2021 SNMMI Highlights Lecture: Cardiovascular Track

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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 lecture by Sharmila Dorbala, MD, MPH, a professor of radiology at the Harvard Medical School and Director of Nuclear Cardiology at Brigham and Women's Hospital (Boston, MA), who spoke on highlights from the cardiovascular track at the meeting. 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]).*

It is a pleasure to present the 2021 Cardiovascular Highlights at the SNMMI Virtual Annual Meeting. The Cardiovascular Highlights session represents the key science selected for presentation based on novelty of the research, advances in the field, and thematic tracks. This year, the meeting featured 935 scientific abstracts, of which 75 (7%) were in the Cardiovascular Science track. Of these, 20% were in the basic sciences, with the remaining 80% covering clinical topics. These abstracts showcased research from Canada, China, Denmark, Germany, Japan, Republic of Korea, South Africa, Switzerland, Taiwan, and the United States. Major emerging themes from this year's cardiovascular presentations included: perfusion imaging advances (SPECT flow quantification, peripheral vascular disease); novel molecular tracers (fibrosis imaging, both human and preclinical; mitochondrial function imaging); volumetric SPECT/CT amyloidosis imaging; microcalcification imaging (perioperative myocardial infarction [MI] prediction, total atherosclerotic burden); and machine learning (automatic quantitation of microcalcification and of SPECT and PET myocardial perfusion imaging [MPI]). I have selected 10 key research presentations to highlight these themes, and I urge you to follow the SNMMI Virtual Meeting to get an overview of the entire spectrum of the novel cardiovascular research presented this year.

One highlight of the Annual Meeting is the naming of the Cardiovascular Council Young Investigator Award Winners. The awardees were the presenting authors on investigations from outstanding teams of researchers. In the Basic Science/Preclinical category, the first-place awardee was Felicitas J. Detmer, PhD, (Massachusetts General Hospital/Harvard Medical School; Boston, MA) for "Imaging of mitochondrial function in doxorubicin-induced cardiotoxicity." Recognized in second place was Benjamin Wilk (Western University; London, Canada) for "Myocardial glucose suppression interferes with the detection of inflammatory cells with FDG PET in a canine model of myocardial infarction." The third-place award in this category went to Zhao Liu, PhD, (Yale University; New Haven, CT) for "Assessment of lower extremities flow using dynamic ^{82}Rb PET: Acquisition protocols and quantification methods." The first-place Cardiovascular Council Young Investigator Award in the Clinical category went to Ananya Singh, MS, (Cedars-Sinai Medical Center; Los Angeles, CA) for "Improved risk assessment of myocardial SPECT using deep learning: Report from the REFINE SPECT registry." The second-place award was presented to Sarah Boughdad, MD, PhD, (CHUV; Lausanne, Switzerland) for "^{68}Ga-DOTATOC PET/CT to detect immune checkpoint inhibitor-related myocarditis." The third-place award in this category went to Xuezhu Wang (Peking Union Medical College Hospital/Chinese Academy of Medical Science; Beijing, China) for "Dynamic analysis of ^{11}C-PIB PET/CT in amyloid light-chain cardiac amyloidosis." I will be highlighting several of these presentations in this lecture.

Sharmila Dorbala, MD, MPH

Brenande de Oliveira Brito et al. from the University of Ottawa Heart Institute (Canada) reported that "SPECT blood flow improves per-vessel sensitivity of myocardial perfusion imaging to detect ischemia" [26]. They studied 172 patients who underwent SPECT MPI and blood flow quantitation. Their results showed that myocardial blood flow assessment had higher sensitivity than MPI on a per-vessel basis to detect hemodynamically obstructive disease compared to the per-patient basis, where there was no significant difference. Figure 1 shows imaging data from an example patient, in whom the stress and rest perfusion SPECT images demonstrate a perfusion defect. Coronary angiography, however, confirmed previous obstructive coronary artery disease (CAD). The polar maps show reduced peak stress myocardial blood flow and myocardial flow reserve in all 3 vascular territories. This research is important, because quantitational SPECT myocardial blood flow is now feasible with some of the modern solid-state SPECT cameras and, as SPECT is widely available, routine use of quantitative SPECT in clinical practice may enable better identification of the extent of hemodynamically significant obstructive CAD.

Liu et al. from Yale University/Yale University School of Medicine and Bridgeport Hospital (all in New Haven,

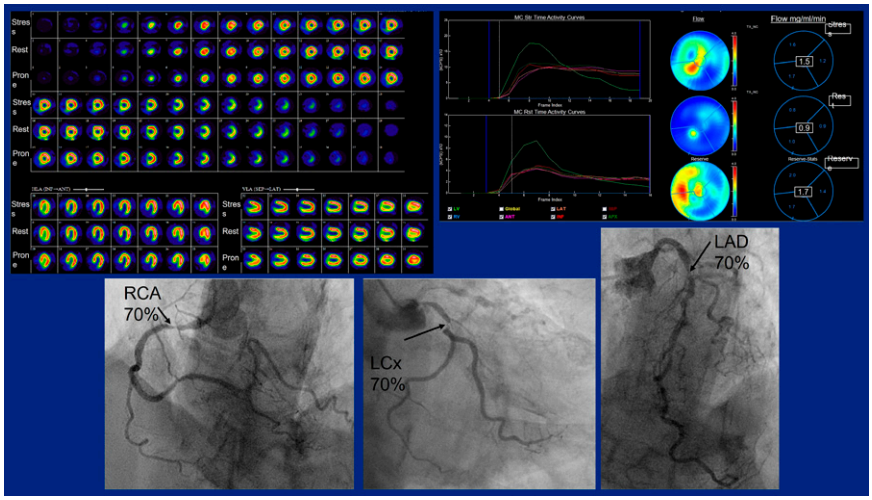

FIGURE 1. SPECT blood flow and per-vessel sensitivity of myocardial perfusion imaging (MPI) to detect ischemia. Imaging data from example patient who underwent SPECT MPI and blood flow quantitation. Stress and rest perfusion SPECT images (top left) demonstrate a perfusion defect. Polar maps show resting blood flow (top), stress blood flow (middle), and myocardial flow reserve (bottom), indicating reduced myocardial flow reserve and peak stress flow in all 3 vascular territories. Coronary angiography confirmed previous obstructive coronary artery disease. These results indicated that SPECT myocardial blood flow assessment can improve the sensitivity of ischemia detection by MPI.

CT) reported on "Assessment of lower extremities flow using dynamic ^{82}Rb PET: Acquisition protocols and quantification methods" [53]. The aim of this study was to investigate and optimize data acquisition protocols and quantitative data processing methods for dynamic ^{82}Rb PET imaging in an established porcine model of peripheral arterial disease through tracer candidate modeling. Their report also included initial human studies. The researchers acquired a 7-minute single-bed dedicated cardiac imaging scan to define the gold standard input function from the left ventricle (LV) blood pool scan, followed by a 2-minute single-bed scan of the abdominal aorta and then 5.5-minute multiple fast continuous-bed motion scanning for the lower extremities. The estimated arterial input function on the images was validated with blood sampling in animal models. The authors noted that the peak input function derived from the abdominal aorta was consistently about 60% underestimated compared to the LV function. They used a single-compartment model to measure K_1 values. In an acute ischemic hindlimb imaged at rest and stress in the pigs (Fig. 2), K_1 values were lower in ischemic than nonischemic limbs. After developing and refining their investigational technique in the animal model, the authors studied 4 healthy humans and 1 diabetic patient (Fig. 2). The K_1 values in the diabetic patient were much lower than those in healthy subjects. The authors concluded that "It is feasible to quantify skeletal muscle blood flow in the lower extremities using dynamic ^{82}Rb PET." These results are important because peripheral arterial disease is a major public health problem. Imaging of peripheral arterial disease and blood flow to the lower extremities is emerging as a novel application in nuclear cardiology. This project opens the door to perfusion imaging in peripheral arterial disease—an entirely new cardiovascular application.

