INAHTA

Joint Project

Positron Emission Tomography

Experience with PET and Synthesis of the Evidence

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International Network of Agencies for Health Technology Assessment

Positron Emission Tomography: Experience with PET and Synthesis of the Evidence

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Established in 1993 the International Network of Agencies for Health Technology Assessment (INAHTA) provides a forum for the identification and pursuit of interests common to health technology assessment agencies. INAHTA consists of non-profit agencies throughout the world that assess health care technologies, relate to a regional or national government and are funded at least 50 percent by public sources.

INAHTA joint projects are collaborations among member agencies to evaluate medical technologies of mutual interest. In 1996 INAHTA completed its first joint project on bone density measurement. In 1999 INAHTA conducted joint projects in telemedicine and prostate cancer screening, in addition to PET scanning.

INAHTA Newsletter provides updates on recently published reports, current initiatives and activities among member agencies, new projects within the Network, recent developments and trends in health policy research, publications in the field and upcoming events. *INAHTA Newsletter* is published quarterly in English, Spanish and French.

Information about *INAHTA Newsletter*, INAHTA and its members, including links to member agencies' websites and the database of published reports and current projects, is available on the web at www.inahta.org or from the INAHTA Secretariat directly.

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International Network of Agencies for Health Technology Assessment
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AETS	Agencia de Evaluación de Tecnologías Sanitarias SPAIN
AETSA	Agencia de Evaluación de Tecnologías Sanitarias de Andalucía SPAIN
AHCPR	Agency for Health Care Policy and Research, Center for Practice and Technology Assessment USA
AHFMR	Alberta Heritage Foundation for Medical Research CANADA
ANAES	L'Agence Nationale d'Accréditation et d'Evaluation en Santé FRANCE
CAHTA	Catalan Agency for Health Technology Assessment SPAIN
CCOHTA	Canadian Coordinating Office for Health Technology Assessment CANADA
CEDIT	Comité d'Evaluation et de Diffusion des Innovations Technologiques FRANCE
CETS	Conseil d'Evaluation des Technologies de la Santé CANADA
CVZ	College voor Zorgverzekeringen/Health Care Insurance Board THE NETHERLANDS
DIHTA	Danish Institute for Health Technology Assessment DENMARK
DIMDI	German Institute for Medical Documentation and Information GERMANY
DSI	Danish Institute for Health Services Research and Development DENMARK
ETESA	Unidad De Tecnologías De Salud CHILE
FINOHTA	Finnish Office for Health Care Technology Assessment (Stakes) FINLAND
GR	Health Council of the Netherlands (Gezondheidsraad) THE NETHERLANDS
HSC	NHS Horizon Scanning Center UNITED KINGDOM
ICTAHC	Israel Center for Technology Assessment in Health Care ISRAEL
INHEM	Instituto Nacional de Higiene Epidemiologia y Microbiologia Infanta CUBA
ITA	HTA Unit of the Institute of Technology Assessment, Austrian Academy of Science AUSTRIA
MSAC	Medicare Services Advisory Committee AUSTRALIA
NCCHTA	National Coordinating Centre for Health Technology Assessment UNITED KINDGOM
NHSCRD	NHS Centre for Reviews and Dissemination UNITED KINGDOM
NZHTA	New Zealand Health Technology Assessment NEW ZEALAND
OSTEBA	Basque Office for Health Technology Assessment (OSTEBA) SPAIN
SBU	Swedish Council on Technology Assessment in Health Care SWEDEN
SFOSS	Medical Technology Section of the Swiss Federal Office of Social Security SWITZERLAND
SMM	The Norwegian Centre for Health Technology Assessment NORWAY
SWISS/TA	Swiss Science Council/Technology Assessment SWITZERLAND
TNO	TNO Prevention and Health THE NETHERLANDS
VATAP	US Department of Veterans Affairs Technology Assessment Program USA

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INAHTA JOINT PROJECT
Positron Emission Tomography:
Experience with PET and Synthesis of the Evidence
Executive Summary

- INAHTA conducted this joint collaboration in response to an increasing global interest in the clinical potential of positron emission tomography (PET). The project documents PET use and related public health coverage in countries represented by INAHTA members and synthesizes technology assessments of PET conducted by INAHTA members and three private US organizations. It considers all PET systems, that is, conventional full ring models, newer partial ring models and SPECT cameras modified for imaging positron emitters.

- PET is a functional imaging technology that uses a radioactive tracer to assess perfusion and metabolic activity in the human body. Introduced first as a research tool, PET has undergone technological advances that make it feasible for clinical use.

- PET's availability is still quite limited, as evidenced by the low numbers and relative under use of scanners in each country or region. Most health systems used their PET scanners for both research and diagnostic purposes, but there were wide variations in use across systems. Local regulatory policies and the availability of private funding sources likely contributed to these differences.

- The vast majority of reimbursed clinical PET activity is concentrated in relatively few health systems and is confined to comparatively few indications.
    - Public health systems in Australia, Switzerland, Denmark and the US (VHA) conducted 85% of the activity.
    - The most frequently covered PET indications, presented in descending order, were for diagnosing head and neck cancer, lung cancer and lymphoma followed closely by differentiating brain tumor from radiation necrosis and diagnosing colorectal cancer, breast cancer and melanoma.
    - 70% of the oncology activity comprised melanoma, lung cancer staging, and an undefined category of "other". The vast majority of neurology activity was for distinguishing brain tumor from radiation necrosis and for localizing epileptic foci in potential surgical candidates with intractable epilepsy.

- Many health systems refer to US experiences, particularly Medicare policy, to establish local reimbursement policy. In the US in 1997, supporters of clinical PET were instrumental in changing FDA regulation of PET drugs. As a result, Medicare has expanded coverage of PET scans beyond cardiac perfusion imaging to include diagnosing indeterminate solitary pulmonary nodules, recurrent metastatic melanoma and recurrent colorectal cancer and staging non-small cell lung cancer, Hodgkin's and non-Hodgkin's lymphoma.

- Regarding PET's utility, evidence of diagnostic accuracy is largely based on traditional full ring PET, is limited by bias and often relates only to small patient numbers. In all of the advocated clinical indications there was uniform agreement that critical research is needed to define the clinical and economic consequences of using PET on treatment decisions and health outcome relative to other methods now in clinical use.

- Many INAHTA agencies identified clinical PET as a major research priority and are initiating rigorous evaluation efforts. Most recommended that, if used at all, PET should be used under research protocols designed to evaluate PET's relative cost-effectiveness.

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INTRODUCTION

At the fifth annual meeting of the International Network of Agencies for Health Technology Assessment (INAHTA) in 1997, members initiated a joint project on positron emission tomography (PET) scanning in clinical medicine in response to a growing interest in the technology worldwide. INAHTA members have experienced different motivations or hindrances to the diffusion of PET, and their assessments reflect the different health care system environments. One goal of this collaborative effort is to bring together the range of experiences into a broadly applicable document. A collaborative INAHTA project drawing on an array of approaches and research questions will expand the scope of individual agencies' assessments.

Four agencies agreed to coordinate the project: The Agency for Health Care Policy and Research (AHCPR), United States; Agencia de Evaluación de Tecnologías Sanitarias (AETS), Spain; Basque Office for Health Technology Assessment Health Department (OSTEBA), Spain; and the Department of Veterans Affairs Technology Assessment Program (VA TAP), United States.

This report will document:

I. the use of PET and public health care coverage policies for PET in countries represented by INAHTA members,
II. a synthesis of technology assessments of PET conducted by INAHTA members and three private US organizations.

Interest in PET now extends beyond the traditional full ring PET scanners to partial ring models and to single photon emission computed tomography (SPECT) modified for imaging positron emitters. Thus, the scope of this project will include positron emitting imaging modalities that use principles of *coincidence detection or high energy 511 keV collimation* to form the raw image.

BACKGROUND

PET is a minimally invasive imaging procedure that uses a radioactive tracer to assess perfusion and metabolic activity in various organ systems of the human body. The tracer decays 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 traveling in opposite directions. The high energy photon is subject to less absorption or scatter by tissue.

A positron camera (tomograph) arranged in a ring around the patient detects the two photons simultaneously (coincidence detection) to produce cross-sectional tomographic images. Traditional PET scanners come in full ring and, more recently, partial ring models. Dual-headed SPECT cameras with coincidence detection capability and multi-headed SPECT cameras adapted for high energy 511 keV collimation are now available for imaging positron emitters.

Relative to other nuclear medicine technologies, traditional PET systems provide superior image quality and quantitative information (Lewellen 1999).

Charged particle accelerators (e.g. generators and cyclotrons) produce the radiopharmaceuticals used in PET scanning. Both generators and cyclotrons are commercially available. Most PET facilities use cyclotron-produced, short-lived positron emitting radionuclides. These are principally oxygen (O-15), nitrogen (N-13), carbon (C-11) and fluorine (F-18). Radionuclide generators typically use longer-lived parent radionuclides to produce a single radiopharmaceutical for routine use, the most common being rubidium (Rb-82) chloride.

Ter-Pogossian (1992) summarized the development of PET from a research instrument to a diagnostic test. Since the invention of the first cyclotron and discovery of the positron in the 1930s, PET has been used in the study of basic physiology. Over the years, advances in detector instrumentation, knowledge of the properties of many short-lived positron emitters, and rapid chemical labeling procedures allowing for *in vivo* nuclear medicine imaging contributed to the development and understanding of PET as a research tool.

Further advances have made PET more feasible for clinical use:

- greater ease of operation, reliability and competitive pricing of cyclotrons;
- less expensive and easier-to-install accelerators for generating PET radionuclides;
- lower cost and more accessible generator-produced radionuclides; and
- improved sensitivity and resolution of PET instrumentation.

Despite technical improvements and an increasing interest in its clinical uses, PET has evolved slowly as a clinical tool relative to other imaging modalities such as CT or MRI. Ter-Pogossian (1992) noted two important barriers limiting PET's acceptance and use in clinical medicine. PET, unlike CT and MRI, was initially developed for research purposes, and PET requires a charged particle accelerator, usually a cyclotron, to produce short-lived positron emitters as tracers for PET studies. Thus, the clinical use of PET using these tracers had been largely restricted to affiliated research departments equipped with cyclotrons and expertise in radiochemistry.

Early clinical PET studies were first conducted in the brain for localizing seizure foci and differentiating causes of dementia. Cardiology studies followed using PET with Rb-82 to trace tissue perfusion and FDG to trace tissue metabolism. More recently, whole body scanning capability has generated considerable attention in using PET to manage oncology patients.

Like many large diagnostic imaging systems, PET is an expensive technology to purchase and maintain. Technical improvements now permit a wider of range of options for buyers of PET. Several PET manufacturers provided the following costs approximated in USD, which may not necessarily reflect the actual negotiated costs (personal communications 1999). Full ring models range from $1.25 to $1.5 million USD, partial ring models cost $900,000 USD, and cyclotrons sell for $1.5 million USD. There may be additional costs associated with installation, construction and operation.

The costs of traditional PET systems are prohibitive for many providers. Accordingly, many are upgrading more readily available dual-headed gamma cameras for coincidence imaging. The cost

of the upgrade is $250,000; dual-headed gamma cameras without the upgrade sell for $400,000 to $600,000 (personal communications 1999). A strontium generator for producing Rb-82 costs $300,000 USD (ECRI 1996).

Annual operating costs for a PET facility can vary considerably and are often related to the complexity of operations (Flynn 1996). Typically, PET facilities that conduct only clinical scans offer the least costly alternative. Mobile PET scanner models and regional suppliers of radiopharmaceuticals such as F-18 fluorodeoxyglucose (FDG) may eliminate the need for an on-site cyclotron. Adding research capability can increase the complexity of operations, as radiolabeling complex tracer substances may require an on-site cyclotron and expertise in radiochemistry. Other research personnel may be needed for patient care, computer function and data analysis. A cyclotron and radiochemistry lab may require a larger facility.

