2021 SNMMI Highlights Lecture: Oncology and Therapy, Part 2

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From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 30 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 2021 Highlights Lectures were delivered on June 15 as part of the SNMMI Virtual Annual Meeting. In this issue we feature the second part of the lecture by Heiko Schöder, MD, MBA, chief of the Molecular Imaging and Therapy Service at Memorial Sloan Kettering Cancer Center (New York, NY) and a professor of radiology at the Weill Medical College of Cornell University (New York, NY), who spoke on oncology and therapy highlights from the meeting. The first part of the lecture appeared in the October issue of Newsline. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine *(2021;62[suppl 1]).*

In the first part of this lecture, presentations on clinical diagnostics (including fibroblast-activated protein inhibitors [FAPI], innovations in prostate cancer diagnosis and staging, and other applications) and several new therapies were reviewed.

New Targets for Radionuclide Therapy: Other Therapy Approaches

We will highlight just a few of the many abstracts that were submitted on novel targets for radionuclide therapies. The first target is the insulin-like growth factor (IGF) receptor, which is relevant for proliferation, inhibition of apoptosis, protein synthesis, and also regulating metabolism. Juneau et al. from the Centre Hospitalier de l'Université de Montréal (Canada), Princess Margaret Hospital (Toronto, Canada), Roswell Park Comprehensive Cancer Center (Buffalo, NY), CDE Dosimetry Services (Knoxville, TN), Fusion Pharmaceuticals, Inc. (Hamilton, Canada; Boston, MA), and CHU de Québec/Université Laval (Québec City, Canada) reported on "Preliminary dosimetry results from a first-in-human phase 1 study evaluating the efficacy and safety of ^{225}Ac-FPI-1434 in patients with IGF-1R [IGF type-1 receptor]–expressing solid tumors" [74]. IGF-1R is a tyrosine kinase receptor implicated in breast, prostate, lung, and other cancers. As is common in these studies, the researchers used an ^{111}In-labeled analog with identical antibody and bifunctional chelate for biodistribution studies and patient selection based on quantification of IGF-1R–expressing targets and organ-based dosimetry prior to therapy. The aim of the study was to evaluate the safety and tolerability of both ^{111}In-FPI-1547 and ^{225}Ac-FPI-1434 in patients with advanced refractory solid tumors and to determine the recommended phase 2 dose of the ^{225}Ac-labeled compound in patients with IGF-1R–expressing tumors. Results were available for 13 patients from the single-dose portion of the study, and avidity in at least 1 lesion was demonstrated in each patient. Dosimetry determined all 13 to be eligible for therapeutic administration of ^{225}Ac-FPI-1434, and 12 received at least 1 such administration (range, 0.80–4.2 MBq) with no drug-related serious adverse events and/or dose limiting toxicity. Figure 1 shows high uptake in a 69-year-old man with castrate-resistant prostate cancer and liver metastasis and emphasizes the promise of theranostic pairs that facilitate patient-specific treatment planning. We look forward to future data that will tell us more about how this agent can be integrated into the armamentarium of treatment options for prostate cancer.

Heiko Schöder, MD

The next interesting target addressed by presenters at the SNMMI meeting was transforming growth factor-β (TGF-β) and its role in the tumor immune environment as a source for therapeutic applications. TGF-β has many functions involved in promotion of angiogenesis, activation of cancer-associated fibroblasts, increased fibrosis, and escape from immune surveillance—all of which contribute to a more favorable environment for tumor growth and metastasis. Burvenich et al. from La Trobe University (Melbourne, Australia), Olivia Newton-John Cancer Research Institute (Melbourne, Australia), Austin Health Melbourne (Australia), University of Melbourne (Australia), and EMD Serono Research & Development Institute (Billerica, MA) reported on "Preclinical evaluation of ^{89}Zr-Df-radiolabeled bispecific anti-PD-L1/TGF-βRII fusion protein bintrafusp alfa" [66]. They used a next-generation programmed death ligand-1 (PD-L1) targeting molecule that allows simultaneous targeting of PD-L1 and "trapping" of TGF-β. The aim of the study was to establish the ^{89}Zr-radiolabeling of the investigational agent and characterize in vitro and in vivo both the ^{89}Zr-Df-M7824 and ^{89}Zr-Df-control radioconjugates. The process involved converting a so-called immune-excluded tumor into an inflamed tumor, thereby reenergizing the tumor immune microenvironment, allowing targeted binding

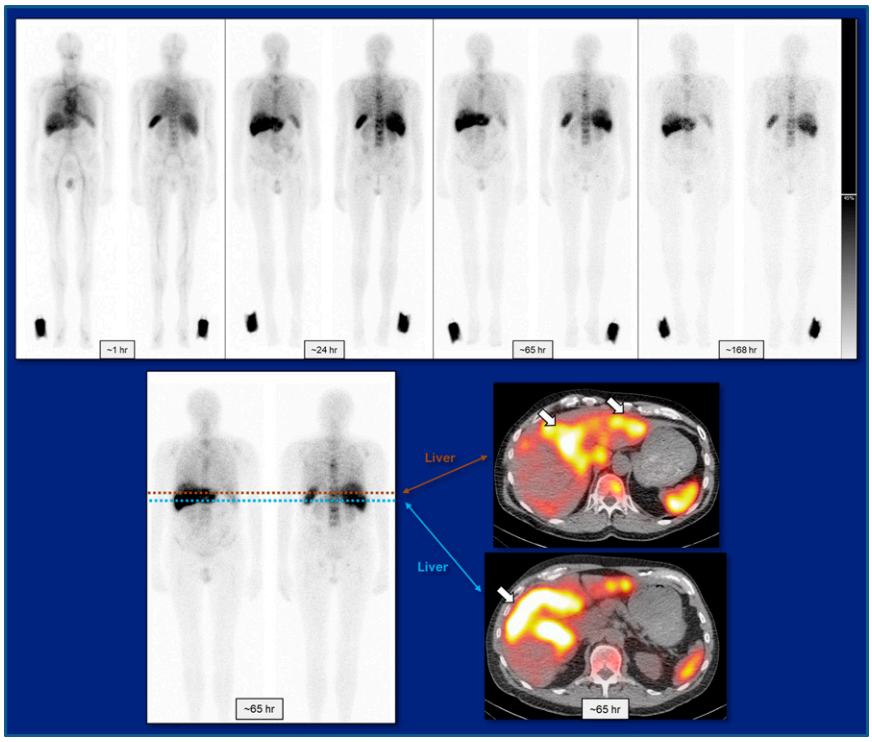

FIGURE 1. First-in-human phase 1 study evaluating efficacy and safety of ^{225}Ac-FPI-1434 in patients with insulin-growth factor type-1 receptor–expressing solid tumors. Images acquired in a 69-year-old man with castrate-resistant prostate cancer and liver metastasis. Top: Paired anterior/posterior images acquired at (left to right) 1, 24, 65, and 168 h after injection. Bottom: Corresponding SPECT/CT views of the liver at 65 h. The study emphasized the promise of theranostic pairs that facilitate patient-specific treatment planning.

to PD-L1 on tumor cells and "trapping" TGF-β, thereby inhibiting 2 mechanisms that would otherwise interfere with antitumor immune response. Figure 2 shows quantitative PET analysis of tumor, liver, lungs, and bone in mice at days 2 and 7 after injection, which allowed direct comparison with the biodistribution data available for these imaged mice. Tissue uptake assessed via PET analysis corresponded with the biodistribution results, and the authors concluded that PET imaging using ^{89}Zr-Df-bintrafusp-α was suitable for use in clinical trial studies. A bioimaging study was subsequently opened at Austin Health focusing on ^{89}Zr-M7824 PET in patients with advanced or metastatic non–small cell lung cancer and high PD-L1 expression receiving M7824 alone or in combination with chemotherapy. Sometimes, in scientific discovery and development, not all is always well that ends well. Since this abstract was submitted for presentation at this meeting, Merck, the company sponsoring the first trial, has stopped clinical trials with this drug because accumulating data did not prove promising in terms of meeting endpoints in progression-free survival in lung cancer (*1*) and, more recently, biliary duct cancer (*2*). This is perhaps a cautionary tale. If, for example, molecular imaging such as this had been employed earlier for patient selection, documentation of target engagement, and documentation of response (or lack thereof), substantial funds could have been saved as compared to conducting a clinical trial and then concluding that the treatment was not working as expected.

