U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Nuclear Medicine Injection Infiltrations

ACMUI Meeting

April 3, 2019

Good morning and thank you for the opportunity to present.

I'm Ron Lattanze and I'm the CEO of Lucerno Dynamics. At Lucerno we've developed a device – called LARA - that provides insight into nuclear medicine injection infiltrations, which are sometimes referred to as extravasations.

Infiltration Agenda

- Presentation – Ron Lattanze
  - Overview
  - Incidence
  - Patient implication/impact
  - Solution
  - Request NRC and ACMUI reconsider a 1980 decision regarding infiltrations
- Q&A – Ron Lattanze, Dr. David Townsend, and Dr. Daniel Sullivan

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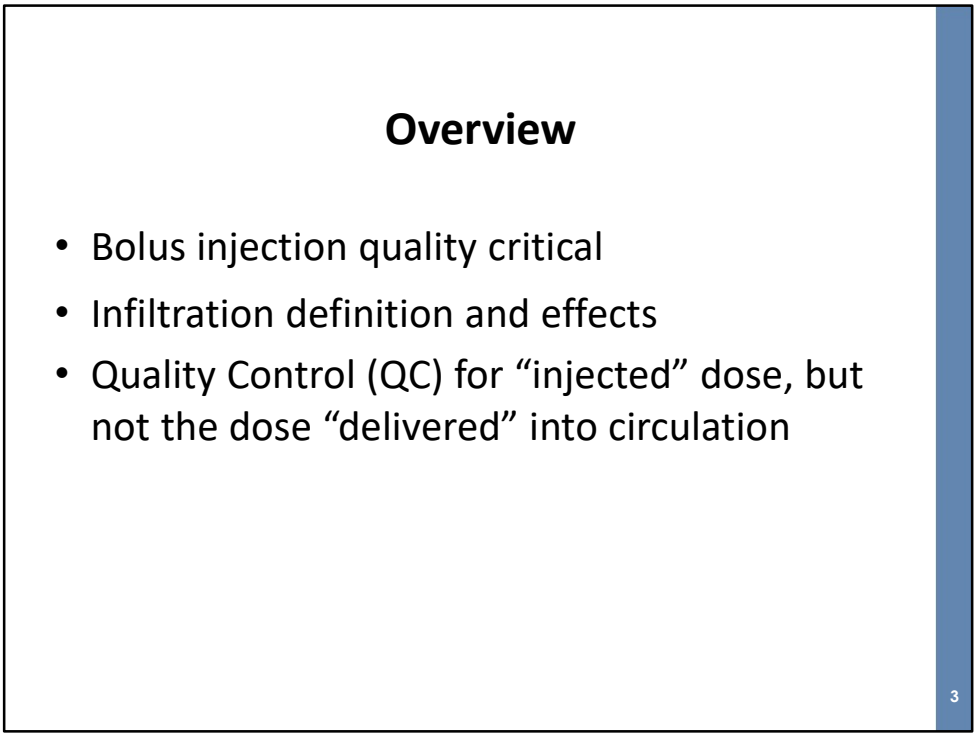
I'll be covering a lot of material in a short amount of time, so I've prepared comments that describe infiltrations, their incidence, and patient impact. I'll also share evidence that infiltrations can nearly be eliminated and will conclude with a request that the NRC and ACMUI reconsider a 1980 decision regarding infiltrations.

ANIMATE In anticipation of questions after my comments, I'd like to introduce Dr. David Townsend who is attending this meeting by phone. David is Lucerno's Scientific Adviser and receives no compensation. He's the co-inventor of the PET/CT scanner and a Fellow of IEEE. He's received many awards, including the IEEE Healthcare Medal and the SNMMI Paul C. Aebersold Award.
And this is Dr. Dan Sullivan, the former NCI Associate Director, Division of Cancer Treatment and Diagnosis, and the former Director of the NCI Cancer Imaging Program. He's a Science Adviser for the RSNA and Founder of the Quantitative Imaging Biomarkers Alliance. Dan consults with Lucerno to review our scientific paper submissions.
David and Dan are here to answer questions related to infiltration effects on Nuclear Medicine imaging studies and on patients in this ERA of precision medicine.



