

Health Policy Advisory Committee on Technology

Technology Brief

Gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography scans for diagnosing and restaging recurrent prostate cancer

August 2016



Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures –
Surgical



Royal Australasian
College of Surgeons

HealthPACT

emerging health technology

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For further information, contact the HealthPACT Secretariat at:

HealthPACT Secretariat
c/o Healthcare Improvement Unit, Clinical Excellence Division
Department of Health, Queensland
Level 2, 15 Butterfield St
HERSTON QLD 4029

Postal Address: GPO Box 48, Brisbane QLD 4001

Email: HealthPACT@health.qld.gov.au Telephone: +61 7 3328 9180

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This Brief was commissioned by Queensland Health, in its role as the Secretariat of the Health Policy Advisory Committee on Technology (HealthPACT). The production of this Brief was overseen by HealthPACT. HealthPACT comprises representatives from health departments in all States and Territories, the Australian and New Zealand governments and MSAC. It is a sub-committee of the Australian Health Ministers' Advisory Council (AHMAC), reporting to AHMAC's Hospitals Principal Committee (HPC). AHMAC supports HealthPACT through funding.

This brief was prepared by Dr Tom Vreugdenburg from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

Summary of findings

Gallium-68 prostate specific membrane antigen (Ga68-PSMA) is a novel tracer for combined imaging with positron emission tomography and computed tomography (PET/CT), which is rapidly diffusing into the Australian private sector. Due to its relatively short half-life (approximately 68 minutes), Ga68-PSMA must be used shortly after production. It is currently being investigated for staging intermediate and high-risk prostate cancer and for re-staging recurrent prostate cancer in patients who experience a rise in prostate specific antigen (PSA) serum level following definitive therapy. Current methods for investigating a clinical recurrence in this population have limited efficacy for diagnosing or restaging recurrent disease. Ga68-PSMA PET/CT, however, may provide additional information or replace a raft of conventional imaging modalities, including bone scans, CT, magnetic resonance imaging (MRI) and C11/F18-fluoromethylcholine PET/CT.

Three studies were identified that compared the diagnostic accuracy of Ga68-PSMA PET/CT with a valid reference standard in patients with recurrent prostate cancer.¹⁻³ The reported sensitivity of Ga68-PSMA PET/CT ranged from 77 per cent to 94 per cent, and specificity ranged from 93 per cent to 100 per cent. Only one study with a valid reference test included a relevant comparator test, in which Ga68-PSMA PET/CT demonstrated higher sensitivity (87% vs 71%), specificity (93% vs 87%), PPV (76% vs 67%) and NPV (97% vs 89%) compared to F18-labelled choline PET/CT.²

In addition to accuracy, three studies investigated the impact of Ga68-PSMA PET/CT on patient management.⁴⁻⁶ The most recent prospective study reported a major change to the management plan in 20 of 70 patients (29%) due to Ga68-PSMA.⁶ One study found that Ga68-PSMA PET/CT changed the management strategy in a moderate or major way for 24 of 38 (63%) patients.⁴ In the final study, the initial management plan based on CT, MRI or bone scintigraphy was changed in 29 of 57 (51%) patients, due to additional information provided by Ga68-PSMA.⁵ Changes to patient management across these studies included expanding the planned volume or area of radiotherapy, the addition of androgen deprivation therapy, or the cancellation of radiotherapy in favour of systemic therapy.

Although a strong focus of existing and ongoing research is on the use of Ga68-PSMA PET/CT to identify and restage recurrent prostate cancer, it is also being investigated for use in pre-operative staging to inform surgery and radiotherapy planning. The evidence suggests that Ga68-PSMA PET/CT is sensitive to detect prostate cancer, but it is not yet clear where it is best placed in the treatment pathway, i.e. either before or after surgery, or both. In addition, Ga68-PSMA PET/MRI is being investigated as a potential alternative to Ga68-PSMA PET/CT, but the clinical results to date suggest the technology is in the early stages of investigation.

HealthPACT Advice

HealthPACT noted that, compared to F18 PET/CT imaging, the diagnostic accuracy of detecting metastases at diagnosis or at recurrence of prostate cancer is improved when Ga68-PSMA PET/CT imaging is used. Although the current evidence base is small, studies have described meaningful changes in patient management with reduced morbidity. It should be noted access to Ga68-PSMA PET/CT would be limited to patients in major centres due to the short half-life of the tracer.

Ga68-PSMA PET/CT is disseminating rapidly in Australian clinical practice despite limited patient outcome and cost-effectiveness data. There are currently around 30 sites in Australia providing this investigation, which should provide sufficient capacity for the predicted annual number of recurrences of prostate cancer. In addition, where Ga68-PSMA PET/CT sits in clinical practice, whether it should be used as a primary or secondary diagnostic tool, has yet to be determined. HealthPACT does not support public investment in Ga68-PSMA PET/CT in clinical practice at this time, and recommends that data on patient outcomes, treatment pathways and cost-effectiveness be collected under the auspices of a controlled clinical trial. Given the rapid dissemination of this technology, HealthPACT recommends that the evidence around Ga68-PSMA PET/CT be reviewed in 12 months.

Technology, Company and Licensing

Register ID	WP238
Technology name	Ga68 prostate-specific membrane antigen (PSMA) PET/CT scans
Patient indication	Patients suspected of having a recurrence of prostate cancer following radical prostatectomy

Description of the technology

The first signs of prostate cancer recurrence following surgical removal of the prostate gland (radical prostatectomy) can be detected by a rising prostate-specific antigen (PSA) level in the blood.⁷ PSA is a protein produced by prostate cells, which can be over produced due to infection, enlargement, inflammation, or cancer of the prostate gland. Although a rising PSA level may identify a possible recurrence before clinical symptoms develop, a PSA score alone cannot differentiate between local, regional or systemic recurrence of disease.⁸ Therefore, advanced imaging techniques are required to identify the site of recurrence, in order to target therapies appropriately.

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is expressed by nearly all prostate cancers, particularly aggressive, metastatic and hormone-refractory carcinomas.^{7,8} When a molecule that binds to PSMA is combined with the radioisotope gallium-68 (Ga68), the resultant radiopharmaceutical (known as Ga68-PSMA) allows a positron emission tomography (PET) scanner to identify prostate cancer cells.⁹ Ga68-PSMA is reportedly able to detect small, recurrent prostate tumours when PSA rises in the blood following radical prostatectomy.⁹⁻¹¹ If a follow-up scan detects the presence of recurrent cancer, treatment options may include further local treatment with additional surgery or radiation therapy, or systemic androgen deprivation therapy.¹²

PET imaging can detect energy emitted by tracers known as radiopharmaceuticals. Radiopharmaceuticals are designed to identify specific cell types, effectively allowing a PET scanner to detect cells that have a particular function.¹³ While PET is able to identify the uptake of radiopharmaceuticals in specific cell types, it cannot show the anatomical structures in which the tracer is present. To provide this detail, the results of PET scans are often overlapped with a computed tomography (CT) image, which sharpens the PET scan and provides a high-resolution image of the patient's anatomy.¹⁴ Therefore, a combined PET/CT image provides information about the presence of cells with a specific function, as well as their precise location within the body. An example of a CT, PET and combined PET/CT image of prostate cancer using a radiopharmaceutical tracer is provided in Figure 1.

