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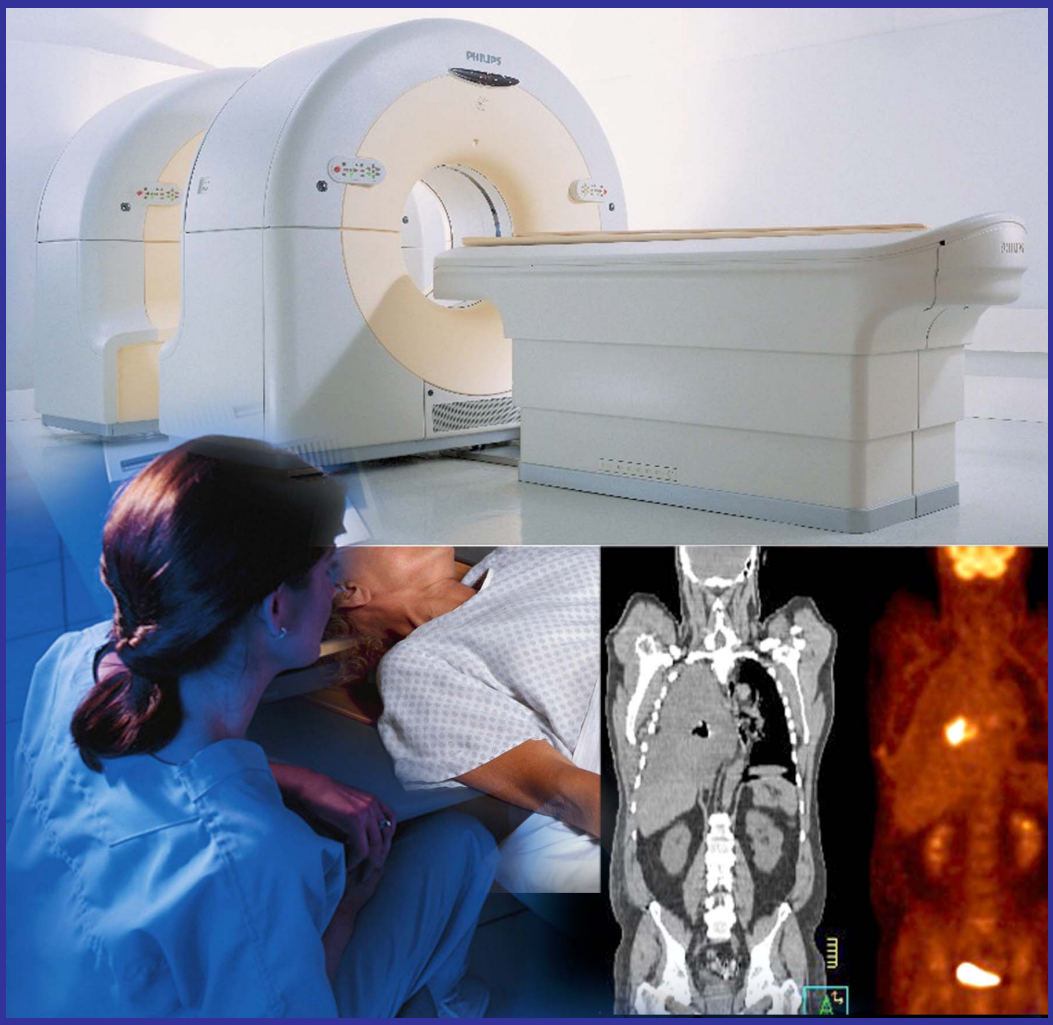
ICES Institute for Clinical Evaluative Sciences

Health Technology Assessment of Positron Emission Tomography (PET) - A Systematic Review -



ICES Investigative Report

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ICES PET HTA Expert Panel, February 27, 2001

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Purpose of this Report

This health technology assessment of Positron Emission Tomography (PET) was requested by the Committee on Technical Fees, a committee consisting of membership from the Ontario Ministry of Health and Long-Term Care (MOHL-TC), the Ontario Medical Association (OMA) and the Ontario Hospital Association (OHA). The Institute for Clinical Evaluative Sciences (ICES) was asked to a) review the existing literature about the diagnostic accuracy, effect upon patient outcomes and cost-effectiveness of PET, b) identify clinical indications for which PET is likely to be shown to be diagnostically accurate and cost-effective in the near future, c) estimate the number of patients in Ontario who may benefit from PET, given current information about its diagnostic accuracy, effectiveness and cost-effectiveness, and d) identify areas of clinical research related to PET that are of importance to Ontarians. This report was to consider the clinical use of PET only, not basic research using PET.

What is Positron Emission Tomography?

PET is an innovative technology that has been in use since the 1970s. In contrast to Computed Tomography or Magnetic Resonance Imaging which both provide images based upon anatomy, PET creates images that reflect biochemical processes and blood flow. Most radioisotopes used in clinical PET are combined with organic compounds. The most commonly used isotope is F18-fluorodeoxyglucose (FDG), which competes with glucose for absorption and metabolism in a wide variety of cells. Because cancer cells often use glucose at higher rates than normal or benign tissue, FDG can potentially identify a primary or metastatic cancer before structural evidence of disease is present. Similarly, metabolic activity within the brain, heart and other organs can be reflected by uptake of FDG.

A fully dedicated PET scanner has a sophisticated detection system that identifies photons of a specific energy that are traveling 180 degrees to each other, and complicated electronics that convert the photons that have been detected into a reconstructed image. Radioisotopes are used in this process and are produced by a cyclotron. Most radioisotopes used in PET have a short half-life, and therefore must be produced by a cyclotron located at the same site, or within a few hours travel from the scanner.

The average amount of time required for each scan varies from 30 minutes for a brain scan to 60 minutes for a whole body scan. PET has not been shown to have any side-effects in patients.

Cost of PET

The cost of PET scanning includes the cyclotron to produce the isotope (one cyclotron can supply more than one scanner, provided the off-site scanners are within a few hours travel from the cyclotron), the scanners themselves, the personnel needed to maintain the cyclotron and scanner, and the personnel required to ensure flow of patients through the scanner and to interpret the results. The costs of these items vary from region to region, but the best estimate, based upon expert opinion, of these costs in Ontario are: $3-4 million per cyclotron; $1.5-3

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million per scanner; $600 thousand/year maintenance (per scanner and cyclotron); $600 thousand/year employee costs; and $250 thousand/year for other overhead costs.

Methodology of this Health Technology Assessment

An extensive systematic review of peer-reviewed, gray and web-based literature was undertaken, and updated until December 2000. Disorders of interest that were identified a priori were a) oncology (lung cancer, solitary pulmonary nodules, head and neck cancer, breast cancer, lymphoma or Hodgkin's disease, melanoma, colon cancer), b) cardiac disease (assessment of cardiac viability), and c) neurological disease (intractable epilepsy and dementia). Differentiating radionecrosis from recurrence in patients with brain tumours was subsequently added, at the suggestion of our Expert Panel. Because of the prevalence of coronary artery disease, a less systematic review of the usefulness of PET for the diagnosis of coronary artery disease was also undertaken.

The methodological quality of the articles that were identified was graded using a modification of a scheme used by the Veteran's Administration (VA) and the National Health Services Health Technology Assessments (NHS-HTA) of PET scanning. Studies received a score ranging from A (best quality) to C/D (poor quality). An a priori decision was made to concentrate upon A and B articles in this report.

Economic evaluations were identified by a separate literature search.

Administrative databases available at ICES, and the findings of a Canadian study in the case of epilepsy, were used to estimate the number of patients who might benefit from PET scanning, based upon the literature review.

An Expert Panel consisting of individuals with expertise in PET scanning, nuclear medicine, radiology, oncology, cardiology and cardiac surgery, neurology and neurosurgery, internal and family medicine, health economics and a representative of the public was formed. They were provided with a draft of the report and asked to provide written, detailed feedback, and also met face-to-face with the report's authors for a day. The Panel was then provided with a second draft of the report and asked to provide further feedback. The final decision about what to include in the report rested with the authors.

While in the process of writing the report, the authors became aware that L'Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AÉTMIS) in Quebec was also preparing a report on PET scanning. Both groups wrote their report independently, but shared drafts of their reports, and met once for a face-to-face meeting.

PET Scanning in Oncology

The number of Grade B articles found in oncology were solitary pulmonary nodule 2, lung cancer 12, colorectal cancer 2, squamous cancer of the head and neck 5, breast cancer 5, malignant lymphoma or Hodgkin's disease 5, malignant melanoma 3, and brain tumour 0. No Grade A articles were found. The most evidence available was for the diagnosis and staging of lung cancer. None of the studies in oncology assessed the impact of PET scanning on overall

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patient well being or quality of life. However, the effects of PET scanning upon a number of "intermediate outcomes" such as avoidance of thoracotomy in patients with metastatic or inoperable lung cancer was evaluated.

A review of the oncological literature suggests that PET scanning has a role for a) investigation of the solitary pulmonary nodule (some thoracotomies will likely be avoided), b) staging of primary lung cancer/evaluation of mediastinal lymph nodes (some thoracotomies and mediastinoscopies will likely be avoided), c) detection of residual or recurrent lung cancer (some bone scans may be avoided), d) detection of resectable recurrent/metastatic colorectal cancer, e) pre and post-therapy evaluation of squamous carcinoma of the head and neck (some CT scans may be avoided), f) axillary assessment in breast cancer if sentinal lymph node biopsy is not part of the evaluation, g) pre-therapy assessment of lymph node involvement, and evaluation of residual masses after completion of therapy in patients with lymphoma or Hodgkin's lymphoma (some CT scans will likely be avoided), and h) evaluation for silent metastases in malignant melanoma (some CT scans will likely be avoided). In addition to possibly decreasing the utilization of some other diagnostic tests or invasive procedures such as biopsies, more accurate knowledge of the extent of disease with PET scanning may change decisions about the aggressiveness of planned chemotherapy or radiotherapy, which can have important impacts upon mortality and quality of life. Decisions about clinical care vary from patient to patient - PET scanning should only be used if the results of the test will affect patient management.

PET Scanning in Cardiology

We did not review the literature regarding the use of PET to diagnose coronary artery disease with the same degree of rigor as we did evaluating its use to assess viability. A number of studies have shown that PET scanning is useful in diagnosing coronary artery disease, although its sensitivity and specificity is not much better than other non-invasive techniques such as SPECT in the overall population of patients referred for assessment of coronary artery disease. It has been suggested that PET may be superior to other non-invasive techniques in women, patients with left bundle branch block, and those with equivocal results with other non-invasive techniques. However, no studies of high methodological quality supporting this assertion were identified by ourselves or the Expert Panel. Therefore, given the cost of PET scanning, the availability of other non-invasive techniques for the investigation of coronary artery disease, and the poor quality of the evidence that PET scanning improves outcome in patients with suspected coronary artery disease, PET scanning cannot now be recommended for regular clinical use in the investigation of coronary artery disease.

PET scanning has been suggested as a method of identifying ischemic heart tissue in patients with moderate to severe heart failure that is reversible with revascularization procedures such as angioplasty or bypass surgery. One Grade A study was found evaluating the use of PET scanning for cardiac viability, and it failed to show any favourable effect upon outcome compared with SPECT. This study was relatively small (103 patients) and included a number of patients with only mild heart failure, and the generalizability to patients with severe heart failure is unknown. Other studies of poorer methodological quality have suggested potential benefits, although PET's incremental impact upon clinical outcomes (e.g., mortality, avoiding transplantation) compared with other non-invasive modalities was not investigated. Although in our opinion the available evidence does not support the routine use of PET for the assessment of viability at the present

time, the state of evidence is evolving. Accordingly, we suggest that a re-evaluation of cardiac PET be conducted in 2-3 years.

PET Scanning in Neurology

The number of Grade A or B articles was 6 for intractable seizures and 8 for dementia. The literature suggests that PET scanning has a limited role in the investigation of patients with intractable seizures being considered for surgery (may help determine eligibility for surgery and avoid invasive diagnostic testing (e.g., intracranial electroencephalograms)). There is no evidence that PET scanning has a clinical role in the diagnosis or symptomatic management of dementia at the present time.

Economic Evaluations of PET

There were few high quality economic evaluations of PET, and none from Ontario or Canada. It is generally accepted that the sensitivity and specificity of a test are generalizable across borders. However, the costs of tests and interventions, and practice patterns vary widely among regions, making it very difficult to extrapolate cost-effectiveness ratios from one region to another. Therefore, the lack of economic evaluations from Ontario and Canada is unfortunate. The economic evaluations that were reviewed suggested that PET scanning is likely to have a favourable cost-effectiveness ratio in patients with lung cancer, those being investigated for a solitary pulmonary nodule, and patients with malignant lymphoma or Hodgkin's lymphoma. No high quality economic evaluations were found for other cancers, cardiac viability, or neurological indications. One high quality American economic evaluation found PET scanning to have an unfavourable cost-effectiveness profile for the routine diagnosis of coronary artery disease.

Numbers of Patients Who Might Benefit from PET Scanning in Ontario

A review of ICES databases suggest that in 2001 approximately 24,000 patients have the oncologic and seizure disorders that might benefit from PET.

Implementation of PET Scanning - Some Issues to Consider

Suggesting the number and location of PET scanners that should be introduced in Ontario, and the rapidity of their introduction, is not within the mandate of this report. However, planners will need to consider a number of issues including: a) the cost-effectiveness of PET scanning compared with other uses of limited health care resources, b) the number and location of cyclotrons relative to scanners (one cyclotron could serve more than one scanner), c) the need to train and retain highly skilled workers in PET (including physicists, maintenance personnel, and personnel to interpret the images), d) advances in the technology (e.g., the development of a combined CT and PET scanner), and e) how to determine which patients have access to a PET scanner.

Further Considerations

Despite the availability of PET scanning for almost three decades, the number of methodologically high quality studies (and the numbers of patients within those studies) is

distressingly small. It is also possible that publication bias (the preferential publication of studies that show a benefit of PET scanning) may limit the evidence considered in this report. These two factors combine to make any conclusions about the usefulness of PET scanning less definitive than one would like.

Although better diagnostic techniques are welcome, in some instances the lack of dramatically effective therapy to complement the diagnostic tool is the more important issue.

In many instances PET is being compared with diagnostic technologies that themselves have not been rigorously evaluated, and it could be argued that PET is being held to a higher standard than some previous diagnostic tests. However, we believe that standards should improve over time, and given PET's expense and the competing demands for limited health care resources, that it is reasonable to expect the usefulness of PET to be supported by high quality studies prior to its introduction into routine clinical practice.

Clinical Research Priorities for PET Scanning in Ontario

The useful research that could be conducted to more definitively establish the role of PET scanning is substantial. However, three areas of clinical research appear to warrant immediate attention. First, rigorous cost-effectiveness studies using Ontario practice patterns and costs would be very helpful. Second, determining the usefulness of PET scanning for viability in patients with heart failure is a high priority, especially given the conflicting results in the literature and the increasing prevalence of heart failure (one randomized trial is already underway). Third, studies should be done on the optimal methods of managing waiting lists for PET scanning. Accessibility to expertise in clinical research design is mandatory for future research in PET in Ontario.

A registry of all patients having PET scans in Ontario should be developed which can be used for administrative and research purposes. The PET registry could be linked to other provincial databases. Although there are limits to the conclusions that can be drawn from registries, the information provided by such a registry would be very helpful in assessing the impact of PET scanning upon the use of other diagnostic modalities, patient management and outcome in Ontario.

ICES Health Technology Assessment of Positron Emission Tomography

Introduction

Positron Emission Tomography (PET) is an innovative and expensive technology that combines advances in nuclear medicine with those in electronics to offer a unique diagnostic tool with the potential to significantly impact the practice of medicine. Rather than being designed to produce images based upon anatomy, like Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), PET creates two or three-dimensional images that reflect biochemical processes and blood flow. Thus, PET provides information about physiology rather than structure, which may allow clinicians to understand, evaluate and consequently treat patients more effectively than is the case without PET.

Because of its expense, it is important that the incremental benefit of PET compared to existing diagnostic modalities is rigorously evaluated. The Committee on Technical Fees (COTF), a committee consisting of membership from the Ontario Ministry of Health and Long-Term Care (MOHLTC), the Ontario Medical Association (OMA) and the Ontario Hospital Association (OHA), asked the Institute for Clinical Evaluative Sciences (ICES) to prepare an independent health technology assessment of PET. This document includes a review of the literature to determine current knowledge about the diagnostic accuracy of PET, the effect of PET findings upon patient management and outcome, and the cost-effectiveness of PET. An attempt is made to estimate the potential number of patients in Ontario who would benefit from PET scanning, on the basis of current knowledge of the established indications for PET scanning. This can be used as a basis for planning the number of PET scanners that should be introduced in Ontario. On-going research studies are identified and key research questions suggested. This document only evaluates the use of PET as a clinical tool, and does not consider its undoubted value for basic and fundamental clinical research.

Background

Initially developed for commercial use in the mid 1970s, PET has largely been a research tool. Brain imaging was the early focus, but more recently this has been expanded to include every region of the body. The past decade in particular has seen an accelerated interest in the clinical usefulness of PET, especially in cardiology (heart) and oncology (cancer). A number of factors have contributed to the increasing feasibility and use of PET in the clinical realm. Technological progress has resulted in significant improvements in the reliability and cost of the radioisotope-generating cyclotrons; increases in the diversity and imaging characteristics of the radiopharmaceuticals; higher sensitivity and resolution of the images; and lower cost of the PET scanners themselves. Moreover, a growing body of research has suggested there may be a place for clinical PET in certain settings. In the United States, changing FDA regulations regarding the radioisotopes, and increased medicare (Health Care Finance Administration - HCFA) and third party payer reimbursement have also contributed to this trend. As well, the clinical PET community has been a well-organized and effective advocate, lobbying government and other health care agencies to increase access to clinical PET.

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According to a 1999 INAHTA (International Network of Agencies for Health Technology Assessment) survey, [1] Australia, Switzerland, Denmark and the USA (Veterans' Health Administration,VHA) accounted for 85% of publicly reimbursed clinical PET activity. The majority of publicly reimbursed scans were in oncology (65%), followed by neurological indications (25%), and cardiology (6%). With the exception of the VHA, most public health systems have fewer than five PET scanners, and most of these are affiliated with academic centres. Worldwide numbers of PET scanners are difficult to determine, but according to the Institute for Clinical PET (ICP) website, a non-profit American educational foundation, in January 2001, 177 sites existed in the US, and 109 outside. This list appears to be the most comprehensive available but almost certainly underestimates the true number, and does not distinguish between types of PET scanners.

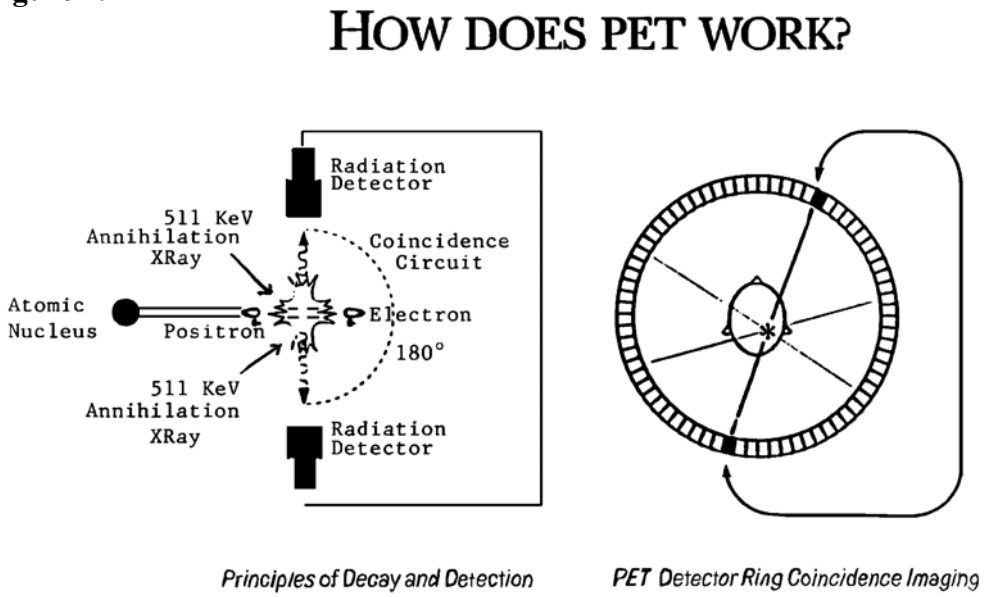
A report from the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), in June 2000 indicated that there are currently 7 PET scanners in Canada (British Columbia (1), Ontario (4) and Quebec (2)) and one planned for Alberta. The PET scanners in Ontario are in Hamilton (2), Ottawa and Toronto. For comparison purposes, there were at least 78 MRI scanners across Canada on the same date.

Pet Technology

1. Overview

All nuclear medicine imaging depends upon the detection of gamma rays or photons (non-visible light) by a camera-like device that records the level of radioactivity originating from a given point in space and time as the radioactive material decays. This information is then transformed by a computer into two- or three-dimensional visible images. In a traditional nuclear imaging device, a stationary single- or double-headed gamma camera records the production of photons as a 2-D picture (resolution about 15 mm). Single Positron Emission Computed Tomography, or SPECT, improves upon the quality of the images by incorporating a rotating camera in varying configurations designed to increase the sensitivity (by collecting or detecting a higher percentage of the photons released) and resolution (by allowing a 3-D image to be reconstructed which then permits the true image [signal] to be better distinguished from irrelevant scatter [noise]). SPECT resolution is about 10 mm.

Figure 1.



Source: http://www.health.state.mn.us/htac/pet.htm [2]

2. Coincident Detection

PET is unique in several respects. As the radioactive isotope decays, a positron, or positively charged electron travels a short distance (minimum of 2-3 mm, the limit of resolution being approached by modern PET cameras) until it collides with a negatively charged electron of nearby atoms in the body tissue (Figure 1). That collision results in conversion of those two particles' mass into energy, a transformation termed the 'annihilation reaction'. This energy takes the form of two photons that travel in opposite directions. Only those photons of a specific energy that are 180 degrees to each other and are detected by the camera within a very narrow window of time (coincident detection) are considered to have originated directly from the point source. All others are interpreted as noise, and are not factored into the reconstruction process. Therefore, the final image is a 2-or 3-D representation of the origin of photons produced by the radioisotope, and so reflects more accurately the true concentration and distribution of the radioisotope.

3. Scintillators

The light-collecting surface area of the detectors in PET cameras is also significantly increased relative to the other nuclear imaging devices. The crucial component in all detectors, or scintillators, is one of several types of crystal that comprises about 50 cc for a typical chest x-ray device, 3000 cc for a SPECT scanner, and about 10000 cc for a dedicated full ring PET camera.[3] This translates into much improved count sensitivity and ultimately image quality and spatial resolution.

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4. Radioisotopes

PET is also unique because of the higher energy of the photons released. Traditional nuclear imaging radioisotopes, such as thallium and technetium, typically release energy in the range of 80 to 400 keV, with SPECT energies typically at about 140 keV. PET detects 511 keV photons. Just as it is more difficult to change the course of an ocean liner relative to a rowboat, these higher energy photons are much less likely to be scattered or absorbed by surrounding tissues before they are detected by the camera. Thus, image quality and resolution is improved as a result of these higher energies involved, just as it is with coincident detection.

The radioisotopes developed for use in PET are based on combining organic compounds such as sugar with positron-emitting isotopes generated in a particle accelerator or cyclotron. The decay rate of these radiopharmaceuticals depends on the half-life (t 1/2)-- the time required for half of the radioactive material to decay. The most commonly used are Carbon (11C), Nitrogen (13N), Oxygen (15O) and Fluorine (18F). They have t 1/2 ranging from 120 seconds (15O) to 110 minutes (18F), so the radioisotopes with shorter half-lives have more limited clinical utility since travel time, and therefore distance from the cyclotron, becomes a limiting factor. Rubidium (82Rb) is also commonly used in cardiology and although it does not require an on-site cyclotron, it does require a 82Rb generator. FDG, or F18-fluorodeoxyglucose, is the agent most commonly used in part because of its long half life, but also because of its ability to compete with glucose--a primary biological source of energy--for absorption and metabolism in a wide variety of cells. Thus, FDG has applications in neurology, cardiology and oncology. For instance, cancer cells are known to often use glucose at higher rates than normal or benign tissue, so FDG can serve to identify areas of increased glucose metabolism, which may help in the detection and staging of cancers. Likewise, brain and heart cells reflect their level of activity by glucose uptake and metabolism, so levels of relatively decreased or increased activity may indicate disease states even before structural evidence of disease is apparent.

5. Scanner Types

There are two main types of scanners: dedicated PET scanners and modified PET scanners. Dedicated PET scanners, while more expensive, also produce better quality images than those of modified PET scanners.

