

The value of improved diagnostic information to AD patients and their families should not be dismissed; however, this value should be quantified in the context of accessibility and accuracy of alternative imaging technologies and of phenotypically or genetically defined subsets of AD. In the absence of effective treatments for AD, an accurate diagnostic test may be needed primarily in research for epidemiologic studies and evaluations of potential therapies.

IX. ONGOING CLINICAL STUDIES AND ON-LINE RESOURCES

Several on-line sources provide useful information about ongoing clinical trials:

- CenterWatch™ Clinical Trials Listing Service [<http://www.centerwatch.com>]
- NIH Clinical Research Studies [<http://clinicalstudies.info.nih.gov/>]
- NCI cancerTrials™ PDQ® database search [<http://cancertrials.nci.nih.gov/>]

These on-line sources were searched in November 1998 for active clinical trials studying the efficacy of FDG PET. Thirty-eight active protocols using FDG PET were retrieved, of which the following six protocols are assessing diagnostic PET for the conditions reviewed in this report.

Table 19: Active NIH Trials of FDG PET in Selected Cancers and Alzheimer's Disease

PROTOCOL	COMMENTS
NCI-94-C-0151 Diagnostic study of PET in patients with stage II-IV or recurrent breast cancer Single-site	Sponsor- NCI Start date 1994 Active accrual for at least 3 years
MSKCC-97046, NCI-G97-1308 Comparison of positron emitter Iodine I ²⁴ Iododeoxyuridine with fludeoxyglucose F 18 (F-18-Fluoro-2-Deoxy-(D)-Glucose) as a tracer for glycolysis on scans and in tumor samples in patients with advanced breast cancer Single site	Sponsor- local funding * Start date (1997) Active accrual for about 1 year
NCI-97-C-0068 Phase II study of Anti-CEA antibody immunoscintigraphy and PET in the localization of recurrent colorectal carcinoma in patients with rising serum CEA levels in the absence of imageable disease by conventional modalities Single site	Sponsor- NCI Start date (1997) Active accrual for 3 years
MSKCC-96079, NCI-G97-1334 Phase II/III Diagnostic Study of Whole Body PET to measure the response to induction chemotherapy of potentially resectable lung and esophageal carcinomas Single site	Sponsor- local funding * Start date (1997) Active accrual open
NCI-98-C-0163 The use of PET and MRI to assess the effects of anti-neoplastic therapy on tumor associated vasculature Unknown	Sponsor- NCI Start date 1998 Accrual pending
81-N-0010 Study of regional cerebral utilization of glucose in organic dementia and Down syndrome by the Laboratory of Neurosciences of The National Institute on Aging Unknown	Sponsor- National Institute of Neurological Disorders and Stroke (NINDS) Start date 1981 Active accrual

* Personal communication: Dr. Steven Larson, Memorial Sloan Kettering Cancer Center, New York

Since there is no central repository for locating active clinical trials of PET, these sources may not provide a complete listing of all multi-site studies evaluating PET as a clinical test.

Consequently, individuals actively involved in the use and evaluation of PET were queried for their knowledge of other relevant cooperative trials.

- NCI is funding a multi-center trial of FDG PET in staging **breast cancer**. The primary goal is to assess the accuracy of PET for detecting the presence, absence, and extent of axillary nodal metastases in women with newly diagnosed breast cancer; a secondary endpoint will evaluate PET for detecting internal mammary nodal disease as a prognostic indicator (personal communication: Dr. Barry Siegel, Washington University, St. Louis, Missouri).
- NCI is sponsoring a new cooperative group within the American College of Surgeons called the American College of Surgeons Oncology Group (ACoSOG) (NIH, 1998). The ACoSOG will design and conduct cooperative trials in surgical oncology. The primary goal of the ACoSOG is to evaluate surgical approaches for diagnosis and treatment of patients with malignant solid tumors. Patients with the most common cancers of the breast, lung, and colo-rectum will be studied initially. Completion of two protocols comparing the incremental value of PET to conventional staging in potentially operable patients with **lung cancer** and esophageal cancer is imminent (personal communication: Dr. Barry Siegel).
- The Southwest Oncology Group (SWOG) is developing a companion study within a Phase III cooperative trial comparing surgery and pre-operative chemotherapy for patients with **lung cancer**. The companion study will evaluate PET in assessing tumor response to chemotherapy. Both studies will be activated in 1999 (personal communication: Suzan Myers, SWOG).

