



**T e c h n o l o g y
A s s e s s m e n t
P r o g r a m**

Office of Patient Care Services

UPDATED INFORMATION FOR VA TECHNOLOGY ASSESSMENT PROGRAM (VATAP) REPORTS

In June 2000, VATAP was relocated within the Veterans Health Administration from the Office of Research & Development to the Office of Patient Care Services. The following report was produced prior to the relocation of VATAP.

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XIV. APPENDIX 1

Methods for the Systematic Review

The MDRC performed a *systematic review* of the published literature to address the diagnostic efficacy of PET in selected cancer applications and Alzheimer's disease. A systematic review differs from a traditional narrative literature review in that it uses a rigorous scientific approach to limit bias and to improve the accuracy of conclusions based on the available data (Guyatt, 1995). 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.

Consistent with established methods for conducting a systematic review, the MDRC developed criteria to select studies for inclusion, conducted a comprehensive search, and appraised the validity of the individual studies in a reproducible fashion using the analytic frameworks presented below.

Search Strategy

An update of the literature was carried out by thoroughly searching the literature published from September 1996 through July 6, 1998. MEDLINE®, HealthSTAR®, EMBASE®, Current Contents®, and BIOSIS® were searched using a range of descriptors: tomography, emission computed; positron emission tomography; gamma camera; PET; and other synonyms. These were combined with the descriptors for Alzheimer's, colorectal neoplasms, breast neoplasms, head and neck neoplasms, and lung neoplasms. Over 400 citations were retrieved.

Inclusion Criteria

All published studies included in this report met the following inclusion criteria:

- 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 positron emission transverse tomography or positron emission coincidence imaging;
- studies using the radiopharmaceutical 2-[¹⁸F]fluoro-2-D-glucose (FDG);
- study not duplicated or superseded by later study with the same purpose from the same institution; and
- 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).

Methodologic standards for studies

The purpose of appraising the literature using clearly defined methodologic criteria is to ensure that studies are evaluated in a consistent, reproducible manner, and that studies included in the report conform to established scientific standards. Studies reviewed for possible inclusion in this report were classified according to the strength of the evidence they provided, and the strongest available evidence for each application was summarized. The strength of a study is based on the overall research design and on the quality of the implementation and analysis. The methodologic standards and the types of studies to which they were applied are summarized below. The standards are also discussed in the MDRC report *Assessing Diagnostic Technologies* (Flynn, 1996).

1. Assign to level of diagnostic efficacy hierarchy

Accurate estimation of the characteristics of a diagnostic test is one of the early steps in the assessment of that test. However, a complete assessment requires further research.

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. The point of the systematic view may be to examine the ultimate value or benefit that is derived from any particular diagnostic examination.

Fryback and Thornbury (1991; 1992) present the most recent manifestation of 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 the next table. The table progresses from the micro, or local level, at which the concern is the physical imaging process itself, to the societal efficacy level. The model stipulates that for a procedure to be efficacious at a higher level in the hierarchy it must be efficacious at the lower levels, but the reverse is not true; this asymmetry is often lost in research reports at Levels 1 and 2. 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.