PART I. PET USE AND REIMBURSEMENT AMONG PROJECT PARTICIPANTS

Interest in clinical PET has changed over the last two decades. Facing an uncooperative US market in the early 1990s, manufacturers looked overseas to increase market share. Lately, clinical PET has gained in popularity in the US and in many other parts of the world. This section explores the changing global interest in clinical PET through the experiences of INAHTA members.

A. Methods

The authors used several strategies to gather data:

1. OSTEBA surveyed 12 INAHTA members, excluding those from the US, and eight non-INAHTA participants in the HTA Europe Project[1] to obtain annual estimates of research and clinical utilization in private and public PET facilities and to gather information on public reimbursement for clinical PET scans performed in 1997 (see Appendix A).
2. Increases in INAHTA membership since 1997 and a continuing interest in PET's clinical potential warranted a new survey. In 1999 OSTEBA surveyed all 31 INAHTA members listed on page i on the availability of public reimbursement for clinical PET scans for the time period July 1, 1998 through June 31, 1999 (see Appendix B).
3. In formulating local policy on PET many public health systems have looked to the US experience. The heterogeneity of the US health care system made it difficult to obtain complete utilisation data for the US and required that a different approach be used. VA TAP and AHCPR reported on the primary factors affecting the diffusion of clinical PET in the US and on trends in coverage for clinical PET, as represented by the major health care payers and providers. For this section the authors searched MEDLINE®, HealthSTAR® and several PET-related web sites to obtain descriptive information, contacted major payers and providers for coverage policies, and obtained reports from technology assessment organizations in the US that conducted evaluations of clinical PET.

[1] HTA Europe is a Project whose aim is to develop a coordinated approach to health care technology assessment in Europe.

B. Results

1. 1997 Survey

Surveyed organizations represented 19 countries and one province. Fifteen HTA agencies (ten INAHTA members and five HTA Europe Project participants) responded indicating a 75% response rate (See Table 1). However, participants from Belgium and Germany did not provide complete information. Since three countries have no PET scanners, survey findings represent 13 countries with 33 PET scanners. Thirty scanners (90.9%) are situated in public health care systems, while only three scanners are situated privately. We observed a high percentage of *whole body PET* (84.8%) relative to *smaller partial body scanners.*

Table 1. 1997 INAHTA PET Survey Respondents by Country or Province

Country or province	*Number of PET scanners*	*Country or province*	*Number of PET scanners*
Australia	3	Germany	2*
Austria	1	Greece	0
Belgium	2*	Ireland	0
Canada (except Québec)	5	The Netherlands	2
Québec (Canada)	1	New Zealand	0
Denmark	3	Spain	2
Finland	2	Sweden	5
France	3	Switzerland	2

* Incomplete questionnaires

Figures 1 and 2 depict PET utilization across countries represented in the survey. The majority used their PET scanners for both clinical and research purposes, but there were exceptions. Austria and Switzerland dedicated their scanners to clinical diagnosis only, while Canada, France and Sweden set aside some of their scanners solely for research. Holland and Denmark performed the most investigative tests, whereas Australia, followed by Spain and Belgium, conducted the most diagnostic studies, bearing in mind the incomplete information received from Belgium.

Fig. 1 Proportion of Research and Clinical PET Use Across Countries in 1997

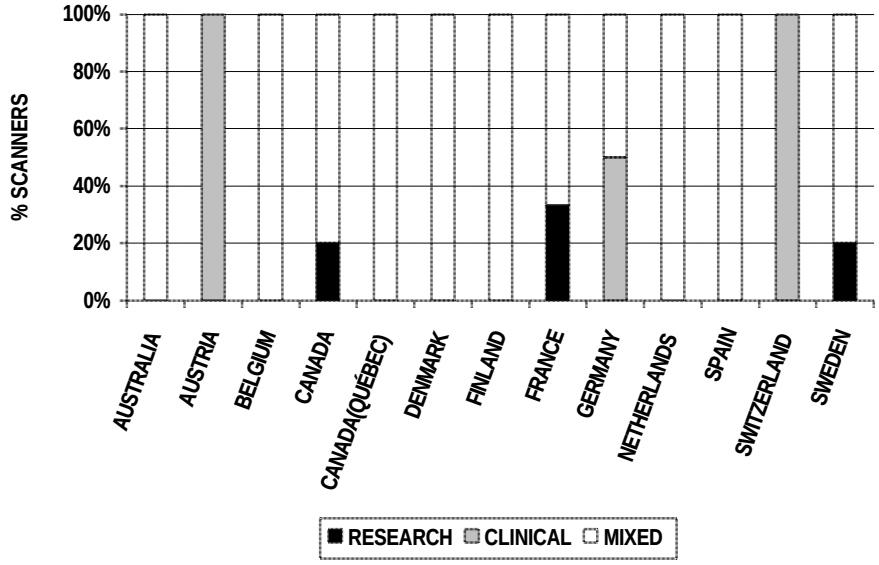
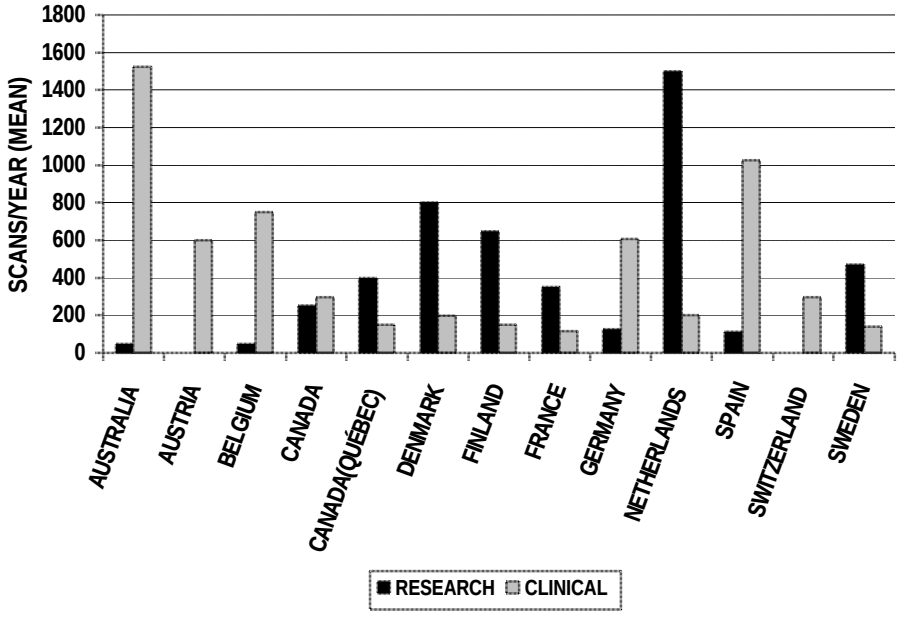


Fig. 2 Average Annual PET Utilization in 1997



Analysis of individual scanner utilization showed that 51.5% of the scanners conducted fewer than 250 clinical scans per year, and 48.5% performed less than 250 scans per year for research purposes (See Table 2). It was very infrequent for an individual scanner to conduct more than 500 scans per year. Accounting for the two incomplete survey results, six (18.2%) scanners were used for clinical use only, three (9.1%) scanners were used exclusively for research. The remainder were used for both research and clinical studies.

Table 2. Average Annual Utilization of 33 PET Scanners in 1997

Average # Scans/year	Number (%) of scanners		Average # Scans/year	Number (%) of scanners	
	Research	Clinical		Research	Clinical
None	4 (12.1)	3 (9.1)	**1001-1250**	1 (3.0)	2 (6.1)
1-250	12 (36.4)	14 (42.4)	**1251-1500**	2 (6.1)	1 (3.0)
251-500	7 (21.2)	5 (15.2)	**> 1500**	0	1 (3.0)
501-750	5 (15.2)	5 (15.2)	**unknown**	1 (3.0)	1 (3.0)
751-1000	1 (3.0)	1 (3.0)	**TOTAL**	33 (100)	33 (100)

Table 3. Diagnostic Uses and Public Reimbursement Among Survey Participants in 1997

		Diagnostic Use	Public Reimbursement	Public Reimbursement
Diagnostic applications		*Number of Scanners (% of total)*	*Number of Scanners (% of total)*	*Number of Countries (% of total)*
Neurology	Epilepsy	27 (81.8)	18 (54.4)	9 (69.2)
	Tumor vs necrosis	27 (81.8)	21 (63.6)	9 (69.2)
	Neurodegenerative disorders	26 (78.8)	14 (42.4)	7 (53.8)
	ACV	5 (15.2)	5 (15.2)	1 (7.7)
	Encephalopathy	2 (6.1)	2 (6.1)	2 (15.4)
	Psychiatry	1 (3.0)	1 (3.0)	1 (7.7)
Cardiology	Myocardial viability	24 (72.7)	16 (48.5)	8 (61.5)
	Myocardial perfusion	19 (57.6)	8 (24.2)	4 (30.8)
Oncology (non-central nervous system)	Lung	21 (63.6)	11 (33.3)	5 (38.5)
	Soft tissue	21 (63.6)	17 (51.5)	7 (53.8)
	Head and neck	18 (54.5)	13 (39.4)	7 (53.8)
	Solitary pulmonary nodules	18 (54.5)	9 (27.3)	4 (30.8)
	Colorectal	16 (48.5)	7 (21.2)	3 (23.1)
	Breast	16 (48.5)	9 (27.3)	4 (30.8)
	Gynecological	14 (42.4)	11 (33.3)	4 (30.8)
	Hematological	12 (36.4)	7 (21.2)	3 (23.1)
	Genitourinary	10 (30.3)	7 (21.2)	3 (23.1)
	Hepatobiliary	7 (21.2)	7 (21.2)	4 (30.8)
	Melanoma	7 (21.2)	5 (15.2)	3 (23.1)
	Adrenal	4 (12.1)	4 (12.1)	1 (7.7)
	Thyroid	2 (6.1)	1 (3.0)	1 (7.7)

Data in Table 3 indicated that there was considerable variability in diagnostic use across the 33 scanners represented in the survey. In general, the most commonly performed diagnostic applications were also the ones most likely to be reimbursed. More than 50% of the PET scanners were used for neurologic diagnoses of epilepsy, neurodegenerative disorders, and distinguishing brain tumor from necrosis, followed by evaluations of myocardial viability, ischemic heart disease, and cancers of the lung, head and neck, and soft tissue.

The majority (>50%) of diagnostic PET scans for epilepsy, distinguishing brain tumor from necrosis, and soft tissue cancers were reimbursed, but coverage for the remaining diagnostic applications was far less common. A comparison of reimbursement among the 13 countries in the survey yielded similar results. It is interesting to note that staging lung cancer, a condition that constitutes a considerable burden to most health systems, was among the most common diagnostic uses but was less frequently reimbursed. Conversely, the slightly lower PET use in head and neck cancer was among the most often reimbursed indications.

2. 1999 Survey

Thirty agencies, representing 18 countries or regions, responded to the survey yielding a response rate of 96%. Survey findings show that Chile, New Zealand, Andalucía (Spain) and Alberta (Canada) had no PET scanners. Providers in Israel, Germany, Norway and Austria used their PET scanners solely for research. Members in Great Britain and France were unable to provide data for their countries.

