**Value Initiative: Research and Discovery Domain**

Richard L. Wahl, MD, FACP, FACNP, and John Sunderland, PhD, MBA

Nuclear medicine and molecular imaging are in the midst of an exciting and dynamic era of growth with new imaging agent approvals, expanding use of radiopharmaceutical therapies, and advances in equipment and artificial intelligence science. While all of these combine to advance the field, we face serious ongoing challenges in reimbursement, regulations, workforce, and broad awareness of nuclear medicine contributions to diagnosing and treating patients. The Value Initiative (VI)—a roadmap for addressing the challenges and demonstrating the true value of the field to a broad set of stakeholders, including patients, referring physicians, medical and science students, industry professionals, regulators, and the public—was launched by SNMMI in 2018. The VI focuses on five domains that guide SNMMI’s strategic plan: Quality of Practice, Workforce Pipeline and Lifelong Learning, Advocacy, Outreach, and Research and Discovery.

The Research and Discovery (R&D) domain is led by chair Richard Wahl, MD, and vice-chair John Sunderland, PhD. The domain’s goal is to advance the development and approval of nuclear medicine and molecular imaging agents, therapies, and technologies. The Clinical Trials Network (CTN), and many of the SNMMI research-oriented councils and centers, fall under the R&D domain.

In January 2021, the R&D domain published the “Mars Shot for Nuclear Medicine, Molecular Imaging, and Molecularly Targeted Radiopharmaceutical Therapy” in *The Journal of Nuclear Medicine* (JNM). The manuscript was authored by representatives from the SNMMI councils and centers. The broad-based vision document outlined the roles of precision imaging and radiopharmaceutical therapy (RPT) in cancer, neuroimaging, and other unmet medical needs and serves as a foundation for future research and development.

In 2020, the R&D domain initiated two important task forces to address advances and challenges in radiopharmaceutical dosimetry and to provide focus and forward-looking strategies on the development of Artificial Intelligence applications across the breadth...
The primary goal of the SNMMI Dosimetry Task Force is to advance the use of dosimetry in radiopharmaceutical therapy. While there have been efforts to harmonize and standardize internal dosimetry calculations, a lack of large-scale studies with which to justify recommendations has made it difficult to develop best practices and methods. The task force launched the Lu-177 Dosimetry Challenge in February of 2021 to collect valuable data from the nuclear medicine community that could guide the efforts to remedy the dosimetry conundrum.

The challenge has been designed with a series of five different tasks, as shown in Figure 1. Participants are given access to the same dataset of two patients treated with Lu-177 DOTATATE. The tasks are performed in order and involve calculating organ and tumor doses starting at different points along the dosimetry analysis pipeline. Participants are provided with template documents to record and submit requested data and are asked to provide a short description of the methods used, along with other important information (e.g., anything that caused particular difficulty). Participants are also asked to record how long each step takes to complete—an important variable for attaining reimbursement for dosimetry calculations. To remove sources of variability for organ and tumor delineation and time-integrated activity (TIA) calculations, volumes of interest and the TIA image are provided to participants for tasks 4 and 5, respectively. The data will be analyzed focusing on determining sources and magnitude of variability.

The challenge was developed by Yuni Dewaraja, Eric Frey, Carlos Uribe, and John Sunderland—a subgroup of physicists belonging to the Dosimetry Task Force (see lead story in this issue). Avery Peterson has been hired as an intern to assist with data analysis. The imaging data for the challenge are hosted in Deep Blue Data—a repository of digital research data—at the University of Michigan.

To date, this challenge has far exceeded our expectations. Over 170 participants have registered from 28 countries, including Colombia, Nepal, the Philippines, and Saudi Arabia, to name a few (Figure 2. Dosimetry Participants Map). Fifteen industry representatives, from software developers to imaging contract research organizations, are also taking part. Several registrants have congratulated the team on the challenge and noted its importance. The task force has received 130...
of nuclear medicine. The Dosimetry Task Force, chaired by Pat Zanzonico, PhD, and George Sgouros, PhD, is charged with identifying the current status and gaps in our applications of radiopharmaceutical dosimetry and developing processes and standards for performing dosimetric measurement of RPT in research and clinical settings. The group also launched an Lu-177 Dosimetry Challenge in January 2021, providing serial SPECT/CT and planar image sets of two patients who received Lu-177 DOTATATE therapy. The goal of the challenge is to identify and quantify variability in radiation absorbed dose calculations across the various steps in the dosimetry workflow. More than 170 professionals from 28 countries have registered, and the group is excited about the robust data set that is developing. The task force is also drafting manuscripts for a JNM dosimetry supplement to be published later this year (see Special Feature in this issue).