A Hierarchical Model of Efficacy for Diagnostic Imaging

Level	Typical Measures of Analysis	Comments
1. Technical efficacy	<ul style="list-style-type: none"> Resolution of line pairs Modulation transfer function Gray scale range Amount of mottle Sharpness 	<ul style="list-style-type: none"> Physical parameters describing technical imaging quality
2. Diagnostic accuracy efficacy	<ul style="list-style-type: none"> Yield of abnormal or normal diagnoses in a case series Diagnostic accuracy (% of correct diagnoses in case series) Sensitivity and specificity in a defined clinical setting Measures of ROC curve height (d') or area under the curve A_z 	<ul style="list-style-type: none"> Joint function of images and observer Also a function of clinician who requests diagnostic procedure, since selection controls specificity of test in clinical practice and sensitivity to the extent that it varies with the spectrum of the disease
3. Diagnostic thinking efficacy	<ul style="list-style-type: none"> Number (%) of cases in series in which image judged "helpful" to making diagnosis Entropy change in differential diagnosis probability distribution Difference in clinicians' subjectively estimated diagnosis probabilities pre-to posttest information Empirical subjective log-likelihood ratio for test positive and negative in a case series 	<ul style="list-style-type: none"> Inducing change in clinicians' diagnostic thinking is a necessary prerequisite to impact on patients. Clinicians may value results which reassure them, but which do not change treatment decisions. Empirical methods to measure change in pretest diagnostic probabilities assumed by clinicians are probably best for determining the absence of diagnostic thinking efficacy, rather than estimating the magnitude of change in diagnostic thinking due to imaging information. Imaging examination result may influence clinician's diagnostic thinking, but has no impact on patient treatment.
4. Therapeutic efficacy	<ul style="list-style-type: none"> Number (%) of times images judged helpful in planning management of the patient in a case series % of times medical procedure avoided due to image information % of times therapy planned pretest changed after imaging information was obtained (retrospectively inferred from patient records) % of times clinicians prospectively stated therapeutic choices changed after test information 	<ul style="list-style-type: none"> In situations where RCTs of decision making with and without the imaging information cannot be performed ethically or because of the momentum for using a particular procedure, asking Level 4 questions may be only efficacy study possible. Integrating negative information about a test from Level 3 and 4 studies may help to direct clinical use away from imaging tests that are not useful or have been supplanted by other tests.
5. Patient outcome efficacy	<ul style="list-style-type: none"> % of patients improved with test compared with no test Morbidity (or procedures) avoided with test Change in quality-adjusted life expectancy Expected value of test information in QALYS Cost per QALY saved with imaging information 	<ul style="list-style-type: none"> Definitive answer re efficacy with respect to patient outcome requires RCT (involving withholding test from some patients). RCTs may be associated with formidable statistical, empirical, and ethical problems and are justified only in carefully selected situations. Weaker evidence may be derived from case control studies or case series. Independent contribution of imaging to patient outcome may be small, requiring very large sample sizes. Decision analytic approach can be alternative to RCT, but the analyses may suffer from the same biases as their secondary data sources. Decision analyses can highlight critical pieces of information and guide future studies.
6. Societal efficacy	<ul style="list-style-type: none"> Cost-benefit analysis from societal viewpoint Cost-effectiveness analysis from societal viewpoint Cost-utility analysis from societal viewpoint 	<ul style="list-style-type: none"> Economic evaluations of evolving technologies do not provide definitive answers, since values and judgments play a significant role in interpretation of results. Cost utility analyses imply at least Level 5 efficacy data or models.

Adapted from Fryback and Thornbury, 1991

Abbreviations: RCT, randomized clinical trial
 ROC, receiver operating characteristics
 QALY, quality adjusted life year

2. Assess the quality of individual studies of diagnostic tests

Criteria for assessing the quality of a diagnostic test evaluation have been defined for use in evidence-based medicine (Haynes and Sackett, 1995). These criteria, listed below, 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.

Evidence-based medicine criteria for evaluating studies of diagnosis

- Clearly identified comparison groups, of which ≥ 1 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).

Haynes and Sackett, 1995

Documentation of test accuracy does not translate into documentation that the test is clinically useful. Sensitivity and specificity, while not as dependent on prevalence of disease as predictive values, can be biased by differences in patient mix in the study population and the patients on whom the test will be used in clinical practice (Sackett et al. 1991). A published study that does not supply valid information needed to calculate posttest probability of disease (i.e., predictive values or likelihood ratios) would not assist clinicians in interpreting its results, or taking action based on those results.

Evidence-based criteria provide a broad quality screen for clinicians who are contemplating using a test in their own patients. A somewhat more detailed set of quality criteria, that expand on those of evidence-based medicine, have been used by the American College of Physicians in evaluations of the literature on magnetic resonance imaging (Kent et al., 1994; Kent and Larson, 1992; Kent and Larson, 1988). These criteria were applied to studies of **diagnostic accuracy and diagnostic thinking efficacy**.

