Technology Assessment Program

Report No. 10

Positron Emission Tomography

Descriptive Analysis of Experience with PET in VA

A Systematic Review Update of FDG-PET as a Diagnostic Test in Cancer and Alzheimer's Disease

Authors: Elizabeth Adams, R.R.T., M.P.H., *Management & Program Analyst*
Karen Flynn, D.D.S., M.S., *Manager, MDRC Technology Assessment Program*

Contributors: Elaine Alligood, M.L.S., *MDRC Information Center Librarian*
Jennifer Cheslog, *MDRC Data Assistant*

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Technology Assessment Program
Management Decision and Research Center (152M)
Health Services Research and Development Service
Office of Research and Development
VA Medical Center
150 South Huntington Avenue
Boston, MA 02130

Tel: (617) 278-4469 FTS: (700) 839-4469 Fax: (617) 278-4438
Elizabeth.Adams@med.va.gov
g.mdrc-ta@forum.va.gov

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Valerie A. Lawrence, M.D.	Medical Consultant, MDRC TA Program Associate Professor, Dept of Medicine University of Texas Health Science Center Audie L. Murphy VA Medical Center San Antonio, Texas
Dr. Matthias Perleth, MPH	Dept. of Epidemiology, Social Medicine and Health System Research Hannover Medical School Hannover Germany
David Hailey, M.D.	Director, Health Technology Assessment Unit Alberta Heritage Foundation for Medical Research Edmonton, Alberta Canada
Paula Corabian	Research Associate, Health Technology Assessment Unit Alberta Heritage Foundation for Medical Research Edmonton, Alberta Canada
Mitchell Burken, M.D.	Medical Officer Coverage and Analysis Group Office of Clinical Standards and Quality Health Care Financing Administration Baltimore, Maryland
Ron Milhorn	Senior Health Insurance Specialist Coverage and Analysis Group Office of Clinical Standards and Quality Health Care Financing Administration Baltimore, Maryland
Captain R.K. Leedham, Jr., R.Ph., M.S., BCNP	Chief Project Management Staff Division of Medical Imaging and Radiopharmaceuticals Center for Drug Evaluation and Research Food and Drug Administration
David Pfister, M.D	Associate Attending Physician Memorial Sloan-Kettering Hospital Associate Professor of Medicine Cornell University Medical College New York, New York
M. Elizabeth Glenn, M.D.	Radiologist Women's Health Center

	Memphis, Tennessee
Lisa Hammond, M.D.	Clinical Investigator, Institute for Drug Development Cancer Therapy and Research Center San Antonio Cancer Institute Staff Oncologist Audie L. Murphy VA Medical Center San Antonio, Texas
James K. Stoller, M.D.	Vice Chairman, Division of Medicine Head, Section of Respiratory Therapy Dept. of Pulmonary and Critical Care Medicine The Cleveland Clinic Foundation Cleveland, Ohio
Dawn Provenzale, M.D.	Director, GI Outcomes Research Duke University Medical Center Senior Research Associate Center for Health Services Research in Primary Care VA Medical Center Durham, North Carolina
Ladislav Volicer, M.D., Ph.D.	Professor of Pharmacology and Psychiatry Boston University School of Medicine Clinical Director/GRECC VA Medical Center Bedford, Massachusetts

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Positron Emission Tomography

PREFACE

The Veterans Health Administration (VHA) has 10 positron emission tomography (PET) imaging facilities and shares ownership and operations with some of its academic affiliates and one with the Department of Defense. Significant resource commitments are associated with the acquisition and operation of these facilities.

In 1996, the MDRC Technology Assessment Program produced a technology assessment report in response to a request from the Office of the Under Secretary for Health for information on VHA's experience with PET. The Advisory Committee for the project provided guidance on the scope and content of the report. The assessment reported the results of: 1) systematic reviews of clinical applications of PET using 2-[F-18]-2-deoxy-D-glucose (FDG) in selected cancers (head and neck, lung cancer staging, solitary pulmonary nodules, breast, and colorectal) and Alzheimer's disease, representing conditions of importance to the veteran population, and 2) surveys of and site visits to VHA PET Centers on PET utilization, center operations, and research activities.

The MDRC found that research into the clinical utility of PET for the selected oncology conditions was in its preliminary stages. Methodological weaknesses in the published literature seriously limited the validity of the available evidence on the accuracy of PET as a diagnostic test, and PET's contribution to improving outcomes had not been systematically assessed. The lack of epidemiological information in these studies made extrapolation of study results to defined VHA populations, and subsequent planning for these populations, difficult.