Dedicated PET scanners can be full or partial ring scanners. Full ring scanners, as their name implies, encircle the patient and so optimize sensitivity and coincidence detection. Partial ring scanners, which rotate around the patient, were developed to reduce costs with a minimal sacrifice in image quality. They require only about half as much BGO (bismuth germanate, a commonly used crystal in the scintillator and the most costly component of the technology). NaI, or sodium iodide, cerium fluoride (CeF3) and barium fluoride (BaF2) are other commonly used crystals in current detectors, each with unique physical properties that affect cost and quality. Lutetium oxyothosilicate (LSO) is a relatively new crystal that can be incorporated into dedicated PET systems.

After non-visible photons contact the crystal, they are converted into flashes of visible light, which are subsequently transformed into amplified electrical signals by photomultiplier tubes. These electrical 'dots and dashes' ultimately serve as the data source for image reconstruction by the associated complex electronics.

Dedicated PET scanners may also operate in 2-D or 3-D modes. In 2-D acquisition mode, lead or tungsten barriers called 'septa' separate adjacent rings of detectors, whereas in 3-D mode these septa are retracted, allowing coincidence detection to occur in three dimensions simultaneously. With the septa in place, there is less background noise or scatter, but at the expense of decreased sensitivity. Alternatively, in 3-D mode detection efficiency or the signal-to-noise ratio is increased, providing eight times greater sensitivity than in 2-D mode but increased scatter as well.

Modified PET scanners come in two varieties: non-coincidence imaging and coincidence imaging gamma cameras. Traditional nuclear medicine gamma cameras use a lead screen with multiple holes (collimator) that open into the crystal portion of the detector. Only photons that are properly oriented will be able to make contact with the crystal; all others are absorbed or deflected by the collimator. This mechanical design element is unnecessary in dedicated PET scanners because coincidence imaging technology enables signal to be accurately separated from noise. Non-coincidence imaging gamma cameras continue to use collimators, although these have been altered to handle the higher energies of PET radiopharmaceuticals. Sensitivity and resolution are significantly reduced as a result of the inherent inefficiencies in this design.

Coincidence imaging gamma cameras, on the other hand, utilise the enhanced performance characteristics of coincidence imaging rather than a modified collimator. These gamma cameras, usually 2- or 3- headed, are rotated around the patient and work in concert with the advanced electronics that enable coincidence detection. They provide images superior to that of non-coincidence imaging cameras, but inferior to dedicated PET scanners.

More recently, CT scanners have been coupled with dedicated PET scanners to optimize correlation of anatomy with physiology, although there is little literature about their clinical applicability.

Given the marked superiority in image quality, and the fact that the vast majority of clinical research has involved dedicated rather than modified PET scanners, this report will exclusively consider dedicated PET's clinical role.

6. Safety

Safety concerns regarding PET have been primarily limited to issues related to the radiopharmaceuticals involved. Silbertstein et al[4] examined 22 PET centres in the US involving a total of almost 82,000 doses of commonly used radiopharmaceuticals and found that no adverse reactions were reported or observed. Furthermore, in March 2000 the US FDA found that commonly produced and used PET drugs (FDG, Fluorine-18, Rubidium-82) "can be found to be safe and effective for certain indications".

Potential complications of the delivery method (typically intravenous injection or inhalation) or to the physical placement of the patient (on a bed, possibly surrounded by a scanner) are not unique to this technology. Thus PET scanning appears to be safe, and in this regard comparable to other nuclear medicine procedures.

7. Procedure

The radioisotope (such as Fluorine-18) is typically generated in a cyclotron by bombarding a target substance with protons or deuterons. Radiochemists then join the organic compound (such as glucose) to the radioisotope, forming the radiopharmaceutical (such as FDG). The drug is then available for immediate use. Isotopes with a relatively long half-life such as FDG can be generated in a cyclotron and then transported to another site with a scanner. The practical upper limit of travel time for this to be feasible in day-to-day practice is about two hours. Because the cyclotron is so expensive, one way of reducing the costs of PET scanning is to link a number of scanners with one cyclotron.

The patient may be initially scanned with gallium (a transmission scan with an external source of radioisotope) to determine the degree to which gamma rays will be absorbed (or attenuated) by body tissues. This allows an 'attenuation correction' to be made by the electronics which further increases the ability of the PET scanner to discriminate between signal and noise, and hence improve image quality. The patient most commonly receives an injection of the radiopharmaceutical and a certain period is required for absorption of the drug before the scanning can proceed. Typically this takes 20 to 30 minutes, but the process depends on the half-life of the radiopharmaceutical involved and the information required. The image is quickly reconstructed by the advanced computing power of the system and is then ready for interpretation. The average amount of time for each scan varies from 30 minutes for a brain scan to 60 minutes for a whole body scan.

Methodology

1. Overview

This health technology assessment consisted of the following steps:

- Reviewing the literature to identify original research evaluating the clinical role and cost-effectiveness of PET scanning;
- Rating the methodological quality of the research, using the research of highest methodological quality to summarize the literature for a number of specific disorders;
- Reviewing previous health technology assessments of PET scanning;
- Sharing a draft document with a number of experts and non-experts about two months before the completion of the report, to obtain their feedback. L'Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AÉTMIS) in Quebec was reviewing PET scanning at the same time. This document was produced independently of that by the AÉTMIS, but the two groups did intermittently discuss methodology and findings during the preparation of this report;
- Using administrative databases to estimate the number of patients in Ontario who would be eligible for PET scanning if it is available for patients for whom there is convincing evidence of its usefulness; and
- Identifying ongoing research projects involving PET scanning.

2. Literature review and assessment of articles

An extensive review of the peer-reviewed, gray and web-based literature was undertaken and updated monthly until December 2000. The databases searched and the search strategies are found in Appendix 1. Abstracts of all peer-reviewed articles were reviewed by two individuals to determine which articles should be photocopied in their entirety - disagreements were resolved by consensus. The major reviews were hand-searched and back-referenced for additional potentially relevant articles. The complete articles with original data were evaluated to determine whether they met the inclusion criteria:

- Studies of PET in the diseases of interest (lung cancer, solitary pulmonary nodules, head and neck cancer, breast cancer, lymphoma or Hodgkin's disease, melanoma, colon cancer, intractable epilepsy, dementia, assessment of cardiac viability) or an economic evaluation of PET; brain tumours vs. radiation necrosis was added subsequently;
- English language studies reporting primary data, published in a peer-reviewed journal; and
- Studies with > 12 human subjects.

Of the 1002 articles found, 386 met the inclusion criteria and were successfully retrieved and subsequently critically reviewed; 83 were review articles and 28 were ultimately unavailable.

Using a grading scheme used by the VA and NHS Health Technology Assessments (HTA) of PET scanning, diagnostic studies were given a rating from A-D (see Table 1) by one reviewer for each section for all articles from 1975-1998, and by two reviewers for each section for all articles from 1999-Jan 2001. Disagreements among reviewers were rare and resolved by consensus. It was decided a priori that grade A and B studies would be given preferential consideration in this review. The economic evaluations were reviewed by two individuals using the checklist by Drummond et al as a guide.[5]

Table 1. Grading Scheme for Diagnostic Studies

GRADE	CRITERIA
A	Prospective studies with broad generalizability to a variety of patients and no significant flaws in research methods.
B	Prospective studies with a narrower spectrum of generalizability, and with only a few flaws that are well described (and impact on conclusions can be assessed).
C	Studies with several methods flaws (e.g., small sample size and retrospective)
D	Studies with multiple flaws in methods (e.g., no credible reference standard for diagnosis)

Adapted from National Health Service Health Technology Assessment, 1999.[6]

3. Expert Panel

The purpose of the panel, convened on February 27, 2001 was to receive comments from experts and non-experts about:

- The clarity, accuracy and completeness of the draft report;
- The types of clinical presentations and diseases in which PET is diagnostically accurate and cost-effective;
- The indications for which PET is likely to be shown to be diagnostically accurate and cost-effective in the next 2-5 years;
- How the use of PET should be monitored; and
- The most important clinical research studies that need to be done immediately to determine the diagnostic accuracy and cost-effectiveness of PET.

Individuals from a variety of academic, non-academic, interventional and non-interventional backgrounds with expertise in cardiology, oncology, neurology, nuclear medicine, family practice, general internal medicine and health economics, as well as a member of the public attended. The attendees are listed prior to the Table of Contents. All participants were mailed the first draft of the report 2 weeks in advance of the meeting with the expectation that they would be prepared to discuss the findings and address the issues outlined above (see Appendix II for a summary of their comments). The panelists were then mailed a second draft of the report and asked to review the revised document.

4. Other HTAs

Using major international health technology institutional websites and references found in the course of the literature search, health technology assessments previously completed were reviewed and summarized. The results can be found in the section entitled "Other Health Technology Assessments" and in Appendix III.

5. Review of Administrative Databases

The administrative databases available at ICES were used to estimate the number of patients who would be eligible for PET scanning, if it was available for the patients for whom the current literature supports its usefulness.

From the CIHI discharge abstract database and from the OHIP billing claims database we identified all residents of Ontario who first had a diagnosis of carcinoma of the lung in fiscal year April 1, 1999 and March 31, 2000.

From the same databases, we identified all residents of Ontario who first had any of the following diagnoses between April 1, 1996 and March 31, 2000, as well as surgical and/or non-surgical procedures: colorectal carcinoma (ICD 153 - 154), head and neck cancer (ICD 140 - 149; 160 - 161), carcinoma of the female breast (ICD 174), Hodgkin's disease and non-Hodgkin lymphoma (ICD 200 - 202), and malignant melanoma (ICD 172). These residents were dichotomized as follows: first diagnosis between April 1, 1996 and March 31, 1999; and first diagnosis between April 1, 1999 and March 31, 2000. The former were used to estimate the frequency of PET scans for indications that involve follow-up of patients with cancer, while the

latter were used to estimate the frequency of PET scans for the initial work-up of residents with suspected or newly-diagnosed cancer.

For all observations, we tabulated the diagnostic imaging procedures billed during fiscal year April 1, 1999 and March 31, 2000.

6. Ongoing Research

Using information available on major institutional health research websites, ongoing PET research projects (as of January 2001) were identified and summarized in Appendix IV.

PET in Oncology

Introduction

We examined the evidence for the clinical applications of PET among seven commonly occurring categories of cancer: carcinoma of the lung, colorectal carcinoma, squamous carcinoma of the head and neck, breast cancer, malignant lymphoma, and malignant melanoma. Gliomas were also considered. We did not include methodological Grade C or D studies in this review. No methodological Grade A studies were identified, primarily because of the small size and non-representativeness of the study population. Accordingly, only Grade B studies will be discussed in this section (see Table 2).

Review of the Evidence

1. Carcinoma of the Lung

a) Diagnosis of the solitary pulmonary nodule

Two recent studies have demonstrated the effectiveness of PET in distinguishing malignant from benign solitary pulmonary nodules (SPN). In a series of 50 cases of SPN with indeterminate clinical/radiological diagnoses after computed tomography (CT), PET had a sensitivity of 100%, specificity of 88%, positive predictive value of 94% and negative predictive value of 100%.[7] Another series of 89 cases demonstrated a sensitivity of 92%, specificity of 90%, positive predictive value of 95% and negative predictive value of 84%.[8]

b) Staging of primary carcinoma of the lung / evaluation of mediastinal lymph nodes

Several recent studies have evaluated the effectiveness of PET in the evaluation of mediastinal lymph nodes in proven or suspected cases of carcinoma of the lung. Evaluation of mediastinal lymph nodes is an important component of estimating the extent of carcinoma of the lung, and the information is frequently used to guide decisions about treatment.

In a study of 50 patients, the sensitivity of PET was 90% compared to 72% for CT. The specificity of PET was 85% compared to 81% for CT.[7] Another study of 96 patients demonstrated that the sensitivity of PET was 98% and the specificity was 94% in the evaluation of mediastinal lymph nodes.[9] A study of 33 patients demonstrated a PET sensitivity of 90%, specificity 97%, positive predictive value 85%, and negative predictive value 98%, which were significantly higher than either CT or mediastinoscopy.[10] The efficacy of PET in the evaluation of mediastinal lymph nodes was examined according to the size of mediastinal lymph nodes, and PET was superior than CT among lymph nodes < 1 centimetre in diameter, between 1 and 3 centimetres, and greater than 3 centimetres.[11] A further publication from the same team of investigators reported the overall comparison of PET and CT scanning in the evaluation of mediastinal adenopathy, using histological status as the gold standard. The sensitivity for PET and CT respectively were: 93% vs. 63%; specificity: 94% vs. 60%; positive predictive value: 92% vs. 50%; negative predictive value 94% vs. 72%.[12] In another study of 97 patients, CT performed poorly compared to PET regarding sensitivity (20% vs. 71%) and positive predictive

value (30% vs. 86%).[13] The specificity and negative predictive values were similar: 90% vs. 97% and 84% vs. 93%.

c) Detection of residual or recurrent carcinoma of the lung

A study of 58 patients who had undergone potentially curative treatment for carcinoma of the lung compared PET to CT as predictors of clinical signs or histologic samples of recurrent carcinoma. The sensitivity was 100% for PET vs. 69% for CT; specificity was 98% for each; positive predictive value 93% vs. 90% and negative predictive value 100% vs. 92%.[14]

d) Detection of bone metastases from primary carcinoma of the lung

A study of 110 patients compared PET to conventional radionuclide bone scanning for the detection of bone metastases. Using clinical and radiological correlation or clinical evolution as the gold standard, the comparison of PET to bone scan demonstrated the following: sensitivity 90% for each; specificity 98% vs. 61%; positive predictive value 90% vs. 35%; and negative predictive value 98% vs. 96%.[15]

e) Potential impact of PET on processes of care for carcinoma of the lung

There is evidence for the efficacy of PET in distinguishing benign from malignant solitary pulmonary nodules (SPN). The use of PET in this context would reduce patient morbidity by reducing the number of thoracotomies.

There is evidence for the efficacy of PET in predicting the histological status of mediastinal lymph nodes in patients with carcinoma of the lung, and that PET is more efficacious than CT. Staging and preoperative procedures prior to attempted resection of carcinoma of the lung vary among practitioners. Among those who use mediastinoscopy as a staging procedure, this procedure would be avoidable if PET were available. Among those who do not use mediastinoscopy and take patients with CT negative mediastinal nodes to resection directly, some thoracotomies might be avoided. It is unclear if the utilization of CT would decrease at all if PET were available, because the anatomical information provided by CT (which is better than that provided by PET) might still be needed.

Although recurrent carcinoma of the lung is usually incurable, residual or recurrent carcinoma may be detected most accurately by PET, and would coincidentally provide better assessment of the possibility of bone metastases which frequently accompany residual or recurrent carcinoma. The number of bone scans would likely decrease.

In addition, PET appears to provide important prognostic information about patients with carcinoma of the lung,[16] and apparently would allow radiation therapy for carcinoma of the lung to be designed in a manner which would reduce the amount of normal lung tissue exposed to radiation.[17,18] However, the impact of this upon clinical outcomes has not been demonstrated.

Table 2. Evaluation of High Grade Oncology Studies

*1. **Lung Cancer** (all B Grade Studies)*

Setting	Author	Year	Country	Pts	Comparison	Blinded	Se / Se (%)	Sp / Sp (%)	PPV/PPV (%)	NPV/NPV (%)	Signif
a) **SPN**	Lowe[8]	1998	USA	89	CT/Histol	Yes	92/-	90/-	95/-	84/-	*
	Bury[19]	1996	Belgium	50	Histol	Yes	100	88	94	100	-
b) **Staging**	Saunders[13]	1999	UK	97	CT/Histol	Yes	71/20	97/90	86/30	93/84	-
	Gupta[12]	1999	USA	103	CT/Histol	Yes	93/63	94/60	92/50	94/72	-
Primary	Graeber[9]	1999	USA	96	CT/Histol	Yes	97/-	89/-	97/-	84/-	-
Nodes	Gupta[11]	2000	USA	54	CT/Histol	Yes	96/68	93/65	86/47	98/82	-
	Graeber[9]	1999	USA	44	CT/Histol	Yes	98/63	94/60	91/64	-	-
	Stokkel[10]	1999	Neth	33	CT/Histol	Yes	90/-	97/-	85/-	98/	-
	Bury[7]	1996	Belgium	50	CT/Histol	Yes	90/72	86/81	-	-	-
	Chin[20]	1995	USA	30	CT/Histol	Yes	78/56	81/86	64/63	89/87	-
c) **Res/Recur**	Bury[14]	1999	Belgium	58	CT/Relapse	Yes	100/69	98/98	93/90	100/92	-
d) **Bone Mets**	Bury[15]	1998	Belgium	110	Bone Scan	Yes	90/90	98/61	90/35	98/96	-

Legend: SPN=solitary pulmonary nodule; Yr=year published; Pts-number of patients; Histol=Histology; CT=Computed Tomography; Se =Sensitivity; Sp=Specificity; Signif=Significant difference; PPV=Positive Predictive Value; NPV=Negative Predictive Value; - =data unavailable; * =CT scans were indeterminate for all 60 malignant SPNs

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2. *Colorectal Cancer* (all B Grade Studies)

Setting	Author	Country	Yr	Pts	Compare	Outcome	Blinded	Se / Se (%)	Sp / Sp (%)	PPV/PPV (%)	NPV/NPV (%)	Signif
a) **Recur**	Imdahl[21]	Germany	2000	71	CT	Loc Rec	Yes	92/88	87/89	76/81	96/93	-
	Imdahl[21]	Germany	2000	71	CT	Liver	-	100/87	98/91	96/83	100/93	-
	Imdahl[21]	Germany	2000	71	CT	Lung	-	94/100	100/100	100/100	98/100	-
Liver Mets	Lai[22]	Australia	1996	34	CT	-	Yes	93	57	89	67	-

3. *Squamous Carcinoma of the Head and Neck Region* (all B Grade Studies)

Setting	Author	Country	Yr	Pts	Compare	Outcome	Blinded	Se / Se (%)	Sp / Sp (%)	PPV/PPV (%)	NPV/NPV (%)	Signif
a) **Node**	Kau[23]	Germany	2000	70	CT/MRI	-	Yes	87/65/88	94/47/41	90/40/51	93/72/83	-
	Benchaou[24]	Switz	1996	48	CT/Palp	-	Yes	72/67/61	99/97/97	89/74/72	99/95/95	-
Lung Mets	Keyes[25]	USA	2000	56	-	-	-	-	-	-	-	One Case
b) **Recur**	Lowe[26]	USA	2000	30	Imag/Ex	Recur	Yes	100/38/44	93/85/100	-	-	p=.013 p=.002
	Lonneux [27]	Belgium	2000	44	CT + MRI	-	Yes	96/73	61/50	-	92/56	-

Legend: Yr=year published; Pts=number of patients; Compare=Comparison modality; CT=Computed Tomography; Loc Rec=Local Recurrence; Se =Sensitivity; Sp=Specificity; Signif=Significant difference; PPV=Positive Predictive Value; NPV=Negative Predictive Value; - =data unavailable

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*4. **Breast Cancer** (all B Grade Studies)*

Setting	Author	Country	Yr	Pts	Compare	Outcome	Blinded	Se / Se (%)	Sp / Sp (%)	PPV/PPV (%)	NPV/NPV (%)	Signif
a) Axilla	Yutani[28]	Japan	2000	38	Histol	-	Yes	50	100	100	69	-
	Smith[29]	Scotland	1998	50	Histol	-	Yes	88	97	-	-	-
b) Bone Mets	Schirrmeister[30]	Germany	1999	34	Bone Scan	-	Yes	-	-	-	-	ROC 1.0 p<0.05
c) Response to Chemo	Smith[31]	UK	2000	30	-	-	Yes	-	-	-	-	DUR Values
d) Mal vs Benign	Avril[32]	Germany	1996	51	Histol	-	Yes	-	-	-	-	p<0.01

Legend: Yr=year published; Pts=number of patients; Compare=Comparison modality; Histol=Histology; Mal=Malignant; Se =Sensitivity; Sp=Specificity;; Sp=Specificity; Signif=Significant difference; PPV=Positive Predictive Value; NPV=Negative Predictive Value; ROC=Receiver Operator Characteristics; DUR=dose uptake ratio; - =data unavailable

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5. ***Lymphoma*** *(all B Grade Studies)*

	Setting	Author	Country	Yr	Pts	Compare	Outcome	Blinded	Se / Se (%)	Sp / Sp (%)	PPV/PPV (%)	NPV/NPV (%)	Signif
a)	**Staging/FU Mal Lymph**	Bangerter[33]	Germany	1999	89	CT	-	Yes	96	94	90	98	-
	Staging Hodgkin's	Bangerter[34]	Germany	1998	44	CT	-	Yes	-	-	-	-	Stage Change
b)	**Residual CT Masses**	Mikhaeel[35]	UK	2000	32	CT	-	Yes	80	96	89	91	-
c)	**Marrow**	Carr[36]	UK	1998	50	Marrow	-	Yes	81	76	62	90	-
		*Moog[37]	Germany	1999	56	Bone Scan	-	Yes	71	87	71	87	-

Legend: Yr=year published; Pts=Patients; Compare=Comparison modality; Se =Sensitivity; Sp=Specificity; Signif=Significant difference; PPV=Positive Predictive Value; NPV=Negative Predictive Value; CT=Computed Tomography; FU Mal Lymph=Follow-up of Malignant Lymphoma; - =data unavailable; *questionable B Grade

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6. *Malignant Melanoma* *(all B Grade Studies)*

	Setting	Author	Country	Yr	Pts	Compare	Outcome	Blinded	Se / Se (%)	Sp / Sp (%)	PPV/PPV (%)	NPV/NPV (%)	Signif
a)	**Staging**	Eigtved[38]	Denmark	2000	38	'Routine'	-	Yes	97/62	56/22	86	83	-
a,b)	**Staging/FU**	Rinne[39]	Germany	1998	52 Prim 48 FU	'Routine'	-	Yes	100/0 100/85	94/80 96/58	-	-	-
c)	**Nodes**	Crippa[40]	Italy	2000	38	Histol	-	Yes	95	84	92	89	-

Legend: Yr=year published; Pts=number of patients; Compare=Comparison modality; Se =Sensitivity; Sp=Specificity; Signif=Significant difference; PPV=Positive Predictive Value; NPV=Negative Predictive Value; Histol=Histology; Prim=Primary disease; FU =Follow-up; -=data unavailable

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2. Colorectal Carcinoma

a) Detection of recurrent/metastatic colorectal carcinoma

PET was performed among 71 patients with a rising carcino-embryonic antigen serum level after therapy for primary colorectal carcinoma, or with other suspicion for recurrent disease. A comparison of PET to CT to detect hepatic metastases revealed: sensitivity 100% vs. 87%; specificity 98% vs. 91%; positive predictive value 96% vs. 83%; and negative predictive value 100% vs. 93%.[21]

b) Potential impact of PET on processes of care for colorectal carcinoma

It is not clear that PET in this context would replace any currently applied investigations; the slightly higher values for PET might slightly reduce the number of laparotomies performed in this clinical setting.

3. Squamous Carcinoma of the Head and Neck

a) Detection of lymph node metastases from newly diagnosed squamous carcinoma of the head and neck

A study of 71 patients compared preoperative PET, CT and MRI (magnetic resonance imaging) for the detection of neck node metastases, with histological ascertainment as the gold standard. The values obtained are in Table 3, and suggest that PET has a markedly superior specificity and positive predictive value.

Table 3. Preoperative Comparison of Imaging Techniques in Neck Node Metastases Detection

	PET (%)	CT (%)	MRI (%)
Sensitivity	87	65	88
Specificity	94	47	40
Positive predictive value (PPV)	90	40	51
Negative predictive value (NPV)	93	72	83

Source: Kau et al[23]

b) Detection of recurrent squamous carcinoma of the head and neck

A study of 44 patients with Stage III or Stage IV head and neck cancer compared follow-up assessment by PET to CT and to clinical examination. PET had a sensitivity of 100% compared to 38% for CT and 44% for clinical examination. All three methods had good to excellent specificity: PET 93%, CT 85%, clinical examination 100%.[26]

c) Potential impact of PET on processes of care for squamous carcinoma of the head and neck

PET may be superior to CT in pre- and post-therapy evaluation of squamous carcinoma of the head and neck and may reduce utilization of CT in this clinical setting.