Methodologic quality of diagnostic accuracy studies

<i>Grade</i>	<i>Criteria</i>
A	<p>Studies with broad generalizability to a variety of patients and no significant flaws in research methods</p> <ul style="list-style-type: none"> • ≥ 35 patients with disease and ≥ 35 patients without disease (since such numbers yield 95% CIs whose lower bound excludes 0.90 if $Se = 1$) • patients drawn from a clinically relevant sample (not filtered to include only severe disease) whose clinical symptoms are completely described • diagnoses defined by an appropriate reference standard • PET studies technically of high quality and evaluated independently of the reference diagnosis
B	<p>Studies with a narrower spectrum of generalizability, and with only a few flaws that are well described (and impact on conclusions can be assessed)</p> <ul style="list-style-type: none"> • ≥ 35 cases with and without disease • more limited spectrum of patients, typically reflecting referral bias of university centers (more severe illness) • free of other methods flaws that promote interaction between test result and disease determination • prospective study still required
C	<p>Studies with several flaws in methods</p> <ul style="list-style-type: none"> • small sample sizes • incomplete reporting • retrospective studies of diagnostic accuracy
D	<p>Studies with multiple flaws in methods</p> <ul style="list-style-type: none"> • no credible reference standard for diagnosis • test result and determination of final diagnosis not independent (diagnostic review and/or test review bias) • source of patient cohort could not be determined or was obviously influenced by the test result (work-up bias) • opinions without substantiating data

Studies that assess the efficacy of diagnostic tests, particularly estimates of sensitivity and specificity, are susceptible to a variety of biases (Begg, 1987). Thornbury et al. (1991) described five aspects of research methodology that may influence accuracy estimates. *Insufficient sample size* may result in failure to detect differences between imaging modalities, if in fact they do exist, and may provide imprecise estimates of imaging accuracy.

Differences among patient populations in the spectrum of disease presentation (case mix) and severity result in *referral bias*. The spectrum of patients needed to assess a diagnostic test will depend on the clinical situation. For example, at initial presentation of abnormality the spectrum should also include patients with no abnormality as well as patients with abnormalities that may be confused with malignancy. For diagnosing recurrent disease the spectrum should include patients with recurrence, patients with no recurrence, and patients with treatment changes that may be confused with malignancy on testing. A wider spectrum of patients would be needed to assess a test when there is a high prevalence of benign conditions (eg. SPN), whereas a test could be assessed in a narrower spectrum of patients with higher prevalence cancers.

Biases related to the appropriate use of a diagnostic reference standard are *work up bias*, *test review bias*, and *diagnostic review bias*. Presence of referral bias and reference standard methodologic biases result in overestimation of true positive rates and underestimation of false positive and negative rates.

Considerable activity in the diagnostic testing literature is focusing on developing study designs and analytic techniques to correct for, or minimize the effect of, these biases. Some of the more common methods for limiting their influence on diagnostic accuracy estimates are presented below:

Biases in Studies of Diagnostic Imaging Tests

Type of bias	Techniques to minimize bias	Comments
Referral/spectrum <i>the influence of spectrum and severity of disease (case mix) on test characteristics</i>	<ul style="list-style-type: none"> referral sources from a variety of medical practice settings in which potential patient subjects are first encountered clearly defined referral define patient groups based on physician's pre-test probability estimate of disease adequate subgroup sizes 	<ul style="list-style-type: none"> ⇒ gives sufficient number and mix of patients needed to define predictive values ⇒ can determine generalizability of study results to own population ⇒ allows subgroup analysis of diagnostic accuracy estimates
Work-up/verification <ul style="list-style-type: none"> results from imaging test determine the choice of patient verified by the gold standard, or study is restricted to biopsy verified cases 	<ul style="list-style-type: none"> all patients have all competing tests prospective study in which all patients receive definitive verification of disease status sufficient follow-up time retrospective adjustments algebraic correction involving regression of empirical disease frequencies against the probability of disease as determined in a predictive model 	<ul style="list-style-type: none"> ⇒ magnitude of the bias is related to association between selection for verification and test result ⇒ maximizes diagnostic certainty ⇒ require test results and covariate data from the source population and verified sample
Test review <i>imaging test interpretation is not independent of final diagnosis, clinical information or results of comparison test</i>	<ul style="list-style-type: none"> randomized, blinded, independent interpretation of imaging test readings with and without clinical information allow sufficient time between readings standardize diagnostic terms and degrees of abnormality document impact of uninterpretable results use multiple readers and determine interobserver variability and methods for resolving differences 	<ul style="list-style-type: none"> ⇒ can determine effect of clinical information on diagnostic probability estimates ⇒ frequency of uninterpretability is an important consideration in the cost-effectiveness of a test
Diagnostic review/incorporation <i>gold standard diagnosis is not independent of imaging test results</i>	<ul style="list-style-type: none"> extensive nodal sampling regardless of imaging results expert interdisciplinary panel to review patient information and revise diagnostic and probability estimates incrementally 	<ul style="list-style-type: none"> ⇒ blinding practitioner to imaging may be impractical, but effect of bias can be minimized ⇒ panel process optimizes the final diagnosis in cases in which biopsy result is and is not available