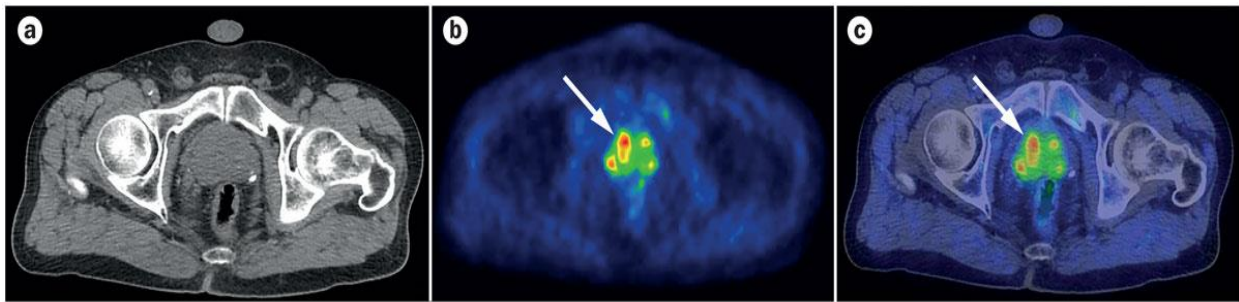


Figure 1 Images of a patient with prostate cancer using (a) CT, (b) PET, and (c) combined PET/CT. Arrows indicate the uptake of a radioisotope tracer within prostate cancer cells (Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Urology*,¹³ copyright 2015)

Company or developer

Currently, there does not appear to be a dedicated supplier of Ga68-PSMA tracers in Australia. Due to its short half-life (approximately 68 minutes), Ga68-PSMA must be used shortly after production. Consequently, it is primarily produced in-house by individual hospitals/private clinics that have an on-site Ga68 generator (Personal communication, University of Melbourne, May 2016). Currently, at least four Ga68 generators are available in Australia (Personal communication, University of Sydney, May 2016), which are manufactured by:

1. Eckhert & Ziegler (Berlin, Germany), distributed in Australia by Imaxeon Pty Ltd (Silverwater, New South Wales, Australia)
2. Isotopen Technologien München AG (Berlin, Germany), distributed by the Australian Nuclear Science and Technology Organization (Hawthorn, Victoria, Australia); and
3. IDB Holland bv (Baarle-Nassau, the Netherlands), distributed in Australia by Global Medical Solutions (Arncliffe, New South Wales, Australia).
4. IRE - IRE EliT (Fleurus, Belgium), distributed in Australia by Global Medical Solutions, Ltd (Arncliffe, New South Wales, Australia)

Reason for assessment

Surgical and radiotherapy treatments for prostate cancer are invasive, and guidelines for surveillance following radical prostatectomy are lacking. In the context of a rising PSA level following radical prostatectomy or radiotherapy, Ga68-PSMA PET/CT imaging has the potential to improve the detection and restaging of remnant or metastatic prostate tumours. In turn, this could improve the effectiveness of therapeutic management, and potentially reduce the use of invasive interventions in cases where watchful waiting would be more appropriate. This technology is currently diffusing into the public and private clinical sectors in Australia, but has not yet been assessed for safety or effectiveness.

Stage of development in Australia

- | | |
|--|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input checked="" type="checkbox"/> Nearly established | |

Licensing, reimbursement and other approval

According to Item 6 of Schedule 5 in the *Therapeutic Goods Regulations 1990* (the Regulations), therapeutic goods that are dispensed, or compounded without advance preparation (extemporaneously), for a particular person are exempt from listing on the Australian Register of Therapeutic Goods (ARTG).¹⁵ Radiopharmaceuticals such as Ga68-PSMA, including their constituent components, fall into this category.^{15, 16} Manufacturing, laboratory and dispensary equipment used in the preparation of therapeutic goods, such as a Ga68 generator, are exempt under Item 7 of Schedule 5 of the Regulations.¹⁵

68-Ga-PSMA PET/CT scans for recurrent prostate cancer are not currently reimbursed through the Medicare Benefits Schedule (MBS). They are currently paid for out-of-pocket by patients in the private system or by individual hospitals in the public system. In addition, there are a number of ongoing clinical trials of Ga68-PSMA PET/CT in Australia, which are funded by various bodies (Movember, Epworth Medical Foundation, Victoria, Australia) and industry sponsorship (Theranostics Australia, Western Australia, Australia). Although combined PET/CT items are not currently reimbursed through Medicare for prostate imaging, the CT component of the scan can be claimed through MBS item 56501 if a dedicated diagnostic CT is also performed at the same time: COMPUTED TOMOGRAPHY - scan of upper abdomen and pelvis without intravenous contrast medium, not for the purposes of virtual colonoscopy, not being a service to which item 56801 or 57001 applies (R) (K) (Anaes.), with a fee of \$385.

Australian Therapeutic Goods Administration approval

- | | |
|--|---|
| <input type="checkbox"/> Yes | ARTG number (s): Ga68 isotopes, PSMA cartridges and Ga68 generators are exempt from listing on the ARTG |
| <input type="checkbox"/> No | |
| <input checked="" type="checkbox"/> Not applicable | |

Technology type

Diagnostic

Technology use

Diagnostic

Patient Indication and Setting

Disease description and associated mortality and morbidity

The prostate gland is found near the base of the bladder and forms part of the male reproductive system (Figure 2). The signs and symptoms of prostate cancer may differ depending on the stage of the disease. In early stages, there may be no symptoms. However, as the disease progresses, symptoms may include the frequent or sudden need to urinate, difficulty urinating, discomfort when urinating, blood in the urine or semen, or pain in the lower back, upper thighs or hips.¹⁸ The majority of these symptoms are caused by an enlarged prostate, which may be due to prostate cancer or as a natural consequence of ageing.¹⁷ Therefore, accurate diagnostic tests are needed to rule out non-cancerous causes of common urinary disturbances.

