Lymphoma is the most common type of blood cancer. Specifically, lymphoma is a cancer that affects lymphocytes, which are a type of white blood cell. Lymphocytes travel through the blood and lymphatic system to defend the body against foreign invaders like bacteria and viruses. Lymphomas usually develop when a change, or mutation, occurs within a lymphocyte, causing the abnormal cell to replicate faster than, or live longer than, a normal lymphocyte. Like normal lymphocytes, cancerous lymphocytes can travel through the blood and lymphatic system and spread and grow in many parts of the body, including the lymph nodes, spleen, bone marrow, and other organs.

Three major categories of cancers that affect lymphocytes are:

- **Hodgkin Lymphoma (HL):** There are five types of HL, an uncommon form of lymphoma that involves the Reed-Sternberg cells. Approximately 8,570 people (4,630 male; 3,940 female) are expected to be diagnosed with HL in the US in 2024.

- **Non-Hodgkin Lymphoma (NHL):** There are more than 90 types of NHL, some of which are more common than others. Any lymphoma that does not involve Reed-Sternberg cells is classified as non-Hodgkin lymphoma. Approximately 80,260 people (44,590 male; 36,030 female) are expected to be diagnosed with NHL in the US in 2024.

- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL):** Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are forms of non-Hodgkin lymphoma (NHL) that arise from B lymphocytes. CLL/SLL are the same disease with slightly different manifestations. Where the cancerous cells gather determines whether it is called CLL or SLL. Leukemic cells develop because of a change that takes place in the cell's DNA. Approximately 21,000 people are diagnosed with CLL/SLL in the US each year.

According to the Lymphoma Research Foundation, more than 100,000 people are diagnosed with lymphoma or Chronic Lymphocytic Leukemia (CLL) each year and there are nearly one million in the US living with, or in remission from, lymphoma. Overall, non-Hodgkin's lymphoma is the fifth most common cancer affecting adults in the US. Hodgkin's lymphoma (HL), also known as Hodgkin's disease, represents about 10 percent of all lymphomas.

Treatment options for lymphoma include chemotherapy and radiation therapy. Effective treatment depends on an accurate assessment of the location and extent of disease at the time of diagnosis, as well as how the patient responds to treatment.

Molecular imaging has become an essential tool in the diagnosis, evaluation and treatment of patients with lymphoma.

**What is molecular imaging and how does it help people with lymphoma?**

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:

- determine the extent or severity of the disease, including whether it has spread elsewhere in the body
- 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
- identify recurrence of disease and help manage ongoing care

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 lymphoma?**

The most commonly used molecular imaging technique for diagnosing and treating lymphoma is positron emission tomography (PET) scanning and PET in conjunction with computer-aided tomography (CT) scanning (PET-CT).

Non-Hodgkin’s lymphoma patients who do not respond to chemotherapy may undergo radioimmunotherapy (RIT).

**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 $^{18}$F-fluorodeoxyglucose (FDG), a compound derived from a simple sugar and a small amount of radioactive fluorine.

Once the FDG 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 FDG is distributed in the area of the body being studied.

Areas where a large amount of FDG accumulates, called ‘hot spots’ because they appear more intense than surrounding tissue, indicate that a high level of chemical activity or metabolism is occurring there. Areas of low metabolic activity appear less intense and are sometimes referred to as ‘cold spots.’ Using these images and the information they provide, physicians are able to evaluate how well organs and tissues are working and to detect abnormalities.

PET-CT is a combination of PET and computed tomography (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 types of scans to be viewed in a single set of images. CT imaging uses advanced 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 lymphoma?
Physicians use PET-CT studies to:
- diagnose and stage: by determining the exact location of a tumor, the extent or stage of the disease and whether the cancer has spread in the body
- plan treatment: by selecting the most effective therapy based on the unique molecular properties of the disease and of the patient's genetic make-up
- evaluate the effectiveness of treatment: by determining the patient's response to specific drugs and ongoing therapy. Based on changes in cellular activity observed on PET-CT images, treatment plans can be quickly altered
- manage ongoing care: by detecting the recurrence of cancer

What are the advantages of PET for people with lymphoma?
For the diagnosis and treatment of lymphoma, PET-CT scans:
- are the most accurate single test to evaluate lymphoma
- have resulted in a change in treatment plan for more than one-third of lymphoma patients registered in the National Oncologic PET Registry (NOPR)
- are recommended for the diagnosis, treatment and restaging for most types of lymphoma by cancer experts, including the National Comprehensive Cancer Network.
- provide the most accurate means of monitoring lymphoma patients. Using PET-CT scans, physicians are able to determine the difference between scar tissue and active disease and discover new tumors before they would be revealed by CT alone.

18F-FDG PET scan of a patient with diffuse large B-cell lymphoma. (A) PET scan (B) CT scan (C) PET/CT scan.
Source: http://jnm.snmjournals.org/content/45/1_suppl/72S.full
Is PET covered by insurance?

PET-CT studies to diagnose and evaluate the effectiveness of treatment for lymphoma are covered by Medicare and Medicaid. Major insurance companies and health maintenance organizations also provide coverage for PET-CT studies for lymphoma. Check with your insurance company for specific information on your plan.

What is radioimmunotherapy (RIT)?

Radioimmunotherapy (RIT) is a personalized cancer treatment that combines radiation therapy with the precise targeting ability of immunotherapy, a treatment that mimics cellular activity in the body's immune system.

In a healthy immune system, certain white cells are able to recognize invading organisms such as bacteria and viruses. The white cell secretes a protein substance called an antibody that identifies a feature of the foreign cell called an antigen. The antibody coats the invading cell, which enables other white cells to destroy it.

In immunotherapy, scientists create monoclonal antibodies in a laboratory that are designed to recognize and bind to the antigen of a specific cancer cell. In RIT, the monoclonal antibody is paired with a radioactive material. When injected into the patient's bloodstream, the antibody travels to and binds to the cancer cells, allowing a high dose of radiation to be delivered directly to the tumor. Several new radioimmunotherapy agents are under development or in clinical trials.

What is the future of molecular imaging and lymphoma?

In addition to increasing our understanding of the underlying causes of disease, molecular imaging is improving the way disease is detected and treated. Molecular imaging technologies are also playing an important role in the development of:

- screening tools for various diseases and medical conditions for at-risk populations
- new and more effective drugs, by helping researchers more quickly understand and assess new drug therapies
- personalized medicine, in which medical treatment is based on a patient's unique genetic profile

In the future, molecular imaging will include an increased use of:

- fusion or hybrid imaging, in which two imaging technologies are combined to product one image
- optical imaging
- new probes for imaging critical cancer processes
- reporter-probe pairs that will facilitate molecular-genetic imaging
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.

The material presented in this pamphlet is for informational purposes only and is not intended as a substitute for discussions between you and your physician. Be sure to consult with your physician or the nuclear medicine department where the treatment will be performed if you want more information about this or other nuclear medicine procedures.