Adapted from Begg (1987), Thornbury et al. (1991), and Webb et al. (1991)

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

The third analytic framework for the literature review will rank the available evidence for the degree to which it supports a causal link between the use of the technology and improved outcomes. Recommendations about the use of a technology should be linked to the quality of the available evidence, with the strength of the evidence dependent on the quality of the available evidence.

Several models for this framework exist that are based on well-established scientific principles of study design. Flynn (1996) used the model below by Cook (1992) to summarize the relative strengths associated with various study designs and to rank the

persuasiveness of their findings between the use of the technology and the outcome of interest:

**Classifications of study designs and levels of evidence
(when high quality meta analyses/overviews are not available)**

<i>Level</i>	<i>Description</i>
I	<p>Randomized trials with low false-positive (alpha) and low false-negative (beta) errors (high power)</p> <ul style="list-style-type: none"> • positive trial with statistically significant treatment effect (low alpha error) • negative trial that was large enough to exclude the possibility of a clinically important benefit (low beta error/high power; i.e. had a narrow confidence interval around the treatment effect, the lower end of which was greater than the minimum clinically important benefit) • meta analysis can be used to generate a pooled estimate of treatment efficacy across all high quality, relevant studies and can reveal any inconsistencies in results
II	<p>Randomized trials with high false-positive (alpha) and/or high false negative (beta) errors (low power)</p> <ul style="list-style-type: none"> • trial with interesting positive trend that is not statistically significant (high alpha error) • negative trial but possibility of a clinically important benefit (high beta error/low power; i.e. very wide confidence intervals around the treatment effect) • small positive trials with wide confidence intervals around the treatment effect, making it difficult to judge the magnitude of the effect • when Level II studies are pooled (through quantitative meta analysis), the aggregate effects may provide Level I evidence
III	<p>Nonrandomized concurrent cohort comparisons between contemporaneous patients who did and did not (through refusal, noncompliance, contraindication, local practice, oversight, etc.) receive treatment</p> <ul style="list-style-type: none"> • results subject to biases • Level III data can be subjected to meta analysis, but the result would not shift these data to another Level, and is not usually recommended
IV	<p>Nonrandomized historical cohort comparison between current patients who did receive treatment (as a result of local policy) and former patients (from the same institution or from the literature) who did not (since at another time or in another institution different treatment policies prevailed)</p> <ul style="list-style-type: none"> • <i>results subject to biases, including those that result from inappropriate comparisons over time and space</i>
V	<p>Case series without control subjects</p> <ul style="list-style-type: none"> • <i>may contain useful information about clinical course and prognosis but can only hint at efficacy</i>

Source: Cook et al. (1992)

Ibrahim (1987) presented a similar framework to display the continuum of study designs and their causal implications.

Continuum of study designs and their causal implications

<i>Level*</i>	<i>Study design</i>	<i>Inference/strength of evidence</i>
I	Randomized controlled trials (RCT) Community randomized trials Systematic reviews of RCTs	Firm
II	Prospective cohort	Moderately firm
III	Before-after with controls Historical cohort	Highly suggestive
IV	Case-control	Moderately suggestive
V	Time series Ecologic correlations Cross-sectional	Suggestive
VI	Anecdote Clinical hunches Case history	Speculative

Adapted from Ibrahim, (1985).