Error! Reference source not found.) It is responsible for producing the majority of seminal fluid that protects and enriches sperm.¹⁷ The term 'prostate cancer' refers to a group of diseases, characterised by the abnormal and uncontrolled growth of cells in the prostate gland. The three main types of prostate cancer are carcinoma, other specific malignant neoplasms and unspecified malignant neoplasms.¹⁷

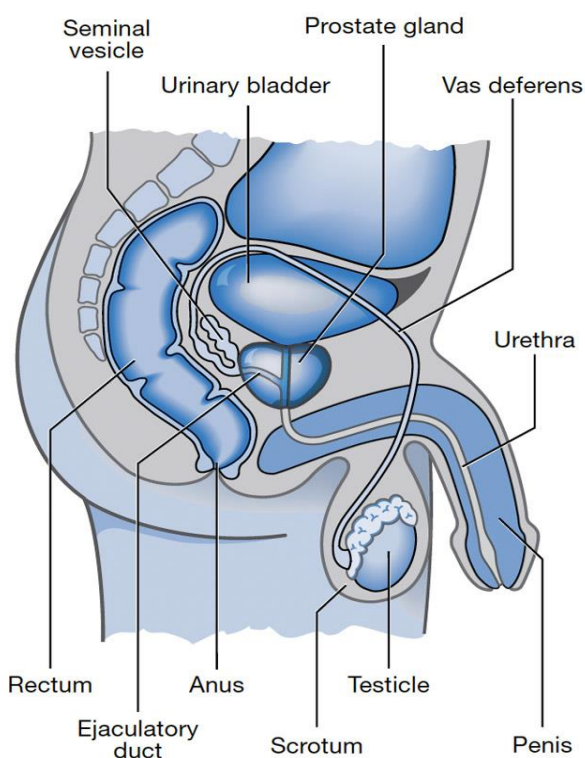


Figure 2 Anatomy of the prostate (Reprinted with permission from the Prostate Cancer Foundation of Australia, copyright 2016)

The signs and symptoms of prostate cancer may differ depending on the stage of the disease. In early stages, there may be no symptoms. However, as the disease progresses, symptoms may include the frequent or sudden need to urinate, difficulty urinating, discomfort when urinating, blood in the urine or semen, or pain in the lower back, upper

thighs or hips.¹⁸ The majority of these symptoms are caused by an enlarged prostate, which may be due to prostate cancer or as a natural consequence of ageing.¹⁷ Therefore, accurate diagnostic tests are needed to rule out non-cancerous causes of common urinary disturbances.

Prostate cancer is the second most common cause of cancer-related death in Australian men behind lung cancer (N = 5,150 deaths) responsible for 3,390 deaths in 2014. The age-standardised mortality rate was 27.6 per 100,000 in 2012, accounting for 3,079 deaths.¹⁷ Similarly, it is the third most common cause of cancer-related death in New Zealand, responsible for 607 deaths in 2012, behind colorectal cancer (N = 664 deaths) and lung cancer (N = 891 deaths).¹⁹ Although prostate cancer is a significant contributor to morbidity and mortality, over 90 per cent of men diagnosed in 2006-2010 were still alive five years after diagnosis, and 84 per cent were still alive 10 years after diagnosis.¹⁷

Biochemical recurrence, defined as a rise in blood PSA level following definitive treatment for prostate cancer (e.g. radical prostatectomy), is a common outcome in prostate cancer.¹² The threshold used to define biochemical recurrence is reported variably in the literature, and differs depending on which treatment was used to treat the primary cancer. In general, a rise in PSA of between 0.2 and 0.4 ng/mL is broadly accepted as indicating a biochemical recurrence of prostate cancer following radical prostatectomy.^{20, 21} Identifying recurrent cancer early has important implications for patients, as earlier initiation of therapy improves patient outcomes.²⁰

Number of patients

Australian incidence of prostate cancer

Prostate cancer is the most commonly diagnosed cancer in Australia, accounting for 17,050 new cases in 2014.²² The age-standardised incidence rate of prostate cancer in Australia was 167.3 per 100,000 in 2011, accounting for 19,993 new cases (Figure 3).

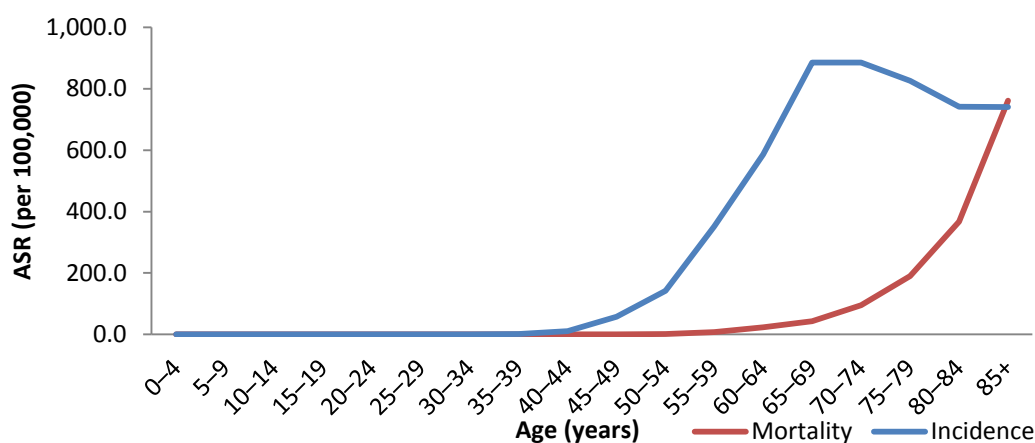


Figure 3 Australian age-standardised rate (ASR) of incidence and mortality of prostate cancer by age, 2012*

*Data from Australian Institute of Health and Welfare, Australian Cancer Incidence and Mortality books.²⁴

In terms of treatment, there were 32,596 separations for prostatectomy across both public and private hospitals in Australia in 2014-15.²³ The 2013/14 National Hospital Mortality Database recorded 32,083 prostatectomies, of which 8,653 were open or closed radical prostatectomies.

New Zealand incidence of prostate cancer

Prostate cancer is the most common cause of cancer in New Zealand men, accounting for 3,155 new diagnoses in 2014. The age-standardised incidence rate (ASR) was 92.8 per 100,000 in 2014, a small decline since 2012 of 98.2 per 100,000.²⁵ This decline is attributable to the rise in population, as the number of new diagnoses (N = 3,129) was similar. Men aged 65-69 had the highest ASR, of 744.8 per 100,000. The incidence of prostate cancer rises sharply from 50-54 years of age, peaking at 60-64. In terms of burden on the hospital system, there were 2,406 separations for malignant prostate cancer in 2012/13 across both private and public systems.^{26, 27} In total, there were 856 open and 465 laparoscopic prostatectomies performed. However, it is not known whether the laparoscopic procedures were for radical prostatectomy.