The remaining respondents provided data for analysis. New Zealand has arranged with a hospital in Melbourne, Australia to provide PET scans for patients with epilepsy who are candidates for surgical treatment, and these data were included under New Zealand in the analysis. Australia provided only aggregate data for each clinical category. Table 4 lists clinical PET applications reimbursed for each of the 11 public health systems within 13 countries or regions, and Table 5 further summarizes these findings. Table 6 provides a relative comparison of reimbursed clinical PET activity in 1999 across health systems.

Data collection time periods varied among some respondents. VA TAP provided data covering June 1997 through July 1998 and only for veterans scanned at VA PET facilities, labeled herein as US (VHA). Data from Switzerland covered January 1998 through December 1998. Denmark and New Zealand provided six months of data from which they estimated annual activity. All other respondents provided data for the time period July 1, 1998 to June 31, 1999.

Table 4. Clinical PET Reimbursement by Public Health System (June 1998-July 1999)

Clinical PET indications		Australia	Basque Region (Spain)	Catalonia (Spain)	Denmark	Finland	Madrid (Spain)	The Netherlands	New Zealand	Québec (Canada)	Switzerland	US (VHA)	TOTAL # SCANS	# Systems Offering Coverage
Neurology	Tumor vs necrosis		10	0	41	0	22	0	0	2	200	3	278	**6**
	Epilepsy		1	0	6	30	8	20	8	21	165	0	259	**8**
	Other		0	0	0	0	0	0	0	1	64	5	70	**3**
	Alzheimer's dementia		1	0	16	5	0	0	0	9	25	11	67	**6**
	Parkinson's disease		0	0	1	20	2	0	0	9	0	2	34	**5**
	Neurodegenerative diseases		1	0	9	20	1	0	0	0	0	1	32	**5**
	TOTAL	***494***	***13***	***0***	***73***	***75***	***33***	***20***	***8***	***42***	***454***	***22***	***1234****	
Cardiology	Myocardial viability		0	0	84	40	0	0	0	6	2	47	179	**5**
	Myocardial perfusion		0	0	0	0	0	0	0	0	65	48	113	**2**
	Other		0	0	0	0	0	0	0	0	0	0	0	
	TOTAL	***22***	***0***	***0***	***84***	***40***	***0***	***0***	***0***	***6***	***67***	***95***	***314****	
Oncology	Other		1	0	526	5	18	0	0	3	0	0	553	**5**
	Lung		0	0	3	8	20	0	0	41	128	246	455	**7**
	Melanoma		9	0	1	0	9	0	0	1	302	21	343	**6**
	Lymphoma		24	1	0	15	9	0	0	51	19	16	135	**7**
	Head and neck		4	0	6	20	15	20	0	7	0	58	130	**7**
	Colorectal		24	0	2	0	6	0	0	3	11	63	109	**6**
	SPN		32	0	0	5	1	0	0	45	0	0	83	**4**
	Breast		3	0	0	10	8	0	0	21	16	1	59	**6**
	Genitourinary		1	0	6	0	5	0	0	1	24	0	37	**5**
	Gynecological		0	0	0	0	2	0	0	7	16	0	25	**3**
	Thyroid		8	1	0	0	2	0	0	1	0	6	18	**5**
	Soft tissue		1	0	1	5	1	0	0	1	0	0	9	**5**
	Hepatobiliary		0	0	3	0	0	0	0	1	0	4	8	**3**
	Pancreas		1	0	1	0	1	0	0	0	0	3	6	**4**
	TOTAL	***1231***	***117***	***2***	***549***	***68***	***97***	***20***	***0***	***183***	***504***	***418***	***3189****	
Other	***TOTAL***										***183***		***183***	
TOTAL		**1747**	**130**	**2**	**706**	**183**	**130**	**40**	**8**	**231**	**1208**	**535**	**4920**	

* includes Australia

Table 5. Summary of the Number of Reimbursed PET Scans by Public Health System (June 1998-July 1999)

Public Health System by Country or Region	Neurology	Cardiology	Oncology	Other	Total
Australia	494	22	1231	0	1747
Switzerland*	454	67	504	183	1208
Denmark*	73	84	549	0	706
US (VHA)*	22	95	418	0	535
Québec (Canada)	42	6	183	0	231
Finland	75	40	68	0	183
Madrid (Spain)	33	0	97	0	130
Basque Region (Spain)	13	0	117	0	130
The Netherlands	20	0	20	0	40
New Zealand*	8	0	0	0	8
Catalonia (Spain)	0	0	2	0	2
TOTAL (% total)	**1234 (25)**	**314 (6)**	**3189 (65)**	**183 (4)**	**4920 (100)**

* data collection periods vary. See page 7.

Table 6. Number of Reimbursed PET Scans per 100,000 inhabitants (June 1998-July 1999)

Public Health System by Country or Region	Neurology	Cardiology	Oncology	Other	Total
US (VHA)*	0.73	3.17	13.93	0	17.8
Switzerland*	6.48	0.95	7.2	2.61	17.2
Denmark *	1.46	1.68	10.98	0	14.2
Australia	2.74	0.12	6.83	0	9.7
Basque Region (Spain)	0.65	0	5.85	0	6.5
Finland	1.5	0.8	1.36	0	3.6
Québec (Canada)	0.6	0.09	2.61	0	3.3
Madrid (Spain)	0.1	0	0.3	0	0.4
The Netherlands	0.13	0	0.13	0	0.3
New Zealand*	0.22	0	0	0	0.2
Catalonia (Spain)	0	0	0.03	0	0.03

* data collection periods vary. See page 7.

Neurology. Neurology indications constituted 25% of all reimbursed clinical PET activity among survey respondents. Excluding Australia, the majority of public health systems offered coverage for clinical PET evaluations in epilepsy, Alzheimer's dementia, brain tumors and neurodegenerative disorders. The survey also revealed considerable variability in the volume of scans for each indication. Of note, PET scans in evaluations of brain tumor and epilepsy comprised 75% of the total volume in neurology.

Switzerland, Australia and Finland reimbursed the most neurologic PET scans. In Switzerland epilepsy and brain tumors constituted 36% and 44%, respectively, of the total volume of neurological diagnostic studies. Finland conducted 60% of neurologic activity in assessments of Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders.

Cardiology. Cardiac indications represented the smallest portion (6%) of reimbursed clinical volume in the survey, of which approximately 60% of the scans were performed for viability determination. Fewer than half of the public health systems surveyed offered funding for myocardial viability determination (five systems) or cardiac perfusion studies (two systems).

US (VHA), Switzerland and Denmark had the highest volume of cardiac PET scans. The volume was roughly equivalent for viability and perfusion in US (VHA), whereas the majority of studies in Switzerland were for myocardial perfusion. Denmark, Quebec and Finland only reimbursed viability studies, while US (VHA) and Switzerland covered both indications.

Oncology. Oncology indications constituted the vast majority (65%) of publically reimbursed diagnostic PET scans. The majority of health systems reimbursed for head and neck cancer, lung cancer and lymphoma, with the remainder in breast cancer, colorectal cancer and melanoma. The highest volume of diagnostic PET scans was in evaluations categorized as "other" primarily in Denmark, but no specific information was made available. Other high volume uses were in lung cancer, lymphoma, head and neck cancer and colorectal cancer.

Further comparison in Table 5 indicates that 85% of reimbursed clinical PET scans were concentrated in four public health systems in Australia, Switzerland, Denmark and US (VHA). Except for Finland, The Netherlands and New Zealand, oncology indications constituted the majority of clinical PET reimbursement.

Table 6 shows the relative comparison of clinical PET activity taking into consideration the volume of patients served by each health system. US (VHA), Switzerland and Denmark reimburse the most PET scans per 100,000 patients. US (VHA) and Denmark concentrated activity in oncology, whereas Switzerland split most of its volume between neurology and oncology indications.

3. Trends in the US

Trends in acceptance and use of clinical PET noted by Ter-Pogossian (1992) persist throughout the 1990s, as most clinical PET activity continues to be concentrated in larger medical centers with affiliated research departments capable of supporting the cyclotrons. Other factors have been identified that influence clinical PET use in the US:

- the complexity and high cost of the technology (Coleman 1992; Flynn 1996);
- Food and Drug Administration regulations (Coleman 1992; Flynn 1996);
- slow development of reimbursement policies by third-party payers (Coleman 1992; Flynn 1996);
- health care reform (Flynn 1996);

- lack of demonstrated clinical utility (Flynn 1996).

Early efforts by PET advocates were ineffective in cultivating acceptance of its clinical potential within health care policy and medical communities. In 1991 individuals, institutions and industry officials in the PET community organized the Institute for Clinical PET (ICP) whose mission is to advance the science of PET and its development in the clinical setting. The ICP actively promotes clinical PET to providers, payers, patients and regulators on behalf of the clinical PET community (ICP 1999).

Complexity/Costs. The initial purchase and maintenance of a PET facility is a major impediment to capital investment in and, as a consequence, access to PET. The primary markets for traditional PET scanners are large regional hospitals and academic institutions.

PET manufacturers are focusing research and development on instrumentation and software that not only improve image quality and scanning performance, but also are lower in cost and user friendly. Lower cost traditional PET systems, mobile units, modified SPECT systems and networks of Radiopharmaceutical suppliers are expanding the market to include smaller hospitals and clinics. The ICP reports that there are approximately 150 PET centers with either traditional PET or modified SPECT systems in the US (ICP 1999).

Regulation--Food and Drug Administration (FDA). FDA has either approved or cleared for marketing both traditional PET cameras and gamma PET cameras to image radionuclides in the body. Considerable controversy has surrounded the jurisdiction of the FDA in regulating PET radiopharmaceuticals. Prior to 1997, FDA had approved only two PET radiopharmaceuticals for clinical PET use:

- Rb-82 limited to rest alone or rest with pharmacologic stress PET scans and 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 metabolism associated with foci of epileptic seizure. Approval for use is restricted to The Methodist Medical Center in Peoria, Illinois.

Supporters in the United States Senate were instrumental in codifying changes to the FDA Modernization Act of 1997 pertaining to FDA regulation of PET (Connell 1999). As a result of this law passing, FDA withdrew its previous regulation of PET drug products and manufacturing guidelines and is drafting new procedures to replace them (FDA 1997). An official ruling on the safety and effectiveness of three PET drugs, F-18 FDG, N-13 ammonia and O-15 water and on the proposed procedures for obtaining marketing approval for them will be forthcoming (FDA 1999).

Reimbursement. To a great extent, reimbursement for PET studies can influence its diffusion into clinical medicine. Because of the controversy surrounding FDA jurisdiction over PET radiopharmaceuticals, many payers have been reluctant to include PET as a covered benefit, until the dispute was resolved. Not surprisingly, the recent changes in the FDA regulation of PET radiopharmaceuticals have had a positive influence on reimbursement for clinical PET in the US.

Medicare—Medicare coverage policies frequently reflect FDA decisions and shape coverage decisions of other payers. Until recently, FDA approval of each site as a manufacturer of PET radiotracers had delayed Medicare reimbursement for clinical PET scans. The Health Care Financing Administration[2] (HCFA) has been continuously reviewing the scientific literature on clinical PET scans and, until the end of 1997, offered limited coverage for PET scans (See Table 7).