The Artificial Intelligence (AI) Task Force has also been developing manuscripts that address the current status of development and implementation of AI in nuclear medicine, molecular imaging, and radiopharmaceutical therapy. Watch for those in JNM this year. In conjunction with the Physics, Instrumentation, and Data Science Council and the Michael J. Fox Foundation, the AI Task Force will launch a data challenge, with data from the Parkinson’s Progression Markers Initiative, addressing the question of the added value of imaging, particularly nuclear medicine imaging, for the identification of clinical progression trajectories in Parkinson’s disease. Prize money totaling up to $25,000 will be awarded to up to three researchers who best answer this question with an AI algorithm.

Performing the increasing variety of radiopharmaceutical therapies is now requiring a more complex array of professional expertise, facilities, resources, and training than the typical nuclear medicine department of yesterday; thus, SNMMI is introducing the Radiopharmaceutical Therapy Centers of Excellence program (www.snmmi.org/rptcoe). Through this program, clinical sites performing RPTs can now apply to be awarded the designation of Clinical or Comprehensive RPT Center of Excellence. These designations provide patients assurance that they will have reliable access to high-quality RPT, which is well-integrated into their pathway of care, delivered by highly qualified therapy teams at technically qualified sites and led by physicians appropriately trained in nuclear medicine.

The rapid growth and excitement associated with the molecular imaging and RPT raises the concern that there may not be enough young talent entering the field to sustain this growth both clinically and in research innovations. In an effort to attract talented students to molecular imaging research, the R&D domain initiated a Discovering MI Study Research Grant. In its inaugural year, five molecular imaging and therapy research grants were awarded to aspiring physicians and scientists not yet committed to a specialty. Based on the success, the number was increased to 10 grants for 2021, which were awarded to a diverse new slate of medical and science students. We congratulate all of the awardees and look forward to their future contributions to the field. New this spring, the R&D domain offered six travel grants to junior faculty members to attend the NCI Cancer Cooperative Groups meetings. The goal of these grants is to increase the number of nuclear medicine physicians contributing to the conduct and design of the cooperative group trials, especially those involving RPT. Each awardee will have a mentor from the same cooperative group to help with the orientation.

As Dr. Wahl assumes the role of SNMMI president, Dr. Sunderland will take the helm as domain chair and continue to innovate for the field of nuclear medicine and the SNMMI.
The SNMMI Clinical Trials Network (CTN) was started in 2009 and has maintained a leadership role in advancing and optimizing the use of molecular imaging and radiopharmaceutical therapies in clinical trials and their dissemination into clinical practice across the globe. The CTN’s work has been distributed across five committees: Scanner Validation and Site Qualification, Education, Database, Radiopharmaceutical Manufacturers, and SPECT. Programs have expanded as the field has grown. CTN’s robust PET/CT scanner validation program is now complemented by the newly developed SPECT/CT scanner characterization for dosimetry. Educational products for the community have included CE courses in research for physicians, technologists, and scientists; reader interpretation training for new agents; and coming soon, online training using full DICOM studies. The CTN database—with extensive data on radionuclide and radiopharmaceutical production capabilities at over 100 institutions—is expanding to include information about the radiopharmaceutical therapy capabilities of sites. With the increased use of more novel isotopes, such as gallium-68, copper-64, and zirconium-89, the Radiopharmaceutical Manufacturers Committee is expanding its auditing capabilities to review these new agents. The CTN is expanding its available expertise and workforce through a new Research Committee to meet these growing activities.

The CTN Research Committee will support the activities of the CTN and the broader Research and Discovery Domain of the SNMMI. Members were selected to provide a larger and more diverse pool of expertise for current and future programs and to increase engagement with the larger molecular imaging community. Individual committee members will engage in CTN projects aligned with their areas of expertise and interests. In addition to work on specific CTN projects, this new pool of research-focused physicians, physicists, and chemists is encouraged to bring new ideas to CTN and help prioritize projects. CTN co-chairs John Sunderland, PhD, and Jonathan McConathy, MD, PhD, welcome the new ideas and energy and are excited to collaborate with the new Research Committee.

The committee comprises Steve Cho, MD (University of Wisconsin); Margaret Daube-Witherspoon, PhD (University of Pennsylvania); Stephen Graves, PhD (University of Iowa); Andrei Iagaru, MD (Stanford University); Suzy Lapi, PhD (University of Alabama, Birmingham); Courtney Lawhn-Heath, MD (University of California, San Francisco); Osama Mawlawi, PhD (MD Anderson, Texas); Yusuf Menda, MD (University of Iowa); Justin Peacock, MD, PhD (Brooke Army Medical Center); Peter Scott, PhD (University of Michigan); and Jeff Yap, PhD (University of Utah). Welcome all!