Diekmann et al. from the Hannover Medical School (Germany) reported that "The area of fibroblast activation exceeds the hypoperfused infarct region in patients with acute myocardial infarction" [135]. The study included 12 patients who underwent cardiac MRI, perfusion SPECT, and ^{68}Ga-FAPI-46 PET/CT at 6–11 days after reperfused acute MI. MRI defined cardiac function and the extent of late gadolinium enhancement (LGE). All patients showed regional FAP signal enrichment at the infarct site relative to blood pool. The extent of FAPI signal was also found to be much greater than that of the perfusion defect. Figure 3 (left) shows an example patient with a matching pattern of a

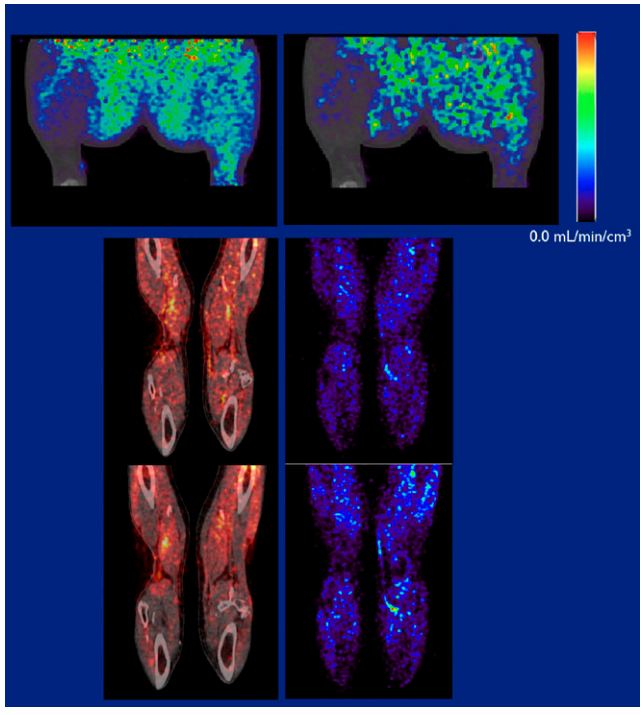

FIGURE 2. Assessment of lower extremities flow using dynamic ^{82}Rb PET. A 1-tissue compartmental model with a blood volume term was used to quantify K_1. Top: Representative K_1 parametric images at rest (left) and adenosine stress (right) in a pig with acute hindlimb ischemia (left in each image). Adenosine stress increased the K_1 heterogeneity and enhanced the relative flow deficit in the ischemia zone. K_1 values were significantly lower in the ischemic limb than in nonischemic areas. Bottom: Representative summed dynamic skeletal muscle images (left) and K_1 parametric maps (right) with ^{82}Rb PET (top) compared to ^{15}O-water PET (bottom) for validation in a control human subject. In humans, K_1 values were much lower in diabetic patients than in healthy controls.

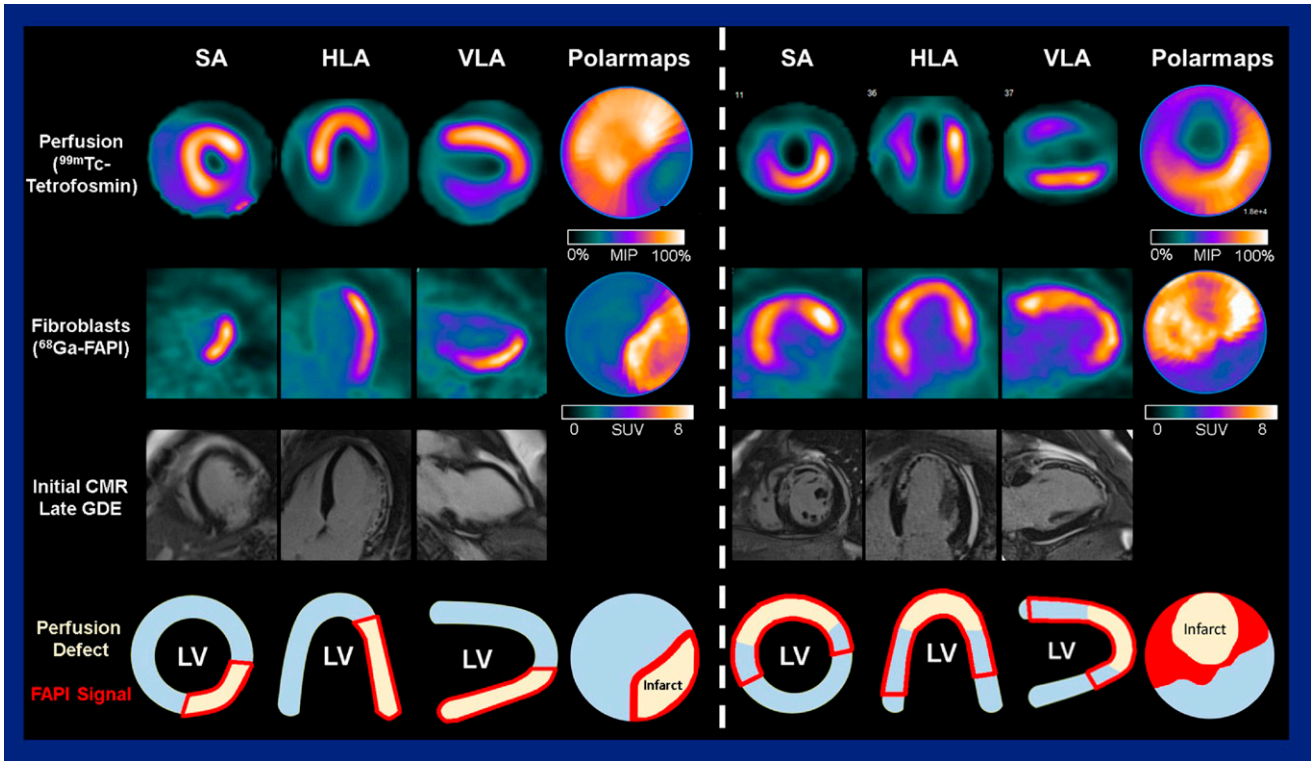

FIGURE 3. Fibroblast activation in patients imaged with cardiac MRI, perfusion SPECT, and ^{68}Ga-FAPI-46 PET/CT at 6–11 days after reperfused acute myocardial infarction (MI). Patient examples show (top to bottom) ^{99m}Tc-tetrofosmin perfusion imaging, ^{68}Ga-FAPI-46 fibroblast imaging, initial cardiac MRI/late gadolinium enhancement, and perfusion defect maps with FAPI signal areas in red. Left block shows a patient example with a matching pattern of perfusion defect and FAPI upregulation. Right block shows a patient in whom FAPI upregulation significantly exceeds perfusion defect and enhanced area on MRI. Fibroblast activation markedly exceeded the hypoperfused infarct region in patients after acute MI and early reperfusion therapy, and the extent of this regional upregulation varied significantly among individuals.

perfusion defect and FAPI upregulation. Figure 3 (right) shows a mismatch pattern in a patient with an anterior wall perfusion defect where the area of FAPI-upregulation significantly exceeded that of the perfusion defect and region of late enhancement on MRI. No relevant signal was observed in remote myocardium or other peripheral organs, including liver, spleen, bone marrow, or lungs. No correlation was detected between the FAP signal and available clinical variables, including measures of myocardial damage. FAP signal was present on MRI in segments with transmural infarct (>75% transmural LGE) and nontransmural infarct (25%–75% LGE). Notably, even among patients with <25% LGE the authors found that about half of segments demonstrated significant FAP signal, suggesting fibroblast activation in the noninfarcted myocardium as well. The authors concluded that the fact that fibroblast activation markedly exceeds the hypoperfused infarct region in patients after acute MI and early reperfusion therapy and that the extent of this regional upregulation varies so significantly among individuals should be further explored to illuminate the underlying mechanisms. This is a study with current relevance, because imaging of activated fibroblasts is of critical importance for development of novel therapies to prevent ventricular remodeling, not only in MI but in a number of other cardiovascular diseases and in heart failure.