Population of interest: incidence of recurrence

There is currently no robust hospital data from Australia or New Zealand on the risk of recurrence of prostate cancer after radical prostatectomy.¹⁷ Estimates in the literature suggest that between 10 and 40 per cent of men who have radical therapy, such as prostatectomy, will experience a recurrence of prostate cancer within five years.^{28, 29} Based on this estimate, and the number of presumed radical prostatectomies noted above, it is estimated that each year between 865 and 3,461 men in Australia, and 132 and 530 men in New Zealand, may be eligible for a follow-up scan with Ga68-PSMA PET/CT due to a recurrence of prostate cancer after surgery.

Speciality

Nuclear Medicine

Technology setting

General Hospital; Private Community Practice

Impact

Alternative and/or complementary technology (substitution)

If Ga68-PSMA PET/CT scanning for prostate cancer proves to be more sensitive and cost effective than existing methods, it will likely replace them rather than be used as an additive technology in the majority of cases (depending on access to the isotope).

Current technology

Australian clinical practice guidelines on the optimal surveillance of recurrence after radical prostatectomy are currently unavailable. Guidelines from the National Comprehensive

Cancer Network (NCCN) have been adopted in several Australian hospitals.³⁰ Based on these guidelines, follow-up investigation after radical prostatectomy is indicated in patients who:

1. have a detectable PSA score, or, who have an undetectable PSA score that rises to detectable levels on two or more occasions; and
2. are suitable candidates for additional therapy.³⁰

A rising PSA level following definitive therapy is indicative of recurrence; however, it is rarely associated with symptoms or findings at physical examination. To appropriately treat any recurrence, it is essential to define its location. Assessments have commenced of the prognostic value of combinations of measures, including, pre-treatment PSA level, Gleason scores, PSA doubling time, PSA kinetics and the presence or absence of surgical margins.^{21, 30, 31} However, at this time, predictive models are insufficient to inform treatment or diagnosis. In particular, it is difficult identify whether a recurrence is localised to the prostate bed or has metastasised to other areas of the body. Therefore, the work-up of patients with biochemical recurrence may include a combination of PSA testing, trans-rectal ultrasound-guided biopsy, and other anatomical or functional imaging.³⁰

Trans-rectal ultrasound (TRUS) and TRUS-guided biopsy

TRUS uses high-frequency sound waves to produce images of the prostate and surrounding tissues. It has been reported that TRUS is not sensitive or specific enough to differentiate recurrence from post-surgical scarring.²¹ It is; however, more sensitive (and less specific) than digital rectal examination for identifying local recurrence (confirmed by biopsy).³² TRUS-guided biopsy of the prostate bed is traditionally the procedure of choice for defining local recurrence. However, it is an invasive procedure that may require multiple biopsies, and it cannot confirm the presence of distant disease. TRUS-guided biopsy after definitive therapy has a reported sensitivity and a specificity of approximately 75 and 66 per cent, respectively.³³

Bone scans

Advanced prostate cancer often spreads to the bones, and as such a bone scan may be needed in patients with a suspected recurrence after prostatectomy.²¹ A radionuclide bone scan, also known as bone scintigraphy, is a nuclear imaging technique used to identify the spread of cancer metastases to the bones.³⁰ Bone scans involve the use of radioactive tracers, which are selectively taken up by areas of increased bone activity. The distribution of the tracer within the patient's skeleton is visualised using a PET or single-photon emission CT (SPECT) scanner. Regions of high tracer uptake indicate a potential site of metastatic disease. Bone scans are of limited use in patients who have a low or slowly rising PSA score after prostatectomy. Less than five per cent of bone scans are positive until the PSA value is above 40-45ng/mL, at which point disease may be widespread.³⁴ Tests with a greater

sensitivity may be able to detect distant metastases before bone scans, offering opportunities for earlier treatment.

Computed Tomography (CT)

CT scans use x-rays to provide an image of a patient's anatomy, which may identify a local or distant spread of disease. Like bone scans, CT is more commonly used to detect metastatic disease in the lymph nodes or bones; however, it is reportedly of limited utility in identifying local recurrence.^{32 35} It has been reported that CT is positive in less than 15 per cent of men with a biochemical recurrence after radical prostatectomy.³³

Magnetic Resonance Imaging (MRI)

MRI uses a magnetic field and pulses of radio wave energy to create high-contrast images of soft tissue, which can be performed with or without contrast agents. In terms of identifying local recurrence, MRI can be performed with an endorectal coil to improve imaging of the pelvis. There are a range of sophisticated MRI techniques available; however, guidelines do not recommend one specific MRI technique over another for evaluating patients with a suspected recurrence.³⁰ It has been reported that the combination of T2-weighted imaging and dynamic contrast-enhanced MRI with endorectal coils has sensitivity of 84 to 97 per cent and specificity of 74 to 89 per cent for detecting local recurrence of prostate cancer. However, the role of MR imaging for detecting distant recurrence is not clear.³⁶

Positron Emission Tomography

Hybrid imaging technologies, including PET/CT with carbon-11 (C11) or fluorine-18 (F18) labelled choline tracers, have also been used to evaluate patients with biochemical failure after radical prostatectomy.³⁶ One study has suggested that MRI and PET/CT may be complementary imaging modalities in identifying recurrent disease with MRI being superior in the detection of local recurrence, whilst PET/CT displays good sensitivity for the diagnosis of lymph node disease. Both modalities appear to be useful in the identification of pelvic bone metastases.³⁶ F18-labelled choline PET/CT scans are commonly used to investigate a potential prostate cancer recurrence.³⁷ A range of other tracers used in PET or SPECT are reported in the literature; however, the frequency of their use in Australia is unclear.³³

Diffusion of technology in Australia

PET/CT scanners are available at selected public and private radiology providers throughout Australia; however, not all have access to a Ga68 generator. The Ga68-PSMA tracer is currently diffusing rapidly within the Australian public and private clinical sector, and is the focus of several ongoing clinical trials in Australian hospitals. Approximately 25 to 30 sites currently offer Ga68-PSMA scans (Personal communication, University of Sydney, May 2016), mainly in New South Wales, Victoria, and Queensland and Western Australia.

International utilisation

Country	Level of Use		
	Trials underway or completed	Limited use	Widely diffused
Australia	✓	✓	
Austria	✓		
Finland	✓		
Germany		✓	
Israel*	✓		✓
Italy	✓		
Japan	✓		
Netherlands		✓	
Russia		✓	
South Africa		✓	
Turkey	✓	✓	
United States of America	✓		
Uruguay	✓		

*Ga68-PSMA PET/CT was recently reimbursed by the government in Israel for (1) staging of intermediate and high-risk prostate cancer and (2) biochemical recurrence (Personal communication, University of Melbourne, May 2016).