CD46 is a transmembrane complement regulatory protein overexpressed in various cancers and highly expressed in aggressive, advanced-state, de-differentiated prostate cancer and with very high overexpression in multiple myeloma. It inhibits complement activation, promotes immune evasion and growth, and regulates cellular metabolism. Wang et al. from the University of California San Francisco and others reported in April of this year on molecular imaging of *prostate* cancer, targeting CD46 using immunoPET with ^{89}Zr-DFO-YS5 in a murine model (*3*). At this meeting, the same group reported on "Molecular imaging of *multiple myeloma* targeting CD46 using immunoPET" [62]. ^{18}F-FDG PET/CT can result in false-negative findings in multiple myeloma, and CD46 targeting holds promise for greater accuracy. They studied the ^{89}Zr-DFO-YS5 tracer in both NSG mice bearing subcutaneous xenograft tumors and in an orthometastatic model of myeloma. Figure 3 shows immunoPET images acquired at 6 and 4 days after injection in subcutaneous and orthometastatic models, respectively. They found that ^{89}Zr-DFO-YS5 binds specifically to CD46+ human MM1s subcutaneous xenografts, with significantly higher uptake than in comparative cold antibody–blocking groups. In the orthometastatic model, ^{89}Zr-DFO-YS5 also demonstrated specific uptake in the bone marrow. Analysis of ex vivo bioluminescence data indicated that heterogeneous osseous tumor involvement correlated with tracer uptake. The authors concluded that this CD46-targeted imaging "shows great potential for clinical translation as an imaging agent, theranostic platform, and companion biomarker in multiple myeloma."

The last target we will look at in this section is a CUB domain–containing protein 1, CDCP1. CDCP1 is a cell-surface, single-pass transmembrane glycoprotein upregulated in multiple malignancies (including but not limited to triple-negative breast cancer, pancreatic ductal adenocarcinoma,

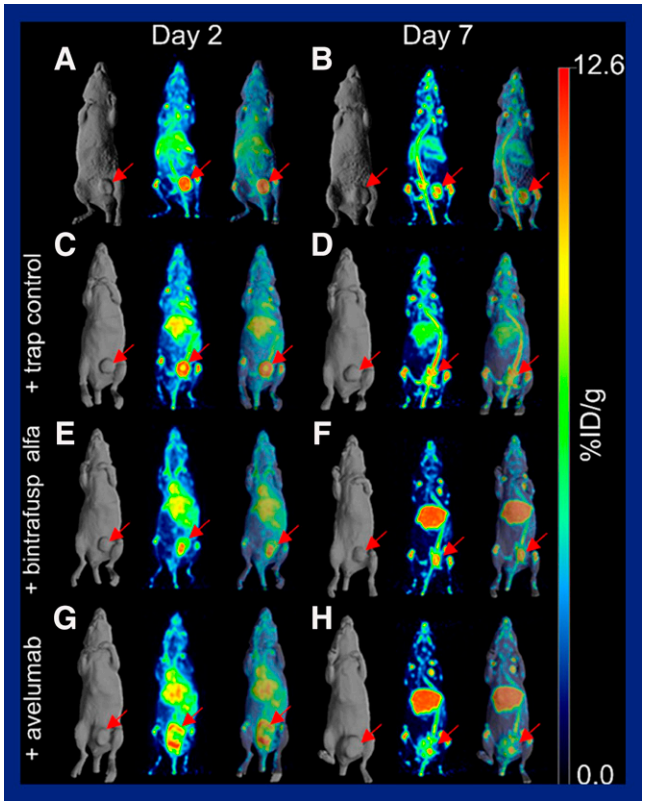

FIGURE 2. Preclinical evaluation of ^{89}Zr-Df-radiolabeled bispecific anti-PD-L1/transforming growth factor-βRII fusion protein bintrafusp alfa. Quantitative PET analysis of tumor, liver, lungs, and bone on days 2 (left 3 columns) and 7 (right 3 columns) after injection allowed direct comparison and correlation with biodistribution data in these mice. (a, b) Baseline imaging; (c, d) trap controls; (e, f) with bintrafusp alfa; and (g, h) with avelumab.

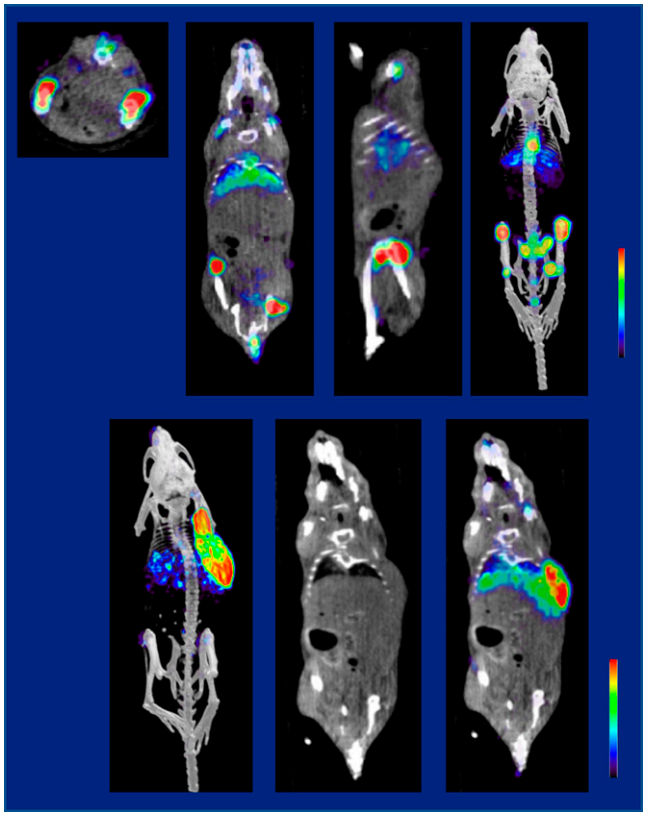

FIGURE 3. Molecular imaging of multiple myeloma targeting CD46 using immunoPET. ^{89}Zr-DFO-YS5, an anti-CD46 antibody, showed high uptake in an orthometastatic myeloma mouse model (top) and in subcutaneous xenografts (bottom). In xenografts, ^{89}Zr-DFO-YS5 bound specifically to CD46+ human MM1s, with significantly higher uptake than in comparative cold antibody–blocking groups. In the orthometastatic model, ^{89}Zr-DFO-YS5 also demonstrated specific uptake in the bone marrow. Ex vivo bioluminescence data indicated that heterogeneous osseous tumor involvement correlated with tracer uptake.

renal cell carcinoma, hepatocellular carcinoma, acute myeloid leukemia, and ovarian cancer) and with relevance to prostate cancer progression. It has a role in cancer growth, survival, and therapy resistance. CDCP1 is being targeted in research with antibody drug conjugates and with radiolabeled antibodies for theranostics. Evans et al. from the University of California San Francisco and PGIMER (Chandigarh, India) reported that "CDCP1 is a novel target for radioligand therapy in metastatic castration-resistant prostate cancer refractory to treatment with PSMA [prostate-specific membrane antigen]–directed radioligands" [92]. Figure 4 shows microCT and PET/CT of their monoclonal antibody 4A06 agent across a number of tumor models. The highest uptake, both in terms of %ID/g and also tumor-to-background ratio, was seen in the PSMA-negative, androgen receptor–negative tumor model. The antibody was also labeled with ^{177}Lu, leading to growth inhibition as shown in the right-hand side of the figure. The authors concluded that these data provide evidence that "CDCP1 can be targeted for radioligand therapy in metastatic cancer-resistant prostate cancer" and "position CDCP1-directed radioligand therapy as a potential complement or alternative to the current repertoire of radioligand therapies."