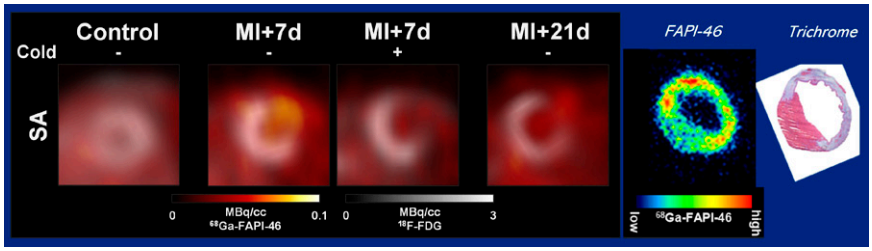

FIGURE 4. Preclinical ^{68}Ga-FAPI-46 for molecular imaging of cardiac fibroblast activation. In vivo PET studies in mice showed (left to right): low background tracer uptake in controls, selective ^{68}Ga-FAPI-46 in a myocardial infarct model at 7 days after infarct, ^{18}F-FDG co-injection uptake at 7 days after infarct, and decline of ^{68}Ga-FAPI-46 uptake by 21 days. Localization of the FAPI signal was confirmed by ex vivo autoradiography (right), where the signal exceeded the Masson trichrome–derived infarct area, suggesting sensitivity to replacement and reactive fibrosis.

Hess et al. from the same group at the Hannover Medical School (Germany) reported on "Preliminary characterization of ^{68}Ga-FAPI-46 for molecular imaging of cardiac fibroblast activation" [134]. They used FAPI here for in vitro and in vivo studies of cardiac fibroblast activation. In vitro studies showed selective ^{68}Ga-FAPI-46 uptake by transfected HT1080 cells overexpressing mouse or human FAP. Human cardiac fibroblasts also exhibited a

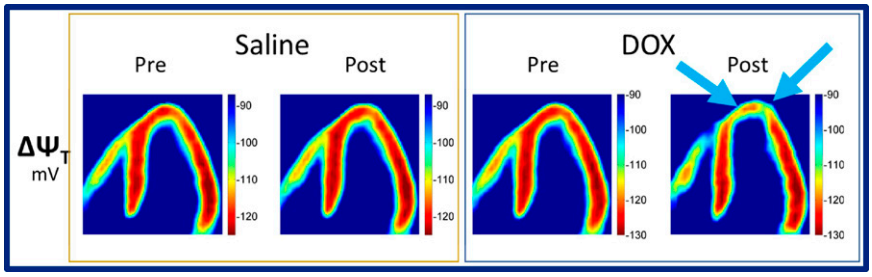

FIGURE 5. Imaging of mitochondrial function in doxorubicin-induced cardiotoxicity. ^{18}F-triphenylphosphonium (^{18}F-TPP^{+}) PET was used to image mitochondrial function in an acute doxorubicin-induced cardiomyopathy porcine model and to explore the utility of the tracer for total membrane potential mapping in monitoring cardiotoxicity during and after chemotherapy. Seven pigs were studied with ^{18}F-TPP^{+} PET before (left in each parametric image set) and after (right in each image set) acute doxorubicin (right set) or control saline (left set) infusions into the mid-left anterior descending (LAD) coronary artery. Results showed local depolarization of total membrane potential during or following doxorubicin infusion in LAD segments but no changes in control segments or after saline infusion.

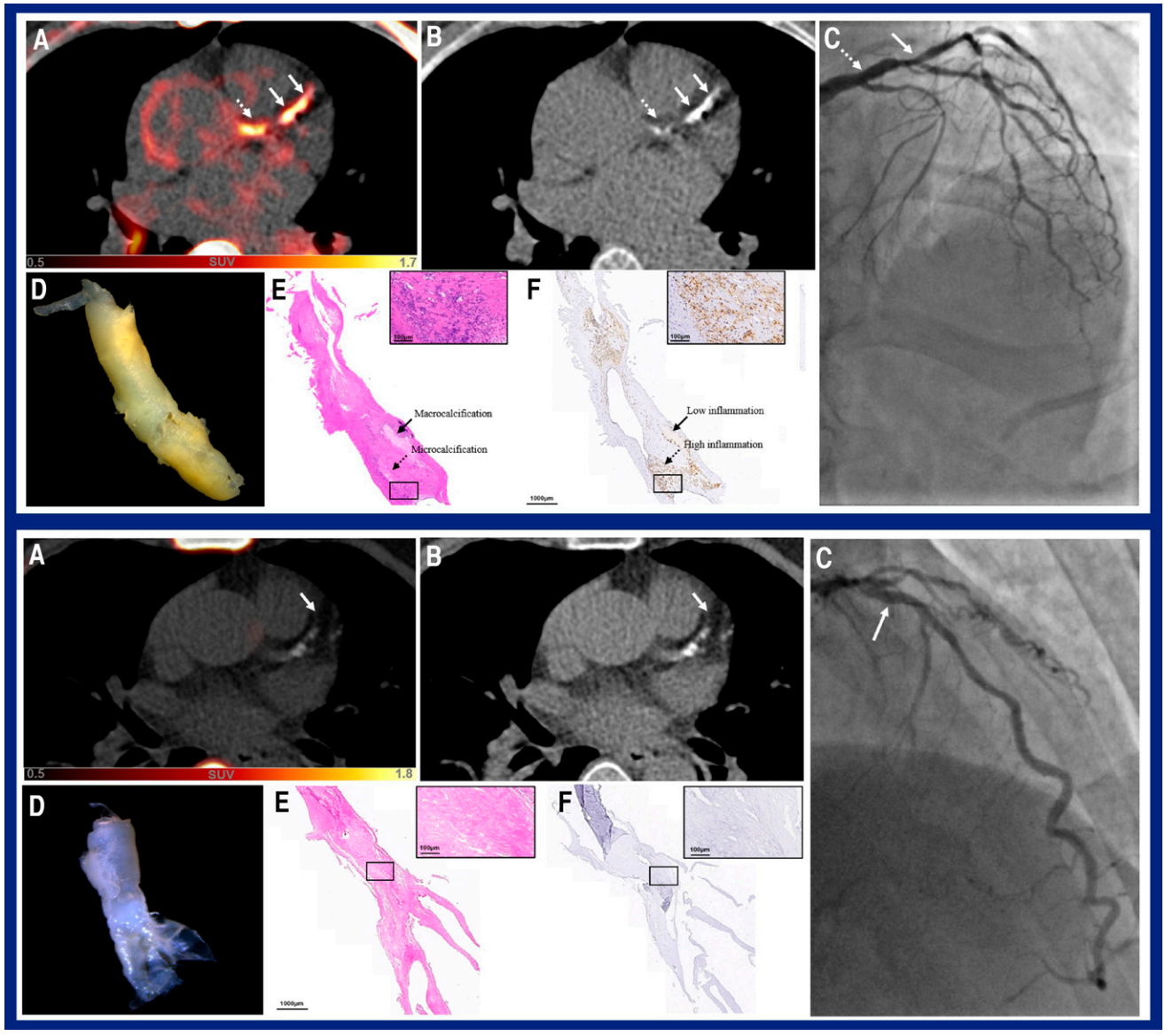

FIGURE 6. Multimodality cardiac imaging for prediction of postoperative myocardial infarction (MI) in example cardiac artery disease patients with (top block) and without (bottom block) postoperative MI. Top block shows: (A) Elevated ^{18}F-NaF uptake on PET at left main (LM) (white dotted arrow) and left anterior descending (LAD) (white solid arrow) arteries on fused PET/CT images. (B) Intense calcium density of LM (white dotted arrow) and LAD proximal stenosis (white solid arrow) on CT. (C) Stenosis at the corresponding lesion site on coronary angiography. (D) Histology and immunohistochemistry of the excised coronary atherosclerotic plaque (inflamed lesion). (E) H&E pathology staining. (F) CD68 immunostaining, with strong expression indicating significant macrophage infiltration in corresponding excised coronary atherosclerotic plaque. Microcalcification (black dotted arrow) and macrocalcification (black solid arrow) regions on H&E corresponded to high (black dotted arrow) and low (black solid arrow) inflammation on immunostaining, respectively. Bottom block shows: (A) Elevated ^{18}F-NaF uptake at proximal LAD (white-solid arrow) on fused PET/CT images. (C) Stenosis of proximal LAD with coronary stent (white solid arrow) on coronary angiography and (B) intense calcium density at the corresponding lesion site on CT. (D) Histology and immunohistochemistry of excised coronary atherosclerotic plaque (noninflamed lesion). (E) H&E pathology staining. (F) CD68 immunostaining indicated no significant macrophage infiltration in corresponding excised coronary atherosclerotic plaque.