Cost infrastructure and economic consequences

Currently there is no Medicare funding for Ga68-PSMA PET/CT for prostate cancer. Some private radiology clinics are providing the service at an out-of-pocket cost of \$600, with bulk billing of the CT component (MBS Item 56501, 75% rebate \$288.75).³⁸ The cost of providing a Ga68-PSMA PET/CT service depends on patient throughput, as the technique relies on expensive capital equipment by way of a PET/CT scanner (\$2M to \$3M) and a Ga68 generator (\$40,000 to \$85,000 depending on generator size and GMP grade) (Personal communication, University of Sydney, May 2016). In addition, significant staff costs, consumable costs, and other setup and logistical costs should be considered. As such, the costs of running a Ga68-PSMA PET/CT service vary considerably, according to:

Staff costs (time)

- Compounding pharmacist/nuclear radiopharmacist
- Nuclear technologist administering tracer/conducting scan
- Radiologist/nuclear medicine specialist reporting

Capital costs

- PET/CT scanners plus ongoing maintenance
- Ge68/Ga68 generator
- PSMA automated synthesis unit

Consumable costs

- Ga68 isotope production
- PSMA cartridges
- Ga68-PSMA tracer synthesis (automated or manual)
- Catheter/IV for administration of contrast

Other costs

- Setup and storage of the Ga68 generator
- Quality control measures

Estimated cost to the healthcare system

Estimating the total cost of Ga68-PSMA PET/CT scans is difficult, due to variation in patient throughput, generators used, radioisotope synthesis methods used and staff available to prepare and administer the tracer. In the absence of published or publically available information regarding the cost components of conducting a Ga68-PSMA scan, clinical advice estimates the per-patient costs related to consumables may range between \$300 and \$500, and the per-patient costs of the synthesis unit may range between \$150 and \$200.

Therefore, based on informed estimates, the cost per-patient will range between \$450 and \$700. Factoring in staff and additional equipment (PET/CT scanner costs between \$2M and \$3M) increases the cost significantly (personal communication, University of Sydney, May 2016).

The recently announced “ProPSMA” trial, funded by the Prostate Cancer Foundation of Australia and Movember, will conduct an economic analysis of Ga68-PSMA PET/CT for cancer diagnosis and impact on management.³⁹ This trial may provide a more robust estimate of the true cost of the technique.

Ethical, cultural, access or religious considerations

The Ga68 isotope is produced using a machine called a gallium generator, and has a half-life of approximately 68 minutes.¹⁰ After Ga68 is produced, it is combined with PSMA in a process that can take between 25 to 35 minutes.^{9,40} Due to the short half-life of the Ga68 isotope, combined with the additional time to compound the tracer, Ga68-PSMA must be produced close to where it is to be used. As such, Ga68-PSMA is currently only available at locations with an on-site Ga68 generator and access to a PET/CT scanner, which restricts access to major urban centres. Similarly, PSMA cartridges can be stored and transported with ease, but require experienced and qualified staff for extemporaneous compounding. As such, it is unclear whether there is a sufficiently trained workforce or PET availability in rural and remote areas of Australia to provide this service.

As with all CT services, patients are exposed to ionising radiation at doses that are equivalent to 500 chest radiographs.⁴¹ It is important that patients, and caregivers, are made aware of the risks associated with CT radiation so that they can make an informed decision about whether to undergo CT or not.

Evidence and Policy

Effectiveness

The use of Ga68-PSMA PET/CT for the diagnosis and staging of recurrent prostate cancer is a rapidly developing area of research. Based on the scope of this Technology Brief, studies were selected based on the following inclusion criteria:

1. **Population**: patients with a biochemical recurrence of prostate cancer following radical prostatectomy
2. **Intervention**: Ga68-PSMA PET/CT imaging
3. **Comparator**: CT, ultrasound (US), Bone scan, MRI, PET/MRI, or PET/CT with other tracers
4. **Outcomes**: diagnostic accuracy (including sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), detection rate) and impact on patient management
5. **Reference test**: biopsy with histological confirmation, or adequate patient follow-up.

Although many of the identified studies met inclusion criteria 1-3, the vast majority did not compare the results of Ga68-PSMA PET/CT with histological confirmation or follow-up, and therefore were unable to report measures of diagnostic accuracy. The absence of an appropriate reference standard is a common limitation in the evidence for existing radioisotopes, as well as existing imaging modalities such as CT and bone scans.³⁷ In total, one study was identified that met all of the inclusion criteria.⁴ As such, the inclusion criteria were broadened to include studies without a relevant comparator, or that reported a mixed population. The results of these studies are presented based on the outcomes of interest, including diagnostic accuracy (three studies) and impact on patient management (three studies).

Diagnostic accuracy of Ga68-PSMA PET/CT

Three studies investigated the diagnostic accuracy of Ga68-PSMA PET/CT with confirmation by a valid reference standard.¹⁻³ Design characteristics of the included diagnostic accuracy studies are described in Table 1. Only one study with histological confirmation of the accuracy results also compared the test to a relevant comparator.²

Sample demographics from included studies are presented in Table 2. Although the inclusion criteria, comparators, and application of reference standards varied slightly across studies, baseline demographic characteristics of the sample populations were similar; In particular, median preoperative Gleason score, age, and PSA score at the time of imaging. The largest difference was the treatment status of patients at the time of scanning, which varied greatly. In particular, the proportion of patients that had a radical prostatectomy is unknown in the trial by Sahlmann et al (2015).³

Table 1 Characteristics of included studies investigating the diagnostic accuracy Ga68 PSMA PET/CT

Study design	Pfister et al 2016 ²	Sahlmann et al 2015 ³	Afshar-Oromieh et al 2015 ¹
Level of evidence	Level III-I diagnostic	Level III-2 diagnostic	Level III-2 diagnostic
Study design	Non-consecutive, retrospective, blinded comparison with a valid reference standard	Consecutive, retrospective, unblinded comparison with a valid reference standard	Non-consecutive, retrospective, unblinded comparison with a valid reference standard
Location (centres)	Germany (1 centre)	Germany (1 centre)	Germany (1 centre)
Inclusion criteria	Patients who underwent salvage lymphadenectomy after PET/CT	Patients with newly diagnosed PCa or recurrence of PCa who underwent PET/CT	Patients who underwent Ga68-PSMA after conventional treatment*
Participants	Ga68-PSMA PET/CT = 28 F18-labelled choline = 38	New PCa = 12 Recurrent PCa = 23	Total sample = 319 Biopsy-confirmed = 42
Intervention	Ga68-PSMA PET/CT	Ga68-PSMA PET/CT	Ga68-PSMA PET/CT
Comparator	F18-labelled choline PET/CT	N/A	N/A
Reference standard	Biopsy with histology	Biopsy with histology	Biopsy with histology
Outcomes	Primary: Diagnostic accuracy per-patient and per-lesion	Primary: Diagnostic accuracy Secondary: SUVmax, T/B ratios	Primary: Diagnostic accuracy Secondary: SUVmax

PCa: prostate cancer; PET: positron emission tomography; CT: computed tomography; PSMA: prostate specific membrane antigen; Ga: gallium; T/B ratio: lesion/background ratio; SUV: selective uptake volume; *226 of 319 patients had prostatectomy prior to Ga68-PSMA, 28 of 319 patients had Ga68-PSMA scan before treatment, to identify potential metastases.