PET is an accurate diagnostic test for dementia of the Alzheimer's type. Studies to determine whether this accuracy extends to confirmed Alzheimer's disease are under way in Europe. Nonetheless, lack of valid estimates of the positive predictive value of PET, parallel developments in other tests, and limited treatment options for Alzheimer's disease argue for continued use of PET primarily as a research tool. ***Accordingly, the evidence as of September 1996 did not support widespread incorporation of PET studies into routine diagnostic strategies for the applications included in the assessment.***

The site visits and surveys confirmed that VHA has made a substantial resource commitment to its PET facilities and that VHA researchers regard PET as an important research tool. Site investigators identified a wide range of research and clinical activities in VHA PET centers, but noted that these activities remained largely uncoordinated. ***The MDRC concluded that VHA should maximize the value of its existing commitment, rather than establish additional PET centers.*** *This could include:*

- *coordinating activities of VHA PET facilities and their academic affiliates to comply with FDA regulations, to identify research areas of interest to VHA, and to design multi-center studies of high methodologic quality;*
- *implementing a VHA PET registry for systematic data collection and for tracking the utility of PET in selected conditions;*
- *supporting rigorous, prospectively designed clinical research that expands the body of PET literature in a methodologically sound manner; and*
- *submitting currently unpublished data from studies of high methodological quality for peer review.*

Positron Emission Tomography
1998 Update

EXECUTIVE SUMMARY

Purpose
After the delivery of the original assessment report, the Under Secretary for Health directed the Office of Patient Care Services to implement the assessment recommendations. VHA PET centers collaborated on the design of the implementation process, which included initiating a multi-center VHA PET registry, supporting prospective research, and this updated systematic review.

To produce this report the MDRC Technology Assessment (TA) Program surveyed VHA PET facilities, used registry data, and conducted systematic reviews of the published PET literature from September 1996 through December 1998 for selected cancers and Alzheimer's disease. This report includes studies using positron emitting coincidence imaging with the radiopharmaceutical FDG to study cellular glucose metabolism.

Background
PET is a minimally invasive nuclear medicine imaging modality that uses the principle of *coincidence detection* to measure biochemical processes within tissues. PET may complement or supplant other imaging modalities, such as radiography, computed tomography (CT), or magnetic resonance imaging (MRI), which rely on predominantly anatomic definitions of disease.

Conventional positron emission coincidence imaging is accomplished using cameras specifically designed, or "dedicated," for imaging positron-emitting radioisotopes. Dual-headed gamma cameras are being adapted for coincidence imaging positron emitters (called "camera-based PET") as a lower cost and more accessible alternative to dedicated PET. Both PET systems have whole body scanning capability.

Key Findings

Cost and Reimbursement
A dedicated PET system costs from $800,000 to $2.5 million, and a cyclotron costs from $1.2 million to $1.7 million, in addition to the costs of installation, construction, and operation. Camera-based PET systems sell for about $850,000. Annual operating costs vary considerably. The charge for a PET scan will depend on these cost factors, as well as the clinical indication, the radiopharmaceutical used, and caseload.

Effective January 1, 1998 Medicare began offering interim provisional coverage for FDG-PET scans using either dedicated or camera-based PET for characterizing solitary pulmonary nodules and initial staging of suspected metastatic non-small cell lung cancer. On or after July 1, 1999 Medicare expanded coverage to include detecting and localizing recurrent colorectal cancer with a rising carcinoembryonic antigen, staging and characterizing Hodgkin's and non-Hodgkin's lymphoma in place of a gallium scan or lymphangiogram, and identifying metastases in melanoma recurrence in place of gallium studies.

The national average payment is $1,980 per scan, excluding the professional component. HCFA will collect and analyze claims data and data from other sources to determine the medical effectiveness of PET in managing these conditions, after which HCFA will decide the extent to which it should modify the coverage policy.

Regulation

Recent changes in FDA regulation now permit PET imaging facilities that manufacture radiopharmaceuticals on-site to continue in accordance with the positron emission compounding standards and the official monographs of the United States Pharmacopoeia. FDA has either approved or cleared for marketing both PET systems to image radionuclides in the body.

