LeukoScan®

For use in diagnostic imaging of the long bones and feet in patients with suspected osteomyelitis, including those with diabetic foot ulcers

May 2003

MSAC application 1056

Assessment report

ISBN 0 642 82375 8

ISSN (Print) 1443-7120

ISSN (Online) 1443-7139

First printed September 2003

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at:

http://www.msac.gov.au/

Hard copies of the report can be obtained from:

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Mr Lachlan Standfield, Mr Warwick Isaacson, Mr Paul Mernagh, Mr Dominic Tilden and Dr Adèle Weston from M-TAG Pty Ltd. The report was endorsed by the Commonwealth Minister for Health and Ageing on 8 August 2003.

Publication approval number: 3375

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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LeukoScan® is presented as a lyophilised powder (0.31 mg per vial) to be reconstituted with sodium chloride and 1100 MBq of technetium-99m. Once it has been reconstituted, LeukoScan® should be injected intravenously after five minutes and before four hours. Imaging should be performed 1–8 hours post-injection.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision-making when funding is sought under Medicare. Medical Technology Assessment Group (M-TAG) Pty Ltd was contracted to undertake a systematic review and economic evaluation of LeukoScan®. A supporting committee with appropriate expertise then evaluated this evidence and provided advice to MSAC.

MSAC's assessment of LeukoScan®

Clinical need

Osteomyelitis is an infection of the bone that is most commonly caused by bacteria. Micro-organisms can enter the bone via the blood supply, by direct introduction from a nearby site of infection, or by a penetrating wound. Increased susceptibility to osteomyelitis may be caused by:

- trauma
- foreign bodies such as implants, which expose sites on the bone to which bacteria can bind
- ischaemia, which reduces the effectiveness of the body's natural defence mechanisms
- diabetes.

Incidence

A total of 3723 patients were diagnosed with primary osteomyelitis in 2000–01 (public hospital: 2927; private hospital: 796) (Australian Institute of Health and Welfare (AIHW): Hospitals Statistics 2000–2001). These figures were based on the principal diagnosis codes (from the Australian modified International Classification of Disease and Related Health Problems, 10th revision [ICD-10-AM] groupings), which are defined as the diagnosis established after study to be chiefly responsible for occasioning the patient's episode of care in hospital. It should be noted that these figures do not include patients treated in the outpatient setting; therefore, they underestimate the total number of patients diagnosed with osteomyelitis each year.

Morbidity and mortality

Acute and chronic osteomyelitis is responsible for considerable morbidity (Hass and McAndrew 1996). It is known that early diagnosis and prompt antibiotic therapy of acute osteomyelitis, before extensive destruction of the bone and conversion to chronic disease, produces the best clinical outcomes for patients with osteomyelitis (Carek et al 2001). Furthermore, if acute osteomyelitis is detected early enough, an aetiological diagnosis made, and antibiotic therapy is successful, surgical debridement of the bone and surrounding tissue is not always necessary. Generally, the patient will be prescribed at least six weeks of intravenous antibiotic therapy for acute osteomyelitis. This is often followed by a period of oral antibiotic treatment. Childhood osteomyelitis often requires shorter duration of therapy, particularly of the intravenous phase. Debridement is critically important in management of chronic osteomyelitis and duration of antibiotic therapy is typically longer (and sometimes indefinite).

Failure to identify osteomyelitis promptly and treat it effectively may result in the need for surgical removal of infected bone and surrounding tissue. In patients with osteomyelitis associated with a prosthetic device, it may be necessary to remove the prosthesis, then to undertake surgical debridement, and packing of the dead space (eg, with antibiotic-impregnated beads or myoplasty). If infection is cleared, the prosthesis can be replaced. In some cases, amputation of the infected limb/extremity may be required.

Data from the National Hospital Morbidity Database were used to assess the morbidity associated with osteomyelitis in Australia. In 2000–01, a total of 583 patients had procedures (in public or private hospitals) that included bones relevant to the LeukoScan® indication (ie, long bones and feet) ***and*** in which osteomyelitis was mentioned in any of the diagnosis codes.

In general, the mortality due to osteomyelitis is low. However, the rate is elevated in patients who have osteomyelitis and associated sepsis, or who have an underlying serious medical condition (eg, immunocompromised patients).

Safety

Preparation and blood handling

There are two main safety issues regarding the preparation and procedure involved in imaging for osteomyelitis:

- the potential for needlestick injury, which is primarily a risk for health care workers; and
- the potential for transmission of blood-borne pathogens to a patient when the procedure involves the withdrawal and reinjection of patients' blood or blood products.

LeukoScan® and gallium-67 scanning (one of the comparators) both require a single injection. Neither of these procedures requires blood handling. In contrast, technetium-99m stannous colloid labelled WBC scanning (the other comparator) requires two injections and the handling of patients' blood. Therefore, the technetium-99m stannous colloid labelled WBC scanning procedure is associated with a greater risk of needlestick injury for health care workers, and misadministration errors for patients. It should be noted that, given the extremely low rates of these events, this safety advantage appears to be marginal.

Exposure to radiation

Exposure to high levels of ionising radiation has been linked with the theoretical possibility of cancer induction and the development of hereditary defects. However diagnostic imaging agents only emit low dose ionising radiation, and to date, have not been linked to any long-term complications when used in the imaging of infection. Nevertheless, it is recognised that ionising radiation doses should be kept as low as possible. As the radiopharmaceuticals labelled with technetium are associated with a lower radiation dose per patient than those labelled with gallium, LeukoScan® and technetium-99m stannous colloid labelled WBC scanning both have a theoretical (albeit marginal) safety advantage over gallium-67 scanning.

LeukoScan®

Theoretical safety issues

As LeukoScan® uses a murine monoclonal Fab there is a possibility that the human immune system might perceive LeukoScan® as foreign and mount an immune response against it. This would produce human anti-mouse antibodies (HAMA) in patients, which might increase the chance of anaphylactic and other hypersensitivity reactions whenever further mouse protein materials were administered. LeukoScan® should therefore be administered in a setting where appropriate cardiopulmonary resuscitation facilities and trained personnel are immediately available in the event of any adverse reaction. In addition, under the Therapeutic Goods Administration (TGA) listed indication for LeukoScan® it is likely that a proportion of patients would require repeat scans.

However, limited data are available regarding the safety and efficacy of re-administration of LeukoScan®. Patients who have previously received murine monoclonal antibodies, from either LeukoScan® or from another product, are more likely to have HAMA. Therefore, administration of LeukoScan® in these patients should be considered only when it has been established that the patient does not have elevated HAMA levels.

Safety data reported in the unpublished study reports

Adverse events occurred at a relatively low frequency in the two unpublished LeukoScan® trial reports (Study 07 and Study 08), and given the patients' clinical course of underlying disease, were considered unrelated to LeukoScan® administration. Furthermore, no induction of HAMA was observed in any patient and the clinical laboratory data revealed no clinically significant changes in haematological parameters following LeukoScan® administration.

Safety data reported in the peer-reviewed publications

In general, safety data were poorly reported in the peer-reviewed publications. However, the available published data suggest that the level of adverse events and the probability of inducing a HAMA response following LeukoScan® administration are both low.

Technetium-99m stannous colloid labelled WBC scanning

No adverse event data were reported in any of the studies of technetium-99m stannous colloid labelled WBC scanning included in the safety evaluation.

Gallium-67 scanning

No adverse event data were reported in any of the studies of gallium-67 scanning included in the safety evaluation.

Effectiveness

Diagnostic accuracy

There are no head-to-head studies of LeukoScan® and the main technologies that it might replace in Australia (ie, technetium-99m stannous colloid labelled WBC scanning or gallium-67 scanning). Furthermore, data were not available to perform an indirect comparison of LeukoScan® with technetium-99m stannous colloid labelled WBC scanning or LeukoScan® with gallium-67 scanning in patients with suspected osteomyelitis of the long bones and feet, including those with diabetic foot ulcers. Consequently, a comparison of the diagnostic accuracy of these testing modalities could not be made. In other words, the comparative diagnostic accuracy of these diagnostic tests remains uncertain.

To aid in the decision-making process, an analysis was undertaken of trials reporting a direct comparison of the diagnostic accuracy of LeukoScan® with indium-111 and technetium-99m labelled hexamethylpropyleneamine oxime (HMPAO) WBC scanning (diagnostic modalities in common usage internationally) in the patient population defined by the TGA approved indication.

In patients with diabetic foot ulcers, the diagnostic accuracy of LeukoScan® compared with indium-111 and technetium-99m labelled HMPAO WBC scanning was not significantly different (81 and 75 per cent, respectively). However, in this patient population, LeukoScan® has a significantly higher sensitivity (92 per cent) than indium-111 or technetium-99m labelled HMPAO WBC scanning (79 per cent; $p < 0.05$), but the specificity of the LeukoScan® test was lower than indium-111 or technetium-99m labelled HMPAO WBC scanning (58 and 67 per cent, respectively). It should be noted that these differences might simply be a function of the threshold at which a positive diagnosis is made.

In patients with suspected osteomyelitis of the long bones, the diagnostic accuracy of LeukoScan® compared with indium-111 or technetium-99m labelled HMPAO WBC scanning was not significantly different (73.9 and 67.0 per cent, respectively). Similarly, the sensitivity for disease detection of LeukoScan® compared with indium-111 or technetium-99m labelled HMPAO WBC scanning was not significantly different in these patients (76.7 and 56.7 per cent, respectively; $p = 0.07$). In this patient group, the specificities of the diagnostic modalities were equal (72.4 per cent).

It is important to note that the data reported in the trials comparing the diagnostic accuracy of LeukoScan® with indium-111 or technetium-99m labelled HMPAO WBC scanning were based on a non-independent, on-site assessment (Harwood et al 1999; Study 08). In this setting, the authors note that the on-site clinician "may have had access to the results of the WBC scans for some patients" when interpreting the LeukoScan® results. This is likely to undermine the comparative analysis of LeukoScan® versus indium-111 or technetium-99m labelled HMPAO WBC scanning.

Change in clinical management and clinical outcomes

There are no head-to-head studies that report either the change in clinical management or the change in clinical outcomes associated with LeukoScan® and technetium-99m stannous colloid labelled WBC scanning or gallium-67 scanning. Furthermore, data were not available to perform an indirect comparison of LeukoScan® with technetium-99m stannous colloid labelled WBC scanning or LeukoScan® with gallium-67 scanning in patients with suspected osteomyelitis of the long bones and feet, including those with diabetic foot ulcers. Consequently, a comparison of the effect of these testing modalities on both the clinical management and clinical outcomes could not be performed and the comparative effect of these diagnostic tests remains uncertain.

Due to lack of available data, it was also not possible to perform a direct comparison of the effect on clinical management or clinical outcomes between LeukoScan® and indium-111 or technetium-99m labelled HMPAO WBC scanning in the appropriate patient groups.

It is clear, however, that a false-negative diagnosis could lead to a delay in the appropriate clinical management of the patient. Based on expert opinion, the possible implications of a false-negative diagnosis for the clinical management and clinical outcomes of patients with osteomyelitis are as follows.

- No change in management or clinical outcomes.

- Surgical debridement and removal of the surrounding infected tissue where none would be required if the infection had been promptly detected and successfully treated, or more extensive surgical debridement than otherwise required. The resultant 'dead space' must then be managed and, if necessary, the bone must be stabilised. Dead space management may involve local myoplasty, free-tissue transfers and the use of antibiotic-impregnated beads or cement. In patients with osteomyelitis associated with a prosthetic device, the prosthesis may have to be removed, followed by surgical debridement, packing of the dead space (eg, with antibiotic-impregnated beads or myoplasty) and, if infection is cleared, prosthetic replacement. This process would be associated with a marked increase in morbidity and temporary or possible permanent disability.

- In more severe cases, a delay in the clinical management of a patient may require amputation of the affected limb or extremity (eg, the diabetic foot).

- In rare cases, a delay in the detection of osteomyelitis may have the potential to cause death (eg, due to septicaemia, especially in immunocompromised patients).

In the case of a false-positive diagnosis, expert opinion suggests that the patient is likely to receive unnecessary and intensive antimicrobial treatment. The antimicrobial therapy chosen for treatment of osteomyelitis is dependent on the microbial aetiology of the infection and the *in vitro* antibiotic susceptibility profile of the pathogen detected. In general, patients in Australia are treated with a course of parenteral antibiotics while in hospital, followed by a period of 'hospital in the home' care, where parenteral antibiotic therapy is completed. If necessary, the patient may then be treated with a course of oral antibiotics. However, in the case of a false-positive diagnosis (eg, a patient with a soft-tissue infection but no underlying osteomyelitis), it is likely that a 'cure' will be achieved earlier in this intensive treatment programme than if the patient had true osteomyelitic disease. Some patients may have limited removal of healthy bone to attempt to confirm the diagnosis.

With regard to patient relevant clinical outcomes the implications of a false positive diagnosis may include the following.

- Limited removal of healthy bone to attempt to confirm the diagnosis, which may be accompanied by an increase in morbidity and disability.

- Increased time in hospital and in 'hospital in the home' care for the administration of parenteral antibiotics.

A false-positive diagnosis also has implications with regard to resource use. These are discussed in the following economic sections.

Cost-effectiveness

The review of effectiveness presented in this assessment found that there was no evidence of superiority of LeukoScan® relative to the main comparator, gallium-67 scanning. Therefore a formal cost-effectiveness analysis on the basis of this conclusion would show that LeukoScan® is a dominated intervention, because it has greater costs without providing additional benefits.

Therefore, an economic analysis was conducted to explore the cost-effectiveness of LeukoScan® based on the nominally better accuracy of LeukoScan® when compared with indium-111 and technetium-99m labelled HMPAO WBC scanning. In patients with suspected osteomyelitis of the long bones or feet, LeukoScan® more accurately identified disease-positive patients than technetium-99m labelled HMPAO WBC scanning, at an incremental cost of $24,056 per additional patient free of osteomyelitis. In patients with diabetic foot ulcers and suspected osteomyelitis, the incremental cost of LeukoScan® per additional patient free of osteomyelitis was $26,348. These analyses indicate that the incremental cost of LeukoScan® per additional patient free of osteomyelitis is greater than the cost of treating a patient with osteomyelitis.

Recommendation

LeukoScan® is safe and as effective as current methods of WBC scanning, but is more costly. MSAC recommends that additional funding is justified for patients who do not have access to ex-vivo WBC scanning.

- The Minister for Health and Ageing accepted this recommendation on 8 August 2003 -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of LeukoScan®, which is a diagnostic test for suspected osteomyelitis. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at **Appendix A**. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for LeukoScan® for use in diagnostic imaging when investigating patients with suspected osteomyelitis in long bones and in feet, including those with diabetic foot ulcers.

Background

LeukoScan®

The procedure

LeukoScan® is a radiopharmaceutical used in the detection of osteomyelitis. LeukoScan® consists of a small murine monoclonal antibody fragment (Fab), sulesomab, formulated for labelling with technetium-99m (^{99m}Tc). When the patient presents for examination, LeukoScan® is labelled with technetium-99m by a proprietary method, and is administered via an intravenous injection.

Following injection, the radiolabelled Fab reacts with the normal cross-reacting antigen (NCA-90). These antigens are present on the surface of virtually all neutrophils (a type of white blood cell). Hence, LeukoScan® targets areas where neutrophils have accumulated and therefore may be useful in determining the location and extent of infection and inflammation in bone in patients with suspected osteomyelitis. Since the white blood cells (WBCs) are not removed from the patient, LeukoScan® can be considered *in vivo* WBC labelling.

LeukoScan® is presented as a lyophilised powder (0.31 mg per vial) to be reconstituted with sodium chloride and 1100 MBq of technetium-99m. Once it has been reconstituted, LeukoScan® should be injected intravenously after five minutes and before four hours. Imaging should be performed 1–8 hours post-injection.

Intended purpose

LeukoScan® is currently approved by the Therapeutic Goods Administration (TGA) in Australia for:

> "use in diagnostic imaging for the investigation of suspected osteomyelitis in long bones and in feet in patients, including those with diabetic foot ulcers".

In line with the indication, this assessment will consider the case for public reimbursement of LeukoScan® in:

- adult patients with suspected osteomyelitis in the long bones or feet
- adult patients with suspected osteomyelitis *and* diabetic foot ulcers.

The safety and effectiveness of LeukoScan® in children below the age of 18 have not been established. Therefore, at this stage, the use of LeukoScan® is contraindicated in children.

This evaluation will consider the role of LeukoScan® in adult patients in whom there is a high clinical index of suspicion of osteomyelitis based on a positive bone scan.

Early diagnosis of osteomyelitis is essential because prompt intravenous antibiotic therapy may prevent necrosis of the bone and further morbidity. In some more advanced cases, surgical intervention may be needed.

Diagnosis is, however, a resource-intensive task, generally requiring a blood test for a WBC count, a plain radiograph, a three-phase bone scan with technetium-99m and, at present, gallium-67 citrate scanning and/or *ex vivo*, autologous radiolabelled WBC scintigraphy.

For autologous radiolabelled WBC scintigraphy, a sample of the patient's blood is collected and the WBCs are labelled with a radioisotope. In Australia, the most common method of *ex vivo* WBC labelling involves combining the patient's blood with a technetium-99m stannous colloid. Labelling of the WBC occurs by phagocytic engulfment of the radiocolloid.

Two other *ex vivo* WBC labelling methods used commonly elsewhere involve hexamethylpropyleneamine oxime (HMPAO) that has been labelled with technetium-99m, or oxine that has been labelled with indium-111. After re-injection into the patient, the radiolabelled white cells accumulate at the sites of inflammation, which can then be seen on the ensuing scan. The *ex vivo* radiolabelling of the WBCs with the technetium-99m labelled HMPAO or indium-111 labelled oxine techniques is technical, labour-intensive, and requires blood handling that poses potential infection risks to patients, clinicians and technicians. In contrast, although the technetium-99m stannous colloid labelling requires handling of patients' blood, it is far less labour intensive than the two aforementioned methods.

It is suggested that LeukoScan® is a faster and more convenient way to investigate patients with suspected osteomyelitis than technetium-99m HMPAO WBC scanning, requiring fewer clinical facilities. LeukoScan® is also likely to be faster and more convenient than technetium-99m stannous colloid labelled WBC scanning. This potentially allows greater patient access compared with the technetium-99m stannous colloid labelled WBC scanning. In addition, LeukoScan® avoids the need for blood handling and therefore offers potential safety advantages to the patient and to the operator.

Clinical need/burden of disease

Osteomyelitis is an infection of the bone that is most commonly caused by bacteria. Micro-organisms can enter the bone via the blood supply, by direct introduction from a nearby site of infection or by a penetrating wound. Increased susceptibility to osteomyelitis may be caused by:

- trauma
- foreign bodies such as implants, which expose sites on the bone to which bacteria can bind
- ischaemia, which reduces the effectiveness of the body's natural defence mechanisms
- Diabetes.

Incidence of osteomyelitis

A total of 3723 patients were diagnosed with primary osteomyelitis in 2000–01 (public hospital: 2927; private hospital: 796) (Australian Institute of Health and Welfare (AIHW): Hospitals Statistics 2000–2001). These figures were based on the principal diagnosis codes (from the Australian modified International Classification of Disease and Related Health Problems, 10th revision [ICD-10-AM] groupings), which are defined as the diagnosis established after study to be chiefly responsible for occasioning the patient's episode of care in hospital. It should be noted that these figures do not include patients treated in the outpatient setting and therefore they underestimate the total number of patients diagnosed with osteomyelitis each year.

Morbidity and mortality associated with osteomyelitis

Acute and chronic osteomyelitis is responsible for considerable morbidity (Hass and McAndrew 1996). It is known that early diagnosis and prompt antibiotic therapy of acute osteomyelitis, before extensive destruction of the bone and conversion to chronic disease, produces the best clinical outcomes for patients with osteomyelitis (Carek et al 2001). Furthermore, if acute osteomyelitis is detected early enough, an aetiological diagnosis made, and antibiotic therapy is successful, surgical debridement of the bone and surrounding tissue is not always necessary. Generally, the patient will be prescribed at least six weeks of intravenous antibiotic therapy for acute osteomyelitis. This is often followed by a period of oral antibiotic treatment. Childhood osteomyelitis often requires shorter duration of therapy, particularly of the intravenous phase. Debridement is critically important in management of chronic osteomyelitis and duration of antibiotic therapy is typically longer (and sometimes indefinite).

Failure to identify osteomyelitis promptly and treat it effectively may result in the need for surgical removal of infected bone and surrounding tissue. In patients with osteomyelitis associated with a prosthetic device, it may be necessary to remove the prosthesis, then to undertake surgical debridement, and packing of the dead space (eg, with antibiotic-impregnated beads or myoplasty). If infection is cleared, the prosthesis can be replaced. In some cases, amputation of the infected limb/extremity may be required.

