MYOCARDIAL PERFUSION IMAGING: Obtaining Optimal Images during Technetium-99m Shortages

PROGRAM OBJECTIVES

Upon completion of this program, participant will be able to:

- Gain a better understanding of the Molybdenum supply challenges
- Evaluate and assess imaging options and alternative protocols
- Understand how to obtain high quality studies using alternative methods
- Discuss the advantages and disadvantages of each method
- Use clinical and technical knowledge to aid interpretation

INTRODUCTION

During the last few years, it has been challenging to consistently provide quality nuclear medicine studies because of ongoing supply issues our industry has had to face. Many departments are using older equipment and the Molybdenum-99 (Mo-99) supply problems are becoming more difficult to address globally.

The United States has been researching alternative means for domestic isotope production since aging reactors issues began several years ago. Currently there are no reactors in the US that are dedicated to manufacturing Mo-99 the parent isotope of technetium-99m used to manufacture Mo-99/Tc-99m generators.¹

In May 2009, the National Research Universal (NRU) reactor in Chalk River, Ontario was taken offline by the Atomic Energy of Canada Limited (AECL) for immediate repair after a heavy water leak was identified. The shutdown of the NRU reactor has extended into the first quarter of 2010. This reactor produces approximately 30% of the world's supply of Mo-99.²

The January 2010 status report from the AECL stated that the NRU reactor repairs are scheduled to be completed in February 2010 but depending on the challenges with the repair process, the NRU return-to-service schedule could extend into April. This, coupled with the scheduled six month shutdown in late February 2010 of the High Flux Reactor (HFR) located in the Netherlands, has increased the need to use alternative methods to stretch the capacity of the limited supply of Tc-99m generators.

There are a number of options available to help maintain high quality standards for your facility. The Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories (ICANL) encourages laboratories to maintain their high standards for quality imaging during these shortages. Currently accredited labs are required to have written protocols for all alternative procedures performed during an isotope shortage but are only required to have them in their procedure manual. They recommend referring to the current American Society of Nuclear Cardiology (ASNC) guidelines for imaging protocol and tracer options. These options range from alternate tracers to a variety of protocol options as well as different imaging modalities. Implementing and researching some of these options will help you maintain your patient volumes and throughput without sacrificing image quality. Simple modifications to your daily routine can potentially have a significant impact on the nuclear medicine community overall. The key is to understand these differences and when they are considered clinically appropriate. Some can even be implemented with only a minor impact to the overall facility. Many of these options and alternative methods will be addressed in this course.

MYOCARDIAL PERFUSION IMAGING (MPI) PROTOCOLS

1 Day MPI Protocols

Tc-99m tracer protocols

One day Tc-99m tracer protocols using sestamibi or tetrofosmin are performed basically in the same manner with few minor differences. The most commonly used protocol is to inject a low dosage (approx 8-12 mCi Tc-99m sestamibi or tetrofosmin) at rest and the resting SPECT scanning can be performed in approximately 30-60 minutes depending on the optimal imaging time for each pharmaceutical. The stress injection (approx 24-36 mCi Tc-99m sestamibi or tetrofosmin) is given at peak exercise or peak infusion for pharmacologic testing. The stress test can be done shortly after the rest scan is complete as long as there is at least a 1:4 ratio of rest dosage to stress dosage per ASNC guidelines to avoid radiation crosstalk. If this is not possible during the times of Tc-99m shortages, there should be at least two hours from rest injection to stress image to decrease "shine-through" from the rest dosage. The post-stress SPECT scan should be acquired with gating since left ventricular ejection fractions are the most accurate when acquired with the higher dosage. This protocol is the most popular due to patient throughput and convenience. Testing can be completed in 3-4 hrs or less depending on camera efficiency.

Testing can also be done with the stress portion as the low dosage and the rest portion as the higher dosage. This protocol uses the same ratio logic for dosing to avoid crosstalk, using a 1-4 ratio of stress dosage to rest dosage. The stress portion is performed first and post-stress SPECT images are acquired based on the ASNC guidelines for exercise and pharmacologic testing. The rest portion is to be done 2.5-4 hours later per ASNC guidelines. The rest injection is given after the post-stress gated SPECT images are acquired with the rest scan performed approximately 30-45 minutes later depending on the pharmaceutical used. Again the higher dosage should be used for gating. It is optional to acquire gating at both rest and stress in either of these protocols.

