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A Look at PET: Past, Present, and Its Prospect for the Future "Two Steps Forward, One Step Back"

Continuing Education for Nuclear Pharmacists
And
Nuclear Medicine Professionals

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STATEMENT OF LEARNING OBJECTIVES:

The following lesson constitutes an introduction and overview for the series of lessons entitled:

A Look at PET: Past, Present, and Its Prospect for the Future.

The series learning objectives are:

1. Describe the development and utilization of cyclotrons,
2. Explain the development and utilization of USP chapters.
3. Describe the currently available machines, synthesis equipment, and quality assurance implementation procedures necessary to ensure patient safety.
4. Explain the value of continuous improvements to targetry and circuitry and the need for improvements in labeling complexity and efficiency.

The above objectives are specific to the accompanying lessons, whereas, this lesson has the broader learning objective:

1. Describe the technical, medical, financial, scientific and regulatory forces that have shaped the practice of PET.

COURSE OUTLINE

Presented at 2009 Annual APhA Meeting

A LOOK AT PET: PAST, PRESENT, AND ITS PROSPECT FOR THE FUTURE "TWO STEPS FORWARD, ONE STEP BACK"

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The subtitle and thematic approach for this lesson is: ***"Two Steps Forward, One Step Back"***, a theme that implies that the progress of PET has not been a smooth progression from an infancy technology to a full-fledged clinical tool, but rather, that advances have been met with, in some cases, losses in functionality and capability and a degradation in the value of PET services. In this perspective on PET, the following questions will be examined:

- Where have we been?
- Where are we now?
- Where are we going?

As an illustrative example of the transitions that have been experienced in PET over the last 20 years, the University of Iowa PET Imaging Center will be used. These questions will be examined with respect to facilities, personnel, imaging equipment, chemistry equipment, study mix and finances and reimbursement issues and how these forces evolved the practice of PET at the University of Iowa and throughout the U.S.A.

OVERVIEW OF THE UNIVERSITY OF IOWA PET IMAGING CENTER (1989 – 2009)

The University of Iowa is a state-supported, Big Ten university contained within a single campus and consisting of a collection of eleven colleges – Medicine, Pharmacy, Nursing, Dentistry, Public Health, Liberal Arts and Sciences, Engineering, Education, Law, Business and Graduate. Current enrollment is approximately 30,000 students with about 5,200 graduate and 4,200 professional students. The student population is comprised of 62% Iowans, 23% from adjoining states and 6.5% international students from 110 countries. Within this complex is the University of Iowa Hospitals and Clinics (UIHC), a 684 bed tertiary care center housing 200 specialty and sub-specialty clinics in a 3.5 million square feet facility. The hospital has 8,000 staff including

over 1,500 nurses, 650 staff physicians and 675 residents and fellows. Each year, there are more than 27,000 inpatient and 850,000 outpatient visits to UIHC. UIHC's Holden Comprehensive Cancer Center became an NCI-designated comprehensive cancer center in 2000, seeing approximately 32,000 patients with a diagnosis of cancer each year. The University of Iowa ranks 13th nationally among public universities for NIH funding. [All statistics from the University of Iowa webpages found at http://www.uiowa.edu/facts/index.html.]

Within this environment in the late 1980s, the departments of Radiology, Neurology, Psychiatry and Cardiology along with the College of Medicine (now Roy J. and Lucille A. Carver College of Medicine) collaborated on the establishment of the University of Iowa PET Imaging Center (UIPIC). A $6 million investment was made to purchase the cyclotron and scanner and the collaborating entities paid to outfit the laboratories and provide yearly operational support. In exchange, the entities received PET imaging services. The UI PET Imaging Center was essentially a second-generation PET facility. Pioneering facilities like UCLA, Johns Hopkins, Washington University in St. Louis, and the University of Michigan were well-established institutions at this time. However, the alluring research potential of PET was attracting a new group – a "second generation" of institutions such as UI and Massachusetts General Hospital (MGH)[1]. At this time, there were approximately 25 PET Centers world-wide, each with not only PET scanners but cyclotrons and full PET radiopharmaceutical production capabilities.

Facilities

Schematics of the UIPIC facilities as they appeared in the early 1990s and today are presented in Figure 1. The pink areas are dedicated to chemistry and laboratory operations. The cyclotron and hot (i.e., radioactive), cold (non-radioactive) and quality control labs occupy the same footprint as they did initially. The original physics and electronics lab was needed along with the machine shop because of the requirement to create ancillary equipment (e.g., on-line blood detector), produce targets, and repair scanner, chemistry and cyclotron parts. This space has now been converted to a research chemistry lab and the physics and electronics functions have been moved to the space previously occupied by the computers needed to operate the original scanner.

[1] Because of construction delays, the original scanner and cyclotron designated for delivery to the University of Iowa was delivered to MGH instead.

The VAX server and computers and power conditioning unit are no longer necessary since current scanners require only standard PCs or Sun computers.