Experience in VHA

- VHA continues its moratorium on adding more dedicated PET facilities within the system. Many VA medical centers are modifying dual-headed gamma cameras for coincidence detection.
- A survey of active funded research at VHA PET sites underscores the importance of PET as a basic research tool. Most of the research is in neurology and cardiology and is funded by a range of private and public VA and non-VA sources.
- There has been an increase in the number of diagnostic PET scans, particularly in oncology. Lung cancer staging was the most common oncology indication among VHA PET sites in FY 1998.
- VHA is maximizing its investment in PET by developing a PET registry to collect critical patient information, funding rigorous, prospectively designed clinical research, and tracking the published peer-reviewed PET literature available in the public domain.
- The MDRC TA Program is coordinating a joint project with other members of the International Network of Agencies for Health Technology Assessment (INAHTA) to produce a report on the use of PET among countries represented by INAHTA members.

Evidence of effectiveness

The existing evidence argues against routine clinical use of PET for diagnosing Alzheimer's disease until more effective treatments and risk modification interventions for Alzheimer's disease are developed, and until meaningful and robust predictive values are obtained from an ongoing European multicenter PET study. The systematic reviews indicate that the data supporting the use of either dedicated or camera-based PET system with FDG in managing patients with selected cancers are deficient.

- The evidence for using camera-based PET in oncology is limited to one small preliminary study in the tertiary-care setting, comparing camera-based PET to dedicated PET using no suitable reference standard. Accordingly, it did not meet the inclusion criteria for this review.
- Included studies assessed dedicated PET as a complement to or replacement for anatomic imaging modalities, as a noninvasive alternative to invasive procedures, or as a method for increasing the diagnostic certainty for performing an invasive procedure. Studies focused on the technical feasibility of using dedicated PET and on defining diagnostic accuracy in the tertiary care setting.

- Studies generally enrolled highly selected patients and failed to adequately describe the previous work up or the size or composition of the referral base from which the patient sample was drawn. All had at least one of the methodologic biases often found in diagnostic imaging test evaluations, and their presence will tend to inflate estimates of diagnostic accuracy. Methods for defining disease on PET imaging have not been standardized and may limit the generalizability of findings across institutions.
- The few studies reporting the influence of PET on changes in diagnostic certainty and/or treatment planning were usually retrospective case series that were not originally designed to document these changes and were not systematically conducted or reported as such. Some authors used likelihood ratios and predictive values to define PET's clinical usefulness, but proper interpretation of these estimates is conditioned on what was known about the patient before the test and on deriving PET results independently of other test results. None of the studies met both conditions, and the influence of PET on diagnostic certainty and subsequent treatment planning could not be determined.

Conclusions/Recommendations

- VHA continues its commitment to delivering high quality patient care and to rational resource management through its support of VHA PET centers, carefully appraising the PET literature to identify areas in need of research, and funding rigorous, prospective clinical research.
- The prevailing evidence does not support the use of either dedicated or modified camera-based PET as a diagnostic test for the applications in this review. The TA Program identified several methodologically rigorous studies of other diagnostic imaging modalities that could serve as models for designing higher quality PET research.
- Systematic reviews from other technology assessment agencies, which used methods similar to VHA's, derived similar conclusions. As in VHA, patients with cancer constitute a considerable burden to the health systems represented by these agencies, and there is growing support for assessing either PET modality in the work up of these patients. Accordingly, agencies identified the uses for PET in oncology, particularly staging non-small cell lung cancer, as major topics for research.
- Several cooperative trials, including a VHA Cooperative Study of PET in solitary pulmonary nodules, are ongoing or planned. Clinicians should await the results of these efforts before incorporating PET into routine diagnostic strategies.
- Individuals interested in clinical PET would benefit from an accessible central repository containing information on existing and proposed rigorously designed cooperative trials of PET. This source could help guide the diffusion of PET into clinical care, as its usefulness and contribution to improved patient outcomes are appropriately evaluated.

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I. INTRODUCTION

VHA is committed to improved quality of care and outcomes for veterans and to rational resource management. As health care decision making transitions from a rationale based on resources and opinions to a rationale based on evidence from research, VHA uses technology assessment (TA) processes and information to guide evidence-based decisions. Health Services Research and Development Service, through the Management Decision and Research Center (MDRC), produces and disseminates TA information in the form of systematic reviews of the literature. VHA uses these reviews to support clinical policy and focus on areas in need of further research.