*For simplicity, the numerical order was reversed for this review to align with the levels found in the previous table.

Levels IV, V, and VI are observational (nonexperimental) studies. Observational studies are subject to many forms of bias, which can diminish the accuracy of their findings. They do not provide strong evidence linking interventions with the observed outcomes; however, they can be useful for generating hypotheses for future research. Levels II and III are considered quasi-experimental designs. They are commonly used in health care and provide stronger evidence than can be obtained from observational studies. Level I studies are true experimental studies and provide the most persuasive evidence for linking interventions with the observed outcomes.

Both frameworks will be used to appraise the strength of the evidence that links use of PET with desired outcomes, particularly to effect change in diagnosis and treatment management.

XV. APPENDIX 2

Models of High Quality Efficacy Studies of Diagnostic Imaging Technologies

Study	Highlights of study design
Mushlin (1993) MRI vs. CT in patients with suspected multiple sclerosis	<ul style="list-style-type: none"> ▪ multi-site study with well-defined referral sources and filters, included patients with an uncertain diagnosis, representing those in whom the tests might be used ▪ sufficient sample size ▪ all patients receive all tests under evaluation ▪ independent, blinded image interpretation ▪ varying degrees of abnormality on the images were noted to permit calculation of receiver-operating characteristics (ROC) analysis and likelihood ratios for summary comparisons ▪ sufficient follow-up to permit reasonable diagnostic certainty ▪ use of technology that is representative of what is available and widely used in most medical communities
Stark (1987) MRI vs. CT in patients diagnosed with liver metastases	<ul style="list-style-type: none"> ▪ included patients with and without disease, and patients with benign disease commonly confused with metastases ▪ independent, blinded interpretation of each test and gold standard diagnosis ▪ used ROC analysis to permit comparison of tests over a range of confidence levels and diagnostic thresholds
Webb (1991) MRI vs. CT to determine extent of disease in patients with non-small cell bronchogenic carcinoma	<ul style="list-style-type: none"> ▪ multi-site study with a detailed description of the filter through which patients entering into the study were passed (to reduce referral bias) ▪ data dichotomized to analyze lower and advanced stage disease ▪ blinded, independent interpretation of test results and interobserver variability calculated ▪ independent pathologic data available for all patients analyzed ▪ use of standardized forms for data analysis ▪ extensive nodal sampling not limited to abnormal results on imaging ▪ assessed influence of sampling procedure on results
Rifkin (1990) MRI vs. transrectal ultrasonography to determine extent of disease in surgical candidates with probable localized prostate cancer	<ul style="list-style-type: none"> ▪ large consecutive case series and a multi-site study ▪ used standardized forms for data analysis ▪ blinded, independent interpretation of test results using a five-point grading scale appropriate for ROC analysis ▪ lesions identified on diagnostic imaging were matched with pathological findings using a computer algorithm
Thornbury (1993) MRI vs. plain CT vs. CT myelography in patients with acute low-back pain and radicular pain	<ul style="list-style-type: none"> ▪ patients with a range of probability of disease were included, based on initial clinical diagnosis before imaging ▪ sample size sufficient to provide reasonable statistical power ▪ MRI and one of the two CT tests were performed in all patients ▪ follow-up time sufficient to permit reasonable diagnostic certainty ▪ randomized, unpaired blinded interpretation of all tests ▪ use of an expert interdisciplinary panel to determine true diagnosis ▪ data collection provided information for use in a cost-effectiveness analysis
Zerhouni (1996) CT vs. MRI in staging colorectal carcinoma	<ul style="list-style-type: none"> ▪ multi-institutional study with well defined and described study population and referral filter ▪ all subjects received either histopathologic, follow-up verification, or corrected for work up bias using technique of Gray et al (1984) ▪ well-defined positivity criteria ▪ blind, independent interpretation of each test compared to joint interpretation ▪ standardized surgical form for data collection of extent of disease for gold standard determination ▪ extensive quality control procedures to monitor data collection and compliance ▪ data analysis stratified based on pre-test knowledge of disease