We will look briefly at increasing interest in photodynamic therapy. Those of you who regularly attend the World Molecular Imaging Congress may be familiar with recent advances. The 3 principal components are the light source, the photosensitizer, and the generation of reactive oxygen species, which lead eventually to targeted and irreversible tissue damage. Of note, it does not matter how the light is created (X-rays, Cerenkov luminescence, or radioluminescence). Most recently, researchers have looked at ways to combine photodynamic therapy with chemoimmunotherapy or targeted radionuclide therapy. Jeon et al. from Seoul National University (Republic of Korea) reported on "Photodynamic therapy induced by a combination of scintillating liposome and radiolabeled antibody" [97]. Europium is a rare earth metal that can be excited and then eliminates the radioluminescence. In this very intriguing presentation, they described using a europium-loaded scintillating liposome and a ^{177}Lu-labeled human epidermal growth factor receptor 2–targeting antibody (Fig. 5). In in vivo and ex vivo murine studies they showed that the europium liposome/^{177}Lu-antibody combination achieved 8-fold higher

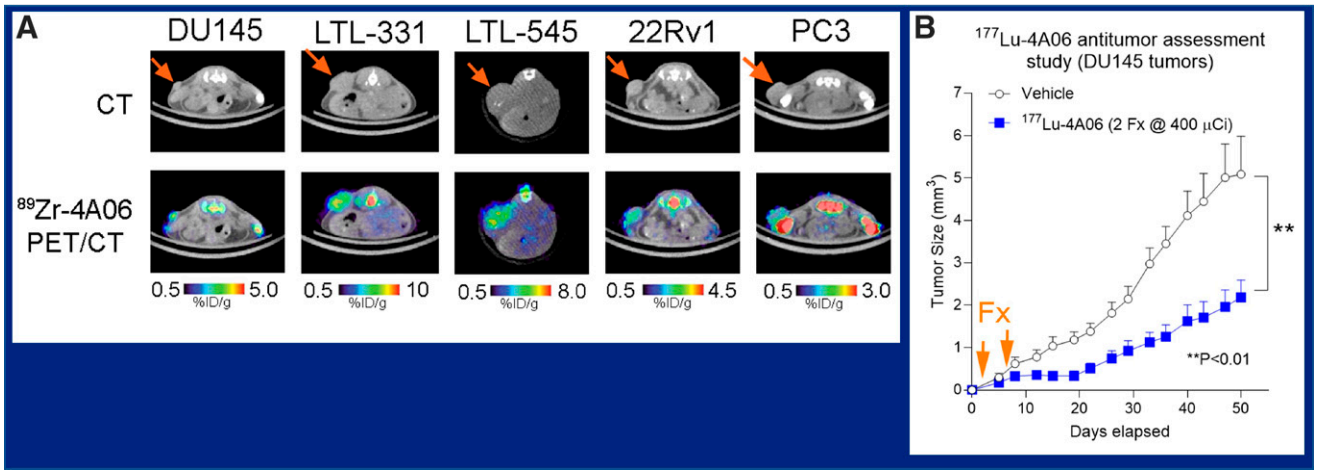

FIGURE 4. CDCP1 as a novel target for radioligand therapy in metastatic castration-resistant prostate cancer refractory to treatment with PSMA–directed radioligands. (A) CT (top row) and ^{89}Zr-4A06 PET/CT (bottom row) images in tumor cell lines (left to right): DU145, LTL-331, LTL-545, 22Rv1, and PC3. (B) Labeling the 4A06 agent with ^{177}Lu led to growth inhibition, showing promise for CFCP1-directed therapy.

radioluminescence than Cerenkov imaging. When combined with the photosynthesizer Victoria blue for photodynamic therapy, reactive oxygen species production was similar to a much greater amount of 100 μCi of ^{177}Lu-antibody alone but with only 10% of the radioactivity, with no apparent cytotoxicity. In in vitro studies, the combination showed a 2.5-fold higher cell-killing effect compared to ^{177}Lu-antibody alone. The authors concluded that a novel treatment strategy using this photodynamic therapy approach could, with further validation, "lower the systemic adverse effect while enhancing the treatment efficacy of ^{177}Lu conjugated theranostic radiopharmaceuticals."

New Techniques: Methods for Data Analysis

A number of new techniques and types of instrumentation were presented at this meeting, many dealing with motion correction, including data-driven motion correction,

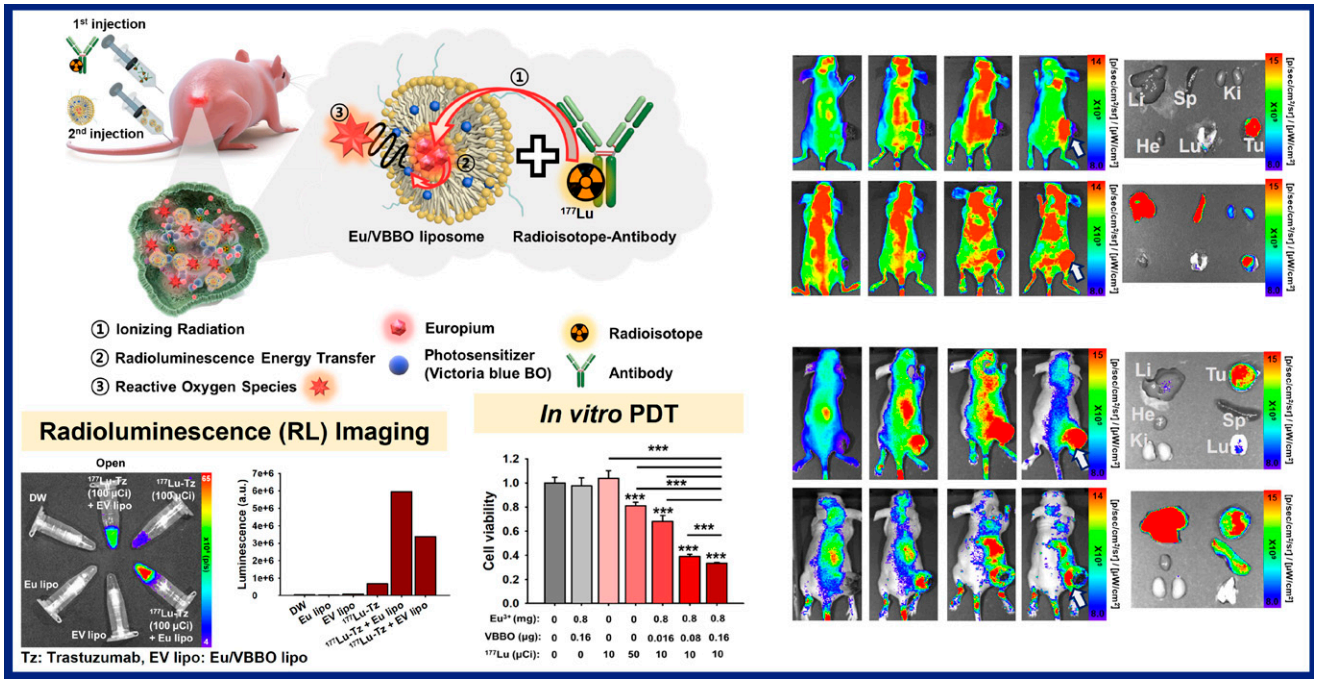

FIGURE 5. Photodynamic therapy induced by a combination of a europium-loaded scintillating liposome and a ^{177}Lu-labeled human epidermal growth factor receptor 2–targeting antibody. Left block: Schematic of labeling and imaging. Right block: In vivo targeting shown in (top block) SK-OV-3 tumor-bearing model (HER2+) at (left to right) 0, 2, 24, and 48 h after treatment with (top row) trastuzumab or (bottom row) the liposome/antibody photodynamic therapy; and (bottom block) CT-26 tumor-bearing model (EGFR+) at (left to right) 0, 2, 24, and 48 h after treatment with (top row) cetuximab or (bottom row) the liposome/antibody photodynamic therapy. Ex vivo radioluminescence images at far right. The technique has the potential to enhance the treatment efficacy of ^{177}Lu conjugated theranostic radiopharmaceuticals and lower adverse systemic effects.