**Spotlight: Technegas™**

Geoffrey Schembri, BSc (Medicine), FRACP, FAANMS, DDU
Nuclear Medicine and PET, Royal North Shore Hospital, Sydney Australia

In the mid ‘70s, ventilation/perfusion imaging was gaining traction for use in the diagnosis of pulmonary emboli (PE). At the time, both Xenon gas (\(^{133}\)Xe) and \(^{99m}\)Tc-based aerosols were available as the ventilation agents. \(^{133}\)Xe suffered from high radiation dose, low energies for imaging, and a single projection. The aerosols were nebulizer-based and produced images often degraded by central airway deposition and limited peripheral penetration. The lung is designed to prevent particles reaching the alveoli. Technegas™, a technetium-labeled nanoparticle, was developed to provide gas-like penetration but “sticks” to the alveoli/terminal bronchioles upon contact with the ease and safety of a technetium-based agent.

Eight years of research led to the development of Technegas in Australia. The first machines were utilized in Australia in 1986 and have spread to many parts of the world since then. Technegas consists of hexagonal flat crystals of technetium metal cocooned in multiple layers of graphite sheets, completely isolating the metal from the external environment. Each particle is from 5 to 30 nm in cross-section and 3 nm thick, and the particle is suspended in an argon carrier gas. Being hydrophobic, they resist clumping.

In the diagnosis of PE, Technegas allows for static images of ventilation to be obtained in multiple planar projections. SPECT (with subtraction images) was initially investigated in 1986\(^1\); however, it did not see widespread utilization until dual-headed gamma cameras became commonplace. SPECT and SPECT/CT have reported greater sensitivity and specificity\(^2-4\), reducing...
the indeterminate rate to less than 5% and 1%, respectively\(^{[5,6]}\). SPECT imaging allows for quantification; V/Q ratio maps can be produced providing assistance to reporters. Quantification also allows for the possibility of measuring clot burden at baseline and measuring resolution and residual clot burden. Technegas’ utility, however, extends beyond just PE. Technegas is an excellent marker of regional ventilation, which allows for it to be applied to a number of other medical indications, including studies into conditions such as asthma, COPD\(^{[7]}\), and pulmonary hypertension. It also allows for radiotherapy planning, surgical planning for lung cancer, volume reduction surgery, and endobronchial valve insertion.

The improved resolution with SPECT/CT does require the reporting doctor to be aware of new variants and findings. It is common now to identify fissures, to visualize the imprint of large vessels, and to be able to appreciate the effect of dynamic lung compression during SPECT acquisition.

### References


---

**Figure 1.** Xenon ventilation (upper) restricted to posterior view. Technegas planar imaging (lower) allows multiple projections of high count.

**Figure 2.** High resolution ventilation SPECT allows for visualization of increased counts in the dependent component of the lung. This is considered due to ventilation being distributed evenly with the lungs expanded during inhalation; then the activity becomes denser as dynamic compression occurs during the study.

**Figure 3.** Planar images demonstrate mild inhomogeneity of perfusion. The SPECT images resolve multiple small PE.
In the News: The FIND Act of 2021

Christina Arenas, JD, MPH — SNMMI Associate Director, Health Policy

On April 28, President Biden told Congress to let Medicare negotiate drug prices this year. “That won’t just help people on Medicare – it will lower prescription drug costs for everyone,” he addressed the nation; however, for drug pricing reform to be sustainable and of any serious value, the United States needs to look at technology, broadly defined, and not focus only on prescription drugs. “It’s simply too big a battle to engage in for too small a gain,” former Health Care Financing Administration (now the Centers of Medicare and Medicaid Services (CMS)) Administrator Gail Wilensky, PhD, stated, referring to the president’s remarks.

SNMMI and its partners, the Medical Imaging and Technology Alliance (MITA) and Council on Radionuclides and Radiopharmaceuticals (CORAR), have been working together for over a decade to reform CMS’s bundling of diagnostic radiopharmaceuticals. Though packaged payment models may work in certain instances, they have created a significant disincentive for using a small subset of innovative diagnostic drugs in hospitals; consequently, Medicare beneficiaries are not getting access to these medically-necessary diagnostic drugs for diseases such as cancer, Alzheimer’s and Parkinson’s.