XVI. APPENDIX 3**Active Funded Research at VHA PET Facilities as of October 1, 1998**

<i>Site</i>	<i>Study Title/Number</i>	<i>Funding/Sponsor</i>	<i>Start/Completion Dates</i>
St. Louis	18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) Imaging in the Management of Patients with Solitary Pulmonary Nodules (CSP 27)	\$2,306,632 - funded by VHA ORD Cooperative Studies Program	1998/5 year project
West Haven	Neurobehavioral Correlates of Mental Stress Ischemia (R01 HL59619-01A1)	\$1,300,000 - NIH National Heart, Lung and Blood Institute	1998-2001
	Psychological, CNS and Myocardial Mechanisms in Mental Stress Ischemia	\$374,000 - Merit Review Award	1998-2000
	CNS Correlates of Mental Stress Induced Myocardial Ischemia in Women	\$100,000 - Charles A. Dana Foundation, Neuroscience Research Program on Brain-Body Interaction	Starts 1998, duration 3 years
	Study to Determine the Effect of Atorvastatin on the Progression of Atherosclerosis	\$210,000 - Parke-Davis Pharmaceutical Research	1998-1999 (6-month project)
	Impact of PET on Patient Care Algorithm	\$50,000 - funded by VHA Office of Patient Care Services	1998-1999
	PET Measurement of Cerebral Blood Flow Correlates of Memory in Posttraumatic Stress Disorder	\$421,094 - Career Development Award	10/1/97-9/30/00
	PET Measurement of Hippocampal Function (Memory) in Depression	\$56,500 - National Alliance for Research in Schizophrenia and Depression, Young Investigator Award	7/1/97-6/30/99
	Cerebral Metabolic Correlates of AMPT-induced Depressive Relapse	\$306,000	7/1/96-6/30/99
	PET Measurement of Cerebral Blood Flow Correlates of Traumatic Memory in PTSD	\$850,000 per year	Continuing Renewal
	Hippocampal Function in Gulf War Combat-related PTSD	\$299,400	7/1/98-6/30/02
	Hippocampus in Women with Abuse-related PTSD	\$967,000 - NIMH	1/1/99-12/30/02
	PET Measurement of Benzodiazepine Receptor in Anxiety	\$850,000 per year - National Center for Posttraumatic Stress Disorder Grant	Continuing Renewal
	PET Measurement of Cerebral Blood Flow Correlates of Conditioned Fear	\$850,000 - National Center for Posttraumatic Stress Disorder Grant	Continuing Renewal
	Transmyocardial Laser Revascularization in Chronic Canine Model of Ischemia	\$80,000 - United States Surgical Corp.	10/96-12/98
	Dynamic SPECT BMIPP Imaging comparison with Perfusion and FDG Accumulation	\$149,400 - Nihon Mediphysics	3/96-6/99
PET Neuroreceptor Imaging (Serotonin-2A and Serotonin-1A)	<ul style="list-style-type: none"> • \$100,000 - National Institute of Mental Health Clinical Research Center • \$55,000 - VA Schizophrenia Research Center 	<ul style="list-style-type: none"> • 10/1/96-9/30/01 • 10/1/94-12/31/99 	
Minneapolis	Quantitative Assessment of Functional Connectivity in the Hereditary Ataxias (PO1 NS33718)	\$87,720 - Sponsored by NIH/NINDS	1/1/95-12/31/99
	Spatial and Temporal Patterns in Functional Neuroimaging (P20 MH57180)	\$1,113,418 - Sponsored by NIH	\$9/30/96-9/29/01
	Correlation of Cholinergic Reserve and Cognitive Function with Positron Emission Tomography (LOI-96-001)	\$106,446 - With the Alzheimer's Association	10/15/96-10/14/98
	Motor Cortex and the Control of Dynamic Force	\$75,500 - Merit Review Award by VA	11/1/96-10/30/01
	Functional MRI of Human Motor Cortex (5R01 NS32437-02)	\$150,178 - Sponsored by NIH.NINDS	4/1/95-3/30/98