4. Carcinoma of the Breast

a) Detection of axillary lymph node metastases

A study of fifty patients with carcinoma of the breast compared PET imaging of the axilla to histological examination of resected axillary lymph nodes. The sensitivity of PET was 90%, specificity 97%, positive predictive value 95%, and negative predictive value 92%.[41]

b) Detection of bone metastases

A study of 34 patients with carcinoma of the breast compared the PET image of the bones to regular radionuclide bone scanning. The area under the receiver-operating characteristic (ROC) curve was 1.00 for PET and 0.82 for bone scanning ($p<0.05$). The PET scan changed the treatment recommendation for 4 of 44 patients, compared to what would have been recommended if only information from the bone scanning was available.[30]

c) Early assessment of response to chemotherapy

A study of 30 patients receiving neoadjuvant or primary chemotherapy for carcinoma of the breast underwent PET evaluation before the first course, and after the second and fifth courses of chemotherapy. Regression of PET uptake in the primary tumour or lymph nodes was related to histological evidence of response to therapy.[31]

d) Potential impact of PET on processes of care for carcinoma of the breast

These clinical applications appear to provide additional information that may be used in the selection of therapy for carcinoma of the breast. It is unclear if PET would replace the utilization of any currently used assessment procedures.

The practice regarding axillary assessment varies widely at present. Some practitioners perform axillary dissection routinely for most patients with newly diagnosed carcinoma of the breast, whereas others perform it only if a sentinel lymph node biopsy is positive. A sentinel node biopsy consists of injecting the patient's breast cancer with a blue dye and nuclear medicine marker 24 hours before surgery. By the time of surgery the injected material has been taken up by the lymph nodes in the axilla. The surgeon can then identify and biopsy the first lymph node in the axilla, which is examined histologically during the operation. Proponents of this technique maintain that if this node does not contain metastases, then the axilla need not be dissected. A randomized trial of this approach is now underway. For surgeons routinely performing axillary dissection, PET might reduce the rate of axillary dissection in patients with PET-negative axillary imaging. Among those performing sentinel node biopsy, the rate of axillary dissection has already been reduced to those patients with a positive-sentinel lymph node biopsy.

The diagnosis of bone metastases in newly diagnosed patients and patients being followed after treatment of breast cancer is a major clinical issue. PET appears to be more effective than

radionuclide bone scanning in the detection of bone metastases due to carcinoma of the breast. If PET is used instead of bone scan, this would be a major shift in nuclear medicine practice in breast cancer.

Neoadjuvant, or primary chemotherapy prior to surgery and/or radiation therapy, at present is applied chiefly in the setting of locally advanced breast cancer, a small subset of the population of newly diagnosed breast cancer patients. It is unclear if information from PET about a poor prognosis or response to chemotherapy would prompt a change in therapy that would improve clinical outcomes (because of the likelihood in this clinical setting that other therapies would also fail).

5. Malignant Lymphoma and Hodgkin's Disease

a) Staging of newly diagnosed malignant lymphoma and Hodgkin's disease

The extent of disease, or stage, of malignant lymphoma or Hodgkin's disease is a key factor in the choice of therapy. A change in staging assignment can lead to the omission or addition of either radiation therapy or chemotherapy. In a study of 44 patients with Hodgkin's disease, changes in stage and treatment recommendation were made for 14% of patients.[34]

A study of 89 patients focusing on the evaluation of lymphoma involving hilar or mediastinal lymph node regions in the chest compared PET to concurrent or ultimate histological evidence of involvement. The results for PET were sensitivity of 96%, specificity of 94%, positive predictive value of 90%, and negative predictive value of 98%.[33]

b) Evaluation of residual post-treatment masses

After completion of therapy, patients treated for malignant lymphoma and Hodgkin's disease may have residual masses detected on CT at anatomic locations that were involved by lymphoma prior to treatment. It is frequently unclear if the residual masses contain residual neoplasm. A retrospective study of 32 patients with residual masses detected on CT evaluated PET, and observed patients for relapse / progressive disease at the anatomic locations of interest. Using relapse / progressive disease as the gold standard, PET demonstrated sensitivity of 80%, specificity of 95%, positive predictive value of 89%, and negative predictive value of 91%.[35]

c) Detection of bone marrow involvement by malignant lymphoma or Hodgkin's disease

Although bone marrow involvement is uncommon in Hodgkin's disease, it is common in non-Hodgkin's malignant lymphoma. In a series of 50 patients (38 with non-Hodgkin's malignant lymphoma and 12 with Hodgkin's disease), PET was compared to bone marrow biopsy (the gold standard for bone marrow involvement). The results for PET were: sensitivity of 81%, specificity of 76%, positive predictive value of 62%, and negative predictive value of 90%.[36]

d) Potential impact of PET on processes of care for malignant lymphoma and Hodgkin's disease

One PET study may be able to replace a series of sequential CT scans in patients with residual masses of indeterminate nature after completion of therapy. It is unclear whether PET would

replace any staging investigations, such as CT scans, or bone marrow biopsies, prior to the selection and initiation of therapy for malignant lymphoma or Hodgkin's disease.

6. Malignant Melanoma

a) Staging of newly diagnosed malignant melanoma

A study of newly diagnosed patients with high-risk malignant melanoma (i.e., thickness >1.5 mm) compared PET to 'conventional imaging' consisting of radiography, sonography, CT, and MRI. The results for PET compared to 'conventional imaging' were sensitivity, 100% vs. 85%, and specificity 96% vs. 68%.[39]

b) Follow-up of malignant melanoma

The detection of silent metastases among malignant melanoma patients compared PET to 'routine methods' including clinical examination, radiography, CT, ultrasound and serum profiles of liver enzymes. The results for PET compared to 'routine methods' were sensitivity 97% vs. 62%, and specificity 56% vs. 22%.[38]

c) Potential impact of PET on processes of care for malignant melanoma

It appears that a single PET study could replace the tests that allow assignment of stage to a patient with malignant melanoma, or evaluate for the presence of metastases for a patient who has a lymph node recurrence for which the treatment might be a radical lymph node dissection. In malignant melanoma, treatment options are few, and staging investigations or investigations to detect asymptomatic metastases are warranted only if there is a treatment decision to be made.

7. Glioma

a) Distinguishing recurrent glioma from radiation necrosis

No Grade A or B studies testing the efficacy of PET in distinguishing recurrent glioma from radiation necrosis were found.

b) PET as an improved method for radiation treatment planning

No Grade A or B studies testing the efficacy of PET in radiation treatment planning were found.

c) Potential impact of PET on processes of care for glioma

The use of PET in the processes of care for glioma is not established by the literature, and remains an experimental question.

8. Cost-effectiveness of PET in Oncology

The literature contains five economic evaluations of PET for the staging of lung cancer and one each for the evaluation of solitary pulmonary modules and the staging of lymphoma and Hodgkin's disease. These evaluations suggest that PET scanning for these indications fall within the range of what is generally considered cost-effective. More details are provided in the section on cost-effectiveness.

Summary of Oncological Indications Reviewed

On the basis of the evidence reviewed, there are roles for PET in the following clinical settings:

- **Carcinoma of the lung:** diagnosis of solitary pulmonary nodules; staging the mediastinal lymph nodes; and evaluation for residual or recurrent malignancy or bone metastases (if the result in these latter situations will influence therapy);

- **Colorectal carcinoma:** detection of recurrent colorectal carcinoma (if the result will influence therapy);

- **Squamous carcinoma of the head and neck:** staging lymph nodes in the neck (if the result will influence therapy); detection of recurrent carcinoma (if the result will influence therapy);

- **Carcinoma of the breast:** axillary assessment if sentinel lymph node biopsy is not part of the evaluation;

- **Malignant lymphoma or Hodgkin's disease:** pre-therapeutic assessment of lymph node regions involved, especially in the chest, and assessment of bone marrow involvement; assessment of residual masses on CT scan after completion of therapy;

- **Malignant melanoma:** staging investigations or evaluation for silent metastases (only if the result will influence therapy); and

- **Glioma:** experimental use only.

PET in Cardiology

Introduction

The literature discusses two main indications for PET in cardiology - the evaluation of coronary artery disease (CAD) and the assessment of viability. The objective of this evaluation is to examine the incremental benefit of PET over and above other available non-invasive diagnostic tests in cardiac disease.

Coronary Artery Disease

Many studies have demonstrated the efficacy of PET in diagnosing coronary artery disease.[42-48] However, given the existence of a number of other non-invasive diagnostic tests, the cost of PET, and the fact that PET is unlikely to replace coronary angiography, it seem highly unlikely that PET will routinely supplement other available non-invasive methods for diagnosing coronary artery disease in the population as a whole. In addition, one high quality economic evaluation conducted in the United States has found PET scanning to be extremely cost-ineffective for this indication.[49] At this time, we feel that there is little evidence to support the wide-spread use of PET over currently available diagnostic strategies for the assessment of CAD. Therefore, we decided not to undertake a systematic evaluation of PET for CAD for the purposes of this report.

However, PET may be a useful non-invasive test in certain subgroups of patients. For example, PET may have specific roles for patients in whom attenuation artifact with single positron emission computed tomography (SPECT) is expected.[50] Another recent study conducted in Ontario suggests that FDG PET compared to SPECT may be diagnostically useful in obese females.[51] However, the methodological quality of the studies in these patient subgroups is poor, and the degree to which small incremental benefits in diagnostic accuracy translate into important clinical benefits is unclear. No cost-effectiveness studies have examined PET for the diagnosis of CAD in these subgroups, nor have any cost-effectiveness studies been conducted in Canada, where costs and practice patterns are different from other jurisdictions (e.g., United States).

In summary, current evidence does not support the routine use of PET for CAD, although the role of PET in CAD should be re-evaluated if higher quality information becomes available.

Left Ventricular Viability

In contrast to CAD, current tests for the evaluation of viability are suboptimal, and PET's ability to assess tissue function makes it a logical test to consider for this indication. Patients with left ventricular (LV) dysfunction who are considered for revascularization have a higher risk but a greater potential long-term mortality benefit from surgery, compared with patients with normal or mildly impaired LV function.[52-54] Available evidence suggests revascularization of patients with viable myocardium results in improved outcomes.[55] Therefore, distinguishing metabolically active, or viable myocardium from non-viable myocardium becomes an important strategy for risk-stratification in these patients.[56,57]

Patients with LV dysfunction may still have viable myocardium due to 'hibernation'. While the pathophysiology of hibernating myocardium is still somewhat controversial, it is believed that chronic low blood flow due to significant epicardial stenosis is a possible mechanism.[58-60] In the setting of a severe decrease in blood flow, myocardial metabolism switches from free fatty acids to glucose uptake.[61] The gold standard for determining whether a patient has hibernating myocardium is improved LV function after revascularization.[56,57]

Patients who require viability assessments represent only a small proportion of the total CAD population.[62,63] However, because CAD is common, the actual number of patients may be considerable. They are patients with predominant heart failure symptoms (rather than angina) who are being considered for revascularization or cardiac transplantation. Those hospitalized with acute coronary syndromes will not be assessed with PET because the majority will have myocardial 'stunning' rather than hibernation.

The purpose of any non-invasive assessment of viability is to distinguish 'reversible' causes from 'irreversible' causes or scar. There are many available methods of detecting viable myocardium. The main non-invasive tests are dobutamine echocardiography, SPECT Sestimibi, SPECT thallium, and FDG imaging (with SPECT or PET cameras).

Review of the Evidence

In total, 332 abstracts, 113 articles (89 primary studies and 24 review articles), and 6 HTAs were reviewed. Only one published study met grade 'A' criteria and it will be discussed in detail. All remaining studies were of poorer methodological quality (grade C and D). Despite our a priori decision to only consider Grade A and B studies in this report, we decided to discuss the better quality C/D studies, those that either strongly supported or refuted the clinical benefit of PET, were pivotal in other HTAs, or were conducted in Ontario. The most common reasons for classifying studies as C or D were the following: small sample size, sample bias with non-consecutive patients, retrospective design, incomplete follow-up/revascularization, or the assessment of PET imaging was unblinded to clinical or other imaging related information.

1. Results of studies of PET for viability assessment

a) Diagnostic studies (predicting segmental wall improvement following revascularization)

There were no A or B quality studies evaluating the accuracy of PET in predicting recovery of LV function after revascularization. Table 4 illustrates the results of some of the better quality C/D studies evaluating the diagnostic accuracy of PET for predicting segmental recovery of LV function following revascularization. A noteworthy limitation is that several of the studies listed examined patients with mild-moderate rather than severe LV dysfunction. Table 5 illustrates how PET compared to other non-invasive modalities in predicting improvements in segmental function. PET had similar sensitivity but superior specificity, when compared to thallium rest-redistribution. When compared to dobutamine echocardiography, PET had marginally inferior sensitivity but similar specificity, suggesting comparable accuracy. Nonetheless, the comparability of PET with dobutamine echocardiography for viability is still controversial. For example, one recent prospective study examined segmental LV function recovery after bypass surgery in 30 patients with a mean LVEF of 25% and suggested that PET had better sensitivity

(99% vs. 60%, p<0.0001), but worse specificity (33% vs. 62%, p<0.0001) when compared to dobutamine echocardiography.[64] In this study, overall accuracy rates favored PET over dobutamine echocardiography (71% vs. 61%, p = 0.01). Moreover, the superiority of PET over dobutamine echocardiography was even greater in the worst functioning (akinetic) segments. However, the degree to which these differences in accuracy rates for segmental recovery translate into important clinical benefits of PET over other available modalities is unknown.

Table 4. Sensitivity and Specificity of Selected Better Quality C/D Grade Studies of FDG18 PET in Predicting Segmental Recovery

Study	Year	No. of Patients	Mean LVEF % (+/- SD)	Sensitivity % (no. of segs)	Specificity % (no. of segs)	Predictive values % (where provided)
Tillisch[65]	1986	17	32 (14)	95	80	PPV 85 NPV 92
Tamaki [66]	1989	22	NA	78	78	PPV 78 NPV 78
Tamaki[67]	1991	11	NA	100	38	-
Carrel[68]	1992	23	34 (14)	94	50	-
Marwick[69]	1992	16	NA	71	76	PPV 68 NPV 79
Lucignani[70]	1992	14	38 (5)	93	86	-
Gropler[71]	1993	34	NA	83	50	PPV 52 NPV 81
Knuuti[72]	1993	48	53 (11)	92	85	-
Paolini[73]	1994	17	28 (4.9)	88	79	-
Tamaki[74]	1995	43	41 (NA)	83	91	PPV 76 NPV 92
Gerber[75]	1996	39	33 (10)	75	67	-
Baer[76]	1996	42	40 (13)	92	88	-
Vom Dahl[77]	1996	193	45 (12)	92	35	PPV 61 NPV 80
Maes[78]	1997	23	41(13)	83	50	-
Pagano[79]	1998	30	24 (7)	99	33	PPV 66 NPV 96
Schoder[80]*	1999	40	30 (6)	93	81	PPV 87 NPV 90
Zhang[81]	1999	60	44 (15)	76	86	PPV 88 NPV 73

Legend: SD=standard deviation; PPV=positive predictive value; NPV=negative predictive value; -=not reported;
* Retrospective

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Table 5. Sensitivity and Specificity for the Different Imaging Techniques in Predicting Segmental Recovery *(based on weighted mean values)*

Technique	No. of Patients	Sens (%)	95% CI	Spec (%)	95% CI
Tc-99m MIBI*	207	83	77-89	69	63-74
LDDE	448	84	82-86	81	79-84
Tl-201 reinjection*	209	86	83-89	47	43-51
F-18 FDG-PET	332	88	84-91	73	69-77
Tl-201 rest-redistribution*	145	90	87-93	54	49-60

Legend: CI=confidence interval; LDDE=Low-dose Dobutamine Echocardiogram;
*imaging techniques not involving PET (eg SPECT)
Source: adapted from Bax, J.J. et al 1997[82]

b) Studies assessing clinical improvement following revascularization

Table 6 summarizes the results of ten studies that evaluated the ability of PET to improve clinical outcome when used as a diagnostic test to identify patients suitable for surgery. Nine studies examined mortality, three studies examined functional status and quality of life, and one study examined changes in global LV function. There was one 'A' quality study. This study conducted in the Netherlands by Siebelink et al,[83] was a randomized, controlled, double-blinded clinical trial of 103 patients with LV dysfunction who were being considered for revascularization. Patients were randomized to receive 13N- ammonia /18FDG PET or 99m-Tc-sestamibi SPECT in order to help the clinicians determine the best management strategy (i.e., PTCA [coronary angioplasty], CABG [bypass surgery], medical therapy). Clinical decisions were based on information obtained from the test, but without knowledge of which non-invasive modality was used. The study was designed to detect a 20% absolute difference in cardiac event-free survival (with a baseline event rate of 20% in the SPECT arm). The primary outcomes were cardiac death, MI, and unintended revascularization after a mean follow-up of about 28 months. Unintended revascularization was defined as PTCA or CABG performed due to worsening of the patient's clinical condition, rather than the PTCA or CABG assigned by the revascularization team when patient management was determined. The results demonstrated that the prevalence of the mean amount of normal, nonviable and jeopardized myocardium was not different between PET and SPECT. Moreover, the frequency of medical therapy/PTCA/CABG was similar between PET and SPECT (in the PET group 24% underwent PTCA, 29% CABG and 47% medical therapy, compared with 28%, 24% and 48% respectively in the SPECT group). Finally, there was no difference in cardiac event-free survival in the two arms (78% in the PET group versus 76% in the SPECT group). Despite its methodological strengths, the study by Siebelink et al has several important limitations. Only 35% of patients had a LV ejection fraction (30% and the mean NYHA functional class (see glossary) was about 2.5--a relatively high functional status

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compared to a severe heart failure population. Accordingly, the generalizability of these results to patients with moderate to severe LV dysfunction, the spectrum of most interest, is not known.

The relatively healthy cohort examined by Siebelink et al might also explain why the two tests identified similar amounts of normal, nonviable and jeopardized myocardium as the relative accuracy of PET in detecting myocardial viability over other non-invasive tests may depend on the extent of LV dysfunction at baseline. As well, the sample size in this study was relatively small, as were the number of deaths or MIs after randomization (i.e., absolute number of deaths/MIs: 6 vs. 4 in PET vs. SPECT groups respectively). Accordingly, the study was not powered sufficiently to detect differences in these outcomes. Nonetheless, this study provides the best quality evidence published thus far about the effect of PET upon clinical decisions and outcomes in heart failure patients being considered for revascularization, and raises doubts about whether PET is more useful than existing diagnostic tests.

The remaining nine studies were all methodologically poorer in quality, although the majority (8) examined an appropriate spectrum of patients (i.e., ischemic cardiomyopathies with the majority having heart failure rather than anginal symptoms). Methodological limitations common to all studies included the potential for pre-selection bias (i.e., no description of how patients were selected for referral to the PET centre or for myocardial revascularization). Only four studies evaluated outcomes without knowledge of the PET result. With one exception[84], no study examined the incremental predictive value of PET over other non-invasive viability modalities. Soufer et al prospectively studied 37 patients, in whom PET and SPECT (MIBI) results were concordant in 131 (71%) of the 185 segments studied. Of the 54 discordant segments, 39 were PET-viable/SPECT non-viable (with a predominance of inferior segments) and 15 were PET non-viable/SPECT viable (with a predominance of apical segments). A subset of 13 patients was referred to CABG, with data on pre and post LV function recovery provided on only 11 such individuals. The authors provided no information as to why patients were, or were not referred for revascularization. There was a significant improvement of regional ejection fraction, from 36% to 48% ($p < 0.001$) in the 12 segments that were PET viable/SPECT non-viable, accompanied by improved regional wall motion in all but one segment. There was no apparent improvement of regional ejection fraction (39% to 40%, p = ns) and only one improvement in regional wall motion in the 7 segments that were PET non-viable/SPECT viable.

c) Does PET influence medical decision making?

A study by Beanlands et al[85] evaluated physician perspectives in 87 patients referred to the Ottawa Heart Institute between February and December 1995. All patients received FDG-PET and technetium-99m SPECT (with the exception of 2 patients receiving a thallium-201 resting study as a substitute for sestamibi). Before knowledge of the PET data, the physicians were asked to indicate their intended management (i.e., a choice of work-up for cardiac transplantation, medical therapy, revascularization, or uncertain) if PET data were not available. Physicians were re-surveyed after PET data were made available and physicians were once again asked to state their intended management. The results suggested that the majority of physicians had their management influenced by PET data (50/87, 57%). The definition of viability or scar on PET redirected therapy from transplant workup to revascularization in 7 of 11 (63%), from medical therapy toward revascularization in 8 of 18 patients (44%), and from revascularization to medical therapy in 16 of 38 patients (42%). In summary, there was poor agreement between pre-

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and post-PET management plans (kappa=0.182). Moreover, the impact of PET increased as preoperative LV function became poorer. However, this study did not examine actual treatments. Therefore, we have no information on whether the intended management correlated with the actual management. Moreover, this study compared PET with sestamibi in clinical decision-making. It is possible that other non-invasive modalities such as thallium or dobutamine echocardiography could have also influenced physician referral behaviour.

PET has also been studied as a method of identifying cardiac transplantation candidates who would benefit from revascularization instead. Two of these reports are abstracts but there is one full publication. This retrospective observational study from UCLA by Louie et al, examined 207 patients with ischemic cardiomyopathy referred for heart transplant evaluation. Among these 207 patients, 131 met predefined criteria for cardiac transplantation, 54 did not satisfy criteria for transplantation and had undergone aggressive medical therapy and 22 were selected for coronary revascularization (NYHA IV). Among the 22 patients, 12 had preoperative PET. All 10 patients with viability on PET survived revascularization, whereas the two patients without viability died following revascularization. While this study did not provide sufficient details on the selection of patients for revascularization, it raises the possibility that PET may have a role in determining whether patients with end-stage ischemic cardiomyopathy should undergo CABG or cardiac transplantation.

d) Cost-effectiveness studies

No economic evaluations of FDG-PET for myocardial viability in order to avert/select patients for cardiac transplantation have been published. Two cost-effectiveness studies evaluating PET for the diagnosis of coronary artery disease are discussed further in the section on cost-effectiveness.

2. Other HTA results

Appendix III includes the results of other HTAs examining the role of PET for myocardial viability. The majority of these suggested either a limited or no role for PET. This document is the only HTA to incorporate the first randomized controlled trial evaluating PET- vs. SPECT-guided revascularization.

Summary

PET scanning has been suggested as a method of identifying ischemic heart tissue in patients with moderate to severe heart failure that is reversible with revascularization procedures such as angioplasty or bypass surgery. One grade A study[83] was found evaluating the use of PET scanning for cardiac viability, and it failed to show any favourable effect upon outcome compared with SPECT. This study was relatively small (103 patients) and included a number of patients with only mild heart failure. Other studies of poor methodological quality have suggested potential benefits, although PET's incremental value over other available non-invasive modalities was not clearly evaluated. Nonetheless, this one "negative" grade A study cannot be used to conclude that PET scanning has no role for the assessment of viability.

Fortunately, Beanlands et al in Ottawa are currently conducting a multi-centre randomized controlled trial evaluating the long-term outcomes and cost-effectiveness of PET in patients with severe LV dysfunction in whom revascularization is being considered. This study will address many of the methodological limitations of the current literature and will provide important insight into the incremental clinical and economic usefulness of PET in the assessment of viability over and above other available non-invasive modalities.

It is our opinion that while the available evidence does not support the routine use of PET for the assessment of viability at the present time, the state of evidence is evolving. Accordingly, we suggest that a re-evaluation of cardiac PET be conducted in 2-3 years.

Table 6. Studies Assessing Clinical Improvement Following Revascularisation *(all but one* are C/D Grade)*

Study	Year	Main Outcome Measure(s)	Results	Methodological Criteria					
				Pts	Selection	Spectrum	Blinded	Revasc	Other
***Siebelink**[83]	2001	13N/FDG-PET vs. 99Tc-sestamibi SPECT	No difference between PET and SPECT in cardiac event-free survival (death, MI, revascularization) at 28+/-1 mos	103	RCT	LVEF ≤30% in only 35% of sample; NYHA-2.5	Yes	50% revascu-larized in each grp	Only Grade A study found.
Marwick[86]	1999	Functional capacity, QOL; Mortality; F/U 17 mos Compared PET to dobutamine echo.	All received PET, 47/63 also received dobutamine echo. Degree of improvement of exercise capacity correlated with the extent of viability by PET (r=0.54, p<0.001). In contrast, extent of viability by dobutamine echo did not correlate with improved exercise capacity. Multivariate analysis: Extent of viability by PET predicted improved exercise capacity and change in functional class, but not improved QOL. No deaths in cohort.	63	?Consecutive ?CABGs Pre-selection bias	Mean EF = 28%	No	63/63 CABG	Prospective; Many patients did not receive dobutamine echo; Incremental benefits unknown.
Pagano[79]	1998	Functional capacity, QOL; Mortality	Viability correlated with change in EF; No correlation between viability and functional capacity and QOL.	35	Pre-selection bias	Mean EF =23%	Yes	31/35 CABG	Prospective; Incremental benefits unknown.
Beanlands[87]	1998	Mortality 17+/- 7 mos	FDG-PET guided revascularization and triage: Early Revasc < 35d mean = 12 d (O% preop; 11% post-op mortality; LVEF from 24% to 29%) vs. Late Revasc ≥35d mean = 145 d (24% preop; 7.8% post-op mortality, LVEF change not significant)	46	Pre-selection bias	All EF < 35% Mean EF = 26% majority had angina	No	35/46	Prospective; why 35 days chosen as cutoff between early and late revasc was unclear; Incremental effects of PET over usual waiting-lists unknown; Incremental benefits unknown.