The Facilitating Nuclear Diagnostics (FIND) Act of 2021, soon to be introduced this month in the House, seeks to fix the patient access issue by allowing diagnostic radiopharmaceuticals (whose mean cost per day is equal to or above $500) to be reimbursed separately in the outpatient hospital space. Since 2008, these new diagnostic drugs were allowed a pass-through period of two to three years where they were paid separately; however, after that term expired, the drugs were bundled in with their scans, making their reimbursement rate sometimes as low as 7% of their pass-through rate. The FIND Act is budget neutral and waives co-payments for Medicare beneficiaries.

Unfortunately, the passage of this bill and its predecessor, HR 3772, did not come in time to alleviate many of those with dementia symptoms seeking a diagnosis that would prompt a tailored care plan. Three Alzheimer’s diagnostic drugs were packaged last fall. These same drugs were used in the Imaging Dementia Evidence for Amyloid Scanning (IDEAS) trial, where more than 18,200 Medicare beneficiaries enrolled; however, now that the second IDEAS trial (called New IDEAS) is beginning this year, none of the hospitals invited (to date), who also participated in the original study, have accepted—with the only exceptions being the two hospitals associated with the New IDEAS Study leads. The hospitals who did not accept the invitation to participate cited the reimbursement impact of the policy packaging.

As our legislators look to medical technology to reform our health care system, we cannot emphasize enough the benefit that high-value radiopharmaceuticals bring, and we hope legislators will seal their approval with co-sponsorship.

Tech Essentials

Radiopharmaceutical Therapy Program for Nuclear Medicine Technologists

Tina M. Buehner, PhD, CNMT, FSNMMI-TS

Radiopharmaceutical therapy (RPT) is an element of nuclear medicine and molecular imaging that is rapidly evolving as more therapeutic radiotracers continue to emerge. The SNMMI and SNMMI-TS continue to address RPT from a quality and excellence standpoint. The SNMMI has developed a Radionuclide Therapy Task Force comprising leadership from the Therapy Center of Excellence, Clinical Trials Network, Outreach Committee, and Quality and Evidence Committee, led by Richard Wahl, MD, and Dan Lee, MD. The Therapy Centers of Excellence Task Force was formed to outline the criteria that facilities must meet to be considered RPT Centers of Excellence. These designations will assist patients in identifying high-quality radiopharmaceutical therapy centers for their respective treatments.

The SNMMI-TS Molecular Therapy Task Force—led by James Crowley, MHA, CNMT, and Seyed Mohammadi, CNMT, RT(N) (CT), PET—work closely with the society to streamline therapy initiatives between the society and Technologist Section and to ensure consistency with the society’s therapy strategic plan. Nuclear medicine technologists (NMTs) play an essential role in RPT through their assistance in various therapeutic procedures. Performing these treatments often requires resources and training in addition to the entry-level NMT education. The SNMMI-TS Molecular Therapy Task Force is continuing to identify NMTs who have therapy-specific training consistent with the criteria for the Therapy Centers of Excellence. One option currently being evaluated is a Therapy Badging Program for NMTs that can be used to recognize those who have completed this additional training. These electronic badges can be included on resumes, curricula vitae, or online professional networking sites, such as LinkedIn, and can distinguish those who have therapy-specific training from those who do not. These therapy badges may also be used by employers to recognize NMTs as having advanced training within their therapy centers.

The SNMMI-TS Molecular Therapy Task Force is continuing to define and develop the criteria for each specific therapy badge. More details to come in the near future.
Focus on the Interns

CTN Intern 2021–2023
Patricia Edem, PhD
Radiochemist, British Columbia Cancer Center, Vancouver, Canada

As the incoming Clinical Trials Network (CTN) intern for the SNMMI, I am looking forward to being part of a great team for the next two years. My background includes a PhD in chemical biology from McMaster University, Hamilton, Ontario in 2016. I then worked as a chemist at Rigshospitalet, the national hospital of Denmark (Copenhagen), until 2019. Currently, I am a radiochemist at the British Columbia (BC) Cancer Center in Vancouver and am particularly interested in the field of theranostics. Developing novel agents for diagnosis and therapy, concurrently, presents exciting opportunities and novel challenges. While I am with the CTN, I hope to work closely with members of the society to expand my knowledge base and offer my experience as a chemist within this interdisciplinary network. Working with the CTN will expose me to the various regulatory and translational challenges facing our field while offering solutions to combat them. Knowledge gained from this experience will surely benefit me in the future as our field expands. For that, I am excited to learn and be of service!