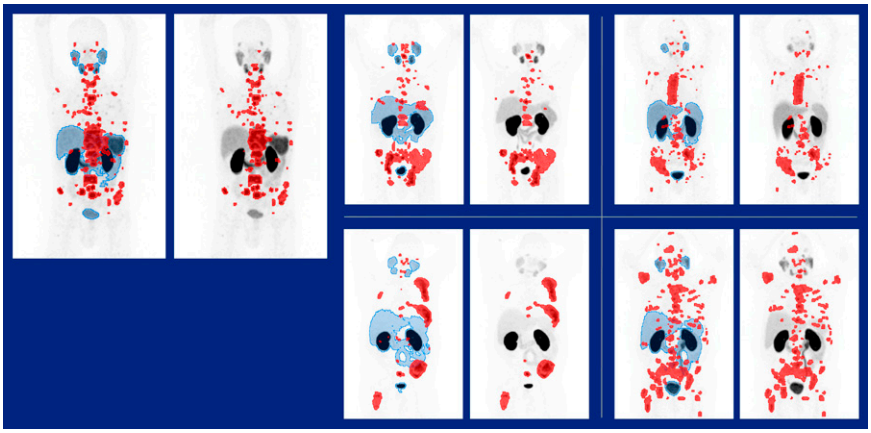

FIGURE 6. Total tumor burden quantification on ^{68}Ga-PSMA-11 PET/CT through deep learning autosegmentation of organs for automatic physiologic uptake removal. Paired images shown using data from patients in clinical trial treatment for end-stage metastatic castrate-resistant prostate cancer. Left image in each pair shows proposed artificial intelligence total tumor burden segmentation after physiologic uptake removal (red) and volume of uptake correctly removed by the algorithm (blue). Right images show ground truth tumor segmentation (red), as segmented by 3 investigators.

and, of course, ever-expanding whole-body imaging capabilities. I will highlight only a few.

Artificial intelligence (AI) is becoming increasingly relevant and available for clinical practice and to support multicenter clinical trials. Niman et al. from MIM Software, Inc. (Cleveland, OH) and St. Vincent's Hospital (Sydney, Australia) reported on the "Improved clinical feasibility of total tumor burden quantification on Ga-PSMA-11 PET/CT through deep learning autosegmentation of organs for automatic physiological uptake removal" [1327]. Their question was whether an AI algorithm can intelligently segment tumor and subtract normal background. They used data from the ^{177}Lu-PSMA-617 and idronoxil trial in men with end-stage metastatic castrate-resistant prostate cancer (LuPIN) to create CT-based organ volumes of interest and automatically remove the majority of PET physiologic uptake. Figure 6 shows the ground truth, as segmented by 3 investigators, compared with results from the algorithm, very nicely identifying tumor lesions and subtracting normal background across a number of patients. The authors concluded that application of fully automatic organ-based physiologic uptake removal results in very similar volumes to those produced by manual editing of total tumor burden volumes, suggesting also that "minimal additional time would be necessary if used in the clinical workflow."

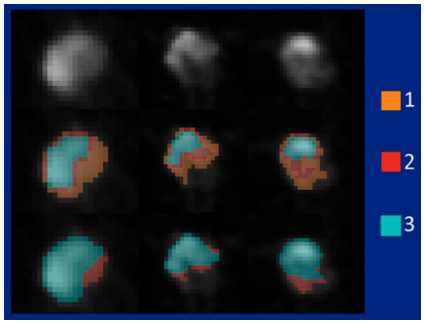

FIGURE 7. Artificial intelligence (AI) tool for detection and quantification of primary prostate tumors, bone metastases, and lymph node lesions in PSMA PET/CT. Images show ^{68}Ga-PSMA PET foci (top row) on the prostate in (left to right) axial, coronal, and sagittal views. Middle row depicts manual annotation without AI assistance. Bottom row depicts manual annotation with AI assistance. Orange pixels were annotated by only 1 reviewer; red by 2; and blue by all 3.

Borelli et al. from Sahlgrenska University Hospital (Gothenburg), Eigenvision AB (Malmö), Chalmers University of Technology (Gothenburg), University of Gothenburg, Skåne University Hospital (Malmö), and Lund University (Malmö; all in Sweden) reported that an "AI tool decreases interobserver variability in the analysis of PSMA PET/CT" [1006]. The aim of this study was to address current challenges in interobserver variability by developing an AI tool for detection and quantification of primary prostate tumors, bone metastases, and lymph node lesions in PSMA PET/CT studies. The tool was based on a previously developed CT-based segmentation approach (*4*) and was applied to direct segmentation of lymph node lesions in ^{68}Ga-PSMA imaging in 10 patients referred for initial staging of prostate cancer (*5*). Total lesion uptake was analyzed with and without AI assistance. The AI tool was found to have significantly lower interobserver variability in prostate tumors, bone metastases, and lymph node metastases. Figure 7 shows differences in human reader and AI identification. The authors concluded that "this AI tool may help in facilitating comparison of studies from different centers, pooling data within multicenter trials, and performing metaanalysis." (They also added that the AI tool developed in this project is available upon reasonable request for research purposes at www.recomia.org).

We will close out these highlights with images from the Penn PET Explorer developed by Joel Karp, PhD, and colleagues. Pantel et al. from this group at the University of Pennsylvania (Philadelphia) reported on "Human research studies on the PennPET Explorer" [55]. The prototype for this whole-body PET device had a 64-cm axial field of view. The expanded scalable PennPET Explorer has a 1.12-m field of view, and the group showed human studies illustrating the resulting benefits. In addition to clinical studies with ^{18}F-FDG, the group has conducted research using ^{89}Zr-Df-IAB22M2C (an anti-CD8 minibody for immune imaging), ^{18}F-(2)FA (for nicotine receptor imaging), ^{18}F-FNOS (for inflammation imaging), ^{18}F-fluoroglutamine (for glutamine metabolism), and ^{11}C- and ^{18}F-trimethoprim (for infection imaging). The increased sensitivity afforded by the extended

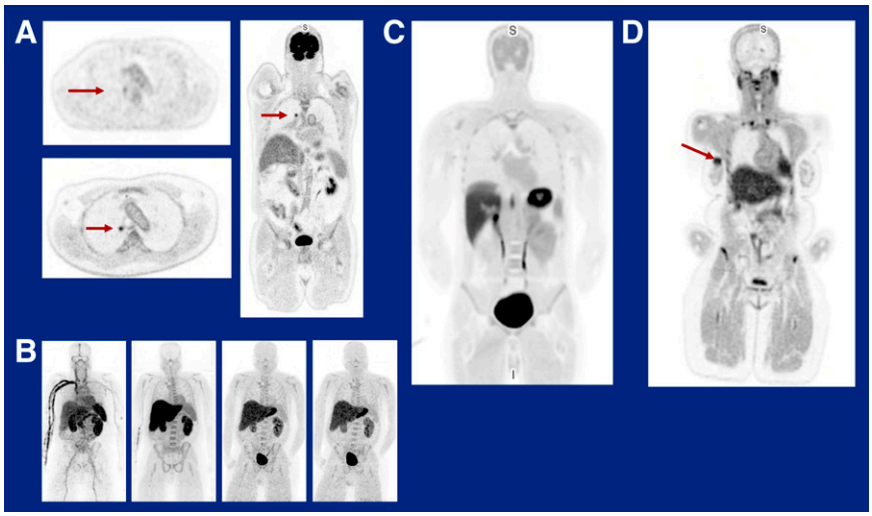

FIGURE 8. Human research studies on the PennPET Explorer with extended axial coverage. Whole-body imaging with: (A) ^{18}F-FDG in lung cancer, with insets of (top) standard-of-care imaging at 1 h after injection and (bottom) PennPET Explorer imaging at 2 h 20 min after injection; (B) ^{11}C-trimethoprim in infection imaging (left to right) at 50–69 s and 7–8, 90–95, and 120–130 min; (C) ^{18}F-FNOS for assessment of lung inflammation (normal subject); and (D) ^{18}F-fluoroglutamide in breast cancer. The increased sensitivity afforded by the extended axial coverage provides possibilities for a wide range of clinical and research applications.

axial coverage of whole-body PET imagers can be leveraged for numerous clinical and research applications (Fig. 8). They showed examples of imaging performed in 3 settings: (1) as part of a clinical standard-of-care (SOC) PET/CT scan using a U.S. Food and Drug Administration (FDA)–approved tracer without administration of additional radiotracer; (2) with PET/CT imaging as part of research studies, with specific radiotracers and protocols dictated by the relevant studies; and (3) imaging with an FDA-approved radiotracer without concomitant SOC imaging, with an injected activity that could be lower than that used for SOC imaging. The results across the spectrum of applications showed good whole-body kinetics, very nice uptake, and high sensitivity. The authors are now focusing on optimizing the many potential associated protocols.