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Study	Year	Main Outcome Measure(s)	Results	Methodological Criteria					
				Pts	Selection	Spectrum	Blinded	Revasc	Other
Haas[88]	1997	Death; Mean F/U ~ 12 mos.	Viability studies permit selection of patients who are at low risk of serious periop complications. Compared 2 grps: *Grp A* with angina Sx and angio (no PET) vs. *Grp B* with PET viability to supplement clinical and angio info (scar ≥40% meant no CABG); Listed baseline characteristics well matched; Grp A higher perioperative event rate (30d mortality = 11.4% vs. 0%, p =0.04) ; 30d to 1-yr mortality equivalent (2.9%)	76	Consecutive 3-vessel disease and poor LV function referred for CABG	Mean EF =29%. No signif. difference between Grp A&B All EF <35%	No	100% CABG	Retrospective; Non-randomized; Incremental benefits unknown.
Soufer[84]	1995	Global LV function – incremental over MIBI-SPECT	71% Concordance Discordance: + PET/ - SPECT 36% to 48%, (p<0.001) - PET/+ SPECT 39% to 40%, (p = ns)	37	Pre-selection bias	Mean EF = 44%	LVEF blinded	13 CABG	Prospective
Di Carli[89]	1995	Functional status	Extent of PET mismatch correlated linearly with % improvement in functional status (r=0.87, p<0.001); Multivariate analysis: Extent of PET mismatch and age predicted improvement in functional status	41	Consecutive referrals for PET and CABG; Pre-selection bias	Mean EF = 28%	Yes	36/41 CABG	Prospective; No assessment of regional or global EF change; Incremental benefits unknown.
Di Carli[90]	1994	Mortality; mean follow-up 13.6 months	Overall mortality = 15%; Multivariate analysis: predictors of survival were less extensive mismatch (p=0.02) revascularization (p=0.04); Among Medical Rx only (n=50), ROC = 5% cut-off for extent of mismatch: If mismatch>5% of myocardium, annual survival=55%; if mismatch ≤5%, annual survival was 92%. Among Revascularized, extent of mismatch also predictive of survival. Medical vs. Revascularization: Survival = if no mismatch	93	Consecutive referrals for PET at UCLA Pre-selection bias	Mean EF =25% 68% NYHA III-IV	No	43/93	Retrospective; Incremental benefits unknown.

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Study	Year	Main Outcome Measure(s)	Results	Methodological Criteria					
				Pts	Selection	Spectrum	Blinded	Revasc	Other
Lee[91]	1994	Non-fatal ischemic events; Death 17+/- 9 mos.	Medical Rx FDG+ = 48% vs. Revasc Rx FDG+ = 8% (p< 0.001) vs. Revasc Rx FDG- = 5%; Cox: FDG+ No Revasc predicted non-fatal; age + LV dysfunction predicted death	137	Pre-selection bias	Majority with angina; only 19% with CHF Sx;	No	50%; decision clinical	Retrospective; Incremental benefits unknown.
Eitzman[92]	1992	MI, death, cardiac arrest	Medical Rx FDG+ = 50% vs. Revasc Rx FDG+ = 11% vs. No Revasc FDG- = 12.5% vs. Revasc Rx FDG- = 7.1%, (p < 0.01)	82	Pre-selection bias	Mean EF =34%	Yes	40/82	Retrospective; Incremental benefits unknown.

Legend: angio=coronary angiography; CABG=heart bypass surgery; CAD=coronary artery disease; d=days; EF=ejection fraction; F/U=follow up; Incremental benefits unknown= Incremental benefits of PET over other imaging modalities were unknown; LV=left ventricle; mos=months; NYHA=New York Heart Association Class; QOL=quality of life; Rx=treatment; Revasc=Revascularized; ROC=receiver operating characteristics; Rx=Treatment; Sx=symptom(s); *only 'A' Grade study

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PET in Neurological Diseases

Introduction

Functional neuroimaging using PET can provide information regarding the biochemical characteristics of the nervous system that may not be identified by anatomical neuroimaging techniques such as CT and MRI. The clinical application of PET has been explored in a number of different neurological disorders, including epilepsy, dementia, movement disorders, and stroke. Unfortunately, the conclusions of many of these studies are limited by poor methodology. In this section, we focus on two neurological conditions where there is the best evidence available evaluating the potential role of PET — pre-surgical evaluation of patients with intractable epilepsy, and the diagnosis of Alzheimer's disease. In general, the majority of articles were of poor methodologic quality because they did not include consecutive patients, had incomplete follow-up, or the assessment of PET by the investigators was unblinded to patient diagnosis. Only methodological Grade A or B studies are discussed in detail in this section, although the conclusions are based upon a complete review of the literature (Tables 7 and 8).

Review of the Evidence

1. Pre-Surgical Evaluation of Intractable Epilepsy

a) Introduction

Antiepileptic drugs are the initial treatment for patients with epilepsy. These drugs provide complete seizure control in the majority of patients with epilepsy, with a lower rate in patients with temporal lobe epilepsy.[93] Patients with epilepsy who are not adequately controlled on standard drug regimens represent a special population with medically intractable epilepsy. Although the formal definition of "intractability" is a topic of discussion in the epilepsy literature[94], patients with seizures refractory to medical treatment may be considered for surgical management. Over the past decade, there has been a dramatic increase in the awareness of the role surgery may play in the management of these epileptic patients. Despite this, relatively few patients undergo this surgical procedure. It is estimated that 352 patients in Canada[95] receive surgical treatment each year.

Patients with intractable epilepsy being considered for epilepsy surgery may undergo a range of investigations including electroencephalogram (EEG), MRI, CT and invasive studies using depth electrodes. FDG-PET provides information complementary to these studies that may benefit the patient in two ways. Many patients have alterations identified on ictal EEG records and structural abnormalities on MRI that predict good outcomes after surgical intervention. The finding of interictal unilateral temporal hypometabolism ipsilateral to the EEG focus may be a valuable procedure for the localization of the seizure focus and may do away with the need for invasive evaluations using depth electrodes in some selected patients that do not have definitive abnormalities on EEG and MRI testing. The finding of widespread interictal hypometabolism with PET in the setting of well-localized EEG discharges may suggest more diffuse cerebral dysfunction and may predict a poor outcome of surgery. In these circumstances, FDG-PET may help identify patients less likely to benefit from surgery.

b) Using PET to localize Epileptogenic Foci

We reviewed 20 original investigations focusing on the role of PET in intractable epilepsy management (Tables 7a and 7b). Of these 20 articles, six[96-101] were given a grade of B. No paper was judged to be grade A. In general, these studies had small sample sizes. This may reflect the small number of patients with intractable epilepsy who undergo pre-surgical evaluation. Only one of the six studies of higher quality evaluated pediatric patients.[98]

The studies examined patients with both temporal lobe and extra-temporal lobe epileptogenic foci. The radioisotope commonly used in the neurological studies with PET is [^{18}F] fluorodeoxyglucose (FDG). Some of the studies also considered the value of [^{11}C] flumazenil-PET (FMZ-PET), because there is reduced FMZ binding in epileptic patients.[97,98] The studies employed a variety of PET scanners of different ages and with different spatial resolutions. One of the six studies[99] directly compared three different PET scanners. The scans were done during interictal periods in the vast majority of cases.

Helveston et al[96] compared qualitative PET interpretation to qualitative MRI interpretation and hippocampal formation volumetric assessment (HVMR) – a quantitative method of MRI interpretation. Qualitative PET methods are used rather than quantitative methods, even though quantitative methods are known to reduce the variability of the measurement. The goal was to lateralize seizure foci in 16 consecutive adults with intractable temporal lobe epilepsy. Correct lateralization was confirmed by determination of the Engel classification (i.e., an examination of the clinical outcomes one year after surgery). PET was correctly lateralizing in nine (56%) patients, non-lateralizing in six (37.5%), and incorrectly lateralizing in one (6%). In comparison, qualitative MR imaging was correctly lateralizing in six (37.5%), nonlateralizing in six (37.5%), and incorrectly lateralizing in four (25%). HVMR was correctly lateralizing in all (100%). This study evaluating a small number of patients suggests that both PET and HVMR are sensitive techniques for the lateralization of epileptic foci in patients being considered for epilepsy surgery. However, HVMR was superior to PET.

Ryvlin et al[97] compared PET using different radioisotopes (FDG and FMZ) to localize the seizure foci. This study prospectively recruited one hundred consecutive patients undergoing a pre-surgical evaluation for intractable partial epilepsy. The results using both forms of PET imaging were compared to intracranial EEG recordings and MRI. The value of PET in predicting surgical outcome, however, was only partially reported. The authors concluded that FMZ-PET (reduced FMZ binding in epileptic patients) was not superior to FDG-PET in this population, but did provide some useful complementary data.

Ho et al[100] compared qualitative interictal FDG-PET interpretation with ictal SPECT to determine if the seizure focus was identified. Thirty-five patients with intractable temporal lobe epilepsy who had undergone both SPECT and PET were retrospectively identified for this study. To be included, localization of the seizure focus by MRI or EEG abnormalities was required. One pair of independent blinded observers were then asked to analyze the SPECT scans, while a second pair of observers analyzed the PET scans. The scans were graded using a standardized protocol. The two SPECT observers correctly lateralized seizure foci with certainty in 89% of patients, while the PET observers only correctly lateralized the foci in 63% of patients. Unfortunately, the value of this study is questionable, given the fact that in the real world, it is

unlikely that either SPECT or PET would be necessary if MRI or EEG localization was already available. Ictal SPECT is unlikely to be a clinically useful technique since it is hard to predict and perform scans during a seizure.

Ryvlin et al[101] also compared FDG-PET with SPECT in patients with temporal lobe epilepsy. Lateralization on EEG was still required for inclusion into the study, but there was an important difference between this study and the one discussed above by Ho et al.[100] The twenty patients in the Ryvlin study were divided into two groups of ten, one group with normal MRI results and the other with abnormal MRI results. In the patients with normal MRI results, PET exhibited focal hypometabolism in 80%, while SPECT demonstrated corresponding hypoperfusion in only 20%. In the patient with MRI abnormalities, the sensitivities for PET and SPECT were 100% and 90%, respectively. Unfortunately, this study did not contain information on the long-term clinical outcomes of the patients. The small number of patients also limit the conclusions that can be drawn from this study.

Muzik et al[98] also compared FMZ-PET, FDG-PET and intracranial EEG. Ten children with intractable extra-temporal lobe epilepsy underwent all three investigations. Sensitivities and specificities for determining the focus of seizure onset were then calculated for the two PET techniques, using different cutoff thresholds for the asymmetry of radioisotope uptake. Receiver operating characteristics (ROC) curve analysis was then performed. The authors concluded that FMZ-PET might have advantages over FDG-PET in some of these patients, and might help to guide intracranial EEG electrode placement.

Henry et al[99] examined the reproducibility of 241 qualitative PET interpretations in patients with partial epilepsy using three different PET scanners. The kappa statistic, a measure of agreement between observers, was moderate (0.54 and 0.55) for the two PET scanners with low spatial resolution. This level of agreement might be considered adequate for clinical application of these tests, and is comparable to the level of agreement seen for many elements of the clinical examination. Interestingly, the agreement was almost perfect (kappa = 0.96) for the PET scanner with the best spatial resolution. This study therefore suggests that the replicability of the interpretations using the newer PET scanners is substantially better than that for the older scanners.

c) Other HTA results

Appendix III includes several health technology reports (adapted from the report prepared by the INAHTA) which evaluated the role of PET in intractable epilepsy. In general, the conclusion of these health technology reports is that there is evidence supporting a role for PET in the evaluation of patients with intractable epilepsy who are candidates for surgery.

d) Cost-effectiveness studies

We identified no studies that evaluated the cost-effectiveness of using PET in the pre-surgical evaluation of patients with intractable epilepsy.

e) Limitations of the evidence and future directions

We have demonstrated that there is some limited evidence supporting the potential role of PET to complement the role of other diagnostic tests being used in the pre-surgical evaluation of patients with intractable epilepsy. However, in general the studies were of relatively poor quality and evaluated small numbers of highly selected patients. Further, while intractable epilepsy is a problem among children, only one[98] of the six higher quality studies evaluated the pediatric population.

In the future, it would be optimal if studies were designed that evaluated patients with intractable epilepsy being considered for neurosurgery and who did not have localizing information available from other diagnostic procedures (e.g., EEG or MRI). Such studies should assess if FDG-PET pre-operatively decreases the use of invasive diagnostic procedures (i.e., depth electrode placement) and improves surgical outcomes. Furthermore, studies should also be conducted in patients likely to be undergoing the procedure; therefore, children should be adequately evaluated.

f) Summary

Our systematic review demonstrates a limited role for PET in the evaluation of patients with intractable epilepsy being considered for neurosurgery. First, PET may decrease the need for invasive diagnostic procedures, thus preventing potentially serious adverse events. Second, PET may facilitate localization of seizure focus and thus improve surgical outcomes. However, there is a need to compare PET to other non-invasive diagnostic procedures such as HVMR in high quality clinical trials. Overall quality of the research evidence is relatively poor and more definitive studies would be welcome.

2. PET in the Diagnosis of Dementia

a) Introduction

The diagnosis of dementias such as Alzheimer's disease may involve the use of information provided from a variety of sources including history and physical examination, neuropsychological testing, and neuroimaging. In many cases, based on this information the diagnosis of Alzheimer's disease can be made in a manner consistent with the criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) working group.[102] In some cases the diagnosis remains uncertain. In these more difficult cases functional neuroimaging techniques such as PET may assist in determining whether a patient likely has Alzheimer's disease. Establishing a definitive diagnosis of Alzheimer's disease, however, requires histopathological examination post-mortem.

Alzheimer's disease is the most common form of dementia in adults in North America.[103] Given the recent emergence of drug therapy that may improve symptoms of Alzheimer's disease, there is a renewed interest in the early differentiation of Alzheimer's disease from other causes of dementia. Studies have explored the role of functional neuroimaging with PET to improve our ability to diagnose Alzheimer's disease. Specifically, the studies we reviewed explored whether

PET may provide information to assist in differentiating Alzheimer's Disease from other causes of dementia and predict the progression of disease.

In this section we describe specific studies, although our conclusions are based on a systematic review of the entire literature.

Tables 8a and 8b summarize information on the 16 original investigations we reviewed that focus on the role of PET in Alzheimer's disease. Of these studies, eight[104-111] were given a grade of B. One study graded C [112] warranted discussion, and was therefore included. No paper was judged to be graded A. The studies are reviewed below by categories of major focus.

b) Using PET to diagnose Alzheimer's disease and to differentiate Alzheimer's disease from other causes of dementia

In clinical practice it is often difficult to differentiate Alzheimer's disease from other forms of dementia. An important application of PET has been to provide unique information complementary to other clinical investigations to facilitate the diagnosis of Alzheimer's disease. A number of investigators[108,111] have demonstrated that a PET scan finding of bilateral temporoparietal hypometabolism is highly associated with probable Alzheimer's disease, although other patterns have also been identified.

Fazekas et al[106] compared CT, MR, and PET among patients with Alzheimer's disease and normal controls. They studied 30 patients with the clinical diagnosis of Alzheimer's disease (six *possible* and 24 *probable* Alzheimer's disease) and 25 age-matched controls. Using visual interpretation, PET scans were rated as normal in 21 of 25 control patients. In contrast, among 30 patients with Alzheimer's dementia only one PET scan was described as normal. They conclude that PET is a sensitive marker of Alzheimer's disease although the group of Alzheimer's disease patients evaluated were primarily those with *probable* Alzheimer's disease. Salmon et al[111] evaluated the cerebral metabolic distribution patterns for degenerative dementias using PET scans obtained from 129 patients being evaluated for the differential diagnosis of dementia. Of this group, 65 patients had a diagnosis of probable Alzheimer's disease. Among the probable Alzheimer's disease group, 97% had abnormal PET scans. The vast majority of these showed bilateral or unilateral temporoparietal hypometabolism.

The paper by Duara et al[105] examined 87 patients with clinically diagnosed Alzheimer's disease and compared their PET and MRI findings to those of normal healthy controls, normal young controls, and patients with multi-infarct dementia. The results suggest that PET does not have a good sensitivity in comparing multi-infarct dementia to Alzheimer's disease. Thus, this paper provides evidence that suggests FDG-PET should not be used in the diagnosis of Alzheimer's disease.

Mendez et al[112] explored the role that PET may play in differentiating patients with dementia and leukoaraiosis into either those with Alzheimer's disease with cerebrovascular changes or those with vascular dementia. A total of 30 patients with dementia and leukoaraiosis were evaluated. The results suggest that patients with dementia and severe leukoaraiosis who have PET findings that demonstrate bilateral temporoparietal hypometabolism likely have predominant Alzheimer's disease rather than vascular dementia. Those who do not display this pattern on PET likely have

vascular dementia. These findings suggest that PET may have a role in helping to differentiate Alzheimer's disease from vascular dementia when patients have leukoaraiosis.

There has been interest in comparing the role of PET to that of SPECT in assisting in making the diagnosis of Alzheimer's disease. PET is not readily available in many centres while (SPECT) is much more available and much less expensive. Mielke et al[110] compared the role of PET and SPECT in differentiating patients with probable Alzheimer's disease (n=20) from normal controls (n=13) or those with vascular dementia (n=12). Comparing the metabolic and perfusion ratio by ROC curves, PET differentiated Alzheimer's disease from normals only marginally better than SPECT. Identifying differences between Alzheimer's disease and vascular dementia was much better achieved by PET. Metabolic differences between normals and Alzheimer's disease patients were less obvious in old age. This study was conducted using patients with probable Alzheimer's disease and therefore does not help with the clinical problem of making a diagnosis which is likely more common in atypical or milder cases of Alzheimer's disease.

For PET to be a useful tool to aid in the diagnosis of Alzheimer's disease it is important that there be good agreement between reviewers interpreting PET scans. Hoffman et al[108] designed a study to evaluate inter- and intra-observer agreement in the interpretation of PET scans in a range of patients from normal controls through to those with probable Alzheimer's disease (i.e., normal controls, mild cognitive impairment, *possible* Alzheimer's disease, *probable* Alzheimer's disease). The kappa statistics in this study were in the "moderate agreement" range (between 0.4 and 0.55). These results suggest that both the intra- and inter-observer reliability for the interpretation of FDG PET studies is acceptable for clinical use. Burdette et al[104] compared the use of three-dimensional stereotaxic surface projection with that of standard transaxial display in PET in Alzheimer's disease. The investigators evaluated 39 patients with probable Alzheimer's disease and 40 patients without Alzheimer's disease. They found improved sensitivity and specificity in dementia with three-dimensional stereotaxic surface projection relative to standard transaxial display (94% and 99% versus 79% and 88%). These findings suggest that the accuracy of detecting Alzheimer's disease is improved with the use of three-dimensional stereotaxic surface projection in PET. Kippenhan et al[109] explored the role of using neural-network classification of PET scans to provide a systematic quantitative approach to differentiating patients with Alzheimer's disease from normal patients. This work suggests a possible future role of metabolic neuroimaging by using it to predict disease probabilities based on a metabolic profile.

c) Using PET to predict the progression of dementia

Patients presenting to a neurologist for the evaluation of dementia often request information on their prognosis. While this is an extremely important issue, at present there is no good method to provide patients or their families with this information on an individual basis. PET scanning has been proposed as a possible diagnostic tool that may help predict the progression of dementia. Herholz et al[107] conducted a prospective multi-center cohort study in 186 patients with *possible* or *probable* Alzheimer's disease to evaluate whether PET can be used to predict the progression of cognitive decline in Alzheimer's disease, based on the initial severity of FDG hypometabolism. The difficulty is that they have not reported the data in a way that clarifies the study's main objective. There is a poor follow-up rate of only 74% (49/77). The conclusions of the study are flawed since there is a "floor effect" of the PET data. In other words, if a patient

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has mild symptoms and relatively high glucose metabolism at the beginning of their follow-up, there is more potential for change compared to a patient with more advanced symptoms and lower metabolism at baseline. Their conclusions are therefore circular. At present there is no good evidence to suggest that PET plays an important role in predicting the progression of Alzheimer's disease.

d) Other HTA results

Appendix III includes health technology reports that evaluated the role of PET in Alzheimer's disease.

In general, the conclusion of these health technology assessment reports is that the evidence does not currently support the routine clinical use of PET for the diagnosis of Alzheimer's disease. Several of these reports comment on the lack of therapies available to cure or prevent Alzheimer's disease, making it of little value to make earlier or more accurate diagnosis of Alzheimer's disease. This situation may change should more effective therapies for the symptomatic treatment for dementia become available.

e) Cost-effectiveness studies

We could find no studies evaluating the cost-effectiveness of PET for the evaluation of dementia.

f) Limitations of the evidence and future directions.

There are limitations to our systematic review. First, in Alzheimer's disease the diagnosis is generally based on clinical information because the definitive diagnosis requires an autopsy. There are relatively few histologically proven cases of Alzheimer's disease because this type of diagnosis requires histopathological examination post-mortem.

Second, many of the studies examined patients with probable Alzheimer's disease, the more advanced form of this type of dementia. While PET scan findings are more likely to be consistent in this group, the diagnosis is usually relatively easy to determine using established diagnostic criteria. Clinical diagnoses of Alzheimer's disease made using the NINCDS-ADRDA criteria is accurate in 90% of cases.[113] It would be more useful to evaluate the role of PET in patients with atypical or milder forms of dementia. At present, PET has been evaluated in fewer such patients.

Third, PET is not as successful at differentiating changes consistent with Alzheimer's disease from older adults with no evidence of cognitive impairment. However, the vast majority of people with dementia are older, and therefore older adults are the group most likely to require this evaluation.

In the future, it would be optimal if studies were designed to look at the value of PET in diagnosing early, undifferentiated dementia (when clinical criteria may be equivocal) among older adults. Good quality studies might also consider the role of PET in predicting progression early in the course of the disease. Improving the accuracy of both the diagnosis of early dementia and the prediction of disease progression could influence decisions about future care and enrolment in clinical trials.

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g) Summary

Our systematic review fails to demonstrate a role for PET in the clinical evaluation of patients with suspected or established dementia. While some studies suggest that PET may help differentiate Alzheimer's disease from other causes of dementia, these studies were conducted primarily among patients with more advanced forms of dementia where the diagnosis is usually relatively easy to determine using established diagnostic criteria. The overall quality of the research evidence is poor and we await more definitive studies.