moderate specific tracer uptake. Imaging in healthy control mice showed low background tracer accumulation in myocardial regions and liver, with rapid renal clearance. FAP expression on PET tended to be higher in mice 7 days after MI than in control mice (Fig. 4), with upregulation in infarct areas declining by 21 days. Co-injection of unlabeled precursor lowered the infarct FAP signal on day 7. Localization of the signal was confirmed by ex vivo autoradiography, where the FAP signal exceeded the Masson trichrome–derived infarct area, suggesting sensitivity to replacement and reactive fibrosis. The authors concluded that their findings support the feasibility of FAP imaging for cardiac fibroblast activation in mice but noted that the low absolute uptake in this animal model may complicate quantitative measurements in vivo. The clinical data presented in the previous study and the preclinical data presented in this study set the stage for innovative future investigations in imaging activated fibroblasts in various cardiovascular diseases.

Detmer et al. from the Massachusetts General Hospital/Harvard Medical School (Boston, MA) reported on "Imaging of mitochondrial function in doxorubicin-induced cardiotoxicity" [51]. These investigators used a novel tracer, ^{18}F-triphenylphosphonium (^{18}F-TPP^{+}), for PET imaging of mitochondrial function in an acute doxorubicin-induced cardiomyopathy model and to explore the utility of the tracer for total membrane potential mapping in monitoring cardiotoxicity during and after chemotherapy. Seven pigs were studied with ^{18}F-TPP^{+} PET after acute doxorubicin or control saline infusions into the mid-left anterior descending (LAD) coronary artery. The results showed local depolarization of total membrane potential during or following doxorubicin infusion in LAD segments but no changes in control segments or after saline infusion (Fig. 5). The results of this study are significant, because mitochondrial dysfunction forms the basis for a number of cardiomyopathies. If these results are validated in a larger study and in human studies, novel tracers such as ^{18}F-TPP^{+} can enhance molecular imaging of cardiomyopathies and our understanding of mitochondrial dysfunction.

Watanabe et al. from Kanazawa University Hospital (Japan) reported on "Volumetric evaluation of ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) SPECT/CT in patients with transthyretin cardiac amyloidosis (ATTR-CA): Optimization and correlation with cardiac functional parameters" [137]. In a retrospective study of 43 patients assessed with ^{99m}Tc-PYP SPECT/CT for ATTR-CA, the researchers evaluated aortic blood pool ^{99m}Tc-PYP activity using SUV_{max} in the ascending aorta at the level of the pulmonary artery bifurcation; total volume of the myocardial region where ^{99m}Tc-PYP uptake was >1.0×, >1.2×, and 1.4× of the aortic blood pool SUV_{max} within the left and right ventricular myocardium (defined as cardiac metabolic volumes); and conventional planar heart-to-contralateral lung uptake ratio. Thirty-seven of the patients had undergone endomyocardial biopsy. The key findings in this study were that the cardiometabolic volume of 1.2× aortic blood pool activity achieved the highest sensitivity and specificity (91% and 100%, respectively) for identifying patients with ATTR-CA, with overall accuracy better than that of the other metrics. The authors also showed that volumetric evaluation of amyloid activity using the cardiac metabolic volume 1.2× correlated linearly with brain natriuretic peptide, a measure of heart failure, and correlated inversely with left ventricular ejection fraction. This study is important because it adds to the growing body of literature supporting the use of volumetric SPECT-based methods for evaluating the disease burden of cardiac amyloidosis.

Wen et al. from the Beijing Anzhen Hospital/Capital Medical University (China) and the Vienna General Hospital (Austria) reported on "Comparative analysis of multimodality cardiac imaging for prediction of postoperative myocardial infarction" [1665]. These researchers aimed to validate and compare the value of coronary microcalcification, macrocalcification, stenosis, and serum inflammatory biomarkers in postoperative MI prediction. The prospective study included 75 patients with CAD scheduled for coronary artery bypass graft procedures. Patients underwent cardiac ^{18}F-NaF PET imaging, coronary artery calcium scoring, coronary angiography, and plaque analysis. Figure 6 shows multimodality cardiac imaging in CAD patients with (top block) and

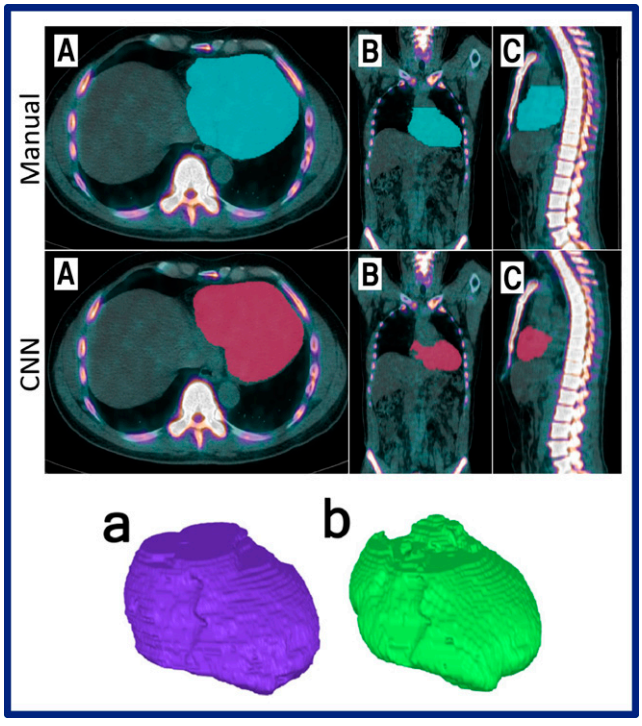

FIGURE 7. Global cardiac atherosclerotic burden assessed by fast automated artificial intelligence (AI)–based heart segmentation in ^{18}F-NaF PET/CT scans. Top block: Axial (a), coronal (b), and sagittal (c) reconstruction of manual (top row) and convolutional neural network (CNN)–based (bottom row) heart segmentation in the same patient. Bottom block: 3D reconstruction of manual (left) and CNN-based (right) segmentation of the heart. The automated method was much faster than the manual method (averages of 1 and 30 minutes, respectively). The CNN method provided values for segmented volume and SUV_{total} that were about 20% lower than manually obtained values, whereas SUV_{mean} and SUV_{max} values were comparable.

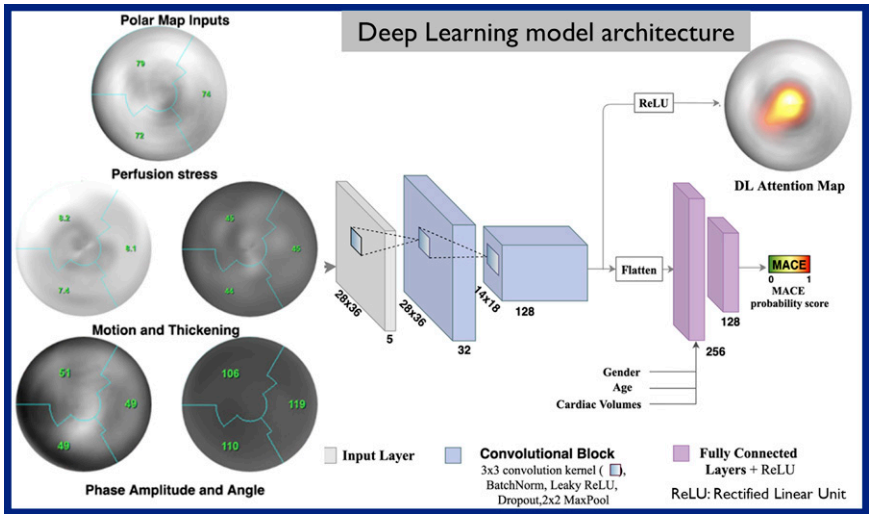

FIGURE 8. Improved risk assessment of myocardial SPECT using a novel deep-learning network for prediction of major adverse cardiac events (MACE). From multiple data sources, deep-learning attention maps were generated, highlighting regions associated with MACE risk as an overlay on polar map images. The deep learning approach was a significantly better predictor of MACE than stress and ischemic total perfusion defect assessment. This image summarizes the model architecture, with the resulting deep-learning attention map at upper right.