X. OTHER SYSTEMATIC REVIEWS OF PET

Since 1996 several organizations have conducted assessments to support evidence-based recommendations for the use of PET as a diagnostic test (See Appendix V). The majority of assessments were qualitative systematic reviews of dedicated PET used in neurology to diagnose and manage patients with medically refractory partial seizures, central nervous system tumors, and cerebrovascular disease. Recent systematic reviews reflect an increasing interest in PET and in other positron imaging modalities to manage patients with non-central nervous system cancers, emphasizing staging non-small cell lung cancer.

For the indications in this review, the findings of assessments with either full text or abstracts in English in the public domain, or otherwise available to the MDRC, are summarized below:

- **There is general agreement that the evidence on FDG-PET for diagnosing, staging or monitoring treatment of primary cancers outside the lung is not firmly established.**
- **There is general agreement that the effect of PET on the management of patients with primary lung cancers is not known.**

The Agencia de Evaluación de Tecnologías Sanitarias (AETS) in Spain, the Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT) in France, and the NHS Health Technology Assessment Programme (NHS HTAP) in the United Kingdom recommend comparative studies of effectiveness and of the diagnostic contribution of

dedicated PET (and, in some cases, coincidence imaging gamma cameras) in patients with lung cancer.

- **Assessment findings and recommendations are mixed regarding the use of PET to diagnose and stage non-small cell lung cancer and solitary pulmonary nodules (SPNs).**

Two agencies, AETS and the NHS HTAP, used VA review methods and frameworks to update and/or expand the first VA PET report (Flynn, 1996). Both reports confirmed VA's original findings that the evidence for the diagnostic efficacy of PET in managing patients with lung cancer was insufficient. Blue Cross/Blue Shield Association found that FDG-PET imaging meet their quality assessment criteria for staging mediastinal lymph nodes and characterizing radiographically indeterminate SPNs, provided the test results could change medical management (HCFA, 1997).

An ECRI quantitative analysis determined that for both lung cancer indications PET is cost-effective when used to confirm resectability, but that PET is not cost-effective when used earlier in the diagnostic algorithm. A SPN strategy using CT for initial diagnosis, needle biopsy to confirm positive results, and PET to confirm negative results attained the greatest life expectancy (Mitchell, 1998).

There are several possible reasons for the discrepancies across these assessments. Variations in criteria for including published studies and for judging the quality of the included studies, in analytical methods, in the rationale for the assessment, and in the focus of the report are likely causes. Often, assessments must be purchased or may require language translation to be systematically evaluated. For this review, the MDRC considered information available only in the public domain in English or with English translation. Proprietary or non-translated reports may have derived different conclusions. Valid comparisons of technology assessments that address similar topics are critical to health care organizations wishing to establish policies based on the best available evidence.

Increasingly, agencies are using quantitative analyses, (e.g., decision analyses, meta-analyses, and cost-effectiveness analyses) to quantify the utility of clinical PET. Many analyses extrapolate existing diagnostic accuracy estimates to population impact, or pool accuracy results from multiple studies. It is important to note that the validity of the studies that are the source of these estimates is an essential consideration when evaluating the robustness of the results (Petitti, 1994).

- **Until recently, agencies considered only dedicated PET scanners, but now are asked to review other positron imaging modalities.**

An expert panel at CEDIT considered coincidence imaging gamma cameras and dedicated PET in their recommendations. The NHS HTAP report will include evaluations of partial ring PET, coincidence imaging gamma cameras, and collimated 511 keV imaging.

PET is a topic for a joint project of the International Network of Agencies for Health Technology Assessment (INAHTA), to which the TA Program belongs. The TA Program is coordinating the project with members from Spain and the Agency for Health Care Policy and Research. Member agencies are collaborating to synthesize their assessments of clinical PET applications into a

single, broadly applicable document. The report will also include a description of the evolution of PET use in the United States and current indications and coverage policies of PET among countries represented by INAHTA members. The report will be available in 1999 on the INAHTA web site at [<http://www.inahta.org>].

XI. CONCLUSIONS

A. Experience in VA

VHA continues to make a substantial resource commitment to its PET imaging facilities. This commitment has the potential to help support two parts of VHA's mission: research and clinical care. The medical community regards PET as an important basic research tool. A survey of active funded research at VHA PET sites underscores this importance, with the vast majority of basic research activity in neurology and cardiology. VHA is maximizing its investment in PET by supporting high quality outcomes research and systematic collection of utilization data.

All VHA PET sites have access to FDG, enabling them to conduct glucose metabolic studies for various clinical applications. The number of PET oncology studies conducted across VHA PET facilities from FY 1994 to FY 1998 has nearly quadrupled, likely reflecting the positive changes in Medicare and private sector reimbursement and changes in practitioners' attitudes. Since VHA continues its moratorium on adding dedicated PET centers to its system, many VA medical centers without access to dedicated PET scanners are adapting existing dual-headed gamma cameras for coincidence detection.