Table 7a. Studies Evaluating the Role of PET Scanning in Patients with Intractable Epilepsy *(all Grade B)*

Study	Year	Comments
Muzik O[98]	2000	10 pts with medically intractable extratemporal lobe epilepsy (?method of identification/source) underwent FDG-PET, FMZ-PET, and intracranial EEG to define sensitivity of the 2 PET methods for finding seizure foci
Ryvlin P[97]	1998	100 consecutive, prospectively identified patients underwent both FDG-PET and FMZ-PET, while control patients either underwent FDG-PET (n=12) or FMZ-PET (n=12) - in order to compare the value of these different forms of PET in preoperative evaluation of refractory partial epilepsy
Helveston W[96]	1996	16 consecutive adult patients with intractable temporal lobe epilepsy undergo PET, qualitative MRI, quantitative MRI – for lateralization of seizure foci
Ho SS[100]	1995	Value of PET and SPECT in lateralizing seizure foci in 35 cases of temporal lobe epilepsy
Henry TR[99]	1993	Reproducibility of 241 PET interpretations using 3 different scanners
Ryvlin P[101]	1992	Clinical utility of PET in 20 patients with temporal lobe epilepsy, 10 with and 10 without MRI abnormalities

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Table 7b. Studies Evaluating the Role of PET Scanning in Patients with Intractable Epilepsy *(all Grade C/D)*

Study	Year	Comments
Hicks RJ[115]	1999	Qualitative audit of the first 2500 modified PET studies conducted in their institution (for a variety of indications)
Muzik O[124]	1998	13 patients (8 children) and 16 controls received semi-automated method of PET interpretation in presurgical evaluation
Blum DE[118]	1998	12 retrospectively identified patients with medically intractable temporal lobe epilepsy and bilat temporal hypometabolism are compared to 12 age-matched controls with unilat hypometabolism re: post-op outcomes
Barrington SF[120]	1998	Qualitative analysis of ictal PET scans vs. EEG in preoperative evaluation for intractable seizures
Lamusuo S[123]	1997	18 patients with intractable epilepsy evaluated preoperatively with PET and different types of SPECTs, compared to post-op course
Duncan JD[117]	1997	15 pediatric patients with intractable epilepsy and seizure foci in close proximity to eloquent cortex were retrospectively identified – their PETs and post-op outcomes were reviewed
Wong CYO[127]	1996	Prediction of surgical outcome by parametric PET imaging in 17 retrospectively identified patients
Snead OC[126]	1996	56 pediatric patients and 44 controls undergo PET and intracranial EEG (13/56 pts) in preoperative evaluation of intractable epilepsy
Delbeke D[116]	1996	38 retrospectively identified patients with intractable temporal lobe epilepsy undergo interictal PET in their preoperative evaluations. PET results were analyzed against post-operative outcomes
Gaillard WD[122]	1995	16 pediatric patients with intractable complex partial seizures had their PETs compared to EEGs; PET scan sensitivity 69%, specificity 100%
Fois A[121]	1995	30 pediatric patients with intractable seizures. If CT/MRI didn't identify seizure focus, then patients went on to SPECT and/or PET
Benbadis SR[119]	1995	In 25 retrospectively identified patients with intractable temporal lobe epilepsy and equivocal/non-lateralizing EEGs, PET lateralization agreed with depth electrodes 67% of the time
Pawlik G[125]	1990	Descriptive summary of authors' experience with PET in preoperative evaluation of intractable epilepsy
Hosokawa S[114]	1989	Diagnostic value of PET in 29 patients with various types of epilepsy, as compared to EEG data are presented in such a way as to make the correlation between PET and EEG difficult to understand

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Table 8a. Studies Evaluating the Role of PET Scanning in Patients with Alzheimer's Disease (AD) *(all Grade B)*

Study	Year	Comments
Hoffman JM[108]	1996	Inter- and intraobserver agreement in PET interpretation in a group of patients with probable AD (96), possible AD (33), mild cognitive impairment (17), normal controls (2) [kappas in "moderate" agreement (approx. 0.4-0.55)]
Burdette[104]	1996	39 patients with probable AD and 40 subjects without AD were studied by comparing their standard PET imaging results with three-dimensional stereotactic surface projections (3D-SSP) of their PET images, to see if 3D-SSP provides any advantage in the visual interpretation of the changes seen in AD
Salmon[111]	1994	PET studies for 129 patients referred for differential diagnosis of dementia were analyzed -- PET findings
Mielke[110]	1994	20 patients with the clinical diagnosis of probable AD and 12 patients with the clinical diagnosis of VD were studied in comparison to a 13 normal persons in a control group -- PET and SPET findings
Kippenham[109]	1994	77 probable AD and 124 normal patients at two different centers -- comparison of classification performance
Herholz[107]	1993	37 patients with the clinical diagnosis of probable AD and 34 healthy controls patients -- comparison of 3 different scanners in different centers
Fazekas[106]	1989	30 patients with clinically diagnosed AD and 25 age-matched normal controls -- CT, PET and MRI findings
Duara R[105]	1989	87 patients with clinically diagnosed AD were compared to 36 normal elderly controls, 50 normal young controls, and 12 patients with multi-infarct dementia – PET and MRI findings

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Table 8b. Studies Evaluating the Role of PET Scanning in Patients with Alzheimer's Disease (AD) *(all Grade C/D)*

Study	Year	Comments
Ohyama M[130]	2000	FDG uptake compared in standardized regions of interest between normals and pts with AD -incomplete reporting
Mendez MF[112]	1999	30 patients with clinical diagnosis of dementia and MRI evidence of leukoariosis underwent PET – divided into 2 groups based on +/- bilateral temporoparietal hypometabolism -Groups then compared (?post hoc subgroup analyses)
Herholz K[128]	1999	Prediction of cognitive decline based on initial severity of FDG hypometabolism -194 patients, 74% follow-up
Kondoh Y[134]	1997	7 patients with probable AD compared with 7 healthy controls – re: PET- derived parameters of glucose metabolism
Messa C[133]	1994	21 patients compared with 10 PET controls and 10 SPECT controls re: diagnosis of AD
Guze BH[129]	1991	21 patients with NINCDS-ADRDA probable AD, 10 unipolar depression, 10 bipolar, 12 young controls, 8 old controls – compared re: PET scans -does PET distinguish between dementia and depression? (unfortunately, pts with depression are much younger than those with AD)
Duara R[131]	1986	21 patients with clinical AD compared to 29 age-matched controls – re: PET scans
DeLeon MJ[132]	1983	24 patients with clinical AD compared to 37 (15 young + 22 old) controls – re: PET scans

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Cost-Effectiveness of PET

Introduction

Decision-making at the policy level involves weighing the incremental costs of diagnostic modalities with the incremental benefits in clinical outcomes, given limited resources and competing options. In other words, once it has been established that a given technology provides additional benefit over an existing alternative, one must consider how much more it will cost to derive the additional benefit of that technology. If the additional benefit is large and the additional costs modest, then this is likely to be a good use of limited resources. On the other hand, if the additional benefit is modest and the additional costs are substantial, limited resources may be more efficiently used elsewhere.

While the number of health economic evaluations has increased in the past few decades, the quality of these evaluations is highly variable.[135] There is a need to standardize economic evaluations in nuclear medicine to increase their quality. Recommendations from previously published general guidelines for economic evaluations[5,136,137] may be applied to studies in nuclear medicine.[138] Although a widely accepted instrument to categorize the quality of such studies does not currently exist, these recommendations can be used to guide discussion about existing studies examining the cost-effectiveness of PET for the various indications covered by this report.

A brief discussion of the key factors considered when reviewing the existing evidence about the cost-effectiveness of PET is warranted. The *perspective of the analysis* affects the costs and outcomes considered in the analysis. For example, the cost of transportation to a hospital may be relevant from a patient's perspective but may not be as important from the perspective of a third party payer. Accordingly, an analysis from the patient's perspective would include transportation costs whereas an analysis from a third party payer perspective would not.

The costs and benefits of a technology should be *compared to all viable existing alternatives*, or at least to the status quo. In situations where additional benefits can only be realized at additional costs, the optimal decision from a cost-effectiveness point of view is to implement the alternative with the lowest incremental cost-effectiveness ratio (ICER) that is equal to or below the value society attaches to a unit of effectiveness. The ICER indicates the additional cost for each unit of additional benefit (i.e., how much more one has to pay to realize the additional benefit).

The *type of economic analysis* refers to the design of the analysis--for example, cost-minimization, cost-benefit, cost-effectiveness, or cost-utility. For the purposes of this review, only simple cost analyses, cost-effectiveness, and cost-utility analyses were considered. Simple cost analyses typically examine the relative costs of a particular technology and compare this to the savings realized by avoiding subsequent procedures or outcomes. For example, a reduced need for unnecessary surgical procedures may be realized with a new diagnostic modality. The costs of both the avoided unnecessary surgical procedures and the diagnostic modality are considered in determining the overall costs. In cost-effectiveness analysis, costs are compared to outcomes that are measured in natural rather than monetary units (e.g., cost per year of life saved). When outcomes are difficult to quantify monetarily, cost-effectiveness analyses are

typically used. For example, the value of a life is difficult to quantify and may be best left as a natural unit. A cost-utility analysis is essentially a form of cost-effectiveness analysis in which the outcomes are adjusted for their quality (e.g., cost per quality-adjusted life years).

Of crucial importance is the selection of *relevant outcome measures* upon which cost-effectiveness analyses are based. Essentially, the effectiveness portion of the cost-effectiveness analysis represents the primary outcome of interest upon which the analysis is based. Tangible health outcomes (e.g., mortality) are usually favoured over surrogate outcomes (e.g., staging).[139]

Costing involves estimating the resources used and their unit costs. Numerous sources of cost estimates exist and there can be substantial geographic variation in costs. Examples of sources of costs include the medical literature, national reimbursement rates, and institution-specific costs. It is generally accepted that the accuracy of a diagnostic test is likely to be similar in different countries. However, the costs of medical care, and practice patterns, vary markedly among countries (and even in centres in one country). Therefore, because of this variation in costs, the results of economic evaluations are often not generalizable beyond the area in which the analysis was done.

The *time horizon* of the study should be long enough to capture all the differential effects of the options being considered.

A great deal of uncertainty often plagues economic evaluations and *sensitivity analyses* are therefore important. Beyond issues of data quality, the findings of the evaluations are dependent on the actual numbers used. Significant variability often exists for these numbers and the robustness of the evaluation to an adequate range of values for these numbers is usually explored through sensitivity analyses. Each important variable in the economic analysis is varied through a pre-specified range to examine how the results change over the range of plausible values. If the results of the analysis do not change significantly, then the analysis is considered to be robust to that particular variable. The main emphasis of the *presentation of results* should be on transparency of the data inputs and methods used.

These basic guiding factors form the basis of the discussion outlined in this section.

Review of the Evidence (Table 9)

1. Oncology

a) Carcinoma of the lung

i) Management of the solitary pulmonary nodule

Only one study has examined the cost-effectiveness of various strategies for managing solitary pulmonary nodules (SPNs). The American study by Gambhir et al[140] utilized a decision analysis model to compare four primary management strategies: 1) wait and watch, in which all patients are observed with serial chest x-rays or alternately serial CT scans (at 3, 6, 12, 24, 52, and 104 weeks over a 2-year period), to determine if the nodule is growing at a malignant rate (i.e., doubling in volume) before the decision to send the patient for biopsy or surgery; 2) surgery (all patients are immediately sent for thoracotomy to remove the SPN if resectable); 3) thoracic CT,

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in which the patient has a high-resolution CT study before a decision for biopsy, surgery, or wait and watch strategy; and 4) thoracic CT-plus-thoracic PET, in which PET scans are performed only in the cases of indeterminate CT scans before the decision for either a biopsy, surgery, or wait and watch strategy. The perspective of the analysis was assumed to be that of the institution, although this was not explicitly stated. The medical literature was surveyed for all relevant clinical information including diagnostic sensitivities and specificities as well as expected survival rates for the various scenarios. Costs were based on US Medicare reimbursement rates. The cost for PET was based on 83% of the institution's billing for thoracic PET and included the technical and professional fees and cost of the FDG tracer. Relative to the CT strategy, the CT-plus-PET strategy was found to avoid costs between the pre-test likelihood ranges of 0.12 – 0.69. When compared to the wait and watch strategy, however, the CT-plus-PET was more costly but revealed modest gains in the number of life-years gained, leading to an incremental cost per life-year saved from approximately $8,000 to $50,000 US over the aforementioned pre-test likelihood range. For higher pre-test likelihoods, the CT strategy was deemed to be the most cost-effective alternative, although an incremental cost-effectiveness ratio of CT-plus-PET relative to CT only was not calculated. Several sensitivity analyses were conducted and revealed the results to be reasonably robust.

ii) Staging of primary carcinoma of the lung / evaluation of mediastinal lymph nodes.

Five primary studies[141-145] examining non-small cell lung cancer (NSCLC) were identified from our search strategy. In NSCLC, the accepted staging modality is computed tomography (CT) from the lung apices to the adrenals.

Two studies examined the cost implications of whole-body PET in staging disease and affecting patient management.[141,142] The first was a Swiss study by von Schulthess et al.[141] Although they labelled this as a cost-effectiveness study the authors actually conducted a cost analysis of 62 NSCLC patients who underwent whole-body PET and CT scanning in a previous study that examined sensitivity and specificity. The perspective of the analysis was not stated, although it was assumed to be that of a third party payer. The authors compared whole body PET scanning with CT being performed only if PET indicated operable disease and surgeons needed CT scans for surgical planning, with CT of three body regions and bone scanning of all patients. The analysis examined impact on patient management. Surgical intervention was the main outcome measure. Although not explicitly stated, it was assumed that the cost data was derived from the institution at which the study was conducted. The costs may not have included additional overhead and personnel costs attributable to PET. The authors demonstrated that unnecessary surgery would be avoided in 6 of 62 patients if whole-body PET scanning was the primary diagnostic modality. The resultant savings outweighed the marginal costs associated with whole-body PET scanning followed by CT scanning. The authors concluded that whole body PET (top of the head to the pelvic floor) is preferable to CT imaging and bone scan in patients with NSCLC.

The second study was an American cost analysis conducted by Valk et al[142] that retrospectively compared the impact of whole-body PET to CT scanning on the management of 72 patients with NSCLC. This subset of patients was non-randomly selected from a group of 99 patients originally participating in a diagnostic study. The main outcome measure was surgery. The perspective of the analysis, although not explicitly stated, was assumed to be that of the

institution. As in the previous analysis, this study examined the impact on patient management, and surgical intervention was the main outcome measure. Sources of cost data included institution-specific costs and Medicare reimbursement rates. It was unclear whether additional costs associated with overhead and personnel for PET, if applicable, were included in the analysis. Planned thoracotomy for diagnostic lung resection was canceled in 5 of 18 patients who had negative PET scans. Pre-thoracotomy mediastinoscopy was avoided in 11 patients with NSCLC, given the findings of the PET scans. As a result, the ratio of savings to cost was calculated to be greater than 2:1 when PET was considered as an addition to conventional staging procedures (i.e., savings of $150,000 US for 72 patients) and greater than 3:1 when replacing CT and bone scanning (i.e., savings of $194,000 US for 72 patients). The costs and benefits of the modified treatments were not considered.

Three studies examined the cost-effectiveness of thoracic PET compared to CT scanning for the staging of NSCLC.[143-145] The first was an American cost-effectiveness analysis conducted by Gambhir et al.[143] A decision analysis model was constructed with two competing strategies, namely CT and PET vs. CT alone. The perspective of the analysis, although not explicitly stated, was assumed to be that of the institution. The outcome of interest was years of life gained. Probability inputs in the models were largely derived from the medical literature and sufficient ranges were assumed for sensitivity analysis. However, costs were based on institution-specific charges. Life expectancy was assumed to be 1 year for patients with unresectable disease and 7 years for surgical candidates in the base models. Two decision models were constructed; a conservative model where anyone with a positive PET scan is referred for biopsy regardless of CT findings and a less conservative model where only those with discordant results between PET and CT scans would be referred to biopsy. The costs in this analysis were institution-specific and did not include costs associated with conservative medical management of patients with non-resectable disease, bone scans or whole-body imaging. It was not clear whether additional operating costs or personnel costs associated with PET were included. Although a cost-effectiveness analysis was originally planned, both models revealed savings in the CT and PET strategy relative to the CT alone strategy without a loss in life expectancy (i.e., average savings of $1,154-$2,267 US per patient). Sensitivity analyses revealed the findings to be reasonably robust, although the cost estimates may have deserved closer scrutiny.

The second study was an American analysis by Scott et al[144] that built on the work of Gambhir et al. Five alternative strategies were compared in this decision analysis model, namely thoracic CT alone, thoracic PET scanning only following a negative CT scan and 3 variations on strategies of CT and PET for all patients. The perspective of the analysis was not explicitly stated but was assumed to be that of the institution. The outcome of interest was years of life gained. Data inputs in the model were largely derived from the medical literature and sufficient ranges of values were assumed for sensitivity analysis. Life expectancy was assumed to be 1 year for patients with unresectable disease and 7 years for surgical candidates in the base model. Medicare reimbursement costs were used as financial inputs. Similar to the Gambhir et al study, the model did not include costs associated with conservative medical management of patients with non-resectable disease, bone scans or whole-body imaging. The results of the analysis indicated that thoracic PET scanning only following a negative CT scan may result in a marginal benefit in life-expectancy (0.007 years per patient) for a marginal increase in cost (i.e., $177 US per patient). The resulting incremental cost-effectiveness analysis was estimated to be $25,286

per life-year saved for this option relative to CT alone. Extensive sensitivity analyses were performed, revealing the findings to be reasonably robust given the assumptions made. The strategy of PET only following negative CT findings was shown to be less costly than CT alone without a loss in life expectancy when the cost of a PET scan was less than $1,700 US. The other CT and PET strategies generally revealed incremental cost-effectiveness ratios of greater than $70,000 US per life-year saved based on the authors' calculations when compared to CT alone and were not considered to be cost-effective. The discrepancy in findings between this study and that of Gambhir et al may be largely attributable to the sources of cost data.

The third study was a Japanese analysis of 2 competing strategies, namely thoracic CT alone vs. thoracic CET plus PET, in the management of NSCLC by Kosuda et al.[145] A decision analysis was conducted for patients in whom stage IIIb or less NSCLC was suspected. The perspective of the analysis was not explicitly stated, although it was assumed to be that of the institution. The outcome of interest was years of life gained. Clinical and financial data inputs for the model were largely derived from 56 NSCLC patients at the institution where the study was conducted and were assumed to be fairly inclusive, although additional overhead and personnel costs associated with PET were not included in the analysis. Life expectancy was assumed to be 1 year for patients with unresectable disease and 7 years for surgical candidates in the base model. Although the authors conclude that CT+PET is not cost-effective, a comparison of costs and outcomes for CT+PET relative to CT alone reveals an incremental cost-effectiveness ratio of approximately $2,600 US per life-year saved (assuming 140 yen = $1 US), which appears to be relatively attractive. It should be noted, however, that the cost of a PET scan was significantly less than that found in the American studies. This study demonstrates reasonable cost-effectiveness of a CT+PET strategy in an environment with a very different cost structure and health policy environment compared with the United States. The study also notes, however, that additional costs associated with personnel and depreciation of PET equipment may be quite substantial (e.g., over $1,000 per PET scan). Such costs are typically excluded from economic evaluations.

b) Hodgkin's Disease and Lymphoma

i) Staging of Hodgkin's disease and lymphoma

Two primary studies examining the staging of Hodgkin's disease (HD) were found.[139,142] The first evaluation was an American cost analysis conducted by Valk et al[142] that examined the medical records of 30 patients to compare the costs associated with whole-body PET compared to conventional CT scanning for the staging of Hodgkin's disease. Although not explicitly stated, the perspective of the analysis appeared to be that of the institution. Costs associated with subsequent treatment were also considered, although details of how these costs were derived and applied were not provided. The authors report that PET changed the staging of HD in 5 of 25 newly diagnosed patients and 6/6 patients with recurrence. This change in stage resulted in treatment change in 3/25 newly diagnosed patients and 3/6 patients with recurrent disease. Since the costs associated with these treatments were comparable, although these costs were not explicitly reported, cost savings with PET were not demonstrated. The outcomes associated with the changes in treatment strategy as a result of PET, were not analyzed. Therefore a cost-effectiveness analysis was not done.

The second evaluation was an American study examining the utility of whole-body PET for staging HD and non-Hodgkin's lymphoma (NHL). This cost analysis by Hoh et al[139] prospectively examined the medical records of 18 patients to compare the accuracy of conventional imaging studies to PET and the respective costs. All patients had a whole-body PET study after completing conventional staging tests that were selected by the oncologist. These conventional methods for staging HD and NHL included chest radiographs, CT or MRI of the neck, chest, abdomen, pelvis, bone scan, gallium scan, liver-spleen scan, lymphangiogram and laparotomy. Costs were limited to those associated with staging only and did not extend to subsequent management of disease. The perspective of the analysis was assumed to be that of the institution, although this was not explicitly stated. The average cost of diagnostic procedures was calculated as the mean cost from five local hospitals. Costs such as routine blood testing or other minor procedures were not included in the analysis. Accurate staging was performed in 17 of 18 patients using whole-body PET vs. 15 of 18 patients using conventional staging methods. Driven by the multiple CT scans performed in the majority of patients, the total staging cost associated with the conventional approach was substantially higher than that of PET (i.e., $68,192 vs. $37,850 US, respectively). Only one whole-body PET scan was conducted for each patient, whereas 33 CT scans were conducted (i.e., one patient may have a CT scan of the chest and a CT scan of the pelvis or abdomen) in the conventional approach. Sensitivity analyses were not conducted.

c) Malignant Melanoma

i) Staging in patients at increased risk of malignant melanoma

A Swiss study by von Schulthess et al[141] retrospectively examined records of 100 patients with an increased risk of metastatic melanoma to compare the costs of two staging strategies involving whole-body PET with that of a conventional approach (i.e., clinical data, chest x-ray, ultrasound of the abdomen and lymph nodes). The perspective of the analysis, although not explicitly stated, was assumed to be that of the institution. Similarly, cost information was assumed to be derived from institution-specific estimates. The authors concluded that a strategy involving PET may be cost-saving in patients with known metastases. Estimates of cost-effectiveness were not explicitly stated. Based on numbers provided, a whole-body PET strategy excluding CT scans of the brain would result in a cost of approximately 440 Swiss francs (the Swiss franc and Canadian dollar are of similar value) per patient relative to CT scanning alone. A PET strategy mandating CT scans of the brain would result in a cost of approximately 500 Swiss francs per patient relative to CT scanning alone. Subsequent financial and therapeutic consequences following staging were not included in the analysis and precluded any conclusions of cost-effectiveness.

ii) Management of malignant melanoma.

An American study by Valk et al[142] retrospectively examined the records of 45 patients who had undergone PET imaging for metastatic or recurrent melanoma over a 2-year period to compare the costs of management associated with whole-body PET relative to CT scanning of the chest and abdomen. Twenty-nine of these patients were referred with known tumour recurrence for evaluation of resectability. The perspective of the analysis was not explicitly stated, although it was assumed to be that of the institution. Estimates of costs were also not explicitly described for

this indication. The authors report that the PET findings directed change in 16 of 45 patients (36%), avoided surgery in 5 patients, and initiated surgery in three patients. Numerous details of this analysis were lacking and the financial and clinical impact of the change in management strategies was not considered. Regardless, the authors report a savings-to-cost ratio of 2:1 when PET was used as an additional procedure and approximately 4:1 when replacing CT scanning.

d) Other Cancers

Two studies conducted by Valk et al[142] as part of a larger study examined the management of recurrent colorectal cancer and recurrent head and neck cancer according to different diagnostic approaches.

i) Recurrent colorectal cancer

The records of 68 patients were reviewed retrospectively to compare costs between whole-body PET and CT scanning of the abdomen and pelvis with respect to management outcomes. As described previously, the perspective of the analysis was assumed to be that of the institution. Cost estimates were derived from US Medicare reimbursement rates. The details of how these costs were applied to the analysis were not clear. Change in surgical management was directed by the PET findings in 24 patients, with avoidance of unnecessary surgery in 15 of these patients. In five cases where CT findings were negative, PET findings spared patients from surgery. Savings resulting from avoidance of unnecessary surgical procedures were compared to costs. The authors conclude a savings-to-cost ratio of 2:1 when PET is considered as an additional procedure as compared to greater than 4:1 when PET is considered to replace CT scans of the abdomen and pelvis.

ii) Recurrent head and neck cancer

The records of 29 high-risk patients with locally advanced tumor or recurrent disease were retrospectively examined to compare costs associated with whole-body PET relative to conventional preoperative evaluation using only chest x-ray and biochemical liver-function tests. The perspective of the analysis, although not stated, was assumed to be that of the institution. The derivation and application of cost data was also not explained. PET findings demonstrated that palliative treatment rather than attempted curative surgery was indicated in 9 of the 29 patients examined. Comparison of PET costs to costs of the contraindicated surgical procedures demonstrated a savings-to-cost ratio of approximately 2:1. Many of the details necessary for evaluation of the validity of the findings were lacking in this evaluation.