Data from the National Hospital Morbidity Database (2000–2001) were used to assess the morbidity associated with osteomyelitis in Australia. All procedures that included bones relevant to the LeukoScan® indication (ie, long bones and feet) and in which osteomyelitis was the principal diagnosis code were included. As principal diagnosis codes are defined as "the diagnosis established after study to be chiefly responsible for occasioning the patient's episode of care in hospital", it is possible that some patients with osteomyelitis might be treated under a different principal diagnosis code. For example, a patient with a diabetic foot ulcer might have had diabetes listed as the principal diagnosis code. Therefore, data are reported not only on the number of procedures with osteomyelitis as the principal diagnosis code, but also on the number of procedures with any mention of osteomyelitis in the diagnosis code (**Table 1**). The true number of procedures for patients with osteomyelitis will fall between the values reported.

It should also be noted that the numbers of procedures reported in **Table 1** are only included as an indication of the morbidity associated with osteomyelitis. These data are not representative of the number of nuclear imaging services provided, as the patients may have been diagnosed through a range of other methods such as clinical examination or plain radiography.

Table 1 Procedures with osteomyelitis as the principal diagnostic code and procedures with any mention of osteomyelitis in the ICD-10-AM code, performed in public and private hospitals in 2000–01

ICD-10-AM code	Bones involved	Public hospitals		Private hospitals		Total procedures (public and private)	
		Principal diagnosis	Any diagnosis	Principal diagnosis	Any diagnosis	Principal diagnosis	Any diagnosis
1420	Humerus	9	11	7	10	16	21
1437	Radius or ulna	22	25	12	12	34	37
1475	Hand	28	35	41	49	69	84
1494	Pelvis or femur	37	52	27	34	64	86
1525	Fibula or tibia	84	98	53	67	137	165
1577	Other musculoskeletal sites	23	26	9	11	32	37
1549	Foot	60	85	53	68	113	153
	Total	**263**	**332**	**202**	**251**	**465**	**583**

Source: Australian Institute of Health and Welfare (AIHW): National Hospital Morbidity Database 2000–2001.
Abbreviation: ICD-10-AM, International Statistical Classification of Disease and Related Health Problems, 10th revision, Australian Modification.

The morbidity of patients with osteomyelitis secondary to the diabetic foot was investigated by considering those who had diabetes listed as a concomitant condition and who had undergone a procedure performed on the foot. In 2000–01 in both public and private hospitals, between 28 and 53 procedures relating to osteomyelitis were performed on the foot in patients who had diabetes listed as a concomitant condition (**Table 2**). Hence, the number of procedures in this subgroup is relatively small compared with the number in the long bone subgroup. It should be noted, however, that these data are only for hospital inpatients and therefore exclude all patients treated as outpatients.

Table 2 Procedures performed on the foot in public and private hospitals for patients with osteomyelitis as the principal diagnostic code and those with any mention of osteomyelitis in the ICD-10-AM code, cross referenced with any diagnosis of diabetes

ICD-10-AM code	Bones involved	Public hospitals		Private hospitals		Total procedures (public and private)	
		Principal diagnosis	Any diagnosis	Principal diagnosis	Any diagnosis	Principal diagnosis	Any diagnosis
1549, with diabetes as a concomitant condition	Foot	17	34	11	19	28	53

Source: Australian Institute of Health and Welfare (AIHW): National Hospital Morbidity Database 2000–2001.
Abbreviation: ICD-10-AM, International Statistical Classification of Disease and Related Health Problems, 10th revision, Australian Modification.

In general, the mortality due to osteomyelitis is low. However, the rate is elevated in patients who have osteomyelitis and associated sepsis, or who have an underlying serious medical condition (eg, immunocompromised patients).

Estimated new patients annually

The number of new patients who present for nuclear imaging with a high index of suspicion for osteomyelitis, and who have already had a positive bone scan, cannot be determined from existing data. It is therefore necessary to derive an estimate from the number of existing nuclear imaging procedures currently used for the detection of osteomyelitis. Patients who would be eligible for LeukoScan® could currently be imaged under any of the Medical Benefits Scheme (MBS) item numbers listed in **Tables 3** and **4**. However, these imaging services are used not only for patients with suspected osteomyelitis but also for those with other diseases, such as infection of unknown origin, lymphoma or inflammatory bowel disease.

Therefore, in order to estimate the number of patients who would fall within the proposed LeukoScan® indication, expert opinion was required. Two estimates were sought:

- the percentage of patients who would undergo the various types of scan for osteomyelitis (to exclude patients scanned for conditions other than suspicion of osteomyelitis)
- the proportion of these who would have osteomyelitis consistent with the proposed indication (to exclude patients with suspected osteomyelitis outside the TGA listed indication – ie, other than in long bones and other than secondary to diabetic foot ulcers).

Table 3 Diagnostic gallium-67 scanning services reimbursed under the MBS that were used between July 2000 and June 2001 and the proportion and number, based on the combined ranges of three nuclear medicine specialists, estimated to be relevant to the LeukoScan® indication

ICD-10-AM code	Item number description	Number of services (July 2000 – June 2001)	Proportion of services estimated to be relevant to the LeukoScan® indication	Number of services estimated to be relevant to the LeukoScan® indication
61429	Whole body study using gallium-67	920	< 5%	Up to 46
61430	Whole body study using gallium-67 with SPECT, one body region	110	< 5%	Up to 5
61450	Localised study using gallium-67	276	80–90%	221–248
61453	Localised study using gallium-67 with SPECT	41	< 5%	Up to 2
Combined expert opinion estimate of the total number of scans relevant to the LeukoScan® indication				**221–300**

Source: HIC Professional Statistics – MBS Item Statistics 2000–2002.
Abbreviations: HIC, Health Insurance Commission; ICD-10-AM, International Statistical Classification of Disease and Related Health Problems, 10th revision, Australian Modification; MBS, Medical Benefits Scheme; SPECT, single photon emission computed tomography.

Table 4 Diagnostic technetium-99m labelled WBC scanning services used between July 2000 and June 2001 and the proportion and number, based on the combined ranges of three nuclear medicine specialists, estimated to be relevant to the LeukoScan® indication

ICD-10-AM code	Item number description	Number of services (July 2000 – June 2001)	Proportion of services estimated to be relevant to the LeukoScan® indication	Number of services estimated to be relevant to the LeukoScan® indication
61433	Whole body study, planar with ^{99m}Tc labelled WBC	262	< 5%	Up to 13
61434	Whole body study, SPECT, with ^{99m}Tc labelled WBC	58	< 5%	Up to 3
61454	Localised study, planar with ^{99m}Tc labelled WBC	256	50–90%	128–230
61457	Localised study, SPECT, with ^{99m}Tc labelled WBC	52	< 5%	Up to 3
Combined expert opinion estimate of the total number of scans relevant to the LeukoScan® indication				**128–249**

Source: HIC Professional Statistics – Medical Benefits Schedule (MBS) Item Statistics 2000–2002.
Abbreviations: HIC, Health Insurance Commission; ICD-10-AM, International Statistical Classification of Disease and Related Health Problems, 10th revision, Australian Modification; MBS, Medical Benefits Scheme; SPECT, single photo emission tomography; ^{99m}Tc, technetium-99m; WBC, white blood cell.

For patients with suspected osteomyelitis of long bones or those with diabetic foot ulcers who have suspected osteomyelitis, the overwhelming majority of the scans with gallium-67 citrate and technetium-99m labelled WBCs would be conducted using localised planar studies (item numbers 61450 and 61454, respectively) (**Table 3** and **Table 4**). Only a small number of relevant patients would be scanned under any of the other item numbers.

Hence, based on the opinion of three nuclear imaging specialists, it is estimated that between 221 and 300 gallium-67 scans and between 128 and 249 technetium-99m labelled WBC scans are conducted in the relevant patient group each year. However, this represents only those patients treated outside of the public hospital system. Similarly, it excludes the smaller number of scans reimbursed by the Department of Veterans Affairs. If this figure is upscaled by the public:private ratio (based on the principal diagnosis codes ratio of 2927:796, or 3.68:1), then it is estimated that a total of 813–1104 gallium-67 scans and 471–916 technetium-99m labelled WBC scans are performed annually in patients who would fall within the proposed LeukoScan® indication. Since it is possible for patients to have repeat scans for chronic conditions and/or have both gallium-67 and technetium-99m labelled WBC scans, these figures should be viewed as number of scans, rather than number of patients.

In summary, the best estimate of the number of scans performed annually within the TGA-approved indication for LeukoScan® is 1284–2020.

Existing procedures

In Australia, patients with suspected long bone osteomyelitis within the LeukoScan® indication undergo a number of diagnostic procedures. These include clinical examination, plain radiography and a three-phase technetium-99m bone scan.

For patients who would fall within the proposed LeukoScan® indication the nuclear imaging procedures currently used to detect osteomyelitis are gallium-67 scanning and

technetium-99m labelled WBC scans, as listed in **Table 3** and **Table 4**, respectively. The level of reimbursement for these two types of scan is dependent on whether they are: whole body planar, whole body single photon emission computed tomography (SPECT), localised planar, or localised SPECT. As stated above, the majority of scans for patients in the proposed LeukoScan® indication will be localised planar studies.

It is important to note that there is no public reimbursement of indium-111 WBC labelled scans. In addition, consultation with clinical experts revealed that the technetium-99m stannous colloid method is currently the most common WBC labelling method in Australia. The technetium-99m HMPAO WBC labelling method, which is in common use internationally, is not currently registered by the TGA for this indication. However, the technetium-99m HMPAO WBC labelling method is used in some Australian hospitals where it has been evaluated and granted approval by local ethics committees.

Comparators

The comparators for the evaluation that are currently listed on the MBS are gallium-67 citrate scanning and WBC scanning using technetium-99m stannous colloid. These are the two diagnostic procedures consistent with the Medical Services Advisory Committee (MSAC) definition of a comparator – that is, the current diagnostic procedure(s) most likely to be replaced if the new diagnostic procedure is recommended for listing. Expert opinion suggests that within the proposed LeukoScan® indication gallium-67 citrate scanning is used more frequently than technetium-99m stannous colloid.

It should be noted that in the existing literature, indium-111 and technetium-99m labelled HMPAO WBC scanning are used frequently in international settings. However, while technetium-99m labelled HMPAO WBC scanning is used in some Australian hospitals under local ethics committee approval, it, along with indium-111 WBC scanning, is not listed on the MBS. Therefore, they are not appropriate comparators in the context of this evaluation.

Reference standard

The recommended methodology for investigating the accuracy of a new diagnostic test is to compare the diagnosis made with the new test with the true disease status. However, it is often not feasible to determine the disease status of a patient unequivocally. Therefore, in many disease states, a proxy measure – such as another diagnostic test or clinical judgement – must be used. The best available measure of disease is called the reference standard. Both the LeukoScan® and the comparator results must be independently compared with the reference standard to assess accuracy. In this way, the difference in accuracy between LeukoScan® and the comparator can be determined.

Currently, the best way of determining whether osteomyelitis is present in patients with suspected disease of the long bones and feet, including those with diabetic foot ulcers, is bone biopsy and histology or culture. For pragmatic reasons, it was decided (on the basis of expert opinion) that studies reporting long-term clinical follow-up as a reference standard would also be included in the assessment.

Marketing status of the technology

LeukoScan® obtained registration as a diagnostic radiopharmaceutical from the TGA following the Australian Drug Evaluation Committee meeting on 7–8 February 2002. The Australian Registry of Therapeutic Goods number for the drug is ARTG 82071. The TGA-listed indication for LeukoScan® is:

> "Use in diagnostic imaging for the investigation of suspected osteomyelitis in long bones and in feet, including those with diabetic foot ulcers".

The safety and effectiveness of LeukoScan® in children below the age of 18 have not been established. Therefore, at this stage, the use of LeukoScan® is contraindicated in children.

In Europe, LeukoScan® was recommended for approval by the Committee for Proprietary Medicinal Products (CPMP) in their meeting on 15–16 October 1996. This recommendation was accepted by the European Agency for the Evaluation of Medical Products (EMEA). Marketing authorisation was granted under the following indication:

> "LeukoScan® is indicated for diagnostic imaging for determining the location and extent of infection/inflammation in bone in patients with suspected osteomyelitis, including patients with diabetic foot ulcers.
>
> When a bone scan is positive and imaging with LeukoScan® is negative, infection is unlikely. When a bone scan is negative, imaging with LeukoScan® may rarely show a positive response and this may indicate early osteomyelitis."

LeukoScan® is currently under review by the US Food and Drug Administration.

Current reimbursement arrangement

The Medicare Benefits Schedule includes nuclear medicine imaging item numbers for WBCs labelled with technetium-99m. The current wording of the MBS item number appears to be ambiguous, as it does not specify whether the WBCs must be labelled *ex vivo* or *in vivo*. Currently, WBC labelling is performed by extracting blood from the patient, processing and labelling the WBCs *ex vivo*, and then reinjecting them into the patient. In contrast, the LeukoScan® agent is labelled with technetium-99m *in vitro* and then injected into the patient. After the LeukoScan® agent is injected into the patient it 'labels' the patient's WBCs *in vivo* by binding to an antigen present on virtually all neutrophils. Therefore, it is possible that reimbursement for LeukoScan® may be sought under the current MBS item number. This assessment report considers the addition of a separate MBS item number at a price premium specifically for LeukoScan®.

Approach to assessment

Review of literature

Studies of LeukoScan®

The medical literature was searched to identify relevant studies and reviews for the period between 1980 and 2002. Searches were conducted via the following primary databases:

- Premedline
- Medline 1966 to current
- Embase 1980 to current
- Econlit 1969 to current.

The search terms used included the following:

- Fractures; bony callus; osteomyelitis; osteitis; diabetic foot; diabetic feet; diabetic ulcer/s; diabetic foot ulcer/s; diabetic feet ulcer/s; diabetes mellitus; foot disease; skin ulcer; fracture.
- LeukoScan; sulesomab; sulesomab Tc 99m; immu-mn3; anti-leukocyte; antigranulocyte; Fab; fragment antigen binding; granulocyte antibody; antibodies, monoclonal; hybridomas; monoclonal antibodies; radiopharmaceutical agent.

Complete details of the literature searches performed using the Medline and Embase databases are presented in **Appendix D**.

Searches of the following secondary databases/sites were also performed:

- British Columbia Office of Health Technology Assessment
- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
- Centre for Health Program Evaluation (Monash University, Australia)
- Centre for Reviews and Dissemination (University of York, UK)
- Cochrane Library database
- Health Economics Research Group (Brunel University, UK)
- Health Information Research Unit (HIRU) internal database (McMaster University, Canada)

- International Network of Agencies for Health Technology Assessment (INAHTA) (Sweden)
- International Society of Technology Assessment in Health Care (Canada)
- National Health and Medical Research Council Australia publication list
- National Health Service (UK)
- Health Services Technology Assessment Texts. National Information Center on Health Services Research and Health Care Technology (HSTAT database) (US)
- Swedish Council on Technology Assessment in Health Care (SBU)
- US Office of Technology Assessment 1974–1995 (closed)
- US Health Care Financing Administration (HCFA).

Inclusion criteria

- For studies of diagnostic accuracy, the study must compare LeukoScan® with an appropriate reference standard. (Currently, the best available indicator of the presence of osteomyelitis is a combination of bone biopsy and histology or culture. For pragmatic reasons, it was decided that studies reporting long-term clinical follow-up as a reference standard would also be included in the assessment.)
- Initially, all publications that reported the use of LeukoScan® and included patients that might be relevant to this assessment were included in the review. If, after review, it was found that the publication did not report the diagnostic accuracy of LeukoScan® specifically in adult patients with suspected acute or chronic osteomyelitis in long bones or in feet, including those with diabetic foot ulcer, the study was excluded from the effectiveness review. For completeness, the details of these publications are listed in **Appendix C**.
- Use of LeukoScan® as currently approved by the Therapeutic Goods Administration (TGA).
- Reporting of an appropriate outcome (eg, diagnostic accuracy, effect on clinical management and/or clinical outcomes).

Exclusion criteria

- Non-systematic reviews or opinion pieces.
- Non-human or *in vitro* studies.
- A study with 20 or fewer patients receiving the correct intervention as currently approved by the TGA (those with ≤ 20 patients were assessed for relevant safety data).

Publications that duplicated all or some of the patient data in other included trials were included in the first instance. They were then reviewed, and excluded if necessary. Similarly, publications that failed to report outcomes adequately were also excluded after review. Original study reports were sourced from the applicant. The evaluators used more detailed data from the study reports as an alternative to that reported in publications, where necessary.

The flow chart in **Figure 1** summarises the exclusion of studies from the safety and effectiveness review of LeukoScan®. A total of 188 references were identified by the search, of which seven met the criteria to be considered as evidence in the safety review, and six were initially included in the effectiveness review. A complete list of the excluded citations identified in the literature search is included in **Appendix E**, together with reasons for exclusion from the reviews.

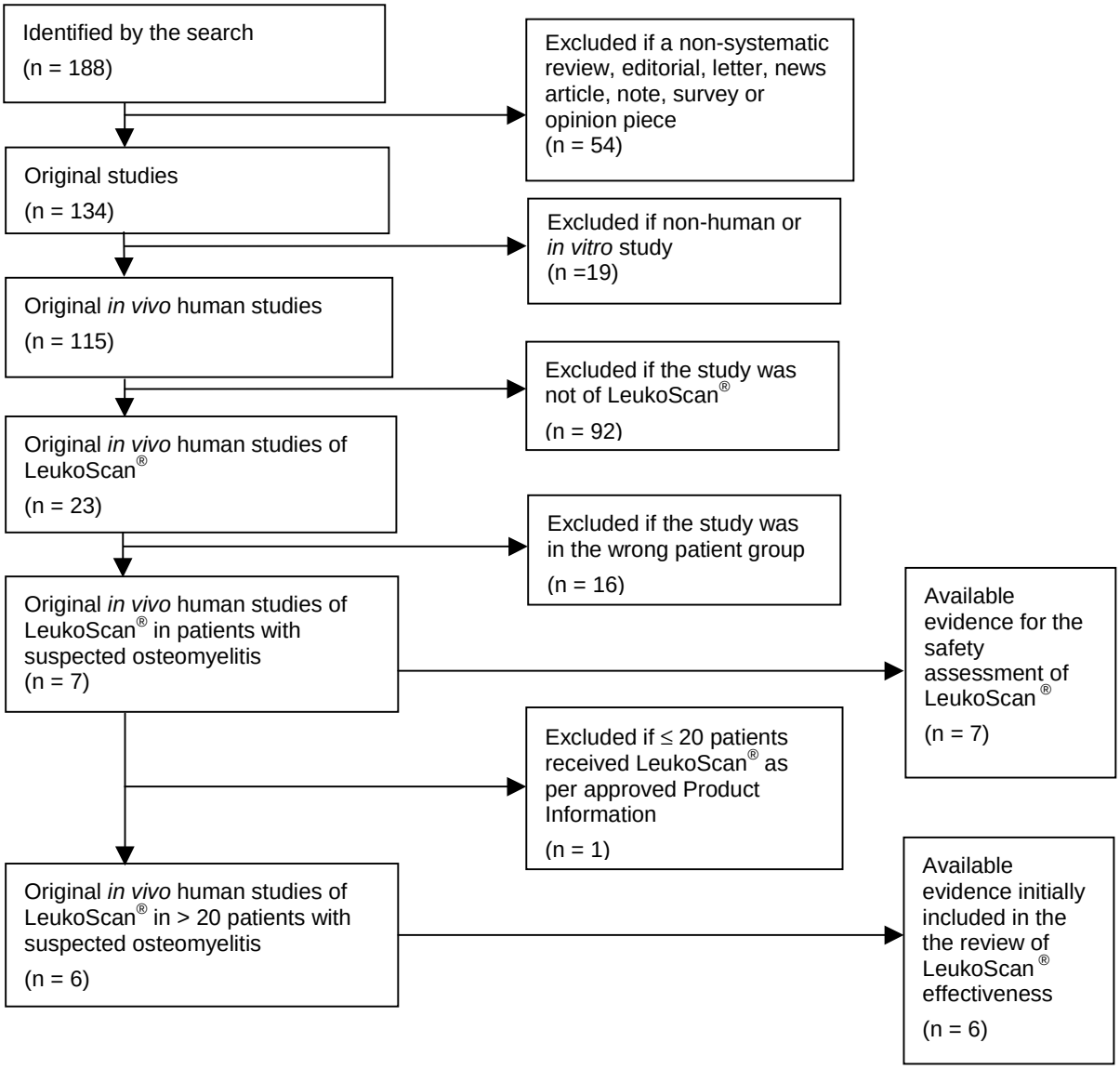

Figure 1 Reasons for exclusion of published reports identified by the literature search

The six studies identified described the diagnostic accuracy of LeukoScan® in various settings. No studies were identified that adequately described the change in clinical management or the change in clinical outcomes directly attributable to LeukoScan®.

