Increasing Patient Volume in PET: Are You Ready?

David W. Dick, PhD and Richard L. Wahl, MD

There has been tremendous growth in the field of positron emission tomography (PET) over the past ten years, with seven new PET drug approvals since the implementation of 21 CFR 212. Recent news regarding approval for a redosing study for an amyloid therapeutic is promising, and the FDA is currently reviewing an NDA for a PSMA-targeting PET imaging drug for prostate cancer. Approval of either of these drugs—let alone both—is expected to result in a significant increase in the volume of patient PET scans. Thus, the PET community must make changes to meet the expected demand.

The Clinical Trials Network (CTN) recently surveyed PET imaging sites regarding their current capacity and plans for expansion. The survey revealed that 54% of sites are at >75% capacity, and 80% of sites are >50% capacity. When asked how they would increase capacity, the majority of sites said that they would extend hours as needed rather than adding additional PET/CT cameras.

Many commercial PET drug manufacturers are already operating at capacity, which has often limited availability of approved PET drugs. Adding additional PET drugs to the increased production of already approved drugs (i.e., amyloid imaging agents) further strains the supply chain, requiring commercial PET drug manufacturers to rethink their operations. Investing in additional cyclotrons is not a near-term solution; the cost and infrastructure associated with their installations is prohibitive. Therefore, it is most likely that commercial drug manufacturers must expand operating hours and hire more personnel to meet the future clinical need for new PET drugs. It is very likely that the current “à la carte” method of ordering PET drugs whenever they are needed is no longer going to be feasible. Setting “time windows” during the day for when a specific PET drug is available is more likely, allowing commercial PET drug manufacturers the ability to produce multiple PET drugs in a given day using existing equipment and personnel.

Given that more than five million Americans are living with Alzheimer’s Disease, the approval of an amyloid therapeutic is expected to significantly increase the volume of PET scans being performed using any of the amyloid imaging agents, as patients need baseline/eligibility scans as well as follow-up scans to assess therapeutic response. In the United States, almost 200,000 new cases of prostate cancer occur each year. While there are currently two approved PET drugs for prostate cancer (C-11 choline and F-18 fluciclovine), the PSMA agents currently under development and moving toward potential FDA approval could shift paradigms in prostate cancer.
The COVID-19 pandemic has reached most countries and is placing extraordinary stresses on societies and individuals. While the thousands of people and families who have suffered deaths and severe illnesses have appropriately been the focus of the response, the impact on the economy and medical research have the potential for serious long-term negative effects on molecular imaging (MI) research. A sustained downturn in MI research will slow scientific discovery and medical care for patients including those with cancer, heart disease, and neurological disorders and ultimately prevent or delay the availability of improved new diagnostics and therapeutics to patients. As we address the acute medical and societal responses to COVID-19, we need to begin identifying and addressing the threats to continued progress in MI.

There have been several responses to COVID-19 that directly affect MI research. Most centers in the United States have suspended diagnostic imaging research to protect study participants and staff. Some centers have experienced furlough or layoffs of technologists and staff who support research. The limited availability of personal protective equipment (PPE) such as masks, gloves, gowns and face shields and other medical supplies may interfere with radiopharmaceutical production and administration to patients and study participants. Preclinical research has been similarly affected and, in some cases, animals have had to be euthanized due to lack of adequate staff to care for the animals. The economic downturn from COVID-19 is likely to be sustained and may reduce the amount of institutional and governmental funding available for MI research.

The Research and Discovery Department of SNMMI sent a survey to institutions in the US to assess the status of their preclinical and clinical research programs by asking these crucial questions:

- What are the long-term potential problems?
- How do research programs start again safely?
- How will funding for non-COVID-19 research be allocated?
- Will there be adequate capacity for imaging research study participants?

Recently, nuclear medicine has benefited from the approval of new imaging agents and therapeutics, and there are a number of promising agents in various stages of development. To sustain this progress, investigators, institutions, industry and funding agencies involved in nuclear medicine and molecular imaging research must work together to address the challenges wrought by COVID-19. Information from this survey will help more clearly identify the logistical and financial problems caused by COVID-19 and develop best practices to manage these problems. Our long-term hope is that making informed decisions for prioritizing activities and resources will help maintain robust MI research and ensure that new diagnostic and therapeutic agents are available to support scientific discovery and improve patient care and outcomes.