without (bottom block) postoperative MI. On the left are patient images showing intense ^{18}F-NaF activity in the coronary arteries and calcified plaque, with corresponding angiography showing obstructive coronary disease. Pathology data indicated microcalcification and macrocalcification regions corresponding to areas of high and low inflammation on immunostaining. In contrast example patient images without postoperative MI showed no significant ^{18}F-NaF uptake at the proximal LAD on PET/CT, stenosis of the proximal LAD with coronary stent on coronary angiography, and intense calcium density at the corresponding lesion site on CT. Pathology, however, showed no significant macrophage infiltration in excised coronary atherosclerotic plaques. This study showed that coronary microcalcification activity was substantially higher in patients who developed postoperative MI, whereas calcium score and baseline coronary stenosis level (SYNTAX score) did not differ between the groups. They also found increased inflammatory infiltration and CD68 expression in plaques showing ^{18}F-NaF uptake. High-risk plaques quantified by ^{18}F-NaF PET had significantly higher target-to-background ratios (TBRs) compared to low- and medium-risk plaques, and a lesional TBR $\geq$1.30 had a high diagnostic accuracy for detecting such high-risk plaques and thereby detecting patients likely to develop postoperative MI.

On a related topic, Skovrup et al. from Odense University Hospital (Denmark), University of Southern Denmark (Odense), Sahlgrenska Academy/University of Gothenburg (Sweden), Eigenvision AB (Malmo, Sweden), and Chalmers University of Technology (Gothenburg, Sweden) reported on "Global cardiac atherosclerotic burden assessed by fast automated artificial intelligence (AI)–based heart segmentation in ^{18}F-sodium fluoride PET/CT scans: Head-to-head comparison with manual segmentation" [29]. Heart segmentation in the study was based on a convolutional neural network (CNN) used in ^{18}F-NaF PET/CT scans of 29 healthy control subjects and 20 patients with angina pectoris, compared with data obtained by manual segmentation in the same scans. The researchers found that the automated method was much faster than the manual method (averages of 1 and 30 minutes, respectively). The CNN method provided values for segmented volume and SUV_{total} that were about 20% lower than manually obtained values, whereas SUV_{mean} and SUV_{max} values were comparable. The important point here is that we can use technology now to estimate in an unbiased fashion the total amount of atherosclerotic burden in these patients. Figure 7 includes examples of 3D reconstruction with both the manual and automatic methods. Automatic methods for estimating the burden of atherosclerosis add to the growing body of literature on machine learning for diagnosis, quantitation, and risk assessment in evaluation of heart disease.

The next 2 presentations are on a similar theme. Singh et al. from Cedars-Sinai Medical Center (Los Angeles, CA), University of Calgary (Canada), Assuta Medical Centers (Tel Aviv, Israel), Ben Gurion University of the Negev (Beer Sheba, Israel), Columbia University Irving Medical Center/New York Presbyterian Hospital (New York, NY), Oregon Heart and Vascular Institute/Sacred Heart Medical Center (Springfield, OR), University of Ottawa Heart Institute (Canada), University Hospital Zurich (Switzerland), Yale University School of Medicine (New Haven, CT), Cardiovascular Imaging Technologies LLC (Kansas City, MO), and Brigham and Women's Hospital (Boston, MA) reported on "Improved risk assessment of myocardial SPECT using explainable deep learning: Report from the REFINE SPECT registry" [50]. In this large study of 20,401 patients undergoing SPECT MPI, the authors reported on development and evaluation of a novel deep-learning network for prediction of major adverse cardiac events (MACE). The deep-learning network was developed with polar map image inputs of raw perfusion and gated derived maps of motion, thickening, phase angle, and amplitude combined with age, sex, and end-systolic and -diastolic volumes. A novel part of this approach is the use of deep-learning attention maps, highlighting regions associated with MACE risk as an overlay on polar map images (Fig. 8). These maps can be generated in less than 1 second to explain results to summarize results for physicians. The authors showed that their deep learning approach was a significantly better predictor of MACE than stress and ischemic total perfusion defect assessment. The authors concluded that the use of a

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SNMMI Adopts Family Leave Statement

The SNMMI Women in Nuclear Medicine Committee, Nuclear Medicine Program Directors Committee, and Diversity, Equity and Inclusion Task Force announced on November 12 the collaborative creation of an SNMMI Family Leave Statement. The statement, which was adopted by the SNMMI Board of Directors on November 1, is included here in its entirety:

SNMMI believes in communities, families, and partnerships where each person's values and needs are held in high regard and that a family's benefits, burdens, and responsibilities are shared among all its members. Caregiver responsibilities are part of a family's natural life cycle, from birth to death, encompassing self, partner, parents, and children.

The benefits of leave are well established, and supported family/medical leave promotes equity, creates a more inclusive environment, and contributes to a person's well-being. Employers and training programs with equitable workplaces must address family/medical leave to support their current employees and trainees and attract and retain future employees and trainees.

To that end, SNMMI believes that:

- Taking family/medical leave should not prevent a person from having a successful career in nuclear medicine and molecular imaging.
- Employers should develop transparent policies regarding family/medical leave and make that information readily available to current and prospective employees.
- Employers should inform all employees of their leave entitlements, including those provided under federal (*1*) and state laws and relevant NIH (*2*) and institutional policies.
- Training program directors and supervisors should inform all trainees of their leave entitlements, including those provided under federal (*1*) and state laws and relevant NIH (*2*), ACGME (3), institutional, and specialty board (*3,4*) policies.
- Employers, supervisors, and training program directors should ensure that employees and trainees eligible for leave are supported in taking leave.
- Employers, supervisors, and training program directors should provide lactation support and accommodations in accordance with federal law (*5*) during the postpartum period.

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deep-learning network allows for prediction of MACE directly from polar map images with improved accuracy compared to automatic quantitation of perfusion.

Authors from the same group extended this approach to ^{82}Rb PET perfusion imaging with similar results. Singh et al. from Cedars-Sinai Medical Center (Los Angeles, CA) and the University of Calgary (Canada) reported on "Explainable prediction of all-cause mortality from myocardial PET flow and perfusion images using deep learning" [28]. Here their goal was to develop and evaluate a novel explainable deep-learning network for prediction of all-cause mortality directly from PET MPI flow and perfusion polar map image data. The study included 3,206 patients referred for regadenoson (91%) and adenosine (9%) stress and rest ^{82}Rb PET. The deep learning approach was trained using stress and rest polar map image data of raw perfusion, myocardial blood flow, spill-over fraction, and myocardial flow rate combined with end-systolic and -diastolic volumes, age, and sex. Over a mean follow-up of 4.7 years, 654 patients died. Again, the deep learning model had a much better accuracy for predicting all-cause mortality. Survival curves presented by the authors emphasized the potential value of deep learning in prediction of adverse outcomes. Deep-learning attention maps generated from these results showed again the value of rapid aggregation of individual patient data for physician assessment. These presentations are very important, because the field of machine learning and AI is rapidly growing not only in cardiac imaging but in all of medicine. Quantitation is one of the biggest assets of nuclear cardiology, and we hope that studies such as this will advance further risk estimation using PET and SPECT MPI.

Thank you all for your attention. Although I was able to highlight only a few of the many cardiovascular research papers presented at this meeting, I urge you to look at the entire meeting available online to see the full spectrum of outstanding research. I want to end by congratulating Omar Mahmood, MD, PhD, and the entire SNMMI Scientific Program Committee for a fantastic meeting and for inviting me to present these highlights.