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 1999). These dimensions consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence (**Table 5**). The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 5 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *p* value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a]See **Table 6**.

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in **Table 6**.

Table 6 Designations of levels of evidence

Level of evidence[a]	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

[a]Modified from NHMRC (1999).

As NHMRC levels of evidence are designed for studies of therapeutic interventions, they are not always appropriate for assessing the quality of studies of diagnostic test accuracy. Therefore, levels of evidence specifically designed for the systematic review of studies that aim to determine the accuracy of diagnostic tests were also used to classify the available evidence (**Table 7**).

Table 7 Levels of evidence specific to studies of the accuracy of diagnostic tests

Level of evidence[a]	Study design
1	An independent, masked comparison with reference standard among an appropriate population of consecutive patients
2	An independent, masked comparison with reference standard among non-consecutive patients or confined to a narrow population of study patients
3	An independent, masked comparison with an appropriate population of patients, but reference standard not applied to all study patients
4	Reference standard not applied independently or masked
5	Expert opinion with no explicit critical appraisal, based on physiology, bench research, or first principles

[a]From Bandolier (2002).

A diagnostic-accuracy-specific checklist (based on guidelines issued by the Cochrane Screening and Diagnostic Tests Methods group) was also applied to assess the quality of the evidence available for the technology in question (**Appendix G**). Health care intervention evidence was considered using the NHMRC levels of evidence.

The Cochrane Screening and Diagnostic Tests Methods group checklist comprises the following:

- patient selection bias
- blinding (test conduct and/or assessment of result)
- diagnosis made independent of other clinical information
- order effect (avoid verification bias)
- accuracy of gold standard
- any treatment between diagnostic tests (avoid treatment bias)
- inclusion of all patients, including those with grey-zone results
- quality of reporting.

Review of literature on comparator therapies

At the time of assessment there were no head-to-head studies identified that directly compared LeukoScan® with WBC scanning using technetium-99m stannous colloid or gallium-67 scanning. For this reason, it was necessary to conduct an additional systematic review of the comparator diagnostic modalities, WBC scanning using technetium-99m stannous colloid and gallium-67 scanning, and then to consider the feasibility of undertaking an indirect comparison.

No studies were identified that adequately described the change in clinical management or the change in clinical outcomes directly attributable to LeukoScan®. Therefore, the comparator searches were limited to studies describing the diagnostic accuracy of technetium-99m stannous colloid labelled WBC scanning and gallium-67 scanning. The comparator search was also restricted to the Medline and Embase databases. Separate searches were conducted for the two comparators (details of the search strategies are included in **Appendix D**). After the removal of duplicate citations, 82 unique citations were obtained in the technetium-99m stannous colloid labelled WBC search, and 145 in the gallium-67 search. The following inclusion/exclusion criteria were then applied to determine whether these citations should be included in this assessment.

Inclusion criteria

- The study must compare technetium-99m stannous colloid labelled WBC scanning or gallium-67 scanning with an appropriate reference standard. (Currently, the best available indicator of the presence of osteomyelitis is a combination of bone biopsy and histology or culture. For pragmatic reasons, it was decided that studies reporting long-term clinical follow-up as a reference standard would also be included in the assessment.)

- Initially, all publications that reported the use of technetium-99m stannous colloid labelled WBC scanning or gallium-67 scanning and included patients that may be relevant to this assessment were included in the review. If, after review, it was found that the publication did not report the diagnostic accuracy of technetium-99m stannous colloid labelled WBC scanning or gallium-67 scanning specifically in adult patients with suspected acute or chronic osteomyelitis in long bones or in feet, including those with diabetic foot ulcer, the study was excluded from the effectiveness review. For completeness, the details of these publications are listed in **Appendix C**.

- Reporting of an appropriate outcome (ie, diagnostic accuracy).

Exclusion criteria

- Non-systematic reviews or opinion pieces.

- Non-human or *in vitro* studies.

- A study with 20 or fewer patients receiving the correct diagnostic test (those with ≤ 20 patients were assessed for relevant safety data).

After application of the above criteria to the abstracts of the retrieved citations, three publications reporting the results of technetium-99m stannous colloid labelled WBC scanning, and 11 reporting the results of gallium-67 scanning were identified for the initial effectiveness review (and five or 19 for the safety review, respectively).

The flow chart in **Figure 2** summarises the exclusion of studies from the safety and effectiveness review of technetium-99m stannous colloid labelled WBC scanning. A complete list of the excluded citations identified in the literature search is shown in **Appendix E**, together with reasons for exclusion from the review.

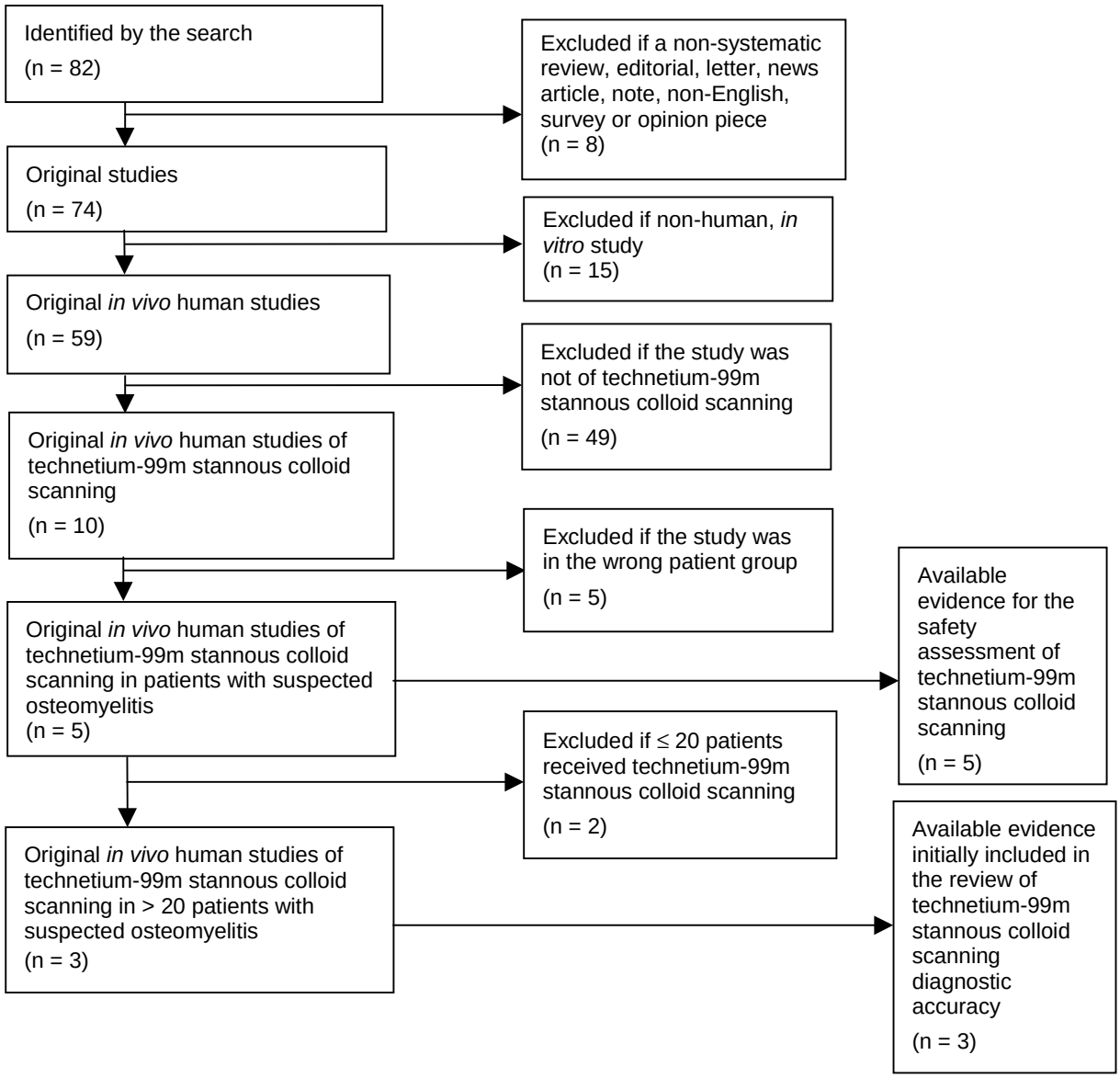

Figure 2 **Reasons for exclusion of published reports of technetium-99m stannous colloid labelled WBC scanning identified by the literature search**

The flow chart in **Figure 3** summarises the exclusion of studies from the safety and effectiveness review of gallium-67 scanning. A complete list of the excluded citations identified in the literature search is included in **Appendix E**, together with reasons for exclusion from the review.

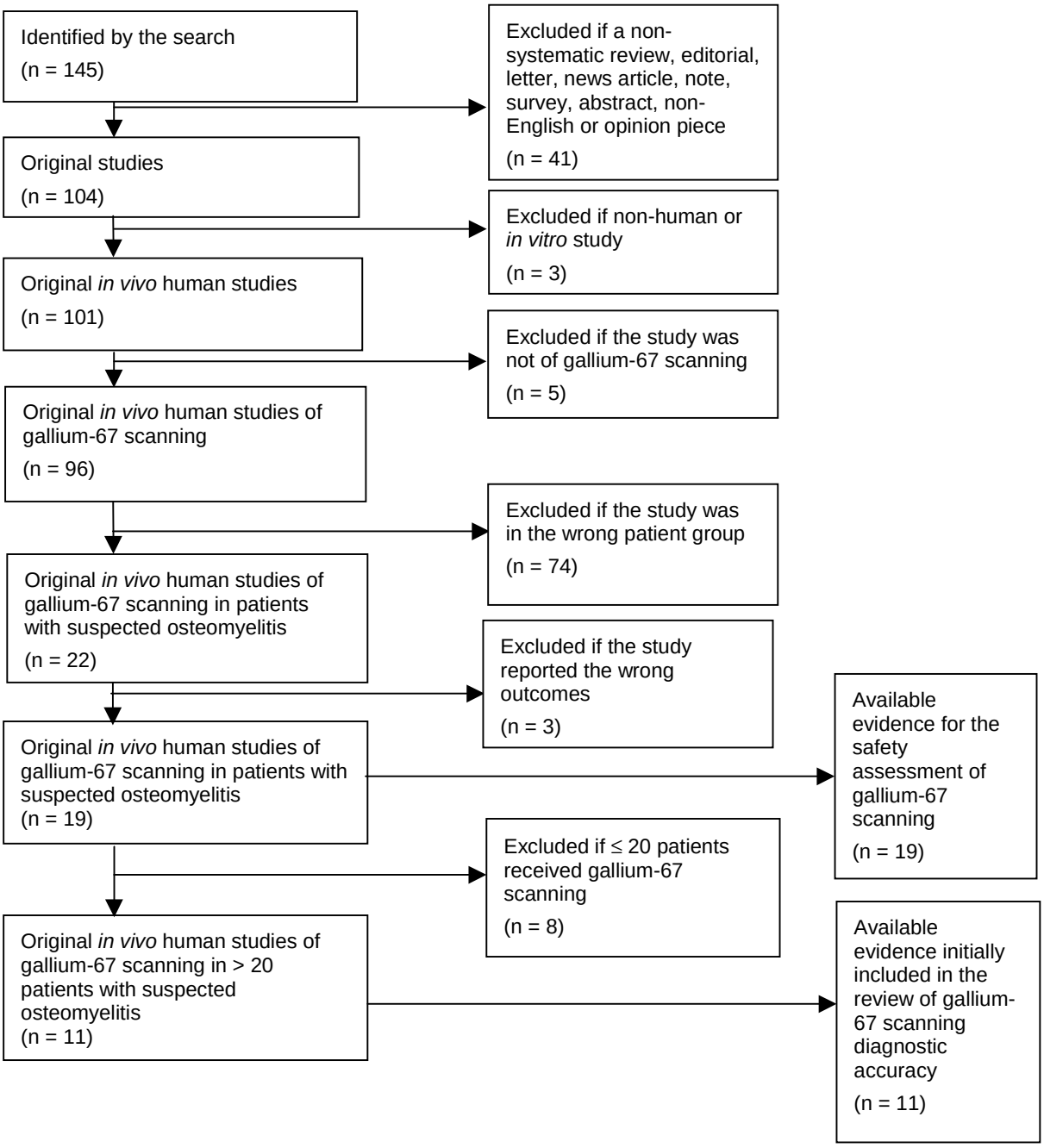

Figure 3 Reasons for exclusion of published reports of gallium-67 scanning identified by the literature search

Additional searches

Additional searches were conducted to examine the following:

- clinical need associated with osteomyelitis
- economic evaluations of LeukoScan®.

Expert advice

A supporting committee with expertise in nuclear medicine, infectious diseases and orthopaedics was established to evaluate the evidence and provide advice to the Medical Services Advisory Committee (MSAC) from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the supporting committee is provided at **Appendix B**.

Results of assessment

LeukoScan®

As shown in **Table 8**, a total of seven relevant publications were identified in the LeukoScan® literature search. Two relevant unpublished LeukoScan® trial reports IMDMN3-07 (Study 07) and IMDMN3-08 (Study 08) were sourced directly from the applicant.

A total of two trials (data reported in five publications: Study 07; Study 08; Harwood et al 1999; Hakki et al 1997; Harwood et al 1994) were included in the effectiveness assessment of LeukoScan®. One publication described a study with fewer than 20 patients falling within the LeukoScan® indication and, in accordance with the exclusion criteria, was excluded from the effectiveness assessment (Becker et al 1994). Three other publications that may have reported pertinent data were included in the first instance. However, after full review, these publications were excluded from the effectiveness assessment (Ryan et al 2002; Devillers et al 2000; Becker et al 1996). Detailed explanations of the reasons for the exclusion of these publications are presented below. All these publications/reports were included in the safety assessment of LeukoScan®.

Two of the trials identified were multicentre, prospective, single group studies with sequential measurements performed in the same patients (ie, the patient was acting as their own control) (Study 07; Study 08; Hakki et al 1997; Harwood et al 1999; Harwood et al 1994). One study reported a retrospective review of case notes (Ryan 2002).

No studies were identified that adequately described the change in clinical management or the change in clinical outcomes directly attributable to LeukoScan®.

Table 8 LeukoScan® studies identified

First author (year)	Design	Included in safety review	Included in efficacy review
Unpublished study reports			
Study 07	All patients included in Harwood et al (1999)	See Harwood et al (1999)	See Harwood et al (1999)
Study 08	Prospective, multicentre, single-group, with sequential diagnostic measurements	✓	✓
Publications			
Ryan (2002)	Retrospective review of case notes	✓	x
Devillers (2000)	Prospective, with sequential diagnostic measurements	✓	x
Harwood (1999)	Prospective, multicentre, single-group, with sequential diagnostic measurements.	✓	✓
Hakki (1997)	All patients included in Harwood et al (1999) and Study 08	See Harwood et al (1999) and Study 08	See Harwood et al (1999) and Study 08
Becker (1996)	Open-labelled, prospective, multicentre, phase I/II, single-group, with sequential diagnostic measurements	✓	x
Becker (1994)	Prospective, single-group, with sequential diagnostic measurements	✓	x
Harwood (1994)	All patients included in Harwood et al (1999) and Study 08	See Harwood et al (1999) and Study 08	See Harwood et al (1999) and Study 08

Ryan et al (2002) performed a retrospective review of case notes in 55 patients. Case notes were available in 51 patients and a final clinical diagnosis was discernable in 47. The patient population included those with possible infection of: a total knee replacement (n = 23); a total hip replacement (n = 3); an internal fixation device (n = 8), septic arthritis (n = 4); chronic osteomyelitis (n = 2); an infected fracture site (n = 2); and five others. It was not reported whether the study was performed in consecutive patients. The study did not include a comparative test. The diagnosis derived from three-phase bone scintigraphy followed by imaging with LeukoScan® was compared with the eventual clinical diagnosis determined by patient case notes (ie, the reference standard). This clinical diagnosis was usually presumptive, based on clinical improvement without necessarily carrying out any other investigations. Furthermore, the results of culture from the identified infection sites were not available for many patients. Therefore, the strength of a positive diagnosis within the study varied from case to case. Consequently, the results of this study were excluded from the effectiveness analysis of LeukoScan®. For completeness, the characteristics of this study are reported in **Appendix C**.

The study by Devillers et al (2000) was prospectively designed, with sequential diagnostic measurements in a single group of patients. The patient population selected for this study included hospitalised patients with a low or moderate index of suspicion of bone or joint infection. This assessment report is focused on the use of LeukoScan® in patients with a high index of suspicion of osteomyelitis. Therefore, this study was excluded from the effectiveness analysis. For completeness, the characteristics of this study are reported in **Appendix C**.

The study by Becker et al (1996) was of a prospective, open-labelled, multicentre, phase I/II, single-group design, with diagnostic tests performed in sequential order. It was not reported whether the study was performed in consecutive patients. The trial was designed to evaluate the safety, tolerance and efficacy of LeukoScan® in patients thought to have acute infection (osteomyelitis, soft-tissue or abdominal infection). To qualify for the trial, patients had to have a high index of suspicion of having an abscess or an inflammatory process, and one or more of the following: at least two cultures testing positive for the same organism and symptoms that could be localised to a particular anatomical region; focal infection or inflammatory process or both delineated by computed tomography (CT), ultrasonography, radionuclide bone scan, magnetic resonance imaging (MRI), or conventional radiotherapy; localised pain lasting more than three days; or leucocyte counts greater than 10,000/μL.

A total of 53 patients were enrolled in the Becker et al (1996) study. Of these, 21 were suspected of having osteomyelitic lesions. The trial employed a range of administered antibody amount (0.1 mg–1.0 mg) to assess the diagnostic potential of the antibody. The diagnostic accuracy of LeukoScan® was compared with that of indium-111 labelled oxine and technetium-99m labelled hexamethylpropyleneamine oxime (HMPAO) white blood cell (WBC) scanning. Patient data and final diagnoses were obtained by biopsy or other standard diagnostic techniques, such as CT scanning, surgery, MRI or ultrasound. Results of the study were reported only at the level of suspected osteomyelitic lesion, not at the patient level. In addition, the trial was performed in patients suspected of having various acute infections (eg, osteomyelitis, soft-tissue or abdominal infections), not just those with osteomyelitis. Therefore, the results of this study were excluded from further consideration in the effectiveness analysis of LeukoScan®. For completeness, the characteristics of this study are reported in **Appendix C**.

Review of comparator scans

It should be noted that in standard clinical practice gallium-67 or technetium-99m stannous colloid labelled WBC scans are often interpreted in conjunction with the patient's three phase technetium-99m bone scan. However, given the need to perform an indirect comparison, studies which only reported diagnostic accuracy based on the joint reading of these scans were excluded from further indirect assessment.

Technetium-99m stannous colloid labelled WBC scanning

As shown in **Table 9**, five publications were identified in the literature search for technetium-99m stannous colloid labelled WBC scanning. Of these, two publications reported on fewer than 20 appropriate patients and, in accordance with the exclusion criteria, were excluded from the effectiveness assessment (Boyd et al 1993; Southee et al 1988). The remaining three publications that may have reported pertinent data were included in the first instance (Chik et al 1996; Gutfilen et al 1994; Schroth et al 1981). However, after full review, these studies were excluded from the indirect comparative effectiveness assessment of LeukoScan® and technetium-99m stannous colloid labelled WBC scanning. Detailed explanations of the reasons for the exclusion of these publications are presented below.

All studies were reviewed for the safety assessment of technetium-99m stannous colloid labelled WBC scanning.

Table 9 Relevant technetium-99m stannous colloid labelled WBC scanning studies identified

First author (year)	Design	Included in safety review	Included in efficacy review
Chik (1996)	Single-group study, with sequential diagnostic measurements	✓	x
Gutfilen (1994)	Single-group study, with sequential diagnostic measurements, and case study	✓	x
Boyd (1993)	Prospective, simultaneous diagnostic measurements in consecutive patients	✓	x
Southee (1990)	Case study	✓	x
Schroth (1981)	Single group, with sequential diagnostic test and reference standard tests	✓	x

NB: As there were no data available to describe how LeukoScan® *per se* changed clinical management or changed clinical outcomes, the review of the comparator trials was limited to studies of diagnostic accuracy only.

