Joint NIBIB/NCI/SNMMI Workshop on Directly Imaging Targeted Radionuclide Therapy Isotopes

I. George Zubal, PhD, National Institute of Biomedical Imaging and Bioengineering, Bethesda, MD, and Jacek Capala, PhD, DSc, National Cancer Institute, Bethesda, MD

The National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Cancer Institute (NCI), and SNMMI organized a virtual workshop titled "Engineering New Instrumentation for Imaging Unsealed Source Radiotherapy Agents" on August 16 and 17, 2021. The impetus for this workshop was introduced by an earlier Newsline article, "Time for a next-generation nuclear medicine γ camera?" (2020;61[7]:16N), asking whether we need to reconsider instrumentation used for theranostic methods with electron- and α-emitting unsealed sources for recently emerging cancer therapies.

The workshop convened physicians and scientists from relevant fields to investigate the clinical challenges of treating cancer and to discuss possible technical developments in imaging instrumentation for improving outcomes. Panel sessions focused on the clinical applications of radiopharmaceutical therapy (RPT), as well as isotope production and dosimetry's roles in delivering safe and effective therapies. The workshop was moderated by George Zubal, PhD, Program Director for Nuclear Medicine (NIBIB), and Jacek Capala, PhD, DSc, Program Director, Radiation Research Program, Division of Cancer Treatment and Diagnosis (NCI).

Kris Kandarpa, MD, PhD, Director of NIBIB's Research Sciences and Strategic Directions, opened the workshop with a welcome message outlining NIBIB's mission to develop imaging methods that lead to personalized precision medicine. He encouraged participants to evaluate recent achievements in PET and consider how similar future improvements could be achieved with α-emitter imaging.

Session 1: Overview of Diagnostic/Therapy Practice

The first workshop session started with a talk by Steven Larson, MD (Memorial Sloan Kettering Cancer Center; New York, NY), describing the therapeutic advantages of α-emitting isotopes. Alpha particles are characterized by double-strand break triggering, high linear energy transfer, relatively short range, greater relative biological effectiveness, and a low oxygen enhancement ratio. Dr. Larson and his team have demonstrated 3 separate therapy protocols that work quite well, with good therapeutic indices associated with cures. Reporting from the same institution, John Humm, PhD, covered specific classes of α-emitting radionuclides, which can be simple (those that decay to stable or non–α-emitting progeny) or complex (those with radioactive α-emitting progeny). He pointed to ^{211}At as possibly the best α emitter that does not exhibit problematic progeny. This has great potential if concerns about its challenging radiochemistry can be resolved. He emphasized dosimetry problems with imaging α-emitting radionuclides, related to the limited resolution of current SPECT cameras, where images of α sources cannot provide accurate information at the relevant cellular target level for microdosimetry.

Daniel Pryma, MD (University of Pennsylvania; Philadelphia) explained current RPT practices using ^{131}I-MIBG, which was developed in 1980 and received therapeutic FDA approval in 2018. Several dosimetric challenges are associated with these studies, including the fact that dosimetry image acquisition requires several visits to the imaging department. Work is being done to use population inputs and information about typical patient kinetics to simplify this process. Michael King, PhD (University of Massachusetts Medical School; Worcester), reviewed manufacturers who have developed dedicated cardiac SPECT systems. These have smaller heads to get closer to patients or 2 heads oriented at 90° for efficient acquisition over 180°. Other advancements (new radiopharmaceutical developments, imaging system design optimization, software advances, and guidelines/standards) facilitated by medical societies have played a role in establishing and enhancing the clinical utility of cardiac SPECT. The hope is that SPECT will also play a role in similar developments for unsealed source radiotherapy agents. The last speaker in this session, Robert Mach, PhD (University of Pennsylvania; Philadelphia), detailed his research findings indicating that SPECT is comparable to PET in studies with high target density or in studies with lower target density in a control group. He further noted that SPECT can be used to separate the photopeaks between ^{123}I and ^{99m}Tc to quantify uptake of the 2 isotopes and measure both terminal density and cerebral blood flow. This could be applied to imaging parent and progeny isotopes in RTP, which is not possible with PET because of the 511-keV emissions of all PET isotopes.

Panel Discussion: Sarah Cheal, PhD (Memorial Sloan Kettering; New York, NY), Robert Miyaoka, PhD (University of Washington School of Medicine; Seattle), Emilie Roncali, PhD (University of California Davis), and Vikram Bhadrasain, MD (NCI) participated in a discussion and Q&A with session presenters. Several interesting topics were raised, including ^{213}Bi dosimetry, comparison to external-beam doses, and development of cameras for specific tasks. Other topics included antibodies in theranostics and sensitivity of SPECT for dosimetry imaging. This led to a discussion of possible new γ detectors and collimator-less cameras. Concluding comments addressed the SNMMI Dosimetry Challenge and ways in which customizing doses to specific patients could improve outcomes.

Session 2: Overview of Imaging

The next workshop session began with an overview from Ben Tsui, PhD (Johns Hopkins University School of Medicine;

Baltimore, MD), who summarized SPECT development over the past decades. He noted that 2 major breakthroughs have made quantitative SPECT more practical: maximum-likelihood expectation maximization and ordered-subset expectation maximization algorithms. In addition, quantitative SPECT has several important implementation requirements, including good quality of SPECT images, good quality of CT images, and accurate alignment of SPECT and CT images to reduce misregistration of image artifacts and to apply attenuation corrections. Also from Johns Hopkins, Eric Frey, PhD, reminded attendees that, when conducting targeted radionuclide therapy, the main objectives are to avoid significant toxicity in normal tissues and to deliver a lethal dose to tumors; hence, it is necessary to image both large and small organs to obtain accurate voxels for 3D dosimetry. He explained issues that must be addressed to achieve these improvements: new detector materials with improved energy resolution and better intrinsic spatial resolution, novel collimation geometries, improved intrinsic resolution, and more detector areas with larger axial fields of view.

The third speaker in the session, Ling-Jian Meng, PhD (University of Illinois at Urbana-Champaign), reviewed a proposed camera design applying the concept of hyperspectral SPECT imaging, which could allow multiisotopic, multifunctional molecular imaging using various combinations of radiotracers. Based on his innovative sensor work, his team has been developing preclinical and clinical imaging systems that show promise for routine imaging in humans. He concluded that, given improvements in sensor spatial resolution and sensitivity, it may be time to revisit Compton cameras as a possibility to improve SPECT imaging. Todd Peterson, PhD (Vanderbilt University; Nashville, TN), presented his unique camera design integrating a high-purity germanium detector camera with a MicroCAT II CT scanner. Using this system, he was able to demonstrate multiisotope capabilities and compared his camera to other systems, demonstrating that germanium could set very narrow photopeak energy windows. His team is also working on mechanical cooling to reduce power consumption. Lars Furenlid, PhD (University of Arizona; Tucson), oversees a lab that develops technologies to image γ rays, principally for SPECT, which are either semiconductor- or scintillator-based. His current designs include a third-generation cross-strip cadmium telluride detector, a hybrid photomultiplier tube/silicon photomultiplier (SiPM) scintillation camera, and a third-generation large-area ionizing radiation quantum imaging detector camera. He summarized the many opportunities for fundamental advancements in SPECT imaging of α emitters, noting that development is needed in the theory of mathematics as well as new mathematical observers, estimation methods, and spectrum-aware reconstruction methods. Also needed are larger area high-Z semiconductors; high-Z, high-light-output scintillators; large-area gaseous or solid-state electron multipliers; and advances in SiPMs.