For example, after delivery of the original MDRC PET technology assessment (Flynn, 1996), the Under Secretary for Health directed the Office of Patient Care Services to implement the assessment findings and recommendations. As a result, VHA continued its moratorium on adding more dedicated PET scanners to its system. A new VHA cooperative study incorporated study design suggestions from the initial assessment. VHA PET Center Directors were instrumental in designing the implementation strategies, which included initiating a multi-center VHA PET registry, completing a rigorous single-site outcome study, and updating the 1996 MDRC PET systematic review.

In this update, the MDRC used evidence-based medicine frameworks and methodology to produce systematic reviews of the peer-reviewed PET literature from September 1996 through December 1998. It reviews the performance of dedicated PET systems and gamma camera systems with coincidence detection capabilities in selected cancers of the head and neck, breast, and colo-rectum, lung cancer staging, solitary pulmonary nodules, as well as Alzheimer's disease. The report also contains:

- clinical and research experience across VHA PET facilities;
- VHA implementation strategies for recommendations made in the first report;
- ongoing multi-site clinical trials of PET for the indications reviewed in the report;
- findings and recommendations from reviews of PET conducted by other technology assessment agencies; and
- a description of an international collaboration studying PET use among countries represented by the collaboration.

II. DESCRIPTION OF TECHNOLOGY

A. Instrumentation

Positron Emission Tomography (PET) is a minimally invasive nuclear medicine imaging modality that uses radiopharmaceuticals to capture and measure biochemical processes within tissues. PET, like other nuclear medicine techniques, defines disease in terms of quantifiably abnormal regional chemistry. PET may complement other imaging modalities, such as radiography, computed tomography (CT), or magnetic resonance imaging (MRI), which rely on predominantly anatomic definitions of disease.

PET imaging employs radioactive isotopes that decay by emitting a positively charged electron, called a positron, from the nucleus. The positron collides with a negatively

charged electron resulting in two high energy (511 keV) photons that travel in opposite directions. PET uses the principle of *coincidence detection* to form the raw image. That is, radiation detectors are arranged in a ring around the patient to allow for simultaneous (coincidence) detection of the two photons. The exact site of origin is recorded, and a cross-sectional image is displayed.

Dedicated PET systems are optimized for high energy dual photon coincidence detection. Two modified forms of single photon emission computed tomography (SPECT) are now available for imaging positron emitters and may be a less costly alternative to dedicated PET (Jarrit and Acton, 1996):

- dual-headed SPECT cameras adapted for coincidence detection, called "camera-based" PET, or
- multi-headed SPECT cameras adapted with special collimators for high energy (511keV) photon absorption.

Both Jarrit and Acton (1996) and Coleman (1997) emphasized that neither modified SPECT system is optimized for clinical use, particularly in oncology. Lower sensitivity restricts their use to studies using isotopes with longer half-lives, and performance and cost data comparing either system to dedicated PET are limited. These authors caution against the premature use of these systems, which could be detrimental to the future acceptance of both dedicated PET and modified PET systems.

In light of recent federal regulatory changes (See Section 111-Regulation and Reimbursement) this report will address only dual-headed gamma cameras adapted for coincidence imaging ("camera-based" PET) and dedicated PET systems.

B. Radiopharmaceutical

The most widely used radiopharmaceutical in PET imaging is the cyclotron-produced FDG. FDG is a D-glucose analog used to study cellular glucose metabolism. Since many diagnostic PET studies rely on FDG, its availability is critical to a facility that wishes to conduct clinical studies using either dedicated or camera-based PET systems.

C. Data analysis

PET and other nuclear medicine image patterns represent spatial and temporal arrangements of the physiological or biochemical process under investigation. There are many ways to detect and compare these patterns such as visual analysis of metabolic patterns, region of interest (ROI) analysis where the regions are hand-drawn or placed (sometimes with coregistration with anatomic images), and neural networks. PET data may be managed by using absolute metabolic values or by normalizing to a reference value to generate metabolic ratios.

D. Potential roles for PET

Flynn (1996) summarized the general rationale for the use of PET in oncology. PET may detect abnormalities in tissue biochemical and physiological processes caused by many forms of cancer. Reliance on tumor histology and anatomy limits the oncologist's tools

for selecting optimal treatment, and adding metabolic data from PET may expand the oncologist's ability to optimize treatment. Finally, monitoring metabolic responses to treatment could allow early redirection of therapy. Several potential applications for PET in oncology were noted:

- Detecting tumors (which may employ coregistration techniques that combine PET and anatomic imaging into a single image);
- Staging (particularly using whole-body imaging methods) although there is a lower limit to the size of metastases that can be detected by PET;
- Detecting local disease recurrence, since anatomically-based imaging is often limited by the effects of treatment;
- Predicting tumor response to chemotherapy; and
- Monitoring treatment.