Most nuclear medicine studies are based on the **ASSUMPTION** that the radiopharmaceutical is injected as a bolus, where the entire dose is delivered in just a few seconds. The injection is usually followed by a saline flush and an uptake period, prior to imaging. This process tends to ensure that by the time the patient is imaged, the low background noise and high counts in organs or lesions of interest results in a high sensitivity study.

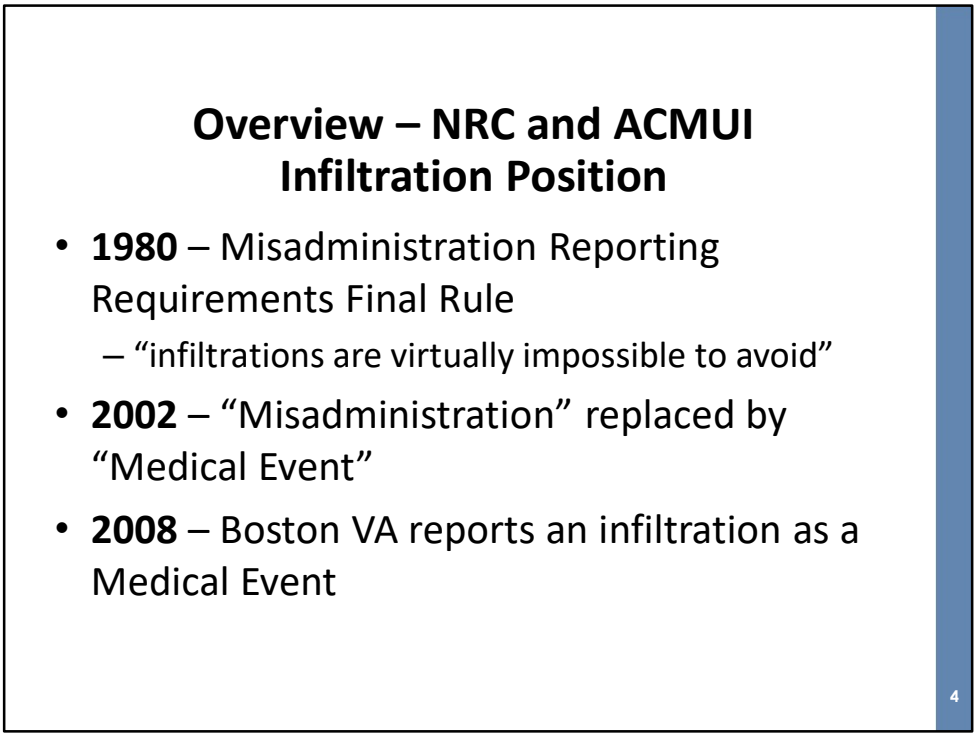
ANIMATE An infiltration results when some or all of the dose intended for a patient’s vein is injected into the tissue near the vein. This not only exposes this tissue to unintended radioactivity, it increases noise, reduces effective counts, and reduces image sensitivity. And, image quantification is incorrect and understated.

ANIMATE Because the **injected** dose is an input to the image quantification formula, quality control measures are in place to ensure dose accuracy. Clocks are synchronized in nuclear medicine departments to account for radioactivity decay. And technologists, after injecting and flushing the delivery syringe, measure the dose left in the syringe and subtract this amount for a “***net injected***” dose. These QC measures increase the accuracy of the **net** dose approximately **1-2%**.

Despite the accuracy that QC provides for the net dose, there remains the **assumption** the net dose is **actually delivered** into the patient circulation.

Until recently, there's never been routine monitoring to confirm the delivery into the circulation. This is important, because an infiltration error can dwarf the effects of any errors resulting from residual or unsynchronized clocks.

To better understand the NRC position on infiltrations, I've reviewed historical records.



In 1980, the NRC published a Final Rule on Misadministration Reporting Requirements. From a review of the supplementary information supporting this rule here are my interpretations of the NRC conclusions regarding misadministrations:
The NRC emphasized their role in protecting patients from unintended radiation exposure and from compromised diagnostic procedures that could impact care.