Panel Discussion: The panel discussion for this session focused on topics concerning germanium detectors for scatter rejection, higher sensitivity imaging systems, and associated reconstruction methods. Additional discussions covered microdosimetry and high-energy photon imaging with camera geometries positioned close to the patient.

Session 3: Overview of Isotopes: Dosimetry and Future Directions

Session 3 opened with an overview from Jehanne Gillo, PhD (U.S. Department of Energy [DOE]; Germantown, MD), of the DOE Isotope Program (DOE-IP), which has a mission to produce and distribute radioisotopes that are not commercially available. She described a dramatic increase in the numbers of reactor- and accelerator-based isotope production facilities at DOE National Laboratories and their academic partners, providing diagnostic and therapeutic radioisotopes, including α emitters (^{223}Ra, ^{221}At, and ^{225}Ac, as well as ^{227}Ac used by Bayer to obtain ^{223}Ra for production of Xofigo). In addition to production and distribution of currently used isotopes, the DOE-IP also operates a discovery arm focused on identifying new radioisotopes that might be of interest to the RPT community. A funding opportunity announcement to support research on new isotopes entering preclinical and clinical trials was recently issued (https://www.isotopes.gov/FOA-Advancing-Novel-Medical-Isotopes-for-Clinical-Trials). DOE has also started an isotope traineeship to apply advanced manufacturing techniques to isotope production.

Douglas Van Nostrand, MD (Georgetown University Medical Center; Washington, DC), provided a comprehensive overview of radioiodine as a paradigm of theranostics. He pointed out its diagnostic (^{123}I and ^{124}I) and therapeutic (^{131}I) utility, facilitating: (1) definition of maximal safe administered therapeutic activity to minimize unacceptable side effects; (2) determination of minimal administered activity to achieve desired therapeutic outcomes; and (3) assessment and mitigation of altered genomic cancer molecular biology (redifferentiation). These permit ^{131}I therapy in patients with negative scans and enhance therapeutic results in patients with positive scans. Because MEK-inhibitors increase iodine accumulation in tumor cells (which can be monitored by PET) the ^{124}I/^{131}I theranostic pair allows successful treatment of non–iodine-avid tumors.

In contrast to external-beam radiotherapy, where the absorbed dose can be precisely inferred from measurements, tissue absorbed dose in nuclear medicine must be approximated using different models. Wesley Bolch, PhD (University of Florida; Gainesville), presented 3 principal methods to compute tissue absorbed dose: (1) direct Monte Carlo (MC) radiation transport simulation; (2) dose-point kernel (DPK) convolution; and (3) the Medical Internal Radiation Dose (MIRD) S-value formalism. Because of the high degree of accuracy, MC simulations are the reference standard for tissue dosimetry and the most reliable tool for computing radionuclide S-values. DPK convolution is commonly used at the voxel level, between the application regimes of S-value and direct MC methods. S-values, the most practical

method because of the link to the MIRD schema, are applicable at any scale, although the underlying approximations of the method mostly limit their use to the organ and suborgan levels.

Yuni Dewaraja, PhD (University of Michigan; Ann Arbor), presented advances in SPECT and PET imaging for patient-specific dosimetry, focusing on imaging methods used for ^{90}Y and ^{177}Lu. ^{90}Y can be imaged by both SPECT and PET. SPECT detects bremsstrahlung that has continuous energy spectra. MC reconstruction, model-based scatter estimation, and deep learning–based scatter estimation are used to enable quantification of the bremsstrahlung. The main challenges in PET imaging of ^{90}Y are low positron yield and coincidences with bremsstrahlung photons. These challenges can be addressed by dedicated reconstruction algorithms and new instrumentation, such as time-of-flight, digital, and whole-body PET. A relatively low intensity of γ rays is a challenge for SPECT imaging of ^{177}Lu, which requires efficient counting methods, application of deep learning, and joint dual-photopeak reconstruction or the option of combining SPECT with data from ^{68}Ga PET.

Panel Discussion: The panelists addressed the limitations of current dosimetry methods and the latest progress in development. Uncertainty in dose estimates was deemed the major problem. Contributing factors, particularly for bone marrow and small structures (metastases), include definition of the region of interest, low signal, and reliability of data obtained using standard partial-volume correction methods. Several methods to improve the reliability of dose estimates and the need to define standards for the whole dosimetry workflow were mentioned. Barriers to wider adoption of radioiodine treatment and challenges and opportunities in combining RPT with conventional radiation therapy were also discussed.

Keynote Overview: Peering into the Black Box of Cancer Therapy

In the keynote lecture, George Sgouros, PhD (Johns Hopkins University School of Medicine; Baltimore, MD) addressed RPT efforts in the context of conventional systemic cancer therapies. He described the latter using a black box analogy, in which inputs are mechanism, target validation, preclinical model toxicity, patient selection, genomics, and theranostics. Treatment is the black box itself, and outputs are tumor response, time to progression, overall survival, quality of life, and clinical toxicity. In this scenario, researchers can understand mechanisms by changing inputs and looking at responses; this is the long-standing process for agents that cannot be imaged. This approach, unfortunately, is not effective. In a paper published in 2018, Wong et al. examined the success rate of oncologic drugs and found that 97% of cancer drugs evaluated in humans fail (*Biostatistics.* 2018;20: 273–286). Many of these agents are targeted therapies blocking signaling pathways that control cancer cell growth, division, and spread. In many cases, targeted therapies miss their target; a 2019 paper by Lin et al. found that many cancer drugs work as a result of off-target effects (*Sci Transl Med.* 2019;11[509]:eaaw8412). Consequently, over the past decade the cost of cancer drugs has gone up, but the clinical benefits of those drugs have not increased proportionately, adding to financial concerns.

RPTs present a promising alternative. They are administered systemically and regionally and can target metastatic cancer, leading to radiation-induced DNA damage and killing cells rather than controlling cell behavior. Their efficacy depends on differential delivery of radiation, which can be assessed by imaging. Dr. Sgouros presented several examples of such approaches in clinical trials using ^{131}I, ^{90}Y, ^{213}Bi, ^{223}Ra, ^{227}Th, ^{212}Pb, and ^{225}Ac. In 1 example, implementation of personalized dosimetry in hepatic artery infusion of ^{90}Y microspheres for hepatocellular carcinoma doubled patient survival time, without changing the agent or the patient population. These examples showed that imaging and individualized dosimetry-based treatment planning can further improve RPT outcomes.