CTN Intern 2019–2021
Eunkyung Angela Park, MD, PhD
Clinical Assistant Professor, Division of Nuclear Medicine, Department of Radiology, University of Iowa

It has been a great privilege to serve as a CTN intern during the last two years. I learned and now understand how academia, companies, and SNMMI work together to bring novel radiopharmaceuticals to the clinic by organizing and implementing clinical trials. I came to appreciate the collaborative effort behind the scenes that enables us to use molecular imaging and therapy in the daily practice of caring for our patients. We were fortunate that the COVID-19 pandemic did not hinder us in our mission to facilitate and expand the use of molecular imaging.

Tech Tip
The Virchow’s Node: A Devilish Problem
Diane Soulek, BS, CNMT, NCT, PET, RT(N), NMTCB(CT)

The Virchow’s node, also known as the “Seat of the Devil,” poses a special problem when performing Axumin exams.

- **What is a Virchow’s node?**
  - A lymph node in the left supraclavicular region near the sternocleidomastoid muscle; it takes lymph supply from the abdominal cavity and is a common site of distant lymph node metastasis from abdominal and pelvic cancers.

- **Why is it a problem?**
  - Left arm injections of Axumin can lead to left supraclavicular vein stasis, which can be misinterpreted as false-positive uptake in Virchow’s node.

- **How is it remedied?**
  - Always use the RIGHT arm for these injections—help prevent a false-positive!

For much of PET’s history, only two Food and Drug Administration (FDA)-approved radiopharmaceuticals were available for clinical use: $^{82}$Rb-chloride (1989) and $^{18}$F-FDG (1994). Both radiotracers secured a foothold in PET clinics offering cardiology or oncology services, with $^{18}$F-FDG quickly becoming one of PET’s most powerful diagnostic tools.

Over the past 20 years, PET has grown to include 15 FDA-approved radiopharmaceuticals. Many tracers have seen limited use due to various reasons: absence of an onsite cyclotron ($^{13}$N-ammonia, $^{11}$C-choline), lack of reimbursement ($^{18}$F-sodium fluoride), or absence of successful anti-amyloid treatments (amyloid and tau imaging agents). For tau and amyloid agents, the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) Study aims to change the Centers for Medicare & Medicaid Services (CMS) policy of non-coverage of scans by assessing the impact of amyloid PET on patient outcomes.

Since 2016, six new radiopharmaceuticals have received FDA approval. These have unique preparation requirements, uptake times, scan durations, and decay-in-storage (DIS) constraints. $^{18}$F-fluciclovine (2016) patient preparation involves no strenuous exercise for 24 hours prior to the scan and no food or drink (including water) for four hours before the scan; additionally, bladder emptying must be done at least 30 minutes before radiotracer injection. Once positioned on the scanner, $^{18}$F-fluciclovine is injected in the patient’s right arm, and the target uptake time is 3–5 minutes—a dramatic change from FDG’s uptake period of 60–90 minutes.

If offering neuroendocrine tumor imaging or somatostatin receptor (SSR) targeted tracers, $^{68}$Ga DOTATATE (2016), $^{68}$Ga-DOTATOC (2019), and/or $^{64}$Cu-DOTATATE (2020) are available options. Patients must hold long-term and short-term SSR analogs for 28 days and 12–48 hours, respectively. In contrast to $^{18}$F FDG, no dietary restrictions are required. Patients may talk, read, and use cell phones during the uptake period of 45–90 minutes. Depending on institutional and regulatory guidelines, patients may be released following injection. With its 12.7-hour half-life, $^{64}$Cu DOTATATE requires separate DIS practices when compared to $^{18}$F- and $^{68}$Ga-based processes.

PET’s most daunting juggling act is just beginning. $^{18}$F-fluoroestradiol and $^{68}$Ga-PSMA-11 received approval in 2020; however, $^{68}$Ga-PSMA-11 currently can be manufactured, imaged, and reimbursed by CMS at only two New Drug Application (NDA)-sponsoring academic sites, while limited additional sites continue imaging under the Investigative New Drug (IND) mechanism. $^{18}$F-fluoroestradiol currently has highly limited commercial delivery options, but delivery pathways should dramatically increase in upcoming months. The FDA is reviewing a $^{68}$Ga-PMSA kit that may be available in late 2021. $^{18}$F-DCFPyL approval for prostate cancer is on the horizon, and $^{18}$F-flurpiridaz myocardial perfusion clinical trials are nearing their end. As departments incorporate new tracers and varying protocols, PET imaging must juggle logistical challenges similar to those experienced in nuclear medicine.