Dual Isotope MPI Protocol

Dual isotope imaging has been used for years however its use has recently increased as an alternative to the technetium-only based protocols in an effort to stretch the limited availability of Tc-99m during times of shortage. Dual isotope is performed using Thallium-201 (Tl-201) thallous chloride as the resting imaging agent and the Tc-99m sestamibi or tetrofosmin dosage as the stress imaging agent. This option allows for a significant decrease in time from rest injection to rest scan since imaging is to be done within 10-15 minutes maximum since Tl-201 redistributes out of the myocardium very quickly. The advantage of this protocol is that Tl-201 is more readily available especially during a Tc-99m shortage and an unused dose can be salvaged and used later in the day or even the following day due to its physical half-life of 73.1 hours.

There is less intestinal and liver uptake with TI-201 but the images will be more diffuse in comparison to the crisper Tc-99m tracer images. The interpreting physician will need to become familiar with these differences especially when comparing TI-201 rest to Tc-99m stress images.

The upside of this protocol is that the Tc-99m stress portion can be done immediately after the Tl-201 rest images are acquired since there is virtually no radiation crosstalk since the principle emissions from Tl-201 are 68-80 keV verses 140 keV with Tc-99m. This allows for more rapid throughput compared to the Tc-99m protocol. Since imaging timing is critical with Tl-201, the camera must be readily available whereas with Tc-99m tracers you have more imaging flexibility. The camera must be peaked and calibrated for both Tl-201 and Tc-99m using this protocol option. It is best to check with your camera manufacturer before you proceed with switching isotopes. Many cameras will require new uniformity corrections and some of the older camera models will require longer imaging times due to decreased count efficiency. These factors need to be taken in consideration and schedule patients accordingly.

Thallium Stress/Rest Protocol

Thallium imaging was originally introduced in the 1970's but has seen a bit of a reemergence due to the medical isotope production problems. Some facilities in remote areas are only able to receive Tl-201 during the shortage periods. They have to adjust their patient scheduling accordingly thus reducing patient throughput in comparison to the more efficient Tc-99m tracer protocols.

In this protocol, the stress portion is done first using a 2.5-4.0 mCi Tl-201 dosage at peak exercise or peak infusion for pharmacologic studies. Images must be acquired within 10-15 minutes to capture the stress perfusion images before tracer redistribution occurs. If gating is desired, the post-stress SPECT images are the only option due to the lack of counts in the delayed images. The resting image acquisition is done 3-4 hours later. A resting injection is not needed for the delayed images but physicians may also obtain 18-24 hour delayed images to further assess viability. A 1-2 mCi Tl-201 injection is given after the initial delayed images to increase the target to background count ratio.

As with the dual isotope protocol, the camera must be readily available for the post-stress images. The camera must be calibrated for Tl-201 and new uniformity corrections may be needed prior to switching to this protocol. The quantitative software may also

need to be adjusted for Tl-201. Check with your manufacturer for recommendations. Since most quantitative software was designed using Tc-99m tracers the databases may not provide accurate results.

MPI: Obtaining Optimal Images during Technetium-99m Shortages

MYOCARDIAL PERFUSION IMAGING (MPI) PROTOCOLS

2 Day MPI Protocols

Tc-99m tracer Stress/Rest and Rest/Stress

The two day protocol whether done as rest/stress or stress/rest yields the highest quality study since there is the lowest target to background ratio especially when the dosage is approximately 24-36 mCi for each injection. In times of Tc-99m shortages, some cardiologists have modified their standard protocol to use lower activity dosages. There is no image crosstalk when imaging is performed at least 18-24 hours apart and scheduling can be a bit more flexible.