Keynote Overview Q&A: The panel discussion focused on obstacles to implementing dosimetry for RPT, including: a need for more examples (preferably randomized clinical trials) showing that dosimetry has a huge impact; a need for consistent, well-validated, and standardized dosimetry methodologies; lack of knowledge of radiation and radionuclide therapy; reimbursement challenges; and the need for multiple scans. Panelists noted that some of these problems can be addressed by simplifying dosimetry procedures and enhancing education of both patients and physicians.

Conclusion

This workshop represented a first step in evaluating and combining physicians' needs for cancer treatment and imaging scientists' knowledge of instrumentation and dosimetry calculations to improve cancer treatment outcomes. We invite the community to view the recorded sessions of this workshop under "Engineering New Instrumentation for Imaging Unsealed Source Radiotherapy Agents" at the NIBIB events page (https://www.nibib.nih.gov/NIBIB-Webinars-and-Conferences). NIBIB looks forward to continuing this workshop in early 2023 with additional discussions and a review of progress made based on insights and discussions from the workshop reported here.

DOE and HHS Certify Sufficient ^{99}Mo Supplies

On December 20, U.S. Secretary of Energy Jennifer M. Granholm and U.S. Secretary of Health and Human Services (HHS) Xavier Becerra jointly certified the achievement of a sufficient supply of ^{99}Mo made without using highly enriched uranium (HEU) to meet the needs of patients in the United States. According to a press release from the agencies, this certification "paves the way for a nuclear nonproliferation milestone and supports U.S. companies by triggering a congressionally mandated ban on exports of HEU for foreign medical isotope production." HEU is a sensitive and critical product in terms of nuclear proliferation, and the Department of Energy (DOE) National Nuclear Security Administration (NNSA) works to minimize the global civilian use and availability of HEU.

"Doctors and patients across the globe can be confident that the critical medical isotope ^{99}Mo will be there when they need it, and we can provide that assurance without making any further exports of HEU," said Granholm. "Today's certification is another example of DOE's world-leading expertise creating win–win outcomes that make the world safer while advancing jobs, improving health care, and increasing the quality of life here at home."

^{99}Mo is used in more than 40,000 medical diagnostic procedures in the United States each day. For decades, the United States had no capability for domestic production of the isotope. To ensure a stable supply, HEU was exported to foreign medical isotope producers that used the material to produce ^{99}Mo for the U.S. and global markets.

Achieving a sufficient supply of ^{99}Mo produced without the use of HEU is the result of significant accomplishments by DOE, HHS, and the commercial ^{99}Mo industry. The DOE NNSA has provided financial and technical assistance to help global ^{99}Mo producers convert from HEU to low-enriched uranium (LEU). DOE/NNSA has also supported development of a domestic production capability for non-HEU ^{99}Mo by awarding more than $200 million in cost-shared cooperative agreements with commercial entities, providing technical support from the U.S. National Laboratories, and establishing a Uranium Lease and Take-Back Program for industry.

HHS's role in achieving this milestone included approvals for use of ^{99}Mo produced by global suppliers using LEU and the 2018 FDA approval of the New Drug Application for the ^{99}Mo production system of NorthStar Medical Radioisotopes, one of NNSA's commercial partners. Both the DOE and HHS noted that they will continue to work together and with commercial entities to further bolster the U.S. supply of non-HEU ^{99}Mo.

"With more than 80% of diagnostic imaging in the U.S. relying on nuclear medicine isotopes like ^{99}Mo, the FDA has a key role to play to ensure a sufficient supply is available for critical daily medical procedures," said Acting FDA Commissioner Janet Woodcock, MD. "We're pleased to partner with DOE and other federal partners to contribute to this important achievement."

U.S. Department of Energy
U.S. Department of Health and Human Services

FDA Approves New ^{68}Ga Kit for Prostate Cancer PET

Telix Pharmaceuticals (Melbourne, Australia; Indianapolis, IN) announced on December 20 that the U.S. Food and Drug Administration (FDA) had approved Illucix (TLX591-CDx), the company's kit for preparation of ^{68}Ga-gozetotide (^{68}Ga–prostate-specific membrane antigen [PSMA]-11). The product is approved for PET imaging in patients with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or in whom recurrence is suspected based on elevated serum prostate-specific antigen levels.

The FDA first approved ^{68}Ga-PSMA-11 PET for prostate cancer imaging in December 2020, but access was available only through the University of California Los Angeles and the University of California San Francisco. "The approval of Illucix will give patients considerably improved access to PSMA PET imaging, an advanced diagnostic tool that was recently included in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Prostate Cancer," said A. Oliver Sartor, MD, Medical Director of the Tulane Cancer Center (New Orleans, LA). "With patient doses able to be prepared onsite or via commercial radiopharmacy networks, either via generator or cyclotron, Illucix delivers flexible patient scheduling and on-demand access throughout the day."

According to a Telix press release issued on December 20, Illucix can be prepared with ^{68}Ga via either GE's FASTlab cyclotrons or in nuclear pharmacies and health care centers using the Eckert and Ziegler GalliaPharm generator or the IRE ELiT Galli Eo generator. Along with a 4-hour shelf life after radiolabeling, these generation options will allow expansion of PSMA PET in prostate cancer. "This product offers a level of flexibility and accessibility to health care professionals we really haven't seen before in this class of products and may help us provide better patient experiences as a result," said Dr. Sartor. With a distribution network encompassing more than 140 nuclear pharmacies through an agreement with Cardinal Health and PharmaLogic, Telix noted that Illucix will be available to more than 85% of eligible PET imaging sites in the United States.

Telix Pharmaceuticals

SNMMI to Host Summits on Artificial Intelligence and Patient Access

Richard L. Wahl, MD, SNMMI President

Advances in medical technology are improving patient care as never before. At the same time, great health disparities exist, and not all patients have access to these advances; urban and rural populations can be underserved. SNMMI recognizes that in order to provide high-quality patient care, we need to support the growth of the field as well as fight for access for all.

Next month SNMMI will host back-to-back summits on 2 hot topics in nuclear medicine, molecular imaging, and radiopharmaceutical therapy: artificial intelligence and patient access to and health disparities in nuclear medicine procedures. Held at the end of March in Bethesda, MD, the summits will provide opportunities for in-depth discussions on these highly relevant topics.

The Artificial Intelligence Summit, organized by the SNMMI Artificial Intelligence Task Force, will be held March 21 and 22. Attendees will include stakeholders in academia, medical device manufacturing and pharmaceutical companies, start-up companies, hospital administrators, and end users of artificial intelligence technology. Representatives from the Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services, and National Institutes of Health will also attend.