2. Cardiology

a) Coronary Artery Disease

i) Diagnosis of coronary artery disease

Two American studies[49,146] utilizing decision analysis models have been conducted to explore the cost-effectiveness of PET in the diagnosis of coronary artery disease (CAD). The first study by Patterson et al[146] compared four primary strategies for the diagnosis of CAD, namely exercise ECG, SPECT, PET and angiography. Angiography was assumed to be conducted subsequent to positive or non-diagnostic findings for any of first three strategies listed. The perspective of the analysis was not explicitly stated, although it was assumed to be societal. The primary outcome

measure was quality-adjusted life years (QALYs) over a 10-year follow-up period. Clinical data were derived from the published literature. A key assumption in this analysis was the addition of 3 QALYs over 10 years as a result of the correct diagnosis of CAD. The analysis also assumed equal test accuracy in the detection of severe coronary disease and more limited coronary disease. The sensitivity and specificity for PET was assumed to be 0.95 for both in the base case analysis. Costs were derived from literature values for fees, the sources of which were not entirely clear. The only major cost aside from the diagnostic tests was associated with incurring a myocardial or cerebral infarction which was estimated to be $40,000 US. Discounting of costs and outcomes over the follow-up period appear not to have been conducted. The authors conclude that a pre-test likelihood of CAD (pCAD) below 0.7 would favor the use of PET over the other strategies based on the cost/QALY ratio, whereas a pCAD greater than 0.7 would favor the use angiography as the primary diagnostic strategy. Sensitivity analyses were conducted to test the robustness of the model, although the ranges of values of certain variables were quite narrow, limiting any statements of model robustness. This study has many flaws. Overall costs were not displayed separately from overall outcomes making the results not transparent. Incremental cost/QALY relative to a base strategy were not provided. The sensitivity and specificity assumed for PET seem high, and the assumption that making a diagnosis of CAD leads on average, to three extra QALYs over ten years is unrealistic.[142]

The second study by Garber et al[49] compared initial testing with coronary angiography to five other initial strategies, namely exercise treadmill testing, planar thallium imaging, SPECT, stress echocardiography and PET. This study used meta-analysis of published literature to provide summary estimates of clinical variables used in their Markov model examining patients over a 30 year follow-up period. However, several PET studies were reviewed but not used in the meta-analysis and no explanations were provided for the exclusion of these other studies. The analysis assumed a sensitivity of 0.91 and specificity of 0.82 for PET. The estimated survival of patients with CAD treated surgically or medically was based on one study, as were estimates of angina patterns experienced after surgical or medical intervention. The perspective was clearly stated as societal. The simulated patient population reflected men and women age 45, 55 and 65 years of age with a 25% to 75% pretest risk for coronary disease. The primary outcome measures were expressed as life-years, QALYs, costs and cost/QALYs. Although a societal perspective was used, the analysis explicitly incorporated only costs arising from the testing strategies and treatment of coronary disease and its complications. Outpatient and diagnostic costs were based on Medicare payments. The authors concluded that PET is not cost-effective in any scenario relative to echocardiography, SPECT and immediate angiography. For example, the incremental cost-utility ratio for PET relative to SPECT was estimated to be $640,000 US/QALY. This was largely driven by very modest gains in life-years (i.e., several days) that may be realized with PET at a substantial cost. The results were reasonably transparent, and extensive sensitivity analyses were appropriately conducted to demonstrate the robustness of the results. The quality of this economic evaluation was felt to be high.

ii) Selection of patients for angiography

One American evaluation using decision analysis modeling examined the costs and accuracy of noninvasive nuclear cardiology testing in the diagnosis of CAD relative to angiography.[147] Six competing strategies were compared, direct referral to angiography; initial PET testing followed by angiography if PET findings were positive; initial SPECT testing followed by angiography if

SPECT findings were positive; initial exercise electrocardiography testing followed by PET if exercise electrocardiography findings were positive and then referral to angiography if PET findings were positive; initial exercise electrocardiography testing followed by SPECT if exercise electrocardiography findings were positive and then referral to angiography if PET findings were positive; and initial exercise electrocardiography followed by angiography if exercise electrocardiography findings were positive. The perspective of the analysis was not explicitly stated. The medical literature was the primary source of clinical data and institutional costs of the diagnostic tests were used. The outcome was defined as the yield, or the proportion of all patients who were categorized correctly as normal or as having CAD. Angiography findings were viewed as the basis of a definitive diagnosis. The results compared the costs and yields of the competing strategies as percentages relative to angiography. The study simply examined costs and outcomes in isolation of each other rather than providing measures of cost-effectiveness or incremental cost-effectiveness. The authors subjectively conclude that in low risk patients (i.e., pCAD=20%) initial exercise electrocardiography testing followed by either PET or SPECT may be the most cost-effective approach; in intermediate risk patients (pCAD=50%), initial PET or SPECT testing may be the most cost-effective approach; and in high risk patients (pCAD=80%), direct referral to coronary angiography may be the ideal approach. Sensitivity analyses exploring the robustness of the findings were not undertaken. Since a formal cost-effectiveness analysis was not truly conducted, the findings of this study are speculative at best.

b) Assessment of Viability

No studies retrieved.

3. Neurology

No studies retrieved.

Summary

Limited evidence about the cost-effectiveness of PET currently exists to guide decision-making. In particular, there are no Canadian studies. Such Canada-specific studies are needed to guide decision-making in a Canadian context because of the large variability in regional costs and health infrastructures among different nations. The currently available evidence, however, suggests that PET may be attractive from a cost-effectiveness perspective in the management of SPN, staging of primary carcinoma of the lung, and staging of HD and NHL. Evidence for other types of cancer, while indicating potential usefulness of PET, is generally of low quality and precludes any definitive conclusions regarding the cost-effectiveness of PET. Although conflicting evidence exists for the use of PET in the diagnosis of CAD, PET does not appear to represent a practical alternative to existing diagnostic approaches in the majority of patients. These recommendations are based only on currently available evidence and may change as more evidence becomes available. The conclusions of this report reflect a *conservative approach* to efficient resource utilization in that the use of PET is recommended for the most well supported indications from a cost-effectiveness perspective. It must also be acknowledged, however, that a careful assessment of feasibility issues such as the availability and retention of skilled human resources, geographic disparities in need and availability of PET, and legal and ethical factors will significantly impact costs associated with PET. All such issues must be considered in

totality in arriving at reasonable estimates of costs associated with the large-scale introduction of healthcare technologies through a single payer (i.e., the government). Although currently available cost-effectiveness analyses are not so comprehensive, they do provide some guidance as to which areas of PET utilization should be given priority.

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Table 9. Summary of Health Economic Evaluations of PET

Indication(s)	Management of SPN	Staging of primary carcinoma of the lung / evaluation of mediastinal lymph nodes				
Study	Gambhir[140]	Von Schulthess[141]	Valk[142]	Gambhir[143]	Scott[144]	Kosuda[145]
Year	1998	1998	1996	1996	1998	2000
Study Design	Decision Analysis Model	Retrospective Record Review (n=62)	Retrospective Record Review (n=72)	Decision Analysis Model	Decision Analysis Model	Decision Analysis Model
Alternatives	Wait and watch surgery Thoracic CT Thoracic CT + PET	3-region CT + bone scan Whole-body PET + CT	Whole-body CT Whole-body PET	Thoracic CT Thoracic CT + PET	Thoracic CT Variations of thoracic CT + PET	Thoracic CT Thoracic CT + PET
Form of Evaluation	CEA	Cost Analysis	Cost Analysis	Cost Analysis	CEA	CEA
Outcome Measures	Life-years saved	N/A	N/A	Life-years saved	Life-years saved	Life-years saved
Perspective	Not stated	Not stated	Not Stated	Not stated	Not stated	Not stated
Costing Sources	US Medicare	Not stated	US Medicare	Institution	US Medicare	Institution
PET:CT Cost Ratio	2.6	1.3	N/A	1.7	5.3	N/A
Time Horizon	Unlimited	N/A	N/A	Unlimited	Unlimited	Unlimited
Results	CT + PET most cost-effective ($8K-50K US/life-year saved) if pre-test likelihood 0.12-0.69	Savings in avoiding unnecessary surgeries apparent with PET + CT strategy relative to CT + bone scan strategy	Savings in avoiding unnecessary surgeries apparent with PET relative to CT; saving : cost ratio may be as high as 3:1.	Savings of $1,154-2,267 US per patient by avoiding unnecessary surgeries apparent with CT + PET relative to CT alone	Thoracic PET only following negative CT study most cost-effective at $25,286 per life-year saved	ICER of $2,600 US per life-year saved for CT + PET; this was concluded to be not cost-effective
Sensitivity Analyses	Several scenarios revealed results to be robust	None	None	Several scenarios revealed results to be robust	Several scenarios revealed results to be robust	Several scenarios revealed results to be robust
General Comments	Overall, a good study. Quality of life and subsequent management costs were not considered.	Swiss study. May avoid unnecessary surgery in about 10% of patients with PET. Costs were modeled.	All patients were from one physician. Costs were modeled. Detailed accounts of patients given.	Findings consistent in two different scenarios assessed; costs may not be entirely inclusive.	Overall, a good study; PET: CT cost ratio higher than other studies.	Japanese study. Clinical data from 1 center used in analysis.

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Table 9. Summary of Health Economic Evaluations of PET *(cont'd)*

Indication(s)	Staging of HL and NHL		Malignant Melanoma		Recurrent Colorectal Cancer	Recurrent Head & Neck Cancer
Study	Valk[142]	Hoh[139]	Von Schulthess[141]	Valk[142]	Valk[142]	Valk[142]
Year	1996	1997	1998	1996	1996	1996
Study Design	Retrospective Record Review (n=25)	Prospective Evaluation (n=18)	Retrospective Record Review (n=100)	Retrospective Record Review (n=45)	Retrospective Record Review (n=68)	Retrospective Record Review (n=29)
Alternatives	Conventional staging Whole-body PET	Whole-body PET 'Conventional' diagnostics	Whole-body CT Whole-body PET	CT (chest and abdomen) Whole-body PET	CT (abdomen and pelvis) Whole-body PET	X-ray and liver function tests Whole-body PET
Form of Evaluation	Cost Analysis	Cost Analysis	Cost Analysis	Cost Analysis	Cost Analysis	Cost Analysis
Outcome Measures	N/A	None	None	N/A	N/A	N/A
Perspective	Not Stated	Not Stated	Not stated	Not stated	Not stated	Not stated
Costing Sources	Not Stated	Institution	Not stated	Not stated	US Medicare	Not Stated
PET:CT Cost Ratio	N/A	1.0 (PET vs. abdomen & pelvis CT)	0.73	N/A	N/A	N/A
Time Horizon	N/A	N/A	N/A	N/A	N/A	N/A
Results	PET imaging may not be justified on the basis of direct cost savings.	Savings to cost ratio was nearly 2:1 as a result of PET replacing numerous isolated tests routinely conducted by oncologists.	Cost of whole-body PET is less than whole-body CT at the study institution, thereby rendering whole-body PET as less costly.	Savings: cost ratio of PET was 2:1 when used as an additional procedure and 4:1 when used in isolation. Driven by surgery avoidance.	Savings: cost ratio of PET was 2:1 when used as an additional procedure and 4:1 when used in isolation. Driven by surgery avoidance.	Savings: cost ratio of PET was 2:1. Driven by surgery avoidance in 9/29 patients.
Sensitivity Analyses	None	None	None	None	None	None
General Comments	Outcomes associated with changes in treatment strategy as a result of PET not analyzed.	Analysis limited to costs of diagnostic tests and did not consider changes in treatment strategy.	Analysis limited to staging costs.	Financial details not stated. Changes in therapeutic management explained.	Cost of surgical procedures initiated as a result of PET not included in analysis.	Financial details not stated. Significant proportion of patients potentially affected.

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Table 9. Summary of Health Economic Evaluations of PET *(cont'd)*

Indication(s)	Diagnosis of CAD		Selection of Patients for Angiography
Study	Patterson[146]	Garber[49]	Maddahi[147]
Year	1995	1999	1997
Study Design	Decision Analysis Model	Decision Analysis Markov Model	Decision Analysis Model
Alternatives	Exercise ECG SPECT PET Coronary angiography	Exercise treadmill testing Planar thallium imaging SPECT Stress echocardiography PET	Direct referral to coronary angiography Various combinations of PET, SPECT, and ECG
Form of Evaluation	CEA	CEA	Cost Analysis
Outcome Measures	Quality-adjusted life-years (QALYs)	Life-years, QALYs	Yield (correct diagnosis)
Perspective	Not stated	Societal	Not stated
Costing Sources	Medical literature	US Medicare	Institution
PET:ECG Cost Ratio	5.5	13.6	N/A
Time Horizon	Unlimited	30 years	N/A
Results	PET is the most cost-effective alternative when pCAD<0.70. Angiography is favored if pCAD>0.7.	PET is the least cost-effective alternative in numerous scenarios.	In low-risk (pCAD=20%) and intermediate risk (pCAD=50%), PET may be cost-effective. In high-risk patients (pCAD=80%) direct referral to angiography may be warranted.
Sensitivity Analyses	Numerous sensitivity analyses conducted to explore robustness of findings. Ranges of some variables may have been restrictive and limited proper testing of robustness.	Numerous sensitivity analyses conducted to explore robustness of findings. Survival benefit assumptions may have warranted more extensive testing.	None.
General Comments	Reasonably extensive study. Crude cost-utility ratios were provided where incremental analyses would have been more appropriate. Assumption of extension of life given diagnosis of CAD unrealistic. Separation of costs from outcomes were not transparent.	High quality evaluation. Clinical data derived from meta-analysis of literature, however certain studies were excluded from review without explanation. All major criteria of conducting proper health economic analysis were met.	Analysis limited to comparison of costs of diagnostic tests and yield in isolation of each other. Conclusions based on subjective assessments of potential 'cost-effectiveness'.

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Other Health Technology Assessments

Summary of Other HTAs

Thirty-six assessments are summarized in Table 10 and Appendix III and they reflect the breadth of international focus on this emerging technology during the period between1990-2000. More recently, interest has grown significantly. From 1990-1994, only two HTAs were done whereas from 1995-1997 and 1998-2000, 14 and 20 reviews respectively, were completed. The majority (22) have been systematic reviews, 8 have been reviews in either an unspecified or less rigorous form, 4 involved expert or Delphi panels, two have been surveys and two were cost-effectiveness analyses. Several studies encompassed more than one approach.

The vast majority of the reviews were inconclusive due to either paucity of evidence (quantity or quality) or lack of consistent results among the studies reviewed. Almost universally it was noted that further investigations were necessary before definitive conclusions could be reached. In some instances positive trends were found, suggesting a potentially appropriate role for PET. Of these, lung cancer and medically refractory epilepsy were the indications for which there was the most enthusiasm for PET.

In cardiology, equal numbers of HTAs evaluated perfusion and viability indications. For each indication, three evaluations found a positive role for PET, while seven were uncertain because of insufficient or conflicting evidence.

Oncological conditions comprised the majority of indications studied (83 of 124). Lung, head & neck, colorectal, SPN and breast cancers were the 5 most commonly evaluated. Of these, there was the most support from the use of PET in lung cancer and SPN. Although brain tumours were less frequently reviewed, several recommendations were favourable. The bulk of the findings, however, were inconclusive.

With respect to neurology, Alzheimer's disease and medically refractory epilepsy were reviewed in a total of 19 HTAs. Although several reviews found PET to be effective in the diagnosis of AD, routine use was not recommended given the current lack of markedly beneficial therapy for the disease. However, there was support for use of PET in refractory epilepsy in five studies.

The generally inconclusive or negative conclusions of HTAs are in marked contrast with many positive review articles in the medical (particularly the radiological) peer-reviewed literature. This may reflect a difference in perspective with the "medical" reviews focussing primarily on diagnostic accuracy, and the HTAs considering the effect on patient management, outcome and cost-effectiveness compared with existing technologies.

Table 10a. General Summary of HTAs Completed from 1990-2000

36 HTAs (1990-2000)	Number of HTAs
1990-1994	2
1995-1997	14
1998-2000	20
Systematic Review	22
Other Review	8
Panel (Expert or Delphi)	4
Survey	2
Cost Effective Analysis	2

*Note: Some assessments used several approaches.

Table 10b. Summary By Indication (1998-2000)

Indication	Number of HTAs	Favourable to Use of PET	PET not indicated	Neutral* to Use of PET
Cardiology				
Perfusion	5	2	0	3
Viability	6	2	0	4
Oncology				
Brain	4	2	0	2
Breast	9	2	0	7
Head & Neck	7	1	0	6
Lung	10	5	0	5
Lymphoma	5	2	0	3
Melanoma	6	1	0	5
Colorectal	8	3	0	5
SPN	7	3	1	4
Neurology				
AD	6	0	0	6
Epilepsy	8	4	0	4

* Neutral indicates either conclusions were equivocal or that insufficient evidence was available to recommend the use of the technology (This HTA's recommendation about PET for cardiac viability would be rated as "neutral".)
Indications were not specifically addressed in the conclusions column for some assessments. One HTA examined unspecified oncology indications so it was omitted from this chart.

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ICES PET HTA Panel Summary

An expert panel met on February 27, 2001 to discuss the first draft of this report. The summary of their comments are listed below (please see Appendix II for more details).

- General agreement regarding oncology and neurology findings;
- Enthusiasm from some members about the potential for PET in assessing cardiac viability and detection of CAD in certain patient subgroups;
- Agreement on possible role in intractable epilepsy evaluation;
- Agreement on PET's accuracy in diagnosis of Alzheimer's disease but essentially no clinical role due to lack of affect upon clinical outcome;
- Recommendation that brain tumours be considered in this report;
- Consensus on importance of (and acknowledgement of current lack of) Canadian-based cost-effectiveness studies;
- Importance of establishing a province-wide network to guide the delivery and planning of PET given its complexity and cost;
- Limitations of the available studies were noted, and better quality studies in recent years recognized; and
- Support for the need for further research.

Estimate of Number of Individuals Eligible for PET Scanning in Ontario

1. Oncology

Potential utilization of diagnostic imaging procedures during fiscal year April 1, 1999 to March 31, 2000 in clinical settings where there is evidence of benefit from Positron Emission Tomography.

Please see the methods section for a description of the analyses performed. The frequency of utilization of diagnostic imaging procedures during the fiscal year under study in this report reflects only the number of PET procedures that would have been required in fiscal year 1999-2000 and will not reflect the number of PET procedures required in any future year. Patients just diagnosed in fiscal year 1999-2000 were assumed to have undergone tests for the *initial work-up* of suspected or diagnosed cancer, while those diagnosed between 1996 and 1999 were assumed to have undergone tests for the *follow-up* of their cancer. Where a list of the frequencies of diagnostic imaging procedures is given, any resident may have undergone one or more of the procedures. It is not possible to determine if the frequencies of the procedures we have studied are appropriate, too high, or too low. To test the reliability of these estimates it would be necessary to conduct a random sample chart review or a prospective cross-sectional study. Either of these approaches would be expensive and time-consuming. In addition, Cancer Care Ontario has reliably predicted an average 3% annual increase in the number of residents newly diagnosed with cancer for the past two decades. This must be considered in the process of deciding what the supply of PET procedures will be for the evidence-based clinical applications described by this HTA.

a) Carcinoma of the lung (ICD 162)

During fiscal year April 1,1999 and March 31, 2000 (FY 99 - 00):

1,951 residents of Ontario first had an ICD 162 diagnosis and underwent one of the following: resection of the lung cancer, attempted resection, or mediastinoscopy. Among these, 1,678 underwent CT chest, 959 underwent CT abdomen, 559 underwent CT brain, and 872 underwent radionuclide bone scanning.

4,067 residents of Ontario first had a diagnosis of ICD 162 but did not have a resection or attempted resection. Among these, 3,012 underwent CT chest, 2,081 CT abdomen, 1,401 CT brain, and 1,655 radionuclide bone scanning.

ESTIMATE FOR PET FOR LUNG CANCER IN FY 99 - 00: 6,018

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b) Colorectal carcinoma (ICD 153 - 154)

During fiscal year 1999-2000, among those with a first diagnosis and resection of colorectal carcinoma, or attempted resection between April 1, 1996 and March 31, 1999, ***3,025*** underwent CT of the abdomen and pelvis and 3,694 underwent ultrasound of the abdomen as follow-up procedures to detect recurrences.

ESTIMATE FOR PET FOR COLORECTAL CANCER IN FY 99 - 00: 3,025

c) Head and neck cancer (ICD 140-149; 160-161)

During fiscal year 1999-2000, 2,592 residents of Ontario had an ICD diagnosis of 140-149 or 160-161 for the first time. Among these, 413 underwent CT of the head and neck and 379 underwent MRI of the head and neck. ***714*** people had either one or the other or both. Note: these numbers do not include persons who had radiotherapy planning CT scans in cancer centres.

4,427 residents of Ontario who first had an ICD diagnosis of 140-149 or 160-161 between April 1, 1996 and March 31, 1999, were alive and living in Ontario, according to the Registered Persons Database (RPDB). Among these, 378 underwent CT of the head and neck and 363 underwent MRI of the head and neck as followup procedures. ***693*** people had one or the other or both.

ESTIMATE FOR PET FOR HEAD AND NECK CANCER IN FISCAL YEAR 1999 - 2000: 1,407

d) Carcinoma of the female breast (ICD 174)

During fiscal year 1999-2000, 8,720 women resident in Ontario first had an ICD 174 diagnosis and breast cancer surgery. Among these ***3,525*** underwent radionuclide bone scanning.

3,268 women resident in Ontario who first had an ICD 174 diagnosis between April 1, 1996 and March 31, 1999 underwent bone scanning.

ESTIMATE FOR PET FOR BREAST CANCER IN FY 99 - 00: 6,793

e) Hodgkin's disease and non-Hodgkin lymphoma (ICD 200- 202)

During fiscal year 1999-2000, 2,749 residents first had an ICD diagnosis 200 - 202. Among these ***2,362*** underwent CT scanning and / or bone marrow biopsy.

2,857 residents in Ontario who first had an ICD diagnosis 200 - 202 during fiscal years 1996 to 1998 underwent CT scanning and / or bone marrow biopsy.

ESTIMATE FOR PET FOR HODGKIN'S / NON-HODGKIN LYMPHOMA FY 99 - 00: 5,219

f) Malignant melanoma

During FY 99 – 00, according to the Canadian Institute for Health Information (CIHI) in-patient and out-patient databases, 1,005 residents of Ontario first had a diagnosis of ICD 172. Among these, ***505*** underwent lymph node dissection and/or chest radiography and/or CT scanning and/or abdominal ultrasound. ***116*** underwent bone scanning.

410 residents of Ontario who first had an ICD 172 diagnosis between April 1, 1996 and March 31, 1999, underwent lymph node dissection and/or chest radiography and/or CT scanning and/or abdominal ultrasound as follow-up procedures, and ***97*** underwent bone scanning.

ESTIMATE FOR PET FOR MALIGNANT MELANOMA FY 99 - 00: 1,128

TOTAL ESTIMATE FOR PET FOR EVIDENCE-BASED CLINICAL APPLICATIONS IN ONCOLOGY FY 99 - 00:

LUNG CANCER	**6,018**
COLORECTAL CANCER	**3,025**
HEAD AND NECK CANCER	**1,407**
BREAST CANCER	**6,793**
HODGKIN'S / NON-HODGKIN LYMPHOMA	**5,219**
MALIGNANT MELANOMA	**1,128**
TOTAL	**23,590**

2. Neurology

a) Intractable Seizures

It is estimated that 352 patients in Canada[95] receive surgical treatment each year for intractable seizures. As of July 2000, the population of Ontario was 11.67 million, and that of Canada, 30.75 million (Statistics Canada 2000 Census data). Based on the fact that the population of Ontario comprises 38% (11.67/30.75) of the population of Canada, and the assumption that patients with intractable seizures are uniformly distributed across the country, on an annual basis, approximately 118 patients (352/3) undergo surgical treatment for intractable seizures in Ontario. Since this number represents only a portion of the patients who would be potential surgical candidates (perhaps double or triple this number would be investigated), a rough estimate of those who would potentially benefit from having a PET scan would be from ***300-400*** patients. This indication for PET scanning, therefore, represents a relatively small number of patients.

Implementation of PET Scanning

Some Issues to Consider

Suggesting the number and location of PET scanners that should be introduced in Ontario, and the rapidity of their introduction, is not within the mandate of this report. The previous section provides planners with an estimate of the number of patients who might benefit from PET scanning for the oncological indications for which PET scanning likely provides some benefit beyond currently existing diagnostic modalities, as well as for the investigation of refractory epilepsy. Planners must be aware that some patients with rarer cancers that have not been well studied may benefit from PET as well.

There is currently no convincing evidence for the incremental outcome benefits of PET over existing diagnostic modalities for the determination of cardiac viability, or for the diagnosis of coronary artery disease. However, it is possible that future research will show that PET is a cost-effective diagnostic test for these indications. This could have considerable impact upon the need for PET because of the increasing incidence of heart failure and the prevalence of coronary artery disease.

Resources available for health care are limited, and the demand for those resources continues to increase. Therefore, planners must weigh the benefits and costs of PET scanning with the benefits and costs of other investments in health care such as home care, radiotherapy machines, new medications, etc. Unfortunately, although some tentative guidelines exist about what is good value for money for therapeutic interventions[148] similar guidelines are not available for diagnostic tests. Decisions about resource allocation are often difficult, and involve considerations of effectiveness (or accuracy in the case of diagnostic tests), cost, cost-effectiveness, availability of resources, alternative uses of those resources, ethics and politics.

The location of PET scanners depends upon the distribution of patients with the disorders that would benefit from PET scanning. Most patients with cancer are investigated in non-university centers, and this should be taken into account when planning the location of scanners. However, because of the need to monitor the outcomes of patients having PET scans, and the need for continued clinical research into the usefulness of PET scanning, it is crucial that a centre with a PET scanner is dedicated to the careful collection of data about the patients scanned, and is an active member of a network of PET scanners in Ontario. Planning should take into account the fact that one cyclotron can supply a number of nearby scanners with isotope.

