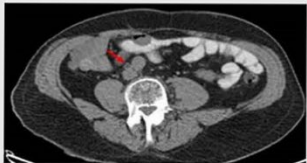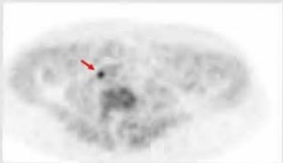# Molecular Imaging and Prostate Cancer

The American Cancer Society's estimates that there will be about 299,010 new cases of prostate cancer in the United States in 2024. When detected early, prostate cancer has more than a 95 percent cure rate. Screening for prostate cancer is performed with a simple blood test measuring PSA level (prostate-specific antigen) and starts at the age of 55. Screening may start as early as the age of 40 for men with increased risk factors. Once prostate cancer is diagnosed, treatment may be highly individualized, and molecular imaging technologies dramatically improve how prostate cancer is localized and treated.

Treatment options include surgery to remove the prostate, radiation therapy, and hormonal or chemotherapy. Determining whether prostate cancer has spread to the lymph nodes or other parts of the body is critical for making appropriate decisions on whether and how to treat prostate cancer. In addition to improving the accuracy of prostate cancer diagnosis, molecular imaging tools can provide detailed information about the cancer that helps patients and their physicians choose the best treatment option.
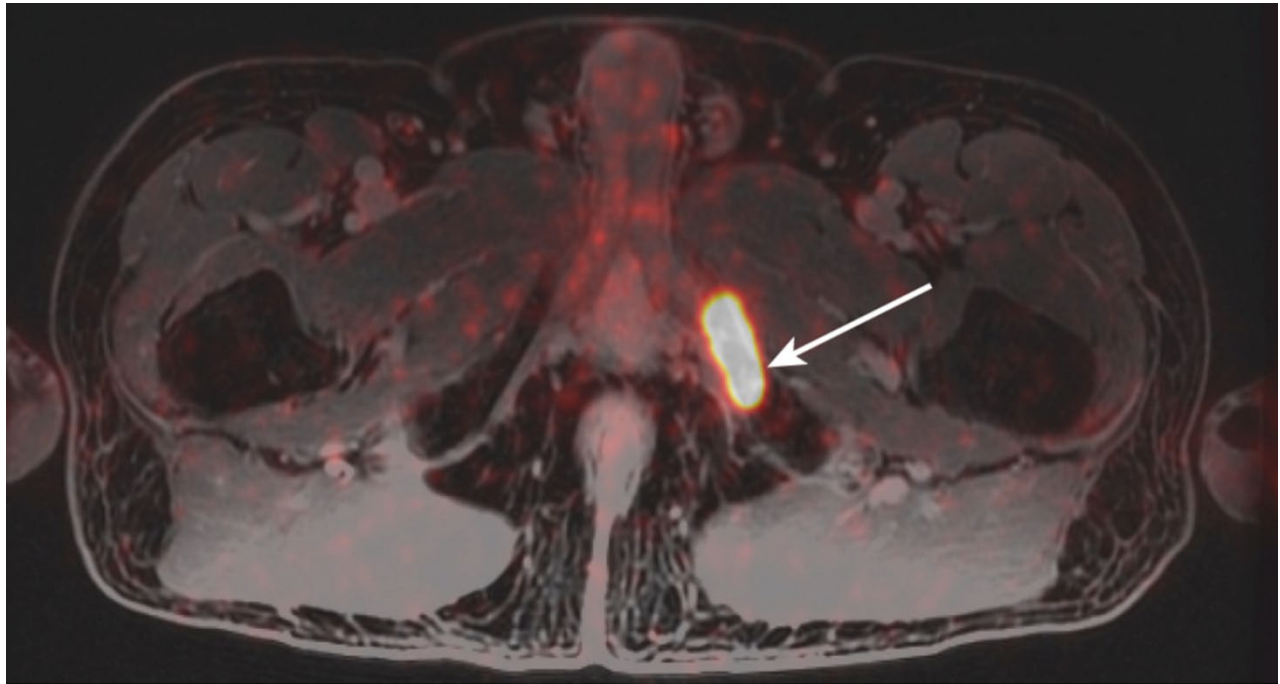
What is molecular imaging, and how does it help people with prostate cancer?