They emphasized reporting is needed to identify root cause and then prevent recurrence and stated that referring physicians and patients should be notified. Interestingly and in apparent contrast to these conclusions, the NRC reached the decision that an infiltration should NOT be considered a misadministration. Their decision was supported by the following justification: infiltrations frequently occur in otherwise normal intravenous and intraarterial injections and
ANIMATE: are virtually impossible to avoid.

ANIMATE: In 2002, the term "misadministration" was replaced with the term "medical event" in the regulations. Additionally, reporting and notification conditions and limits for these events were established in SUBPART M.

ANIMATE: In 2008, a Boston VA patient was infiltrated. Aware of Subpart M, the VA reported a medical event to the NRC, based on their estimate that the infiltration may have exceeded the effective dose equivalent limit to tissue. The NRC requested that the VA retract the report, referencing the 1980 decision that infiltrations should **NOT**

be considered a misadministration.
The NRC shared this decision with the ACMUI and according to the December 2008 meeting minutes, the ACMUI supported the NRC decision and rationale and passed a motion that quote: **at this time, NRC should continue its policy of NOT requiring infiltrations of diagnostic dosages to be reported as Medical Events - unquote**.

Few centers have ever shared their infiltration rates, but the limited available global data support the idea that NUCLEAR MEDICINE infiltrations can occur frequently.

Nuclear Medicine Infiltration Rates Are High

- 2006-17 Published data:
  - 15.2% (3% - 23%)
- 2017 Alberta QI, 9 centers:
  - 15.0% (0% - 28%)
  - 20.0% (8% - 44%)
- 2018 Lara QI, 7 centers:
  - 6.2% (2% - 16%)

2018 SNMMI Highlights Lecture: General Nuclear Medicine

Heather A. Jacene, MD, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA

From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting was originated and presented for more than 10 years by Henry N. Wagner, Jr, MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. Each year Newsline publishes these lectures and selected images. The 2018 Highlights Lectures were delivered on June 26 at the SNMMI Annual Meeting in Philadelphia, PA. In this issue we feature the lecture by Heather A. Jacene, MD, assistant professor in the Department of Radiology at Dana-Farber Cancer Institute, Brigham and Women's Hospital,and Harvard Medical School (Boston, MA), who spoke on highlights in general nuclear medicine.

Two studies from the same institution reported on the results of quality improvement projects related to a challenge we all probably face every day in our PET/CT clinics: radioactivity infiltration at the injection site, resulting in reduced image quality and incorrect quantitation (Fig. 9). Often the arm is extended out of the field of view, so we do not know that this infiltration has occurred, although biodistribution can sometimes provide clues. Townsend et al. from A*STAR-NUS Clinical Imaging Research Centre (Singapore), Duke University (Durham, NC), Lucerno Dynamics, LLC (Cary, NC), the University of North Carolina (Chapel Hill), and other centers reported on "Multicenter assessment of infiltration rates in FDG PET/CT scans: Detection, incidence, and contributing factors". The group presented a new technology, Lara sensors (Lucerno Dynamics, LLC), that can be placed on the patient's arm. The sensors yield data to derive time–activity curves describing the quality of the injection. The investigators found a range of infiltration rates across multiple PET/CT centers, with an average of 15.2%. This result supports the findings in 7 previously published single-center studies. The results suggest not only that infiltration is common but is many instances may go undetected. In the second phase of the above study (phase 2) by members of the same consortium, similar assessments were made after institution of quality improvement plans at 4 PET/CT centers. Wong et al. from A*STAR-NUS Clinical Imaging Research Centre (Singapore), Duke University (Durham, NC), Lucerno Dynamics, LLC (Cary, NC), and the University of North Carolina (Chapel Hill) reported on "Use of a novel detection device to reduce 18F-FDG infiltration rates".