Summary

Several oncologic themes and questions emerged from presentations and related discussions at this meeting. We need to define how many PSMA-based probes are really needed in the future, and which should be applied when and in what settings. FAPI is the focus of a growing number of promising applications and excitement, but it is important to think now about methods of quantification to better define its role in the clinic and clinical trials. In the rapidly expanding field of radionuclide-based therapy, the VISION and TheraP trials have helped to establish the role of ^{177}Lu-PSMA. My appeal to you is to make sure that the nuclear medicine community maintains ownership of these new treatments.

I would like to conclude with a few tasks that we should collaboratively undertake for the future. We need to better define the role of diagnostic or therapeutic PSMA in various states of disease. We should continue to define the role and place of α emitters in various therapies (a topic which I did not cover in this lecture because of time limitations). We must encourage appropriate and timely clinical translation of the many molecules that are coming forward, as well as ensure that these are suitable for specific applications. We need to establish artificial intelligence solutions for nuclear medicine agents for clinical trials. Finally, I believe we need to establish and proactively pursue models of "co-opetition" with radiation oncology, medical oncology, and surgical oncology for theranostic applications.

REFERENCES

1. Merck KgaA. Update on the Intr@pid clinical program including Lung 037 study. Darmstadt, Germany: Merck KGaA; January 20, 2021. Available at: https://www.emdgroup.com/en/news/bintrafusp-alfa-037-update-20-01-2021.html. Accessed on September 20, 2021.
2. Merck KGaA. Statement on phase II study of bintrafusp alfa in first-line treatment of biliary tract cancer. Darmstadt, Germany: Merck KGaA; August 23, 2021. Available at: https://www/emdgroup.com/en/news/bintrafusp-alfa-update-23-08-2021.html. Accessed on September 20, 2021.
3. Wang S, Li J, Hua H, et al. Molecular imaging of prostate cancer targeting CD46 using immunoPET. *Clin Cancer Res.* 2021;27(5):1305–1315.
4. Trägårdh E, Borrelli P, Kaboteh R, et al. RECOMIA: A cloud-based platform for artificial intelligence research in nuclear medicine and radiology. *EJNMMI Phys.* 2020;7(1):51.
5. Borelli P, Larsson M, Ulén J, et al. Artificial intelligence-based detection of lymph node metastases by PET/CT predicts cancer-specific survival. *Clin Phys Function Imaging.* 2021;41(1):62–67.

NRC Rejects Petitions to End Reliance on LNT Model

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Editor's note: *Newsline encourages perspectives on issues affecting the nuclear medicine community. This month we feature commentary on a longstanding effort to secure regulatory reassessment and invalidation of the linear-no-threshold (LNT) radiation model, which posits a linear relationship between dose and health risk and denies the existence of a threshold below which there is no harm, suggesting that radiation has the potential to cause harm at any dose level and that the sum of small exposures poses the same risk as a single larger exposure. Responses to this commentary are welcome.*

The Nuclear Regulatory Commission (NRC) on August 17 issued their rejection of three 6-year-old petitions requesting repudiation of the linear-no-threshold (LNT) model. The petitions maintained that the model is scientifically false and does more harm than good (*1*). The NRC contends that by overestimating radiation risk, adherence to the LNT model protects the public and radiation workers. The NRC relies on recommendations of authoritative scientific organizations that include the International Commission on Radiological Protection (ICRP), the National Council on Radiation Protection and Measurements (NCRP), and the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation. It is our contention that unless NRC's policies comply with scientific evidence, they are as likely to *endanger* as to protect, and they directly contribute to avoidable early deaths.

Following ICRP and NCRP recommendations, the NRC concedes that no evidence supports the LNT model. Nevertheless, the NRC defends it, ignoring the fact that it was disproven at its 1940s birth in favor of a threshold model (*2*), as well as by data from the Life Span Study (LSS) of atomic bomb survivors (considered to be the gold standard for estimating radiation effects in humans) and the International Nuclear Workers Study (*3–5*). Even the most recent examination of the LSS data in 2017 by Grant et al. (*6*) concluded: "At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies." This stands in stark contrast to NCRP's 2018 Commentary 27, which wrongly asserted that Grant's study provided *strong* support for the LNT model.

Ever-expanding experimental and observational (epidemiologic) evidence demonstrates a threshold of radiation dose and/or dose rate below which harm disappears and the net effects on health, after the organism responds to protect itself, are beneficial (*3*). Such a threshold is common for many chemical and physical agents (e.g., oxygen, sunlight, water, vitamins, aspirin) and is called hormesis. The nonlinearity of net effect at low doses is a consequence of the biologic response of the exposed organism to the damage, a homeostatic defense mechanism, which is either repair of damaged DNA or removal of unrepaired cells through cell suicide and/or cleanup by the immune system.

The burden of proof should fall on the claim that radiation is an exception and causes harm even at low doses, which would imply that neither repair nor removal occurs. Although the evidence of benefit (which is forced to bear the burden in this argument) keeps multiplying as its mechanisms become further elucidated, the NRC and its advisers pretend otherwise. As the NRC notes, NCRP past-president John D. Boice, Jr., ScD, admitted that "the LNT model is not an appropriate mechanism to assess radiological risk," while at the same time advising that "[LNT is] a prudent basis for the practical purposes of radiological protection."

NRC indicates that NCRP Commentary 27 updated its assessment of currently available epidemiologic evidence and concluded that "the LNT model (with the steepness of the dose–response slope perhaps reduced by a DDREF [dose and dose rate effectiveness factor] should continue to be utilized for radiation protection purposes." DDREF has no physiologic basis, but its invocation indicates the realization that LNT is false. They refuse to admit that a dose (or dose-rate) threshold exists, but, in direct contradiction, state: "NCRP defines high dose rate as a dose rate above which recovery and repair processes are unable to ameliorate the radiation damage." The DDREF is an arbitrary mathematic construct that simply reduces the slope by a factor of 2 at doses $<$200 mSv, thereby artificially retaining linearity in this low-dose region while precluding hormesis by ruling out an initial *negative* slope.

Commentary 27 admitted that the LNT model's denial of a threshold "… likely cannot be scientifically validated by radiobiologic or epidemiologic evidence in the low-dose range" but claimed that "the preponderance of epidemiologic data is consistent with the LNT assumption, although there are a few notable exceptions." But a threshold has been found, repeatedly and for decades, from sources around the world (*4*). In short, the LNT model has been proven false in numerous studies (*3*,*7–9*), and hormesis has been proven to exist at low doses and dose rates (*3*).

The NRC, again following NCRP and ICRP, favors studies that *claim* to provide evidence for the LNT model. However, such studies employ circular reasoning, inaccurate dose estimates, violation of proper frequentist statistical procedures (including misassignment of the null hypothesis to represent the favored hypothesis [i.e., the LNT model],

making it more difficult to reject the model and wrongly interpreting failure to reject as equivalent to proof thereof), failure to seek confounders, and so on, all of which mask hormetic effects (*3*,*10*).