Originally, a single patient preparation room accompanied the single PET scanner room with its corresponding control room and "uptake room" – a room designed for analysis of blood samples and to provide a space for the investigator to observe the subject and to operate stimulation protocols. The scanner room was over-sized in order to provide the "distance" needed (i.e., time-distance-shielding) to minimize staff and researcher radiation exposures (from potentially very high doses such as 100 mCi of [^{15}O]-based radiopharmaceuticals) while remaining in communication with subjects/patients. The patient preparation room has become a dispensary equipped with a laminar flow hood for dispensing of PET radiopharmaceuticals and secured with proximity card access. The single preparation/single scanner room concept has been replaced by the clinically-oriented traffic flow with six patient preparation rooms and a nursing station to service three scanner rooms – two for PET/CT units and one PET-only research scanner. One of these prep rooms was specifically designed to create the controlled environment needed for the uptake period for brain scans. A single control room is used for both PET/CT scanners, providing for efficient use of technologist staff. The scanner rooms, outfitted with large leaded-glass windows, are designed for visibility of the patient while maintaining a minimum footprint for the scanners. An enlarged waiting room and a formal reception area are now part of the facility. Office space has been minimized requiring that the majority of the faculty offices are now located outside of the facility.

All of these facility changes have been geared toward the progression from a personnel-intensive research and technical development environment to a higher throughput clinical operation. Imaging and control rooms have needed to comply with the shielding requirements for not only PET but CT as well and have benefited from the shrinking footprint of the needed acquisition and processing computer systems. Chemistry facility changes have been geared toward the separation of clinical and research radiopharmaceutical preparations and the dispensing functions with an eye toward regulatory compliance with future cGMPs, USP <797> and USP <823>. Future changes will be dictated by the needs imposed by new regulatory requirements, especially in the areas involved in radiopharmaceutical synthesis and dispensing functions, and to accommodate new imaging modality combinations (e.g., PET/MRI).

Figure 1. The University of Iowa Hospitals and Clinics, Positron Emission Tomography Imaging Center, as configured in the early years (left hand panel) and currently (right hand panel). The pink areas are dedicated to chemistry. The yellow areas are accessible to the public. The blue areas are dedicated to patient care (imaging and physician reading). The green areas are dedicated to support services and offices.

Personnel

The UIPIC was designed by a physicist and a chemist with prior PET experience at the University of Michigan. Joining the staff were a nuclear medicine technologist, a nurse and a research scientist with pharmacokinetic experience – none of whom had any PET training of any kind. The staff was a total of 4.5 full-time equivalents (FTEs). The current staff is as detailed in Table 1 for a total of 18.5 FTE.

Table 1.

STAFF OF THE UI PET IMAGING CENTER 2009	
Physics:	**Technical Staff:**
Ph.D. Physics - Director	**Chief Technologist**
Ph.D. Physics – Associate VP for Research (UI)	Senior NMT with PET Certification, credentialed for CT operation (3 FTE, 2 PTE)
Chemistry:	**Nursing Staff:**
Ph.D. Chemist – Research Chemistry	**Clinical nurse specialist (RN)**
Ph.D. Chemist – Clinical Chemistry	Staff nurse (RN) (2 FTE)
M.S. Chemist – Clinical Chemistry	
B.S. Chemist – Clinical Chemistry	
Data Analysis:	**Engineering Staff:**
Ph.D. Pharmacokineticist	Engineer III (BS)
Graduate student (physics) (0.5 time)	Engineer I (MS)
	Receptionist/scheduler
	Research Assistant III (small animal imaging)

Bolded individuals are members of the original staff.

In the 20 years of operation, there has been a significant increase in the number and diversity of personnel required to operate the UIPIC. The staffing mix changes reflect the shift from a focused research laboratory to a center that provides routine daily clinical studies along with research employing a variety of PET radiopharmaceuticals and also operates as a small animal imaging core. Of note, there is no individual employed as a pharmacist at the UIPIC because radiopharmaceuticals are prepared under the "Practice of Medicine" regulations of the State of Iowa. No PET radiopharmaceuticals are distributed outside of the institution. In addition, there are no individuals employed as "cyclotron" operators since this position is not mandated by state law. All of the technical, chemistry, physics and engineering staff are trained in cyclotron operation and routinely perform these operations. In addition, all PET technologists are credentialed in both PET and CT (for operation of a PET/CT unit only).

Future personnel needs will likely reflect the additional regulatory burdens imposed by cGMPs (i.e., QA and clerical positions), third-party-payer authorization (i.e., clerical positions) and clinical study complexity (e.g., nurse or PA to monitor ECG) or new combination modalities. Economic constraints resulting from changes in reimbursement (see below), mandated by administrators from bench-marking analyses, and limitations in grant funding will require shifts in personnel toward the most cost-effective mix that still maintains operational effectiveness and

meets regulatory requirements. Expensive personnel like pharmacists and scientists may become luxuries in operations focusing on clinical throughput only.

Imaging Equipment

The UIPIC originally had a single GE4096 whole-body PET scanner. This BGO (bismuth germanate) scanner had 8 detector rings resulting in 15 slices of image data within the 10 cm axial field-of-view (FOV). This 1990 state-of-the-art scanner was a huge leap forward when compared to the single or two-slice brain-only scanners that were available in the 1980s. This scanner had 2D acquisition in the dynamic, static and wobble modes. Display software was limited to transaxial slices only, whether activity-based or parametric images. However, a number of parametric models (e.g., autoradiographic [^{15}O]water blood flow model, autoradiographic [^{18}F]fluorodeoxyglucose (FDG) cerebral metabolic rate model) as well as hardware and software tools for the acquisition and analysis of arterial blood curves were supplied with the scanner's operation software system. Attenuation correction utilized [^{68}Ge] transmission images with the rod source manually inserted when required for imaging. In the mid-1990s, software upgrades provided for the capability to acquire whole-body images as well as display these images in the standard orthogonal planes (i.e., transaxial, coronal, and sagittal). This change in software capability significantly improved the utility of FDG for clinical non-neurological uses such as whole-body oncology studies.