Table 7. HCFA-Approved Medicare Benefits for PET Scanning

Date	Indication(s)	Conditions for coverage
March 1995	Cardiac Perfusion Imaging Using Rb-82	• Medically necessary • Does not unnecessarily duplicate other covered diagnostic tests • Does not involve investigational drugs or procedures using investigational drugs • Used in place of SPECT or in addition to an inconclusive SPECT • Not for screening asymptomatic patients
January 1998	SPNs and Non-Small Cell Lung Cancer (NSCLC) Using FDG	• Uses traditional PET scanners or coincidence imaging gamma cameras • To characterize SPNs initially detected, usually by CT • To stage mediastinum in patients with confirmed primary NSCLC • Payment for the use of routine biopsy following a negative PET scan will be denied for these conditions, unless the claim is supported by evidence explaining the medical necessity of the biopsy
March 1999	Additional Oncology Indications Using FDG	• 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 • Identifying metastases in melanoma recurrence in place of gallium studies

Source: HCFA 1998

Intense pressure on the part of clinical PET advocates has influenced expansion of PET coverage in oncology and inclusion of SPECT with coincidence detection capability (Anonymous 1998). Interim coverage for PET scans is conditioned upon its ability to provide useful information for the management and treatment of patients with these conditions. HCFA will use the claims process to evaluate the impact of PET on clinical care and determine the extent to which they should modify future policy.

[2] Health Care Financing Administration of the Department of Health and Human Services administers the Medicare, Medicaid, and Child Health Insurance Programs. In addition, HCFA performs a number of quality-focused activities including development of coverage policies. http://www.hcfa.gov/

Veterans Health Administration (VHA)—Currently, VHA has ten PET scanners, and nearly all share operations with academic affiliates. VHA does not have a national coverage policy for PET scans; coverage decisions are made by each institution. Access to VHA PET centers is limited, and they are not evenly distributed throughout the system. Consequently, many VA medical centers without traditional PET facilities are upgrading dual-headed gamma cameras for coincidence imaging, or are affiliating with local PET centers in the private sector.

VHA is capitalizing on its investment in PET in several ways:

- by establishing a registry to collect important utilization data from VHA PET centers;
- by funding prospective outcomes research; and
- by conducting regular systematic review updates to track new data in the literature.

Private sector carriers—The ICP has successfully lobbied national and local carriers and is actively involving patients in its lobbying efforts (ICP 1999; Connell 1999). The ICP reports that, since 1996, there has been an increase in the number of insurance carriers now covering PET scans (See Table 8). Table 8 is not a complete listing of all carriers with approved coverage policies for PET, but it does illuminate the trend in PET coverage among private sector carriers in the US in recent years. Coverage decisions emphasize PET's use in oncology, particularly of the lung. However, most still reimburse on a case-by-case basis, and many require pre-approval.

Table 8. Approved PET Indications of Selected Private Carriers in the US

Source=ICP (personal communication: Ruth Tesar, ICP, May 1998).

Carrier	Approved indications
California Blue Cross	Lung, colorectal, head and neck, melanoma, SPN
California Blue Shield	Lung, colorectal, head and neck, melanoma, SPN
Empire BC/BS New York	SPN, lung cancer staging
Cigna/Health Source Provident	Colorectal, head and neck, melanoma, lung
Duke University	Brain tumors, colorectal
Kaiser-Permanente*	Epileptic foci when not identified by other means SPN in selected low risk patients
Aetna/USHealthCare**	Cardiac-Rb^{82} Brain tumor vs. necrosis, epileptic foci, and lung cancer on a case-by case basis Others, not specified
United Health Care	Several, not specified
Several, not specified	Brain tumors
Many, not specified	Epilepsy
Few, not specified	Cardiac-Rb^{82}

*personal communication: M. Sugarman, Kaiser-Permanente (May 1999)
**personal communication: R. McDonough, M.D., Aetna/USHealthCare (May 1999)

Health care reform. Unless otherwise noted, background information on health care reform is taken from Zelman (1996). Over the last two decades health care reform initiatives related principally to payment system restructuring are driving more explicit decisions about the use of health care resources. This section presents a condensed account of the current and most relevant reforms measures and the impact of these measures on the diffusion of PET into clinical care.

The introduction of a prospective, pre-determined payment system (called the Prospective Payment System) in 1983, departed from the traditional retrospective fee-for-service system. This has had a dramatic effect on health industry behavior (Holmes 1992). The new system of payment sharply curtailed public sector revenue to providers, who responded by increasing premiums to private payers, including employers. Private insurers quickly adopted the new payment system, which further decreased revenue to providers.

As premiums continued to rise at an alarming rate, payers, providers and consumers became more value-driven. Maximizing outcomes and productivity while containing costs have resulted in a growth in underwriting practices, managed care alternatives, outcomes research and patient consumerism. Increasingly, government intervention is sought: 1) to protect consumer value by lowering or limiting the rise in costs and maintaining or elevating quality, and 2) to foster or maintain competition, for example, by establishing basic minimum standards of care and requiring evidence of cost-effectiveness for benefit coverage.

In the above scenario, regulation and reimbursement primarily defined the market for PET. Early proponents for clinical PET sought to capitalize on a cutting-edge technology that showed potential both as a clinical tool and as a source of revenue (Flynn 1996). However, PET was introduced into clinical medicine when trends in health care decision making were transitioning from a rationale based primarily on resources and opinions to a rationale derived from research findings.

Today in response to reform pressures decision makers, who seek to optimize patient care by investing in diagnostic technologies, are insisting on scientific evidence that supports improved patient outcomes and cost-savings in addition to safety and improved diagnostic performance. The clinical research community is beginning to collaborate on evaluations of PET's utility in selected clinical areas (Adams 1998).

Clinical utility. Flynn (1996) reviewed assessments, guidelines and policy statements on clinical PET use produced by US organizations through 1994. Early findings or comments about the use of PET in clinical applications were generally based on expert opinion and non-systematic qualitative reviews. Comments emphasized PET's clinical "potential" in several areas, mainly neurology and cardiology, and its ability to provide unique clinical information. The added value of this information was not proven.

Since 1994 emphasis has shifted toward more rigorous methods of technology assessment. Results of such assessments of PET from US organizations published after 1994, which are in the public domain or otherwise made available to the authors for this report, are included and discussed in Part II.

C. Summary/Discussion

INAHTA members' experiences with PET since 1997 show wide variations in use and public reimbursement for clinical scans. PET's availability and use is still quite limited, as evidenced by the small numbers and relative under use of scanners in each country or region. Most PET scanners are confined to academically affiliated facilities, and most health systems (excluding VHA) have fewer than five PET scanners. FDG is the most common radiotracer used in clinical PET studies, and its availability is critical to PET facilities wishing to conduct diagnostic tests. FDG produced on-site requires a cyclotron, and commercial vendors of FDG can vary regionally.

The majority of PET scanners are used for both research and diagnostic studies, but there are exceptions. Local regulatory policies and funding sources may explain the variations in PET use among survey participants. For example, regulatory policies that stress clinical research to address gaps in knowledge of PET's clinical utility may explain the high frequency of research studies in some countries. In countries with a high concentration of clinical studies, private funding sources may be available to enhance clinical activity that would otherwise not be covered with public funding. The size and geographic distribution of the population served by each health system may further contribute to the variations in use.

The latest utilization data show that most clinical PET activity is concentrated in relatively few health systems and primarily in a few select indications in oncology and neurology. Whereas public financing is available for several oncology indications, nearly 70% of the volume is confined to evaluations of melanoma, lung cancer staging, and an undefined category of "other." Similarly, reimbursement is available for a number of neurological indications, but the vast majority of neurological PET activity is confined to distinguishing brain tumor versus radiation necrosis and to localizing epileptic foci in potential surgical candidates with intractable epilepsy.

High cost and technical complexity, regulatory policies, value-driven health care decision making and lack of demonstrated clinical utility had hampered the diffusion of clinical PET in the US. However, PET use and acceptance have been on the rise, particularly since 1997. Lower cost PET systems, mobile units, modified SPECT systems and commercialization of radiopharmaceuticals allow smaller hospitals and clinics to offer clinical PET capability. Well-organized promotions by the clinical PET community both in the US and abroad have been instrumental in supporting initiatives that increase demand for the technology and in changing policies that now permit limited reimbursement for PET despite the continued lack of evidence supporting its clinical or economic benefit.

PART II. SYNTHESIS OF TECHNOLOGY ASSESSMENTS OF PET

Several INAHTA members have conducted technology assessments of PET in response to the needs of their health care systems. Likewise, several private TA organizations in the US have evaluated PET for a range of clinical indications to support clinical policy makers. Each assessment addressed various research questions using an array of approaches. Synthesizing the assessments will expand the scope of each assessment into a single, comprehensive document.

A. Methods

The authors surveyed each INAHTA member for completed technology assessments on the clinical utility of PET. Three private US organizations also agreed to collaborate on the project: Blue Cross Blue Shield Association Technology Evaluation Center (BCBSA TEC), Emergency Care and Research Institute (ECRI), and HAYES, Inc. (HAYES).

B. Results

Appendix C contains information abstracted from each PET assessment. Full reports from INAHTA members are kept on file at the VA TAP; reports from BCBSA TEC, ECRI, and HAYES are proprietary. Thirty-one assessments from 13 organizations were synthesized for this review. The assessments reflect a variety of motivations for conducting the assessment, research questions, inclusion criteria and methodologies. As is the nature of health care technology assessment, organizations produced assessments for decision-makers in response to pressures to use or evaluate PET for one or more clinical indications.

Most assessments were qualitative systematic reviews and focused on evaluations of PET's clinical utility. The remainder comprised quantitative analyses, non-systematic reviews, report syntheses and expert panel consensus. ECRI, BCBSA TEC and MSAC used quantitative methods to analyze PET's utility and/or its economic impact in health care. Reports from CEDIT (Baffert 1999) in France and SFOSS in Switzerland outlined proposals for systematically evaluating PET in several clinical indications within their respective health systems; VA TAP (Adams 1998) reported results of an ongoing system-wide PET registry data collection effort.

To the extent that the inclusion criteria were either specified in the report or made available to the authors of this synthesis, most reports appraised literature published or otherwise available since 1990. BCBSA TEC (1997) and AHCPR (1998) extended their literature searches to 1985 and 1977, respectively. Organizations used electronic data sources extensively. Several reports included literature published in a range of languages, thus helping to minimize potential language bias. Unless otherwise stated, assessments appraised studies using PET with FDG, reflecting the radiopharmaceutical most often used in clinical PET studies.

All organizations assessed traditional full ring PET systems. Partial ring PET scanners, gamma cameras (SPECT) modified for coincidence detection and 511 keV collimated PET imaging are newly available, lower cost alternatives to traditional full ring PET systems but are not yet optimized for clinical use. However, they attract considerable interest, and their rapid diffusion into clinical care could have a substantial impact on national health systems. Accordingly, AHFMR,

CEDIT, NCCHTA and VA TAP addressed one or more of the alternatives to traditional PET in their reviews.

Report syntheses and updates are ongoing efforts of participating agencies to track the PET literature and are included in this report. OSTEBA and AETS (1995) synthesized several reports, including those from INAHTA members. AETS and NCCHTA used methodologies similar to VA TAP to expand on the VA TAP (Flynn 1996) report, and VA TAP updated its review in 1998. BCBSA TEC is in the process of updating its assessments, but the updates are not yet available to the authors of this synthesis. HAYES continues to update its assessments and has made them available for this report.

The major uses for clinical PET are grouped into three main categories: neuropsychiatry, cardiology and oncology. Technology assessments of PET in each category are discussed below. Indications for which assessment findings disagree or make for compelling discussion are described in more detail within each category.

1. Neuropsychiatry

Early PET activity focused on clinical and research indications in neurology and psychiatry. PET allows the qualitative and quantitative evaluation of cerebral physiology and the study of the biochemical bases for clinical diseases. The majority of indications in Table 9 employ FDG to study glucose metabolism using traditional PET systems.