Grant et al. (*6*) unwittingly provided an illustrative example of misassignment of the null hypothesis in their recent reanalysis of the LSS data. They reported: "The evidence of a threshold dose below which there was no dose response was examined using linear-quadratic threshold models for males and linear threshold models for females. There was no [*sic*] evidence of a threshold for females (estimated threshold dose of 0.08 Gy). *This was not significantly different from 0* ($P = 0.18$), and the upper 95% confidence bound was 0.2 Gy. For males, the best estimate for a threshold dose was 0.75 Gy. Similarly, *this was not significantly different from 0* ($P = 0.49$)" [italics our emphasis]. Note that their implied null hypothesis, acceptance of a threshold at zero dose (equivalent to "no threshold"), is both illegitimate and completely arbitrary, since, from this approach, one could also validly choose a nonzero threshold anywhere between zero and the upper bound (i.e., anywhere between 0 and 750 mGy for males).

Tacitly admitting that the LNT model is unsupported by evidence, NCRP says "current judgment by national and international scientific committees is that no alternative dose response relationship appears more *pragmatic or prudent for radiation protection purposes* than the LNT model on the basis of available data, recognizing that the risk [for doses] <100 mGy [<10 rad] is uncertain but small" [our emphasis]. Despite the fact that the LSS data clearly exhibit an initial negative slope indicative of hormesis when the low-dose data are carefully examined (*8*,*11*), pragmatism and prudence are allowed to trump scientific validity.

Scientifically, NRC acts as though the evidence against the LNT model and in favor of hormesis is inconclusive. Pragmatically, despite the preponderance of evidence for hormesis, its policy appeals to the precautionary principle, which holds that when there is uncertainty (real or pretended), prudence demands erring on the side of caution. This might be justified if: (1) the promotion of the LNT model carried little to no harm; (2) its implied directive to use x-ray and CT doses as low as reasonably achievable (ALARA) were without negative consequences; and/or (3) it were acknowledged that a threshold actually exists and that hormesis should be universally recognized. None of these is the case. The ICRP LNT-derived principle of "optimization," generally practiced by radiologists, promotes the widespread misconception among physicians and the public that the LNT model accurately describes the effects of low-dose ionizing radiation (*5*). This misconception can inflict devastating harm on public health and safety.

One such harm has been radiophobia-driven forced evacuations, such as that in 2011 after the tsunami-caused Fukushima Daiichi nuclear event (*7*). This resulted in massive loss of homes, communities, jobs, property, and lives. The Japanese government admits to some 2,000 evacuation-caused deaths of elderly individuals who would have been far safer if allowed to shelter in place. The concomitant stresses have produced a sharp rise in heart attacks, strokes, alcoholism, divorces, joblessness, despair, and suicide.

LNT-derived radiophobia also induces many people to avoid medically indicated CT scans and other imaging, with consequent missed or delayed diagnoses and ineffective treatments (*5*). CT imaging with insufficient radiation produces similar outcomes. Alternative methods to CT and x-rays are widely encouraged, such as longer-duration MR studies requiring sedation for children or exploratory surgeries risking blood loss, infection, and, in some cases, death.

Misguided attempts to evade imaginary risks deprive adults and children of the far greater benefits of low-dose radiologic examinations, including accurate and timely diagnoses, effective therapies, lives saved, improved quality of life, avoidance of unnecessary surgeries, reduced hospital stays, and reduced costs, or, in the case of negative examinations, greater peace of mind.

Effective risk management and public communication regarding radiation incident-related evacuation policies and medical imaging are not possible until the LNT model and its corollary, ALARA, are universally acknowledged as scientifically and pragmatically indefensible. To properly manage and communicate risk at low radiation doses, the complete spectrum of possible health outcomes must be acknowledged (*7*).

The unintended side effects of a policy are as important as the intended direct effects. The need for a 2-sided assessment to replace simplistic 1-sided epidemiologic studies that misassign the role of the null to a then unrejectable hypothesis (*10*) remains unacknowledged by the NRC and its advisory organizations (and their overlapping memberships who generally reinforce the others' conclusions). In effect they comprise not several independent voices, but a single voice, diminishing the overall authority of their consensus (*12*).

Although the NRC's rejection of the petitions purports to address our criticisms, these criticisms are merely listed, followed by evidence-free "disagreements"—the very transgression of which the NRC wrongly accuses the petitioners. NRC simply declares that they bear no responsibility for resulting forced evacuations, imaging avoidance, or nondiagnostic CT scans. We let the reader judge such protestations of innocence.

It is long past time for the NRC and authoritative scientific organizations to forgo falsely presumed pragmatic prudence in favor of scientific accuracy. Erring in either direction from a scientifically valid policy inevitably endangers public health and safety, and recognition of this fact requires acknowledgment of the negative side effects of such deviation. Only then will the dangers be preventable.

REFERENCES

1. Nuclear Regulatory Commission. Linear no-threshold model and standards for protection against radiation. *Fed Reg.* 2021;86:45923–45936.

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Advocating for Expanded Access

Richard Wahl, MD, SNMMI President

Advances in medicine are being made every day across the globe, revolutionizing the diagnosis and treatment of a wide variety of diseases. However, if not accessible to the patients who need them, these medical innovations are essentially ineffective.

The field of nuclear medicine and molecular imaging has produced many new advances in the past few years—the development of imaging agents for prostate cancer, Alzheimer disease, and breast cancer among the most recent. To ensure that patients have access to these advances, the SNMMI is working diligently to educate lawmakers, payers, physicians, and other government agencies about diagnostic radiopharmaceuticals.

In partnership with the Council on Radionuclides and Radiopharmaceuticals and the Medical Imaging and Technology Alliance, SNMMI has helped develop major legislation, the Facilitating Innovative Nuclear Diagnostics (FIND) Act of 2021 (H.R. 4479/S. 2609), to address the imbalance in Medicare's reimbursement structure for radiopharmaceuticals. Medicare currently packages payment for diagnostic radiopharmaceuticals into the payment for molecular imaging tests conducted by nuclear medicine providers in hospital outpatient facilities. These packaged rates are often the same, whether they involve a high-volume, lower-cost diagnostic radiopharmaceutical or a low-volume, higher-value precision diagnostic tool that can facilitate more targeted treatment. As a result, Medicare reduces reimbursement for the higher-cost products to the point that providers simply cannot afford to provide these services, limiting or preventing their availability to patients.

If passed, the FIND Act would ensure that Medicare patients have access to precision diagnostic nuclear imaging studies prescribed by their physicians, when clinically appropriate, and that hospitals are appropriately reimbursed for the cost of such tests. This bill would significantly expand patient access to life-saving imaging agents. I encourage all U.S. members of the nuclear medicine and molecular imaging field to contact their members of Congress and share their support for this important bill. Representatives and senators can be contacted through SNMMI's dedicated FIND website at: https://snmmi.quorum.us/campaign/34856/. Every voice matters in helping to pass the FIND Act.

SNMMI is working to educate payers and physicians about issues with the payment structure for diagnostic radiopharmaceuticals. SNMMI is also reaching out to patients regarding the FIND Act. It is critical that patients help us gain traction for this bill by informing their providers when appropriate access is not available.

Richard Wahl, MD

In addition to the access issues addressed by the FIND Act, patients face other challenges in receiving innovative nuclear medicine procedures to guide their treatment. With any new medical advance, physicians question how to make it available and how to ensure it is paid for. This is happening right now as providers try to navigate use of the newly U.S. Food and Drug Administration–approved prostate-specific membrane antigen (PSMA) imaging agents. To make the process as easy as possible for physicians, a new set of appropriate use criteria has been developed to guide the use of PSMA PET imaging agents. SNMMI developed the criteria in collaboration with the American College of Nuclear Medicine, American Urological Association, Australia and New Zealand Society of Nuclear Medicine, American Society of Clinical Oncology, European Association of Nuclear Medicine, and American College of Physicians. The National Comprehensive Cancer Network (NCCN) has also issued new guidelines for PSMA PET imaging. Many physicians consider NCCN guidelines to be the standard for cancer care, and these guidelines will assist physicians in use of the new agents to improve care and outcomes for patients with prostate cancer.