Studies of Alzheimer's disease and other neurologic and psychiatric conditions predate studies of PET for other diagnostic applications and are prevalent in the PET literature. PET allows qualitative and quantitative evaluation of cerebral physiology and exploration of the biochemical bases for clinical diseases. FDG PET brain studies have been used for many research and clinical purposes related to the central nervous system. These include (Hoffman, 1993):

- defining the magnitude and distribution of normal local cerebral glucose metabolism, and the effects of age and sex on metabolism;
- locating seizure foci in patients with partial complex seizures who are potential surgical candidates for temporal lobectomy;
- assessing brain tumors for degree of malignancy at diagnosis, persistent post operative tumor, differentiating high- from low-grade tumors and radiation necrosis from persistent tumor;
- evaluating schizophrenia, affective disorders, obsessive-compulsive disorder;
- studying cerebral metabolism in cerebrovascular disease; and
- defining regions of altered glucose metabolism in various forms of dementia such as Alzheimer's disease, Pick's disease, and Huntington's disease.

Expanded roles for PET in selected applications will be discussed in Section VIII Published Findings for each application.

III. REGULATION AND REIMBURSEMENT

A. The Food and Drug Administration (FDA)

FDA has either approved or cleared for marketing dedicated PET scanners and coincident imaging gamma cameras to image radionuclides in the body. To date, the FDA has approved two PET radiopharmaceuticals for clinical use:

- Rubidium (^{82}Rb), limited to rest alone or rest with pharmacologic stress PET scans, is used for noninvasive imaging of the perfusion of the heart for the diagnosis and management of patients with known or suspected coronary artery disease.

- FDG indicated for identifying regions of abnormal glucose hypometabolism associated with foci of epileptic seizure. Approval for use is restricted to The Methodist Medical Center in Peoria, Illinois.

In the Food and Drug Modernization Act, which was signed into law on November 21, 1997, Congress directed the FDA to develop new approval procedures and appropriate current good manufacturing practice requirements for PET drug products. FDA may not require the submission of new or abbreviated new drug applications for PET drug products, which are not adulterated, for a period of 4 years after the date of enactment of the Modernization Act or for 2 years after FDA develops the new procedures, whichever is longer. FDA has begun developing these procedures.

In the meantime, PET drug products may be manufactured for clinical use providing they are produced in accordance with the positron emission compounding standards and the official monographs of the United States Pharmacopoeia. These standards are to assure that PET drug products are safe and have the identity, strength, quality, and purity that they are represented to possess.

B. Health Care Financing Administration (HCFA) and Medicare

A health technology review conducted by the Center for Practice and Technology Assessment (formerly the Office of Health Technology Assessment), Agency for Health Care Policy and Research (1998) provided the basis for Medicare's first coverage policy for PET scans performed on or after March 14, 1995 (HCFA, AB972760):

- PET scans using Rubidium (^{82}Rb), done at rest or with pharmacological stress, for noninvasive imaging of the perfusion of the heart for the diagnosis and management of patients with known or suspected coronary artery disease. Coverage is limited to PET scans used in place of SPECT or following an inconclusive SPECT scan, which provide information deemed necessary to determine treatment intervention.

In an agreement with the Chairman of the Senate Appropriations Committee in late 1997, the Secretary of Health and Human Services committed to expanding Medicare coverage of PET scans on an interim basis to include diagnosing solitary pulmonary nodules and initial lung cancer staging (Stevens, 1997). Effective January 1, 1998, FDG-PET scans will be covered when performed using either dedicated or camera-based PET system to image radionuclides in the body for the following conditions (HCFA, 3b4120):

- characterizing solitary pulmonary nodules (SPNs) for the primary purpose of determining the likelihood of malignancy to plan treatment. Coverage is limited to claims that include evidence of the initial detection of a primary lung tumor, usually by CT.

- initial staging of suspected metastatic non-small cell lung cancer in thoracic (mediastinal) lymph nodes in patients with pathologically confirmed primary lung tumor, but whose extent of disease has not yet been established. Coverage is limited to claims that include evidence of confirmed primary tumor, concurrent CT, and follow-up lymph node biopsy.