Table 9. Assessments of Clinical PET in Neuropsychiatry by Organization and Indication

Organization	Report Date	Alzheimer's disease	Parkinsonism	Other neurodegenerative disorders	Epilepsy	Brain tumor					Cerebrovascular disorders	Other
						Differential diagnosis	Grading malig-nant gliomas	Recurrence vs. necrosis	Guiding stereo-tactic biopsy	Monitoring treat-ment		
AETS	May 1999	✓	✓		✓			✓				✓
AHCPR	Jul 1998				✓							
AHFMR	Aug 1998				✓							
BCBSA TEC	Mar 1997				✓	✓	✓	✓	✓	✓	✓	✓
CAHTA	1993	✓						✓				
CAHTA	1996											✓
CAHTA	1997											✓
HAYES	Jul 1997	✓	✓	✓	✓						✓	✓
MSAC	Nov 1990				✓							
NCCHTA	Feb 1999	✓	✓		✓						✓	
OSTEBA	Sep 1998	✓			✓							✓
VA TAP	Sep 1996	✓										
VA TAP	Dec 1998	✓										

Intractable epilepsy. The majority of patients with epilepsy use anti-epileptic medication to control seizure activity. Among patients whose seizures remain uncontrolled with medication (medically refractory or intractable epilepsy), most suffer from temporal lobe epilepsy. Resective temporal lobe surgery has been shown to be an effective treatment for appropriately selected patients with medically refractory complex partial seizures to avoid progressive brain injury due to uncontrolled seizures and the adverse effect of anti-epileptic medication.

Patients undergo pre-surgical evaluation to identify and delineate the epileptogenic foci and to determine resectability. In many cases the decision to proceed with surgery can be made based on information from a detailed history, observation and review of non-invasive electrophysiologic, neurophysiologic and structural imaging and can result in good postsurgical outcomes. Other tests such as invasive electroencephalography (EEG), MRI and functional imaging modalities may be used to help identify additional surgical candidates. Interictal (between seizures) PET using FDG records glucose hypometabolism that appears to be associated with the epileptogenic zone. PET has been suggested in the work up of these patients to complement MRI data and potentially to supplant or reduce the use of invasive EEG.

Eight organizations appraised the literature on PET for the pre-surgical localization of epileptogenic foci in patients with medically refractory complex partial seizures. Reports focused primarily on the use of interictal FDG PET to measure hypometabolic regions of the temporal lobe. Findings conflict regarding the quality of the available evidence on which to establish PET's efficacy for this indication. BCBSA TEC found that FDG PET imaging for these patients met their methodologic quality criteria; other assessments remarked on the limited quantity and quality of evidence available to establish PET's clinical utility.

Assessments suggested that the diagnostic accuracy of interictal FDG PET was comparable or superior to other functional imaging modalities used to confirm epileptogenic foci indicated by EEG or structural lesions on MRI. However, available evidence was insufficient to support replacing either invasive EEG or structural imaging with PET and had not supported using PET for many patients with non-temporal lobe epilepsy.

PET could potentially benefit a small minority of patients whose epilepsy is difficult to manage, but its impact on patient management decisions, eventual outcome and costs are as yet unknown. Several reports suggested that the use of PET in managing patients with intractable epilepsy be done in the context of well-designed prospective research protocols.

Alzheimer's disease[3]. In Alzheimer's disease (AD) the primary role of diagnostic testing has been the differential diagnosis of AD from reversible or treatable diseases. Functional imaging technologies have been used to improve diagnostic certainty and provide information on the pathophysiologic basis of AD and can aid in early diagnosis. While there is no cure for AD,

[3] A definitive diagnosis of AD is based on a typical clinical picture and histopathologic findings in samples of brain tissue at autopsy. In the absence of histologic confirmation of AD, patients are referred to as having a diagnosis of Dementia of the Alzheimer's Type (DAT). For simplicity, in this report AD is used to mean patients with DAT.

psychosocial techniques and drug therapies aimed at slowing disease progression are now available to help improve quality of life.

For differentiating Alzheimer's disease from other dementias, assessments generally agreed that the diagnostic accuracy of PET appeared comparable or superior to competing technologies like CT, MRI, SPECT or EEG, but was little and of low quality. Assessments concurred on the need for additional rigorous study. Reports acknowledged the importance of improved diagnostic information to AD patients and their families for coping and for future planning, but the value of improved diagnostic information to management of AD patients or to the improvement in clinical results was unknown. Further, the potential utility and accuracy of PET in AD should be viewed in the context of no available effective cure and of the accessibility and accuracy measurements of other diagnostic modalities, many of which have been more rigorously studied.

Brain tumors. For managing patients with brain tumors, primarily gliomas, BCBSA TEC found that in none of the indications was there sufficient scientific evidence to permit conclusions about the effect of PET on health outcomes. In the differential diagnosis of radionecrosis versus residual or relapsing tumor, CAHTA (1993) concluded that PET's diagnostic performance was superior to conventional diagnostic techniques (CT, MRI). AETS (1999) similarly pointed out that while PET appeared to be superior to MRI for this indication, PET was not superior to SPECT. Further, PET's impact on clinical management was undocumented, the overall quality of available evidence was limited, and further controlled study of PET was warranted.

Cerebrovascular and other neurodegenerative and neuropsychiatric disorders. Studies employ a variety of radiotracers with PET to evaluate cerebral metabolism and perfusion, to map cerebral regions and to locate receptor sites within the brain. Potential indications include differential diagnosis, assessing response to therapy and improved knowledge of disease mechanisms.

Reviews of the evidence recognized PET's contribution to the knowledge of the biochemical and physiological mechanisms of many cerebrovascular and neuropsychiatric conditions, but it was unclear whether the added information improved patient management or outcomes. Evidence comprising small and methodologically inconsistent studies and lack of normative data prevented definitively establishing PET's efficacy or cost-effectiveness for these indications. AETS, NCCHTA and OSTEBA recommended further prospective study to define the contribution of PET in these areas.

2. Cardiology

There is an extensive array of noninvasive strategies for diagnosing coronary artery disease (CAD). For patients with chronic left ventricular dysfunction who are being considered for revascularization by coronary artery bypass surgery or angioplasty, there is a need to accurately determine whether the myocardium is viable and likely to respond to improved blood flow. Traditionally, clinicians use noninvasive coronary perfusion imaging in these patients to diagnose and evaluate CAD and to determine viable and hibernating myocardium for potential

response to revascularization. Conventional techniques identify viable tissue by measuring perfusion, contractile reserve and cell membrane integrity (Cowley 1999). Standard coronary perfusion imaging consists of single photon emission computed tomography (SPECT) and planar scintigraphy using intravenous administration of thallium-201 or technetium-99m sestamibi during exercise or pharmacologic stress. These techniques often employ delayed imaging methods to identify viable tissue. Technetium-99m is also used for gated blood pool scanning to measure left ventricular ejection fraction (the capacity of the heart muscle to contract). Stress echocardiography further assesses global and regional wall motion abnormalities that may not be present at rest, and the use of magnetic resonance technologies in this area is evolving.

Traditional PET systems reportedly offer higher quality images over conventional testing. PET can image and quantify myocardial perfusion with a variety of tracers such as nitrogen-13 ammonia, oxygen-15 water, or rubidium-82. Most PET studies of myocardial viability utilize the radiotracers FDG and, to a lesser extent, C-11 acetate to detect active metabolism.

In this setting the metabolic information from PET may improve patient selection for revascularization and consequently the likelihood of successful surgery. PET may offer cost savings by eliminating unnecessary angiography and revascularization in inappropriate patients. Coincidence detection SPECT, high energy SPECT and 511 keV collimated positron imaging have been advocated as less costly, technically simpler and potentially more accessible alternatives to traditional PET systems.

Table 10. Assessments of Clinical PET in Cardiology by Organization and Indication

Organization	Report Date	Myocardial perfusion	Myocardial viability	Monitoring treatment response
AETS	Dec 1995	✓	✓	
AHCPR	Jan 1995	✓		
AHFMR	1999 (pending)		✓	
BCBSA TEC	Oct 1995	✓		
BCBSA TEC	1996	✓		
CAHTA	1993	✓	✓	
CEDIT	Apr 1998	✓	✓	
HAYES	May 1997	✓	✓	✓
HAYES	Jul 1999	✓	✓	
MSAC	Nov 1990	✓	✓	
NCCHTA	Feb 1999	✓	✓	
OSTEBA	Sep 1998	✓	✓	

Myocardial perfusion. AHCPR and BCBSA TEC confined their reviews to studies using the tracer rubidium-82, and BCBSA TEC further restricted its review to studies of patients at

intermediate risk of having CAD.[4] BCBSA TEC produced a cost-effectiveness analysis (Garber 1996) using the societal perspective and analytic assumptions from their 1995 clinical assessment. CEDIT appraised studies on the use of coincidence detection SPECT for conventional scintigraphy.

Reports generally agreed on the comparable or superior performance of PET to other myocardial perfusion imaging alternatives, particularly to thallium-201 SPECT, but the extent of the improvement in performance and its contribution to managing patients with CAD was unclear. PET was more costly than all other individual noninvasive strategies, and it had not been able to replace coronary angiography as the definitive standard for assessment of CAD in most symptomatic patients. PET for patients at intermediate risk as determined by BCBSA TEC was an unlikely cost-effective alternative to immediate angiography or to other noninvasive tests such as stress echocardiography or SPECT. Consideration should be given to the most overall cost-effective approach, but at present, evidence is needed to establish the relative cost-effectiveness of PET in diagnosing CAD.

Coincidence detection SPECT has the theoretical advantage of being able to image both positron-emitting and gamma-emitting radiopharmaceuticals. CEDIT found that there was no scientific evidence to support the use of coincidence detection SPECT as a replacement for conventional scintigraphy. Experts agreed that for either myocardial perfusion or viability studies no practical problem arose when coincidence detection SPECT was carried out using technetium and higher energy radiotracers, but that the quality of coincidence detection SPECT using low energy thallium could not be guaranteed.

Myocardial viability. For determining myocardial viability and/or predicting risk for cardiac events, most assessments found that PET appeared to have comparable sensitivity and superior specificity to other modalities, but the studies comparing PET's diagnostic performance to other functional imaging modalities were few and methodologically flawed. With regard to improving the likelihood of successful revascularization and cost savings, the data were insufficient to confirm the relative cost-effectiveness of PET. AHFMR determined that the data were similarly limited for all other functional imaging modalities (SPECT, dobutamine echocardiography and MRI). However, CAHTA suggested a limited role for FDG-PET for patients with inconclusive results on delayed thallium-201 reinjection imaging. HAYES (1999) concluded from the evidence that PET information is clinically useful only for patients who are suitable candidates for revascularization.

NCCHTA identified as a major research priority the relative cost-effectiveness of coincidence detection SPECT and 511 keV collimated PET for selecting patients for myocardial revascularization. AHFMR stated that any use of PET for this indication in Alberta, Canada should be associated with prospective studies involving long-term follow up.

[4] defined as 25% – 75% probability of having either a 50% or greater left main coronary artery occlusion or a 70% or greater occlusion of any other coronary artery.

Monitoring response to treatment. HAYES (1997) concluded that PET's efficacy had not been firmly established for assessing the effects of pharmacologic therapy or risk factor modification techniques in subjects with CAD, hypertension or cardiomyopathy.

3. Oncology (non-central nervous system tumors)

Reliance on tumor histology and anatomy limits the oncologist's tools for selecting the most favorable treatment. Since tumor metabolism and blood flow often differ from adjacent tissue, adding functional information may expand the oncologists' ability to optimize treatment. PET has been used to detect, stage and grade tumors, discern recurrence from treatment changes, predict tumor response to therapy and monitor response to therapy. FDG is the most commonly employed radiopharmaceutical in PET cancer studies.