Currently the UIPIC has a PET-only scanner, utilized primarily for research purposes, two PET-CT scanners used for both research and clinical purposes, and a third PET/CT which resides in the Department of Radiation Oncology and is utilized for clinical diagnostic imaging and treatment simulations. The PET-only scanner has both 2D and 3D capability, 63 slices in a 15.5 cm FOV and [^{68}Ge] transmission imaging (in-dwelling rod sources). The two PET-CT scanners (2-slice CT and 40-slice CT) have 47 and 81 slices in the whole-body mode over 16.2 cm FOV, respectively. Both scanners operate in 3D mode only with CT-based attenuation correction. In addition, the UIPIC operates a PET-only small animal scanner and has a PET-SPECT-CT small animal scanner on order.

The changes in the specifications for PET scanners over the last 20 years are presented in Table 2. There are obvious improvements in FOV, image planes, and resolution. However, there are

some shortfalls associated with this progression in PET scanner technology. First, the conversion from PET-only to PET/CT scanners has significantly improved the speed of imaging (especially the time needed for attenuation correction) and provides the frequently invaluable co-registered anatomical image. However, this conversion comes at a significant cost with respect to radiation dosimetry. Although, low-dose CT imaging can potentially be used for attenuation correction, this results in an essentially uninterpretable image, minimizing the utility of the bimodal imaging approach. Wu, et al.[1] found mean effective doses for [^{68}Ge]-based transmission imaging for brain, cardiac and whole-body studies to be 2 - 3, 8 - 13 and 20 - 26 mrem, respectively. These same studies employing high-speed CT (i.e., lower quality) would entail radiation doses of 22, 325 and 881 mrem, respectively. Whereas, in the high quality mode, producing images comparable to usual diagnostic quality CT images, the radiation doses would be 45, 566 and 1897 mrem, respectively. In comparison, the H_e from a 5 mCi dose of FDG is 500 mrem[2]. Frequently, two CT scans will be acquired per PET scan, the first for attenuation correction purposes, generally a low dose scan, and a second with CT contrast enhancement for diagnostic co-registration purposes, significantly increasing the patient's radiation doses associated with their diagnostic procedures. The escalating radiation exposures from CT examinations have become a source of concern, especially for pediatric patients[3]. Therefore, the movement toward PET/CT scanners exclusively could potentially limit the usefulness of PET technologies in general, for pediatric patients and for research involving radiopharmaceuticals administered under the RDRC mechanism due to regulation-imposed radiation exposure limitations for these types of studies.

Table 2.

SPECIFICATIONS FOR LEGACY AND CURRENT PET SCANNERS

Specification	Original BGO Scanner	Current BGO Scanners	Current High-Resolution LSO Scanners*
Number of crystals	4096	<11,000	24,336 (32,448)
Number of detector rings	8	24	39 (52)
Number of contiguous image planes (slices)	15	47	81 (109)
Slice spacing (mm)	6.5	3.75	2.0
Transaxial resolution (mm)	6.5	~6.0	4.2

Specifications are for the GE4096 WB scanner, a current generic BGO (bismuth germanate) and a current high-resolution LSO (lutetium oxyorthosilicate) scanner (e.g., Siemens Biograph TruePoint PET/CT scanners with values for a fourth set of detector rings in parentheses). Information on current scanners available at: http://www.medical.siemens.com/webapp/wcs/stores/servlet/ProductDisplay?productId=143899&storeId=10001&langId=-1&catalogId=-1&catTree=100001,12788,12756*275083511&level=0.

The conversion from 2D to 2D/3D to 3D only scanners has the advantage of improved sensitivity and therefore, lower doses of PET radiopharmaceuticals and/or reduced scanning times for similar mCi doses. However, the large number of additional corrections required for scatter, randoms and deadtime when operating in the 3D mode compared to the 2D mode, may potentially compromise the quantitative accuracy of the images. Furthermore, the improved sensitivity comes at the expense of more restrictive count rate limitations. For example, the ECAT EXACT HR+ has count rate correction capability within ±5% up to 4.2 μCi/cc in the 2D mode whereas these same specifications are only met up to 0.63 μCi/cc when in the 3D mode [ECAT EXACT HR+ specifications, Siemens Medical, 2003]. Advances in picoelectronics are reversing this trend in count rate limitations. In addition, the storage requirements for 3D raw data are approximately a factor of 4 larger than the space needed for the storage of 2D sinograms.

In this same vein, newer scanners have gravitated to list-mode acquisitions as opposed to dynamic acquisitions. List mode is particularly advantageous when the time course for tracer delivery is unknown *a priori* or when flexibility is needed for shifting data acquisition windows based on other physiological measures and for gating data based on respiratory or cardiac cycles (e.g., radiation therapy treatment planning or gated [^{82}Rb] imaging, respectively). However, the processing of list-mode data may be very time and computer-intensive. If the binning sequence is known *a priori*, establishing a dynamic acquisition sequence is much more time efficient from a data processing point-of-view, but this capability may no longer be available.

Future directions for equipment development will be directed toward continued improvements in resolution, sensitivity and FOV leading to enhanced throughput and niche markets such as positron emission mammography (e.g., PEM (Naviscan, Inc.)) or brain-only units (e.g., NeuroPET™ (PhotoDetection Systems, Inc.)).