The Chik et al (1996) study was of single-group design, with diagnostic tests performed in sequential order in patients with a painful joint prosthesis. It was not reported whether this study was performed in consecutive patients. Evaluation of the scintigraphic images was performed independently and in a masked fashion. Patients were permitted to receive antibiotic therapy during the study period. The final diagnosis of infection was based on microbiological culture or long-term (six months) clinical follow-up. The trial was performed exclusively in patients with prosthetics, and was therefore unsuitable for comparison with the patient populations presented in Harwood et al (1999) and Study 08. Therefore, this study was excluded from further analysis. For completeness, the characteristics of this study are reported in **Appendix C**.

Gutfilen et al (1994) compared the sensitivity and specificity of a novel method, of labelling WBCs with technetium-99m using stannous chloride in 25 patients with suspected osteomyelitis. The stannous chloride method of labelling WBCs presented in this study was distinct from the method most commonly used to label WBCs in Australia. The effect of the difference in labelling methods on diagnostic accuracy is unclear. The patients included in the study were described simply as having suspected osteomyelitis. Histological studies were performed to confirm the diagnosis. The publication did not report the diagnostic work-up required for patient inclusion in the study, nor whether the study was performed in consecutive patients. In addition, neither the bone type (ie, whether it was a long bone) or anatomical position of the suspected osteomyelitis were reported, and it was not apparent whether patients with prosthetics were included in the trial. Therefore, this study was excluded from further analysis. For completeness, the characteristics of this study are reported in **Appendix C**.

The Schroth et al (1981) study was poorly reported. Forty-two patients with a diagnosis of a suspected septic loosening of an endoprosthesis were examined using technetium-99m stannous colloid labelled WBC scanning. The final patient diagnosis was based on bacteriological and histological examinations. It was not reported whether the study was retrospective or prospective in design, whether it was performed in consecutive patients, or whether evaluation of the radiographic images was masked. The anatomical position of the prosthetics under investigation was not indicated, and there were no details provided regarding the diagnostic work-up required for inclusion in the study. The trial was performed exclusively in patients with prosthetics, and was therefore unsuitable for comparison with the patient populations presented in Harwood et al (1999) and Study 08. Therefore, this study was excluded from further analysis. For completeness, the characteristics of this study are reported in **Appendix C**.

Gallium-67 scanning

Nineteen publications were identified in the gallium-67 literature search (**Table 10**). Of these, eight studies had fewer than 20 appropriate patients and, in accordance with the exclusion criteria, were not included in the effectiveness assessment (Yapar 2000; Weinstein 1993; Ivancevic 1990; Moreno 1987; Alazraki 1985; Gavin 1984; Firooznia 1983; Sugarman 1983). The remaining 11 publications that may have reported pertinent data were included in the first instance. After full review, 10 of these studies were excluded from the indirect comparative effectiveness assessment of LeukoScan® and gallium-67 scanning. Detailed explanations of the reasons for the exclusion of these publications are presented below.

Hence, only one trial was included in the effectiveness assessment of gallium-67 scanning (Johnson et al 1996).

It should be noted that many of the publications identified in the gallium-67 scanning search are over 10 years old. This reflects the fact that gallium-67 scanning has been adopted as standard practice, and as such, there has not been the need for more recent trials of its diagnostic accuracy.

All studies were reviewed for the safety assessment of gallium-67 scanning.

Table 10 Relevant gallium-67 scanning studies identified

First author (year)	Design	Included in safety review	Included in efficacy review
Yapar (2000)	Prospective, single group, with diagnostic tests performed in sequential order	✓	x
Johnson (1996)	Prospective, single group, with diagnostic tests performed in sequential order	✓	✓
Sorsdahl (1993)	Prospective, single group, with diagnostic tests performed in sequential order	✓	x
Weinstein (1993)	Single group, with sequential diagnostic tests	✓	x
Ivancevic (1990)	Single group, with sequential diagnostic tests	✓	x
Seabold (1989)	Prospective, single group, with diagnostic tests performed in sequential order, in consecutive patients	✓	x
Tumeh (1988)	Retrospective review of clinical records	✓	x
Moreno (1987)	Case series	✓	x
Sugarman (1987)	Case-control	✓	x
Tumeh (1987)	All patients included in Tumeh et al (1986)	See Tumeh et al (1986)	See Tumeh et al (1986)
Tumeh (1986)	Retrospective review of clinical records in consecutive patients	✓	x
Alazraki (1985)	Single group, with gallium-67 scans performed coincidentally	✓	x
Al Sheikh (1985)	Prospective, single group, with diagnostic tests performed in sequential order in consecutive patients	✓	x
Esterhai (1985)	Prospective, single group, with diagnostic tests performed in sequential order	✓	x
Gavin (1984)	Retrospective review of clinical records	✓	x
Schauweker (1984)	Prospective, single group, with diagnostic tests performed in sequential order in consecutive patients	✓	x
Firooznia (1983)	Single group, with gallium-67 scans performed in a portion of patients	✓	x
Sugarman (1983)	Single group, with diagnostic tests performed in sequential order	✓	x
Rosenthall (1982)	Retrospective review of clinical records in consecutive cases	✓	x

NB: As there were no data available to describe how use of LeukoScan® *per se* led to a change in clinical management or a change in clinical outcomes, the review of the comparator trials were limited to studies of diagnostic accuracy only.

The study by Sorsdahl (1993) was a prospective, single-group study, in which diagnostic tests were performed in sequential order. It was not reported whether the study was performed in consecutive patients or whether the scan evaluations were masked. A total of 110 adult patients with 126 sites of suspected osteomyelitis were included in the study. No further details were reported about the diagnostic work-up required for entry into the study.

The investigators compared images of affected sites with contralateral or adjacent normal (ie, unaffected) bony background areas. The images of the affected and unaffected areas were acquired for the same time period. Ratios of the average counts in affected and unaffected regions were calculated. To minimise dependence on the region size and shape, average counts per unit area (expressed as counts per pixel) were used. All open fracture patients received prophylactic antibiotics, which may mean that some infected fractures were classified as 'non-infected fractures' because they had been cured before the diagnosis of osteomyelitis could be confirmed. The study reported diagnostic performance only at the level of the suspected osteomyelitic lesion, not at the patient level. Furthermore, the anatomical regions of suspected osteomyelitis were not reported (eg, vertebral, diabetic foot, long bone) and it was not reported whether patients with prosthetics were included in the study. Therefore, the study was excluded from further analysis. For completeness, the characteristics of this study are reported in **Appendix C**.

The Seabold et al (1989) study was a prospective study in which diagnostic tests were performed in sequential order in consecutive patients. The study was conducted to compare three-phase bone scanning, combined technetium-99m methylene diphosphonate (MDP)/indium-111 WBC scanning, and combined gallium-67/technetium-99m MDP scanning. The study included 54 consecutive patients with 55 delayed union or non-union fracture sites. Five patients received antibiotics for concurrent infections and were omitted from the analyses in an effort to exclude false-negative culture results. The remaining 49 patients were analysed using three-phase bone scanning and combined technetium-99m MDP/indium-111 WBC scanning. Forty-five patients were also assessed with gallium-67 scintigraphy. The combined technetium-99m MDP/indium-111 WBC scanning results and the combined gallium-67/technetium-99m MDP scanning results were interpreted in a masked fashion (ie, without knowledge of the patients' histories or clinical findings). The study only reported the diagnostic accuracy of gallium-67 and technetium-99m MDP scanning together and was therefore inappropriate for this assessment. Hence, the results of this study were excluded from further consideration in the effectiveness analysis of gallium-67 scanning. For completeness, the characteristics of this study are reported in **Appendix C**.

The retrospective review of clinical records in consecutive patients reported by Tumeh et al (1988) compared the roles of scintigrams (ie, three-phase bone scans and gallium-67 scans), plain radiographs and CT scans. The clinical records of 27 patients were reviewed, all of whom had prior bone infection, had undergone three-phase technetium-99m MDP scans, gallium-67 scans, plain radiographs and CT scans, and had surgical proof of active or inactive disease. Patients with surgical devices or prostheses were excluded from the analysis. The results of the three-phase bone scans and gallium-67 scans were assessed together, while different observers read the plain radiographs and CT scans without knowledge of each other's data. All scans were assessed without knowledge of the final results.

This study did not distinguish between the anatomical positions of the suspected osteomyelitis (eg, vertebral, diabetic foot, long bone) and was therefore not suitable for use in an indirect comparison with LeukoScan®. It should also be noted that it is likely that the patients included in this study are a subset of those reported in Tumeh (1986, 1987). However, this could not be confirmed from the data presented in the publication. For completeness, the characteristics of this study are reported in **Appendix C**.

The Sugarman et al (1987) study was of a case-control design. The primary objective of the trial was to determine the optimal way to decide whether bone infection was present beneath a pressure sore. The study was conducted in 385 patients with spinal cord injuries and 17 other debilitated individuals, all of whom had pressure sores. The results of the gallium-67 scans performed in this study were poorly reported: they were reported only at the level of the pressure sore, and for a small proportion of the included patients. Therefore, this study was excluded from further analysis. For completeness, the characteristics of this study are reported in **Appendix C**.

The retrospective review of clinical records in consecutive patients published by Tumeh (1986, 1987) investigated the three-phase bone scanning and gallium-67 scanning patterns associated with active osteomyelitis. Initially, clinical records were analysed in 149 patients, all of whom had previous bone infections or old fractures (with or without infection) and who had undergone both three-phase bone scanning and gallium-67 scanning. Patients with normal bone scans and joint prostheses were then excluded, leaving 136 patients. Those with other orthopaedic devices, such as pins and plates, were not excluded from the analysis. Both scintigraphic studies were read by the same radiologist, who did not know the final diagnosis. The study did not distinguish between the anatomical positions of the suspected osteomyelitis (eg, vertebral, diabetic foot, long bone) and was therefore not suitable for use in an indirect comparison with LeukoScan® in the identified patient groups of interest. For completeness, the characteristics of this study are reported in **Appendix C**.

The publication by Al-Sheik et al (1985) described a prospective, single-group study, with diagnostic tests performed in sequential order. The study included 21 consecutive orthopaedic patients with suspected subacute or chronic osteomyelitis and abnormal findings at radiological examination. Because this study included only those with subacute or chronic osteomyelitis, the study population is unlikely to be representative of all patients presenting with long-bone osteomyelitis (ie, it excludes those with acute long-bone osteomyelitis). It was therefore excluded from further analysis. For completeness, the characteristics of this study are reported in **Appendix C**.

The Esterhai et al (1985) study was prospectively designed with diagnostic tests performed in sequential order. The trial investigated the diagnostic effectiveness of technetium-99m MDP scanning and gallium-67 scanning when used to evaluate patients with possible subclinical osteomyelitis complicating fractures that have failed to heal. Unfortunately, the study did not report the diagnostic accuracy of gallium-67 scanning alone. Therefore, the results of this study were excluded from further consideration in the effectiveness analysis of gallium-67 scanning. For completeness, the characteristics of this study are reported in **Appendix C**.

The Schauweker et al (1984) study was prospectively designed with diagnostic tests performed in sequential order in 57 consecutive patients. All patients underwent three-phase bone scanning and indium-111 WBC scanning. A total of 29 patients also received gallium-67 scans. Three nuclear medicine physicians assessed the scan results without knowledge of the clinical or pathological status of the patients. Where readings differed, the final result was determined by consensus. The study did not report the anatomical position of the suspected osteomyelitis (eg, vertebral, diabetic foot, long bone) and was therefore deemed unsuitable for further analysis. For completeness, the characteristics of this study are reported in **Appendix C**.

Rosenthall et al (1982) reviewed the case notes of 500 consecutive patients suspected of having septic disease of bone, joint or adjacent soft tissue. Only 223 case notes contained documentation reliable enough to determine the disease state of the patient. Of these, only 159 patients (32 per cent of all cases reviewed) were referred with an initial clinical suspicion of osteomyelitis. Thirty-one patients were considered to have a final positive disease status on the basis of one or more of the following criteria: local fluid or tissue culture positive for bacteria, blood culture positive for bacteria plus localised signs of bone pain and tenderness, biopsy histologically consistent with osteomyelitis, and progressive radiographic bone changes. Another 34 patients were considered to have very high probability of the disease based on clinical evaluation only, the accepted clinical criteria being localised bone tenderness, warmth, swelling, fever and a favourable response to antibiotic treatment. However, this method of assessment does not appear to exclude the possibility of the patient having a soft-tissue infection rather than osteomyelitis. The remaining 94 patients were proven not to have osteomyelitis.

This study was not considered suitable for inclusion in this assessment due to the high number of patients excluded from the initial analysis of case notes (68 per cent), the inclusion of children in the analysis, and the clinical criteria used to define a patient with osteomyelitis. Furthermore, the study did not report the diagnostic accuracy of gallium-67 scanning alone. Therefore, the results of this study were excluded from further consideration in the effectiveness analysis of gallium-67 scanning. For completeness, the characteristics of this study are reported in **Appendix C**.

Is it safe?

LeukoScan®

Theoretical concerns regarding the use of LeukoScan® relate to use of a murine monoclonal antibody fragment (Fab). There is a possibility that the human immune system might perceive LeukoScan® as foreign and mount an immune response against it, producing human anti-mouse antibodies (HAMA).

In subjects with HAMA, there may be a greater chance of anaphylactic and other hypersensitivity reactions whenever mouse protein materials are administered to patients. Therefore, LeukoScan® should be administered only in a setting where, in the event of an adverse reaction, appropriate cardiopulmonary resuscitation facilities and trained personnel are immediately available. Furthermore, there is also a concern that the presence of HAMA in a patient will diminish the efficacy of imaging due to an increased rate of elimination of the labelled cells.

Under the Therapeutic Goods Administration (TGA) listed indication for LeukoScan® it is likely that a proportion of patients would require repeat scans. However, limited data are available regarding the safety and efficacy of re-administration of LeukoScan®. Patients who have previously received murine monoclonal antibodies, from either LeukoScan® or from another product, are more likely to have HAMA. Therefore, administration of LeukoScan® in these patients should be considered only when it has been established that the patient does not have elevated HAMA levels.

Adverse event data

Assessment of the safety of LeukoScan® in the diagnostic testing of patients with suspected osteomyelitis included comparative and non-comparative studies. Studies that described the use of LeukoScan® in different patient groups (eg, patients with inflammatory bowel disease) were excluded from the safety review.

The unpublished study reports provided thorough evaluations of the safety of LeukoScan®. It is important to note that LeukoScan® Study 07 and Study 08 reported all adverse events, including those consistent with the underlying disease, but not related to LeukoScan® administration. By contrast, safety reporting in the published literature was of a poor standard. The studies either did not report any safety data or provided very minimal data. None of the studies reported adverse events unrelated to the radiopharmaceutical administration. Therefore when considering the safety data presented it should be noted that expert opinion suggests that the level of adverse events associated with LeukoScan® and the comparator scans are similarly low in incidence.

A summary of adverse events reported in Study 07 and Study 08 is provided in **Table 11**. In addition, Harwood et al (1999) reported safety data for an additional 48 patients with suspected osteomyelitis secondary to diabetic foot ulcer recruited following the initial Study 07 report.

Table 11 Adverse events – LeukoScan®

Study	Total number of patients	Drop-outs[a]	Patients experiencing adverse events n (%)	Total number of events experienced	Relationship of patients experiencing adverse events to LeukoScan® administration			
					Unrelated/ remote	Unknown	Possible	Probable
Study 07	102	0	17 (16.7)	33	15	2	0	0
Study 08	130	0	16 (12.3)	33	12	2	2	0
Harwood (1999)	150[b]	0	21 (14.0)	39	21		0	0

[a]A dropout was defined as any patient who was lost to follow-up for a period of ≥ 7 days in the 30-day adverse event follow-up period after LeukoScan® administration.
[b]Includes patients in Study 07 (102) and an additional 48 patients recruited following the Study 07 report.

Of the 17 patients in Study 07 experiencing adverse events following LeukoScan® administration, one patient (1.0 per cent) died, three patients (2.9 per cent) experienced a total of four serious/unexpected adverse events, and 14 patients (13.7 per cent) experienced a total of 28 non-serious adverse events. One patient experienced both a serious/unexpected adverse event and a non-serious adverse event. With two exceptions, the clinical investigator judged these events as being either of remote relationship or unrelated to LeukoScan® administration. The two exceptions were non-serious adverse events of unknown relationship to LeukoScan® administration: nausea in one patient, and cough, backache, nausea and vomiting in another.

Of the 16 patients in Study 08 experiencing adverse events following LeukoScan® administration, three patients (2.3 per cent) died, six patients (4.6 per cent) experienced a total of 13 serious/unexpected adverse events, and 10 patients (7.7 per cent) experienced a total of 17 non-serious adverse events. Two patients experienced a serious/unexpected adverse event prior to death, while another patient experienced both a serious/unexpected adverse event and a non-serious adverse event. With four

exceptions, the clinical investigator judged these events as being either of remote relationship or unrelated to LeukoScan® administration. The four exceptions included two patients with non-serious adverse events of unknown relationship to LeukoScan® administration: rhinorrhoea in one patient, and nausea/emesis in another. The other exceptions were two patients with non-serious adverse events that were possibly related to LeukoScan® administration: a rash in one patient and eosinophilia in the other.

Clinical laboratory data

Blood glucose, phosphorous and alkaline phosphate levels, and several of the haematological parameters, showed small but statistically significant changes from baseline. However, the authors of Study 07 and Study 08 did not consider these differences to be clinically significant and they were deemed to be consistent with the clinical course of the patients' underlying disease.

Antibody assays

In Study 07 and Study 08, serum was collected from patients at 4–6 weeks and 3–4 months following LeukoScan® administration for the determination of HAMA titres for both the intact immunoglobulin G (IgG) antibody and the Fab.

Of the 85 patients in Study 07 and the 84 patients in Study 08 who had both pre-injection and post-injection (1–4 months) determination of HAMA titres, no patient had a positive HAMA response to the Fab. Five patients (5.9 per cent) in Study 07 and two (2.4 per cent) in Study 08 developed a positive boost response (ie, an increase in HAMA titre for a patient with HAMA present at baseline) to the intact IgG antibody.

Additional safety data reported in the peer-reviewed publications

In general, safety data were poorly reported in the peer-reviewed publications. However, the available published data suggest that the level of adverse events and probability of inducing a HAMA response following LeukoScan® administration are both low.

Harwood et al (1999) reported safety data for 150 patients, of whom 102 had been included in the Study 07 report. No patient died or dropped out of the study. Of the 150 patients enrolled, five patients experienced a total of six unrelated serious adverse events (one sepsis, five cardiac events), while 18 patients experienced 33 non-serious adverse events (two had both serious and non-serious events). The events were not considered either possibly or probably related to LeukoScan® administration.

None of the 96 patients who had both a pre-injection and at least one (1–4 months) post-injection HAMA determination developed a positive HAMA response or a positive boost response (an increase in HAMA titre in those with HAMA present at baseline) to the Fab. Clinical, chemical and haematological analysis did not reveal any clinically significant changes from baseline following LeukoScan® administration.

Becker et al (1996) reported no adverse events and no significant abnormalities in the blood or urine of the 53 patients following administration of LeukoScan®. Of the 13 patients tested for HAMA before and up to four months following administration, none had an elevation in HAMA. This publication included patients from Becker et al (1994).

No safety data were reported in the studies by Ryan et al (2002) and Devillers et al (2000).

Technetium-99m stannous colloid labelled WBC scanning

No adverse event data were reported in any of the studies of technetium-99m stannous colloid labelled WBC scanning included in the safety evaluation.

The only safety data available were from a small kinetic sub study of 10 patients included in Schroth et al (1981). The total trial population in this study included patients with suspected abdominal abscesses as well as those with septic loosening of an endoprosthesis. Therefore, it was not possible to determine whether the patients in the kinetic sub study fell within the LeukoScan® indication. Consequently these data have not been presented in this assessment.

Gallium-67 scanning

No adverse event data were reported in any of the studies of gallium-67 scanning included in the safety evaluation.

Theoretical safety comparisons between LeukoScan®, technetium-99m stannous colloid labelled WBC scanning and gallium-67 scanning

Preparation and blood handling

There are two main safety issues regarding the preparation and procedure involved in imaging for osteomyelitis:

- the potential for needlestick injury, which is primarily a risk for health care workers; and
- the potential for transmission of blood-borne pathogens to a patient when the procedure involves the withdrawal and reinjection of patients' blood or blood products.

LeukoScan® and gallium-67 scanning both require only a single injection with no blood handling. This represents a safety advantage over technetium-99m stannous colloid labelled WBC scanning, which involves a short five-step procedure where blood is drawn from the patient for WBC labelling before reinjection.