Molecular imaging is a type of medical imaging that provides detailed pictures of what is happening inside the body at the molecular and cellular levels. Where conventional imaging methods such as x-ray (radiographs), computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) predominantly offer anatomical pictures, molecular imaging allows physicians to see how the body functions and measures its chemical and biological processes.

	Conventional images	Molecular images
Type of scans	Radiographs, US, CT, MRI	Biological Photon/Single-photon emission (PET, SPECT)
Identification of lesions is based on	Anatomy Size Shape Location	Biological pathways Over expression of receptors Overuse of different metabolic pathways
Example	CT below pointing on a tiny lymph node that appears normal in anatomy	Same Lymph node with fluciclovine PET tracer uptake indicating abnormal biology. Biopsy proven to be prostate cancer spread to lymph node

Molecular imaging can also use both morphologic and physiologic in a "Hybrid" image. By superimposing the precise location of abnormal metabolic activity (from PET) in a tissue or an organ against the detailed anatomic image (from CT or MRI) we can get information from two different types of scans in a single set of images.

The image below is a PET/MRI. The arrow is indicating a bone metastasis in the left inferior public ramus.

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Molecular imaging offers unique insights into the human body that enable physicians to personalize patient care.

Overall 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:

- Provide early localization of primary and recurrent disease before it is seen in conventional images (such as US, CT, MRI).
- Determine the extent or severity of the disease, including whether it has spread elsewhere in the body
- Personalize therapy based on the unique biologic characteristics of the patient and the molecular properties of a tumor or other disease
- Determine a patients' response to specific drugs and accurately assess the effectiveness of a treatment regimen and adjust treatment plans quickly in response to changes in cellular activity

- Assess disease progression
- Identify recurrence of disease and help manage ongoing care
- Determine appropriateness or eligibility for new therapies

Nuclear medicine molecular imaging procedures involve the use of radiation in small amounts that are relatively non-invasive, safe, and painless. Consult with your health provider for specific information on the safety and benefits of molecular imaging for your care.

More information about nuclear medicine and radiation can be found in our Factsheet: Nuclear Medicine and Radiation Safety

How does molecular imaging work?

When disease occurs, the biochemical activity of cells begins to change. For example, cancer cells may multiply much faster, resulting in increased demand for energy compared with normal cells. Brain cells affected by dementia require less energy than normal brain cells. Heart cells that suffer from lack of oxygen due to vessel occlusion will have less perfusion than adjacent healthy cells. The use of different molecular imaging helps to locate these abnormal processes for diagnosis and treatment.

Molecular imaging may diagnose a disease before there are anatomical changes. Most times, the anatomical changes that are seen on CT or MRI scans are a direct result of the abnormal cellular activity that occur in the disease process. For example, cancer cells may form a mass or tumor. With the gradual loss of brain cells, overall brain volume may decrease. Similarly, the heart muscle cells that lack oxygen will stop contracting, and the overall heart function deteriorates. Molecular imaging excels at detecting the cellular changes that occur early in the course of the disease, often well before structural changes can be seen on conventional imaging. Similarly, molecular imaging can detect treatment-induced cellular activity changes earlier than structural changes.

Most molecular imaging procedures involve an imaging device, and an agent, or a probe. A variety of imaging agents are used to visualize cellular activity, such as the chemical processes involved in metabolism, specific receptors, oxygen use, or blood flow. In molecular imaging, the imaging agent is known as a radiopharmaceutical or radiotracer. This compound includes a pharmaceutical structure attached to a minimal amount of radioactive element.

Once the imaging radiotracer 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 showing how the imaging agent is distributed in the body. This distribution pattern helps physicians determine how well organs and tissue function.

What are the molecular imaging technologies used for prostate cancer?

Several molecular radiotracers demonstrate the ability to diagnose and guide the treatment of prostate cancer using different pathophysiology processes that are related to prostate cancer metabolism and cell growth. These include metabolic radiotracers such as FDG, ^{18}F-Fluciclovine, and choline as well as agents that target the prostate-specific membrane antigen (PSMA). These radiotracers utilize positron emission tomography (PET) scanning in conjunction with computer-

aided tomography (CT) to identify sites of disease. Additional molecular imaging radiopharmaceuticals that specifically target prostate cancer bone metastases include sodium fluoride PET and bisphosphonate bone scans.

What is a PET Scan?