Chemistry Equipment

The UIPIC started with a Scanditronix MC-17 cyclotron (dual particle), two large Von Gahlen hot cells, an Anatech RB-86 Robotic Arm and Stations for automated chemistry syntheses and an in-house developed [^{15}O]water maker. Today, the cyclotron remains the same units as was

originally installed with software improvements for enhanced automated operation. In addition to the original two hot cells, four Von Gahlen mini-hot cells and three Comecer stainless steel hot cells with HEPA-filtered air capability have been installed. In place of the robot for automated syntheses, a number of commercial "boxes" have been acquired, specifically, two Nuclear Interface (NI) FDG synthesis units, a NI fluorination unit, a NI [^{11}C] unit, a Siemens Explora (FDG) unit, a GE methyl iodide unit and an Advion Microfluidic System. An in-house built unit for the production of [^{11}C]acetate has been added to free up the commercial [^{11}C] units for other more complicated syntheses.

The evolution of cyclotrons and chemistry equipment are topics for the subsequent lessons. However, it is obvious that the trends are toward more automated syntheses in "clean" environments that are conducive to routine production needed for clinical operations and in response to current and impending PET radiopharmaceutical requirements and regulations. In the least, these evolutions are extremely costly changes since synthesis units run in the multiple tens of thousands of dollars and collections of hot cells potentially in the hundreds of thousands of dollars.

Study Mix

The UIPIC, because of its founding as a consortium of departments, was tasked with performing research, primarily [^{15}O]water brain mapping studies. FDG was a secondary tracer and studies using this tracer were initiated after the brain mapping studies were begun. Some exploratory work on the clinical potential of cardiac imaging with [^{13}N]ammonia and [^{11}C]acetate was conducted but was abandoned due to the lack of reimbursement at the time, and the cyclotron-intensive/labor-intensive tracer production for only marginal improvements in diagnostic utility over current SPECT myocardial perfusion agents. With reimbursement and the image-display improvements detailed above, the clinical use of FDG, primarily for oncologic purposes exploded in the late 1990s. During this same time period, much of the research brain mapping work migrated to fMRI, limiting the research [^{15}O]water studies to indications requiring absolute quantitation or in cases where MRI artifacts may be problematic. Recently, diagnostic CTs, with and without contrast enhancement, and myocardial perfusion studies using [^{82}Rb] have been

added to the study mix. See Figure 2 for an illustration of this progression in the number and mix of studies.

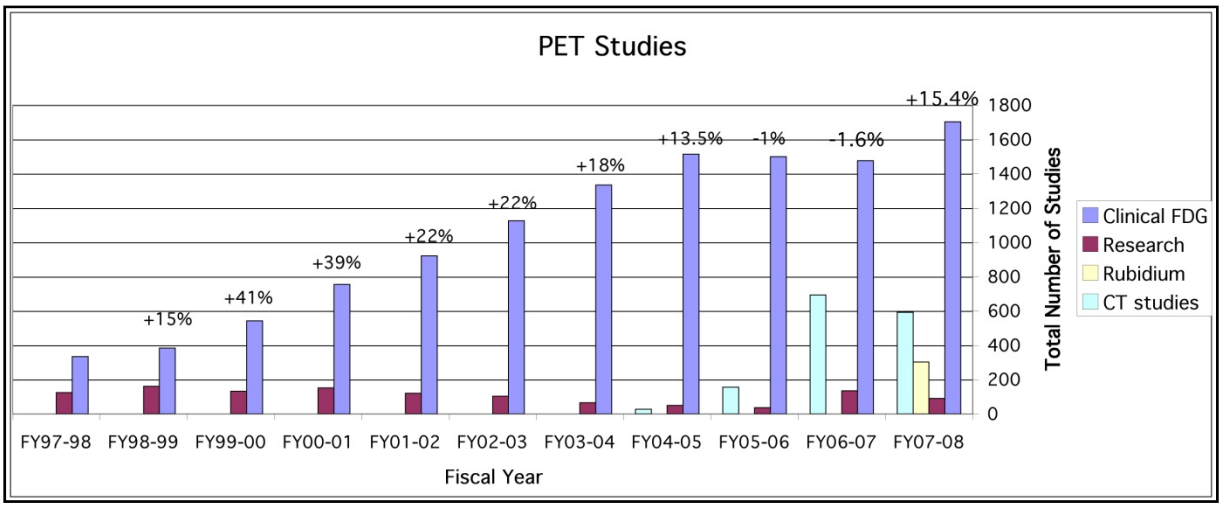

Figure 2. The study mix for the University of Iowa PET Imaging Center (UIPIC) for the decade from fiscal year (FY) 1997-98 to fiscal year 2007-08. The percentage values are the increase from the previous fiscal year for FDG clinical studies. The decrease in the number of studies from FYs 2005-2007 was due in part from renovations and equipment moving and upgrades that reduced clinical productivity.

In economic terms, the total billables for FY 97-98 was $935,400 of which 15.2% was research-based revenue primarily from [^{15}O]water brain mapping work. In FY 07-08, the total billables were $10,886,600 of which 1.1% was research-based revenue from a broader repertoire of studies. Included in this recent revenue increase is revenue from performing clinical CT scans and [^{82}Rb] myocardial perfusion imaging for only a part of this fiscal year.