PET scanning is a sophisticated enterprise, requiring highly trained personnel. This includes radiation chemists, nuclear medicine technicians, physicists and nuclear medicine physicians. At the present time in Canada there is an acute shortage of radiation chemists. As well, establishing a number of PET scanners in Ontario will require the training of a number of physicians to interpret the scans. It is important that this training be of sufficient length and quality. Thus, the introduction of greater PET scanning capacity in Ontario carries with it the need for increased training and retention of highly qualified personnel.

This report has only considered dedicated PET scanners. The technology will almost certainly change in the future, and it is important that high quality studies are undertaken of the new diagnostic modalities to determine their incremental benefit.

Managing the waiting list for a diagnostic test is difficult. Currently, access to other expensive diagnostic technologies such as magnetic resonance imaging is done implicitly with no formal rules or guidelines, but rather, by judgement based on a variety of factors including clinical need, accessibility, aggressiveness of the ordering physician, and opinion of the radiologist. An attempt to develop a scientific approach to the management of waiting lists for coronary angiography in Ontario[149] similar to the management of the waiting lists for bypass surgery[150,151] is now underway (Cardiac Care Network Angiography Registry). Consideration should be given to the development of a standardized method of managing the waiting lists for PET scanning.

Further Considerations

Despite the availability of PET scanning for almost three decades, the number of methodologically high quality studies (and the number of patients within those studies) is distressingly small. This raises the real possibility that publication bias (the preferential publication of studies that show a benefit of PET scanning) has occurred, which means the evidence considered in this report has over-estimated the actual benefit of PET scanning. These two factors combine to make the conclusions in this report about the usefulness of PET scanning less definitive than one would like.

The generally poor quality of the evidence for diagnostic tests has been recognized for decades,[152] yet little seems to have improved (although our subjective impression is that the quality of studies of PET have increased considerably during the last two to three years). This may be because there is no regulatory requirement for manufacturers to demonstrate that diagnostic tests improve patient care or outcome. This is in marked contrast to the regulations for drugs that require manufacturers to demonstrate efficacy in randomized trials prior to clinical use. In the future, consideration should be given to establishing more stringent requirements for the quality of evidence required before diagnostic tests are introduced into routine clinical use.

It must be remembered that a diagnostic test is only one step in the continuum of clinical care that involves the patient recognizing symptoms, the history and physical examination, diagnostic testing, and therapy. In some instances the lack of a demonstrably effective and cost-effective therapy is a more important impediment to clinical management than the lack of a highly accurate diagnostic test. For example, the new therapies for the management of dementia symptoms are only marginally effective, and many cancers do not have effective therapies. Conversely, a more accurate diagnostic test may have considerable therapeutic implications. For example, if PET scanning is found to accurately identify a number of heart failure patients who would benefit from revascularization, who are not currently being revascularized, more resources for revascularization will be required.

In many instances PET is being compared with diagnostic technologies that themselves have not been rigorously evaluated, and it could be argued that PET is being held to a higher standard than some previous diagnostic tests. However, as mentioned previously, we believe that standards should improve over time, and given PET's expense and the competing demands for limited health care resources, that it is reasonable to expect the usefulness of PET to be supported by high quality studies prior to its introduction into routine clinical practice.

Clinical Research Priorities for PET Scanning in Ontario

The useful research that could be conducted to more definitively establish the role of PET scanning for a number of diseases is overwhelming. However, three areas of *clinical* research appear to warrant immediate attention. Rigorous cost-effectiveness studies using Ontario practice patterns and costs would be very helpful. Determining the usefulness of PET scanning for viability in patients with heart failure is a high priority, especially given the conflicting results in the literature and the increasing prevalence of heart failure (one randomized trial coordinated at the Ottawa Heart Institute is already underway). Studies should be done on the optimal methods of managing waiting lists for PET scanning.

Accessibility to expertise in clinical research design is mandatory for future research in PET in Ontario.

In addition to research designed to generate new knowledge about the use of PET for new indications, useful research into the manner in which PET is being used in the province for "established" indications must be undertaken. We strongly suggest that a registry of all patients having PET scans in Ontario should be developed. This registry, with patient consent, would collect a small amount of baseline information on patients having a PET scan. The registry could then be linked to other databases available in Ontario that provide information about admissions, surgical procedures, visits to physicians, drugs utilized and mortality. Linking this information would provide a relatively inexpensive way of determining whether the benefits suggested in the literature (for example unnecessary surgeries avoided) are realized in actual practice. This information would also be invaluable for the cost-effectiveness studies mentioned previously.

The need to perform research on PET scanning, and the desire not to introduce PET scanning until its impact on patient care has been demonstrated, are both logical and worthwhile goals, but unfortunately they are also reminiscent of the 'chicken and the egg' analogy. It is impossible to do research on PET scanning without a PET scanner. If one does not introduce a PET scanner until there is evidence of its benefit, one will not have a PET scanner with which to do the research. A lesser version of this problem will arise when PET scanners are introduced in Ontario to meet the established clinical need. There will be an understandable desire to use the scanners primarily for patient care. However, when planning for the introduction of PET scanners, the need to have some scanner time dedicated to research must be recognized. The funding for the research could come from various sources including peer reviewed granting agencies such as the Canadian Institutes of Health Research, infrastructure grants from organizations such as the Canada Foundation for Innovation, the diagnostic industry, and the Ministry of Health and Long-Term Care (which could allow a certain amount of PET scanning time to be dedicated to research). It is beyond the mandate of this report to determine which combination of these or other options is chosen.

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APPENDICES

Appendix I

Summary of Literature Searches

Relevant literature was searched in the databases of Medline, on OVID-CDROM, HealthStar and Cancerlit on OVID Online, Cochrane Library (issue 4, 2000) and the Internet.

Medline and HealthStar, Cancerlit
These searches were performed on the following subset databases: 1997- September 2000, 1993-1996, 1992-1987, and 1975-1986.HealthStar and CancerLit were searched from 1975-September 2000. The search was limited to English language articles. The search was updated monthly to and including December 2000. The main HTA reports and various journal articles were back searched to ensure comprehensiveness.

MeSH and textwords were used. Most, though not all MeSH were "exploded" to include the narrower terms. Terminology was adjusted for changes in MeSH over the years. This related mostly to headings for positron emission tomography and FDG. The strategies were purposely left broad.

The search was divided into 4 separate sections, cardiology, neurology, oncology and costs. A general search on costs was included with all the disease specific strategies. The specific strategy for costs was expanded. Duplication between the sets was not removed.

The specific areas were as follows- * indicates an "exploded" term:

Heart diseases*
Myocardial ischemia*
Epilepsy*
Dementia*
Parkinson disease
Huntington disease
Colorectal neoplasms*
Breast neoplasms*
Lung neoplasms*
Lymphoma*
Melanoma*
Cost and cost analysis*
Outcome and process assessment (health care)*
Models, economic*
Tomography, emission-computed*
Gamma cameras*
Fludeoxyglucose f 18

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The following are the search strategies performed on MEDLINE and HealthStar

Cardiac: 1997-2000

1. tomography, emission-computed/ec,td,ut
2. exp tomography, emission-computed/
3. "coincidence imaging".tw.
4. fludeoxyglucose f 18/
5. pet.tw.
6. "positron emission tomography".tw.
7. "gamma camera$".tw.
8. (2 or 3 or 5 or 6 or 7) and 4
9. exp myocardial ischemia/
10. exp heart diseases/ri
11. 8 and (9 or 10)
12. exp myocardial ischemia/di or exp heart diseases/di
13. 12 and 8
14. exp diagnosis/ and (9 or exp heart diseases/)
15. 14 and 8
16. 11 or 13 or 15
17. rubidium radioisotopes/
18. rubidium/
19. "13n ammonia".tw.
20. (17 or 18 or 19) and (2 or 3 or 5 or 6 or 7)
21. fludeoxyglucose f 18/du
22. 21 and (exp myocardial ischemia/ or exp heart diseases/)
23. 22 or 20
24. 23 or 16
25. l/24 lg=en
26. 25 not animal/

Cardiac: 1975-1996

1. (deoxyglucose or "deoxy-glucose" or fluorodeoxyglucose).tw.
2. (18fluorodeoxyglucose or fludeoxyglucose or fdg$ or 18fdg).tw.
3. ("f-18-dg" or "fluoro-2-deoxy-d-glucose" or "2fluoro-2deoxyglucose").tw.
4. 1 or 2 or 3 or "fluoro-d-glucose".tw.
5. tomography, emission-computed/ec,td,ut
6. exp tomography, emission-computed/
7. "coincidence imaging".tw.
8. fludeoxyglucose f 18/
9. pet.tw.
10. "positron emission tomography".tw.
11. "gamma camera$".tw.
12. (6 or 7 or 9 or 10 or 11) and 8
13. exp myocardial ischemia/
14. exp heart diseases/ri
15. 12 and (13 or 14)
16. exp myocardial ischemia/di or exp heart diseases/di
17. 16 and 12
18. exp diagnosis/ and (13 or exp heart diseases/)
19. 18 and 12
20. 15 or 17 or 19
21. rubidium radioisotopes/
22. rubidium/
23. "13n ammonia".tw.
24. (21 or 22 or 23) and (6 or 7 or 9 or 10 or 11)
25. fludeoxyglucose f 18/du
26. 25 and (exp myocardial ischemia/ or exp heart diseases/)
27. 26 or 24
28. 4 and (6 or 7 or 9 or 10 or 11)
29. 28 and (13 or 14 or 16 or 18)
28. 27 or 29
29. l/30 lg=en
30. 31 not animal/

Neurology: 1997-2000

1. tomography, emission-computed/ec,td,ut
2. exp tomography, emission-computed/
3. ”coincidence imaging".tw.
4. fludeoxyglucose f 18/
5. pet.tw.
6. "positron emission tomography".tw.
7. "gamma camera$".tw.
8. (2 or 3 or 5 or 6 or 7) and 4
9. exp epilepsy/
10. exp dementia/
11. exp radiotherapy/
12. 8 and (9 or 10 or 11)
13. "postop$ radiation".tw.
14. 13 and 8
15. Parkinson disease/
16. Huntington disease/
17. (15 or 16) and 8
18. 13 and (2 or 3 or 5 or 6 or 7)
19. fludeoxyglucose f 18/du
20. 19 and (9 or 10 or 11 or 15 or 16)
21. 12 or 14 or 17 or 18 or 20

Neurology: 1975-1996

1. tomography, emission-computed/ec,td,ut
2. exp tomography, emission-computed/
3. “coincidence imaging".tw.
4. fludeoxyglucose f 18/
5. pet.tw.
6. "positron emission tomography".tw.
7. "gamma camera$".tw.
8. (2 or 3 or 5 or 6 or 7) and 4
9. exp epilepsy/
10. exp dementia/
11. exp radiotherapy/
12. 8 and (9 or 10 or 11)
13. "postop$ radiation".tw.
14. 13 and 8
15. Parkinson disease/
16. Huntington disease/
17. (15 or 16) and 8
18. 13 and (2 or 3 or 5 or 6 or 7)
19. fludeoxyglucose f 18/du
20. 19 and (9 or 10 or 11 or 15 or 16)
21. 12 or 14 or 17 or 18 or 20
22. (deoxyglucose or "deoxy-glucose" or fluorodeoxyglucose).tw.
23. (18fluorodeoxyglucose or fludeoxyglucose or fdg$ or 18fdg).tw.
24. ("f-18-dg" or "fluoro-2-deoxy-d-glucose" or "2fluoro-2deoxyglucose").tw.
25. 22 or 23 or 24 or "fluoro-d-glucose".tw.
26. 25 and (2 or 3 or 4 or 6 or 7)
27. 26 and (9 or 10 or 11 or 13 or 15 or 16)
28. 21 or 27
29. l/28 lg=en
30. not animal/

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Oncology: 1997-2000

1. tomography, emission-computed/ec,td,ut
2. exp tomography, emission-computed/
3. "coincidence imaging".tw.
4. fludeoxyglucose f 18/
5. pet.tw.
6. "positron emission tomography".tw.
7. "gamma camera$".tw.
8. (2 or 3 or 5 or 6 or 7) and 4
9. exp colorectal neoplasms/ or breast neoplasms/
10. exp "head and neck neoplasms"/ or exp brain neoplasms/
11. exp lung neoplasms/
12. exp lymphoma/
13. exp melanoma/
14. 8 and (9 or 10 or 11 or 12 or 13)
15. fludeoxyglucose f 18/du
16. 15 and (9 or 10 or 11 or 12 or 13)
17. 14 or 16
18. l/17 lg=en
19. 18 not animal

Oncology: 1975-1996

1. (deoxyglucose or "deoxy-glucose" or fluorodeoxyglucose).tw.
2. (18fluorodeoxyglucose or fludeoxyglucose or fdg$ or 18fdg).tw.
3. ("f-18-dg" or "fluoro-2-deoxy-d-glucose" or "2fluoro-2deoxyglucose").tw.
4. 1 or 2 or 3 or "fluoro-d-glucose".tw.
5. tomography, emission-computed/ec,td,ut
6. exp tomography, emission-computed/
7. "coincidence imaging".tw.
8. fludeoxyglucose f 18/
9. pet.tw.
10. "positron emission tomography".tw.
11. "gamma camera$".tw.
12. (6 or 7 or 9 or 10 or 11) and 8
13. exp colorectal neoplasms/ or breast neoplasms/
14. exp "head and neck neoplasms"/ or exp brain neoplasms/
15. exp lung neoplasms/
16. exp lymphoma/
17. exp melanoma/
18. 12 and (13 or 14 or 15 or 16 or 17)
19. fludeoxyglucose f 18/du
20. 19 and (13 or 14 or 15 or 16 or 17)
21. 4 and (6 or 7 or 9 or 10 or 11)
22. 21 and (13 or 14 or 15 or 16 or 17)
23. 18 or 19 or 20 or 22
24. ..l/23 lg=en
25. 24 not animal/

Cost Effectiveness: 1997-2000

1. exp tomography, emission-computed/
2. "coincidence imaging".tw.
3. pet.tw.
4. "positron emission tomography".tw.
5. "gamma camera$".tw.
6. exp tomography, emission-computed/ec,sn,td,ut
7. exp "costs and cost analysis"/
8. exp "outcome and process assessment (health care)"/
9. exp models, economic/
10. (1 or 2 or 3 or 4 or 5) and (7 or 9)
11. fludeoxyglucose f 18/ec
12. fludeoxyglucose f 18/
13. 12 and (7 or 9)
14. 6 or 10 or 11 or 13
15. ..l/14 lg=en
16. 15 not animal

Cost Effectiveness: 1975-1996

In these databases the same search without the FDG terms was performed.

The Cochrane Library was searched using the MeSH terminology for PET and textwords.

GRAY LITERATURE

Internet searches were performed using the Alta Vista and Google search engines. Going directly to HTA and PET centre sites and using their links identified most other relevant sites. The following is a list of major sites visited.

Website	Organization
www.hcfa.gov	Health Care Financing Administration (US)
www. bcbs.com/	BlueCross BlueShield Association (US)
www.health.gov.au:80	Government of Australia
www.inahta.org	International Network of Agencies for Health Technology Assessment (Sweden)
www.ncchta.org	National Coordinating Centre for Health Technology Assessment, Southampton (UK)
www.update-software.com/National/nrr-frame.html	National Research Register (UK)
www.va.gov/resdev/prt/petreport.htm	VA Research & Development (US)
www.cc.emory.edu/RADIOLOGY/pet.html	Emory University (US)
www.dihta.dk	Danish Institute for Health Technology Assessment
www.cc.nih.gov/petlinks.html	NIH Clinical Center Pet Department
www.health.state.mn.us	Health Technology Advisory Committee (Minnesota, US)
www.ctsnet.org	The CardioThoracic Surgery Network
www.ecri.org	Emergency Care Research Institute (US)
www.hta.nhsweb.nhs.uk/	Health Technology Assessment (UK)
www.pet.med.va.gov:8080/	Minnesota VA (US)
www.nzhta.chmeds.ac.nz/	New Zealand HTA
www.icppet.org/	Institute for Clinical PET (US)
www.austin.unimelb.edu.au	Austin and Repatriation Medical Centre (Australia)
www.york.ac.uk/inst/crd/welcome.htm	NHS Centre for Reviews and Dissemination (UK)
www.mja.com.au	eMJA (Australia)
www.ahfmr.ab.ca//frames3.html	Alberta Heritage Foundation for Medical Research
www.ahrq.gov/	Agency for Healthcare Research & Quality (US), formerly
www.ahcpr.gov/	Agency for Health Care Policy & Research.

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Appendix II

ICES PET Panel, February 27, 2001

Please note: The comments of the Panelists described in this Appendix refer to the *first* draft of this report. A number of their comments have been incorporated into the final report.

1. Questionnaire Feedback

a) General Comments

In general, there was agreement amongst the panelists about the overall conclusions in the oncology and neurology sections. There was more disagreement regarding cardiac viability and CAD indications.

Near universal agreement was expressed about PET's possible role in lung cancer. Other oncological indications were suggested, the two most common being esophageal (4) and thyroid (2) cancer.

Evidence for cardiac viability was felt to be better than was reflected in the initial draft of the report. It was also noted that PET may be useful in the diagnosis of CAD, in particular for subgroups such as obese patients or those with equivocal SPECT results. In addition, PET was thought by some to have a potential role in evaluating patients who are cardiac transplant candidates to determine whether bypass surgery is an option instead.

The importance of having Canadian studies was frequently stressed, as was the importance of considering installation, operating and training costs, and cost-effectiveness.

Additional comments included the need to balance PET's research and clinical uses, that infrastructure for PET should be addressed, and that continuing changes in the technology should also be considered. Outcomes such as quality of life and morbidity were also felt to be a significant component in determining the effectiveness of PET. Sixteen specific references were provided by panelists. The difficulties of prioritizing patients and addressing the problems of waiting lists were also raised.

b) Research Agenda

(Feedback was received in response to the following question: If you were establishing a research agenda for PET in Ontario, what would be your 5 most important topics?)

From the 33 questionnaires mailed to the panelists, 26 questionnaires were received, each completed to varying degrees (79% response rate). 19 included comments pertaining to the research agenda. The single greatest number of suggestions were related to oncology (35), followed by those in cardiology (11), cost-effectiveness (9), general issues (7), neurology (5),

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and other areas (4). There was overlap between cost-effectiveness and both oncology and cardiology. Overall, the suggestions were very general and non-specific.
In oncology, the main areas of interest involved exploration of PET's potential role in screening (both primary and secondary) (5), staging (6), treatment planning (5), evaluating response to treatment (7), evaluating new chemotherapeutic agents (3), and cost-effectiveness (1). General comments reaffirmed the importance of further research in cancer diagnosis, and specific cancers were noted, namely lung (3), breast (3), colorectal (2), prostate (2), lymphoma (2), myeloma (1) and brain (1).

Primary screening was mentioned once in connection with breast cancer, and staging and cost-effectiveness was also mentioned once with regards to lung cancer. On the other hand differentiating recurrent disease vs. scar tissue (secondary screening), and other comments about staging, treatment planning, evaluating treatment response, and evaluating new chemotherapeutic agents were not linked to any specific cancer. Treatment planning suggestions included assessment of radiotherapy treatment volumes and evaluation of tumour characteristics.

In cardiology, further clarification of the possible roles for PET in CAD was suggested (3), with two of these specifically suggesting that particular subgroups of the CAD population be the focus of future research. Regarding viability, 8 comments supported more research in that area—including examination of 5-year survival outcomes, and its role in assessing potential transplant patients. A single mention was made of investigating FDG-SPECT applications in cardiology.

Neurology research suggestions were limited to looking at PET in dementia (diagnosis, assessment, prognosis) (3); psychiatry (1) and stroke (1).

More general comments suggesting that PET research centres be established to validate cost-effectiveness data in Canada and address questions on the PET research agenda (2). Research directed towards improvement of the technology itself (2), development of new radiopharmaceuticals (4), and evaluation of the impact of the information provided by PET on clinical decisions, and other outcomes such as quality of life were also mentioned (3). On one occasion the question of whether PET should be a replacement for or an adjunct to other existing technologies was raised, as was the issue of exploring the appropriate balance between research and service use of PET.

Apart from the general suggestion that more studies into PET's cost-effectiveness be done, the main focus in economic evaluation was on the need for studies from Ontario and Canada (3).

Other areas of suggested research included PET's possible role in infectious and autoimmune diseases (3) and gene therapy (1).

Appendix III

Summary of Other Health Technology Assessments and Reviews

Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
AETS	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	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	1999	Alzheimer disease
		Parkinsonisms
		Epilepsy
		Brain Tumours
		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 tumoural 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 PET's utility in handling of specific clinical situations, and its contribution in improving therapeutic results.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
						• 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	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 management, and therapeutic decisions in cardiac patients.
AHCPR	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 seizures can be defined.
AHFMR	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	• PET would be used as a complement to anatomical imaging methods such as MRI and would increase the cost of management.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
					Methodologic quality based on: • Study design • Description of study • population • Diagnostic method • Determination of diagnostic accuracy and validity • influence on management • influence on outcomes	• 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 Allbertan patients with MRE should be in the context of well designed studies to evaluate Pet's clinical & economic impact.
AHFMR	1999	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 1 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 diagnosis. 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 viability 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.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations

BCBSA TEC	1997	Lung Cancer
		Breast Cancer
		Pancreatic Cancer
		Colorectal Cancer
		Head and Neck Cancer
		Lymphoma
		Melanoma
		Musculo-skeletal Tumours
		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 tumours because the scientific evidence did not permit conclusions concerning the effect of the technology on health outcomes.
						NOTE: As of the INAHTA report date , this TEC assessment was currently being updated and these conclusions may have changed based on additional evidence review.

BCBSA TEC	1997	Neurologic indications: • Differential dx of symptomatic intracranial masses	MEDLINE 1985 - February 1997	Systematic review	Criteria as above	• FDG PET imaging does not meet BCBSA TEC criteria for any of the CNS tumour indications reviewed because the scientific evidence did not permit conclusions concerning the effect of the technology on health outcomes. *NOTE: As of the INAHTA report date, this TEC assessment was currently being updated and these conclusions may have changed based on additional evidence review.*

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
		• Differentiation of low-grade and high-grade brain tumours • Guidance of stereotactic biopsy or biopsies of documented intracranial masses • Recurrent brain tumour from radionecrosis • Monitoring treatment response in patients with brain tumours				
BCBSA TEC	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.
BC135A TEC	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.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
						* 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	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 Rb-82 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	Myocardial perfusion Myocardial viability Brain tumour 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 tumour 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	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 that 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.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
CAHTA	1997	PET & Stereotactic Surgery for patients with neuropsychiatric disorders	Medline 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 with different neuropsychiatric disorders. Study results are questioned due to their methodological limitations. PET is still an experimental technology.
CEDIT	1998	FDG-PET and coincidence detection PET (CDPET) imaging in Assistance Publique-Hopitaux de Pads (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 centre 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	1998	CDPET for conventional scintigraphy	Not specified	Expert panel	Criteria not specified	• Evidence is non-existent • Using CDPET to conduct scans using Technetium 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	1999	Patient-care protocols in AP-HP to evaluate FDG-PET in: lung cancer digestive cancer lymphoma ENT 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.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
		Future clinical research programs in: biliary tract cancer melanoma childhood cancer				• Organizing committee will supervise PET Canter 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	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.
HAYES	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 non-invasive 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, multicentre 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.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
HAYES	1999	Myocardial perfusion Myocardial viability	Medline HEALTHSTAR EMBASE Current Contents Additional Info: FDA, the ACC, and the AHA 1966-7199	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 non-invasive method for detecting the presence and severity of CAD in symptomatic patients and for diagnosing CAD in asymptomatic individuals	• Evidence suggests that PET is the most accurate and reliable non-invasive strategy for detecting the presence and severity of CAD. PET will not replace 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	1997	Alzheimer's d. (AD)
		Huntington's d.
		Wilson's d. (WD)
		Parkinson's d. (PD)
		Epilepsy
		Schizophrenia
		Addiction, chronic substance abuse
		ADHD
		Head trauma
		Cerebrovascular dis.
			MEDLINE
			EMBASE
			Current Contents
			HealthSTAR
			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 due to 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 to 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.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
HAYES	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 differentiatingrecurrence and treatment-induced changes with FDG PET **D** for monitoring response to treatment with C11-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.
HAYES	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 benign from malig. lesions and staging with FDG PET *Urinary bladder:* **C** fordetecting perivesical tumor growth and distant mets and for early detection of 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.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
					Colorectal: **C** for 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 tumours, staging, and detecting recurrence.	