Table 2 Sample demographics of included diagnostic accuracy studies

Demographic characteristics	Pfister et al 2016 ²	Sahlmann et al 2015 ³	Afshar-Oromieh et al 2015 ¹
Number of patients	Ga68-PSMA = 28 F18-labelled choline = 38	New PCa = 12 Recurrent PCa = 23	Total sample = 319 Biopsy-confirmed = 42
Gleason score	≤ 7 = 34 > 7 = 20 Unknown = 12	Median = 7 (range = 6 to 9)	Median = 7 (range 5 to 10)
PSA level @ imaging	Median = 2.5 µg/l (range 0.3 to 8.4 µg/l)	Median = 2.4 µg/l (range 0.13 to 30.0 µg/l)	Median = 4.59 µg/l (range 0.01 to 41395 µg/l)
Age	Median = 66 years (range 46 to 79 years)	Median = 71 years (range 49 to 78 years)	Median = 68 years (range 46 to 86 years)
Prior treatment	Prostatectomy = 56 Radiation therapy = 8 HIFU = 2	Prostatectomy = unclear Radiation therapy = unclear ADT = 4	Prostatectomy = 226 Radiation therapy = 177 ADT = 86

ADT: androgen deprivation therapy; PCa: prostate cancer; CT: computed tomography; PSMA: prostate specific membrane antigen; PET: positron emission tomography; T/B: lesion/background ratio; PSA: prostate specific antigen; HIFU = high intensity focussed ultrasound.

In Ga68-PSMA studies, the maximum standardised uptake value (SUVmax) is used to measure the uptake of the tracer by prostate cancer cells. Higher SUVmax values indicate a greater likelihood of cancer being present; however, biopsy is needed to confirm whether a site of increased uptake is cancerous.³ SUVmax is commonly applied in clinical practice as a semi-quantitative way of identifying potential sites of a tumour recurrence, and is considered to be more reproducible and reliable than the mean uptake (SUVmean).^{1, 3} As demonstrated in Table 3, confirmed sites of recurrence were associated with higher

SUVmax values. In addition, Sahlmann et al demonstrated that SUVmax increased significantly between one-hour post injection and three hours post-injection.³ This may indicate a benefit for delayed imaging after administration of Ga68-PSMA contrast, but noting that a greater amount of contrast is required to produce reliable images at three hours post injection.³ Importantly, effective cut-offs to differentiate metastatic and normal sites of uptake are currently unknown.³

Table 3 Median SUVmax of lesion types identified by Ga68-PSMA PET/CT

Lesion type	Sahlmann et al 2015 ³		Afshar-Oromieh et al 2015 ¹
	Median SUVmax 1HPI (range)	Median SUVmax 3HPI (range)	Median SUVmax (range)
Axillary lymph nodes	1 (range 0.4 to 2)	0.8 (range 0.3 to 0.9)*	N/A
Benign lymph nodes	1.4 (range 0.8 to 2.5)	1.1 (range 0.7 to 1.5)*	N/A
Lymph node metastases	9.8 (range 2.0 to 37.3)	15.2 (range 3.7 to 57.2)*	7.0 (range 1.0 to 122.5)
Primary PCa	11.6 (range 4.3 to 64.4)	18.2 (range 5.2 to 107.6)*	7.1 (range 3.0 to 40.0)
Local recurrence	17 (range 6.1 to 20)	15.5 (range 4.7 to 25.1)	11.3 (range 2.4 to 22.8)
Bone metastases	5.8 (range 1.3 to 27.6)	7.2 (range 1.6 to 43.4)*	9.8 (range 1.6 to 115.4)
Soft tissue metastases	N/A	N/A	6.0 (range 0.7 to 47.5)

HPI: hour post injection; N/A: not applicable; SUV: standardised uptake value; *3HPI SUVmax score was significantly higher than 1HPI score, all P values were <0.02.

A summary of the reported per-lesion diagnostic accuracy of Ga68-PSMA PET/CT is presented in Table 4. The reported sensitivity value ranged from 77 per cent to 94 per cent, and specificity ranged from 93 per cent to 100 per cent. Only one study with a valid reference standard included a relevant comparator test. In this trial, Ga68-PSMA PET/CT demonstrated higher sensitivity (87% versus 71%), specificity (93% versus 87%), PPV (76% versus 67%) and NPV (97% versus 89%) compared with F18-labelled choline PET/CT.²

Table 4 Per-lesion diagnostic accuracy of Ga68-PSMA PET/CT

	Pfister et al 2016 ²	Sahlmann et al 2015 ³	Afshar-Oromieh et al 2015 ¹
Sensitivity (n)	89% (53/61)	94% (not reported)	77% (98/128)
Specificity (n)	93% (230/247)	99% (not reported)	100% (318/318)
PPV (n)	76% (53/70)	89% (not reported)	100% (98/98)
NPV (n)	97% (230/238)	99% (not reported)	91% (318/348)

NPV: negative predictive value; PPV: positive predictive value.

Impact of Ga68-PSMA on patient management

Characteristics of the included studies are outlined in Table 5.

Table 5 Characteristics of studies investigating the impact of Ga68-PSMA PET/CT on patient management

Study design	van Leeuwen et al 2016 ⁶	Sterzing et al 2016 ⁵	Morigi et al 2015 ⁴
Level of evidence	Level IV intervention	Level IV intervention	Level IV intervention
Study design	Prospective case series with pre-test and post-test managements outcomes	Retrospective case series with pre-test and post-test management outcomes	Prospective case series with pre-test and post-test management outcomes
Location (centres)	Australia (1 centre)	Germany (1 centre)	Australia (1 centre)
Inclusion criteria	Patients with a biochemical recurrent of prostate cancer after radical prostatectomy, considered for salvage radiotherapy	Patients with a new PCa diagnosis, or recurrent PCa after radical prostatectomy	Patients with a rising PSA level after radical prostatectomy who were considered for, but had not commenced, systemic therapy
Participants	N = 70	Recurrent PCa = 42 New PCa=15	N = 38
Intervention	Ga68-PSMA PET/CT	Ga68-PSMA PET/CT	Ga68-PSMA PET/CT
Prior test	Contrast-enhanced CT	MRI, CT, bone scintigraphy	F18-fluoromethylcholine PET/CT
Comparator	N/A	N/A	N/A
Reference standard	Histological follow-up when available (N = 3)	N/A	Histological follow-up when available (N = 9)
Outcomes	1. Proportion of patients with a changed management strategy after Ga68-PSMA PET/CT 2. Detection rate	1. Proportion of patients with a changed management strategy after Ga68-PSMA PET/CT	1. Proportion of patients with a changed management strategy after Ga68-PSMA PET/CT 2. Detection rate

CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; PCa: prostate cancer; PSMA: prostate specific membrane antigen.