The 2 day protocol is recommended for overweight patients (>250 lbs or body mass index > 30) or in female patients where significant breast attenuation is anticipated.⁶

The various protocols, based on the American Society of Nuclear Cardiologists (ASNC) imaging guidelines for stress protocols and tracers updated in 2009, are summarized in Table 1.⁶

Table 1 – Summary of Available MPI Imaging Protocols

Imaging Protocol	1st Injection	Delay (approx.)	1st Image*	2nd Injection	Delay (approx.)	2nd Image*
1 Day Tc-99m Rest/Stress	8-12 mCi Tc-99m (rest inj.)	30-60 minutes	15-30 minutes	24-36 mCi Tc-99m** Per stress protocol (peak exercise/infusion)	15-60 minutes	12-25 minutes
1 Day Tc-99m Stress/Rest	8-12 mCi Tc-99m (stress inj.) Per stress protocol	15-60 minutes	15-30 minutes	Approx 3-4 hrs recommended post stress injection 24-36 mCi Tc-99m** (resting injection)	30-60 minutes	12-25 minutes
1 Day Dual Isotope	2.5-4.0 mCi Tl-201 (rest inj.)	10-15 minutes	15-30 minutes	24-36 mCi Tc-99m** Per stress protocol (peak exercise/infusion)	15-60 minutes	12-25 Minutes
2 Day Tc-99m Rest/Stress	24-36 mCi Tc-99m** (rest inj.)	30-60 minutes	15-30 minutes	24 hrs after rest study - 24-36 mCi Tc-99m** Per stress protocol (peak exercise/infusion)	15-60 minutes	12-25 Minutes
2 Day Tc-99m Stress/Rest	24-36 mCi Tc-99m** (stress inj.) Per stress protocol	15-60 minutes	12-25 minutes	24 hrs after stress study - 24-36 mCi Tc-99m** (resting injection)	30-60 minutes	12-25 Minutes
Thallium Stress/Rest with Viability (optional)	2.5-4.0 mCi TI-201 (stress inj.) Per stress protocol	10-15 minutes	15-30 minutes	2.5-4.0 hrs recommended delay for resting images	N/A	15-30 minutes (1-2 mCi Tl- 201 optional for viability at 18-24 hrs)

^{*} Imaging time is based upon published ASNC recommendations, which is dependent upon the counting efficiency per recommendations of the camera manufacturer.

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^{**} Higher dose is recommended for gating purposes.

Stress Only (Resting optional) MPI Protocol

Tc-99m tracer protocol

There have been at least three clinical studies conducted recently to support stress-only myocardial perfusion imaging. Some clinicians have considered selectively using stress-only imaging when the stress images are normal. These studies have shown that acquiring a rest study after a normal stress study has not changed the previous diagnosis or treatment.

Another study is being published in the January 19, 2010 issue of the *Journal of the American College of Cardiology* which further supports the results of the previous studies. The study authors, Dr. Su Min Chang and colleagues have stated, "Our results indicate that additional rest imaging is unnecessary in patients with a normally appearing initial stress SPECT. Selectively targeting rest imaging to appropriate patients should lower cost by eliminating unnecessary imaging time and radiopharmaceutical doses, improve laboratory throughput, and significantly lower radiation exposure in a substantial percentage of patients." Since concern had been raised over the safety of this imaging strategy, the study consisted of 27,540 consecutive patients who underwent SPECT with Tc-99m radiotracers at their institution from 1999 to 2007. After an average follow-up of 4.5 years, they concluded that there were no significant differences in outcomes between the stress-only and stress-plus-rest groups.⁷

These studies have used similar approaches for determining the necessity of resting images. The stress images are obtained and then a decision is made by the interpreting physician as to whether to proceed with resting images. A normal stress perfusion study with an ejection fraction of 50% or greater and no stress EKG abnormalities is considered completely normal and resting images are not obtained. Patients who cannot exercise are at a higher risk for cardiac events so this strategy may be best for patients that can exercise adequately. Attenuation correction and prone imaging may help reduce the rest studies by reducing attenuation artifacts on the stress images.

The limitation of this protocol is in evaluating the transient ischemic dilatation (TID) ratio; this is a calculation comparing the rest quantitative data to the stress quantitative data. The highest risk is when balanced ischemia is present which would appear as normal perfusion but this possibility decreases significantly if all the stress testing results and previous history are available for the interpreting physician. Low risk patients with low to moderate probability of ischemia are the target group of patients for this protocol.