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
HAYES	1999	Malignant lymphoma Malignant melanoma Breast cancer colorectal cancer	MEDLINE EMBASE Current Contents HealthSTAR 1966-3199 for lymphoma, melanoma and breast cancer; 1985-3199 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.
MSAC (formerly NHTAP)	1990	Myocardial perfusion Myocardial viability localization of epileptic foci in surgical candidates with medically 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.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations

OSTEBA	1998	Head & neck
		colorectal
		breast
		lung
		SPN
		brain
		pancreatic
		melanoma
		soft tissue
		myocardial perfusion
		myocardial viability
		epilepsy
		West infantile spasms
		Lennox-Gastaut syndr.
		Alzheimer's
			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 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.

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations

SFOSS	1999	Lung cancer
		head and neck
		melanoma
			Not applicable	Proposed evaluation registries and multicentre 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 multicentre 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

VA TAP	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 multicentre PET study. • VA should maximize the value of its existing commitment, rather than establish additional PET centres.
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 co-operative 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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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
			• **Additional Reviews**			
Council of Medical Imaging (OMA)	**July 1999**	Cardiac: perfusion viability transplantation Neurology: epilepsy dementia movement dis. brain tumours Oncology: lung breast colon lymphoma head and neck other	No search criteria identified	Expert clinical panel	None	• Useful in diagnosis of SPN • Lung cancer: staging, monitoring response to chemotherapy, distinguishing scar from recurrence • Breast cancer: initial staging and assessing response to therapy • Colon cancer: detection of local recurrence and regional metastases • Lymphoma: staging and response to therapy • Head and neck cancers: pre-surgical staging • Potential role in melanoma, cancers of ovary, esophagus, thyroid, pancreas, bone and muscle • Cost-effective for cardiac perfusion and viability • Localization of epileptogenic foci in intractable seizures • Research role for PET in dementia and movement disorders • Brain tumours: to distinguish scar from recurrence • Encourage: a province-wide approach to policy, reimbursement and implementation with heart disease and cancer given the primary emphasis; further cost-effectiveness research; networking between industry, research and educational arms of the PET community

NHS R&D HTA (NCCHTA)	1999	Cardiac:
		perfusion
		viability
		Neurology:
		Alzheimer's dis.
		dementia
		epilepsy
		Parkinson's dis.
		Stroke
			Ovid MEDLINE (1996-98) and Cochrane Library (1998 #2)	Systemic review based on VHA review of 1996
				
				3-round Delphi panel
					EBM criteria used for grading quality of evidence
					
					Fryback and Thornbury scale used for classifying included articles
						• Paucity of evidence regarding cost-effectiveness in all of studied clinical indications
						• Many reports on diagnostic accuracy limited because they are subject to bias and often use small sample sizes
						• Delphi panel established 4 most important research priorities:
						  • Relative cost-effectiveness (CE) of full ring PET vs. gamma camera with coincidence imaging vs. current diagnostic strategies in:
						  i) Pre-surgical staging of lung cancer
						  ii) Staging and monitoring treatment response in breast cancer

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
		Oncology: breast lung colorectal head and neck SPN				• Partial ring vs. full ring PET in oncology • Relative CE of gamma camera PET with coincidence imaging vs. 511keV collimated gamma camera imaging in assessing myocardial viability in selecting patients for revascularization
INAHTA	1999	Cardiology: perfusion viability Neurology: epilepsy tumour vs. necrosis neurodegenerative disorders ACV (?) encephalopathy psychiatry Oncology: lung soft tissue head and neck SPN colorectal breast gynaecological haematological genitourinary hepatobiliary melanoma adrenal thyroid	1997-1999 collaboration of INAHTA's members (31 in 1999) MEDLINE, HealthSTAR and PET-related web sites for descriptive material, major payers and HTA reports from USA	Survey of membership and systematic review	None in addition to that incorporated in each of the collaborator's assessments	• PET is now feasible for clinical use but research: • Largely based on full-ring PET • Limited by bias • Often only small patient numbers • Wide variation in use of PET for research and diagnosis • Public health systems in Australia, Switzerland, Denmark and US (VHA) accounted for 85% of PET activity • Critical research required to define clinical and economic consequences of using PET relative to other current modalities

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations

HTAC (Minnesota)	1999	Oncology:
		brain
		head and neck
		pituitary
		thyroid
		urinary
		kidney
		lung
		breast
		esophageal
		pancreatic
		ovarian
		prostate
		testicular
		malig. melanoma
		colorectal
			Unknown	Literature review (methods not described)	None noted	• PET improves diagnostic accuracy in these selected cancer patients:
						  • Evaluating SPN
						  • Staging lung cancer
						  • Brain tumour recurrence vs. necrosis
						• Better designed, multi-centred studies with larger patient samples need to be done
						• PET accessibility should be limited to patients where an essential clinical question has a reasonable likelihood of being answered
						• Numbers of PET sites should remain limited due to expenses and staffing involved
						• Whenever possible, selected patients should be assured access to PET if it is clinically appropriate
						• PET institutions should define appropriate clinical settings for PET

Commonwealth Report (MSAC)	2000	Cardiac:
		viability
		Neurology:
		medically refractory epilepsy
		Oncology:
		NSCLC
		melanoma
		malignant glioma
		colorectal cancer
			Ovid MEDLINE 1966-Jan 2000
			Cochrane Library
			Websites of HTA organisations including: INAHTA; NHS Economic Evaluation Database; Economic and HTA databases; York Health Technology Assessment Database
				Systematic review	Inclusion criteria noted but absolute grading of studies was not done	• Insufficient evidence to draw definitive conclusions regarding clinical- and cost-effectiveness of FDG-PET
						• In most indications, FDG-PET is additive to current diagnostic algorithms
						• FDG-PET is safe
						• Further evaluation is necessary
						• Restricted funding approved for the following:
						  • SPN workup
						  • NSCLC staging pre-operatively or before radiotherapy
						  • Guiding biopsy in primary brain tumours
						  • Differentiating structural changes from local recurrence of colorectal cancer
						  • Differentiating radiation necrosis from recurrent glioma
						  • Pre-operative evaluation of patients considered for resection of colorectal liver or lung metastases
						  • Pre-operative evaluation of patients considered for

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Organization	Year	Indications Studied	Sources and Dates Covered in Search	Assessment Type	Quality Assessment	Conclusions/Recommendations
						resection of apparently limited metastatic disease from malig. Melanoma • Evaluation of patients with refractory epilepsy considered for surgery where other diagnostic modalities are inconclusive • Cardiac viability assessment for possible revascularization in patients with CAD and impaired LV function, where standard diagnostic modalities have been negative

Source: Adapted from INAHTA, November 1999

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Appendix IV

Ongoing PET Research

The following projects were identified by searching the following institutional websites as of January 2001: NRR, CIHR, NIH, all INAHTA and ISHTAC member sites, ICP, NHS and the VA.

Neurology

Project	Reference Number and Dates	Primary Contact
1. A double-blind, multicentre, flexible dose, L-Dopa controlled study of Ropinirole, to investigate a)Neuroprotective effect as measured by 3D pet scanning, and b) Ophthalmological safety, in patients with early Parkinson's disease. [multi-centre study]	NRR Project: N0232063389 Start date: 01/01/1997, End date: 31/12/2002	Dr David Park
2. Assessment of cerebral oedema, regional cerebral blood flow, oxygenation and glucose metabolism in severe head injury using positron emission tomography and magnetic resonance imaging.	NRR Project: N0287023102 Start date: 05/12/1997, End date: 05/12/2000	Prof John D Pickard
3. Cerebral metabolic, perfusion and electrophysiological changes on emergence from coma.	NRR Project: N0287040867 Start date: 19/02/1999, End date: 19/02/2002	Prof John D Pickard
4. Characterization and imaging of cerebral physiology in acute stroke: (1) Inflammation following acute stroke.	NRR Project: N0287040869 Start date: 17/03/1999, End date: 01/03/2002	Dr Elizabeth Anne Warburton
5. Characterization of protein binding and partitioning of PET tracers in blood from normal subjects and patients with acute brain injury.	NRR Project: N0287042228 Start date: 24/05/1999, End date: 24/05/2002	Dr David Krishna Menon
6. Comparison of 2D and 3D H2 15O PET CBF measurement in volunteers and after acute brain damage: repeatability and response to variations in arterial CO2 concentration.	NRR Project: N0287022658 Start date: 05/12/1995, End date: 30/11/2000	Prof John D Pickard
7. F-18 flurodeoxyglucose positron emission tomography (18FDG PET) of carotid artery atherosclerosis.	NRR Project: N0544074076 Start date: 18/04/2000, End date: 18/04/2003	Prof Peter Leslie Weissberg
8. Functional imaging studies (PET and MRI) of the structural basis for functional recovery in aphasia.	NRR Project: N0287052562 Start date: 09/09/1999, End date: 09/09/2002	Dr Elizabeth Anne Warburton
9. Imaging inflammatory processes in acute stroke using the PET ligand PK11195.	NRR Project: N0544074093 Start date: 22/02/2000, End date: 22/02/2003	Dr Elizabeth Anne Warburton

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Project	Reference Number and Dates	Primary Contact
10. Prospective clinical evaluation of mild to moderate Huntington's disease (HD) using the CAPIT-HD protocol.	NRR Project: N0287022664 Start date: 22/05/1995, End date: 28/05/2001	Prof John R Hodges
11. Regional cerebral blood flow, oxygenation and glucose metabolism in subarachnoid haemorrhage/intracerebral haematoma using PET and MRI.	NRR Project: N0287023103 Start date: 05/12/1997, End date: 05/12/2000	Prof John D Pickard
12. The early diagnosis, differentiation and clinical course of dementia: Alzheimer's, frontotemporal and vascular types. PET component.	NRR Project: N0287040801 Start date: 13/01/1999, End date: 13/01/2002	Prof John R Hodges
13. A double-blind, madopar controlled, multicentre study of ropinirole in the treatment of de-novo Parkinson's disease.	NRR Project: N0016000859 Start date: 10/07/1992, End date: 30/12/2000	Prof David Brooks
14. A long term phase III multicentre safety and efficacy study with idazoxan on levodopa-induced dyskinesias in Parkinson's disease.	NRR Project: N0016028034 Start date: 01/10/1997, End date: 01/10/2001	Prof David Brooks
15. A PET study of opiate receptor changes in drug addiction.	NRR Project: N0016000874 Start date: 01/10/1998, End date: 01/10/2002	Prof David Brooks
16. A PET study of prefrontal lobe function in normal volunteers.	NRR Project: N0016001185 Start date: 01/06/1998, End date: 31/12/2001	Dr PM Grasby
17. A PET study of the dopaminergic system in depression.	NRR Project: N0016066593 Start date: 01/03/2000, End date: 28/02/2003	Prof PM Grasby
18. A PET study on function of the dopaminergic system in Gilles de la Tourette syndrome.	NRR Project: N0016000857 Start date: 01/01/1995, End date: 31/12/2000	Prof David Brooks
19. A Prospective Neurobiological Study of a First Episode Schizophrenia Cohort	NRR Project: N0292005362 Start date: 01/03/1998, End date: 28/02/2001	Dr Eileen Joyce
20. Flumazenil pet in diagnosis of apertial vs generalized seizures.	NRR Project: N0013076049 Start date: 01/01/1997, End date: 01/01/2005	Dr Kate Blake
21. Flumazenil pet in localization in epileptic foci in epileptic encephalopathies.	NRR Project: N0013076050 Start date: 01/01/1997, End date: 01/01/2005	Dr Kate Blake
22. Investigation of microglial activation in MS subgroups using PET: correlation with clinical, MRI and immunological markers of disease activity	NRR Project: N0263083152 Start date: 10/10/1996, End date: 01/05/2003	Dr R Kapoor

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Project	Reference Number and Dates	Primary Contact
23. Spinal cord imaging: A comparison of MRI and PET scanning in patients presenting with myelopathy	NRR Project: N0411057556 Start date: 22/11/1999, End date: 30/08/2001	Dr R J Coleman
24. PET studies in addiction	NRR Project: N0264060190 Start date: 01/10/1997, End date: 30/09/2002	Prof David Nutt
25. Brain Function in panic disorder: PET studies, CAMH	2000-2001 $63,018	Brown, Gregory M
26. The use of neuroimaging in dementia evaluation. A medical technology report	Study design: Primary Research, Systematic Review, Copenhagen University Hospital--DIHTA (project start: 2000 end: 2001)	Dr Steen G. Hasselbalch

Cardiology

Project	Reference Number and Dates	Primary Contact
1. Comparison of intra coronary doppler studies and dobutamine stress left ventricular angiography with pet scan and dobutamine stress echocardiogram for the assessment of viability of infarcted myocardium	NRR Project: N0542075135 Start date: 01/03/2000, End date: 28/02/2002	Dr P M Schofield
2. Comparison of left ventricular volumes measured with gated C150 PET, Magnetic Resonance Imaging (MRI) and echocardiography.	NRR Project: N0016048318 Start date: 01/03/1999, End date: 01/02/2001	Professor Paolo G Camici
3. Development of ECG-Gated Myocardial SPECT and Comparison with FDG PET for the Detection of Hibernating Myocardium in Patients with Ischaemic Left Ventricular Dysfunction	NRR Project: N0201082378 Start date: 01/04/2000, End date: 31/03/2001	Professor SR Underwood
4. Myocardial oxidative metabolism and blood flow in myocardial stunning.	NRR Project: N0016027993 Start date: 01/12/1997, End date: 01/12/2000	Dr Edward Barnes
5. The use of MRI in the assessment of left ventricular impairment and its recovery: a PET-MRI comparative study.	NRR Project: N0411013188 Start date: 01/01/1998, End date: 31/12/2000	Dr T Redpath
6. To compare the use of collimated and coincidence gamma camera PET for myocardial viability.	NRR Project: N0231084965 Start date: 01/01/1998, End date: 31/05/2001	Dr John Fleming
7. Outcome and cost-effectiveness of FDG PET in LV dysfunction (PARR 2) University of Ottawa Heart Institute	2000-2001 $220,500	Beanlands, Robert S
8. Serial evaluation of myocardial perfusion using	2000-2001 $69,522	Dekemp, Robert A

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Project	Reference Number and Dates	Primary Contact
SPECT imaging, University of Ottawa 9. Post-Stress Left Ventricular Contractile Dysfunction: Does It Represent Persistent Myocardial Ischemia or Stunning?	NHLBI: 96-H-0031 (?active)	NA
10. Myocardial Fluorodeoxyglucose Imaging Using SPECT: A Cost Effective Alternative to pet	NHLBI: 95-H-0128 (?active)	NA
11. Determination of Regional Myocardial Blood Flow and Glucose Metabolism Using PET	NHLBI: 92-H-0207	NA

Oncology

Project	Reference Number and Dates	Primary Contact
1. Evaluation of PET in determining complete response after neoadjuvant chemotherapy in primary breast cancer.	NRR Project: N0143030169 Start date: 05/09/1997, End date: 31/12/2000	Dr Andreas Makris
2. Evaluation of PET with FDG in primary Breast Cancer	NRR Project: N0143056132 Start date: 01/01/2000, End date: 31/03/2001	Dr Andreas Makris
3. Evaluation of Positron Emission Tomography in primary breast cancer [multi-centre study]	NRR Project: N0143043360 Start date: 01/04/1999, End date: 31/03/2002	Dr Andreas Makris
4. PET imaging of patients with carcinoma of the oesophagus [multi-centre study]	NRR Project: N0143030251 Start date: 01/01/1998, End date: 01/01/2001	Dr Wai Lup Wong
5. The role of PET in the assessment, planning and follow up of patients receiving novel fractionation schemes in the treatment of locally advanced head and neck cancer	NRR Project: N0143078816 Start date: 01/09/2000, End date: 01/09/2003	Prof Michele Saunders
6. A comparison of pet scanning and sentinel node biopsy in the detection of subclinical nodal metastases in patients with malignant melanoma.	NRR Project: N0013076837 Start date: 01/04/1997, End date: 01/06/2001	Dr Kate Blake
7. Assessment of tumour response to chemotherapy by FDG-PET	NRR Project: N0256057433 Start date: 15/11/1999, End date: 01/05/2001	Prof RHJ Begent
8. Development of PET for the study of tumour physiology and response to treatment.	NRR Project: N0016001553 Start date: 01/01/1993, End date: 31/12/2000	Dr Pat Price
9. Longitudinal study of SPET and PET scanning in the evaluation of patients with low-grade gliomas	NRR Project: N0263083107 Start date: 01/07/2000, End date: 30/06/2003	Dr J Rees

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Project	Reference Number and Dates	Primary Contact
10. The role of pet scanning in the management of patients with cancer of the head and neck.	NRR Project: N0013075992 Start date: 01/04/1992, End date: 30/04/2002	Dr Kate Blake
11. The role of positron emission tomography (PET) in the follow up of patients with a history of colorectal carcinoma	NRR Project: N0263066759 Start date: 01/02/2000, End date: 30/01/2002	Prof I Taylor
12. The role of positron emission tomography (PET) in the pre-operative assessment of colorectal cancer	NRR Project: N0263066760 Start date: 01/02/2000, End date: 31/01/2002	Prof I Taylor
13. Preliminary investigation of glucose and Iodine metabolism using PET in the assessment of the patients with suspected recurrent thyroid cancer	NRR Project: N0063083913 Start date: 01/08/2000, End date: 31/07/2001	Dr E Allan
14. Preliminary investigation of the role of metabolic imaging with Positron Emission Tomography (PET) in managing the cancer patient.	NRR Project: N0063054444 Start date: 01/12/1999, End date: 01/12/2001	Dr N J Slevin
15. Development of correlative analytical techniques for MRI and PET imaging in breast cancer	NRR Project: N0411063772 Start date: 01/08/1999, End date: 31/07/2002	Dr T Redpath
16. Dedicated PET or coincidence gamma camera PET for diagnostics in recurrent colorectal cancer. [Clinical Guidelines]	DIHTA project: start 2000; end 2001	Ass. Prof. Dr Inge-Lis Kanstrup
17. Positron Emission Tomography (PET) scanning ("We will assess the need, location and optimal use of PET scanning in cancer") (HTBS)	By March 2001, NHS Scotland will publish a comprehensive Scottish Cancer Plan that will include national targets for maximum waiting times.	NA
18. The Use of PET and MRI to Assess the Effects of Anti-Neoplastic Therapy on Tumor Associated Vasculature	NCI: 98-C-0163 prospective study (?active)	NA
19. Phase II Study of the Role of Anti-CEA Antibody Immunoscintigraphy & PET in the Localization of Recurrent Colorectal Carcinoma in Patients with Rising Serum CEA Levels in the Absence of Imageable Disease by Conventional Modalities	NCI: 97-C-0068 (?active)	NA

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Other

Project	Reference Number and Dates	Primary Contact
1. Improved Methods Using High Performance Computing For Triple Oxygen Pet In Critically Ill Patients	NRR Project: N0544074220 Start date: 01/11/1999, End date: 31/10/2002	Dr T Adrian Carpenter
2. A programme of radiopharmaceutical development for PET and SPECT.	NRR Project: N0016028453 Start date: 01/01/1993, End date: 31/12/2000	Professor Vic W Pike
3. Positron Emission Tomography: an economic evaluation [Systematic Review]	DAHTA at DIMDI--German HTA	(Completed Project not yet published)
4. Positron Emission Tomography [Systematic Review]	DAHTA at DIMDI--German HTA	Perleth M.

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Appendix V

Glossary of Organizations

AETMIS	Agence d'Évaluation des Technologies et des Modes Intervention en Santé (formerly CETS), Montreal (Quebec)
AETS	Agencia de Evaluación de Tecnologias Sanitarias, Madrid (Spain)
AHCPR	Agency for Health Care Policy and Research, Center for Practice and Technology Assessment (USA)
AHFMR	Alberta Heritage Foundation for Medical Research, Edmonton (Alberta)
BCBSA TEC	Blue Cross-Blue Shield Association Technology Evaluation Center (USA)
CAHTA	Catalan Agency for Health Technology Assessment, Barcelona (Spain)
CCOHTA	Canadian Coordinating Office for Health Technology Assessment, Ottawa (Ontario)
CEDIT	Comité d'Evaluation et de Diffusion des Innovations Technologiques Assistance. Publique Hôpitaux de Paris, Paris (France)
ECRI	Emergency Care Research Institute, Plymouth Meeting (Pennsylvania)
Hayes	Hayes, Inc., Lansdale (Pennsylvania)
ICES	Institute for Clinical Evaluative Sciences, Toronto (Ontario)
ICP	Institute for Clinical PET (USA)
MOH	(Ontario) Ministry of Health
MSAC	Medical Services Advisory Committee, Canberra (Australia)
NCCHTA	National Coordinating Centre for Health Technology Assessment, Southampton (UK)
NHSCRD	NHS Centre for Reviews and Dissemination University of York, York (UK)
OMA	Ontario Medical Association, Toronto (Ontario)
OSTEBA	Basque Office for Health Technology Assessment, (Spain)
VATAP	Veterans Affairs, Technology Assessment Program, Boston (USA)

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Glossary of Terms

511 keV Collimation	Type of modified PET with a collimator adapted for the higher energies of PET technology retrofitted into a conventional gamma camera.
Annihilation Reaction	The conversion of mass into light energy (2 photons) as a result of collision of a positron from the radiopharmaceutical with an electron within the body's tissues.
Coincidence Imaging	1. type of modified PET primarily involving retrofitting gamma cameras with new electronics and software 2. unique feature of PET technology based on near simultaneous arrival of photons at opposite poles of the detector, allowing all non-coincident events to be interpreted as noise
Collimator	Lead sieve that serves to filter out photons originating directly from the region of interest from those produced by scatter. The size and shape of the holes also factors into the camera's sensitivity and specificity. (bigger holes=more sensitive, but less specific)
Computed Tomography (CT)	the process of reconstructing a 2- or 3-D image from its 1-D projections from all angles
Crystals	Three main types 1. BGO (bismuth germinate)—best for F-18 and C-11 (isotopes with longer t1/2 lives) 2. CeF3 (cerium fluoride) or BaF2 (barium fluoride)—best for TOF systems 3. NaI (sodium iodide)—better suited for SPECT than PET scanners Newer LSO—lutetium oxyothosilicate
Detector	crystal (eg BGO) + photomultiplier tubes + electronics
Fwhm	Full width half maximum (a standardized camera setting to allow comparison of resolution and other camera specifications)
FDG	Fluorodeoxyglucose
F-18	Fluorine-18
Gamma Camera	Conventional nuclear medicine imaging device

keV	Kilo-electron-volt (a unit of energy)
MRI	Magnetic Resonance Imaging
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography: a unique advancement in nuclear medicine technology that facilitates imaging of metabolic function as opposed to structure. Using crystal sensors and electronics that are specifically designed to exclude all but near simultaneous arrival of 2 photons originating from the region of interest (coincidence detection) from opposite directions. PET offers improved resolution and image quality over SPECT and traditional nuclear medicine imaging.
Photo-multiplier tubes (PMT)	Portion of camera detector, downstream of the crystals that collects the visible light created from the interaction of the non-visible light of the photon with the crystal.
Positron	Negatively charged electron (antimatter)
ROI	Region of interest
Scintillator	Portion of the camera that contains the crystals (upon which the quality of the images is highly dependent) and the photomultiplier tubes
SPECT	Single photon emission computed tomography
SPN	Solitary pulmonary nodule or solitary lung nodule (SLN)
TOF	Time of Flight PET: a refinement of coincidence imaging that uses the minute differences in arrival times at the detector between coincident photons to increase the accuracy of image reconstruction.

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Glossary of Epidemiological Terms

blinded (masked) study	Observer(s) and/or subjects are unaware of the group to which the subjects are assigned. When both observer and subjects are unaware of treatment assignments, this if referred to as a double-blind trial.
predictive value	In screening and diagnostic tests, the probability that a person with a positive test is a true positive (i.e., does have the disease) is referred to as the 'positive predictive value' or the 'predictive value of a positive test'. Alternatively, the 'negative predictive value' or the 'predictive value of a negative test' is the probability that a person with a negative test does not have the disease.
randomized, controlled trial (RCT)	An epidemiologic experiment in which subjects in a population are randomly allocated into groups, usually call study and control groups, to receive or not to receive an experimental preventive or therapeutic procedure, maneuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. Randomized controlled trials are generally regarded as the most scientifically rigorous method of evaluating the benefits of therapies available in epidemiology.
sample/sampling bias	Systematic error due to study of a nonrandom sample of a population.
selection bias	Errors due to systematic differences in characteristics between those who take part in a study and those who do not. Selection bias invalidates conclusions and generalizations that might otherwise be drawn from such studies.
Sensitivity	The proportion of truly diseased persons in the screened population who are identified as diseased by the screening test.
Specificity	The proportion of truly nondiseased persons who have a negative test. It is a measure of the probability of correctly identifying a nondiseased person with a screening test. (synonym: true negative rate).

Source: Adapted from 'A Dictionary of Epidemiology', 4th Ed., edited by John M. Last, OUP 2001