This explosion in the productivity at the UIPIC reflects the expansion and shift in study mix in PET imaging worldwide and the impact of PET, especially FDG imaging, on medical care. Fueling this growth was the advent and expansion of the commercial availability of FDG, making PET imaging services available beyond institutions with their own cyclotron and chemistry facilities. For example, PET imaging services are now available throughout the state of Iowa as is the case nationwide. Even the community hospital in Iowa City, a metropolitan area of approximately 100,000 has the services of a mobile PET scanner on a routine basis, even with the UIPIC located within a mile of this hospital.

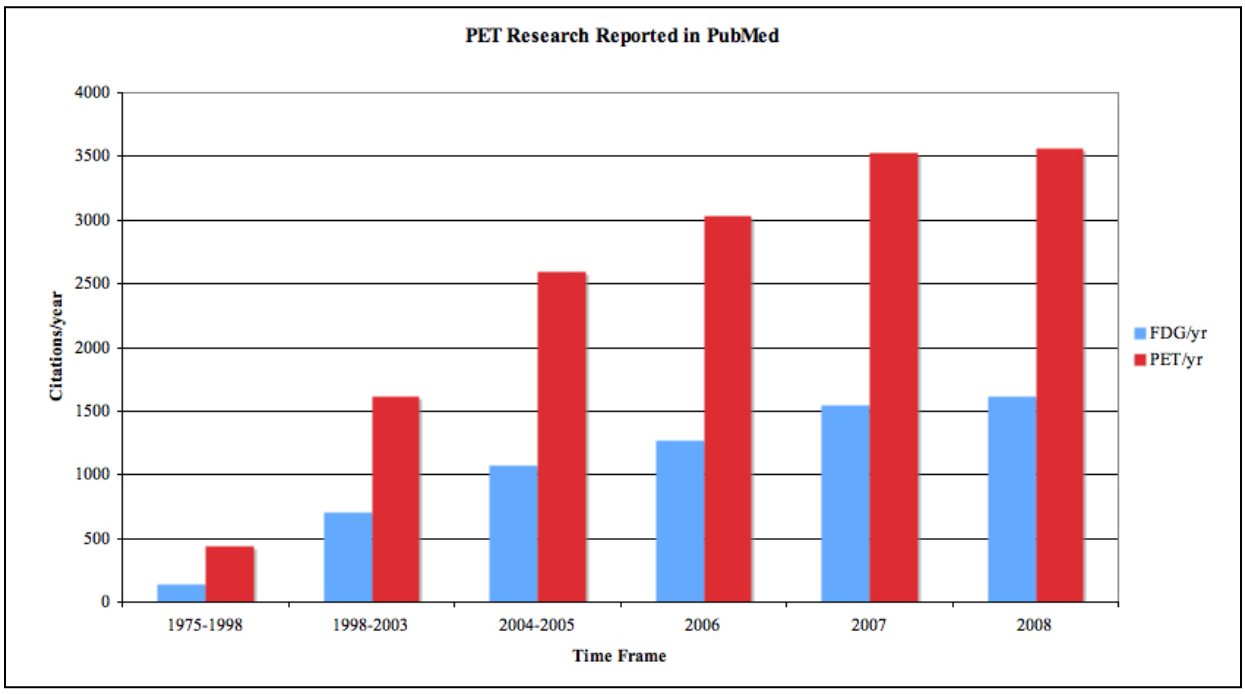

Figure 3. PubMed citations per year for PET in general and FDG specifically.

To understand the future potential of this imaging modality, the direction and balance of the medical research related to PET can provide some insight. Figure 3 illustrates the research productivity for PET as exemplified by PubMed citations. Although research and clinical PET productivity appear to go hand-in-hand, the importance of FDG is a far more significant factor in the clinical PET world than the research world. Yet, reflected in these numbers is the potential for PET to expand beyond an FDG-centric modality if reimbursement and regulatory factors support such an expansion.

Under the Food and Drug Modernization Act of 1997 (FDAMA), a drug that has a USP monograph and that is prepared under the auspices of USP general chapter <823> is legally non-adulterated, therefore, potentially available for clinical use. The PET radiopharmaceuticals that potentially meet these requirements, depending on the qualifications of the facility preparing the radiopharmaceutical, are listed in Table 3. The majority of the USP agents use short-lived radionuclides (i.e., C-11, N-13 or O-15 labeled) which require an on-site cyclotron for their preparation, eliminating commercial distribution. Included in Table 3 is additional information regarding the date of the last revision of the USP Drug Information (USP DI) monograph and the number of PubMed citations for the particular agent within the last 2 years (1/07 through 1/09).

With the exception of FDG, the majority of USP PET radiopharmaceuticals have only a trivial impact on the medical literature. In addition, with the demise of the USP DI in 2004, there is no "official" labeling information available on agents other than the sample labeling available on the FDA's website for FDG (Fludeoxyglucose F 18 Injection [^{18}F] FDG), Ammonia N 13 Injection and Sodium Fluoride F 18 Injection (http://www.fda.gov/CDER/guidance/labsample.pdf) and the package insert for Cardiogen-82® (Rubidium Rb-82 Generator). The information that was previously available in the USP DI, in most cases, was dated. The USP Expert Committee on Radiopharmaceuticals and Medical Imaging Agents lacks the needed resources and support to significantly increase the number of PET radiopharmaceutical standard monographs at the present time. The USP Expert Committee on Radiopharmaceutical Information currently has no forum for the generation and publication of PET radiopharmaceutical drug information monographs.