Ensuring Quality and Safety in Nuclear Medicine Imaging and Therapy

Richard L. Wahl, MD, SNMMI President

The field of nuclear medicine and molecular imaging has seen extraordinary advances over the past several years. From the approval of ^{177}Lu-DOTATATE and the promising published results of the ^{177}Lu-PSMA-617 phase 3 VISION trial in prostate cancer to advances in quantitative SPECT imaging and commercial internal radiation dosimetry software, we have made great strides in providing exceptional patient care. As more patients with prostate cancer benefit from nuclear medicine imaging and therapies, we must be prepared to safely expand our clinical services. SNMMI offers programs and services to ensure the quality and safety of these innovations. By supporting the field in this way, SNMMI helps to pave the road for the growth of nuclear medicine and molecular imaging domestically and around the world. SNMMI helps ensure that appropriately trained professionals, excellent facilities, and the best protocols are available to safely deliver growing patient care services in the radiopharmaceutical therapy space.

SNMMI provides a wide range of educational opportunities to help nuclear medicine physicians, technologists, physicists, pharmacists, radiologists, and others develop expertise in the latest innovations in nuclear medicine and molecular imaging. These educational offerings are presented at SNMMI's Mid-Winter and Annual Meetings and other in-person conferences, as well as virtually through online education programs, case reviews, and continuing education articles in *The Journal of Nuclear Medicine*. A record number of programs have been made available during the pandemic.

The society has taken several steps to ensure that comprehensive education is available on advances in radiopharmaceutical therapy. An inventory of existing SNMMI continuing education material related to therapy—including articles, courses, webinars, videos, specialty conferences, and more—has been curated and reviewed for gaps in content. In addition, SNMMI has conducted a thorough needs assessment for residency training programs. The results of this assessment are being analyzed and used to develop new content for students. SNMMI is also offering support for new therapy fellowships and for practitioners. The Therapeutics Conference in March 2022 will be delivered in person and will provide a comprehensive update on radiopharmaceutical therapies. With such a robust education program, we are confident that our trained nuclear medicine professionals can meet the needs of their patients, serving as their "nuclear oncologists" during their therapeutic interactions.

To ensure excellence in imaging, SNMMI provides guidance for nuclear medicine and molecular imaging professionals through appropriate use criteria, value and quality metrics, and procedure standards. By standardizing best practices to enhance operational efficiency, we can improve the quality of nuclear medicine and molecular imaging.

The SNMMI Dosimetry Task Force has been focused on developing processes and standards for performing dosimetric measurements of radiopharmaceutical therapy in research and clinical settings. A special *JNM* supplement was published in December 2021 comprising 7 articles that address both the rapid progress and the challenges in applying patient-specific radiation dosimetry to guide radiopharmaceutical therapies. The task force is working on reimbursement issues, a compendium of dosimetry software and hardware, and a white paper on the use of dosimetry in drug development and clinical practice, as well as compiling data from the SNMMI ^{177}Lu Dosimetry Challenge. The dosimetry supplement illustrates SNMMI's leadership in this important space, which is likely to be increasingly important in precision nuclear medicine.

Richard L. Wahl, MD

SNMMI is also developing a Radiopharmaceutical Therapy Registry (RaPTR) that will provide the framework to support a community of practices committed to patient-centered imaging and therapy, patient safety, optimized radiation dose, improved outcomes, practice transformation, and innovation through ongoing data collection and quality improvement. RaPTR will initially focus on ^{177}Lu-DOTATATE data, and launch is planned for January 2022.

To further promote quality and safety in therapy, SNMMI has launched a Radiopharmaceutical Therapy Center of Excellence Program (CoE) designed to further raise the quality bar on centers performing radiopharmaceutical therapies. Its mission is to establish criteria and standards to recognize facilities that provide excellence in clinical practice, research, and teaching. Certification and accreditation are planned for these centers, which will provide a clinical and comprehensive level of assessment. These programs will help ensure patients and providers that sites performing therapies meet specific standards. The Therapy CoE is dedicated to advancing quality patient care and promoting health care by ensuring that these centers meet rigorous standards for transdisciplinary, state-of-the-art research focused on developing new and better approaches to preventing, diagnosing, and treating cancer.

In addition, a comprehensive resource for nuclear medicine therapy has been launched for SNMMI members. Available at https://therapy.snmmi.org, the SNMMI Radiopharmaceutical Therapy Central portal provides information and content related to education, research, dosimetry, clinical guidelines, coding and reimbursement, accreditation, and other aspects of radiopharmaceutical therapies. SNMMI will continue to monitor the content of this portal and provide feedback for regular updates.

With the volume of recent advances in radiopharmaceutical therapy, however, challenges still remain. Patient service needs will be large, and we must meet the needs of our patients, safely. A recent survey published in *Advances in Radiation Oncology* showed that more than half of radiation oncologists would like to prescribe radiopharmaceutical therapy but cite infrastructure, interspecialty relations, lack of training, and financial considerations as barriers to doing so. Nuclear medicine facilities generally have training and equipment in place for radiopharmaceutical therapies.

No one can work in a vacuum, and collaboration and teamwork are critical in our efforts to ensure quality and safety. Teams of physicians working together for the best in patient outcomes through effective collaborations are often the best approach. SNMMI will continue its work with its partners to address all aspects related to quality and safety for new innovations in nuclear medicine and molecular imaging. We are confident that with dedicated training and resources, our nuclear medicine and molecular imaging professionals can improve the health of patients around the world and that the term *nuclear oncologist* will be more widely applied to discuss nuclear medicine physician activities in this space.

Regarding LNT: Scientifically Worthless and Increasingly Indefensible

TO THE NEWSLINE EDITOR: I am delighted with the commentary by Siegel, Sacks, and Greenspan in the November issue of *JNM* Newsline (2021;62[11]:17N–18N, 22N) regarding my petition and those of 2 others asking the Nuclear Regulatory Commission (NRC) to cease using the linear no-threshold (LNT) theory as the basis for radiation safety regulation. The authors did an excellent job in this commentary as part of a continuing effort over the years to refute LNT. It is shameful that government regulators have hoodwinked the entire nation with nearly 70 years of LNT-based regulations, including the corollary "as low as reasonably achievable" (ALARA) principle. The NRC-required public dose limit is set at 1 mSv, despite the fact that credible evidence of imaging-related low-dose (<100 mSv) carcinogenic risk is nonexistent. As pointed out in the commentary, NRC lacks necessary in-house expertise and therefore relies on recommendations from the equally misguided International Commission on Radiological Protection (ICRP) and National Council on Radiation Protection and Measurements (NCRP). NRC pays the NCRP for its opinion, and NCRP conveniently gives NRC the opinion it bought and paid for. (One might question the value of the NRC if it lacks the in-house expertise to evaluate radiation science.)

The LNT theory of radiation carcinogenesis is based on 4 assumptions, each of which is obviously incorrect and which together rely on illogical and circular reasoning: (1) The first assumption is that there is no such thing as repair of radiation damage. However, more than 150 genes have been found to be involved in gene repair, and in 2015 the Nobel Prize in Chemistry went to scientists who for more than 40 years had been elucidating the mechanisms of DNA repair. (2) The second assumption (which actually follows from the first) is that LNT is applicable whether a specific dose of radiation is delivered slowly over time or all at once—the putative effect is the same. We know, however, that a given quantity of radiation delivered slowly is much less damaging than the same quantity delivered all at once. Patients in radiation oncology routinely receive high doses given gradually, often over a 6-week period. If the total dose were delivered all at once, repair mechanisms would be overwhelmed and damage to normal tissue would be much greater. (3) The third assumption is that a single radiation interaction causing 1 DNA mutation can cause a fatal cancer. However, stem cells that give rise to cancer contain thousands of mutations, including numerous essential driver mutations. According to J. Michael Bishop, MD, 1989 Nobel laureate discoverer of the oncogene, "A single mutation is not enough to cause cancer. In a lifetime, every single gene is likely to have undergone mutation on about 10^{10} separate occasions in any individual human being. The problem of cancer seems to be not why it occurs, but why it occurs so infrequently." (4) The fourth assumption is that no processes exist at low radiation doses that do not exist at high doses. However, at high doses repair enzymes that exist at low doses are often inhibited from being synthesized.