<i>Site</i>	<i>Study Title/Number</i>	<i>Funding/Sponsor</i>	<i>Start/Completion Dates</i>
	Functional reorganization with cortical motor areas	\$33,000 - Funded by Charles A. Dana Foundation	1/1/95-12/31/98
	Neural mechanisms of drawing movements under different load conditions	\$73,300 - Funded by the National Science Foundation	4/1/97-3/31/00
	Optimizing 3D Iterative Reconstructions for PET (R29 NS33721)	\$71,369 - Sponsored by NINDS	12/1/94-11/30/99
	Regional FDG Uptake in Stunned vs Hibernating Myocardium (R29 HL52157)	\$78,012 - Sponsored by NIH/NHLBI	2/1/96-1/31/01
	Quantitative Magnetic Resonance Assessment of Microvascular Dysfunction (R01 HL58876)	\$194,475 - Sponsored by NIH	9/1/97-8/31/00
	Functional Anatomy of Human Cognition	\$99,000 - VA Merit Review Award	10/1/95-9/30/99
	PET studies of Lexical Processing in Schizophrenia	\$30,000 - Young Investigator Award from NARSAD	7/1/96-6/30/98
	Lexical Processing in the Differential Diagnosis of Mania from Depression	\$12,151 - Funded by Minnesota Medical Foundation	4/1/98-3/31/99
	PET Imaging of Hunger and Satiety	\$38,704 - Minnesota Obesity Center	8/1/96-7/31/97
	Hippocampal and Memory Dysfunction in Normal Aging	\$29,700 - Alzheimer's Disease Association	7/1/96-12/31/97
Buffalo	Positron Emission Tomographic Study of Tinnitus and Auditory Plasticity	\$46,125 - American Tinnitus Association	6/1/96-10/30/97
	Positron Emission Tomographic Studies of the Auditory System	Jane H. Cummings Foundation	6/1/97
	A Comparison of Cerebral Blood Flow in Migraineurs During Headache, Headache Free, and Treatment Periods	\$114,300 - Department of Defense	Start 7/1/95 duration of two years
	PET Studies of Temporal Mandibular Joint Pain	\$20,000 - State University of New York	Start 6/1/97 duration of one year
	Glucose Transport in Stunned and Hibernating Myocardium	\$105,000 - New York State Affiliate, American Heart Association	7/1/97-6/30/00
	Chronic Alterations in Glucose Transport in Hibernating and Stunned Myocardium	\$277,800 - American Heart Association	7/1/96-6/30/01
	Chronic Adaptations to Myocardial Ischemia	\$1,120,447 - NIH and National Heart Blood and Lung Institute	
	PET Studies of Tinnitus and Hearing Loss	\$1,272,652 - NIH and National Institute on Deafness and Communicative Disorders	Starts 1/98 duration of 5 years
	PET Imaging subproject	\$48,240 - NIH and National Institute of Aging	
San Antonio	Fluoxetine Effects on Mood, Cognition & Metabolism	\$507,446 - National Institute of Mental Health	Ends 8/31/98
	Anterior Cingulate Metabolism in Depression	\$99,992 - NARSAD	Ends 9/14/98
	Multimethodological Studies in Cognitive Neuroscience	\$85,440 - Blue List Neurobiology	Ends 12/31/98
	The Role of PET in Conjunction with Maximal Exercise Stress in Assessment of Chronic Stable Coronary Artery Disease	\$25,000 - Dupont Pharmaceuticals, Inc.	Ends 01/01/99
	The Effects of Prozac Treatment on Mood, Cognition and Brain Glucose Metabolism in Patients with Primary Unipolar Depression	\$49,940 - Eli Lilly and Co.	Ends 01/01/99
	PET/TMS Mapping of the Neural Circuitry of Developmental Stuttering	\$100,000 - Dan Foundation	Ends 12/31/99
	Interactive Effects of Mood and Cognition Challenges on Anterior Cingulate Function in Remitted Depression	\$60,000 - NARSAD Young Investigator Award	Ends 06/30/00
	Hunger for Air Study	\$140,000 - Mathers Foundation	Ends 06/30/00
	Investigating the Neural Bases of Chronic Stuttering	\$435,231 - NIH	Ends 11/30/01
Indianapolis	Role of Hemodynamics in In-Vivo Insulin Resistance (R01 DK 42469)	\$207,453 - sponsored by NIH	7/1/95-6/30/00