This summit will kick off with a plenary session on the role of ethics in artificial intelligence, presented by Melissa McCradden, PhD, bioethicist with the department of bioethics at the Hospital for Sick Children (Toronto, Canada). Irène Buvat, PhD, head of the Laboratory of Translational Imaging in Oncology Research at the Institut Curie Research Center (Orsay, France), will then discuss the state of the art in artificial intelligence.

Four panel discussions will follow on standardization initiatives; current challenges; the landscape of artificial intelligence regulations, coverage, and funding; and what end users (physicians, technologists, hospital administrators, etc.) want from artificial intelligence. The speakers from the panel discussions will give updates on current status as well as what is needed from other stakeholders to advance their respective artificial intelligence agendas. The summit will conclude with a session on next steps and a call to action.

The SNMMI Summit on Patient Access to and Health Disparities in Nuclear Medicine Procedures will take place on March 22 and 23, immediately following the Artificial Intelligence Summit. The goal of the summit is to gather representatives from major stakeholders in the nuclear medicine and health equity spaces to identify and address barriers, including health disparities, that prevent patients from accessing high-quality nuclear medicine scans and therapies.

The invitation-only summit will include approximately 120 attendees from nuclear medicine and molecular imaging industry, regulators, legislators, and payers. Although SNMMI has elected to keep this meeting small, we recognize the widespread interest in this topic in the wider oncology and imaging/radiopharmaceutical therapy communities. The meeting will be available online via a webinar for those who would like to listen to the talks and associated discussions.

Richard L. Wahl, MD

Andrew Scott, MD, director of the department of molecular imaging and therapy at Austin Health (Victoria, Australia), will begin the meeting with lessons from *The Lancet Oncology* in regard to global access to nuclear medicine and radiology. Eliseo Pérez-Stable, MD, director of the National Institute on Minority Health and Health Disparities, will follow with a keynote speech on social determinants of health. Richard L. Wahl, MD, Elizabeth Mallinckrodt professor and chair of radiology and director of the Mallinckrodt Institute of Radiology at Washington University School of Medicine (St. Louis, MO), will then speak on the changing landscape in nuclear medicine, with a special focus on areas where patient access limitations are apparent—including both inner urban and rural care delivery spaces.

The summit will also include 6 panels covering a range of topics related to patient access to and health disparities in nuclear medicine procedures. Two panels will be held on the first day of the summit. The first will discuss health disparities in imaging and focus on lessons learned in mammography and prostate imaging, as well as clinical trial participation. A panel on federal regulatory efforts to ensure access to nuclear medicine will conclude the day.

The remaining 4 panels, on the following day, will begin with radiopharmaceutical production and distribution challenges, with a focus on rural America. Next, attendees will learn about the foundational infrastructure of nuclear medicine, followed by appropriate utilization and reimbursement for products. The final panel will be a "Payer Panel," in which insurance companies will discuss what steps are being taken to address social disparities in health care access. The meeting will end with a working session to review solutions and next steps.

SNMMI recognizes that the field of nuclear medicine and molecular imaging is rapidly evolving, and nuclear medicine procedures are fundamental components of many patient care pathways. Through summits like these, our goal is to provide strategic vision and a roadmap to address these changes, demonstrate the true value of the field, and elevate nuclear medicine and molecular imaging. By doing so we can improve access for patients and provide increased value to the medical community, regulators, payers, patients, and the public.

Call to Action for Federal Research Funding

SNMMI and the Academy of Radiology and Biomedical Imaging Research announced on December 14 a partnership to urge the U.S. Congress to pass an FY22 appropriations package with support for the National Institutes of Health (NIH) and biomedical imaging and to curtail the use of harmful continuing resolutions. In early December, Congress passed its second continuing resolution for the 2022 fiscal year, which should have begun on October 1, 2021. That continuing resolution will keep the government funded until February 18, which means there will be no increases in government funding until well after the first third of the 2022 fiscal year. NIH, for example, does not know its final funding level for the year already in progress. NIH and other research agencies cannot issue new funding awards until formal appropriations are determined. In addition, researchers working on existing awards may receive notification of funding cuts to maintain conservative spending levels mandated by the continuing resolution. Early career researchers and those with new proposals are especially adversely affected as they wait for federal support for research plans already determined to be meritorious. In their December 14 statement, SNMMI and the Academy of Radiology and Biomedical Imaging Research said "This extended delay will only hold back research. Already, research has suffered greatly due to the negative scientific and economic effects of the COVID-19 pandemic. We must remain committed to assisting Congress in the nation's recovery from the pandemic and support the continuous funding of scientific and medical research to ensure improved patient outcomes and U.S. competitiveness." Members of the nuclear medicine and molecular imaging and therapy communities were urged to contact their members of Congress to emphasize the importance of biomedical research and the deleterious effects of chronic continuing resolutions. Additional information is available at: https://www.acadrad.org/take-action/#/5.

SNMMI

CMS Grants Pass-Through Payment Status for ^{18}F-Piflufolastat

On November 22, the Centers for Medicare & Medicaid Services (CMS) granted transitional pass-through payment status for ^{18}F-piflufolastat (Pylarify; ^{18}F-DCFPyL), increasing patient access to prostate-specific membrane antigen (PSMA)–based imaging in prostate cancer. The decision was effective as of January 1. The Medicare Transitional Pass-Through Payment program is designed to facilitate patient access to cutting-edge treatments by allowing adequate payment for new agents while permanent reimbursement rates are being established.

^{18}F-piflufolastat is the first fluorinated PSMA agent approved for reimbursement by CMS. The agent, manufactured by Lantheus Holdings (North Billerica, MA), was approved in May 2021 by the U.S. Food and Drug Administration for PET imaging of PSMA-positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected disease recurrence based on elevated serum prostate-specific antigen levels.

"We have been thrilled with the response to Pylarify in the prostate cancer community," said Mary Anne Heino, president and chief executive officer of Lantheus. "Pylarify is a transformative diagnostic tool that identifies disease earlier and more accurately than conventional imaging, providing more information to guide treatment decisions. The granting of transitional pass-through payment status for Pylarify further facilitates patient access to our game-changing PSMA-targeted imaging agent for prostate cancer."

Centers for Medicare & Medicaid Services
Lantheus Holdings

2022 Hal O'Brien Rising Star Award

Attila Feher, MD

Yale University School of Medicine (New Haven, CT) announced in December that Attila Feher, MD, a clinical fellow in cardiovascular medicine at the Yale Translational Research Imaging Center, would receive the Hal O'Brien Rising Star Award at the High Country Nuclear Medicine Conference (HCNMC) to be held in Sun Valley, ID, March 5–8. The award honors junior faculty, postdoctoral trainees, and fellows performing exemplary work in the radiopharmaceutical sciences, clinical applications, or research in oncology, cardiology, and neurology. A $1,000 travel grant included in the award is intended to enable travel to the meeting and presentation of research as part of HCNMC proceedings.

