's tissues and organs, its natural decay includes emission of tiny particles called positrons that react with electrons in the body. This reaction, known as annihilation, produces energy in the form of a pair of photons. The PET scanner, which is able to detect these photons, creates three-dimensional images that show how the radiotracer is distributed in the area of the body being studied.

PET and SPECT scanners are most often combined with CT that produces highly detailed views of the body. The combination of two imaging techniques—called co-registration, fusion imaging, or hybrid imaging—allows information from two different kinds of scans to be viewed in a single set of images. CT imaging uses advances x-ray equipment and in some cases a contrast-enhancing material to produce three-dimensional images.

A combined PET-CT study is able to provide detail on both the anatomy and function of organs and tissues. This is accomplished by superimposing the precise location of abnormal metabolic activity (from PET) against the detailed anatomic image (from CT).

How is PET performed?

The procedure begins with an intravenous (IV) injection of a radiotracer, such as FDG, which usually takes between 30 and 60 minutes to distribute throughout the body. The patient is then placed in the PET scanner where special detectors are used to create a three-dimensional image of the FDG distribution.

Scans are reviewed and interpreted by a qualified imaging professional such as a nuclear medicine physician or radiologist who shares the results with the patient's physician.

How is PET used for Alzheimer’s Disease?

Researchers are exploring the use of PET to:

- help diagnose AD early in the disease process
- differentiate AD from other types of dementia
- monitor the progression of the disease
- determine the effectiveness of new therapies
- gain a better understanding of AD, including its causes and progression

What are the advantages of PET for the brain?

- PET allows metabolic activity to be directly visualized, not inferred.
- PET studies allow abnormal brain function to be detected before structural changes resulting from brain cell death can be seen on CT or MRI.
- PET is highly useful in detecting specific types of dementia, such as Alzheimer's disease and Pick's disease, a type of frontotemporal dementia. In these disorders, early brain damage is
too spread out, or diffuse, and may not impact brain volume or structure that is identifiable on CT or MR.

**Is PET covered by insurance?**

Insurance companies will cover the cost of most PET scans, however, coverage for PET scans that measure brain amyloid plaques is not yet available. Check with your insurance company for specific information on your plan.

**What is the future of molecular imaging and Alzheimer’s disease?**

While molecular imaging technologies such as PET are still primarily research tools, they may one day help physicians to:

- routinely diagnose AD at its earliest stages, which is critical for providing the best possible care
- identify individuals who are at high risk of developing Alzheimer’s disease
- monitor the progress of the disease
- assess patient response to drug treatment
- contribute to the development of targeted drugs and therapies for dementia and Alzheimer’s disease.

**Dementia and Alzheimer’s Disease**

Important research underway includes the National Institute on Aging’s Alzheimer’s Disease Neuroimaging Initiative (ADNI), which is following hundreds of cognitively healthy individuals and others with mild cognitive impairment (MCI) and early Alzheimer’s disease over at least five years. Participants will undergo annual MRI and PET scans so that researchers can assess changes in both the normal aging brain and in individuals with MCI and AD to better understand when and where in the brain degeneration occurs.

By correlating these images with other test results from the study’s participants, such as cognitive function tests and fluid and urine samples, researchers hope to identify valuable biomarkers of the disease process. Researchers hope that this study and future initiatives using the ADNI database will create imaging and biomarker standards for measuring the success of potential treatments.

While molecular imaging technologies such as beta-amyloid imaging with PET are currently only used as research tools, they may soon help physicians to:

- routinely diagnose AD at its earliest stages, which is critical for providing the best possible care
- identify individuals who are at high risk of developing Alzheimer’s disease
- monitor the progress of the disease
- assess patient response to drug treatment
- contribute to the development of targeted drugs and therapies for dementia and Alzheimer’s disease
About SNMMI

The Society of Nuclear Medicine (SNMMI) is an international scientific and medical organization dedicated to raising public awareness about nuclear and molecular imaging and therapy and how they can help provide patients with the best health care possible. With more than 18,000 members, SNMMI has been a leader in unifying, advancing and optimizing nuclear medicine and molecular imaging since 1954.

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