B. Systematic reviews

The prevailing evidence does not support the use of either dedicated or gamma cameras modified for coincidence detection (camera-based PET) as a diagnostic test for the applications in this review. All studies were subject to considerable bias, which will have resulted in overestimating accuracy and clinical value. Several studies presented anecdotal data on the influence of PET on changing diagnostic certainty and treatment planning, but the methods for assessing these changes were not described, and the systematic nature could not be determined.

Caution must be exercised to not apply accuracy estimates from dedicated PET to camera-based PET systems. Whereas dedicated PET scanners are limited primarily to tertiary care institutions, dual-headed gamma camera systems are more widely employed. Technical differences between the two systems and potential differences in the study populations represented across different health facilities emphasize the need for large, rigorous studies of diagnostic efficacy to define the clinical role of camera-based PET.

The TA Program identified several methodologically rigorous studies of other diagnostic imaging modalities that could serve as models for designing future PET research (Appendix II). Incorporating aspects from these studies would correct the methodologic shortcomings of the existing literature and strengthen the evidence on which to base future patient care decisions.

Qualitative systematic reviews produced by other technology assessment agencies, which used methods similar to the VA PET report, reached similar conclusions. Most agencies agree that the effect of positron imaging on managing patients with cancer needs further study. Several cooperative trials and other data collection efforts are ongoing or are being proposed that may address many unanswered questions regarding the utility of FDG PET in the work up of patients with cancer and Alzheimer's disease. **Clinicians should await the results of these efforts before incorporating PET into routine diagnostic strategies.** Nonetheless, variations across studies in study populations, imaging protocols, threshold values, and formulae for calculating quantitative uptake values may limit the generalizability of the findings to other institutions and populations. **Review of recent evidence confirms the conclusions from the original VA PET assessment (Flynn, 1996).**

Information on some of the cooperative trials can be accessed through on-line data sources. **Advocates of clinical PET and decision makers interested in its clinical utility 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.

XII. REFERENCES

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Head and Neck

Included Studies

Diagnostic Accuracy

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Breast Cancer**Included Studies****Diagnostic Accuracy**

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Lung Cancer

Included Studies

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SPN

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Diagnostic Accuracy

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Colorectal Cancer

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Alzheimer's Disease

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XIII. EPILOGUE

On January 28, 1999 the TA Program conducted a final update of the literature by searching the literature published from July 6, 1998 through December 31, 1998 using the same search and appraisal strategies described in Appendix 1. Titles and abstracts of 346 citations were screened. Forty-one were determined to be relevant, and their full text articles were reviewed for potential inclusion in the review.

Thirty articles from the database searches and from end references of initially retrieved articles met inclusion criteria for review. Each included study was classified according to clinical condition and assigned to a diagnostic efficacy level as follows:

Efficacy level*	Head & Neck	Breast	Lung staging	SPN	Colorectal	Alzheimer's
Technical	3	1	6	0	0	7*
Diagnostic accuracy	5	1	5**	1	0	0
Diagnostic thinking			†			
Therapeutic						
Patient outcome				1		
Societal						

*includes 6 overlapping studies from same institution

**includes 3 overlapping studies from same institution (Vansteenkiste, 1998a,b,c)

†diagnostic thinking data and diagnostic accuracy data provided from one study (Vansteenkiste, 1998a)

All of the studies represented are single-site case series. All studies used dedicated PET systems. PET was usually added in the work up to complement anatomic imaging data, and most were retrospective analyses.

As in the main report, recent studies of FDG PET in Alzheimer's disease explore the relationships between regional glucose metabolism and cognitive function and are classified as technical efficacy studies. Several studies of diagnostic PET in oncology met inclusion for review and could be classified at higher levels of diagnostic efficacy. Five studies in lung cancer staging, three from the same institution (Vansteenkiste, 1998a; 1998b; 1998c) were continuations of studies reviewed in the main report with overlapping study populations (Bury, 1998; Weder, 1998)

The diagnostic accuracy studies were further appraised for study quality and content. None of the studies met strict evidence-based medicine criteria for evaluations of diagnostic tests, as the extent of blinding was either not clearly reported or was incomplete. However, two met most of the criteria and had reasonably well reported and designed studies, despite their small sizes (Smith, 1998; Präuer, 1998). All studies used patients with no metastases or with benign diseases as internal controls, and all reported using an objective gold standard. Expanded criteria for methodologic quality of diagnostic accuracy studies used by the American College of Physicians yielded the following quality scores:

Table 20: Methodologic Quality of Diagnostic Accuracy Studies of FDG PET in Selected Cancers

Methodologic Quality Grade*	Head & Neck	Breast	Lung staging	SPN	Colorectal
A					
B					
C		1	3	1	
D	5		2		

Studies received overall quality scores of “D” if the presence of referral bias and methodologic biases related to the association between test interpretation and gold standard diagnosis were not minimized in the study. Studies received a “C” because of small study sizes, incomplete reporting of critical study design elements, and/or a study design that minimized the effect of methodologic biases. Several asserted the potential for PET to directly affect patient management, but this was not systematically assessed in any study.