Table 11. Assessments of Clinical PET in Oncology by Organization and Primary Tumor Site and/or Indication

Note: This section considers only non-central nervous system (non-CNS) primary tumors.

Organization	Report Date	Head & neck	Breast	Lung staging	SPN	Pancreatic	Ovarian	Prostate	Colorectal	Melanoma	Lymphoma	Other
AETS	Oct 1997	✓	✓	✓	✓	✓	✓		✓	✓		
BCBSA TEC	May 1997	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CAHTA	1993	(indications not specified)										
CEDIT	Feb 1998		✓	✓					✓		✓	
CEDIT	Mar 1999	✓		✓						✓	✓	✓
ECRI	May 1998			✓								
ECRI	Jun 1998			✓								
HAYES	Mar 1998			✓		✓	✓	✓				✓
HAYES	Jul 1999		✓						✓	✓	✓	
NCCHTA	Feb 1999	✓	✓	✓	✓				✓			
OSTEBA	Sep 1998	✓	✓	✓	✓	✓			✓	✓		✓
VA TAP	Sep 1996	✓	✓	✓	✓				✓			
VA TAP	Dec 1998	✓	✓	✓	✓				✓			

Staging non-small cell lung cancer (NSCLC) and diagnosing solitary pulmonary nodules (SPN). Assessments disagreed on the degree to which the prevailing evidence supported PET as a strategy for staging NSCLC and diagnosing SPNs. BCBSA TEC's qualitative review and ECRI's quantitative analyses produced the most favorable conclusions based on published evidence. BCBSA TEC determined that FDG PET imaging met their criteria for both lung cancer indications, provided the PET results could change management. After thorough sensitivity analyses ECRI concluded that PET was cost-effective for staging NSCLC PET to confirm resectability based on a negative mediastinum on CT. PET was not cost-effective when used earlier in the diagnostic algorithm or when diagnosing SPNs.

Other agencies found the existing body of evidence on PET's efficacy insufficient to establish a role for PET in staging NSCLC or diagnosing SPNs. Lung cancer constitutes a considerable burden to the health systems represented by INAHTA agencies. Consequently, several advocated rigorous comparative study of PET, including coincidence detection SPECT and partial ring PET versus traditional PET, to alternative strategies to clarify PET's role in staging NSCLC.

All other indications. Based on evidence from 1977 through 1998, reviews were unable to firmly established PET's role in all other oncology indications. Recent 1999 reviews by HAYES confirmed these findings in breast cancer, melanoma and lymphoma but suggested a plausible complementary role for PET with conventional imaging to confirm suspicious post-treatment colorectal cancer recurrence, if results will significantly alter patient management or improve outcome. However, within certain health systems there is focused interest in PET for diagnosing and staging patients with breast cancer, lymphoma and melanoma.

Several agencies stressed the need for further research to define or support the relative contribution of PET in the management of patients with these cancers. Recent assessments by NCCHTA and VA TAP (Adams 1998) advocated rigorous study of positron coincidence imaging alternatives in the oncologic work up. CEDIT (Baffert 1999) and SFOSS are instituting clinical protocols to systematically collect data on the use of PET in selected oncology indications.

C. Summary

Assessments, founded collectively on evidence available since 1977, provide valuable insight into clinical trends and the body of knowledge used to suggest PET's clinical utility thus far. Available research assessed the feasibility of using primarily traditional full ring PET in certain clinical situations and on defining its accuracy as a diagnostic test.

There was uniform agreement that critical research into defining the clinical consequences of using PET on treatment decisions and health outcome has not been studied. While deficiencies in the evidence prevented most organizations from firmly establishing a clinical role for PET, some identified plausible roles in view of the clinical context and PET's availability and diagnostic performance relative to alternative modalities (Table 12).

Differences among report conclusions generally indicated the degree to which the evidence met the assessments' quality assessment criteria, where reported. Other possible reasons may have included the rationale for the assessment, focus of the report, inclusion criteria and analytical methods. Therefore, methodologic transparency is critical to health care organizations wishing to make valid comparisons of technology assessments and establish policies based on the best available evidence.

Table 12. Potential Clinical PET Indications Identified by INAHTA PET Collaboration Participants

Clinical indication	*Evidence suggests…*
Diagnosing seizure foci in intractable epilepsy	• PET's diagnostic accuracy was comparable or superior to other functional imaging modalities used to confirm foci identified by EEG or MRI, but PET is not yet able to replace invasive EEG or structural imaging. • Diagnostic contribution of all functional imaging for this indication is still questioned.
Diagnosing Alzheimer's dementia	PET's diagnostic accuracy was comparable or superior to competing technologies (CT, MRI, SPECT, EEG), but the value of improved diagnostic information to management of AD patients or to improved clinical results was unknown.
Diagnosing brain tumor recurrence vs. radiation necrosis	PET's diagnostic accuracy was superior to conventional diagnostic techniques (CT, MRI) but not to SPECT.
Assessing myocardial perfusion in patients with coronary artery disease (CAD)	• PET's diagnostic accuracy is improved over other imaging alternatives, particularly thallium-201 SPECT, but the extent of improvement is unclear. • PET is more costly than all other individual noninvasive strategies. • PET is unable to replace coronary angiography as the definitive standard for CAD assessment in most patients.
Assessing myocardial viability	• PET has comparable sensitivity and superior specificity to other modalities. • Quality of data for evaluating the performance of SPECT, dobutamine ECHO and MRI are similarly limited.
Diagnosing and staging non-small cell lung cancer	PET may be cost-effective for staging lung cancer to confirm resectability in patients with a negative mediastinum on CT.
Characterizing solitary pulmonary nodules	PET may have utility when other diagnostic tests are inconclusive.

It should be noted that the evidence supporting many technologies used in routine practice and for which coverage policies exist are similarly deficient and often show diagnostic performance inferior to PET (e.g. myocardial viability diagnostic testing). Further, the value of improved diagnostic accuracy with PET or with other modalities is questioned in certain indications for which there is no cure or effective treatment to improve prognosis (e.g. Alzheimer's dementia).

Review of assessments shows both encouraging and disturbing trends in the advancement of knowledge regarding PET's clinical utility. Neuropsychiatric and, to a lesser extent, cardiac clinical indications have been studied since the early 1980s. Yet after almost two decades questions of PET's clinical utility persist and hamper its diffusion into clinical practice.

In recent years there have been positive trends in the regulation and use of PET in oncology in spite of the lack of supportive evidence. As pressure on our health care resources increases, similar trends are seen in the use of lower-cost nuclear medicine systems modified for positron emission coincidence detection. Questions of PET's utility in oncology could follow a path similar to its other indications, unless rigorous, prospective clinical research is conducted.

In light of limited health care resources, some organizations recommended approving use on a case-by-case basis in select indications for which there are limited diagnostic options. Some conditioned PET use on its ability to affect patient management decisions or restricted its use to subgroups of patients who met explicit selection criteria. Most identified clinical PET as a major research

priority for their respective organizations and recommended well-designed prospective clinical studies to assess the relative contribution of traditional and/or modified PET. Several INAHTA agencies reported on rigorous research efforts either underway or proposed within their health systems to help clarify the contribution of PET to clinical medicine, which for now remains elusive.

APPENDIX A. 1997 INAHTA PET SURVEY

1. Number, type and use of PET scanners (human subjects only).

PUBLIC scanners

	Type		Scans/ year	
Organisation and city	Body PET	Small	Research	Clinical

PRIVATE scanners

	Type		Studies/ year	
Organisation and city	Body PET	Small	Research	Clinical

2. Diagnostic application and public reimbursement

		Diagnostic use		**Public Reimbursement**	
Diagnostic applications		Yes	No	Yes	No
Neurology	Epilepsy				
	Tumor vs necrosis				
	Neurodegenerative disorders				
	Other.....				
Cardiology	Viability				
	Ischemic heart disease				
	Other.....				
Oncology	Head and neck				
	Colorectal				
	Breast				
	Lung				
	Solitary pulmonary nodules				
	Haematological				
	Hepatobiliary				
	Soft tissue				
	Genitourinary				
	Gynaecological				
	Other.....				
Other					

APPENDIX B. 1999 INAHTA PET SURVEY

Activity for the time period (1 July 1998 – 30 June 1999)

Diagnostic applications		Public Reimbursement	
		Yes (Number)	No
Neurology	Epilepsy		
	Alzheimer disease		
	Parkinsonisms		
	Neurodegenerative disorders		
	Tumour vs necrosis		
	Other.....		
Cardiology	Myocardial Viability		
	Coronary artery disease		
	Other.....		
Oncology	Head and neck		
	Colorectal		
	Breast		
	Lung		
	Solitary pulmonary nodules		
	Lymphomas		
	Hepatobiliary		
	Pancreas		
	Thyroid		
	Soft tissue		
	Melanoma		
	Genitourinary		
	Gynaecological		
	Other.....		
Other	.....		
	.....		

Type of Reimbursement: __ Case by Case __ Regular Basis __Other……

Number of PET Scans in the Country or Region: …….

Health Care Financing Organisation ……..

Level (National, Regional or Local): ……..

APPENDIX C. INAHTA PET COLLABORATION ASSESSMENTS OF CLINICAL PET

Organiza-tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
AETS	Dec 1995	Myocardial perfusion Myocardial viability	Not specified	Synthesis of reports from ECRI and AHCPR	Criteria not specified	• PET and SPECT appear to perform similarly for diagnosing coronary perfusion in coronary disease and for making subsequent management decisions (AHCPR). • Substituting PET for SPECT or vice versa for determining myocardial viability depends on which is more cost-effective to use (ECRI).
AETS	Oct 1997	Head and neck Recurrent colorectal Breast cancer Lung cancer SPN Pancreatic Metastatic melanoma Ovarian cancer	VA TAP PET report through 1995, MEDLINE and HEALTHPLAN through 1996	Systematic review	EBM criteria used for grading quality of evidence Fryback and Thornbury scale used for classifying selected articles	• No definitive conclusions can be made relative to the contribution of PET in the management of the oncologic patient. • PET seems to offer a good alternative for lung cancer staging and SPN diagnosis. • As there exists no controlled clinical trials, PET is deemed an investigative technology. • Rigorous, clinical trials are needed to assess the clinical benefit of PET in all clinical indications.

AETS	May 1999	Alzheimer disease
		Parkinsonisms
		Epilepsy
		Brain Tumors
		Other less frequent
			MEDLINE 1995-Dec 1997
			Extended to the end of 1998 for radionecrosis vs. Residual-relapsing lesions.
				Systematic review	EBM criteria used for grading quality of evidence
					
					Fryback and Thornbury scale used for classifying the 48 selected articles
						• FDG-PET has proven clinical utility in the management of:
						  • Refractory complex partial seizures and temporal epilepsy candidates for surgery, as a complementary diagnostic and prognostic tool. FDG-PET does not preclude invasive methods in most cases.
						  • Differential diagnosis between radionecrosis and residual or relapsing tumoral lesions.
						  • FDG-PET aids in the early diagnosis of AD. This fact doesn't modify the current clinical management of this disorder.
						• There is a remarkable lack of studies and of methodological quality guided to establish the PET's utility in handling of specific clinical situations, and its contribution in improving therapeutic results.
						• Recommend developing appropriately designed prospective studies mainly to answer questions of great interest for the National Health System in order to use PET most effectively.
						• PET use should be controlled according to a research protocol.