The technetium-99m procedure requires two hollow-bore needle procedures in comparison with the single hollow-bore needle procedure for LeukoScan® and gallium-67 scanning. This is likely to increase the risk of needlestick injury during the technetium-99m procedure. A recent study of the epidemiology of needlestick injury in an Australian tertiary teaching hospital recorded a total of 1836 reported needlestick injuries in a 10-year surveillance period (Whitby and McLaws 2002). These injuries occurred at a higher rate among medical staff, at an annual rate of 10.27 injuries per 100 full-time positions, compared with an annual rate of 8.79 per 100 full-time positions among the nursing staff.

Furthermore, a large US study reported that approximately 400,000 needlestick injuries occur annually among an estimated four million health care workers (Porta et al 1999). This equates to a ratio of one injury per 10 workers each year, which is similar to the findings of Whitby and McLaws (2002). Porta et al (1999) also found that the risk of needlestick injury and the risk of subsequent infection is associated with invasiveness,

frequency, complexity, and extent of blood and body substance exposure during the procedures.

Another way to estimate the safety advantage offered by LeukoScan® and gallium-67 scanning over technetium-99m stannous colloid labelled WBC scanning is to use data from Jagger et al (1992), that reported a rate of 6.9 needlestick injuries per 100,000 needles purchased in a US university hospital. Given that technetium-99m stannous colloid labelled WBC scanning requires twice as many devices (withdrawal and reinjection) as LeukoScan® and gallium-67 scanning, and that there are an estimated 471–916 scans performed annually in Australia, the number of needlestick injuries saved would be 6.9 per 100,000 or 0.032–0.063 needlestick injuries per year.

Furthermore, it should be noted that only a small percentage of needlestick injuries involve needles containing pathogens. Of the needlestick injuries that do contain pathogens, again only a small percentage would lead to infection in the injured individual. In the Australian study by Whitby and McLaws (2002), 127 (6.9 per cent) of the 1836 needlestick injuries involved exposure to potential infection. Five staff sustained needlestick injuries associated with patients positive for human immunodeficiency virus (HIV), 23 associated with hepatitis B virus (HBV), and 99 associated with hepatitis C virus (HCV) patients. No seroconversion indicating HIV, HBV or HCV infection was recorded. Similarly, Jagger et al (1992) found no documented case of infection or infectious disease from the 326-needlestick injuries observed during their 10-month study.

Nuclear medicine procedures that involve withdrawal and reinjection of blood products can also expose patients to pathogens as a result of misadministration of the blood products. A US paper published in 1992 reported on three patients (two in hospitals in the US and one in the Netherlands) who inadvertently received intravenous injections of blood or other material from patients infected with HIV (Grinsberg et al 1992). The authors noted that administration errors in nuclear medicine are relatively rare. They estimated that approximately one misadministration occurred in 10,000 nuclear medicine procedures in the US in the period 1981–1990, and most of these involved an incorrect dose or radiopharmaceutical and/or errors in patient identification. Given the increased awareness of administration errors in recent times and similarity between the US and Australian nuclear medicine settings, it seems reasonable to assume that these data can be applied to patients who fall within the proposed LeukoScan® indication. Therefore, with an estimated 480–920 technetium-99m stannous colloid labelled WBC procedures per year in Australia, this suggests a total of 0.048–0.092 misadministrations could be avoided annually. As with needlestick injury, the risk of any such misadministration leading to infection or infectious disease of a patient is low.

In summary, LeukoScan® offers a safety advantage over technetium-99m stannous colloid labelled WBC scanning by reducing the needlestick injury risk to nuclear medicine technicians, and by reducing the risk of administration errors in patients. However, given the very low rate of these events, this safety advantage appears to be marginal.

Exposure to radiation

Exposure to high levels of ionising radiation has been linked with the theoretical possibility of cancer induction and the development of hereditary defects. However diagnostic imaging agents only emit low dose ionising radiation, and to date, have not been linked to any long-term complications when used in the imaging of infection.

Nevertheless, it is recognised that ionising radiation doses should be kept as low as possible. As the radiopharmaceuticals labelled with technetium are associated with a lower radiation dose per patient than those labelled with gallium, LeukoScan® and technetium-99m stannous chloride labelled WBCs both have a theoretical safety advantage over gallium-67 citrate scanning. The relative radiation dosimetry of the technetium and gallium based compounds is presented in **Table 12**.

Table 12 Relative radiation dosimetry of LeukoScan®, other radiopharmaceuticals used for osteomyelitis imaging and other reference procedures

	Average administered activity (MBq)	Effective radiation dose (mSv)
Radiopharmaceutical		
Technetium-99m LeukoScan	900	9.9
Gallium-67 citrate[a]	185	20.3
Indium-111 labelled WBCs	28	10.0
Reference scan or procedure		
Bone scan (Technetium-99m phosphate)[b]	900	5.2
CT - pelvis	NA	7.3
Plain film X-ray - IVP	NA	4.6
Annual background radiation[c]	NA	2.8

Source: Mountford (1995).
Abbreviations: CT, computed tomography; IVP, intravenous urogram; NA, not applicable; WBC, white blood cell.
[a]Murray and Ell (1994) report an effective dose of 16.5 mSv based on dose of 150 MBq. The standard Australian dose is 185 MBq so the effective radiation dose was therefore upscaled to make the value relevant to the Australian health care setting.
[b]The standard Australian dose for a bone scan is 900 rather than 600 MBq. The effective radiation dose was therefore upscaled to make the value relevant to the Australian health care setting.
[c]Murray and Ell (1994) report a total effective natural dose of 2.4 mSv per annum and a total man-made effective dose of 0.4 mSv per annum, equating to a total background effective dose of 2.8 mSv per annum.

Is it effective?

Available evidence

LeukoScan®

Table 13 provides a summary of the clinical evidence retrieved for review in the effectiveness assessment of LeukoScan®. Levels of evidence were assigned to the studies according to the National Health and Medical Research Council (NHMRC) definitions (NHMRC 1999) and definitions specific to assessing the diagnostic accuracy of diagnostic tests (Bandolier 2002).

A more detailed assessment of study quality was undertaken and a quality score was derived using a modification of the diagnostic-specific checklist published by the Cochrane Screening and Diagnostic Tests Methods group (**Appendix G**). Two evaluators independently scored each of the included studies.

Only two studies reported the diagnostic accuracy of LeukoScan® specifically in patients with suspected osteomyelitis in long bones and in feet, including those with diabetic foot ulcers (Study 08; Harwood et al 1999).

No studies adequately reported whether or how the various imaging modalities led to a change in clinical management or a change in clinical outcomes associated with LeukoScan®.

Table 13 Levels of evidence and study characteristics – LeukoScan®

	Study 08	Harwood (1999)
Level of evidence		
Bandolier (2002)	4	4
NHMRC	III-2	III-2
Quality score[a]	8	8
Diagnostic work-up consistent with Australian setting[b]	x	x
Patient characteristics	Suspected osteomyelitis of the long bones	Suspected osteomyelitis in patients with diabetic foot ulcers
Patient numbers		
LeukoScan®		
n (ITT)	n = 130	n = 150
n (eval)	n = 96	n = 122
Reference standard		
n (eval)	n = 96	n = 123
Comparator		
n (ITT)	n = 130	n = 150
n (eval)	n = 88	n = 111
Reference standard	Bone biopsy	Bone biopsy
Comparator	^{111}In oxine *or* ^{99m}Tc HMPAO WBC scan	^{111}In oxine *or* ^{99m}Tc HMPAO WBC scan

Abbreviations: eval, evaluable patients; HMPAO, hexamethylpropyleneamine oxime; ^{111}In, indium-111; ITT, intention-to-treat; NHMRC, National Health and Medical Research Council; ^{99m}Tc, technetium-99m; WBC, white blood cell.
[a] 0 = poor, 15 = excellent. The quality score is based on the scale described in **Appendix G**.
[b]Diagnostic work-up should consist of preliminary diagnostic investigations such as plain radiography and radioisotope bone scanning (unless not clinically appropriate).

Harwood et al (1999) and Study 08 were of a prospective, multicentre, single-group, non-randomised design, with blinded and un-blinded analyses and diagnostic tests performed in sequential order. It was not reported whether the trials were performed in consecutive patients. The objective of Harwood et al (1999) was to evaluate the safety and efficacy of LeukoScan® for the diagnosis of osteomyelitis in patients with diabetic foot ulcers. Study 08 was designed to evaluate the safety and efficacy of LeukoScan® for the diagnosis of long bone osteomyelitis. It should be noted that a small number of patients included in Study 08 had suspected vertebral osteomyelitis. This presentation is outside of the TGA-listed indication for LeukoScan® (ie, patients with osteomyelitis of the long bones or feet, including those with diabetic foot ulcers). It was not possible to separate these patients from the analysis *post hoc*. However, due to the small number of patients with suspected vertebral disease included in Study 08, it is unlikely that the inclusion of these patients will have a significant effect on the overall diagnostic accuracy reported in the study.

Neither study required that a patient should have a positive or equivocal plain radiograph or three-phase radiographic bone scan prior to trial inclusion. Rather, both trials accepted patients with a "high index of suspicion for osteomyelitis". Neither trial defined how patients with a high index of suspicion for osteomyelitis were identified. Subjects who were treated with antibiotics within the past 30 days were enrolled only if the subject showed no clinical response to antibiotic therapy, *or* if it were already determined that the subject would be undergoing a biopsy of the bone and surrounding soft tissue. Initially,

both trials were designed to compare LeukoScan® with indium-111 labelled WBC scanning. However, indium oxine was not available for a short period of time and technetium-99m HMPAO labelled WBCs were used instead. Final diagnoses were obtained by bone biopsy for histology and/or culture.

The comparative effectiveness of LeukoScan® and indium-111 or technetium-99m HMPAO labelled WBC scanning was determined only by non-independent, informed, unblinded, on-site assessment. Importantly, the authors note that the on-site clinician might have had access to the results of the WBC scans for some patients. This is likely to have undermined the comparative analysis of LeukoScan® and indium-111 or technetium-99m HMPAO labelled WBC scanning. No independent comparative assessment of LeukoScan® was performed in either trial. However, an analysis of LeukoScan® alone was performed in an independent blinded assessment (ie, without knowledge of the patients' clinical data or diagnostic information) and in an independent informed assessment (with knowledge of all clinical data, except the WBC scan results).

Technetium-99m stannous colloid labelled WBC scanning

No studies were identified that reported the diagnostic accuracy of technetium-99m stannous colloid labelled WBC scanning specifically in the TGA-indicated patient population for LeukoScan®.

As there were no studies available that investigated how the use of LeukoScan® influenced changes in clinical management or clinical outcome, no comparison could be made with technetium-99m stannous colloid labelled WBC scanning.

Gallium-67 scanning

Table 14 provides a summary of the single study meeting the inclusion criteria for the review of the diagnostic accuracy of gallium-67 scanning (Johnson et al 1996). Levels of evidence were assigned to the study according to the NHMRC definitions (NHMRC 1999) and definitions specific to assessing the accuracy of diagnostic tests (Bandolier 2002).

A more detailed assessment of study quality was undertaken and a quality score was derived using a modification of the diagnostic-accuracy-specific checklist published by the Cochrane Screening and Diagnostic Tests Methods group (**Appendix G**). Two evaluators independently scored the included study.

As there were no studies identified that adequately described the change in clinical management or the change in clinical outcomes directly attributable to LeukoScan®, no comparison could be made between the two testing modalities.

Table 14 Levels of evidence and study characteristics – gallium-67 scanning

	Johnson (1996)
Level of evidence	
Bandolier (2002)	2
NHMRC	III-2
Quality score[a]	9
Diagnostic work-up consistent with Australian setting[b]	x
Patient characteristics	Adult diabetics with suspected osteomyelitis of the foot or ankle
Patient numbers	
Gallium-67 scan	
n (ITT)	n = 22
n (eval)	n = 22
Reference standard	
n (eval)	n = 22
Comparators	
n (ITT); n (eval)	Plain radiography: 22; 22
	^{99m}Tc MDP: 22; 22
	^{111}In: 22; 22
	^{99m}Tc/^{111}In: 22; 22
Reference standard	Deep culture and histology and/or long-term clinical follow-up
Comparators	Plain radiography; ^{99m}Tc MDP; ^{111}In; ^{99m}Tc MDP/^{111}In

Abbreviations: eval, evaluable patients; ^{111}In, indium-111; ITT, intention-to-treat; MDP, methylene diphosphonate; NHMRC, National Health and Medical Research Council; ^{99m}Tc, technetium-99m.

[a]0 = poor, 15 = excellent. The quality score is based on the scale described in **Appendix G**.

[b]Diagnostic work-up should consist of preliminary diagnostic investigations such as plain radiography and radioisotope bone scanning (unless not clinically appropriate).

The Johnson et al (1996) study was of a prospective, single-group design, with diagnostic tests performed in sequential order. It was not reported whether the study was performed in consecutive patients. The objective of the study was to compare the diagnostic accuracy of gallium-67 scanning, plain radiography (X-ray), technetium-99m MDP bone scanning, indium-111-labelled leucocyte scanning, and a combination of technetium-99m/indium-111 scanning. The radiologists/nuclear medicine physicians were informed of the site of clinical interest, but did not have additional clinical, radiographic or pathological information about patients' true disease states.

The study included 22 patients with suspected osteomyelitis of the foot or ankle. To qualify for inclusion into the study, patients were required to test positive for loss of protective sensibility of the foot by Semmes-Weinstein monofilament pressure aesthesiometry (inability to feel the 5.07 monofilament).

It is important to note that initial treatment was not withheld from patients participating in the Johnson et al (1996) study. At the time of imaging, 16 of the 22 patients had already received 1–14 days of antibiotic therapy. The final diagnosis of osteomyelitis was established for 12 patients by deep culture and histology. The remaining 10 patients were considered disease-negative on the basis of deep culture and histology *and/or* long-term clinical follow-up (3–18 months).

Results

Diagnostic accuracy

There were no head-to-head comparisons of LeukoScan® with technetium-99m stannous colloid labelled WBC scanning or LeukoScan® with gallium-67 scanning. Therefore, the feasibility of performing an indirect comparison of these diagnostic modalities was considered.

Two trials of LeukoScan® were identified in the TGA-indicated patient population (ie, patients with suspected osteomyelitis of the long bones and feet, including those with diabetic foot ulcers) (Harwood et al 1999; Study 08). No trials of technetium-99m stannous colloid labelled WBC scanning were identified in the specific patient population of interest. Therefore, an indirect comparison of the diagnostic accuracy of LeukoScan® and technetium-99m stannous colloid labelled WBC scanning could not be performed.

After review of the studies identified for gallium-67 scanning, it was found that only one study reported the diagnostic accuracy of gallium-67 scanning in an appropriate patient population (Johnson et al 1996). However, this study involved only 22 patients and a considerable proportion of these patients (73 per cent) had received 1–14 days of antibiotic therapy between the time of the reference standard and the various imaging procedures. Furthermore, the prevalence of true disease in the included patient population was lower (55 per cent) than in the patient population included in the Harwood et al (1999) study (68 per cent). Therefore, on their own, the data presented by Johnson et al (1996) were considered inadequate to form the basis of an indirect comparison between gallium-67 scanning and LeukoScan®.

Since indirect comparison of LeukoScan® with technetium-99m stannous colloid labelled WBC scanning and with gallium-67 scanning could not be performed, an alternative approach was needed to aid in the decision-making process. An analysis of trials reporting a direct comparison of the diagnostic accuracy of LeukoScan® with either indium-111 or technetium-99m labelled HMPAO WBC scanning in the TGA-indicated patient population was therefore carried out.

LeukoScan® versus indium-111 or technetium-99m labelled HMPAO WBC scanning

The recommended methodology for investigating the accuracy of a new diagnostic test is to compare the diagnosis made with the new test with the true disease status. However, it is often not feasible to determine the disease status of a patient unequivocally. Therefore, in many disease states, a proxy measure – such as another diagnostic test or clinical judgement – must be used. The best available measure of disease is called the reference standard. Both the LeukoScan® and the comparator results must be independently compared with the reference standard to assess accuracy. In this way, the difference in accuracy between LeukoScan® and the comparator can be determined.

Currently, the best way of determining whether osteomyelitis is present in patients with suspected disease of the long bones and feet, including those with diabetic foot ulcers, is bone biopsy and histology or culture. For pragmatic reasons, it was decided (on the basis of expert opinion) that studies reporting long-term clinical follow-up as a reference standard would also be included in the assessment.

Where possible, the following markers of diagnostic effectiveness were calculated:

- Sensitivity – the ability to detect osteomyelitis among patients in whom it is present.
- Specificity – the ability to detect no osteomyelitis among patients in whom it is absent.
- Accuracy – the proportion of all tests giving the correct result, as proportion of all results (calculated as a diagnostic odds ratio (DOR) from the sensitivity and specificity).
- Positive predictive values (PPV) – the ability to detect positive patients only among positive scans (ie, avoid false-positives).
- Negative predictive values (NPV) – the ability to detect negative patients only among negative scans (ie, avoid false-negatives).

The Harwood et al (1999) trial and Study 08 reported the comparative diagnostic performance of LeukoScan® with patients scanned with either indium-111 labelled WBC or technetium-99m labelled HMPAO WBC. **Table 15** summarises the results of the on-site blinded assessment of all patients who underwent LeukoScan® testing *and* indium-111 labelled WBC scanning or technetium-99m labelled HMPAO WBC scanning *and* biopsy in these two studies.

Table 15 Unblinded on-site assessment of patients with suspected osteomyelitis – LeukoScan® versus technetium-99m labelled HMPAO WBC or indium-111 labelled WBC scanning for patients who underwent each test and bone biopsy

		Harwood (1999)[a]		Study 08	
Diagnostic test		LeukoScan®	^{111}In WBC or ^{99m}Tc WBC scanning[c]	LeukoScan®	^{111}In WBC or ^{99m}Tc WBC scanning[c]
Patient characteristics		Suspected osteomyelitis in patients with diabetic foot ulcers		Suspected osteomyelitis of the long bones	
Sensitivity[b]	% n/N (95% CI)	92% ($p < 0.05$)[d] 69/75 (83, 97)	79% 59/75 (68, 87)	76.7% ($p = 0.07$)[d] 23/30 (58, 90)	56.7% 17/30 (37, 75)
Specificity	% n/N (95% CI)	58% 21/36 (41, 75)	67% 24/36 (49, 81)	72.4% 42/58 (59, 83)	72.4% 42/58 (59, 83)
Accuracy	% n/N (95% CI)	81% 90/111 (73, 88)	75% 83/111 (66, 83)	73.9% 65/88 (63, 83)	67.0% 59/88 (56, 77)
PPV	% n/N (95% CI)	82% 69/84 (72, 90)	83% 59/71 (72, 91)	59.0% 23/39 (42, 74)	51.5% 17/33 (33, 69)
NPV	% n/N (95% CI)	78% 21/27 (58, 91)	60% 24/40 (43, 75)	85.7% 42/49 (73, 94)	76.4% 42/55 (63, 87)

Abbreviations: CI, confidence interval; HMPAO, hexamethylpropyleneamine oxime; ^{111}In, indium-111; NPV, negative predictive value; PPV, positive predictive value; ^{99m}Tc, technetium-99m; WBC, white blood cell.

[a]Data also published in Study 07, Hakki et al (1997) and Harwood et al (1994).

[b]It was only possible to derive *p* values for the difference in sensitivity between LeukoScan® and indium-111/technetium-99m labelled WBC scanning. No significance test was performed for specificity, accuracy, PPV or NPV.

[b]Initially both trials were designed to compare LeukoScan® with indium-111 labelled WBC; however, indium oxine was not available for a short period of time and technetium-99m HMPAO labelled WBCs were then used instead. The results of these testing methods (ie, indium-111 labelled WBC and technetium-99m HMPAO labelled WBCs) were reported as pooled outcomes.

[c]The *p* values pertain to the difference in diagnostic sensitivity between LeukoScan® and indium-111/technetium labelled WBC scanning.

Table 16 shows that the sensitivity of disease detection with LeukoScan® (92 per cent) in patients with diabetic foot ulcers who are suspected of having osteomyelitis was significantly higher than with indium-111 and technetium-99m labelled HMPAO WBC scanning (79 per cent; $p < 0.05$). It should be noted that this difference might simply be a function of the threshold at which a positive diagnosis is made. In contrast, the specificity of the LeukoScan® test was numerically lower than indium-111 and technetium-99m labelled HMPAO WBC scanning in this patient group (58 and 67 per cent, respectively). Therefore, in patients with diabetic foot ulcers, the diagnostic accuracy of LeukoScan® compared with indium-111 and technetium-99m labelled HMPAO WBC scanning was not significantly different (81 and 75 per cent, respectively).