The use of routine biopsy following a negative PET scan is considered inappropriate in these conditions, and payment for biopsy will be denied unless the claim is supported by evidence explaining the medical necessity of the biopsy.

After an expedited review of scientific information presented at a town hall meeting in January 20-21, 1999, HCFA agreed to expand coverage for PET scans performed on or after July 1, 1999 to diagnose and manage the following three indications:

- detecting and localizing recurrent colorectal cancer with rising carcinoembryonic antigen (CEA);
- staging and characterizing both Hodgkin's and non-Hodgkin's lymphoma in place of a gallium scan or lymphangiogram; and
- identifying metastases in melanoma recurrence in place of gallium studies prior to surgery.

Table 1: Pricing of New PET Scan Indications Approved by HCFA*

HCPCS Codes	Description	National Average Payment for Technical Component**
G0125	PET lung imaging of solitary pulmonary nodules using FDG, following CT	$1,980
G0126	PET lung imaging for initial staging of solitary pulmonary nodules using FDG, following CT or of pathologically diagnosed non-small cell lung cancer	$1,980
G0163	PET, whole body, for recurrence of colorectal or colorectal metastatic cancer	$1,980
G0164	PET, whole body, for staging and characterizing lymphoma	$1,980
G0165	PET, whole body, for recurrence of melanoma or melanoma metastatic cancer	$1,980

*From www.hcfa.gov/pubforms/14%5Fcar/3b4120.htm
**technical component only, including payment for radiotracer, using revenue code 404. Claims for professional component should user modifier 26.

Medicare coverage is conditioned on the ability of PET to affect the management and treatment of patients with these cancers. HCFA will collect and analyze claims data, and data from other sources, to determine the medical effectiveness of PET in managing these conditions. After sufficient claims data have been collected, HCFA will decide the extent to which it should modify the coverage policy.

IV. ACCESS AND COST

The Institute for Clinical PET (1999) reports that there are nearly 147 facilities with coincidence detection capability in the United States. There are 10 dedicated PET facilities in the VHA system, making VHA one of the largest owners of dedicated PET scanners by any single health system in the world.

ECRI (1996) reports that the cost of a PET scanner ranges from $800,000 to $2.5 million, excluding costs associated with installation, construction, and operation, and a cyclotron costs from $1.2 million to $1.7 million. Annual operating costs vary considerably and may include personnel salaries, scanner and cyclotron supplies, service and maintenance contracts, equipment amortization, and other indirect costs. Ultimately, what a PET facility charges for a PET scan will depend on these factors, as well as the clinical indication, the radiopharmaceutical used, and caseload (Flynn, 1996).

Currently, there is a moratorium on adding PET facilities in VHA. Many VHA medical centers without access to PET facilities are adapting gamma cameras for coincidence imaging. The cost of upgrading dual-headed gamma cameras for coincidence imaging is approximately $250,000; dual-headed gamma cameras without the upgrade sells for about $600,000 (ECRI, 1996).

V. EXPERIENCE IN VHA

Table 2 lists VHA PET (dedicated) sites and their sharing partners. In all but two sites, both the camera and cyclotron are in the same location. However, ownership of the camera and cyclotron varies across sites (Flynn, 1996). All sites have access to FDG.

Table 2: VHA PET Facilities and Sharing Partners

VHA PET Facility	VISN	Facility Location	Sharing Partner
VA Connecticut Health Care System VAMC West Haven, Connecticut	1	VAMC	Yale University
VA West New York Health Care System VAMC Buffalo, New York	2	VAMC (cyclotron at sharing partner)	State University of New York at Buffalo
VA Pittsburgh Health Care System VAMC Pittsburgh, Pennsylvania	4	Sharing Partner	UPMC Health Systems- Presbyterian
Richard L. Roudabush VAMC Indianapolis, Indiana	11	Sharing partner	Indiana University
VAMC Ann Arbor, Michigan	11	Sharing Partner	University of Michigan Ann Arbor
VAMC Minneapolis, Minnesota	13	VAMC	None
St. Louis VA Medical Center St. Louis, Missouri	15	Sharing Partner	St. Louis University
VA South Texas Health Care System VAMC San Antonio, Texas	17	Sharing Partner-UTHSC	University of Texas Health Science Center
VA Palo Alto Health Care System VAMC Palo Alto, California	21	VAMC (no cyclotron, FDG purchased from private source)	None
VA Greater Los Angeles Healthcare System VAMC West Los Angeles, California	22	VAMC	Individual investigators

Research continues to constitute considerable activity conducted at VHA PET facilities. All VHA PET facilities were surveyed for a list of active funded research at their site. The results of this survey are listed in Appendix III. Most are multi-year studies with funding from a range of private and public VA and non-VA sponsors. The majority of funded PET research is for the study of neurologic conditions, followed by studies in cardiology.