Positron emission tomography (PET) is an imaging technique that is able to localize and quantify the amount of positron emitting radiotracers that accumulate in the body's tissues and organs. These radiotracers decay by the 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 tracer is distributed in the area of the body being studied.

Areas where radiotracers accumulate, are called "hot spots" because they appear more intense than surrounding tissue indicating the presence of a high level of biochemical targets or metabolism. Using these images and the information they provide, physicians can evaluate how well organs and tissues are working and detect abnormalities.

Hybrid PET imaging is a combination of PET and computed tomography (PET/CT) or magnetic resonance (PET/MR) that produces highly detailed images of the body. The combination of two imaging techniques is also called co-registration or fusion imaging. CT imaging uses advanced x-ray equipment and, in some cases a contrast-enhancing material to produce three-dimensional images. MR uses changes in magnetic fields in the body to generate anatomical images. The use of hybrid PET/CT or PET/MR by superimposing the precise location of abnormal pathological activity (from PET) in a tissue or an organ against the detailed anatomic image (from CT or MR) provides information from two different types of scans in a single set of images.

FDG PET Scan

FDG PET scan involves the use of a PET with an ^{18}F-Fluorodeoxyglucose (FDG) radiotracer. FDG is a compound derived from a simple sugar (glucose) and a small amount of radioactive fluorine. FDG accumulates in tissues with high metabolic activity levels, such as the normal brain tissue. Many cancers, including aggressive prostate cancer (also known as high Gleason Score), accumulate high levels of FDG due to their altered metabolism and rapid cell growth. Given the newer available PET tracers, FDG PET is not as commonly used to diagnose prostate cancer. In the past, FDG PET/CT was typically used in patients with known high-grade prostate cancer to determine if the disease has spread to pelvic lymph nodes or the skeleton.

Choline PET Scan

A choline PET scan uses PET and the ^{11}C-choline radiotracer, a positron-emitting radiopharmaceutical. Choline is an essential component of cell membranes and accumulates in tissues with high cellular proliferation (high rate of cell replication). Malignancies, such as prostate cancer demonstrate increased choline uptake and incorporation into their cellular membranes. ^{11}C-choline PET is used in patients with prostate cancer previously treated and now have an increase in prostate-specific antigen (PSA) blood levels suggesting recurrent prostate cancer. Choline is not widely available for commercial distribution in the United States.

Fluciclovine PET

A ^{18}F-Fluciclovine (Axumin**®)** PET scan uses PET and the ^{18}F-Fluciclovine radiotracer. ^{18}F-Fluciclovine is a positron-emitting synthetic amino acid radiotracer that accumulates in prostate cancer cells. Amino acids are essential to cell metabolism and growth, and prostate cancer cells have a much higher nutrient demand compared to normal tissues. Like choline PET, ^{18}F-Fluciclovine PET is used in patients that have previously been treated for prostate cancer and now have a clinical suspicion of recurrent disease and rising PSA blood levels. ^{18}F-Fluciclovine is widely available for commercial distribution in the United States. Since its approval by the FDA, it has been the primary PET tracer for the localization of patients with a history of prostate cancer that present with suspicion of recurrent disease.

Recently, the FDA approved a new generation of PET tracers for prostate cancer imaging using specific receptors on prostate cells called prostate-specific membrane antigen (PSMA).

PSMA Scan

Prostate-specific membrane antigen is a cell surface protein that is commonly overexpressed by prostate cancer cells. Several small molecules targeting PSMA are available for imaging men with prostate cancer using positron emission tomography (PET). Currently available radiotracers include ^{68}Ga-PSMA-11 (LOCAMETZ or ILLUCCIX), and ^{18}F-rhPSMA-7.3 or flotufolastat F 18 (POSLUMA).

According to the United States Food and Drug Administration (FDA), use of these radiotracers is indicated for the following groups of patients: (1) men with newly diagnosed prostate cancer with suspected metastatic disease who are candidates for definitive therapy, (2) men who have already undergone treatment and are suspected of having a recurrence on based an elevated serum prostate-specific antigen (PSA) level, and (3) men with metastatic prostate cancer being considered for treatment with the PSMA-targeted radioligand therapy known as ^{177}Lu-PSMA-617 or lutetium Lu 177 vipivotide tetraxetan (PLUVICTO). Although the FDA stipulates that only ^{68}Ga-PSMA-11 is approved for this third indication, the Society of Nuclear Medicine and Molecular Imaging feels that any of the available PSMA-targeted radiotracers can be used for this purpose.