In response to this void, the Society of Nuclear Medicine (SNM) initiative to establish multicenter investigational new drug applications (INDs) is designed to expand the clinical information available for new PET radiopharmaceuticals with the ultimate goal of securing New Drug Application (NDA) status. The first agent with such an IND is [^{18}F]fluorothymidine, (FLT). Commercial entities are also exploring the potential of various PET radiopharmaceuticals, primarily fluorinated agents, for a variety of uses (e.g., amyloid imaging) as commercially-available PET radiopharmaceuticals using the same types of approval mechanisms that are utilized for conventional nuclear medicine agents. Therefore, the potential exists for expanding the scope of PET clinical utility if these initiatives come to fruition.

The current study mix of PET illustrates that this modality has widespread availability with proven and accepted utility due primarily to the expansion beyond the academic medical centers through commercial involvement. Even in academic medical centers, research has taken a back-seat to the demands of clinical operations and applications. However, PET imaging could be a "one-trick pony" if tracers beyond FDG are not developed into full-fledged clinical radiopharmaceuticals. The future of PET is dependent on guiding new radiopharmaceuticals through the entire maze from idea to IND to NDA to reimbursement.

Table 3.

PET RADIOPHARMACEUTICALS WITH USP MONOGRAPHS IN USP 32		
USP Agent	**USP DI Revision Date**	**Citations in Last 2 years***
Carbon monoxide C-11		1
Flumazenil C-11 injection		0
Mespiperone C-11 injection	6/15/99	0
Methionine C-11 injection	8/24/98	4
Raclopride C-11 injection	6/15/99	2
Sodium acetate C-11 injection	6/8/99	68
Fludeoxyglucose F-18 injection	1/9/03	3,157
Fluorodopa F-18 injection	6/9/99	35
Sodium Fluoride F-18 injection	8/2/98	11
Ammonia N-13 injection	8/2/94	10
Water O-15 injection	4/19/99	141
Rubidium chloride Rb-82 injection		30
Other non-USP PET RPs		3,631

*Values as on January, 2009 for period 1/07 to 1/09.

Finances/reimbursement

As mentioned earlier, the original financial structure of the UIPIC was a core research facility created by a consortium of College of Medicine entities that evolved into a clinical division of the University of Iowa Hospitals and Clinics, Department of Radiology. The decision to reimburse PET clinical studies was pivotal to the survival of PET in the late 1990s both at the University of Iowa and throughout the nation. This financial incentive was the primary impetus to the rapid expansion of these services in the past decade. However, the scope of this reimbursement has been very restrictive as CMS has taken a very narrow approach to payment for PET imaging. For example, the sample labeling for FDG lists (http://www.fda.gov/CDER/guidance/labsample.pdf) the following indications:

- **Fludeoxyglucose F 18 Injection** is indicated in positron emission tomography (PET) imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnoses of cancer.

- **Fludeoxyglucose F 18 Injection** is indicated in positron emission tomography (PET) imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function.

- **Fludeoxyglucose F 18 Injection** is indicated in positron emission tomography (PET) imaging in patients for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

The first indication accepts the general utility of FDG for assessing glucose metabolic abnormalities associated with malignancy. However, reimbursement has been limited to the indications in Table 4, specifically the CMS Nationally Covered Indications. In response to these restrictive reimbursement decisions and to expand the clinical information regarding the impact of FDG imaging on oncologic treatment decision-making, the National Oncology Patient Registry (NOPR) was established. NOPR implemented Medicare's "Coverage with Evidence Development" (CED) Policy that allowed for coverage of previously non-covered cancer indications if prospective registry data were collected to assess the utility of PET and PET/CT. The covered indications are listed in Table 4 under the "NOPR Eligible Indications". After one year of NOPR data gathering, 22,975 studies from 1,178 PET Centers were available for analysis. Approximately, 30% of the enrollments were studies of patients with prostate, pancreas or ovarian cancer. The results of this study found that physicians changed their intended management of their patients in 36.5% of cases after PET imaging[4]. On January 6, 2009, a new draft PET national coverage determination was released by CMS for comment. Specific information on what indications will and will not be covered and whether a new "coverage with evidence development" program will be instituted is slated for an April 6, 2009 announcement.

Table 4.

ONCOLOGY INDICATIONS COVERED BY CMS AND THOSE COVERED UNDER THE NOPR*

Type of Cancer	CMS Nationally Covered Indications	NOPR Eligible Indications
Head and neck cancer	DIR	T
Esophageal cancer	DIR	T
Stomach cancer		DITR
Intestinal (small) cancer		DITR
Colorectal cancer	DIR	T
Anal cancer		DITR
Liver cancer		DITR
Gall bladder cancer		DITR
Pancreas cancer		DITR
Retroperitoneal/peritoneal/pleura cancer		DITR
Lung cancer, non-small cell	DIR	T
Lung cancer, small cell		DITR
Thymus, heart or mediatinal cancer		DITR
Bone or cartilage cancer		DITR
Connective or other soft tissue cancer		DITR
Melanoma	DIR	T
Breast cancer	ITR	
Kaposi's sarcoma		DITR
Uterine cancer		DITR
Cervical cancer	I	DTR
Ovarian cancer		DITR
Prostate cancer		DITR
Testicular, penile and male genitalia cancer		DITR
Bladder cancer		DITR
Kidney cancer		DITR
Eye cancer		DITR
Primary brain cancer		DITR
Thyroid cancer	R	DIT
Lymphoma	DIR	T
Myeloma		DITR
Leukemia		DITR
Solitary pulmonary nodule	D	
Other		DITR

D = Diagnosis; I = Initial staging; T = Treatment monitoring; R = Restaging or recurrence *Information from The National Oncology PET Registry home page, http://www.cancerpetregistry.org/indications.htm, accessed on 2/6/09.