<i>Site</i>	<i>Study Title/Number</i>	<i>Funding/Sponsor</i>	<i>Start/Completion Dates</i>
	SCOR in Sudden Cardiac Death (P50 DK 52323)	\$258,274 - sponsored by NIH	1/1/95-12/31/99
	PET Imaging in the Surgical Management of Melanoma	\$127,918 - Sponsored by NIH	4/1/97-3/31/01
Pittsburgh	Effect of NIDDM on Glucose Transport into Skeletal Muscle	Not available	1998
	The Effect of Troglitazone, Metformin, and Sulfonylurea on Insulin-stimulated Glucose Transport and Phosphorylation, Oxidative Enzyme Capacity and Muscle Composition in NIDDM	Not available	Ongoing
	Echocardiographic Assessment of Myocardial Viability in patients with Impaired Left Ventricular Function	Not available	1998
	The Role of PET Scanning in Staging the Patient with Intrathoracic Malignancies: Non-small Cell Lung Cancer	Not available	1998
West Los Angeles	Pre-frontal Dysfunction in Frontal Lobe Epilepsy	VA Merit Review	
	Psychiatric and Behavioral Disturbances in Alzheimer's Disease	NIMH	
	The Study of Cognitive Processes in Normal Individuals: Activation Studies of the Normal Human Frontal Lobe	Mathers Charitable Foundation	
	Effect of Smoking on Coronary Blood Flow Reserve and Attenuation Effect on Coronary Vasodilator Response of Nitroglycerine	California Tobacco Institute	
	Perception and Modulation of Visceral Sensations	NIH and Astra Pharmaceuticals	
	Central Nervous System Processing of Sensory Information in Irritable Bowel Syndrome (IBS) and Fibromyalgia	CAP	
	Functional Electrical Stimulation on Spinal Cord Injured Patients	VA PM&R R&D	
	Evaluation of Limb Blood Flow with ¹⁵ O-H ₂ O PET	VA PM&R R&D	
	¹⁵ O-H ₂ O Scanning in Schizophrenia; Assessing Training-Related Improvement	Stanley Foundation and/or NARSAD Young Investigator Award	
	Brain Metabolic Changes with Cigarette Craving	California Tobacco institute	
	PET-FDG Imaging of Opioid Dependent Subjects	NIDA	
	Pathogenesis of Symptomatic vs. Silent Myocardial Ischemia	Not Available	
	Assessment of Myocardial Viability Using PET to Determine Benefit for Revascularization	Not Available	
Ann Arbor	Michigan Alzheimer's Disease Research Center	NIA	
	PET study of Biochemistry and Metabolism of CNS	NIND&S	
	Forebrain Mechanisms of Pain and Analgesia	\$300,000 - VA Merit Award	
	Forebrain Responses to Chronic Pain and Its Treatment	NICH&HD	
	Concomitant Chemotherapy and Radiation for Organ Preservation in Patients with Advanced (Stage III, IV) Laryngeal Cancer	University of Mich./VA	
	Combined Hormone Replacement Therapy and Myocardial Blood Flow	VA	

<i>Site</i>	<i>Study Title/Number</i>	<i>Funding/Sponsor</i>	<i>Start/Completion Dates</i>
	Effect of Conjugated Equine Estrogen and Micronized Progesterone on Coronary Artery Endothelial Function as Assessed by Positron Emission Tomography	VA	
	Limbic Blood Flow & Opiate Receptor PET in Posttraumatic Stress Disorder	\$288,500 - VA Merit Award	
	Paroxysmal Dystonia-Choreoathetosis	NIND&S	
	PET Studies of Dopaminergic Neurons in Chronic Severe Alcoholism	NIAA&A	
	Metabolic Imaging of Renal Masses with Positron Emission Tomography	VA	
	Metabolic Imaging of Pancreatic Disease with Positron Emission Tomography	University of Mich./VA	
	Imaging of Intermediary Metabolism in Neoplasia using C-11 Acetate PET	VA	