How is PET performed?

Depending on the specific radiotracer used for the PET study (FDG, choline, fluciclovine, PSMA), patients may be asked to fast or avoid exercise before arriving for the PET study. The procedure begins with an intravenous (IV) injection of the radiotracer followed by a waiting period to allow the radiotracer to distribute throughout the body. The waiting time required depends on the radiotracer and may be short (4 minutes for fluciclovine) or longer (45-90 minutes for PSMA and FDG). The patient is then placed in the PET scanner, where special PET detectors create a three-dimensional image with the radiotracer bio-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.

What is a bone scan, and how is it performed?

A bone scan is a diagnostic imaging test used to determine whether cancer cells have spread to the skeleton. It involves the intravenous injection of a radiotracer that accumulates predominantly in

the bones, where the pattern of accumulation can be detected by a PET scan or gamma camera, depending on the type of radiotracer being used. The resulting two-dimensional or three-dimensional images can detect cancer lesions and various additional processes such as bony fractures, infection, inflammation, and changes secondary to the presence of cancer cells.

The most commonly used radiotracer for bone scans is a bisphosphonate attached to gamma emitting radioactive element ^{99m}Tc that can be detected using a gamma camera. The second commonly used tracer is a ^{18}F-sodium fluoride positron-emitting radiotracer that uses a PET camera and is similar to a bone scan with a higher sensitivity for detecting bone metastases.

What are the advantages of molecular imaging for people with prostate cancer?

- **Diagnosis and staging:**
  - Molecular imaging with PET can identify locally prostate cancer and sites of lymph node or skeletal metastatic disease.
  - While a molecular imaging PET scan may be used in place of a bone scan to determine whether prostate cancer has spread to the bone painlessly, it can also be used in conjunction with a bone scan or MRI to increase the accuracy of skeletal disease identification.
  - PET studies are able to determine the extent of prostate cancer and whether it has spread to the lymph nodes or other parts of the body before traditional imaging technologies such as magnetic resonance imaging (MRI) and computed tomography (CT), which are often unable to detect the spread of prostate cancer cells until later stages when metastases are more pronounced. Of note, MRI better defines local anatomy in the prostate bed and is useful for surgical planning.
- **Plan treatment:**
  - Molecular imaging technologies help physicians select the most effective therapy for prostate cancer, taking into account a tumor's unique molecular properties and whether the cancer is localized or diffuse, or spread out.

Does insurance cover molecular imaging?

Medicare and most private insurance companies will cover the cost of most PET scans. Check with your insurance company for specific information on your plan.

What is the future of molecular imaging and prostate cancer?

Developments underway include:

- New imaging agents for PET scanning of the prostate
- Hybrid imaging in which PET studies are combined with other imaging technologies such as CT or MRI to improve image accuracy and to offer more targeted treatment
- The use of radioligand therapy (RLT) such as ^{177}Lu PSMA-617

New molecular imaging techniques that will:

- Predict the aggressiveness of a tumor
- Predict the outcome of treatment
- Detect genetic markers of the disease
- Assist physicians in developing even more tailored treatment plans

What is Radioligand therapy (RLT) with ^{177}Lu-PSMA-617 in prostate cancer?

^{177}Lu PSMA-617 is a therapeutic radiopharmaceutical that delivers beta-particle radiation selectively to cells with high expression of PSMA. Similar to the ^{68}Ga PSMA-11 (Locametz**®)** or ^{18}F PSMA-DcPyL (Pylarify**®)** radiotracers, the ^{177}Lu PSMA-617 attaches to an extracellular site on the PSMA structure. The difference between the two radiopharmaceuticals is the radioactive element attached to the pharmaceutical. While ^{68}Ga or^{18}F are diagnostic PET radiopharmaceuticals that emit positrons to be detected by the PET scan; ^{177}Lu is a therapeutic element that delivers high energy beta radiation therapy to the cancer and its surrounding microenvironment. The combination of a diagnostic radiotracer followed by the administration of a therapeutic dose is known as Theranostics or Theragnostics (**Ther**apy and Dia**gnostics**). Theranostics agents offer precise radiation targeting mechanisms.

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.