The improvement plans focused on factors identified by the Lara technology in the first study, including patient body mass index, weight, age, glucose, injection sites, and extravasion. Injection screw technique and needle gauge were not associated with differences in infiltration rates. Results varied by adherence to the improvement plans. In the 3 centers that completed the phase 2 study (n = 830 injections), the infiltration rate decreased by 51% as compared to phase 1 (n = 815 injections). In the fourth center, the infiltration rate decreased by >50%. This new technology is quite interesting. Routine incorporation into a busy clinical center for every patient might be challenging, but this technique could be used to train technologists and other professional staff. It also has important implications for clinical trials, for example in qualifying participating clinical trial sites to improve standardization for quantitation.

Heather A. Jacene, MD

FIGURE 9. Reducing radioactivity infiltration at injection sites in PET/CT. Shown is a typical example of infiltration, which can result in reduced image quality and incorrect quantitation and may go undetected when the injection site is out of the imaging field of view. At the SNMMI meeting, researchers presented a new technology, Lara sensors, that can be placed on the patient's arm to provide data for time–activity curves describing the quality of the injection. These data can, in turn, be used to institute quality improvement measures and reduce the frequency and amount of infiltration.

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In the last decade, SLU, OSU, and University of Santiago have conducted six **RETROSPECTIVE** studies of PET/CT injection infiltration rates, **by reviewing images for infiltration evidence**. As stated in one of the studies, rates are likely underreported, because as you can see here, **ANIMATE** injection sites, like this infiltrated site shown by the arrow, are often outside the routine PET/CT imaging field of view.

ANIMATE These six studies retrospectively reviewed 2,804 patient images and found a 15.2% infiltration rate. The studies ranged from 3% to 23%.

ANIMATE In Alberta, 9 centers each retrospectively reviewed 25 consecutive nuclear medicine bone scans for infiltrations on two separate occasions. In the first review of 225 patients, the centers had an average infiltration rate of 15%. The centers' rates ranged from 0-28%. The review of another 225 patient injections had an average rate of 20% and ranged from 8-44%.

From 2016-2018 Lucerno worked with 7 prestigious U.S. PET/CT centers, including MD Anderson, UCLA, Wake Forest Baptist, and UT Knoxville, on a project called Lara QI. This quality improvement project used LARA, our new monitoring device, to help clinicians determine infiltration rates by PROSPECTIVELY comparing the injection arm to the other arm for excess radiotracer, rather than retrospectively reviewing images. While this ensures infiltrations are not missed due to field of view detection issues, the QI project results ALSO likely underrepresent real infiltration rates. That's because of

the **observer or trial effect.** Before beginning infiltration rate measurement in Lara QI, all technologists were trained on the importance of high-quality injections. They knew their **INJECTIONS** would be monitored for infiltrated radioactivity.

ANIMATE In the LARA QI measurement phase 2,431 patients were monitored. Investigators found a 6.2% infiltration rate. Centers' rates ranged from 2-16% and technologists' rates from 0-24%.

These results were presented at the SNMMI Annual Meeting last June. During the closing session, a distinguished subject matter expert summarizes, in what is known as the **Highlights Lecture**, selected significant general nuclear medicine presentations from the hundreds shared at that meeting. The Lara QI findings were ***1*** of 12 presentations highlighted last year.

ANIMATE The **Highlights Lecture** was published in the October issue of the Journal of Nuclear Medicine.
Without an easy-to-use detection process, technologists do not receive injection quality feedback, are not aware of infiltrations, and thus can't improve their technique. And when infiltrations **are** identified, there are no reporting requirements in place that lead to root cause investigation, quality improvement, and a reduction in occurrence.

In summary of this slide, the data we've gathered support the NRC position that nuclear medicine injection infiltration rates appear to be high. **But do infiltrations matter?**

Infiltrations Can Matter

50+ references support how diagnostic radiopharmaceutical infiltrations can harm or have harmed patients

~50% of injection sites are outside image FOV

Patient 11490 **MTV** Change

MTV	Day 1	Day 5	Understated
Lesion 1	7.43	11.34	34%
Lesion 2	5.57	10.66	48%
Lesion 3	27.77	41.07	32%
Lesion 4	0.88	2.93	70%

Adversely Affects Treatment Planning

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We do not believe that **all** diagnostic infiltrations matter acutely or to the ensuing patient care. **But some do matter. And they can matter in many ways**.
In 1980, the NRC stated that a misadministration of a diagnostic radiopharmaceutical could compromise the effectiveness of the diagnostic procedure. They were right. A literature review has identified over 50 references that show how infiltrations can harm or have harmed patients – these references are cited in a letter I sent to the NRC yesterday. Examples of how infiltrations may negatively affect patient care include:

Missed disease that impacts staging and treatment, wrong quantification that adversely affects longitudinal assessment scans and treatment planning, false positive results that lead to unnecessary invasive procedures, and repeated imaging that increases patient radiation exposure.