Dr. Feher is being recognized for his work in development of imaging tools to evaluate microcirculation in heart transplant recipients. Albert Sinusas, MD, director of the Yale Translational Research Imaging Center, said, "Attila is one of the best fellows that I have had the pleasure of training over my 30-year career on faculty at Yale. He has received multiple awards, including a recent award for the best manuscript in the *Journal of the American College of Cardiology: CardioOncology.* He is an outstanding clinician scientist who excels both in clinical care and translational and clinical research. He is also a humble and caring person."

The Rising Star Award was created to celebrate the leadership legacy of the High Country meeting and to recognize the vision of Hal O'Brien, MD, in creating a unique and productive format for bringing together leaders from across the spectrum of nuclear medicine and molecular imaging. The conference includes experts from academia and industry, with leaders in medical specialties, the regulatory agencies, and health care researchers in an informal setting to facilitate exchanges of ideas. The Education and Research Foundation for Nuclear Medicine and Molecular Imaging manages the program as an endowed fund to support the award in perpetuity. Each year in July the HCNMC Award Subcommittee initiates a call for nominations directed to the SNMMI Councils and Centers of Excellence and to the American Society of Nuclear Cardiology. The subcommittee reviews nominations and selects the awardee.

A preliminary program for the 2022 meeting, including streaming sessions, is available at: https://www.hcnmc.org/.

FDA Approves Near-Infrared Imaging Agent for Ovarian Cancer

The U.S. Food and Drug Administration (FDA) on November 29 approved Cytalux (pafolacianine), an optical imaging agent indicated in patients with ovarian cancer as a near-infrared adjunct to intraoperative identification of malignant lesions. The drug is manufactured by On Target Laboratories (West Lafayette, IN) and was previously granted Orphan Drug, Priority, and Fast Track designations.

"The FDA's approval of Cytalux can help enhance the ability of surgeons to identify deadly ovarian tumors that may otherwise go undetected," said Alex Gorovets, MD, deputy director of the Office of Specialty Medicine in the FDA Center for Drug Evaluation and Research. "By supplementing current methods of detecting ovarian cancer during surgery, Cytalux offers health care professionals an additional imaging approach for patients with ovarian cancer."

The drug is administered intravenously 1–9 h before surgery and binds to and fluoresces folate receptors. Cytalux is used with a near-infrared fluorescence imaging system cleared by the FDA for specific use with pafolacianine.

The safety and effectiveness of Cytalux was evaluated in 3 trials, including a randomized, multicenter, open-label study of women diagnosed with ovarian cancer or with high clinical suspicion of ovarian cancer who were scheduled to undergo surgery. The study included 134 women (ages, 33–81 y) who received a single dose of Cytalux and were evaluated under both normal and fluorescent light during surgery. More than a fourth of participants (26.9%) had at least 1 cancerous lesion detected under fluorescence imaging not observed by stand-ard visual or tactile inspection.

U.S. Food and Drug Administration
On Target Laboratories

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. We have also added a small section on noteworthy reviews of the literature.

PSMA PET/CT Risk-Stratification Tool

Xiang, from the University of California at Los Angeles, and a multiinstitutional cohort of investigators reported in the December 1 issue of *JAMA Network Open* (2021;4[12]:e2138550) on the prognostic significance of a nomogram developed to model an individual's risk of nonlocalized upstaging of high-risk prostate cancer on prostate-specific membrane antigen (PSMA)–based PET/CT. The researchers also compared the nomogram's performance with that of existing risk-stratification tools. The 15-center, multinational study included 5,275 patients diagnosed with high- or very high–risk prostate cancer (prostate-specific antigen [PSA] >20 ng/mL, Gleason score of 8–10, and/or clinical stage of T3–T4, with no evidence of nodal or metastatic disease on conventional workup). Data calculated in the nomogram for PSMA upstaging included the biopsy Gleason score, percentage positive systematic biopsy cores, clinical T category, and PSA levels. Over a median follow-up of 5.1 y, 1,895 (36%) participants had biochemical recurrence, 851 (16%) developed distant metastases, and 242 (5%) died of prostate cancer. The PSMA upstage probability was significantly prognostic for all clinical endpoints, with 8-y concordance indices of 0.63 for biochemical recurrence, 0.69 for distant metastases, 0.71 for prostate cancer–specific mortality, and 0.60 for overall survival. The PSMA nomogram outperformed existing risk-stratification tools, except for performance similar to that of the Staging Collaboration for Cancer of the Prostate for prostate cancer–specific mortality. Results were validated against secondary cohorts from a national database. The authors concluded that these findings suggest that PSMA upstage probability is associated with long-term, clinically meaningful endpoints, with superior risk discrimination compared with existing tools. They added that "formerly occult, PSMA PET/CT-detectable nonlocalized disease may be the main driver of outcomes in high-risk patients."

JAMA Network Open

SPECT/CT in Complex Foot and Ankle Diagnosis

In an article published on December 7 ahead of print in *Foot & Ankle Specialist*, Ghani et al. from the Royal National Orthopaedic Hospital (Stanmore, UK) reported on an assessment of the value of SPECT/CT in patients with complex but nonarthritic and nonneoplastic foot and ankle pathology with unclear diagnoses after conventional imaging. The retrospective research, which began with a dataset of 297 SPECT/CT foot and ankle studies, found only 18 (age range, 16–56 y) performed for nonarthritic/nonneoplastic diagnoses. The resulting SPECT/CT findings differed from provisional diagnoses in 10 (56%) of the 18 patients, leading to changes in treatment planning and significant improvements in 8 of these 10 patients. In the remaining 8 patients, SPECT/CT was useful in confirming provisional diagnoses, which had been uncertain on conventional imaging. A total of 15 of the 18 patients (83%) showed improvements in symptoms after management affected by SPECT/CT diagnoses. The authors concluded that these results highlight "the added value of SPECT/CT in patients presenting with nonarthritic and nonneoplastic foot and ankle conditions in which there is diagnostic uncertainty after conventional imaging" and noted that in their practice they have found SPECT/CT to be a useful investigative modality in assessing these cases.

Foot & Ankle Specialist

Dual-Tracer PET/CT in Renal Cell Carcinoma

Tariq et al. from the Royal Brisbane and Women's Hospital (Brisbane), the University of Queensland (Brisbane), Redcliffe Hospital, Wesley Urology Clinic/The Wesley Hospital (Brisbane), and the Princess Alexandra Hospital (Brisbane; all in Australia) reported on December 8 online ahead of print in *Urologic Oncology* on dual-tracer ^{18}F-FDG and prostate-specific membrane antigen (PSMA)–based PET/CT compared with standard-of-care imaging for the characterization, staging, and restaging of renal cell carcinoma. The retrospective, multicenter study included 11 patients (mean age, 65.5 y; 7 men, 4 women) who underwent dual-tracer PET/CT after conventional imaging. Indications for referral to dual-tracer PET were staging (36%) and restaging after radical/partial nephrectomy (64%). Mixed patterns of uptake in primary tumor assessment were concordant in 40% and discordant in 60% (20% favoring PSMA and 40% favoring ^{18}F-FDG). Tracer uptake in metastatic disease was concordant in 6 patients (55%), in agreement as negative in 3 (27%), and discordant in 2 (favoring PSMA). PET was superior to standard-of-care imaging for assessment of metastatic disease in 5 patients (45%) and equivalent for the remainder, with resulting management changes in 3 (27%). The authors noted that PSMA tracers and ^{18}F-FDG offer complimentary advantages in PET/CT assessment of primary and metastatic

renal cell carcinoma and that the intensity of avidity of the tracers may assist in prognostication.