In summary, new diagnostic PET drugs and the potential of amyloid therapeutics currently under development demand that PET drug manufacturers and PET imaging sites need to start preparing for an upsurge in the volume of patients needing scans. Adding new equipment, hiring new staff and adjusting to new schedules takes time—it is imperative to plan ahead and be ready for the coming wave.

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management, leading to a much higher volume of PET scans for these patients. These two developments have the potential to double the number of PET studies being performed daily, representing an enormous—albeit welcomed—opportunity for the PET community.

The burden on imaging sites to manage the increased patient activity may result in lengthy waits for PET scans unless the number of PET/CT cameras is increased and the hours of operation expanded. Capacity can also be increased using more sensitive scanners and specialized reconstruction methods to reduce scan times. More sensitive scanners may mean lower administered radioactivity levels, which could stretch available isotope production over more patients. PET centers must adapt by operating like their CT and MRI brethren, utilizing evening time slots to reduce wait times. At many centers, MRs operate around the clock. This necessitates having multiple shifts of technologists and physicians to handle the increased volume and provide adequate coverage for the longer clinical workday. In-house radiopharmaceutical production is also impacted by the need to add personnel to cover expanding clinical demands.

In summary, new diagnostic PET drugs and the potential of amyloid therapeutics currently under development demand
Special Feature
CTN Database Refresh

The CTN maintains a comprehensive database that stores and manages information on over 500 imaging sites, production sites and sites that have both imaging and production capabilities. The database is housed on an online, web-based platform that allows approved sites to enter, edit and update their information.

Database Fields
- Relevant site personnel
- Scanner and dose calibrator inventory
- Research regulatory infrastructure
- Cyclotron and manufacturing equipment
- Radiopharmaceuticals made and used

CTN staff has, in the past, contacted sites annually to update information regarding nuclear medicine scanners and radiopharmaceuticals being used or produced at their site. This also includes the use of cyclotrons or generators that manufacture radionuclides and radiopharmaceuticals. To be effective, the database must stay current so sites can connect with each other and exchange information. This reduces unnecessary workload by a site or team of researchers as they work on projects with current or novel radiotracers. The database can help locate sites using a certain radiopharmaceutical, scanner model, or synthesis module; cross-reference an IND for an agent already in use; and connect pharmaceutical companies to sites having experience with certain radiotracers and radiotherapies. As the use of theranostics grows (see Pathways, January 2020), the CTN database can help.

To ensure that we maintain an up-to-date bank of data, interns from CTN and the Radiopharmaceutical Sciences Council (RPSC) have volunteered to team up on a unique project to “refresh” the database.

Eunkyung and Jessica are dividing up the list of sites and personally contacting the administrator listed in the database. If your site is already part of the CTN database, go online at www.ctndatabase.org and see where you need to update your information. Expect a call or email from Jessica or Eunkyung soon—they can help you with the process.

CTN 2020 Webinar Series

The 2020 Series includes six webinars that address some key—and exciting—areas. With several novel tracers in the later stages of development and a few hopefully to soon become FDA-approved, experts present timely information on the topics listed below.

- There’s a New PET Drug in Town: Manufacturing and Approval Considerations for Your Institution (May 7)
- FES for Breast Imaging
- 68Ga-PSMA for Prostate Cancer
- Writing a Successful NIH Grant Application
- Phantom Analysis Tool: How to Use It
- FDOPA for Movement Disorders and CHI

CTN updates the schedule as speakers, topics and dates are confirmed. Please check the CTN website for information.
**Prostate specific membrane antigen (PSMA)** is highly overexpressed by prostate cancer cells, and thus represents an ideal target for PET imaging. PET tracers targeting PSMA include non-patented free-for-use agents labeled with gallium-68 (68Ga-PSMA-11 and 68Ga-PSMA-I&T) and fluorine-18-based agents under commercial development (18F-DCFPyL, 18F-rhPSMA and 18F-PSMA-1007, among others). Among these, 68Ga-PSMA-11 has been more extensively investigated and used in patients. The uro-oncologist community has accepted and adopted 68Ga-PSMA-11 PET/CT because of its high management impact and superiority to conventional imaging. In the past decade, hundreds of thousands of 68Ga-PSMA-11 PET scans have been performed worldwide, reflecting the rapid and profound clinical adoption by users. Yet in the U.S., PSMA PET is still a clinical research procedure. Patients have access only via clinical trials or under expanded access protocols at a small number of specialized academic centers. In many cases patients need to cover scan and tracer costs without reimbursement (per Title 21(CFR) 312.8).