I could show you many patient cases, but due to time limits I'll only share two.

ANIMATE. Here is a published report of lung lesion patient with an infiltrated PET/CT study, the left image with the infiltration circled in red, that when repeated 3 days later with study parameters kept as constant as possible, the image on the right, revealed a missed metastatic lesion – shown by the arrow. In the infiltrated image on the left, only the lung lesion in the circle was identified. To eliminate the impact of the streaking artifacts that you see emanating from the infiltration and obscuring the torso, the patient was **re-imaged** with his arms over his head just 30 minutes after **this**

infiltrated image was produced. With a clear torso view, the reading physician did not identify any other lesions.
The Day 3 non-infiltrated image on the right, revealed that the Standardized Uptake Value (SUV) of the infiltrated image lesion had been understated by 44%. More importantly it revealed right adrenal metastatic disease. With the infiltrated image guiding treatment, as is commonly done in many centers, the patient would have received loco-regional treatment rather than treatment for metastatic disease. Informed of the Day 3 scan results, the patient chose to spend his last 5 months in hospice care.

The next patient had two PET/CT scans performed 5 days apart in a test-retest study. **ANIMATE:** Imaging parameters were controlled, 4 metastatic lesions were quantified, and the results from the two scans were compared. This example is also important. The first reason is the dramatic effect an infiltration can have on quantification. As you can see from the far-right column, the infiltration caused the SUVs of the four lesions to be understated between **33-54**%.

ANIMATE: and the infiltrated image Metabolic Tumor Volume value calculations were understated between **32-70**%.
Another reason this case is important is, because without the device, **no one would have known to order a repeat scan.** The injection site was in the left hand, outside the imaging field of view. In such a scenario an infiltrated scan would provide the wrong information in assessing disease progression or in developing treatment plans. This latest example is **NOT** unusual.

ANIMATE. From our monitoring of over 14,000 injections, we know injection site locations and estimate that about 50% of injection sites are out of the routine imaging field of view. A meaningful infiltration outside the field of view like the example I just shared, or an infiltration that is seen, but not included in the radiology report, may result in compromised care. And patients and treating physicians would be unaware.

Not only can infiltrations negatively affect care, many exceed NRC reporting limits, similar to the Boston VA case.

Infiltrations Can Exceed Reporting Limits

- Reporting Limit – 0.5 Sievert (Sv) effective dose equivalent to the tissue

	Time between injection and imaging	Estimated infiltration activity at time of imaging	Estimated effective dose equivalent to the tissue from injection to reabsorption time
A	57 mins	4.55 mCi	11.5 Sv (~23x limit)
B	107 mins	0.11 mCi	2.26 Sv (~4.5x limit)

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One medical event reporting limit is 0.5 Sv effective dose equivalent to the tissue. We've worked with physicists, measured visible infiltrations, and used Monte Carlo simulations to show how diagnostic infiltrations can exceed Subpart M reporting and notification limits. In the letter I sent to the NRC yesterday, I've also provided engineering reports to support these findings.

ANIMATE. Example A is the **actual case** I just presented where the hand was out of the imaging FOV. By knowing the injected dose and the tumor quantification changes, and by estimating the reabsorption process, we can calculate how much infiltrated radioactivity was in the hand at time of imaging and that conservatively the infiltration resulted in an effective dose equivalent to the tissue that exceeded the reporting limit by ~23X.