Urologic Oncology

US-Based Respiratory Motion Detection in PET/CT

In an article published on December 10 ahead of print in *Physics in Medicine and Biology*, Madore et al. from the Harvard Medical School/Brigham and Women's Hospital (Boston, MA), the University of Oxford (UK), National Sun Yat-Sen University (Kaohsiung, Taiwan), Amazon Robotics (Westborough, MA), Eindhoven University of Technology (The Netherlands), and the University of Pennsylvania Perelman School of Medicine (Philadelphia) reported on development and testing of small ultrasound-based sensors, referred to as organ-configuration motion (OCM) sensors, that attach to the skin and provide motion-sensitive information to allow respiratory gating during PET imaging. In the study, both a motion phantom with an ^{18}F-FDG solution and imaging in 2 cancer patients were used to test the sensors. In the phantom and in patients, the OCM signals were used to help reconstruct data into time series of motion-resolved images accurately capturing underlying motion. In 1 patient, a single large lesion was seen to be mostly stationary through the breathing cycle. In the second patient, several small lesions were mobile during breathing, and the sensors captured breathing-related displacements. The authors noted that this relatively inexpensive and simple hardware solution, which attaches to the skin rather than walls or ceilings, is advantageous because it can accompany patients from 1 procedure to another, with the potential for gathering more consistent and useful data on breathing motion–related changes.

Physics in Medicine and Biology

Brain Metabolism Patterns and Epilepsy Death Risk

Whatley, from the University College of London/Queen Square Institute of Neurology (UK), and a consortium of researchers from the UK, Canada, and the United States reported on November 23 ahead of print in *Frontiers in Neurology* on a study using ^{18}F-FDG PET to characterize regional brain metabolic differences in patients with epilepsy at high risk of sudden unexpected death. The study included patients with refractory focal epilepsy at high ($n = 56$) and low ($n = 69$) risk of sudden unexpected death who underwent interictal ^{18}F-FDG PET as part of presurgical assessment. Whole-brain analyses were used to explore regional differences in interictal metabolic patterns and were contrasted with regional brain metabolism more directly related to frequency of focal-to-bilateral tonic-clonic seizures. Imaging found that regions associated with cardiorespiratory and somatomotor regulation differed in interictal metabolism. Tracer uptake was increased in the basal ganglia, ventral diencephalon, midbrain, pons, and deep cerebellar nuclei in patients in the high-risk of sudden death group, and uptake was decreased in the left planum temporale. These patterns differed from those associated with focal-to-bilateral tonic-clonic seizure frequency (decreased uptake in bilateral medial superior frontal gyri, extending into the left dorsal anterior cingulate cortex). PET-identified changes in interictal metabolic activity in regions critical to cardiorespiratory and somatomotor regulation in patients considered to be at relatively high risk of sudden death from epilepsy have the potential to elucidate processes that may predispose such patients to sudden death and to identify such patients and affect management.

Frontiers in Neurology

Benzodiazepine and AD: ^{18}F-Florbetapir PET and MRI

In an article published on December 10 ahead of print in *Neuropsychopharmacology*, Gallet, from University Hospital (Angers, France), and French re-searchers in the MEMENTO study looked at data from that cohort correlating benzodiazepine (BZD) use and neuroimaging markers of Alzheimer disease (AD) in nondemented older individuals with isolated memory complaints or light cognitive impairment at baseline. The study's goals were to replicate/assess findings on BZD use and brain amyloid load with ^{18}F-florbetapir PET and to investigate associations between BZD use and hippocampal volume with MRI. Chronic BZD user and nonuser data on multiple-variable clinical, symptomatic, and genetic data were compared. The authors found that BZD users were more likely to manifest symptoms of depression, anxiety, and apathy. Total SUV ratios and hippocampal volumes were significantly lower and larger, respectively, in BZD users than in nonusers. Short-acting BZDs and Z-drugs (Zopiclone/Zolpidem) were more significantly associated with larger hippocampal volumes, with no significant effects associated with dose and duration of BZD use. The authors concluded that these results "support the involvement of the GABAergic system as a potential target for blocking AD-related pathophysiology, possibly via reduction in neuronal activity and neuroinflammation" and noted that additional longitudinal studies may confirm the causal effect of BZDs in blocking amyloid accumulation and hippocampal atrophy.

Neuropsychopharmacology

DCE CT vs PET in Solitary Pulmonary Nodules

Gilbert, from the University of Cambridge (UK), and a large group of UK researchers reported on December 9 ahead of print in *Thorax* on a study comparing the accuracy and cost effectiveness of dynamic contrast-enhanced CT (DCE CT) and PET/CT in diagnosis of malignancy in solitary pulmonary nodules. The prospective multicenter trial included individuals with a solitary pulmonary nodule (range, 8–30 mm) and no recent history of malignancy. The protocol included both types of imaging and either biopsy with histologic diagnosis or completed CT follow-up. A total of 312 participants (53% men, 47% women; ages, 68.1 ± 9.0 y) completed the study, with a 61% rate of malignancy at 2-y follow-up. The sensitivity, specificity, and positive- and negative-predictive values for DCE-CT were 95.3%, 29.8%, 68.2%, and 80.0%, respectively. For PET/CT the respective percentages were 79.1%, 81.8%, 87.3%, and 71.2%. The areas under the receiver

operator characteristic curves for DCE-CT and PET/CT were 0.62 and 0.80, respectively. Combining results from the 2 imaging modalities significantly increased diagnostic accuracy over PET/CT alone. In a cost analysis, DCE-CT was preferred when the "willingness to pay" per incremental cost per correctly treated malignancy was below £9,000. Above £15,500 a combined approach was preferred. The authors concluded that "PET/CT has a superior diagnostic accuracy to DCE-CT for the diagnosis of solitary pulmonary nodules" and that "combining both techniques improves the diagnostic accuracy over either test alone and could be cost effective."