The level of reimbursement, as measured by the Hospital Outpatient Prospective Payment System (HOPPS), has declined significantly over the last few years. The reimbursement rates for the last four years are illustrated in Figure 4 and detailed in Table 5. This decline has manifested in two forms – the reduction in the technical fees associated with the procedure and the decision to bundle radiopharmaceutical costs rather than remain with the cost-to-charge formula. The change in reimbursement rates between 2007 and 2008, the time frame in which the formula for paying for PET radiopharmaceuticals changed, resulted in an effective payment rate for myocardial perfusion agents (i.e., [^{13}N]ammonia or [^{82}Rb]) of $670. Comparing the 2009 to the 2007 rates, the payment for these pharmaceuticals would be $426. At these rates, 45 to 71 myocardial perfusion studies (rest, stress, or rest and stress) would be needed every 28 days to reach the break-even point for the cost of the [^{82}Rb] generator at its current $30,000 plus cost. Using a similar type of comparison (i.e., 2007 – 2008 rates or 2007 – 2009 rates), the effective payment rate for a dose of FDG would be $210 or $181 for PET studies, respectively. Because of the discontinuation of the premium paid previously for a PET/CT over a PET only study, the FDG payment would be even less at $107 or $87 for PET/CT, respectively. A number of value-added features of current PET/CT over PET-only studies are detailed in Table 6. These features, as well as the scanner purchase and operational expenses, frequently add expense to the conduct of the study, yet are no longer rewarded with a premium in reimbursement levels.

Table 5.

HOSPITAL OUTPATIENT PROSPECTIVE PAYMENT SYSTEM (HOPPS) REIMBURSEMENT RATES FOR CMS-COVERED PET INDICATIONS[5, 6]

Study type	2006	2007	2008	2009
Heart image, PET, multiple	$2,484.88	$731.24	$1,400.98	$1,156.87
Tumor image, PET, skull-thigh	$1,150.00	$855.43	$1,057.33	$1,036.92
Tumor image, PET/CT, skull-thigh	$1,250.00	$950.00	$1,057.33	$1,036.92
Pharmaceuticals	FDG, Rb cost-to-charge for RPs > $50/day	FDG, Rb cost-to-charge for RPs > $55/day	Diagnostic RPs are bundled	Diagnostic RPs are bundled

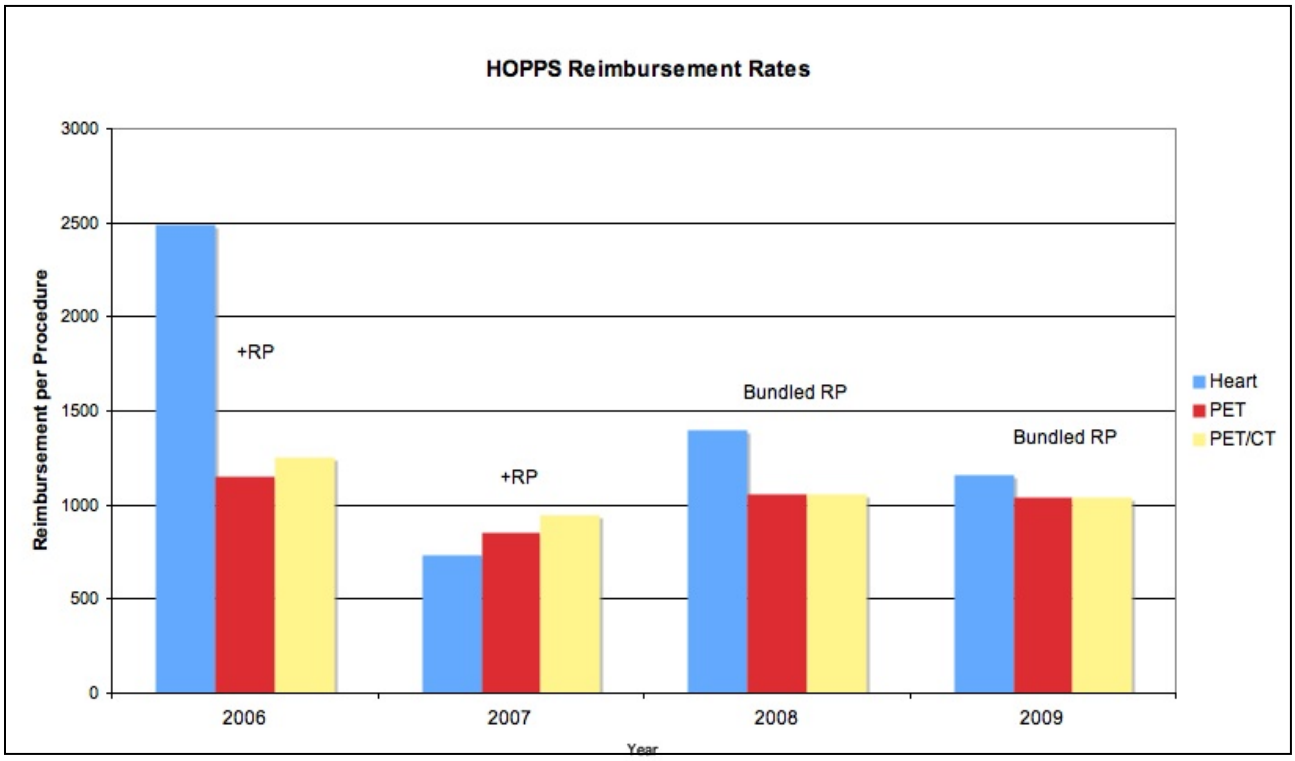

Figure 4. Hospital Outpatient Prospective Payment System (HOPPS) Reimbursement Rates for CMS-covered PET Indications by year.