A positive stress study would still require a resting comparison the following day regardless of the stress imaging results. Ideally patient studies should be interpreted by the physician before the patient is dismissed to determine if the resting scan will be needed. If this isn't possible, you should give all patients a return time for the rest study within 24-48 hrs preferably. If a patient's stress study is considered normal, the rest portion is cancelled. Rest scans can also be worked into the schedule later in the day to accommodate the lab and patient's schedule. The American Society of Nuclear Cardiology (ASNC) believes that for the appropriate use of this strategy it is essential that the interpreting physicians be highly experienced, and that they are to make the decisions about who will benefit from resting images. When in doubt, do the rest study.⁸

PET MYOCARDIAL PERFUSION IMAGING OVERVIEW

Positron Emission Tomography (PET) is used to detect physiologically significant coronary artery narrowing with a view towards aggressive risk factor modification in order to:

- 1. Delay or reverse the progression of atherosclerosis
- 2. Alleviate symptoms of ischemia by medical or revascularization therapy
- 3. Prevent future adverse events
- 4. Improve patient survival

Stress and rest perfusion studies are performed to assess myocardial ischemia and/or infarction. Currently, reimbursement is limited to Rubidium-82 (Rb-82) chloride and Nitrogen-13 ammonia (N-13 ammonia) for myocardial blood flow tracers. Perfusion imaging can also be combined with myocardial metabolism imaging with F-18 FDG for the assessment of myocardial viability.

Patient preparation is similar to SPECT imaging and the main limitation is due to the differences in acquisition protocols for Rb-82 chloride and N-13 ammonia which are related to the duration of uptake and clearance of the radiopharmaceuticals.

Rubidium-82 Chloride Perfusion Imaging

Rb-82 is the decay product of Strontium-82 (Sr-82). Rb-82 chloride is eluted from a Sr-82 generator with 10-50 ml normal saline using a computer-controlled elution pump. The pump is connected directly to the patient via an intravenous line and the generator

is fully recharged every 10 minutes so serial imaging can be performed every 5-6 minutes. The rest and stress myocardial perfusion studies can be completed very quickly since the Rb-82 physical half-life is 75 seconds. The Sr-82 generator is commercially available and is replaced every four weeks so a cyclotron is not needed.

The adult dosages vary depending on the scanner type but the maximum allowable activity is 60 mCi for both rest and stress. Due to the short half-life of this agent, it is primarily limited to pharmacologic stress. Scout scanning is recommended before each injection to ensure proper positioning. This is done as a fast transmission image or with a low dosage of Rb-82 injection (10-20 mCi). The scout scan also estimates circulation times and cardiac blood pool clearance times to obtain optimal injection to imaging delay time. A PET/CT scanner will use a low dose CT scan for patient positioning.

Resting images should be performed before stress to avoid residual stress effects. The patient is infused with Rb-82 chloride for a maximum of 30 seconds and typically images start within 70-90 seconds post-injection. This time will vary depending on whether the patient has reduced left ventricular function. Imaging is performed in the same manner post-stress.⁹

Nitrogen-13 Ammonia Perfusion Imaging

N-13 ammonia is a valuable agent for measuring myocardial blood flow which requires a dynamic acquisition from the time of injection. Absolute flow measurements with ammonia are performed primarily in research settings as they require a high level of expertise and require an on-site cyclotron. The physical half-life is 10 minutes. The dosage is approximately 10-20 mCi of N-13 ammonia but a larger patient may need 25-30 mCi.⁹

F-18 FDG Metabolism Imaging

F-18 FDG is an analog of glucose and is used to image myocardial glucose utilization. The Center for Medicare and Medicaid Services (CMS) has approved reimbursement for the use of F-18 FDG in the evaluation of myocardial viability. F-18 is produced in a cyclotron and decays with a half-life of 109 minutes. The longer half-life allows for greater flexibility for distribution and allows sufficient time to obtain high quality images.

The required dosage is 5-15 mCi depending on scanner type. The main difference between PET and SPECT cardiac imaging is the patient preparation process. Blood glucose levels must be checked prior to injection since FDG enters myocardial cells by the same transport mechanism as glucose... There are several ways to stimulate myocardial glucose metabolism which are described in detail in the current ASNC guidelines for PET.