Two studies were classified either as diagnostic thinking efficacy (Vansteenkiste, 1998a) or patient outcome efficacy (Gambhir, 1998). Expanding on their study reviewed in the main report, Vansteenkiste (1998a) used ROC analysis with PET to calculate optimal accuracy and likelihood ratios (LR) for estimating the probability of nodal metastases in 690 lymph node stations in 68 patients with non-small cell lung cancer. For their study population, a cut-off SUV of 4.40 provided optimal accuracy. Based on these data, the authors suggested that positive LRs for SUVs <3.5 or >4.5 offered high diagnostic value and recommended the following:

- The high negative predictive value of mediastinal CT+PET is sufficient to exclude N2/N3 disease, to exclude malignancy in individual node stations and, therefore, to omit invasive mediastinal staging.
- Despite the high positive predictive value of CT+PET, mediastinoscopy is still advised in patients with a positive mediastinal PET to ensure that no patient with N0 or N1 disease is denied curative resection based on a false positive PET.

LRs can vary with severity of disease in the case mix and positivity criteria (different threshold values) used for interpretation of both imaging tests. There were few benign conditions that may contribute to false positive diagnoses on CT and PET, and only four patients had confirmed N3 disease. The authors calculated positive LRs for both CT and quantitative PET but did not report the probability of nodal metastases before CT. In the absence of knowing the pre-test probability of malignancy, LRs are inconclusive for assessing the impact of the test on diagnosis or treatment planning, and these findings should be interpreted cautiously.

Gambhir (1998) conducted a cost-effectiveness analysis to compare various strategies for diagnosing and managing SPNs. Expanding on a decision analysis by Cummings (1986), the authors incorporated PET into a CT-based strategy for patients with noncalcified solitary pulmonary nodules < 3cm in diameter. They concluded that a CT-plus-PET strategy was the most cost-effective over a wide range of pre-CT probabilities of malignancy (0.12 to 0.69), and offered cost savings over the CT-alone strategy ranging from \$91 to \$2,200 per patient.

The assumptions upon which the analysis is based may affect the stability of the conclusions. PET sensitivity and specificity estimates were based on data from one abstract and biased estimates from three peer-reviewed studies, which were reviewed in the first VA PET report (Flynn, 1996). The model did not account for the possibility of an indeterminate PET scan. Payment and charge data used in the analysis may not adequately reflect true costs or be sufficiently comprehensive to reflect the true work-up of these patients.

The MDRC agrees with the authors' statement that "this analysis is not a substitute for clinical trials, but a guide to the design of clinical trials." The MDRC does not agree with the authors' statement that "there is significant savings when using a PET-based strategy. This warrants a more widespread dissemination of the technology." Given the preliminary nature of the assumptions, a more widespread dissemination of the technology based on the results of this cost-effectiveness analysis would be premature.

Conclusion

Recent studies from 1998 do not provide conclusive evidence to support the use of PET in the work up of patients with the cancers assessed in this report. Prospective, rigorously designed studies with a sufficient spectrum of patients are needed to assess the incremental value of PET in these patients. The impact of PET results on treatment planning has been alleged, but further research designed to assess impact on treatment management and associated costs is needed. The findings from recent 1998 studies confirm the conclusions and recommendations in the main report.

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Background

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Head and Neck

Included Studies

Diagnostic Accuracy

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Breast Cancer

Included Studies

Diagnostic Accuracy

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Technical Efficacy

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Lung Cancer

Included Studies

Diagnostic Accuracy

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Technical Efficacy

Ahuja V, Coleman RE, Herndon J, Patz EF, Jr. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with non-small cell lung carcinoma. *Cancer* 1998; 83(5): 918-924.

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Excluded Studies

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SPN**Included Studies****Diagnostic Accuracy**

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Patient Outcome Efficacy

Gambhir SS, Shepherd JE, Shah BD, Hart E, Hoh CK, Valk PE, et al. Analytical decision model for the cost-effective management of solitary pulmonary nodules. *J Clin Oncol* 1998; 16(6): 2113-2125.

Colorectal Cancer**Excluded Studies**

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Alzheimer's Disease**Included Studies****Technical Efficacy**

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