So, when will 68Ga-PSMA-11 PET become widely available as a standard-of-care procedure?

An FDA New Drug Application (NDA) approval is required to make 68Ga-PSMA-11 PET available in the U.S. Driven by the pressing need for clinical use, a team led by academic investigators from UCLA and UCSF worked together to develop a program to support an academic NDA for 68Ga-PSMA-11, despite the lack of industry support. They conducted a pivotal investigator-initiated clinical trial that established the safety and efficacy profile for initial staging and biochemical recurrence localization.

UCLA and UCSF obtained Prescription Drug User Fee Act (PDUFA) application fee waivers and filed two separate NDAs with the FDA. The two NDAs share the same information for non-clinical and clinical data but have different Chemistry, Manufacturing and Controls (CMC) sections. They both use conventional radiolabeling and are not cold-kit-based. UCLA and UCSF NDAs waived market exclusivity, which enables any site with the ability to manufacture 68Ga-PSMA-11 similar to the UCLA/UCSF NDAs to file abbreviated NDAs (ANDAs) immediately after the NDA approvals, using either NDA’s PET tracer as the Reference Listed Drug (RLD). Based on the latest interactions with the FDA, approval of both NDAs by the end of 2020 looks promising.

There are limitations to making 68Ga-PSMA-11. It has a short half-life of 68 minutes that requires onsite production and prohibits distribution to satellite sites. It is made in small batches of two doses at a time, up to six or eight per day. Cold-kits for rapid one-step 68Ga radiolabeling without manipulation can circumvent these restrictions and, therefore, make it more widely available. Two are currently on their way: 68Ga-THP-PSMA (GalliProst™), developed by GE Healthcare and Theragnostics (Phase 3 trial currently being registered), and TLX591-CDx (Illumet™), developed by Telix (NDA submission anticipated in 2020).

The fluorine-18 based PET agents targeting PSMA are more amenable to distribution and large-scale production due to the longer half-life (110 minutes) and ability to manufacture curies of fluorine on cyclotrons. Progenics’ 18F-DCFPyL is furthest along in clinical development, with an NDA submission anticipated in 2020. Other agents include 18F-rhPSMA (Blue Earth Diagnostics) and 18F-PSMA-1007 (ABX).

After FDA approval, CMS/Medicare approval for reimbursement and integration of PSMA PET/CT into clinical guidelines (NCCN) are the next steps to establish the clinical use 68Ga-PSMA-11.
**In the News: SNMMI Awards Research Grants**

Nuclear medicine (NM), molecular imaging (MI) and targeted radionuclide therapy (TRT) technology is rapidly expanding, and having enough highly trained physicians and scientists is critical for realizing the full potential of recent advances. However, many medical school students are not introduced to nuclear medicine until late in their medical school education, after many may already have selected a different specialty.

SNMMI is excited to offer a new program, “Discovering MI: Student Research Grants,” to help remedy this shortfall. The grant introduces high-achieving medical and science students to molecular imaging and targeted radiotherapy as a potential career path by supporting their participation in a molecular imaging/therapy research project. This grant allows medical students the opportunity to gain valuable research exposure in NM, MI and TRT before they select a residency program and avails science students to NM and MI research opportunities. Recipients receive $5,000 each as a stipend to secure time for their project. After completion of their projects, recipients are required to provide a report on their findings and an evaluation of their experience, which may help SNMMI develop further grant award programs.

SNMMI received 18 high-quality applications from a diverse group of applicants, which made the final decision very difficult. We are pleased to announce and congratulate these five awardees.

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<thead>
<tr>
<th>Name</th>
<th>Mentor</th>
<th>Project Title</th>
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<tr>
<td>Philip Mannes</td>
<td>Carolyn Anderson, PhD</td>
<td>Lysyl oxidase-like 2 targeted PET imaging of matrix remodeling and fibrosis in pulmonary hypertension</td>
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<td>Catherine Meyer</td>
<td>Magnus Dahlbom, PhD</td>
<td>Evaluation of multi- and single-time point dosimetry in Lu-177 PSMA TRT patients</td>
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<td>Peng Lu</td>
<td>Daniel Thorek, PhD</td>
<td>Computational approaches to directly measure alpha particle emitter distribution and small-scale dose on metastatic prostate cancer bone biopsies</td>
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<tr>
<td>Zekun Li</td>
<td>Abhinav Jha, PhD</td>
<td>Quantitative ultra-low count SPECT for alpha-particle therapy</td>
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<td>Amy Zhang</td>
<td>Darko Pucar, MD, PhD</td>
<td>PET/CT features of immunotherapy-related toxicities in endocrine organs</td>
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<td>Yale School of Medicine</td>
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**What’s Happening**