The main limitation with FDG is with diabetic patients because of their limited ability to produce insulin therefore fasting is not recommended. Use of insulin while monitoring blood glucose has yielded satisfactory results along with a delayed image time of 2-3 hours after FDG injection. In a normal patient, the patient should wait a minimum of 45 minutes before starting the static FDG scan. Scan duration is approximately 10-30 minutes depending on scanner type. A 3D scanner will use lower activity dosages but the imaging time is similar to achieve the same count rate and avoid increased scatter. The images are processed similar to SPECT but fused transmission and emission images are preferred.⁹

DECISIONS, DECISIONS, DECISIONS – WHICH PROTOCOL SHOULD I USE?

Clinicians should be mindful of the radionuclide supply challenges nuclear medicine is facing and prepare accordingly. There is no right or wrong answer as to which protocol is best. Many physicians with years of expertise still swear that Tl-201 provides them the information they need to form a confident diagnosis and it also allows for viability options. A huge concern when using Tl-201 as the primary tracer is the level of radiation exposure to the patient compared to the Tc-99m tracers. Facilities tend to lean towards using a higher dosage of Tl-201 to compensate for the lower counting statistics but this exposes the patient to an excessive dose of radiation. See Table 2 below for radiation exposure comparisons. Whole body radiation exposure using Tc-99m tracers results in one-tenth of the exposure versus Tl-201.

Table 2: Comparison of Tl-201 to Tc-99m for Radiation Exposure as it pertains to the Organs and Whole Body Exposure

	TI-201	Tc-99m	Tc-99m	TI-201
	Rest	Rest	Stress	Stress
Option 1	2.5 mCi	-	30 mCi	-
Option 2	4.0 mCi	-	30 mCi	-
Option 3	-	10 mCi	30 mCi	-
Option 4	4.0 mCi	-	-	4.0 mCi

Calculated Dose (rad)

	Option	Option	Option	Option
ORGAN	#1	#2	#3	#4
Adrenals	0.607	0.952	0.044	0.920
Brain	0.566	0.896	0.021	0.880
Breasts	0.338	0.533	0.018	0.520
Gallbladder Wall	0.981	1.446	0.255	1.240
Lower Lrg Int. Wall	3.238	5.038	0.340	4.800
Small Intestine	4.431	6.981	0.255	6.800
Stomach	1.764	2.799	0.053	2.760
Upper Lrg Int. Wall	3.329	5.129	0.466	4.800
Heart Wall	2.539	4.039	0.052	4.000
Kidneys	4.373	6.923	0.173	6.800
Liver	0.955	1.510	0.044	1.480
Lungs	0.443	0.698	0.025	0.680
Muscle	0.452	0.707	0.037	0.680
Ovaries	1.024	1.579	0.137	1.480
Pancreas	0.713	1.118	0.052	1.080
Red Bone Marrow	0.533	0.833	0.045	0.800
Bone Surfaces	0.869	1.364	0.060	1.320
Skin	0.315	0.495	0.020	0.480
Spleen	1.658	2.633	0.047	2.600
Testes	1.850	2.945	0.035	2.920
Thymus	0.444	0.699	0.025	0.680
Thyroid	5.768	9.218	0.024	9.200
Urinary Bladder Wall	0.697	0.982	0.323	0.760
Uterus	0.857	1.322	0.115	1.2400
WHOLE BODY	1.734	2.634	0.274	2.4000

Source: Package inserts for Thallium, Cardiolite⁰, and Myoviewä ^{13, 14, 15}

If TI-201 or dual isotope studies are your only option and you need to change due to ongoing shortages, it is suggested that you proceed as follows:

- 1. Check your Radioactive Material (RAM) license to determine if you facility is licensed to possess TI-210 or if there are any limitations. You should check with your health physicist to confirm this before starting any new procedures to ensure you are within the parameters of your RAM license.
- 2. Contact your camera manufacturer or service engineer prior to using Tl-201 for the first time. Uniformity corrections may need to be done if they have not been done in the past. Peaking of each isotope is required to obtain the best quality study. Most of the newer systems peak automatically so this may only be a problem with older equipment.
- 3. Talk to all of the interpreting physicians and determine their comfort level interpreting TI-201 images because there is a learning curve when comparing them to Tc-99m tracer studies. If you are considering a dual isotope protocol, keep in mind that the images do not compare as well and the TI-201 images will show more lung uptake and less bowel uptake. The quantitative programs are typically automated so you may need to make some manual adjustments to filters and cutoff limits to improve the overall processed study.
- 4. Remember that gating should be done on the high activity dosage and gating using TI-201 may not give as accurate of an assessment for LVEF due to a lower count rate.
- 5. Patient dietary preparation differs slightly with Tc-99m and Tl-201 studies for example, Tl-201 has dairy restrictions where Tc-99m does not. So it is best to refer to the published ASNC imaging guidelines to obtain the best study.
- 6. When using the dual isotope protocol, remember that scheduling will need to be adjusted since Tl-201 requires that the camera is readily available post-injection whether rest or rest/stress. This will limit your imaging flexibility as a result patients may need to return for the stress study later than originally planned.
- 7. With Tl-201 imaging time may need to be increased so this may pose a problem for patient comfort especially on a single head system.
- 8. Work directly with your local radiopharmacy to determine the availability of Tc-99m. Keep in mind that the availability of Tl-201 may also be tight during times of severe shortages.
- 9. Because TI-201 has a longer half-life, separate arrangements for proper storage and disposal must be made.
- 10. Be sure to forewarn patients that Tl-201 may be externally detectable for up to 30 days post study and be prepared to provide them a medical proof source.

If you only feel comfortable with Technetium MPI tracers, there are some ways to help obtain the activity you need. Your local radiopharmacy has probably already mentioned these to your facility but they are worth mentioning again because this is a global problem and you may want to change procedures depending on the patient or their particular clinical indications. They are as follows:

- 1. Limit the schedule to the more pertinent or emergency type patients.
- 2. Order dosages as close to calibration times as possible. Additional deliveries during the day may help you get the activity you need due to additional generator elutions performed by your nuclear pharmacy or additional reserved activity.
- 3. Consider doing the studies on off-peak times during the day or possibly even over the weekends. If a 2 day study is performed, resting scans may be easily performed without requiring that full staffing is available.
- 4. Consider the impact of lowering Tc-99m dosages from 10 mCi to 8mCi for rest and 30 mCi to 25 mCi for stress. Be sure to follow the 1:4 ratio of rest:stress or stress:rest when appropriate. If this is not possible during times of Tc-99m shortages, there should be at least 2 hours from rest injection to stress image to decrease "shine through" from the rest dosage.
- 5. Check the latest notices from your radiopharmacy regarding isotope availability and schedule accordingly. For example, you may be able to do more patients on Wednesday than on Monday and Tuesday, so make Wednesdays a longer testing day and shorten the hours earlier in the week. Direct communication between you and your pharmacy will also ease your burden with rescheduling patients and your local pharmacists will appreciate your thoughtfulness.
- 6. Research the possibility of using a stress-only protocol if the patient is considered low risk to avoid the additional activity and expense of a rest study. This may also allow you to complete more studies.
- 7. Lastly, consider some of the reduced dosing options available by adding one of the innovative imaging hardware/software packages for your camera system.

PET imaging reimbursement is more favorable now but the problem still remains with cost and availability. The location of the PET scanner must be taken in consideration since the 511 keV energy will shine-through and is not a possibility in most nuclear medicine or nuclear cardiology departments due to confined areas. The interpreting physicians and technologists should be properly trained for PET to provide quality studies. As with any new modality, there is a learning curve especially when compared to SPECT. If FDG PET metabolic images are being compared to perfusion images acquired by SPECT, the interpreter should be mindful that there will be differences in soft tissue attenuation, image resolution, and registration problems if acquired on different instruments.⁹

CONCLUSION

Nuclear cardiology as a whole has been subject to much criticism lately due to healthcare reform and reduced Medicare payments. This should not deter technologists or physicians from providing the best study possible. Accreditation is being brought more to the forefront than ever before as the Medicare deadline of 2012 draws nearer. Be prepared and do the research to determine what is working in your facility and make adjustments to areas that need improvement. The isotope shortages may remain for an indefinite period of time so know your options and be prepared. Keep in mind that your solution today may not be relevant tomorrow.

Perform only tests that are clinically appropriate and do the study that will give you the best diagnosis.

AUTHOR INFORMATION

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The author has over 20 years of experience in Nuclear Medicine with the last 6 years devoted to nuclear cardiology. She has served as an ICANL site visitor and reviewer and currently assists facilities to achieve accreditation. She holds certifications in the NMTCB and ARRT-Nuclear. She is an active member of the Society of Nuclear Medicine.

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