ANIMATE. Example B uses actual infiltration data and is very interesting. It shows how the effective dose equivalent of an infiltration can be easily underestimated if one is just using a static PET image. In this example, at the time of imaging, 107 minutes post injection, there was a relatively low amount of activity left at the injection site (~100 micro Curies). However, by using the infiltration resolution data with known infiltration volume data, we can estimate that an infiltration that may appear minor on imaging can actually exceed reporting limits.

Again, not all diagnostic radiopharmaceutical infiltrations will matter to patients, but

some will. Some infiltrations will exceed medical event reporting limits and should be reported, and the referring physicians and patients should be notified.

But there is good news. Infiltrations are *NO LONGER* virtually impossible to avoid. And infiltration rates can be dramatically improved.

Infiltrations Are Avoidable

- 2017 Chemotherapy rates – 0.18%
- 2016 Contrast CT rates – 0.24%
- Monitoring nuclear medicine injection quality can lead to significant and quick improvement

Site	Measure Phase Rate	Standard Error	Improve Phase Rate	Standard Error	Change
A	13.3%	2.1%	2.9%	1.0%	-78%
B	15.7%	4.0%	6.0%	2.6%	-62%
C	12.8%	1.5%	8.7%	1.3%	-32%
D	2.1%	0.6%	1.9%	0.6%	-10%

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Other healthcare injection processes monitor and report infiltrations.

ANIMATE Over the last 40+ years, quality improvement projects have monitored more than a million chemotherapy injections and infiltration rates have continued to decline. A 2017 QI project involved nearly 740,000 patients and found a **0.18%** infiltration rate for **peripheral IV** chemotherapy injections.

ANIMATE – Hundreds of thousands of contrast CT injections have also been studied and because of monitoring and reporting, infiltration rates have continued to decline. Another recent QI project monitored over 450,000 CT injections and found a **0.24%** infiltration rate.

The 1980 belief, which was reaffirmed in 2008, **is NO LONGER accurate in 2019**. Infiltrations are **NOT** virtually impossible to avoid, **today**!

ANIMATE – Now, a device that uses sensors placed on the arms and that adds just 20 seconds to the patient experience, can routinely **help clinicians detect** infiltrations before imaging.

As a result, **ANIMATE** centers can provide individual quality control for each injection with time-activity curves or TACs like this one, indicating no presence of excess radiotracer at the injection site after about 30 seconds post-injection. Here you can

see the injection arm sensor's black curve showing the bolus rise and then quickly drop to the level of activity represented by the reference arm's red curve. But not all TACs look ideal like this one. Unfortunately, many look like this **ANIMATE,** where the injection arm's curve never drops to the level of the reference arm, indicating the presence of excess radiotracer at the injection site!

Just as importantly, by using the device's quality assurance functions, centers can identify factors associated with **their** infiltrations and then put improvement plans in place to correct them. Following a QI process can lead to very low infiltration rates, as we've seen in other healthcare settings.

ANIMATE. In fact, four of the 7 Lara QI centers tried to improve their rates. As you can see by the columns highlighted in red font, each center improved. Their aggregated rate had a statistically significant decrease, from 8.9% to 4.6% ($p<0.0001$). And even better news, measuring and improving results can be accomplished in ~6-8 months. In fact, now, some centers are in sight of 1% infiltration rates.

These results were also presented at the annual meeting last year. The presentation was also **one of 12** selected for the Highlights Lecture.

It appears to us that addressing the infiltration issue is consistent with the goals of all interested parties.

Identifying, Reporting, and Reducing Infiltrations

Consistent with the goals of:

- NRC
- Nuclear Medicine Societies
- Technologists
- Physicians
- Patients

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Minimizing infiltrations seems consistent with the previously stated NRC goals, of protecting patients from unnecessary radiation exposure, as well as from compromised diagnostic studies, of reporting, determining causes, and preventing recurrence, and of ensuring referring physicians and patients are notified of medical events, that exceed reportable limits. Limits, I will add, **that should be agnostic** to whether the source is a diagnostic or therapeutic radiopharmaceutical

Identifying and reporting infiltrations are also in the best interest of Nuclear medicine and molecular imaging societies.

As the NRC knows, the importance of patient safety was a consistent message throughout recent public comments received by the NRC with respect to the training and experience requirements for Authorized Users.