In patients with suspected osteomyelitis of the long bones, the diagnostic accuracy of LeukoScan® compared with indium-111 or technetium-99m labelled HMPAO WBC scanning was not significantly different (73.9 and 67.0 per cent, respectively). Similarly, the sensitivity for disease detection of LeukoScan® compared with indium-111 or technetium-99m labelled HMPAO WBC scanning was not significantly different in these patients (76.7 and 56.7 per cent, respectively; $p = 0.07$). In this patient group, the specificities of the diagnostic modalities were equal (72.4 per cent).

LeukoScan® therefore had a numerically higher sensitivity in patients with diabetic foot ulcers who are suspected of having osteomyelitis than in patients with suspected osteomyelitis of the long bones (92 and 76.7 per cent, respectively). A similar trend was seen when comparing the WBC scanning (indium-111 and technetium-99m labelled HMPAO) diagnostic performance in patients with diabetic foot ulcers who are suspected of having osteomyelitis and those with suspected osteomyelitis of the long bones (79 and 56.7 per cent, respectively).

In contrast, the specificity of the LeukoScan® test was numerically lower in the diabetic foot group than in the long bone group (58 and 72.4 per cent, respectively). The specificity of WBC scanning (indium-111 and technetium-99m labelled HMPAO) was similar in patients with diabetic foot ulcers who are suspected of having osteomyelitis (67 per cent) and in those with suspected long bone osteomyelitis (72.4 per cent).

It is important to note that the data reported in Harwood et al (1999) and Study 08 were based on a non-independent, on-site assessment of LeukoScan® and indium-111 and technetium-99m labelled HMPAO WBC scanning. In this setting, the authors note that the on-site clinician "may have had access to the results of the WBC scans for some patients" when interpreting the LeukoScan® results. This is likely to undermine the comparative analysis of LeukoScan® and indium-111 and technetium-99m labelled HMPAO WBC scanning presented in Harwood et al (1999) and Study 08.

As shown above, there is considerable variation between the diagnostic performance of LeukoScan® in patients with diabetic foot ulcers who are suspected of having osteomyelitis and those with suspected osteomyelitis of the long bones. This is understandable considering that the presence of a foot ulcer in a diabetic patient is likely to be strongly suggestive of underlying osteomyelitic disease. By comparison, a non-diabetic patient with suspected osteomyelitis of the long bones is less likely to have this disease. In fact, Harwood et al (1999) reported the prevalence of confirmed disease in their study population (patients with diabetic foot ulcers) was 68 per cent, while in Study 08 (long bones) it was reported to be 34 per cent (percentages derived from patients who received both tests *and* were assessed by biopsy). Furthermore, osteomyelitic disease may be less ambiguous in the diabetic foot than in long bones. Therefore, due to the clinical

heterogeneity between these patient groups, results from the Harwood et al (1999) study and Study 08 were not pooled within this assessment.

Change in clinical management

No studies adequately reported changes to clinical management directly attributable to the use of LeukoScan® in the appropriate patient population. Therefore, a comparative analysis of the effect of the various testing modalities on clinical management could not be performed.

Delineation of the treatment of osteomyelitis is difficult for several reasons: debridement obscures the impact of antibiotics, the clinical situations and pathogens associated with the disease are heterogeneous, years of follow-up may be necessary to demonstrate sustained remission, and many of the studies of antibiotic therapy have enrolled only small numbers of patients.

However, it is known that the best clinical outcomes are achieved when there is early diagnosis and prompt initiation of antibiotic therapy, before extensive destruction of the bone (Carek et al 2001). If osteomyelitis is detected early enough and antibiotic therapy is successful, surgical debridement of the bone and surrounding tissue is not always necessary.

If a false-negative diagnosis is made, this may delay appropriate clinical management of the patient. Based on expert opinion, the possible implications of a false-negative diagnosis for the clinical management of patients with osteomyelitis are as follows.

- No change in management.
- Surgical debridement where none would be required if the infection had been promptly detected and successfully treated, or more extensive surgical debridement than would otherwise be required. The resultant 'dead space' must then be managed and, if necessary, the bone must be stabilised. Dead space management may include local myoplasty, free-tissue transfers and the use of antibiotic-impregnated beads or cement. In patients with osteomyelitis associated with a prosthetic device, the prosthesis may have to be removed, followed by surgical debridement, packing of the dead space (eg, with antibiotic-impregnated beads or myoplasty) and, if infection is cleared, prosthetic replacement.
- In more severe cases a delay in the clinical management of a patient may require the amputation of the affected limb or extremity (eg, the diabetic foot).

If a false-positive diagnosis is made, the patient is likely to receive unnecessary and intensive antimicrobial treatment. The antimicrobial therapy chosen for treatment of the osteomyelitis is dependent on the microbial aetiology of the infection and the *in vitro* antibiotic susceptibility profile of the pathogen detected. In general, patients in Australia are treated with a course of parenteral antibiotics while in hospital (average length of stay = 10.39 days[1]), followed by a period of 'hospital in the home' care where parenteral antibiotic therapy is completed (parenteral antibiotic therapy is generally given for a

[1]Derived from a weighted average of AR-DRG (Australian-refined diagnosis-related groups) v5 codes I64a and I64b.

minimum period of six weeks). If necessary, the patient may then be treated with a course of oral antibiotic therapy. However, in the case of a false-positive diagnosis (eg, a patient with a soft-tissue infection but no underlying osteomyelitis), it is likely that the patient will be 'cured' earlier in this intensive treatment programme than if there were true osteomyelitic disease. Some false-positive patients may have limited removal of healthy bone in an attempt to confirm the diagnosis.

Change in clinical outcomes

No trials adequately reported changes in clinical outcomes associated with the use of LeukoScan® in the appropriate patient population. Therefore, a comparative analysis of the effect of the various testing modalities on clinical outcomes could not be performed.

The implications of a false-negative diagnosis on clinical outcomes will depend on the length of delay before the disease is detected and the aggressiveness of the osteomyelitic infection. Based on expert opinion, the clinical outcomes associated with a false-negative diagnosis include the following.

- No change in clinical outcome.
- Removal of infected bone and surrounding tissue where none would be required if the infection had been promptly detected and successfully treated, or more extensive removal of infected bone and surrounding tissue than otherwise required, with a resultant increase in morbidity and disability. In patients with osteomyelitis associated with a prosthetic device, the prosthesis may have to be removed, followed by surgical debridement, packing of the dead space (eg, with antibiotic-impregnated beads or myoplasty) and, if infection is cleared, prosthetic replacement. This process would be associated with a marked increase in morbidity and temporary or possible permanent disability for the patient.
- Amputation, with a resultant increase in morbidity and disability.
- In rare cases, a delay in the detection of osteomyelitis may have the potential to cause death (eg, due to septicaemia, especially in immunocompromised patients).

The implications of a false-positive diagnosis on patient-relevant health outcomes are likely to be less severe, and may include the following.

- Limited removal of healthy bone to attempt to confirm the diagnosis, which may be accompanied by an increase in morbidity.
- Increased time in hospital and in 'hospital in the home' care for the administration of parenteral antibiotics.

A false-positive diagnosis also has implications with regards to resource use. These implications are discussed in the following economic sections.

What are the economic considerations?

The review of the clinical effectiveness of LeukoScan® indicated that there is insufficient evidence to prove that LeukoScan® is a superior diagnostic procedure to either of the main comparators (gallium-67 scanning or technetium-99m stannous colloid labelled WBC scanning). The proposed fee for LeukoScan® is also greater than that for either of these comparators. Therefore, a cost-effectiveness analysis would show that LeukoScan® is a dominated intervention – ie, it has greater costs without evidence of additional health benefits.

Nevertheless, an economic analysis was conducted to explore the cost-effectiveness of LeukoScan® based on the nominally better accuracy of LeukoScan® when compared with indium-111 and technetium-99m labelled HMPAO WBC scanning, as reported in Harwood et al (1999) and Study 08. The economic analysis assumes that the diagnostic accuracy of gallium-67 scanning is equivalent to technetium-99m labelled HMPAO WBC scanning. It is therefore assumed that the benefit of LeukoScan® relative to gallium-67 scanning is equivalent to the benefit of LeukoScan® relative to technetium-99m labelled HMPAO WBC scanning, as observed in the clinical trials. The economic evaluation does not compare LeukoScan® with technetium-99m stannous colloid labelled WBC scanning.

Therefore, the economic analysis determines whether LeukoScan® has the potential to be cost-effective relative to the most commonly used diagnostic procedures in Australia if evidence of its greater diagnostic accuracy were confirmed.

The economic evaluation found that LeukoScan® was most cost-effective in patients with suspected osteomyelitis of the long bones or feet. In these patients, LeukoScan® more accurately identified disease-positive patients than technetium-99m labelled HMPAO WBC scanning, at an incremental cost of $24,056 per additional patient free of osteomyelitis. In patients with diabetic foot ulcers and suspected osteomyelitis, the incremental cost of LeukoScan®, compared to technetium-99m labelled HMPAO WBC scanning, per additional patient detected with osteomyelitis was $26,348.

The incremental cost-effectiveness of LeukoScan® relative to gallium-67 scanning, and the assumptions used in the economic evaluation, are described below.

Approach

To assess the value-for-money of a new health intervention, it is necessary to express the incremental cost associated with the new treatment relative to the incremental health benefit gained. When this information is available, an incremental cost-effectiveness ratio (ICER) can be calculated:

$$\text{ICER} = \frac{\text{Cost}_{\text{new technology}} - \text{Cost}_{\text{comparator}}}{\text{Effectiveness}_{\text{new technology}} - \text{Effectiveness}_{\text{comparator}}}$$

When determining the incremental cost of the new technology, several factors should be considered: the costs of the intervention itself; the costs of any downstream management including any costs secondary to misdiagnosis or non-compliance; treatment costs for any adverse reactions; and also any cost-savings achieved.

With respect to incremental effectiveness, there are several ways of expressing the effectiveness of the treatment. It may be expressed as a measured intermediate health outcome (eg, mmHg reduction in blood pressure) or as an end-stage outcome (eg, life-years gained). Alternatively, effectiveness may be expressed as quality-adjusted life-years (QALYs) gained, a measure that incorporates both the quality and the quantity of life-years gained (a cost-utility analysis).

In the current assessment, an economic evaluation was used to determine the cost-effectiveness of LeukoScan® for the detection of osteomyelitis. Patients free of osteomyelitis was the health outcome used to assess the value-for-money offered by LeukoScan®. Hence, the ICER calculated in this economic evaluation was the incremental cost per additional patient free of osteomyelitis. The ICER was calculated for the two indications for LeukoScan® that are the subject of this review: patients who are suspected of having osteomyelitis of the long bones or feet, and patients with diabetic foot ulcers who are suspected of having osteomyelitis. The value-for-money that the ICERs represent can be interpreted by considering the cost-savings and improved health outcomes associated with curing a patient of osteomyelitis.

A summary of the key assumptions used in the economic model are presented below:

- The analysis compared LeukoScan® with both technetium-99m labelled HMPAO WBC scanning[2] and gallium-67 scans. The latter is included as a comparator due to the frequency with which it is used in Australia. Point estimates of the sensitivity and specificity of the diagnostic procedures were derived from the clinical trials. Due to a lack of head-to-head clinical trial data comparing LeukoScan® with the main-comparator (gallium-67 scanning) it has been assumed that technetium-99m labelled HMPAO WBC scanning and gallium-67 scanning have equivalent accuracy.

- The effectiveness of LeukoScan® was based on data from Study 08 (patients with suspected osteomyelitis of the long bones or feet) and Harwood et al (1999) (patients with diabetic foot ulcers who were suspected of having osteomyelitis).

- The true prevalence of osteomyelitis in the economic model was based on the prevalence observed in the pivotal clinical trials. Sensitivity analysis considered different estimates for the true prevalence of the disease. The true prevalence of osteomyelitis was 34 per cent (30/88) in patients with suspected osteomyelitis of the long bones or feet and 68 per cent in patients with diabetic foot ulcers (75/111).

[2]Although Study 08 and Harwood et al (1999) used a combination of technetium-99m labelled HMPAO WBC scans and indium-111 WBC labelled scans, only the former is reimbursed under the Medicare Benefits Schedule. Additionally, it was not possible to perform a comparison with technetium-99m stannous colloid labelled WBC scanning. Consequently, only technetium-99m labelled HMPAO WBC scanning is included in the economic analysis.

- All patients incurred the costs of the initial diagnostic procedures and associated professional attendances. The Medicare Benefits Scheme (MBS) fees used in the analysis were assumed to incorporate the cost of consumable items, professional time and depreciation of capital equipment associated with the procedure.

- Patients in which osteomyelitis was not detected were assumed to incur no further health care costs. A sensitivity analysis includes a case where these patients incur additional follow-up costs of between $1,000 and $10,000 per patient. However, this sensitivity analysis does not incorporate the knock-on effect of these additional costs on altering patient outcomes in the economic model.

- Patients in which osteomyelitis was detected were followed until the completion of the first round of antimicrobial therapy. This therapy included an initial period of hospitalisation and continued with the remainder of the antimicrobial therapy being administered in the 'hospital in the home' setting. The model followed patients until the completion of antimicrobial therapy, at which point the number of patients free of osteomyelitis was estimated based on the probability that the patient was detected with the disease and the probability that the treatment initiated was successful.

- It was assumed that 75 per cent of disease-positive patients were cured following hospitalisation and antimicrobial therapy for osteomyelitis.

- For simplicity, it was assumed that there were no equivocal results and patients received only one diagnostic test. (It is anticipated that the number of equivocal results would be small, so that this assumption would have little impact on the overall results.)

- The costs and health consequences of needlestick injuries were not included in the analysis. Due to the very low rate of these events, the effect of excluding these costs and consequences on the results of the analysis are negligible.

- All costs and outcomes were assumed to occur within a one-year period, hence discounting of costs and health outcomes was not required.

Model structure and variables

The decision-analytic model used in this economic evaluation is presented in **Figure 4**. The tree structure is used to calculate the incremental cost-effectiveness of LeukoScan®.

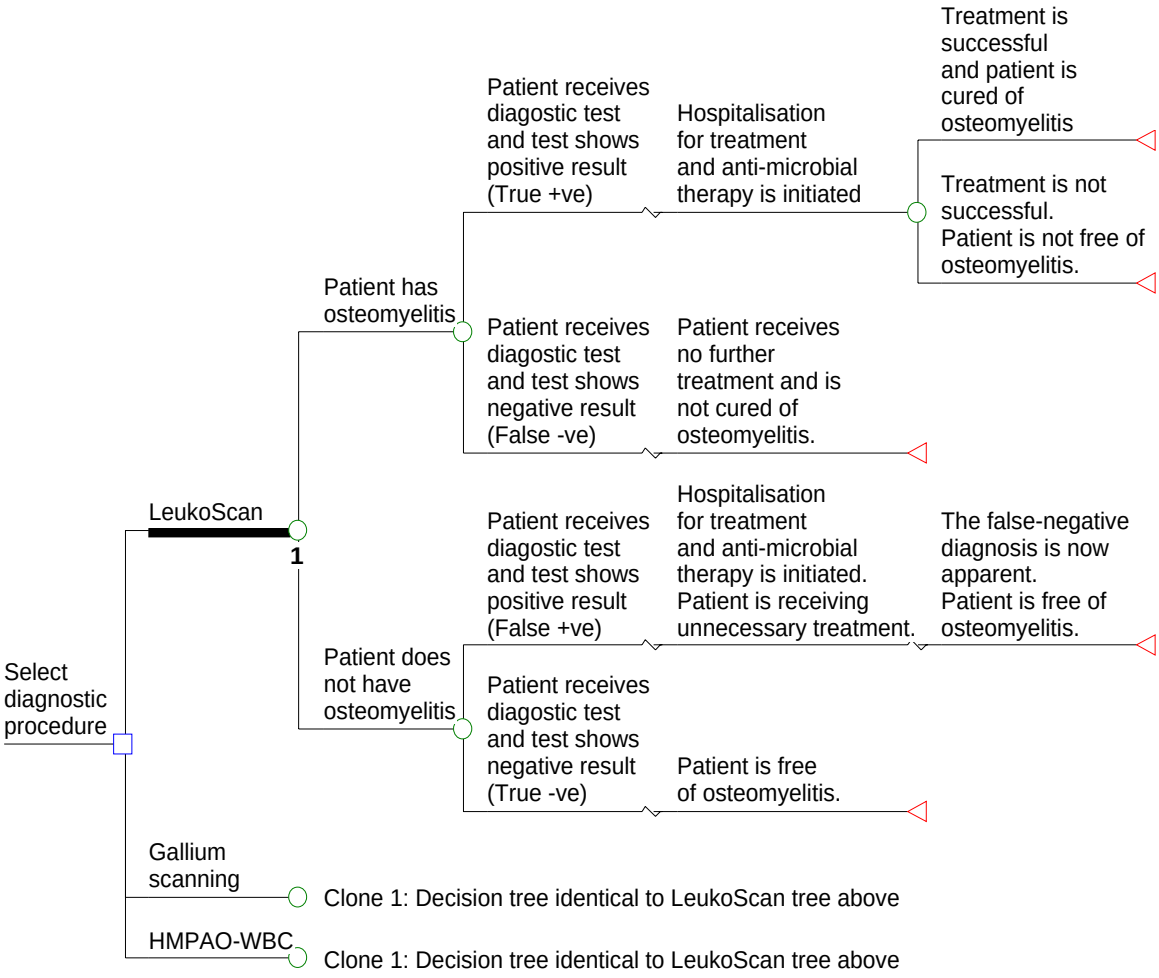

Figure 4 Decision-analytic model

The variables included in the model are described below. The structure of this decision-tree is generic and was applied to each of the patient populations and diagnostic procedures. The probability of a correct diagnosis depends on the patient population and the diagnostic procedure being analysed.

Clinical trial variables

The clinical trial variables used to populate the decision-analytic model were the sensitivity and specificity of the respective diagnostic procedures.

In patients with suspected osteomyelitis in the long bones and feet, LeukoScan® was more sensitive than technetium-99m labelled HMPAO WBC scanning (and, by assumption, the main comparator, gallium-67 scanning), detecting 77 per cent of all diseased patients compared with 57 per cent of diseased patients detected with technetium-99m labelled HMPAO WBC scanning. Also, LeukoScan® had equivalent specificity with technetium-99m labelled HMPAO WBC scanning in this indication (72 per cent).

In patients with diabetic foot ulcers, LeukoScan® was more sensitive than technetium-99m labelled HMPAO WBC scanning (92 vs 79 per cent), but had poorer specificity. LeukoScan® gave a correct negative diagnosis in 58 per cent of patients free of the disease, compared with 67 per cent with technetium-99m labelled HMPAO WBC scanning. The sensitivity and specificity of the respective diagnostic tests applied to the economic model are presented in **Table 16**.

Table 16 Accuracy of diagnostic tests in patients with suspected osteomyelitis

Diagnostic test	Sensitivity % (n/N)	Specificity % (n/N)
Suspected osteomyelitis of the long bones or feet[a]		
LeukoScan®	77% (23/30)	72% (42/58)
Technetium-99m labelled HMPAO WBC scanning	57% (17/30)	72% (42/58)
Gallium-67 scanning (assumed)	57%	72%
Suspected osteomyelitis in patients with diabetic foot ulcers[b]		
LeukoScan®	92% (69/75)	58% (21/36)
Technetium-99m labelled HMPAO WBC scanning	79% (59/75)	67% (24/36)
Gallium-67 scanning (assumed)	79%	67%

Source: [a]Study 08, [b]Harwood et al (1999).
Abbreviations: HMPAO, hexamethylpropyleneamine oxime; WBC, white blood cell.

It is important to note that the lower specificity of LeukoScan® in patients with suspected osteomyelitis of the long bones and feet added to the total cost of LeukoScan®. This was because the resource wastage and consequent costs associated with treatment received on the basis of a false-positive result were included in the economic model.

The true prevalence of disease in patients presenting for diagnosis was also based on data from the clinical trials. The true prevalence of osteomyelitis applied to the economic model was 34 per cent in patients with suspected osteomyelitis of the long bones or feet (30/88) and 68 per cent in patients with suspected osteomyelitis and diabetic foot ulcers (75/111). However, due to the way that patients were recruited to the trials, it is possible that the true prevalence of disease applied in the economic model was overestimated compared with the prevalence of disease in the patient population likely to receive LeukoScan® through the MBS.[3] This would affect the number, and total cost, of patients incorrectly diagnosed with the disease. That is, an overestimate of the prevalence of the disease would lead to an underestimate of the impact of the poorer specificity of LeukoScan® – this is explored in a sensitivity analysis.