In another area of advocacy, SNMMI has been successful in working with the Centers for Medicare and Medicaid Services (CMS) to retire the National Coverage Determination (NCD) for ^{18}F-FDG PET for infection and inflammation imaging. In the absence of an NCD, coverage determinations for PET for infection and inflammation are now made at the discretion of local Medicare Administrative Contractors. Removal of this NCD was accomplished after many discussions and sharing of guidelines and evidence by the SNMMI, American College of Radiology, and American Society of Nuclear Cardiology. This effort and the CMS decision have opened up a path to reimbursement that ultimately will improve access for patients to valuable nononcologic use of FDG PET.

SNMMI is constantly working to make sure that advances in nuclear medicine and molecular imaging are easily available to patients and reimbursed appropriately. We will continue to advocate for expanded access in our efforts to improve the health of patients everywhere.

ACMUI Meets on Extravasation Reporting

On September 2 the Advisory Committee on the Medical Uses of Isotopes (ACMUI) Subcommittee on Extravasations met in a public meeting to review and provide additional recommendations on the Nuclear Regulatory Commission (NRC) Staff Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting. In anticipation of the meeting, SNMMI filed public comments. In a statement issued on the following day, SNMMI noted that this issue "has the potential to negatively impact the future of nuclear medicine." In September 2020, the NRC requested public comment on whether additional rulemaking was needed to require reporting of certain nuclear medicine injection extravasations as medical events. SNMMI and other interested organizations submitted comments in November 2020.

In the most recent comments, SNMMI supported the non–dose-based reporting options found in both NRC staff and ACMUI draft reports. Noting that although a lower regulatory reporting requirement (Option 6) was preferred (because extravasations present low patient safety risk), the comments included recommendations on the subcommittee's preferred option. Option 4 would require reporting when "a patient requires medical attention due to skin damage near the administration site, and the damage is determined to be caused by radiation." Among the SNMMI comments were:

- The phrase "medical attention" is ambiguous. Taken to the extreme, "medical attention" could conceivably include basic IV access care (e.g., compresses, etc.) for temporary injection site bruising, erythema, or swelling. If Option 4 is to be seen as a viable option, the manner and intensity of "medical attention" that would trigger medical event reporting requirements must be clearly defined.
- The injury assessor should be a physician with radiation medicine expertise (i.e., an Authorized User [AU] or AU-eligible physician) who can differentiate normal injection site changes from radiation-caused damage. Option 6 would provide for this physician determination of harm standard, whereas Option 4 does not specify the qualifications for the "radiation damage assessors."

After the September 2 ACMUI meeting, SNMMI stated "We are pleased that the subcommittee supported our recommendations to tailor Option 4 more narrowly to the needs of the nuclear medicine community, and we look forward to the final report."

SNMMI

Sam Gambhir Trailblazer Award

SNMMI and the Education and Research Foundation for Nuclear Medicine and Molecular Imaging, Inc. announced on October 2 that applications are now being accepted for the new Sam Gambhir Trailblazer Award, which will honor midcareer professionals for outstanding achievement and excellence in transformative research (basic science, translational science, or clinical science) and exceptional mentorship. The award is named for Sanjiv Sam Gambhir, MD, PhD, an internationally recognized pioneer in molecular imaging who dedicated his career to developing methods of early disease detection, ushering in a new era of molecular imaging to identify signals of disease in the earliest stages. Gambhir was known for development of PET reporter genes and for his commitment to introducing precision medicine across disciplines. Within the imaging community, he was a leader and scientist with extraordinary expertise, widely known as a kind and generous friend, a nurturing mentor, and a catalyst for collaboration.

Nominees must have been SNMMI members (both U.S. and international applicants are welcome) for at least 5 consecutive years and be no more than 15 years past the last training position. Applications must be submitted by December 22. The awardee will receive $2,000 and will be acknowledged during the Wagner Highlights Lectures at the SNMMI Annual Meeting. For more information on nominating candidates, see: http://www.snmmi.org/applications/Forms/FormDisplay.aspx?FormID=166670.

SNMMI

SNMMI 10th Annual Patient Education Days

Each year the SNMMI Outreach Domain works with the SNMMI Patient Advocacy Advisory Board to hold a Patient Education Day, usually in conjunction with the Annual Meeting. This year's event was held virtually as 3 interactive webinars on August 14, 21, and 28, focusing on neuroendocrine tumors, prostate cancer, and breast cancer, respectively. Nuclear medicine physicians, radiologists, technologists, oncologists, and more than 220 patients, caregivers, and advocates from throughout the United States and the world presented sessions on nuclear medicine and radiation safety as well as disease-specific information. For more information on Patient Education Day and to watch recordings of the sessions, see www.snmmi.org/ped.

SNMMI

Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here.

PET/CT vs CT in FUO

Buchrits et al. from the Beilinson Hospital (Petah-Tikva) and Tel Aviv University (both in Israel) reported on August 20 in the *European Journal of Internal Medicine* (2021;20;S0953-6205[21]00264-8) on a study comparing the efficacy of ^{18}F-FDG PET/CT with that of contrast-enhanced CT in diagnosis of classic fever of unknown origin (FUO). The retrospective study included 303 patients referred for PET/CT for FUO. Final diagnoses, based on clinical, radiologic, and pathology data at latest follow-up (≥6 mo after hospital discharge), served as the gold standard and included infectious diseases in 111 (36.5%) patients, malignancies in 56 (18.4%), and noninfectious inflammatory conditions in 52 (17.1%). In 84 (28%) patients, FUO resolved without definitive diagnoses. Overall sensitivity and specificity for PET/CT were 88.7% and 80.9%, respectively, with corresponding percentages of 75.2% and 90.2% for CT. Analysis indicated that PET/CT was necessary in 79 (26%) patients and that endovascular infection, hematologic malignancy, and large vessel vasculitis were the only factors associated with this necessity. The authors concluded by recommending "PET-CT as the imaging modality of choice for patients with classical FUO, when endovascular infection, hematological malignancy or large vessel vasculitis are suspected."

European Journal of Internal Medicine

PET/CT and RT in Meningiomas

In an article published on August 16 in *Radiation Oncology* (2021;16[1]:151) Kowalski et al. from the University of Maryland School of Medicine and School of Pharmacy (Baltimore, MD) reported on the utility of PET/CT with the somatostatin receptor ligand ^{68}Ga-DOTATATE in conjunction with MR imaging in delineating radiation treatment target volumes and evaluating treatment response. The study included 19 patients who underwent both ^{68}Ga-DOTATATE PET/CT and MR imaging for radiation planning and/or posttreatment follow-up. Ten of the patients underwent both imaging modalities at both timepoints. Meningiomas were grade I in 9 patients and were not biopsied in 8. The majority (10) involved the base of the skull. Ten (53%) patients received postoperative radiation, and 9 (47%) received fractionated radiation treatment. In the subgroup who had undergone planning and posttreatment imaging with both modalities, adaptive thresholding software measured total lesion activity. PET/CT identified intraosseous (4, 22%), falcine (5, 26%), and satellite (3, 19%) lesions and resulted in a change in management for 3 patients. Mean total lesion activity decreased from pre- to posttreatment PET by 14.7%, and maximum total lesion activity decreased by a median of 36%. MR-based meningioma volumes did not significantly change between the 2 acquisitions. The authors concluded that "future studies are warranted to: (1) assess the sensitivity and specificity of ^{68}Ga-DOTATATE PET/CT; (2) evaluate the impact of ^{68}Ga-DOTATATE PET/CT–based planning on treatment outcomes; and (3) assess the prognostic significance of these posttreatment imaging changes."