Let us focus on radiation hormesis at low doses: Low doses of radiation result in stimulation of enzymes that not only repair radiation damage but repair damage caused by other mutagens, the most important being oxygen—yes, oxygen. The cost of being an aerobic organism is huge. According to the late Myron Pollycove, MD, breathing oxygen causes 10,000 DNA mutations/cell/hour. One rem causes 20 DNA mutations/cell/*year*. Oxygen therefore causes 4.4 million times as many mutations per year as 1 rem. Low-dose radiation hormesis is pervasive, having been found in microorganisms, algae, plants, insects, invertebrates, vertebrates, and humans. Unlike low-dose carcinogenic risk, radiation hormesis has been demonstrated to exist.

So why have radiation professionals accepted LNT and not condemned this demonstrably false theory? Ignorance? Laziness? Fear? LNT has become an illogical religion among scientists who need to recognize their problem. It is time to stand up to the regulators, challenge the scientific organizations, and demand change. We should all better educate residents and other physicians, as well as patients, on this issue. LNT is scientifically worthless and indefensible.

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Regarding LNT: NRC Wrongfully Rejects Petitions to End LNT Model Use

TO THE NEWSLINE EDITOR: I would like to offer a historical perspective on the commentary by Siegel, Sacks, and Greenspan in the November issue of *JNM* Newsline (2021;62[11]:17N–18N, 22N) on the Nuclear Regulatory Commission (NRC) rejection of three 6-year-old petitions requesting repudiation of the linear no-threshold (LNT) model. First, I am reminded of a 1980 speech by Lauriston Taylor, who said that studies "calculating the numbers of people who will die as a result of having been subjected to diagnostic X-ray procedures [by applying the LNT model] … are deeply immoral uses of our scientific knowledge" (*1*).

In 1954, soon after President Eisenhower's Atoms for Peace Speech to the United Nations, the Rockefeller Foundation mobilized and managed a National Academy of Sciences (NAS) study of radiation effects "with particular attention to the possible danger to the genetic heritage of man" (*2*,*3*). The 10-year study, by Neel and Schull, on 75,000 children of atomic bomb survivors, showed no evidence of hereditary damage (*2*,*4*). Nevertheless, the NAS rejected these data and in 1956 recommended use of the LNT model to assess the risk of radiation-induced mutations, based largely on controversial studies that irradiated fruit flies.

I previously reviewed the 1957 study by Lewis that linked the incidence of leukemia in atomic bomb survivors to their radiation exposures (*5*). The study was flawed because it combined data in the low-dose Zone D with data in the control Zone E. This concealed the high 1.1-Gy threshold for inducing leukemia, shown in Figure 1 (*6*–*8*).

Discussions in the NCRP about this cancer risk controversy led to a compromise and the NCRP decision in 1960 to adopt policies

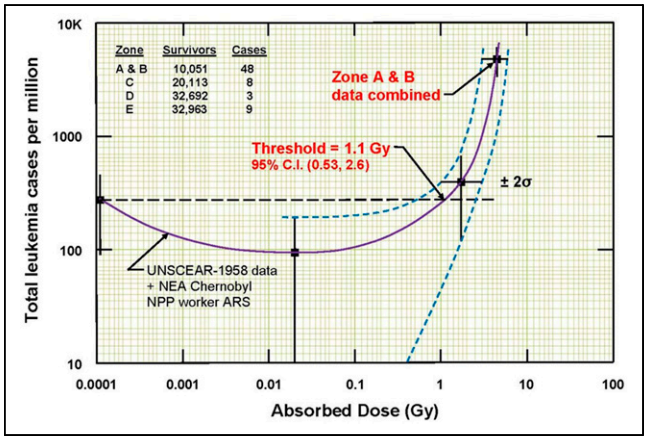

Figure 1. Graph of incidence of leukemia in 95,819 Hiroshima atomic bomb survivors versus absorbed dose, from 1950 to 1957, showing evidence of the threshold at 1.1 Gy for radiation-induced leukemia (*7*). UNSCEAR = United Nations Scientific Committee on the Effects of Atomic Radiation; NEA = OECD Nuclear Energy Agency; NPP = nuclear power plant; ARS = acute radiation syndrome. Blue broken lines show 2-σ error band.

governed by the precautionary principle and the "as low as reasonably achievable" (ALARA) benchmark. This policy included using the LNT model to estimate the risk of radiation-induced cancer (*9*). The NCRP decision was based on widespread public concern over the effects of radiation from fallout and the possibility of new information regarding effects on humans (*10*). The United States and other countries followed the NCRP policy.

This policy has not changed in more than 61 years, despite evidence in 1960 and much more evidence today that contradicts the LNT model and demonstrates that low doses of radiation benefit health (*7*). It was wrong for the NRC to reject the petitions that requested amendment of 10 CFR Part 20 to protect people based on scientific evidence that contradicts the LNT hypothesis. Instead of following the antinuclear NCRP policy based on taking precautions against fearful myths, the NRC should recognize the evidence of radiation's beneficial health effects for exposures that are below thresholds for detrimental effects (*11*).

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Regarding LNT: The Negative Consequences of Reliance on LNT/ALARA

TO THE NEWSLINE EDITOR: I was intrigued by the commentary from Siegel, Sacks, and Greenspan (*1*) regarding 3 petitions (*2*) requesting that the Nuclear Regulatory Commission (NRC) cease using the linear non-threshold (LNT) hypothesis as the basis for radiation safety regulations. These regulations accept the LNT hypothesis and its "as low as reasonably achievable" (ALARA) partner principle. Any challenge to the established NRC dogma merits a thorough and rigorous discussion. Unfortunately, the NRC relied on only a portion of relevant information that supported their position and failed to consider the complete set of data that offers a scientific basis for rejecting the LNT hypothesis. Arguments against the NRC's rejection have considerable merit and must not be ignored by regulators.

By its very nature LNT/ALARA focuses on radiation detriment and not the collective set of repair mechanisms that mitigate the effects of ionizing radiation, particularly at low doses. The NRC does not properly evaluate the well-known repair and mitigative mechanisms, including adaptive response, the human immune system, and DNA repair mechanisms. In addition, hormesis and radiation damage thresholds are not considered (*3*,*4*). Although these comments outline a limited number of concerns, the case against LNT/ALARA is strong (*1*,*2*). In addition, there are numerous negative consequences of perpetuating the reliance on LNT/ALARA including:

(1) LNT/ALARA creates an atmosphere that fosters and perpetuates radiophobia and inhibits research using low-dose radiation in the detection, prevention, and treatment of cancer and other diseases, including COVID-19. Unwarranted fears have effectively retarded research and could result in missed diagnoses in instances where imaging doses are too low to produce adequate tissue resolution (*5*).

(2) The continued development and utilization of nuclear power in the United States and Western Europe have been inhibited by LNT/ALARA exaggerations of the impacts of nuclear accidents. These mischaracterizations reinforce unjustified fears regarding the detrimental effects of radiation (*6*,*7*) and inadvertently promote the use of higher-polluting energy-generating sources.

(3) Increased regulation of radiation and radioactive materials and the associated costs to implement LNT/ALARA compliance further dampen the expansion and use of the beneficial uses of nuclear technology.

(4) Nuclear facilities, particularly in the commercial nuclear power reactors and fuel cycle areas, devote significantly more resources and attention to imagined safety efforts driven by LNT/ALARA than to real industrial safety hazards that have injured workers.