Effectiveness of osteomyelitis treatment

It is assumed in the economic evaluation that 75 per cent of patients correctly diagnosed with osteomyelitis were cured following treatment. This assumption was based on data from clinical trials of oral ciprofloxacin and standard parenteral therapies (Gentry and Rodriguez-Gomez 1989). Clinical success was reported by Gentry and Rodriguez-Gomez in 24 of 31 patients (77 per cent) treated with oral ciprofloxacin, and in 22 of 28 patients (79 per cent) treated with standard parenteral therapies. A systematic review of the effectiveness of treatment following successful diagnosis of osteomyelitis is beyond the

[3]There is also the possibility of an underestimate, though this is not as likely.

scope of this review. Therefore, a conservative value of 75 per cent for the response to treatment following diagnosis of osteomyelitis was applied to the economic evaluation.

Costs

The costs of procedures used for diagnosing osteomyelitis are based on the respective MBS fees for each procedure. The resources used and costs associated with each diagnostic procedure are presented in **Table 17**. The MBS fees used in estimating costs in the economic model were assumed to incorporate the cost of professional time, depreciation of capital equipment and the cost of consumable items used in performing the procedure. However, the current MBS fees might not, in fact, adequately reimburse providers for these resources and are likely to be significantly less than the market rate. Therefore, the fees for the procedures listed in **Table 17** recommended by the Australian Medical Association (AMA Limited, List of Medical Services and Fees, 1 November 2002), were considered in a sensitivity analysis. These fees are an acceptable proxy for the market rates. For simplicity, it was assumed that patients did not receive more than one diagnostic test (ie, there were no equivocal results).

Table 17 Diagnostic costs

Diagnostic procedure	Reference	Cost of medical resources
LeukoScan® scanning	Fee requested by applicant	$779.35
Technetium-99m labelled HMPAO WBC scanning	MBS 61454	$315.65
Gallium-67 scanning	MBS 61450	$360.50

Abbreviations: HMPAO, hexamethylpropyleneamine oxime; MBS, Medicare Benefits Schedule, November 2002; WBC, white blood cell.

In addition to the costs associated with the diagnostic procedures, patients with positive results – whether correct or otherwise – incur the costs of the associated treatment. The cost of this treatment was estimated to be $11,241 per patient and included costs for an initial period in hospital, plus costs for subsequent 'hospital in the home' administration of antimicrobial therapy (**Table 18**).

The cost of the hospitalisation applied in the economic model was based on Australian-Refined Diagnosis-Related Groups (AR-DRGs) I64A and I64B. The cost of 'hospital in the home' administration of antimicrobial therapy was derived from an Australian study of the costs of home intravenous antibiotic therapy by Grayson et al (1995). This study included 10 patients with osteomyelitis treated for an average of 28 days with antibiotic therapies including vancomycin, ceftriaxone and fluconazole. The costs of delivering the therapy comprised the cost of the antibiotics themselves, plus the cost to administer the therapy. The average cost per patient receiving 'hospital in the home' therapy for treatment of osteomyelitis estimated by Grayson et al was $4534. A cost of $5472 per patient was applied to the economic model after inflating the Grayson et al cost to year 2001 values (Australian Institute of Health and Welfare (AIHW) 2002). The total cost of $11,241 per patient referred for treatment was tested in a sensitivity analysis.

Table 18 Costs of treatment initiated by a positive result with LeukoScan®, technetium-99m labelled HMPAO WBC scanning or gallium-67 scanning

Medical resource	Reference	Cost per patient
Hospitalisation	AR-DRGs I64A and I64B	$5769.05
'Hospital in the home' treatment	Grayson et al (1995)	$5472.22
Total cost of treatment per patient		**$11,241.27**

Abbreviation: AR-DRG, Australian-Refined Diagnosis-Related Group (published in the National Hospital Cost Data Collection Hospital Reference Manual version 5).

Patients not detected with osteomyelitis were assumed to incur no health care costs after the diagnostic procedure. A sensitivity analysis includes a case where these patients incur additional follow-up costs of between $1,000 and $10,000 per patient. However, this sensitivity analysis does not incorporate the knock-on effect of these additional costs on altering patient outcomes in the economic model.

The applicant suggested a potential for cost-savings and improved health outcomes due to a lower rate of needlestick injuries with LeukoScan® compared with technetium-99m labelled HMPAO WBC scanning. The risk of needlestick injury was not included in the economic model. Excluding this risk will have no impact on the cost-effectiveness of LeukoScan® relative to gallium-67 scanning, because the risk of needlestick injury is the same with each of these procedures. Excluding the risk of needlestick injury could slightly underestimate the cost-effectiveness of LeukoScan® compared with technetium-99m labelled HMPAO WBC scanning. However, any underestimate is likely to be negligible due to the very low rate of needlestick injuries (6.9 per 100,000 devices sold; Jagger et al 1988) and the fact that the majority of needlestick injuries do not result in transmission of infection (Jagger et al 1988).

Results of the economic evaluation

Total costs

In patients with suspected osteomyelitis of the long bones or feet, the incremental costs of LeukoScan® were $1230 and $1185 per patient when compared with technetium-99m labelled HMPAO WBC scanning and gallium-67 scanning, respectively (**Table 19**). In those with diabetic foot ulcers who were suspected of having osteomyelitis, the incremental cost of LeukoScan® was $1780 and $1735 per patient when compared with gallium-67 scanning and technetium-99m labelled HMPAO WBC scanning, respectively (**Table 20**).

Table 19 Total cost of osteomyelitis detection and initial treatment in patients with suspected osteomyelitis of the long bones or feet

Comparison		Reference	LeukoScan®	Comparator	Incremental
LeukoScan® vs technetium-99m labelled HMPAO WBC scanning					
A	Cost of diagnostic procedure	Table 17	$779.35	$315.65	$463.70
B	Patients testing positive for osteomyelitis[a]	Table 16	44.3% (39/88)	37.5% (33/88)	6.8% (6/88)
C	Treatment costs per patient testing positive for osteomyelitis	Table 18	$11,241.27	$11,241.27	
D	Total health care costs per patient	D = A + (B × C)	$5761.28	$4531.13	$1230.15
LeukoScan® vs gallium-67 scanning					
E	Cost of diagnostic procedure	Table 17	$779.35	$360.50	$418.85
F	Patients testing positive for osteomyelitis	Assume same as B	44.3%	37.5%	6.8%
G	Treatment costs per patient testing positive for osteomyelitis	Table 18	$11,241.27	$11,241.27	
H	Total health care costs per patient	H = E + (F × G)	$5761.28	$4575.98	$1185.30

[a]Includes patients correctly and incorrectly diagnosed with osteomyelitis.
Abbreviations: HMPAO, hexamethylpropyleneamine oxime; WBC, white blood cell.

Table 20 Total cost of osteomyelitis detection and initial treatment in patients with suspected osteomyelitis and with diabetic foot ulcer

Comparison		Reference	LeukoScan®	Comparator	Incremental
LeukoScan® vs technetium-99m labelled HMPAO WBC scanning					
A	Cost of diagnostic procedure	Table 17	$779.35	$315.65	$463.70
B	Patients testing positive for osteomyelitis[a]	Table 16	75.7% (84/111)	64.0% (71/111)	11.7% (13/111)
C	Treatment costs per patient testing positive for osteomyelitis	Table 18	$11,241.27	$11,241.27	
D	Total health care costs per patient	D = A + (B × C)	$9286.26	$7506.01	$1780.25
LeukoScan® vs gallium-67 scanning					
E	Cost of diagnostic procedure	Table 17	$779.35	$360.50	$418.85
F	Patients testing positive for osteomyelitis	Assume same as B	75.7%	64.0%	11.7%
G	Treatment costs per patient testing positive for osteomyelitis	Table 18	$11,241.27	$11,241.27	
H	Total health care costs per patient	H = E + (F × G)	$9286.26	$7550.86	$1735.40

[a]Includes patients correctly and incorrectly diagnosed with osteomyelitis.
Abbreviations: HMPAO, hexamethylpropyleneamine oxime; WBC, white blood cell.

Effectiveness

For each patient with suspected osteomyelitis of the long bones or feet presenting for diagnostic scanning, an additional 6.8 per cent of patients are detected with osteomyelitis when LeukoScan® is used, compared with when technetium-99m labelled HMPAO WBC scanning or gallium-67 scanning is used for diagnosis. Assuming 75 per cent of these patients would be cured of the disease, the model estimated that an additional 5.1 per cent of the patient population would be free of osteomyelitis if LeukoScan® were used for diagnosis compared with technetium-99m labelled HMPAO WBC scanning or gallium-67 scanning (**Table 21**). In patients with diabetic foot ulcer, it is estimated that an additional 6.8 per cent of the population would be free of osteomyelitis when LeukoScan® is used for diagnosis, compared with technetium-99m labelled HMPAO WBC scanning or gallium-67 scanning (**Table 22**).

Table 21 Effectiveness of diagnostic procedures calculated in the economic model for patients with suspected osteomyelitis of the long bones or feet

Row	Comparison	Reference	LeukoScan®	Technetium-99m labelled HMPAO WBC scanning or gallium-67 scanning	Incremental
A	Patients with osteomyelitis	Table 16	0.341 (30/88)	0.341 (30/88)	
B	Sensitivity of diagnostic procedure	Table 16	0.767 (23/30)	0.567 (17/30)	0.200
C	Patients detected with osteomyelitis	A × B	0.261 (23/88)	0.193 (17/88)	0.068
D	Patients cured of osteomyelitis	C × 75%	0.196	0.145	0.051
E	Patients free from osteomyelitis	D + (1 – A)	0.855	0.804	0.051

Abbreviations: HMPAO, hexamethylpropyleneamine oxime; WBC, white blood cell.

Table 22 Effectiveness of diagnostic procedures calculated in the economic model for patients with diabetic foot ulcers who are suspected of having osteomyelitis

Row	Comparison	Reference	LeukoScan®	Technetium-99m labelled HMPAO WBC scanning or gallium-67 scanning	Incremental
A	Patients with osteomyelitis	Table 16	0.676 (75/111)	0.676 (75/111)	
B	Sensitivity of diagnostic procedure	Table 16	0.920 (69/75)	0.787 (59/75)	0.133
C	Patients detected with osteomyelitis	A × B	0.622 (69/111)	0.532 (59/111)	0.090
D	Patients cured of osteomyelitis	C × 75%	0.466	0.399	0.068
E	Patients free from osteomyelitis	D + (1 – A)	0.791	0.723	0.068

Abbreviations: HMPAO, hexamethylpropyleneamine oxime; WBC, white blood cell.

Cost-effectiveness

The cost-effectiveness of LeukoScan® was found to be relatively consistent between the patient populations. Also, the incremental cost-effectiveness ratios were not influenced greatly by which comparator was used. This was because the effectiveness of technetium-99m labelled HMPAO WBC and gallium-67 scanning were assumed to be equivalent, and the costs of these two procedures were similar.

The incremental cost of LeukoScan® per additional disease-positive patient free of osteomyelitis of the long bones or feet was $24,056, compared with technetium-99m labelled HMPAO WBC scanning, and $23,179 compared with gallium-67 scanning.

The incremental costs of LeukoScan® per additional patient free of osteomyelitis with diabetic foot ulcer were $26,348 and $25,684 compared with technetium-99m labelled HMPAO WBC scanning and gallium-67 scanning, respectively.

Table 23 presents the incremental cost-effectiveness ratios for patients with suspected osteomyelitis of the long bones or feet, while **Table 24** presents these ratios for patients with diabetic foot ulcers who are suspected of having osteomyelitis.

Table 23 Incremental cost-effectiveness of LeukoScan® in patients with suspected osteomyelitis of the long bones or feet

Comparison	LeukoScan®	Comparator	Incremental
LeukoScan® vs technetium-99m labelled HMPAO WBC scanning			
Total costs	$5761	$4531	$1230
Patients free from osteomyelitis	0.855	0.804	0.051
Incremental cost per additional patient free from osteomyelitis			***$24,056***
LeukoScan® vs gallium-67 scanning			
Total costs	$5761	$4576	$1185
Patients free from osteomyelitis	0.855	0.804	0.051
Incremental cost-per additional patient free from osteomyelitis			***$23,179***

Abbreviations: HMPAO, hexamethylpropyleneamine oxime; WBC, white blood cell.

Table 24 Incremental cost-effectiveness of LeukoScan® in patients with diabetic foot ulcers who are suspected of having osteomyelitis

Comparison	LeukoScan®	Comparator	Incremental
LeukoScan® vs technetium-99m labelled HMPAO WBC scanning			
Total costs	$9286	$7506	$1780
Patients free from osteomyelitis	0.791	0.723	0.068
Incremental cost per additional patient free from osteomyelitis			***$26,348***
LeukoScan® vs gallium-67 scanning			
Total costs	$9286	$7551	$1735
Patients free from osteomyelitis	0.791	0.723	0.068
Incremental cost per additional patient free from osteomyelitis			***$25,684***

Abbreviations: HMPAO, hexamethylpropyleneamine oxime; WBC, white blood cell.

Sensitivity analyses

Sensitivity analyses were conducted to test the effect of changing key variables on the incremental costs and benefits of LeukoScan® relative to the main comparators (**Table 25** and **Table 26**). Changing the true prevalence of disease in the model population affected the total number of patients detected with the disease and consequently the incremental benefit of LeukoScan®. In addition, changes in the prevalence affected the costs associated with the poorer specificity of LeukoScan® in patients with diabetic foot ulcer. The sensitivity analysis showed that the cost-effectiveness of LeukoScan® improved as the prevalence of the disease increased. This suggests that the cost-effectiveness analysis may be biased in favour of LeukoScan®, given that the clinical trials potentially overestimate the prevalence of disease in normal clinical practice.

The total cost of treatment associated with a positive diagnosis and the probability that the treatment is successful also affected the cost-effectiveness of LeukoScan®.

Analyses were conducted using fees for Medicare services recommended by the AMA. These analyses were performed due to uncertainty with respect to whether the MBS fees (as used in the base case) are representative of the total fee being paid in the community. The AMA fees are consistently greater than the MBS fees, suggesting that the base case MBS fees might not have captured the total cost, including patient out-of-pocket payments, of the services. In these analyses, the cost-effectiveness of LeukoScan®

improved compared with the base case. However, these analyses might be biased in favour of LeukoScan® because there is the potential that the AMA recommended fee for LeukoScan® would be greater than the proposed MBS fee used in these analyses.

Table 25 Sensitivity analysis of patients with suspected osteomyelitis of the long bones or feet

Analysis	Incremental cost of LeukoScan® per additional patient free of osteomyelitis	
	LeukoScan® compared with technetium-99m labelled HMPAO WBC scanning	LeukoScan® compared with gallium-67 scanning
Base case	$24,056	$23,179
True prevalence of osteomyelitis in model population (34% in base case)		
Decreased to 20%	$30,445	$28,950
Decreased to 30%	$25,293	$24,296
Increased to 40%	$22,717	$21,969
Increased to 50%	$21,171	$20,573
Total cost per patient referred for treatment ($11,241.27 in base case)		
Decreased by 50% ($5621)	$16,562	$15,685
Decreased by 25% ($8431)	$20,309	$19,432
Increased by 25% ($14,052)	$27,803	$26,926
Increased by 50% ($16,862)	$31,550	$30,673
Proportion of patients with osteomyelitis who are cured after treatment (75% in base case)		
Decreased to 50%	$36,084	$34,768
Increased to 100%	$18,042	$17,384
Cost of Medicare services based on AMA schedule fees (MBS schedule fees in base case[a]	$21,331	$20,060
Follow-up costs applied to patients not detected with osteomyelitis ($0 in base case)		
$1,000 per patient	$22,723	$21,861
$5,000 per patient	$17,390	$16,524
$10,000 per patient	$10,723	$9853

[a]Technetium-99m labelled HMPAO WBC scan = $455 and gallium-67 scan = $520 (Reference: AMA).
Abbreviations: AMA, Australian Medical Association; HMPAO, hexamethylpropyleneamine oxime; MBS, Medical Benefits Scheme; WBC, white blood cell.

Table 26 Sensitivity analysis of patients with diabetic foot ulcers who are suspected of having osteomyelitis

Analysis	Incremental cost of LeukoScan® per additional patient free of osteomyelitis	
	LeukoScan® compared with technetium-99m labelled HMPAO WBC scanning	LeukoScan® compared with gallium-67 scanning
Base case	$26,348	$25,684
True prevalence of osteomyelitis in model population (68% in base case)		
Decreased to 50%	$33,630	$32,733
Decreased to 60%	$28,962	$28,214
Increased to 70%	$25,627	$24,986
Increased to 80%	$23,127	$22,566
Total cost per patient referred for treatment ($11,241.27 in base case)		
Decreased by 50% ($5621)	$16,605	$15,941
Decreased by 25% ($8431)	$21,476	$20,813
Increased by 25% ($14,052)	$31,219	$30,555
Increased by 50% ($16,862)	$36,090	$35,426
Proportion of patients with osteomyelitis who are cured after treatment (75% in base case)		
Decreased to 50%	$39,521	$38,525
Increased to 100%	$19,761	$19,263
Cost of Medicare services based on AMA schedule fees (MBS schedule fees in base case)[a]	$24,285	$23,323
Follow-up costs applied to patients not detected with osteomyelitis ($0 in base case)		
$1,000 per patient	$25,014	$24,375
$5,000 per patient	$19,681	$19,036
$10,000 per patient	$13,014	$12,363

[a]Technetium-99m labelled HMPAO WBC scan = $455 and gallium-67 scan = $520 (Reference: AMA).
Abbreviations: AMA, Australian Medical Association; HMPAO, hexamethylpropyleneamine oxime; MBS, Medical Benefits Scheme; WBC, white blood cell.

Discussion of cost-effectiveness

The incremental cost-effectiveness ratio calculated in the economic evaluation is not based on a final health outcome. This makes it difficult to compare the cost-effectiveness of LeukoScan® reliably with interventions in other therapeutic areas. Comparisons with other health care interventions can typically be made only when the effect of treatment is represented as a final health outcome such as life-years gained or QALYs gained.

The economic evaluation did not use a final health outcome because of the uncertainty regarding the clinical effectiveness parameters on which any estimate of final health outcomes would be based. Modelling to final health outcomes using epidemiological data was considered unnecessary, given the lack of evidence indicating superior accuracy for LeukoScan®. The economic evaluation presented here used a surrogate health outcome of additional patients free of osteomyelitis. To determine whether LeukoScan® could offer reasonable value-for-money, the incremental cost of LeukoScan® per additional patient free of osteomyelitis was considered against the costs and consequences of patients not free of osteomyelitis.

Potential costs for patients with osteomyelitis include hospitalisation costs and the cost of long-term antimicrobial therapy. Patients with osteomyelitis can be hospitalised for surgery and other complications, including amputation. The cost of these hospitalisations on the health care system range from $4595 to $18,544 (**Table 27**).

Table 27 Costs associated with hospitalisation for osteomyelitis

Description of hospitalisation	Number of separations with osteomyelitis as the principal diagnosis	Cost per separation	Reference
Amputation	781	18,544	AR-DRG v5 Item number I64A
Infect/Inflam of bone & joint w misc musc sys & conn tiss procs w catastr cc	634	16,782	AR-DRG v5 Item number I64B
Infect/inflam of bone & joint w misc musc sys & conn tiss procs w severe cc	157	8232	AR-DRG v5 Item number I12A
Infect/inflam bone & joint w misc musc sys & conn tiss proc w/o cat or sev cc	152	4595	AR-DRG v5 Item number I12B
Osteomyelitis A < 65 + Cscc/A > 64	204	7020	AR-DRG v5 Item number I12C
Osteomyelitis A < 65 – Cscc	24	2929	AR-DRG v5 Item number I07Z
Total	1952		

Abbreviations: AR-DRG, Australian-Refined Diagnosis-Related Group (published in the National Hospital Cost Data Collection Hospital Reference Manual version 5).

Interrogation of the clinical profiles for public and private hospitals (AR-DRG v5.0 and AR-DRG v5.2, 2000–01) revealed that there were 3082 hospitalisations in Australia in which osteomyelitis was the principal diagnosis. Of these hospitalisations, 70.5 per cent were for general osteomyelitis admissions, 27.6 per cent were for surgical intervention (not amputation) and the remaining 1.8 per cent were for amputation (**Figure 5**).