Radiation Oncology

PET and Benign Anthracotic Lymphadenitis

Ivanick et al. from the University of California San Francisco and the Roswell Park Comprehensive Cancer Center (Buffalo, NY) reported in the July issue of the *Journal of Thoracic Disease* (2021;13[7]:4228–4235) on a study exploring the clinical, radiographic, and histologic characteristics of benign anthracotic lymphadenitis in patients referred for endobronchial ultrasound (EBUS)–guided biopsies. Benign anthracotic lymphadenitis is uncommon but has been associated with false-positive PET/CT findings. The retrospective study included 20 patients referred for EBUS-guided biopsies of ^{18}F-FDG PET–positive mediastinal and hilar lymph nodes (with demonstrated anthracotic pigment as the only histologic abnormality) during initial diagnosis or treatment of suspected malignancy. Of note, >90% of patients in this U.S.-based study were born outside of the country and their histories indicated likely exposure to biomass fuel or urban pollution. More than 90% had bilateral ^{18}F-FDG–avid lymph nodes, with an average SUV of 7.9 ± 2.2. The authors concluded that benign anthracotic lymphadenitis may be "an underrecognized cause for PET-positive lymph nodes in patients undergoing work-up for malignancy" and that these results "support the importance of sampling mediastinal and hilar lymph nodes even when SUVs are highly suggestive of malignancy."

Journal of Thoracic Disease

PET/CT Imaging and Utility in COVID-19

In an article published online on August 8 ahead of print in *Clinical*

Imaging (2021;80:262–267), Yeh et al. from Memorial Sloan Kettering Cancer Center (New York, NY) reported on initial imaging findings and potential clinical utility of ^{18}F-FDG PET/CT in patients with confirmed COVID-19. The retrospective review included data on 31 patients (21 men, 10 women; mean ages, 57 ± 16 y) who were diagnosed using real-time reverse transcription-polymerase chain reaction and who had undergone contemporaneous PET/CT imaging for routine cancer care in March and April 2020. Thirteen of the patients had positive PET/CT findings, suggesting a detection rate of 41.9%. Clinical data indicated that patients with positive scans had significantly higher rates of symptomatic COVID-19 infection than those with negative imaging (77% and 28%, respectively), with corresponding percentages of 46% and 0% for hospitalization. ^{18}F-FDG lung avidity was seen in 11 (84.6%) patients (mean lung SUV_{max} = 5.36), and 6 (46.2%) of the 13 positive patients had extrapulmonary PET/CT findings in thoracic lymph nodes. Lung SUV_{max} was not associated with COVID-19 symptoms, severity, or disease course. The detection rate was significantly lower when the scan was performed before the swab test than after (18.8% and 66.7%, respectively). The authors concluded that although ^{18}F-FDG PET/CT has limited sensitivity for detecting COVID-19 infection, "a positive PET scan is associated with higher risk of symptomatic infection and hospitalizations, which may be helpful in predicting disease severity."

Clinical Imaging

PSMA PET/CT Utility in High PSA and Negative Biopsy

Bodar et al. from Amsterdam University Medical Center/VU University, the Netherlands Prostate Cancer Network, Cancer Center Amsterdam, and the Netherlands Cancer Institute (all in Amsterdam, The Netherlands) reported on August 14 online ahead of print in *Urologic Oncology* on the diagnostic performance of prostate-specific membranous antigen (PSMA) imaging to localize primary prostate cancer in men with persistent elevated prostate-specific antigen (PSA) levels and previously negative prostate biopsies. The study included 34 such men (median PSA = 22.8 ng/mL) who underwent imaging with either ^{18}F-DCFPyL at 1 study institution or ^{68}Ga-PSMA–11 at another. Participants were divided into 3 groups for retrospective analysis: (1) those with previous negative multiparametric MR findings (n = 12); (2) those with a positive MR imaging but negative MR-targeted biopsies; and (3) those in whom multiparametric MR imaging was contraindicated. Patients with PSMA-avid lesions then underwent 2–4 PSMA-targeted biopsies in combination with systematic biopsies. PSMA tracer uptake in the prostate suspicious for prostate cancer was observed in 22 (64.7%) patients, in 18 of whom PSMA-targeted biopsies were performed. In 3 (16.6%) of these patients targeted biopsies showed International Society of Urological Pathology scores of 1–2 for prostate cancer. The other men had inflammation or benign findings confirmed at biopsy core histopathology. The authors concluded that "the clinical value of PSMA PET/CT for patients with an elevated PSA level and negative for prostate cancer biopsies was low."

Urologic Oncology

^{11}C-MET PET and Localization in Primary Hyperparathyroidism

In an article published on August 16 ahead of print in the *Scandinavian Journal of Surgery*, Iversen et al. from Aarhus University Hospital (Denmark) evaluated the use of ^{11}C-methionine PET/CT imaging in patients with primary hyperparathyroidism and either persistent primary disease after parathyroidectomy or inconclusive preoperative localization on ultrasound and ^{99m}Tc-sestaMIBI imaging. The study included 36 patients analyzed in 2 groups: (1) with ^{11}C-methionine PET/CT performed before parathyroidectomy (n = 17); and (2) with ^{11}C-methionine PET/CT performed after unsuccessful parathyroidectomy and before reoperation (n = 19). Across the 2 groups, PET/CT identified a true-positive pathologic parathyroid gland confirmed by a pathologist (positive-predictive value of 91%) in 30 (83%) patients. In group 1, 16 (94%) patients had such true-positive imaging findings, resulting in clinical benefit in 13 (76%) patients. In group 2, 14 (74%) patients had true-positive imaging, resulting in a clinical benefit in 9 (47%) patients. The authors summarized their findings that in this setting of patients planned for initial surgery or reoperation of primary hyperparathyroidism and inconclusive conventional imaging, ^{11}C-methionine PET/CT gave parathyroid surgeons clinical benefits in the majority of cases.

Scandinavian Journal of Surgery

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2. Siegel JA, Pennington CW, Sacks B, Welsh JS. The birth of the illegitimate linear no-threshold model: An invalid paradigm for estimating risk following low-dose radiation exposure. *Am J Clin Oncol.* 2018;41:173–177.
3. Sacks B, Meyerson G, Siegel JA. Epidemiology without biology: False paradigms, unfounded assumptions, and specious statistics in radiation science. *Biol Theory.* 2016;11:69–101.
4. Siegel JA, Welsh JS. Does imaging technology cause cancer? Debunking the linear no-threshold model of radiation carcinogenesis. *Technol Cancer Res Treat.* 2016; 15:249–256.
5. Siegel JA, Pennington CW, Sacks B. Subjecting radiological imaging to the linear no-threshold hypothesis: a non sequitur of non-trivial proportion. *J Nucl Med.* 2017;58:1–6.
6. Grant EJ, Brenner A, Sugiyama H, et al. Solid cancer incidence among the Life Span Study of atomic bomb survivors:1958-2009. *Radiat Res.* 2017;187: 513–537.
7. Siegel JA, Brooks AL, Fisher DR, et al. A critical assessment of the linear no-threshold hypothesis: Its validity and applicability for use in risk assessment and radiation protection. *Clin Nucl Med.* 2019;44:521–525.
8. Pennington CW, Siegel JA. The linear no-threshold model of low-dose radiogenic cancer: A failed fiction. *Dose-Response.* 2019;17:1–10.
9. Siegel JA, Greenspan BS, Maurer AH, et al. The BEIR VII estimates of low-dose radiation health risks are based on faulty assumptions and data analyses: a call for reassessment. *J Nucl Med.* 2018;59:1017–1019.
10. Siegel JA, Sacks B, Pennington CW, Greenspan BS. Perseverating on epidemiology and linearity: A journey into the minds of LNT model advocates. *J Nucl Med.* 2019;60[12]:15N–16N.
11. Furukawa K, Misumi M, Cologne JB, Cullings HM. A Bayesian semiparametric model for radiation dose-response estimation. *Risk Analysis.* 2016;36;1211–1223.
12. Sacks B, Siegel JA. Preserving the anti-scientific linear no-threshold myth: authority, agnosticism, transparency, and the standard of care. *Dose-Response.* 2017;15:1–4.