The VA HSR&D Center for Practice Management and Outcomes Research, Office of Research and Development, provided FY 1998 utilization data from the VHA PET registry for the conditions in this report (See Table 3). Of the subjects that had radiopharmaceutical data available, nearly 70% were scanned using FDG, representing the radiopharmaceutical most often used across VHA PET sites.

Given the significant burden lung cancer represents in both the veteran and general populations, not surprisingly lung cancer was the major oncology diagnosis among VHA PET sites in FY 1998. Alzheimer's disease, colorectal cancer, and head and neck cancer have roughly equivalent numbers of veteran and non-veterans scanned, whereas non-veterans comprise a higher portion of subjects with breast cancer, as expected. The distribution of veterans and non-veterans within and across diagnoses may change as evidence of PET's clinical utility is clarified, or if reimbursement policies in either the public or private sector are altered.

Table 3: Diagnostic-specific Utilization Data Across VHA PET Facilities for FY 1998

Diagnosis	*# Veterans*	*# Non-veterans*	*Total (% of all neurology subjects)*
Alzheimer's disease	11	6	17 (3.4%)

Diagnosis	*# Veterans*	*# Non-veterans*	*Total (% of all oncology subjects)*
Lung cancer	246	192	438 (29.4%)*
Colorectal cancer	63	80	143 (9.5%)**
Breast cancer	1	34	35 (2.3%)
Head & neck cancer	58	52	110 (7.4%)

*excludes 8 patients with unknown veteran status
**excludes 2 patients with unknown veteran status

In the 1996 assessment, the TA Program recommended that VHA maximize the value derived from its existing commitment, rather than invest in additional PET centers, and suggested ways in which PET activities could be coordinated across the VHA system (See Preface). Since then, several suggestions have been implemented:

Develop and maintain a VHA PET registry

The VHA Office of Patient Care Services is providing recurring funding to the HSR&D Center for Practice Management and Outcomes Research in Ann Arbor, Michigan to develop and maintain a VHA PET registry. The Center is collecting annual facility utilization data and subject-specific data from all VHA PET facilities.

Support rigorous, prospectively designed clinical research

- The VHA Office of Patient Care Services is providing funding to the VHA Cooperative Studies Center and to the PET Center in West Haven, Connecticut to complete an outcome analysis. The study addresses clinical utility, cost, utilization of other diagnostic studies, and the impact of PET on treatment planning.

- VHA Cooperative Studies Program is funding a multi-year cooperative trial to evaluate the clinical utility of PET in characterizing solitary pulmonary nodules (See Appendix III, St. Louis). The Palo Alto Cooperative Studies Coordinating Center is monitoring the study. Six VHA PET sites and four non-VHA PET sites with VA affiliation are participating. Patient accrual started in August, 1998.

Results from these studies should clarify the evidence on the utility of FDG-PET in the management of patients with selected clinical conditions.

Conduct regular updates of the PET literature

The VHA Office of Patient Care Services also agreed to fund regular systematic review updates of the 1996 MDRC PET Technology Assessment.

VI. METHODS FOR THE SYSTEMATIC REVIEW

Information about the value of PET scanning in selected cancers and Alzheimer's disease was obtained by conducting a ***systematic review*** of the published literature. A systematic review uses a scientific approach to limit bias and to improve the accuracy of conclusions based on the available data. A systematic review addresses a focused clinical question, uses appropriate and explicit criteria to select studies for inclusion, conducts a comprehensive search, and appraises the validity of the individual studies in a reproducible manner. With respect to the diagnostic test literature, the point of a systematic review can be to examine the ultimate value or benefit derived from the test (Guyatt, 1995).

The MDRC uses a review protocol to guide the inclusion, analysis, and summary of evidence for this review (See Table 4 and Appendix 1). The protocol uses three analytic frameworks to appraise the literature, ensuring that studies are evaluated in a consistent, reproducible manner, and that studies included in the report conform to established scientific standards. These frameworks are critical to understanding the report analysis, conclusions, and recommendations.