Thorax

PET/CT Textural Features in Follicular Lymphoma

In an article published in the December 10 issue of *Scientific Reports* (2021;11[1]:23812), Faudemer et al. from Caen University Hospital, Normandy University (Caen), and the Comprehensive Cancer Centre François Baclesse (Caen; all in France) reported on a study assessing the value of baseline ^{18}F-FDG PET/CT radiomics (skeletal textural features) in the diagnosis of bone marrow involvement in patients with follicular lymphoma. The retrospective study included 66 patients newly diagnosed with follicular lymphoma. For visual assessment, patients with obvious bone focal uptake were considered positive. For textural analysis, skeletal volumes of interest were automatically extracted from segmented CT images. Bone marrow biopsy and visual assessment were used as a gold standard in categorizing participants as bone-negative (negative bone marrow biopsy/negative PET) or bone-positive (positive bone marrow biopsy/negative PET, negative bone marrow biopsy/positive PET, or positive bone marrow biopsy/positive PET). Thirty-six patients (54.5%) were classified as bone-negative and 30 (45.5%) as bone-positive. Software analysis identified a cutoff of –0.190 as optimal for diagnosis of bone marrow involvement using a PET predictive score. The corresponding sensitivity, specificity, and positive- and negative-predictive values for PET were 70.0%, 83.3%, 77.8%, and 76.9%, respectively. A significant difference was found between bone marrow biopsy results and visual PET assessments, whereas bone marrow biopsy results and the PET radiomics predictive score were concordant. The authors concluded that "skeleton texture analysis is worth exploring to improve the performance of ^{18}F-FDG PET/CT for the diagnosis of bone marrow involvement at baseline in follicular lymphoma patients."

Scientific Reports

PET/CT Prediction of Urinary Retention After Hysterectomy

Davidson et al. from Chaim Sheba Medical Center (Tel Hashomer), Tel Aviv University (Ramat Aviv), and Hebrew University of Jerusalem (all in Israel) reported on December 14 ahead of print in *Minerva Obstetrics and Gynecology* on a study using ^{18}F-FDG PET/CT to measure residual urinary volume both before and after radical hysterectomy to determine whether scanned abnormal residual bladder volume is predictive of future urinary symptoms. The study included 64 women. Postvoid bladder volumes were $\geq$150 cm^3 on postoperative PET/CT in 24 (38%) patients, with 9 (37.5%) of these experiencing some degree of voiding difficulty. In 3 of the 24 patients, the high bladder volume on PET/CT was seen 2–4 mo before complaints of voiding difficulty. Of the 40 (62%) remaining patients whose postoperative bladder volumes were $<$150 cm^3, only 1 (2.5%) had urinary retention. Symptomatic voiding difficulties were higher in the postvoid volume $\geq$150 cm^3 group than in the $<$150 cm^3 group (13 and 6, respectively). The authors concluded that "measuring bladder volume on postoperative ^{18}F-FDG PET/CT may facilitate early identification of urinary retention, possibly enabling early treatment and possibly preventing complications."

Minerva Obstetrics and Gynecology

Machine Learning and SPECT MPI Polar Maps

In an article published on November 11 in *Frontiers in Cardiovascular Medicine* (2021;8:741667), Marques de Souza Filho et al. from the Universidade Federal Fluminense (Rio de Janeiro, Brazil), Universidade Federal Rural do Rio de Janeiro (Rio de Janeiro, Brazil), the University of Ottawa Heart Institute (Canada), and the Hospital Pró-Cardíaco/Americas Serviços Medicos (Rio de Janeiro, Brazil) reported on a study using machine learning algorithms to differentiate normal from abnormal gated SPECT myocardial perfusion polar map images. The authors analyzed 1,007 polar maps from a database of patients referred for clinically indicated myocardial perfusion imaging. Studies were first visually assessed and reported by experts as a comparative standard. Image features were then extracted using polar map segmentation based on horizontal and vertical slices. Cross-validation divided the dataset into training and testing subsets. All machine learning models (except for 1) had accuracy $>$90% and area under the receiver operating characteristics curves $>$0.80. Overall machine learning precision and sensitivity were $>$96% and 92%, respectively. The authors concluded that machine learning algorithms performed well in image classification and were remarkably capable of distinguishing normal from abnormal polar maps.

Frontiers in Cardiovascular Medicine

Nanoparticle Radioenhancer Plus RIT

Hu et al. from the University of Texas MD Anderson Cancer Center (Houston, TX), Nanobiotix (Paris, France), the Shandong Cancer Hospital and Institute/Shandong First Medical University/Shandong Academy of Medical Sciences (Jinan, China), and the Koc University School of Medicine (Istanbul, Turkey) reported on December 11 in the *Journal of Nanobiotechnology* (2021;19[1]:416) on results from a study of multicombination therapy in which NBTXR3, a clinically approved nanoparticle radioenhancer, was combined with high-dose radiation to a primary tumor plus low-dose radiation to a secondary tumor along with

immune checkpoint inhibitor blockade in a mouse model of anti-PD1–resistant metastatic lung cancer. In the complex protocol, mice were injected with a metastatic mouse lung cancer cell line in the right leg on d 0 for the primary tumor and the left leg on d 3 for the secondary tumor. Immune checkpoint inhibitors (anti-PD1 and anti-CTLA4) were administered intraperitoneally. Primary tumors were injected with NBTXR3 on d 6 and irradiated with 12 Gy on d 7, 8, and 9. Secondary tumors were irradiated with 1 Gy on d 12 and 13. Surviving mice at d 178 were rechallenged with the original lung cancer cell lines, and tumors were monitored. The researchers found that the combination of therapies resulted in significant antitumor effects against both primary and secondary tumors, improving the survival rate from 0 to 50%. Immune profiling in secondary tumors showed that the nanoparticle enhancer plus low- and high-dose radiation increased CD8 T-cell infiltration and decreased the number of regulatory T cells. None of the rechallenged mice developed tumors. These rechallenged mice were found to have higher percentages of CD4 memory T cells and CD4 and CD8 T cells in both blood and spleen than untreated mice. The authors concluded that the NBTXR3 nanoparticle "in combination with radioimmunotherapy significantly improves anti-PD1–resistant lung tumor control via promoting antitumor immune response."

Journal of Nanobiotechnology

Coffee Consumption and Cognitive Decline

Gardener, from Edith Cowan University (Joondalup, Australia), and a consortium of researchers from the Australian Imaging, Biomarkers, and Lifestyle (AIBL) study reported on November 19 in *Frontiers in Aging Neuroscience* (2021;13: 744872) on the results of an investigation of the relationship between self-reported habitual coffee intake and cognitive decline. The report included AIBL data with comprehensive neuropsychological battery assessments from 227 cognitively normal older adults over more than 10 y. The researchers also investigated the relationship between habitual coffee intake and cerebral amyloid-β accumulation in 60 of the individuals and brain volumes in 51. The researchers found that higher baseline coffee consumption was associated with slower cognitive decline in executive function, attention, and performance on the AIBL Preclinical Alzheimer Disease Cognitive Composite assessment and with lower likelihood of transitioning to mild cognitive impairment or AD status over the duration of the study. Higher baseline coffee consumption was also associated with slower amyloid-β accumulation and lower risk of progressing to moderate, high, or very high categories of amyloid-β burden. No associations were noted between coffee intake and atrophy in total gray matter, white matter, or hippocampal volumes. The authors concluded that these results "support the hypothesis that coffee intake may be a protective factor against Alzheimer disease, with increased coffee consumption potentially reducing cognitive decline by slowing cerebral Aβ–amyloid accumulation, and thus attenuating the associated neurotoxicity from Aβ–amyloid–mediated oxidative stress and inflammatory processes."