**Amanda Abbott Joins CTN**

Amanda Abbott, MS, CNMT, RT(N), PET, has worked in both research and the clinic coordinating multimodality imaging research activities and authoring several articles. She has been a member of the SNMMI Technologist Section and New England Chapter since 2006 and became co-chair for the CTN Education Committee in 2016. In this capacity, Amanda has been instrumental in recruiting new members to the committee to help develop educational resources. Before joining the CTN in March 2020 as the Associate Director of Research and Discovery, she was the imaging research manager at the Dana-Farber Cancer Institute. Amanda holds a master’s degree in molecular imaging and therapeutics from Regis College and has served as a PET item writer for the NMTCB. She has been awarded the 2015 ARRT/SNMMI-TS Professional Development Grant, a Partners in Excellence Award for Leadership and Innovation and the SNMMI Outstanding Technologist Award June 2017. Most recently, she received the prestigious SNMMI Technologist Section Editor’s Choice award for the best continuing education article published in JNMT in 2018. We look forward to benefiting from her experience, enthusiasm and knowledge of the field. Amanda can be reached by phone at 703.652.6795 or via email at aabbott@snmmi.org.
TechTalk
50th Anniversary of the SNMMI-TS
Norman E. Bolus, MSPH, MPH, CNMT, FSNMMI-TS

It is interesting to look back at where the entire nuclear medicine (NM) field was when the Society of Nuclear Medicine and Molecular Imaging (SNMMI) was forming a new Technologist Section (TS) in the 1970s. Key events during this decade greatly impacted the field as we know it today. As part of its 55th anniversary commemoration, SNMMI created “Important Moments in the History of Nuclear Medicine” to chronicle the evolution of NM from 1896 to 2008. It included the following events from the 1970s.

1970 FDA announced it would gradually withdraw the exemption granted to radiopharmaceuticals and start regulating them as drugs; change to be completed by January 20, 1977

1971 American Medical Association officially recognized nuclear medicine as a medical specialty
Gopal Subramanian and John McAfee introduced Tc-99m–labeled phosphates for bone imaging

1972 David Kuhl performed the first quantitative measurement of cerebral blood volume in living patients

1973 H. William Strauss introduced the exercise stress-test myocardial scan
Elliot Lebowitz introduced thallium-201 for myocardial perfusion imaging, first proposed by Kawana
David Goldenberg demonstrated that radiolabeled antibodies against a human tumor antigen (CEA) could target and image human tumors in animals

1976 John Keyes developed the first general purpose single photo emission computed tomography (SPECT) camera
Ronald Jaszczak developed the first dedicated head SPECT camera
N. Firusian used strontium-89 to reduce pain from metastatic bone disease

1977 The FDA required manufacturers to obtain an approved new drug application for new and existing radiopharmaceuticals; requirements are essentially the same as those for other prescription drugs

As we celebrate the 50th Anniversary of the SNMMI-TS, we have many activities planned throughout the year. Our largest commemoration is perhaps our Journal of Nuclear Medicine Technology (JNMT) supplement to be published in June 2020. This supplement provides a history of the Technologist Section with congratulatory messages from SNMMI and TS leadership, past presidents and international partners. Sections are devoted to the history of technology and radiopharmaceuticals, describing how foundations and our TS chapters were formed over the years. This “not to be missed” supplement highlights conversations with past TS presidents and includes their fondest memory or experience. Be on the lookout for other commemorative activities and planned events! Go to www.snmmi.org/tech50 for complete details.

Research Essentials
A Reminder for Techs: Career Options in Research
Amanda Abbott, MS, CNMT, RT(N)(CT), PET

Happy 50th anniversary to our SNMMI Technologist Section! It is an exciting time to be a technologist in nuclear medicine (NM). The growth of our field, especially in theranostics, is opening more doors of opportunity for technologists to explore. If you are interested in working in the research area, any one of the following options may be for you.