Table 6.

PREMIUM FEATURES WITH CURRENT SCANNER TECHNOLOGY
Myocardial perfusion studies
CT co-registration allows for exploration of non-cardiac sources of chest pain More rapid attenuation correction ECG gated imaging
Tumor imaging
Anatomical imaging (CT) with automatic co-registration More rapid attenuation correction Use of oral contrast to delineate the GI tract Resolution improvements

CMS and other third-party payers have recognized the utility of PET imaging, but the tracers and indications that are reimbursed (i.e., [^{13}N]ammonia, [^{82}Rb], and FDG) are very restrictive. A tracer, such as sodium fluoride F-18 injection has a HCPCS code for bone scanning (A9580), but is still not reimbursed by CMS[6]. The levels of reimbursement for PET studies have continually declined in the face of increasing costs for manpower, equipment, and regulatory compliance. The potential for expanded reimbursed oncologic indications bodes well for increased numbers of studies, hopefully, sustaining "bottom lines" for PET Centers.

Prospects for the future

The prospects for the future of PET reflect the theme of this lesson – two steps forward, one step back – but that possibly is too pessimistic. Maybe, the math is more akin to three or four steps forward for each step back, but it is definitely a path forward. What is certain is that there will be a greater burden for regulatory compliance and under the current economic conditions, lower reimbursement on a per study basis. Economies of scale may help to relieve the financial squeeze imposed by these factors. New hybrid modalities such as PET/MRI and specialty scanners will enter the market. As evidence continues to grow that PET has the potential to positively influence medical management decisions, the "cost-effectiveness" may offset the "cost" considerations in the control of healthcare spending equation. A new type of drug approval path may be forged by the efforts of professional organizations such as the Society of Nuclear Medicine (SNM) to create multicenter INDs and clinical trials leading to new tracers available for use in meeting the diagnostic, staging and therapeutic monitoring needs of not only cancer but other devastating conditions such as Alzheimer's disease. Commercial entities will find markets for PET radiopharmaceuticals with shelf-life potential such as fluorinated compounds or agents labeled with other long-lived positron emitters such as [^{68}Ga] or [^{124}I]. First and foremost, the PET world needs to remember its roots. The UIPIC, as did the majority of pioneering PET Centers, started as research centers with clinical care an important but secondary objective. The flexibility inherent in positron emission tomography radiopharmaceuticals makes this the premier modality for bringing the promise of molecular imaging to fruition and this promise is the brightest future.

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ASSESSMENT QUESTIONS

1. The following statements regarding current Medicare reimbursement for PET scans is true except

    a) The cost of the PET radiopharmaceutical is bundled with the cost of the procedure.
    b) The reimbursement for studies performed on a PET only scanner is lower than that for a PET/CT scanner.
    c) Reimbursement is limited to specific oncologic, neurologic and cardiology indications only.
    d) The level of reimbursement has progressively decreased over the last few years.
    e) Although [18F]sodium fluoride bone scans have a HCPCS code, this study is not covered by CMS.

2. USP Monographs for PET radiopharmaceuticals are currently available for all of the following agents except

    a) [^{18}F]Fludeoxyglucose
    b) [^{11}C]Acetate
    c) [^{18}F]Fluorothymidine
    d) [^{15}O]Water
    e) [^{11}C]Flumazenil

3. PET scanners have changed significantly with respect to

    a) FOV
    b) Number of slices
    c) Transaxial resolution
    d) Slice spacing
    e) All of the above.

4. NOPR (National Oncology Patient Registry) was established to

    a) Maintain a registry of patients who were imaged with PET in order to monitor them for long-term toxicities to the anti-metabolite, FDG.
    b) Examine the demographics of patients who were imaged with PET in order to determine whether changes are occurring in the incidence and prevalence of cancer.
    c) Collect and analyze data on the utility of PET FDG studies in conditionally covered cancers and indications.
    d) Examine the use of PET in non-Medicare eligible patients.

5. Studies performed on 3D PET/CT scanners compared to PET-only scanners

    a) Will involve significantly larger radiation doses to the patient from the attenuation correction CT scan than from a [68Ge]-based transmission imaging.
    b) Will require higher doses of radiopharmaceuticals to achieve equivalent count-statistics because of reduced sensitivity of the LSO scanner.
    c) Will have a smaller field-of-view (FOV) because of the space requirements of the CT tube.
    d) Will have a poorer transaxial resolution because of the requirements for septa in the scanner gantry.

6. Trends in PET over the past two decades involve all of the following except

    a) Increased numbers and skill-mix of personnel required to operate an imaging center.
    b) Increased numbers of clinical studies performed and their associated revenue.
    c) Increased numbers of papers appearing in the medical literature.
    d) Increased reimbursement rates on a per study basis.
    e) Increased numbers of commercial entities distributing PET radiopharmaceuticals commercially.