The societies are also focused on precision medicine – infiltrations lead to imprecise medicine.

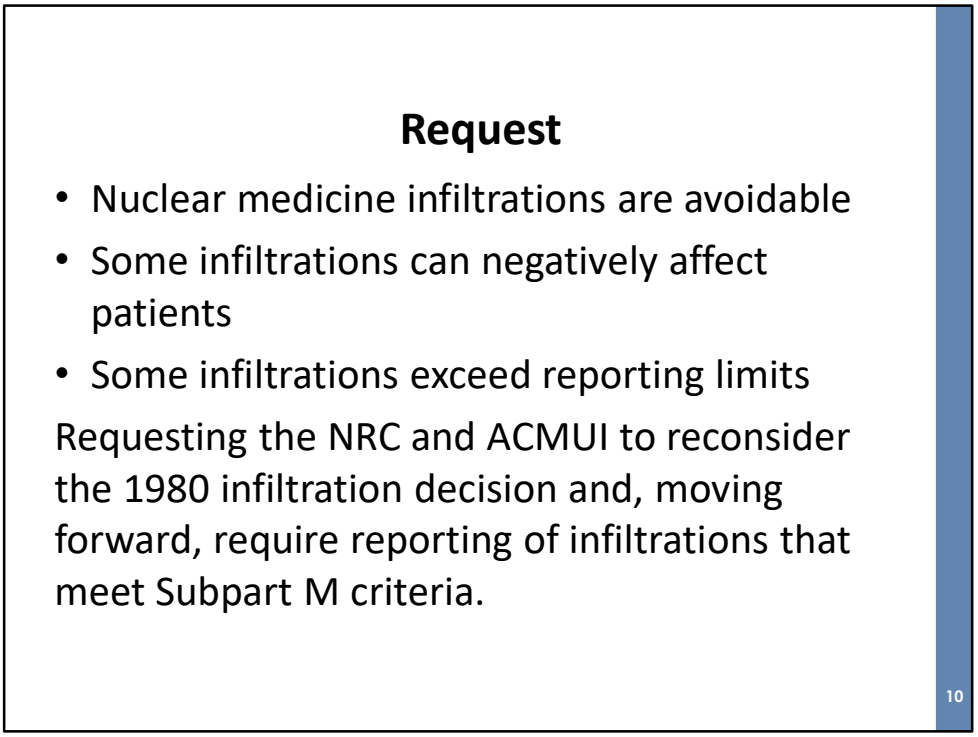
Societies are also aware that in the future, alpha and beta therapeutic injections with their longer half-lives will play an increasingly important role in medicine, and they know that the same personnel delivering diagnostic radiopharmaceuticals today will be delivering radio therapeutics tomorrow.
And the SNMMI knows that infiltrations have no place in their **Quality of Practice**

initiative. The goal of which is to ensure that members are known **for high-quality**, **value-driven** performance and **delivery of patient-centered nuclear medicine practice**.

And when we deal with individual centers, the vast majority of technologists want feedback that they are doing injections properly, physicists want reproducible imaging, safety officers want radioactive material used optimally and safely, and most interpreting and treating physicians want the highest quality imaging to help treat their patients.

Finally, and most importantly, are the patients; it's their life and their care. We've met them, their families, their friends and patient advocacy groups. Their message is clear. They all want the highest quality nuclear medicine injections.

On that point, let me share my last slide.



Now that there is awareness that infiltrations are avoidable, that they can harm some patients, and that they can exceed reporting limits, we are asking the NRC and ACMUI to review the information I sent to the NRC yesterday and reevaluate the 1980 infiltration policy. **Infiltrations that meet Subpart M reporting and notification criteria should be reported.**

This will lead to a reduction in infiltrations and to an improvement in patient care.

Thank you for your attention and we welcome any questions you have.

Discussion and Q&A

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Acronyms

- QI – Quality Improvement
- SUV – Standardized Uptake Value
- MTV – Metabolic Tumor Value
- FOV – Field of View
- mCi – Millicurie
- CT – Computed Tomography
- TAC – Time-activity Curve

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