AHCPR	Jan 1995	myocardial perfusion	Not specified	Health Technology Review	Criteria not specified	• Rb-82 PET and Thallium 201 SPECT appear to be useful for evaluating myocardial perfusion and making further management and therapeutic decision in cardiac patients. • It was not apparent from the available data, which varied over the same wide range, whether improved images with RB-82 PET led to better sensitivities and specificities than those of Thallium 201 SPECT. • PET with Rb-82 is more costly than planar scintigraphy, 201 Thallium SPECT, echocardiography, but costs less than angiography. Whether using a more expensive technology is necessary in particular situations might be considered when making mgmt, and therapeutic decisions in cardiac patients.

Organiza -tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
AHCPR	Jul 1998	Localization of epileptogenic foci	MEDLINE and Healthline from 1977 through 1996	Systematic review	Criteria not specified	• 70-80% of patients with interictal PET scans demonstrated hypometabolism in areas concordant with the epileptogenic foci indicated by other diagnostic tests such as EEG and MRI. • Many PET scans appear to miss a substantial number of EEG-identified foci and appear to indicate abnormalities that were discordant with EEG findings. • Available data were insufficient to determine whether PET scans might serve as a reliable substitute for EEG or what PET contributes to the management of patients with intractable, complex partial seizures. • Further studies are needed before a role for FDG PET in complex partial seizure can be defined.
AHFMR	Aug 1998	medically refractory epilepsy (MRE)	Embase, MEDLINE, HealthStar, ECRI from 1993-Nov 1997	Systematic review	Scope of studies based on Fineberg et al. 1977 classification Methodolgic quality based on: Study design Description of study population Diagnostic method Determination of diagnostic accuracy and validity Influence on management Influence on outcomes	• PET would be used as a complement to anatomical imaging methods such as MRI and would increase the cost of management. • PET has advantages over existing functional imaging methods in terms of accuracy of localization of lesions in patients with MRE. • PET is not helpful for many patients with non-temporal lobe epilepsy. • Quality of the available evidence on PET's performance and impact is limited. • Further work is needed to define PET's role and economic costs and benefits. • Any use of PET in managing Albertan patients with MRE should be in the context of well designed studies to evaluate PET's clinical & economic impact.

Organiza-tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
AHFMR	1999 (release pending)	Functional diagnostic imaging in the assessment of myocardial viability in patients considered for revascularization includes use of FDG PET and some reference also to N-13, C-11 and Rb-82 studies (Two volumes)	MEDLINE, EMBASE, ECRI 1993-November 1998	Systematic review Interest in accuracy, effects on patient management and outcome.	Quality of evidence on accuracy: Poor – Fair Quality of evidence on Outcomes: Poor Detailed criteria for the following attributes: Determination of diag. accuracy & validity Study design Description of study pop. Characteristics of the assessed FDI technique Follow-up & outcome analysis:	• For accuracy, in terms of identifying viable regions of the myocardium, PET and echo seem to offer similar levels of performance. However, given the quality of the studies, there is limited evidence of accuracy of these methods in this application. • There is little information on the contribution of these methods to patient outcomes. There is some evidence that PET is able to predict outcomes, but this is not conclusive. • The promise of PET in assessment of MV is not yet matched by convincing evidence of benefit to health care, data on comparative performance are limited and technical development continues to be rapid. Any use in Alberta should be associated with prospective studies involving long term follow up of patients.

BCBSA TEC	May 1997	Lung Cancer
		Breast Cancer
		Pancreatic Cancer
		Colorectal Cancer
		Head and Neck Cancer
		Lymphoma
		Melanoma
		Musculo-skeletal Tumors
		Miscellaneous
		Thyroid, Parathyroid, Ovarian, Hepatocellular, Thymoma, Prostate, Germ Cell, and esophageal
			MEDLINE
			January 1985 – April 1997
				Systematic review
				(dedicated PET systems only)
					Study design: prospective, retrospective, uncertain
					Representative patient sample: yes, no, uncertain
					PET interpretation: quantitative, qualitative, uncertain
					Masked observers: yes, no uncertain
					Within-subjects comparison of alternative imaging technique: yes, no, uncertain
					Consistent and appropriate reference standard: yes, no, uncertain
					Clear and complete presentation of data to permit 2x2 table calculation
						• FDG PET imaging meets the BCBSA TEC criteria for 2 indications in lung cancer:
						  • Staging mediastinal lymph nodes.
						  • Diagnosing solitary pulmonary nodule in patients in whom chest x-ray and computed tomography have failed to distinguish benign from malignant disease, when the results of the test could change management.
						• FDG PET imaging does not meet BCBSA TEC criteria for all other uses in imaging non-CNS tumors because the scientific evidence did not permit conclusions concerning the effect of the technology on health outcomes.
						• **NOTE: This TEC Assessment is currently being updated and these conclusions may change based on additional evidence review.**

BCBSA TEC	Mar 1997	Neurologic indications: Differential dx of symptomatic intracranial masses Differentiation of low-grade and high-grade brain tumors Guidance of stereotactic biopsy or biopsies of documented intracranial masses recurrent brain tumor from radionecrosis Monitoring treatment response in patients with brain tumors	MEDLINE 1985 – February 1997	Systematic review	Criteria as above	• FDG PET imaging does not meet BCBSA TEC criteria for any of the CNS tumor indications reviewed because the scientific evidence did not permit conclusions concerning the effect of the technology on health outcomes. • **NOTE: This TEC Assessment is currently being updated and these conclusions may change based on additional evidence review.**

Organiza-tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
BCBSA TEC	Mar 1997	medically refractory complex partial seizures in potential surgical candidates	MEDLINE 1985 – Feb 1997	Systematic review	Criteria as above	• FDG PET imaging meets the BCBSA TEC criteria for the evaluation of patients who have medically refractory complex partial seizures and are potential candidates for surgery. All other uses of PET for the management of seizure disorders do not meet BCBSA TEC criteria.
BCBSA TEC	Mar 1997	Detecting Acute Ischemia Assessing Aphasia	MEDLINE 1985 – Feb 1997	Systematic review	Criteria as above	• FDG PET imaging does not meet the BCBSA TEC criteria for the evaluation of cerebrovascular disease because the evidence was not sufficient to permit conclusions about the diagnostic performance characteristics of PET.
BCBSA TEC	1996	PET Myocardial Perfusion Imaging for the Detection of Coronary Artery Disease companion to clinical assessment below		Cost-Effectiveness Analysis from societal perspective		• The CEA compared immediate angiography versus using PET, SPECT, Stress Echo, Planar Thallium, or Exercise Treadmill Testing (ETT) as diagnostic tests to select patients for angiography in a population with intermediate risk* of CAD. The base case was a 55 yr old man with 50% risk of CAD. • CE ratio of PET was quite high and not within the range of other technologies generally accepted to be cost-effective. The incremental cost-effectiveness of PET compared with SPECT was $900,000 per life year or $490,000 per QALY. * defined as 25% – 75% probability of having either a 50% or greater left main coronary artery occlusion or a 70% or greater occlusion of any other coronary artery.
BCBSA TEC	Oct 1995	Myocardial perfusion in patients at "intermediate" risk of having CAD	MEDLINE through Aug 1995	Systematic review and pooled analysis of PET performance	Criteria as above	• PET imaging using ^{82}Rb for the detection of coronary artery disease in patients at intermediate risk* of having coronary artery disease meets the BCBSA TEC criteria. * defined as 25% – 75% probability of having either a 50% or greater left main coronary artery occlusion or a 70% or greater occlusion of any other coronary artery.
CAHTA	1993 (internal use)	Myocardial perfusion Myocardial viability Brain tumor recurrence vs. necrosis Alzheimer's diagnosis Oncology	Not Specified	Literature Review	Criteria not specified (however methodological limitations are addressed)	• For myocardial perfusion, differences in sensitivity and specificity between PET and SPECT (using new isotopes) are negligible. • FDG18-PET can be a support technology to identify myocardial viability and to assess the feasibility for a revascularization procedure for those patients with an inconclusive diagnosis using conventional technologies (Thallium-201 reinjection after 4 hours) • PET has shown to be superior to diagnostic conventional techniques (CT, MRI) in the differential diagnosis between post-radiation tissue necrosis and tumor recurrence. • PET is useful in the differential diagnosis between Alzheimer's and other dementias. However, the therapeutic approach of the Alzheimer patient does not change with the information. This indication is still considered experimental. • PET seems to have a great potential in the early detection of cancer. However, its use is still in the experimental stage.
CAHTA	1996 (briefing)	Autism	Medline 1986-96 Search strategy specified	Synthesis of the scientific evidence	Criteria not specified (however quality of the scientific evidence was addressed and discussed)	• The scientific evidence shows lack of a consistent anatomical or metabolic image which can be associated with the presence of autism. The available studies have a low methodological quality. PET is still an experimental technology for this clinical indication.

Organiza-tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
CAHTA	1997 (briefing)	PET & Stereotactic Surgery for patients with neuropsychiatric disorders	Mediline 1986-1996 Search strategy specified	Synthesis of the scientific evidence	Criteria not specified (however quality of the scientific evidence was addressed and discussed)	• No conclusive scientific evidence has shown a consistent PET brain image pattern associated to different neuropsychiatric disorders. Study results are questioned due to their methodological limitations. PET is still an experimental technology.
CEDIT	Feb 1998	FDG-PET and coincidence detection PET (CDPET) imaging in Assistance Publique-Hôpitaux de Paris (AP-HP)	Not specified	Expert panel	Criteria not specified	• Assessment addressed technical aspects, clinical uses, economics, regulatory issues, and recommendations from the perspective of the AP-HP system • Literature is inconclusive but appears to support positron imaging in prostatic cancer and has potential value in at least 4 areas: bronchopulmonary cancer, colorectal cancer, lymphoma, and breast cancer. • CEDIT recommends establishing a PET center for AP-HP cancer patients for routine oncologic use and funding comparative studies of PET versus CDPET in pre-operative staging patients with lung cancer for diagnostic contribution and effectiveness.
CEDIT	Feb 1998	CDPET for conventional scintigraphy	Not specified	Expert panel	Criteria not specified	• Evidence is non-existent • Using CDPET to conduct scans using Technitium and higher-energy tracers does not seem to pose any problem • The quality of Thallium scans using CDPET is not guaranteed. • CEDIT does not recommend that a comparative study of conventional gamma cameras vs. CDPET using Thallium be carried out.
CEDIT	March 1999	Patient-care protocols in AP-HP to evaluate FDG-PET in : lung cancer digestive cancer lymphoma ENT cancer Future clinical research programs in: biliary tract cancer melanoma childhood cancer	not applicable	not applicable	not applicable	• CEDIT approved recommendations issued in October 1997. • For conditions in which literature is deficient, protocols will include medical/economic studies taking into account feasibility, effectiveness in improving patient care and estimating the population impact. Expected annual patient enrollment=1,600. • Scientific committee will be assembled to oversee patient accessibility and scientific quality, comprised of experts in nuclear medicine, PET, radiopharmacology, disease treatment, scientific methodology and external scientific authority, and representatives from AP-HP and CEDIT. • Organizing committee will supervise PET Center operations and assess accessibility to other hospitals. • CEDIT recommends that AP-HP central pharmacy establish procedures to ensure quality and permanence of FDG supplies.
ECRI	May & June 1998	Non-small cell lung cancer	Multiple sources including Cochrane CD, Current Contents, EMBASE, HealthSTAR, HSRPROJ, IHTA, MEDLINE, various web sites, gray literature from 1990-97	Systematic review, meta-analysis, cost-effectiveness analysis	No specific criteria used	• PET is not cost-effective for diagnosing an SPN as malignant or benign. Instead, CT should be used, with positive results confirmed with needle biopsy. • PET is cost-effective for staging proven NSCLC when it is used only for confirming negative CT findings of suspected metastases (mets) to unresectable lymph nodes of the mediastinum. • Mediastinal biopsy is preferred to PET for confirming positive CT findings of mediastinal node mets.