Frontiers in Aging Neuroscience

Delayed PET and Glioblastoma Conspicuity

In an article in the November 16 issue of *Frontiers in Neurology* (2021; 12:740280), Johnson et al. from the University of Texas MD Anderson Cancer Center and Baylor College of Medicine (both in Houston, TX) reported on a study designed to determine the ideal timepoint for ^{18}F-FDG PET imaging of suspected glioblastoma. The study was intended as part of preparation for future trials involving noninvasive differentiation of true progression from pseudoprogression in glioblastoma. This initial investigation included 16 adults (9 men, 7 women) with suspected glioblastoma who underwent PET imaging at 1, 5, and 8 h after ^{18}F-FDG injection within 3 d before scheduled surgery. Maximum SUVs were quantified for the central enhancing component of the lesion and contralateral normal brain. Results showed statistically significant improvements in maximum SUVs and subjective reader conspicuity of glioblastomas at later time points when compared to the conventional 1-h time point. Tumor-to-background ratios at 1, 5, and 8 h after tracer injection were 1.4 ± 0.4, 1.8 ± 0.5, and 2.1 ± 0.6, respectively. The authors concluded that these findings "demonstrate that delayed imaging time point provides superior conspicuity of glioblastoma compared to conventional imaging."

Frontiers in Neurology

Characterizing BRAF-Mutant Papillary Thyroid Cancer Subtypes

Boucai et al. from the Memorial Sloan Kettering Cancer Center (New York, NY), MD Anderson Cancer Center (Houston, TX), and the Cleveland Clinic (OH) reported on November 23 online ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on a study looking at the feasibility of characterizing the molecular and clinical features of 2 subtypes of BRAF-mutant papillary thyroid cancer by their degree of expression of iodine metabolism genes. The study included data from 227 BRAF-mutant papillary thyroid cancer tumors in the Cancer Genome Atlas (Thyroid Cancer), divided into 2 subgroups based on their thyroid differentiation score (TDS; categorized as high or low). A range of data points were compared between the 2 groups. Seventeen percent of tumors were categorized as high BRAF-TDS and 83% as low. High BRAF-TDS tumors were more common in black and Hispanic patients. High BRAF-TDS tumors were also larger, associated with more tumor-involved lymph nodes, and had a higher frequency of distant metastases. Gene set enrichment analyses showed positive enrichment for RAS signatures in the high BRAF-TDS cohort, with corresponding but less pronounced changes in the low group. Several microRNAs (miR-204, miR-205, and miR-144) were overexpressed in the high group. In a subset of data on clinical patient follow-up, those with high BRAF-TDS tumors had higher complete responses to therapy than those in the low BRAF-TDS tumor group

(94% and 57%, respectively). The authors concluded that "enrichment for RAS signatures, key genes involved in cell polarity, and specific miRs targeting the transforming growth factor β–SMAD pathway define 2 subtypes of BRAF-mutant papillary thyroid cancer subtypes with distinct clinical characteristics and prognosis."

Journal of Clinical Endocrinology and Metabolism

SLN Visualization in Upper Urinary Tract Urothelial Cancer

In an article published on November 23 in the *Journal of Clinical Medicine* (2021;10[23]:5465), Polom et al. from the Medical University of Gdansk (Poland) reported on a radioisotope-based technique for detection of sentinel lymph nodes (SLNs) and analysis of lymphatic outflow in patients with suspected upper-tract urothelial carcinoma (UTUC). The study included 19 such patients (7 men, 12 women; mean age, 73.4 y) who were scheduled for ureterorenoscopy. Staging included ^{99m}Tc-nanocolloid radioactive tracer injection and tumor biopsy (pathology: 8 patients, T0 [42%]; 7 patients, Ta [36%]; and 4 patients, T1 [21%]). 3D reconstruction and image fusion were performed for better localization of lymph nodes, and SPECT/CT lymphagiography was used for detection of SLNs and analysis of radiotracer outflow. SLNs were detected in 2 patients (10%): 1 in whom a single SLN was visualized and another in whom multiple radioactive lymph nodes were visualized. SPECT/CT detected no lymphatic outflow in 17 (89.5%) patients. In 5 of these patients (26.3%), however, gravitational leakage of injected radiotracer to the retroperitoneal space was noted. The authors concluded that these results reinforce the challenging nature of detecting SLNs in the upper urinary tract, with associated difficulties in radiotracer injection during ureterorenoscopy. However, "SPECT/CT lymphangiography in cases of UTUC may provide valuable information about a patient's individual anatomy of the lymphatic system and the position of the first lymph nodes draining lymph with potential metastatic cells from the tumor."

Journal of Clinical Medicine

Reviews

Review articles provide an important way to stay up to date on the latest topics and approaches through valuable summaries of pertinent literature. The Newsline editor recommends several general reviews accessioned into the PubMed database in November and December. Rowe and Pomper, from the Johns Hopkins University School of Medicine (Baltimore, MD), provided an overview of "Molecular imaging in oncology: Current impact and future directions" on December 13 ahead of print in *CA: A Cancer Journal for Clinicians*. In an article in the November 30 issue of *Cancers (Basel)* (2021;13:6026), Guglielmo et al. from the Veneto Institute of Oncology IOV-IRCCS and the University of Padova (both in Italy) surveyed the "Additional value of PET radiomic features for the initial staging of prostate cancer: A systematic review from the literature." The role of "Tau biomarkers in dementia: Positron emission tomography radiopharmaceuticals in tauopathy assessment and future perspective" was outlined by Ricci et al. from the University of Rome Tor Vergata and IRCCS Neuromed (Pozzilli; both in Italy) in the November 30 issue of the *International Journal of Molecular Sciences* (2021; 22[23]:13002). Beuthien-Baumann et al. from the Deutsches Krebsforschungszentrum Heidelberg and the Universitätsklinikum Heidelberg (both in Germany) reviewed "Adapting imaging protocols for PET-CT and PET-MRI for immunotherapy monitoring" in the November 30 issue of *Cancers (Basel)* (2021; 13[23]:6019). In the November 24 issue of *Molecules* (2021;26[23]:7111) Prigent and Vigne from Normandie Université (Caen, France) outlined "Advances in radiopharmaceutical sciences for vascular inflammation imaging: Focus on clinical applications." Rondon et al. from the Université Catholique de Louvain (Brussels, Belgium), the Université Clermont-Auvergne (Clermont-Ferrand, France), and CHU Estaing (Clermont-Ferrand, France) published "Radioimmunotherapy in oncology: Overview of the last decade clinical trials" on November 7 in *Cancers (Basel)* (2021;13[21]:5570).