Assign to Fryback and Thornbury hierarchical model of diagnostic efficacy

Fryback and Thornbury (1991) note that the localized view of the goal of diagnostic radiology would be that it provides the best images and the most accurate diagnoses possible. A more global view recognizes diagnostic radiology as part of a larger system of medical care whose goal is to treat patients effectively and efficiently. Viewed in this larger context, even high-quality images may not contribute to improved care in some instances, and images of lesser quality may be of great value in others.

Fryback and Thornbury (1991; 1992) present an evolving hierarchical model for assessing the efficacy of diagnostic imaging procedures. Their model, with a list of the types of measures that appear in the literature at each level in the hierarchy, is presented in Appendix I. Using this model, it is possible to follow the development of a diagnostic technology and to align current research efforts with a particular level of development.

Assess the quality of individual studies of diagnostic tests using evidence-based medicine criteria

This assessment has adopted evidence-based medicine criteria as a requirement for assignment of studies to the "diagnostic accuracy" level of the hierarchy. These criteria will be applied to individual studies in the report. If the criteria are not met, the study will generally be considered insufficiently rigorous to provide the basis for patient care decisions. However, such studies often provide useful information on the technical characteristics of a diagnostic test or may provide information necessary to subsequent diagnostic accuracy studies.

Evaluate the strength of the evidence supporting a causal link between the use of the technology and improved outcomes of care

Recommendations about the use of a technology should be linked to the quality of the available evidence, which ultimately depends on the strength of the evidence. The strength of the evidence relates to the overall research design and to the quality of the

implementation and analysis, i.e. how well bias and confounding factors are controlled in the design and conduct of a study. Attributes that strengthen the validity of findings include: ***randomized*** (vs. nonrandomized), ***controlled*** (vs. uncontrolled), ***blinded*** (vs. unblinded), ***prospective*** (vs. retrospective), ***large*** (vs. small), ***multi-site*** (vs. single site), and ***contemporaneous*** (vs. historical) ***controls.***

Table 4: Systematic Review Protocol

1) Conduct search of MEDLINE and other databases. Also search end references from retrieved articles and listings of English language, public domain technology assessments.

2) Apply inclusion criteria to search:
   - English language articles reporting primary data and published in a peer review journal (not abstracts)
   - studies $\geq$ 12 human subjects (not animal studies) with the disease of interest
   - studies using dedicated PET systems or gamma camera systems adapted with 511 keV coincidence imaging capability
   - studies using the radiopharmaceutical 2-[^{18}F]fluoro-2-D-glucose (FDG)
   - study not duplicated or superseded by subsequent study with the same purpose from the same institution
   - study design and methods clearly described (i.e. sufficient information to judge comparability of case and control groups, details of imaging protocol, whether visual or quantitative analysis of PET data used, or type of PET quantitative data analysis used)

3) Retrieve full text articles meeting inclusion criteria.

4) Review full text articles and assign to level of Fryback and Thornbury (1991) diagnostic efficacy hierarchy.

5) To assess methodologic quality, apply evidence based medicine criteria to studies of diagnostic tests:
   - clearly identified comparison groups, $\geq$ 1 of which is free of the target disorder.
   - either an objective diagnostic standard (e.g. a machine-produced laboratory result) or a contemporary clinical diagnostic standard (e.g. a venogram for deep venous thrombosis) with demonstrably reproducible criteria for any subjectively interpreted component (e.g., report of better-than-chance agreement among interpreters).
   - interpretation of the test without knowledge of the diagnostic standard result (no test review bias).
   - interpretation of the diagnostic standard without knowledge of the test result (no diagnostic review bias).

6) To further refine judgment of methodological quality, grade **diagnostic accuracy or thinking efficacy** studies:
   Grade A- Studies with broad generalizability to a variety of patients and no significant flaws in research methods
   Grade B- Studies with a narrower spectrum of generalizability, and with only a few flaws that are well described (and impact on conclusions can be assessed)
   Grade C- Studies with several methods flaws, small sample sizes, incomplete reporting or retrospective studies of diagnostic accuracy
   Grade D- Studies with multiple flaws in methods, no credible reference standard for diagnosis, evidence of work up, test review, or diagnostic review bias, or opinions without substantiating data

7) Evaluate quality of studies at each efficacy level; conduct meta analyses if appropriate.
8) Rank the evidence for the degree to which it supports a causal link between technology use and improved outcomes.

Modifications made to the grading system accounted for the degree to which bias could be reasonably minimized in the study design, given the nature of the clinical work up. More