(*Continued on page 22N*)

MPFS and OPPS Final Rules Expand Nononcologic PET Coverage

On November 9 SNMMI issued comments on the newly finalized Centers for Medicare and Medicaid Services (CMS) Medicare Physician Fee Schedule (MPFS) and Hospital Outpatient Prospective System (OPPS) rules. SNMMI summarized and provided commentary on the highlights of the final rules:

- CMS removed the "exclusionary language" from NCD 220.6 Positron Emission Tomography (PET) Scans. This will leave nononcologic PET indications (unless noted by NCD 220.6.1–220.6.20) to the discretion of local Medicare Administrative Contractors (MACs). The SNMMI applauded the coverage decision, noting that it resulted from years of work by SNMMI and industry partners, saying in a press release: "We resoundingly agree that 'local contractor discretion provides an immediate avenue to potential coverage in appropriate candidates for nononcologic indications.' Various new PET agents for nononcologic indications are currently in FDA trials. Retiring the national noncoverage policy for nononcologic indications upon the agents' FDA approval will eliminate the regulatory bottleneck leading to Medicare beneficiary access issues."
- CMS did not retire national noncoverage decisions for amyloid PET (220.6.20) and NaF (220.6.19). SNMMI noted that the society is working with CMS to rectify coverage decisions for both: "We hope CMS will change its position on amyloid PET when they release their national coverage analysis decision on Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease on January 12, 2022."
- The PFS final rule cuts the conversion factor to $33.59 in CY 2022 from $34.89 in CY 2021. This follows the expiration of the 3.75% payment increase, a 0.00% conversion factor update, and a budget neutrality adjustment. SNMMI reported that the society is working with the medical community to prevent cuts to physician reimbursement.
- CMS delayed implementation of the payment penalty phase of the Appropriate Use Criteria program to the later of January 1, 2023, or the January 1 that follows the end of the current public health emergency.
- CMS will be phasing in the clinical staff wage increase over 4 years. As a result, the impact to nuclear medicine procedure codes will not be as acute as in the proposed rule (3%–4% decrease versus a 10%–15% decrease).
- The final CY 2022 OPPS Rule included no changes to what the SNMMI termed the "inequitable" reimbursement policy of precision diagnostic radiopharmaceuticals. These drugs continue to be packaged after the expiration of a 3-year pass-through period. SNMMI urged members and interested members of the community to send a letter to Congress in support of the Facilitating Innovative Nuclear Diagnostics (FIND) Act, legislation aiming to expand patient access through appropriate payment. More information is available at: https://snmmi.quorum.us/campaign/34856/.

SNMMI

U.S., Canada, UK Collaborate on Good Machine Learning Practice

On October 27, the U.S. Food and Drug Administration (FDA), Health Canada, and the United Kingdom Medicines and Healthcare Products Regulatory Agency jointly issued the "Good Machine Learning Practice for Medical Device Development: Guiding Principles" to identify 10 principles that are important in development of Good Machine Learning Practice (GMLP). GMLP is intended to advance high-quality artificial intelligence/machine learning–enabled medical device development. The 10 principles identify areas in which alignment in efforts related to research, building resources and tools, regulatory policies, regulatory guidelines, international harmonization, and consensus standards could be developed by the International Medical Device Regulators Forum, international standards organizations, and other collaborative bodies to advance the maturation of GMLP.

In a press release, FDA said that these guiding principles could be used to either specifically tailor practices applicable to health care, create new practices, or adopt from practices that have been proven in other domains. "With artificial intelligence and machine learning progressing so rapidly, our 3 regulatory agencies, together, see a global opportunity to help foster good machine learning practice by providing guiding principles that we believe will support the development and maturation of good machine learning practice," said Bakul Patel, director of the FDA Digital Health Center of Excellence in the Center for Devices and Radiological Health. The GMLP guiding principles are available at: https://www.fda.gov/medical-devices/software-medical-device-samd/good-ma chine-learning-practice-medical-device-development-guiding-principles.

U.S. Food and Drug Administration

DOE Tri-Lab Project and ^{225}Ac

In a news feature released on November 17, the Department of Energy (DOE) Oak Ridge National Laboratory (ORNL; TN) described a national laboratory collaborative effort to provide accelerator-produced ^{225}Ac for therapeutic use. Since 2014, the DOE Isotope Program has sponsored the Tri-Lab research project with a goal of production of large batches of ^{225}Ac more quickly and more frequently in anticipation of regulatory approval of routine use in clinical treatment. A number of private and global public/private partnerships are also addressing the challenge to safely and reliably produce ^{225}Ac.

ORNL currently produces the majority of the world's ^{225}Ac by harvesting it from a supply of ^{229}Th, produced by ^{232}Th targets irradiated in proton accelerators at Los Alamos and Brookhaven National Laboratories. However, the amount of the radioisotope currently "milked" from the ^{229}Th "cow" (about 1 Ci/year) is not enough even for large-scale clinical trials, and options for scaling up production are limited. In June, ORNL processed the largest batch of ^{225}Ac ever put into its inventory,

processed from targets irradiated at Brookhaven, which produces ^{225}Ac using a high-energy proton beam. "We demonstrated that the accelerator route can generate about 60% of the current annual supply of ^{225}Ac in just 12 days," said Dmitri Medvedev, a scientist in the Brookhaven Collider Accelerator Department.

In 2020, FDA acknowledged receipt of a drug master file for the Tri-Lab accelerator-produced ^{225}Ac, outlining details about the facilities and processes used in manufacturing, processing, packaging, and storing the radioisotope to ensure that the product meets specifications. "The drug master file is one step forward toward this ultimately being used in an FDA-approved product," said Roy Copping, who leads the Tri-Lab production program from the ORNL side. Researchers at ORNL are currently looking at 2 ways to further increase output: processing batches more frequently and processing larger targets. As part of the Tri-Lab effort, a research and development team developed in-cell technology to manage gas created in the production process. The team began developing the technology in November 2020, spent several months testing it outside the hot cell, then implemented it in the hot cell in April 2021. The technology benefits production at ORNL and is extensible to future target processing at Brookhaven and Los Alamos. For more information about the Tri-Lab effort, see: https://www.isotopes.gov/sites/default/files/2021-01/Actinium225Brochure%20-%20FINAL%20for%20web_sm.pdf.

Oak Ridge National Laboratory

Gene Therapies for Rare Diseases

On October 27 the National Institutes of Health (NIH), U.S. Food and Drug Administration (FDA), 10 pharmaceutical companies, and 5 nonprofit organizations announced a partnership to accelerate development of gene therapies for individuals who suffer from rare diseases. Although ~7,000 rare diseases have been identified, only 2 heritable diseases currently have FDA-approved gene therapies. The new Bespoke Gene Therapy Consortium (BGTC), part of the NIH Accelerating Medicines Partnership program and project-managed by the Foundation for the National Institutes of Health, is intended to optimize and streamline the gene therapy development process.

"Most rare diseases are caused by a defect in a single gene that could potentially be targeted with a customized or 'bespoke' therapy that corrects or replaces the defective gene," said NIH Director Francis S. Collins, MD, PhD. "There are now significant opportunities to improve the complex development process for gene therapies that would accelerate scientific progress and, most importantly, provide benefit to patients by increasing the number of effective gene therapies."

Gene therapy development for rare diseases is time consuming and expensive. NIH cited numerous challenges, including limited access to tools and technologies, lack of standards across the field, and a "1-disease-at-a-time" approach to therapeutic development. A standardized therapeutic development model that includes a common gene delivery technology (a vector) could allow for a more efficient approach to specific gene therapies, saving time and cost.

A clinical component of BGTC-funded research will support between 4 and 6 clinical trials, each focused on a different rare disease, expected to be rare, single-gene diseases with no gene therapies or commercial programs in development but with substantial groundwork already in place to rapidly initiate preclinical and clinical studies. For these trials, the BGTC will aim to shorten the path from studies in animal models of disease to human clinical trials. The BGTC also will explore methods to streamline regulatory requirements and processes for FDA approval of safe and effective gene therapies, including developing standardized approaches to preclinical testing.

NIH and private partners will contribute ~$76 million over 5 years to support BGTC-funded projects. This includes about $39.5 million from the participating NIH institutes and centers, pending availability of funds. Additional information and a complete list of participating NIH entities, industry partners, and nonprofit groups is available at: https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/bespoke-gene-therapy-consortium.

National Institutes of Health

(Continued from page 20N)

(5) Following the Fukushima-Daiichi accident, more than 100,000 individuals were evacuated and forced to abandon their family farms, homes, and jobs. The physical and psychological harm caused by these LNT/ALARA–driven evacuations vastly outweigh the imagined hazard of low levels of ionizing radiation.

I offer the following rallying cry to those seeking to use reason and scientific evidence to overthrow the LNT/ALARA dogma (with apologies to Winston Churchill): We shall challenge the proponents of LNT/ALARA in scientific journals, at conferences, in the media, on the internet, in public forums, and in classrooms. We shall defend valid science, whatever the cost may be.

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