Organiza -tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
HAYES	May 1997	myocardial perfusion myocardial viability monitoring response to treatment for cardiac disorders	Medline HEALTHSTAR EMBASE Current Contents Additional Info: FDA, the ACC, and the AHA	evidence-based evaluation or systematic review	HAYES Rating system: [description] **B** rating for use as a noninvasive method for detecting the presence and severity of CAD, determining myocardial viability, and assessing response to therapy in symptomatic patients **D** for diagnosing myocardial viability in subjects with LBBB	• The evidence of PET's efficacy is fraught with methodologic flaws and inconsistent methodology. • PET's efficacy for assessing response to revascularization, pharmacologic intervention, or risk factor modification in subjects with CAD, HTN, or cardiomyopathy is not firmly established. • Because of limited availability, multicenter trials or meta-analyses are required to confirm efficacy. Additional study is needed to determine the cost-effectiveness of PET and to clarify controversial issues.
HAYES	Jul 1999	myocardial perfusion myocardial viability	Medline HEALTHSTAR EMBASE Current Contents Additional Info: FDA, the ACC, and the AHA 1966-7/99	evidence-based evaluation or systematic review	**A** rating for determining myocardial viability in individuals with CAD and left ventricular dysfunction (LVD) who are suitable candidates for revascularization **B** rating for use as a noninvasive method for detecting the presence and severity of CAD in symptomatic patients **D** for diagnosing CAD in asymptomatic individuals	• Evidence suggests that PET is the most accurate and reliable noninvasive strategy for detecting the presence and severity of CAD. PET will not replace cor. angiography in most symptomatic patients with suspected CAD. • The primary cardiac indication is assessing myocardial viability and identifying those with CAD and LVD who are at high risk for cardiac events and who would most benefit from revascularization. PET information is clinically useful only in those in whom successful revascularization is likely.

HAYES	July 1997	Alzheimer's d. (AD)
		Huntington's d. (HD)
		Wilson's d. (WD)
		Parkinson's d. (PD)
		Epilepsy
		schizophrenia
		addiction, chronic substance abuse
		ADHD
		head trauma
		cerebrovascular disease
			MEDLINE
			EMBASE
			Current Contents
			HealthSTAR
			1ascuto May, 1997
				evidence-based evaluation or systematic review	**C** for all indications except:
					B for localizing seizure foci in subjects with intractable epilepsy
					D for assessing ADHD, head trauma, and schizophrenia
						• For the applications reviewed, the efficacy of PET has not been firmly established dueuto the paucity of evidence or quality of evidence available for each. Data suggest that:
						  • FDG PET, particularly in combination with surface EEG, is highly effective in localizing seizure foci
						  • FDG PET is valuable in understanding mechanisms of disease and drug intervention, which could lead to improved management of many conditions
						  • In identifying foci, PET may be superior uto MRI, CT and SPECT.
						  • FDG PET may be comparable or better than other current diagnostic modalities in differentiating AD from other neurologic diagnoses.
						  • PET may have limited value in assessing certain psychiatric or psychologic disorders, as well as cerebrovascular disorders and ischemia.

HAYES	March 1998	lung cancer	Medline-MESH 1992-1997 completed 11/24/97	evidence-based evaluation or systematic review	**B** for differentiating benign and malignant lesions and for staging with FDG PET **C** for differentiating recurrence and treatment-induced changes with FDG PET **D** for monitoring response to treatment with C-11-MET PET	• The efficacy of PET for each application reviewed has not been firmly established due to the paucity and/or quality of available evidence. • No cost-effectiveness studies could be found regarding the use of PET for lung cancer. It has not been proven in most cases whether the additional information provided by PET translates into improved patient management or outcomes. • Further study is required to define the role of PET for each application.

Organiza -tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
HAYES	March 1998	other oncology indications: breast, pancreas, colorectal, ovarian, prostate, urinary bladder, pituitary, thyroid, neuroendocrine, gastrointestinal, testicular, kidney, malig. melanoma, and lymphoma	Medline-MESH 1992-1997 completed 11/24/97	evidence-based evaluation or systematic review	Breast: **C** for differentiating benign versus malignant lesions, staging, and treatment monitoring Pancreas: **C** for differentiating ben. from malig. lesions and staging with FDG PET Urinary bladder: **C** for detecting perivesical tumor growth and distant mets and for early detection of recurrence Colorectal: **C** foe detecting and staging, identifying recurrence, and monitoring treatment response with FDG. Ovarian: **C** for differentiating benign and malignant lesions and identifying recurrence. Malig. melanoma: **C** for disease staging. Malig. lymphoma: **C** for detecting and staging disease, clarifying tumor grade, identifying recurrence, and monitoring treatment response. Prostate: **D** for detecting and grading tumors, staging, and detecting recurrence.	• The efficacy of PET for each application reviewed has not been firmly established due to the paucity and/or quality of available evidence. • No cost-effectiveness studies could be found for PET oncologic imaging. It has not been proven in most cases whether the additional information provided by PET translates into improved patient management or outcomes. • Further study is required to define the role of PET for each application.
HAYES	Jul 1999	malignant lymphoma malignant melanoma breast cancer colorectal cancer (CRC)	MEDLINE EMBASE Current Contents HealthSTAR 1966-3/99 for lymphoma, melanoma and breast cancer; 1985-3/99 for colorectal cancer	evidence-based evaluation or systematic review	not specified	• Evidence suggests that PET may prove to be a feasible replacement for one or more standard tests used in the oncologic work up. • For patients with malignant lymphoma, malignant melanoma, or breast cancer, further study is needed to compare PET with alternative strategies and to prove improved clinical outcome with the use of PET. • For patients with CRC, PET could be considered medically necessary when used in conjunction with normal or equivocal results on conventional imaging to confirm suspicion of recurrence post-treatment, if the results will significantly alter patient management or improve outcome. • Additional study is needed to compare PET with alternatives for diagnosing primary CRC and detecting recurrence, and to define criteria for selecting which patients would benefit from PET.

Organiza-tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
MSAC (formerly NHTAP)	Nov 1990	Myocardial perfusion Myocardial viability Localization of epileptic foci in surgical candidates with medical refractory epilepsy grading malignant cerebral gliomas recurrent glioma vs. radiation necrosis	Not specified	Narrative review with cost analysis	Criteria not specified	• Sufficient case has not yet been established for routine use of PET as a clinical service in Australia. • If proposed PET units are introduced into Australia, they should be subject to a coordinated evaluation of clinical and cost benefits. No further units should be considered until evaluations are completed.

NCCHTA	Feb 1999	Head and neck cancer
		Breast cancer
		Lung cancer
		SPN
		Colorectal cancer
		Alzheimer's Disease
		Cerebrovascular disorders
		Epilepsy
		Parkinson's Disease
		Dementia
		Myocardial perfusion
		Myocardial viability
			Ovid MEDLINE and Cochrane Library from 1996-98	Systematic review
				(updates and expands 1996 VA TAP report)
				three-round Delphi survey to identify research priorities for the NHS
						• Under Council review
						• Report includes myocardial and neuropsychiatric applications and all positron imaging modalities
						• Evidence related to diagnostic accuracy is limited by bias and often relates only to small patient numbers.
						• Evidence is needed on the cost-effectiveness of positron imaging modalities in all of the advocated clinical indications
						• Research priorities identified in descending order:
						  • relative cost-effectiveness of full ring PET and gamma camera PET to pre-operatively stage patients with lung cancer
						  • compare partial ring to full ring PET in oncology
						  • relative cost-effectiveness of full ring PET and gamma camera PET to stage and monitor treatment response in patients with breast cancer
						  • relative cost-effectiveness of gamma PET to collimated 511 keV positron imaging for selecting patients for myocardial revascularization surgery

Organiza-tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations

OSTEBA	Sep 1998	head & neck
		colorectal
		breast
		lung
		SPN
		brain
		pancreatic
		melanoma
		soft tissue
		myocardial perfusion
		myocardial viability
		epilepsy
		West infantile spasms
		Lennox-Gastaut syndrome
		Alzheimer's d.
			Cochrane Library, INAHTA, ACP Journal Club from 1994-1998, PET reports from AETS, AHCPR, VA	Literature synthesis, utilization survey		• Studies of good methodologic quality are needed to establish PET's role in routine clinical practice
						• In certain situations PET may have complementary utility, possibly a future with hybrid or fusion imaging
						• PET could be appropriate on a case by case basis, taking into account characteristics of the disease, patient conditions, the diagnostic problem, the quality of the complementary information that can be obtained and its possible influence in clinical decision making.
						• It may be appropriate to initiate a registry of all cases in which the problem occurs, to advance knowledge of the practical value of PET.
						• There is agreement regarding PET's utility for the following:
						  • diagnosing SPNs when other diagnostic tests are inconclusive
						  • staging lung cancer
						  • localizing epileptic foci in medically refractory temporal lobe epilepsy
						• Although PET seems to help in the diagnosis of patients with Alzheimer's disease, no therapy exists that can cure or improve the prognosis. The information that can be applied is not relevant from the clinical-therapeutic point of view.
						• For the remaining indications in light of the existing discrepancies, it is appropriate to await the results of new studies. The results from the INAHTA PET collaboration will be available in November of 1999 will provide more on this subject.
						• Gamma cameras with coincidence detection capability that offer diagnostic capability and advantages (lower cost and simpler technology) with respect to PET are now marketed, are being studied and can be the future of emission tomography.

SFOSS	1999	lung cancer:
		head and neck
		melanoma
			not applicable	proposed evaluation registries and multicenter studies
				(pending)
					not applicable	• SFOSS proposed to their federal committee the following to generate a solid basis for cost-effectiveness studies:
						  • continue evaluation registries to collect a minimal data set
						  • standardize multicenter protocols for PET in head and neck, melanoma, and lung cancer, others to be determined later
						  • make available central data collection only to participating facilities
						  • define reimbursement and quality control criteria, for both PET and coincidence imaging SPECT
						  • make reimbursement available only to institutions participating in registries
						  • establish a working group to oversee PET scanning protocols
						
						Status: Under review

Organiza -tion	Report Date	Indications studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
VA TAP	**Sept 1996**	Head and neck cancer Breast cancer Lung cancer SPN Colorectal cancer Alzheimer's disease	MEDLINE, HealthSTAR, EMBASE, Current Contents, and BIOSIS from 1991 through Sep 1996	Systematic review	EBM criteria used for grading quality of evidence Fryback and Thornbury scale used for classifying included articles	• Research into the clinical utility of PET for selected oncology conditions is preliminary. The evidence of FDG-PET's diagnostic accuracy is methodologically weak, and PET's contribution to improving outcomes has not been systematically assessed. • PET is an accurate test for dementia of the Alzheimer's type. However, evidence argues against routine clinical use of PET for diagnosing AD until more effective treatments and risk modification interventions are developed, and until meaningful and robust predictive values are obtained from an ongoing European multicenter PET study. • VA should maximize the value of its existing commitment, rather than establish additional PET centers.
VA TAP	**Dec 1998**	Head and neck cancer Breast cancer Lung cancer SPN Colorectal cancer Alzheimer's disease	MEDLINE, Health, Current Contents, from Sep 1996-Dec 1998	Systematic review	EBM criteria used for grading quality of evidence Fryback and Thornbury scale used for classifying included articles	• The prevailing evidence does not support using either dedicated or camera-based PET using FDG as a diagnostic test for the applications in this review. • Several cooperative studies of PET are ongoing or planned in the US. Clinicians should await the results of these efforts before incorporating PET into routine diagnostic strategies.

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