Three studies investigated the impact of Ga68-PSMA PET/CT on the clinical management of patients with recurrent prostate cancer after radical prostatectomy. In all three studies, investigators recorded the proposed clinical management plan based on initial imaging or clinical judgement and any changes to the management plan after additional information was obtained through a Ga68-PSMA PET/CT scan. Sterzing et al (2016) and van Leeuwen et al (2016) reported that initial management was based on conventional imaging.^{5,6} In contrast, Morigi et al (2015) did not report the initial management plan, but compared the impact on management of both F18-labelled choline PET/CT and Ga68-PSMA PET/CT.⁴ van Leeuwen et al and Morigi et al also reported detection rates, but did not confirm these with a reference standard for the entire sample population. As reference-confirmed accuracy results were presented previously, only the reported impact on patient management is reported here.

Sample demographics of the included change in management studies are reported in Table 6. As in the diagnostic accuracy studies, Sterzing et al reported some overlap in the eligible population in terms of disease status, but this was accounted for in the analysis to an extent.⁵ Other demographic characteristics were broadly similar across the included studies.

Table 6 Sample demographics of included change in management studies

Demographic characteristic	van Leeuwen et al 2016 ⁶	Sterzing et al 2016 ⁵	Morigi et al 2015 ⁴
Number of patients	N = 70	Recurrent PCa = 42 New PCa = 15	N = 38
Gleason score	7, N = 46 8 to 10 = 24	Median 8 (range 5-9)	6 or 7, N = 23 8 or 9, N = 15
PSA level at imaging	Median 0.2 ng/mL (IQR 0.12 to 0.32 ng/mL)	Median 3.0 ng/mL (range 0.16 to 113 ng/mL)	Mean 1.72 ± 2.54 ng/mL (range 0.04 to 12.0 ng/mL)
Age	Median 67 years (range 60 to 71 years)	Median 70 years (range 53 to 83 years)	Mean 60 years (range 54 to 81 years)
Prior treatment	Radical prostatectomy: N = 70*	Radical prostatectomy: N = 42	Radical prostatectomy: N = 34 Radiotherapy: N = 4 Surgery + salvage radiotherapy: N = 12

NR: not reported; PCa: prostate cancer; PSA: prostate specific antigen; *patients previously treated with radiotherapy or systemic therapy were excluded.

The recent study by van Leeuwen et al reported a major management impact in 29 per cent (20/70) of patients.⁶ Prior to Ga68-PSMA, all patients were considered for salvage radiotherapy. The site of the detected recurrence had an important impact on patient management. All 50 patients with no change in management were either PSMA-negative, or PSMA-positive in the prostate bed or seminal vesicles only. The main impact of Ga68-PSMA was in patients with disease beyond the prostate bed, in which a positive scan led to:

- An expansion of radical radiotherapy to include pelvic lymph nodes in five patients
- Cancelled radiotherapy in one patient
- Salvage radiotherapy to the pelvic lymph nodes with additional anti-hormone therapy in six patients (avoiding radiotherapy to the prostate bed)
- Specifically targeted radiotherapy of individual lesions in seven patients
- Salvage radiotherapy plus specifically targeted radiotherapy in one patient.

In the second study, Morigi et al reported a major or moderate change to the clinical management plan in 65 per cent (24/38) of cases, of which 54 per cent (13/24) were attributable solely to Ga68-PSMA PET/CT findings.⁴ In the other cases 11 (46%), Ga68-PSMA and F18-fluoromethycholine PET/CT both contributed to the change in management strategy, but Ga68-PSMA was more influential in four of those cases. In no case was a change in management solely attributed to F18-fluoromethycholine PET/CT. Therefore, Ga68-PSMA PET/CT had a major or moderate impact to the treatment strategies for all 24 patients.

In the final study, Sterzing et al found that Ga68-PSMA PET/CT changed the initial disease staging based on CT, MRI or bone scanning in 51 per cent (29 of 57) of patients.⁵ Of these patients, four had a change in tumour stage after a primary diagnosis of prostate cancer, and 25 had a change following a recurrence of prostate cancer. Based on the change in tumour staging, all 29 patients had a change in their therapeutic management plan. In total,

four patients (14%) had their radiation plan cancelled in favour of systemic therapy, eighteen patients (62%) had their radiotherapy regimen expanded to include additional lymph nodes, and eight patients (28%) had the radiation field expanded to include either para-aortic node region or inguinal node region.

Safety

There were no adverse events or other related safety issues identified in the included studies.

Economic evaluation

No cost-effectiveness studies were identified.

Ongoing research

The use of Ga68-PSMA for diagnosing prostate cancer, or prostate cancer recurrence, is an active area of ongoing research. There are at least five ongoing trials of the technology for currently underway in Australia, and six in the United States (Table 7), as identified on www.clinicaltrials.gov and <http://www.anzctr.org.au/>. In addition to the prostate cancer trials, there is one small (N = 10) ongoing trial in Australia that aims to determine the diagnostic sensitivity Ga68-PSMA PET for the characterisation of metastatic kidney disease compared to conventional CT (Trial ID ACTRN12615000854538). The trial is currently recruiting in Queensland, and is due to complete enrolment in August 2016.