• Preclinical Technologist: Work in the preclinical setting, testing novel tracers and radionuclide therapies on small animals and providing critical information to help move these tracers and therapies into clinical trials.

• Research Technologist: Serve as a liaison between the research world and the clinic space by facilitating site activities for inclusion in clinical trials. This includes reviewing imaging manuals, acquiring phantom scans, building scanner acquisition and reconstruction protocols, preparing for/attending site initiation visits, ensuring clinical trial protocols are followed accurately and submitting imaging data to study sponsors.

• Image Analyst: Work with nuclear medicine physicians on quantitative image analysis. Drawing regions of interest around tumors provides sponsors and clinicians information on the efficacy of the study drug in reaching its target or if a patient is responding to treatment.

• Author: Become a published author. Participating in a research study provides an opportunity to submit an abstract to the SNMMI for a meeting poster or oral presentation, submit an article to the JNMT (always looking for continuing education articles), write a piece for an SNMMI newsletter such as the TS Uptake or CTN Pathways, and explore other publication avenues.

Technologists are on the forefront of advancing novel tracers and radionuclide therapies toward approval. I encourage you to get involved in the fascinating field of research with its many components and opportunities for enhancing your career. It really is an exciting—and gratifying—time to be a nuclear medicine technologist!
The rapid rise in the number of patients with Alzheimer’s disease (AD), currently the sixth-leading cause of death in the United States, results in substantial costs to society, including the impact of the disease on patients and caregivers as well as the financial strain on the health care system. Indeed, the current estimated 5.8 million people in the United States living with dementia due to AD is projected to reach 13.8 million by 2050. Furthermore, there are millions of undiagnosed individuals living with mild cognitive impairment (MCI) who have AD pathology (e.g., elevated amyloid β [Aβ]), but can carry out their everyday activities despite subtle memory and thinking problems beginning to develop.

While some advances have been made over past decades for AD diagnosis and symptom treatment across the AD dementia stages (mild, moderate, and severe AD), new early detection diagnostic modalities and therapies are urgently needed. Currently available treatments are not approved for MCI and they do not slow the progression of AD, however, new therapeutic modalities are being explored. One promising area of focus for AD research is targeting Aβ. Several Aβ-targeting agents are in late-stage clinical development for the treatment of early AD (i.e., MCI due to AD and Mild AD). As disease-modifying therapies (DMTs), these agents may have the potential to slow disease progression by reducing underlying AD pathology (e.g., Aβ plaques or tau tangles) and may also alleviate some of the significant costs to society.

To fully realize the potential of DMTs if approved, more efficient and effective processes for detecting individuals with early AD are needed. The earlier patients are detected, the greater the window for non-pharmaceutical and pharmaceutical interventions to lessen the burden of AD. This will require that resources and testing modalities are available and reimbursed in such a way that primary care physicians can readily detect, screen, and refer patients with suspected early AD to specialists who can confirm the diagnosis. In addition, confirmation of Aβ pathology will be necessary for early AD diagnosis and for future approved DMTs to be initiated as appropriate. This confirmation currently relies on two modalities:

1. Amyloid positron emission tomography (PET), for which three amyloid tracers are approved but not reimbursed by CMS, and
2. Cerebrospinal fluid (CSF), for which there is currently no FDA-approved assay.

An urgent call to action is imperative to optimize the management of patients and to ensure only appropriate individuals receive a DMT once approved: nuclear medicine and imaging communities should begin to make the necessary preparations so the amyloid PET infrastructure is in place and that more of the ~2,400 PET sites across the nation have experience in performing amyloid PET scans.

References:
Introducing “PAT”—SNMMI’s PET/CT Phantom Analysis Toolkit—Free for SNMMI Members!

SNMMI’s new cloud-based automated Phantom Analysis Toolkit (PAT) is designed to provide rapid, reliable, and reproducible fully automated phantom analysis for the four most common PET phantoms currently in use for clinical trials and clinical practice.

How it works:
1. Name your Upload/Analysis
2. Select the phantom type (ACR PET Phantom, CTN Oncology Phantom, NEMA Image Quality Phantom, or Uniform Phantom)
3. Select and Upload the phantom DICOM image files
4. Enter the phantom radioactivity fill and time data
5. Submit for analysis
6. Complete analysis back in just a few minutes. (Note: analysis time depends upon both cloud server and the size of the phantom data set.)

Meet your program accreditation requirements—check out “PAT” today!

www.snmmi.org/PAT