The Prostate Cancer Foundation of Australia and Movember recently funded the “ProPSMA trial”, a randomised controlled trial of Ga68-PSMA PET/CT versus conventional imaging for staging of high-risk prostate cancer. The primary endpoint is accuracy, and secondary endpoints include management impact and economic analysis. This multi-centre trial will take place in seven sites around Australia, and is due to commence in late 2016.³⁹

Table 7 Ongoing clinical trials of 68-GA-PSMA PET/CT or PETMRI for detecting or staging prostate cancer

Trial ID; Site; Country	Study design	n	Aim/Intervention(s)	Outcome measure(s)	Status; Estimated completion date
ACTRN12616000186459; Princess Alexandra Hospital and Greenslopes Private Hospital Queensland, Australia	Diagnostic accuracy study	30	To investigate the diagnostic accuracy of 68-Ga-PSMA PET/MRI in men with a biochemical recurrence of prostate cancer following definitive therapy	Sensitivity, specificity, and impact on patient management of 68-Ga-PSMA PET/MRI compared to other imaging (e.g. staging CT, bone scan or MRI)	Not yet recruiting; TBD
ACTRN12615001324505; Peter MacCallum Cancer Centre Victoria, Australia	Non-randomised, single arm case series	14	To investigate the safety and uptake of 68-Ga-PSMA in prostate tumours and normal tissue	Safety, biodistribution, radiation dosimetry, optimal imaging time and expression of PSMA relationship to 68-Ga-PSMA	Recruiting; June 2016

Trial ID; Site; Country	Study design	n	Aim/Intervention(s)	Outcome measure(s)	Status; Estimated completion date
ACTRN12615001183572; Epworth Healthcare Victoria, Australia	Diagnostic accuracy study	150	The first phase is to determine whether 68-Ga-PSMA PET/CT can be used to identify locally recurrent prostate cancer in men with rising PSA following radical prostatectomy.	Proportions of participants with positive/negative PSMA-PET results	Recruiting; May 2018
ACTRN12615000608561; Sir Charles Gairdner Hospital Western Australia, Australia	Diagnostic accuracy study	40	To determine the efficacy of 68-Ga-PSMA PET/CT for detecting recurrent prostate cancer in patients with rising PSA following radical prostatectomy	Detection of the disease on initial and follow-up imaging, assessment of impact on patient management.	Recruiting; TBD
ACTRN12614000783628; Brisbane Urology Clinic Queensland, Australia	Diagnostic accuracy study	20	To evaluate the ability of 68-Ga-PSMA PET/MRI to detect local prostate cancer foci	Detection of local prostate cancer, correlation of the intensity of 68-Ga-PSMA uptake with Gleason Grade, tumour volume and grade	Recruiting; TBD
NCT02611882; USA	Diagnostic accuracy study	225	To determine the diagnostic accuracy of 68-Ga-PSMA PET/CT or PET/MRI in: 1) treatment naïve patients 2) prostatectomy patients 3) patients with castrate resistant disease	Sensitivity and specificity of 68-Ga-PSMA for detecting metastatic disease	Recruiting; December 2020
NCT02678351; USA	Diagnostic accuracy study	200	To determine the diagnostic accuracy of 68-Ga-PSMA PET/MRI in patients with suspected prostate cancer	Per cent of patients with true lesions, sensitivity and specificity of 68-Ga-PSMA PET/MRI	Not yet recruiting; February 2021
NCT02673151; USA	Diagnostic accuracy study	200	To determine the diagnostic accuracy of 68-Ga-PSMA PET/CT in patients with suspected prostate cancer	Per cent of patients with true lesions, sensitivity and specificity of 68-Ga-PSMA PET/CT	Not yet recruiting; February 2021
NCT02488070; USA	Case series	10	To determine the bioavailability of 68-Ga-PSMA in patients with a suspected prostate cancer recurrence	Biodistribution of 68-Ga-PSMA, number of patients who complete the examination	Ongoing, not recruiting; June 2017
NCT02282137; USA	Comparative diagnostic accuracy study	208	To determine the diagnostic accuracy of 68-Ga-PSMA PET/CT compared to conventional imaging in patients with suspected prostate cancer recurrence	Diagnostic accuracy of 68-Ga-PSMA and conventional imaging	Recruiting; December 2015
NCT01496157; USA	Diagnostic accuracy study	24	To evaluate 68-Ga-PSMA PET/CT for prostate cancer detection and aggressiveness at initial diagnosis	Detection of primary prostate cancer, detection of metastatic disease at initial staging	Ongoing, not recruiting; January 2015

CT: Computed Tomography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; PSA: Prostate Specific Antigen; PSMA: Prostate Specific Membrane Antigen; RP: radical prostatectomy; TBD: To Be Determined.

Other issues

Conflicts of interest

One included study, Pfister et al (2016), reported that several authors received consultancy fees, speaker fees, travel reimbursement or research grants from a number of pharmaceutical companies.² No other studies reported a conflict of interest.

Other PET tracers under development

Nuclear imaging of prostate cancer is a burgeoning area of research, with many tracers either currently in use or under development internationally. In addition to Ga68-PSMA, other tracers include 11C/18F-choline, 18F-FACBC, 18F-DCFPyLis, 18F-Bombesin, Ga68-DOTA-Bombesin and radiolabelled uPAR.³⁷ Each tracer has strengths and weaknesses in relation to Ga68-PSMA and it is unclear from the literature which will prove to be the most efficacious.

PET/CT compared with PET/MRI

The spatial resolution of the CT component of a PET/CT scan is a commonly cited limitation of the technique compared to other hybrid imaging methods.³⁷ In particular, PET/MRI is an area of interest, due to the relative benefits of spatial resolution and lack of exposure to ionising radiation. A recent study by Afshar et al compared the feasibility of Ga68-PSMA PET/CT with Ga68-PSMA PET/MRI in a sample of 20 patients with a biochemical recurrence of prostate cancer.⁴² The authors noted that PET/MRI provided higher lesion contrast and spatial resolution compared to PET/CT, allowing for subjective improvements in image interpretation. From a total of 75 lesions, four lesions that were unclear on PET/CT were characterised using PET/MRI. However, PET/MRI images often had image artefacts around the urinary bladder and kidneys. This early feasibility study showed that PET/MRI may be promising technique, but requires further research to optimise imaging of Ga68-PSMA uptake in the kidney and urinary bladder.

Other indications

There is a growing body of literature examining the efficacy of Ga68-PSMA for the pre-operative staging of intermediate and high-risk prostate cancer prior to prostatectomy or radiotherapy.⁴³ Ga68-PSMA may be able to identify distant metastatic disease not seen on conventional imaging, which may in turn avoid unsuitable curative intent therapies. In addition, studies have investigated the use of Ga68-PSMA in restaging patients with known metastatic disease to assess response to systemic therapy and to assess the suitability for Lu-177 PSMA radionuclide therapy.⁴⁴

Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the [HealthPACT web site](#).

Total number of studies	6
Total number of Level III-1 diagnostic studies	1
Total number of Level III-2 diagnostic studies	2
Total number of Level IV intervention studies	3

Search criteria to be used (MeSH terms)

Search terms: ((prostate) AND PSMA) AND (((((68Ga) OR (68)Ga) OR Gallium-68) OR Gallium 68) OR [68Ga])

Date searched

29/03/2016

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