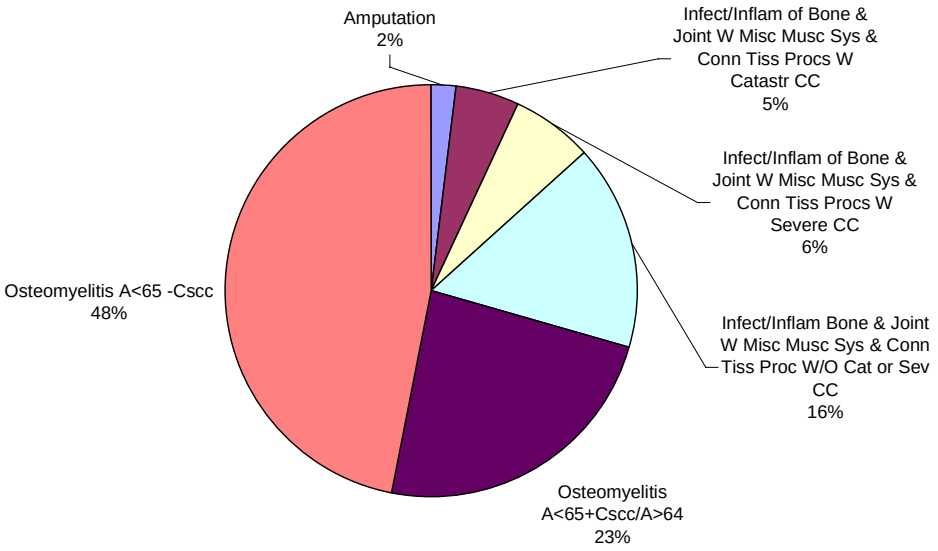

Figure 5 Hospitalisations for osteomyelitis by description of hospitalisation

Given that only a proportion of all patients with osteomyelitis are hospitalised, it is unlikely that the cost of hospitalisations avoided would offset the incremental cost of LeukoScan® per additional patient free of osteomyelitis (approximately $25,000). However, other benefits of avoiding osteomyelitis include lower treatment costs for chronic osteomyelitis and improved health outcomes associated with avoiding amputation and surgical intervention.

Comparing the cost and consequences of illnesses in other therapeutic areas may help to put the incremental cost of LeukoScan® per additional patient free of osteomyelitis into perspective. Shiell and Law (2001) estimated that preventing a single case of hepatitis C would release health care resources valued at approximately $6000. For LeukoScan® to be considered cost-neutral, it would need to release resources associated with downstream osteomyelitis management to the value of approximately $25,000. This seems unlikely given that prevention of hepatitis C releases costs of only $6000 per patient. Given that LeukoScan® is not a cost-neutral intervention, the additional costs need to be considered against the additional number of patients free of osteomyelitis and the consequent better health outcomes.

Kinlay (1996) estimated the incremental cost of coronary angioplasty was $10,930–$12,682 per additional patient free of angina. This suggests that the cost and consequences of osteomyelitis would have to be approximately double those of angina for LeukoScan® to be as cost-effective as coronary angioplasty.

The review of effectiveness presented earlier in this report found that there was no evidence of superiority of LeukoScan® relative to the main comparator. Therefore a formal cost-effectiveness analysis on the basis of this conclusion would show that LeukoScan® is a dominated intervention, because it has greater costs without providing additional benefits. The economic analysis conducted above calculated incremental cost-effectiveness ratios based on a nominally better accuracy for LeukoScan® compared with technetium-99m labelled HMPAO WBC scanning. These analyses showed that the incremental cost of LeukoScan® per additional patient free of osteomyelitis was greater than the cost of treating a patient with osteomyelitis. In addition, the cost-effectiveness of LeukoScan® did not compare favourably with that of coronary angioplasty.

Aggregate financial impact of LeukoScan®

Consistent with the perspective of this assessment report, the following calculations of the aggregate financial implications of LeukoScan® are based on it's TGA approved indication. That is, the financial implications are based on listing LeukoScan® for:

- adult patients with suspected osteomyelitis in the long bones or feet; and
- adult patients with suspected osteomyelitis *and* diabetic foot ulcers.

It is estimated that LeukoScan® would cost the MBS up to a total of $120,082–$188,915 in the first year of listing, increasing to $265,705–$418,010 by the third year of listing. However, there would be fewer gallium-67 and technetium-99m labelled HMPAO WBC scans as a result of introducing LeukoScan®. Therefore, the net impact of introducing LeukoScan® on the MBS was estimated to be $67,462–$106,131 in the first year of listing and $149,272–$232,048 by the third year of listing. The impact of LeukoScan® across the entire health care budget was estimated to be $219,460–$345,256 in the first year,

increasing to $485,956–$763,944 in the third year of listing. It should be noted that the recommended restrictions are likely to reduce these amounts.

The following assumptions were used to derive the estimated financial impact for LeukoScan®.

- Advice from the supporting committee indicated that the annual number of patients presenting for diagnosis across each of the indications considered in this review is between 1284 and 2020.

- The supporting committee also advised that 60 per cent of these patients would present with suspected osteomyelitis of the long bones or feet. The remaining 40 per cent of this population would be presenting with diabetic foot ulcer.

- It was assumed that the patient population will grow by 3.1 per cent per annum. This is in line with the growth in recent years in the total number of similar procedures being performed on the MBS. It was also assumed that the availability of LeukoScan® would not result in any additional growth in the number of patients presenting for this diagnostic procedure. It is unlikely that the use of LeukoScan® would improve access to diagnostic scanning for patients with suspected osteomyelitis in rural or remote areas of Australia. While the access associated with LeukoScan® is better than that of technetium-99m labelled HMPAO WBC scanning, it is no different from that of gallium-67 scanning. Patients with accessibility problems that potentially preclude the use of technetium-99m labelled HMPAO WBC scans are already likely to receive gallium-67 scans. Hence, the introduction of LeukoScan® was considered unlikely to result in more patients being scanned.

- The total financial impact was based on advice from the applicant indicating that LeukoScan® would be used in 12 per cent of the eligible patient population in the first year of listing and in 25 per cent of eligible patients in subsequent years.

- The net financial impact assumed that 58 per cent of patients using LeukoScan® would have otherwise received gallium-67 scans and 42 per cent of patients using LeukoScan® would have otherwise received technetium-99m labelled HMPAO WBC scans. This was based on Health Insurance Commission (HIC) data indicating the relative use of gallium-67 and technetium-99m labelled HMPAO WBC scans.

- The costs per patient were based on those estimated by the economic model.

- The results of the financial implications are calculated from two different perspectives: the MBS budget perspective and the total health care perspective.

The aggregate financial implications of LeukoScan® are calculated in **Table 28** to **Table 32**. **Table 28** estimates the size of the eligible patient population and the estimated extent of use of LeukoScan® in this population. The costs per patient using LeukoScan® are based on those estimated in the economic model (**Table 29**).

Table 28 Total eligible population and estimated extent of use of LeukoScan®

Row	Parameter	Reference	Year 1	Year 2	Year 3
A	Total eligible patient population (patients with suspected osteomyelitis of the long bones or feet, including those with diabetic foot ulcer)	Supporting committee, with growth rate based on HIC data	1284–2020	1323–2082	1364–2145
B	Proportion of eligible population with suspected osteomyelitis of the long bones or feet	Supporting committee	60%	60%	60%
C	Total eligible population of patients with suspected osteomyelitis of the long bones or feet	C = A × B	770–1212	794–1249	818–1287
D	Proportion of patients in eligible population using LeukoScan® [a]	Applicant	12%	25%	25%
E	Total number of patients with suspected osteomyelitis of the long bones or feet who will receive LeukoScan®	E = C × D	92–145	198–312	205–322
F	Proportion of eligible population with diabetic foot ulcer	Supporting committee	40%	40%	40%
G	Total eligible population of patients with diabetic foot ulcer	G = A × F	514–808	529–833	545–858
H	Proportion of patients in eligible population using LeukoScan® [a]	Applicant	12%	25%	25%
I	Total number of patients with diabetic foot ulcers who will receive LeukoScan®	I = G × H	62–97	132–208	136–215

[a]Although the applicant suggests a take-up rate for only the first and second year, it has been assumed that the second year's take-up rate also applies in the third year.
Abbreviation: HIC, Health Insurance Commisiion.

Table 29 Per patient component costs of scanning and treatment

Row	Parameter	Reference	LeukoScan®	Gallium-67 scans	Technetium-99m labelled HMPAO WBC scan
Patients with suspected osteomyelitis of the long bones or feet					
A	Total health care costs	Table 23	$5761.28	$4575.98	$4531.13
B	Cost of scan (MBS)	Table 17	$779.35	$360.50	$315.65
C	Other health care costs	C = A – B	$4,981.93	$4,215.48	$4,215.48
Patients with suspected osteomyelitis in patients with diabetic foot ulcers					
E	Total health care costs	Table 24	$9286.26	$7550.86	$7506.01
F	Cost of scan (MBS)	Table 17	$779.35	$360.50	$315.65
H	Other health care costs	H = E – F	$8,506.91	$7,190.36	$7,190.36

Abbreviations: HMPAO, hexamethylpropyleneamine oxime; MBS, Medical Benefits Scheme; WBC, white blood cell.

The aggregate cost of LeukoScan® and the aggregate substituted expenditures associated with reduced numbers of gallium-67 and technetium-99m labelled HMPAO WBC scans are presented in **Table 30** and **Table 31,** respectively.

Table 30 Aggregate costs associated with LeukoScan®

Row	Parameter	Reference	Year 1	Year 2	Year 3
Patients with suspected osteomyelitis of the long bones or feet					
A	Number of LeukoScan® procedures	Table 28	92–145	198–312	205–322
B	Cost of LeukoScan® to the MBS	A × $779.35 (Table 29)	$72,049–113,349	$154,693–243,364	$159,423–250,806
C	Other health care costs	A × $4981.93 (Table 29)	$460,569–724,571	$988,860–1,555,682	$1,019,097–1,603,253
D	Total health care costs	A × $5761.28 (Table 29)	$532,618–837,920	$1,143,552–1,799,046	$1,178,520–1,854,058
Patients with suspected osteomyelitis and diabetic foot ulcers					
E	Number of LeukoScan® procedures	Table 28	62–97	132–208	136–215
F	Cost of LeukoScan® to the MBS	E × $779.35 (Table 29)	$48,033–75,566	$103,128–162,243	$106,282–167,204
G	Other health care costs	E × $8506.91 (Table 29)	$524,298–824,830	$1,125,687–1,770,941	$1,160,109–1,825,093
H	Total health care costs	E × $9286.26 (Table 29)	$572,331–900,395	$1,228,816–1,933,183	$1,266,391–1,992,297
Total eligible population					
I	Number of LeukoScan® procedures	A + E	154–242	330–520	341–537
J	Cost of LeukoScan® to the MBS	B + F	$120,082–188,915	$257,821–405,607	$265,705–418,010
K	Other health care costs	C + G	$984,867–1,549,401	$2,114,547–3,326,623	$2,179,206–3,428,346
L	Total health care costs	D + H	$1,104,949–1,738,315	$2,372,368–3,732,229	$2,444,911–3,846,355

Abbreviations: MBS, Medical Benefits Scheme.

Table 31 Aggregate substituted expenditures

Row	Parameter	Reference	Year 1	Year 2	Year 3
Patients with suspected osteomyelitis of the long bones or feet					
A	Number of LeukoScan® procedures	Table 28	92–145	198–312	205–322
B	Proportion of gallium-67 scans that are substituted	Supporting committee	58%	58%	58%
C	Proportion of technetium-99m labelled HMPAO WBC scans that are substituted	Supporting committee	42%	42%	42%
D	Costs of diagnostic procedures substituted by LeukoScan®	($360.50 × A × B) + ($315.65 × A × C)	$31,572 -$49,670	$67,787–106,643	$69,860–109,904
E	Other health care costs substituted by LeukoScan®	($4215.48 × A × B) + ($4215.48 × A × C)	$389,712–613,099	$836,727–1,316,347	$862,313–1,356,598
F	Total health care costs substituted by LeukoScan®	($4575.98 × A × B) + ($4531.13 × A × C)	$421,285–662,769	$904,515–1,422,990	$932,173–1,466,503
Patients with suspected osteomyelitis and diabetic foot ulcers					
G	Number of LeukoScan® procedures	Table 28	62–97	132–208	136–215
H	Proportion of gallium-67 scans that are substituted	Supporting committee	58%	58%	58%
I	Proportion of technetium-99m labelled HMPAO WBC scans that are substituted	Supporting committee	42%	42%	42%
J	Costs of diagnostic procedures substituted by LeukoScan®	($360.50 × G × H) + ($315.65 × G × I)	$21,048–33,113	$45,191–71,096	$46,573–73,270
K	Other health care costs substituted by LeukoScan®	($7190.36 × G × H) + ($7190.36 × G × I)	$443,156–697,177	$951,474–1,496,867	$980,568–1,542,638
L	Total health care costs substituted by LeukoScan®	($7550.86 × G × H) + ($7506.01 × G × I)	$464,205–730,291	$996,665–1,567,962	$1,027,141–1,615,908

Abbreviations: HMPAO, hexamethylpropyleneamine oxime; MBS, Medical Benefits Scheme; WBC, white blood cell.

The net financial implications of LeukoScan® are presented in **Table 32**. The net financial impact associated with the diagnostic procedures alone ranged from $67,462 in the first year of listing to $232,048 in the third year of listing. The net impact of LeukoScan® was greater for the total health care budget ($219,460–$763,944) due to the treatment costs associated with a greater number of patients being initiated on treatment when LeukoScan® is used for diagnostic scanning.

Table 32 Net financial impact of LeukoScan®

Row	Parameter	Year 1	Year 2	Year 3
Patients with suspected osteomyelitis of the long bones or feet				
A	Cost of diagnostic procedures	$40,477–63,679	$86,905–136,720	$89,563–140,901
B	Other health care costs	$70,857–111,473	$152,132–239,336	$156,784–246,654
C	Total health care costs	$111,334–175,151	$239,038–376,056	$246,347–387,555
Patients with suspected osteomyelitis and diabetic foot ulcers				
D	Cost of diagnostic procedures	$26,985–42,452	$57,937–91,147	$59,709–91,147
E	Other health care costs	$81,141–127,652	$174,213–274,074	$179,541–282,455
F	Total health care costs	$108,126–170,105	$232,150–365,221	$239,249–376,389
Total eligible population				
G	Cost of LeukoScan® to the MBS	$67,462–106,131	$144,842–227,867	$149,272–232,048
H	Other health care costs	$151,998–239,125	$326,345–513,410	$336,325–529,109
I	Total health care costs	$219,460–345,256	$471,188–741,277	$485,596–763,944

Abbreviations: MBS, Medical Benefits Scheme.

Conclusions

Safety

Adverse events

LeukoScan® appears to be well tolerated. Adverse events observed in Study 07 and Study 08 occurred at a relative low frequency and, given the clinical course of the underlying disease, were considered unrelated to LeukoScan® administration. Furthermore, no induction of human anti-mouse antibodies (HAMA) was reported in any patient in Study 07 and Study 08, and the clinical laboratory data revealed no clinically significant changes in haematological parameters following LeukoScan® administration.

In the peer-reviewed publications, safety data were generally poorly reported. However, the available published data also suggest that the level of adverse events and probability of inducing a HAMA response following LeukoScan® administration are both low.

No adverse event data were reported in any of the studies of technetium-99m stannous colloid labelled white blood cell (WBC) scanning or gallium-67 scanning included in the safety evaluation. Therefore, the relative safety of LeukoScan® and the comparators could not be assessed.

Blood handling

LeukoScan® and gallium-67 scanning both require a single injection. Neither of these procedures requires blood handling. In contrast, technetium-99m stannous colloid labelled WBC scanning requires two injections and the handling of patient's blood. Therefore, the technetium-99m stannous colloid procedure is associated with a greater potential risk of needlestick injury for health care workers and misadministration errors for patients. It should be noted that, given the extremely low rates of these events, this safety advantage appears to be marginal.

Exposure to radiation

Exposure to high levels of ionising radiation has been linked with the theoretical possibility of cancer induction and the development of hereditary defects. However diagnostic imaging agents only emit low dose ionising radiation, and to date, have not been linked to any long-term complications when used in the imaging of infection. Nevertheless, it is recognised that ionising radiation doses should be kept as low as possible. As the radiopharmaceuticals labelled with technetium are associated with a lower radiation dose per patient than those labelled with gallium, LeukoScan® and technetium-99m stannous colloid labelled WBC scanning both have a theoretical safety advantage over gallium-67 citrate scanning.

Effectiveness

Diagnostic accuracy

There are no head-to-head studies of LeukoScan® and technetium-99m stannous colloid labelled WBC scanning or gallium-67 scanning. Furthermore, data were not available to perform an indirect comparison of LeukoScan® with technetium-99m stannous colloid labelled WBC scanning or LeukoScan® with gallium-67 scanning in patients with suspected osteomyelitis of the long bones and feet, including those with diabetic foot ulcers. Consequently, a comparison of the diagnostic performance of these testing modalities could not be made. In other words, the comparative diagnostic performance of these diagnostic tests remains uncertain.

To aid in the decision-making process, an analysis was undertaken of trials reporting a direct comparison of the diagnostic accuracy of LeukoScan® with indium-111 and technetium-99m labelled hexamethylpropyleneamine oxime (HMPAO) WBC scanning in the patient population defined by the Therapeutic Goods Administration (TGA) approved indication.

In patients with diabetic foot ulcers, the diagnostic accuracy of LeukoScan® compared with indium-111 and technetium-99m labelled HMPAO WBC scanning was not significantly different (81 and 75 per cent, respectively). However, in this patient population, LeukoScan® has a significantly higher sensitivity (92 per cent) than indium-111 or technetium-99m labelled HMPAO WBC scanning (79 per cent; $p < 0.05$), but the specificity of the LeukoScan® test was lower than indium-111 or technetium-99m labelled HMPAO WBC scanning (58 and 67 per cent, respectively). It should be noted that these differences might simply be a function of the threshold at which a positive diagnosis is made.

In patients with suspected osteomyelitis of the long bones, the diagnostic accuracy of LeukoScan® compared with indium-111 or technetium-99m labelled HMPAO WBC scanning was not significantly different (73.9 and 67.0 per cent, respectively). Similarly, the sensitivity for disease detection of LeukoScan® compared with indium-111 or technetium-99m labelled HMPAO WBC scanning was not significantly different in these patients (76.7 and 56.7 per cent, respectively; $p = 0.07$). In this patient group, the specificities of the diagnostic modalities were equal (72.4 per cent).

It is important to note that the data reported in these trials were based on a non-independent, on-site assessment of LeukoScan® and WBC scanning (Harwood et al 1999; Study 08). In this setting, the authors note that the on-site clinician "may have had access to the results of the WBC scans for some patients" when interpreting the LeukoScan® results. This is likely to undermine the comparative analysis of LeukoScan® and indium-111 and technetium-99m labelled HMPAO WBC scanning.

Change in clinical management

There are no head-to-head studies that report changes in clinical management associated with LeukoScan® and technetium-99m stannous colloid labelled WBC scanning or gallium-67 scanning. Furthermore, data were not available to perform an indirect comparison of LeukoScan® with technetium-99m stannous colloid labelled WBC

scanning or LeukoScan® with gallium-67 scanning in patients with suspected osteomyelitis of the long bones and feet, including those with diabetic foot ulcers. Consequently, a comparison of the effect of these testing modalities on clinical management could not be performed. In other words, the comparative effect of these diagnostic tests on clinical management remains uncertain.

Data were not available to perform a direct comparison of the effect on clinical management of LeukoScan® with indium-111 and technetium-99m labelled HMPAO WBC scanning in patients with suspected osteomyelitis of the long bones and feet, including those with diabetic foot ulcers.

Delineation of the treatment of osteomyelitis is difficult for several reasons: debridement obscures the impact of antibiotics, the clinical situations and pathogens associated with the disease are heterogeneous, years of follow-up may be necessary to demonstrate sustained remission, and many of the studies of antibiotic therapy have enrolled only small numbers of patients.

However, it is known that the best clinical outcomes are achieved when there is early diagnosis and prompt initiation of antibiotic therapy, before extensive destruction of the bone (Carek et al 2001). If osteomyelitis is detected early enough and antibiotic therapy is successful, surgical debridement of the bone and surrounding tissue is not always necessary.

Based on expert opinion, if a false-negative diagnosis is made this may delay appropriate clinical management of the patient. The possible implications of a false-negative diagnosis for the clinical management of patients with osteomyelitis are as follows.

- No change in management.
- Surgical debridement where none would be required if the infection had been promptly detected and successfully treated, or more extensive surgical debridement than otherwise required. The resultant 'dead space' must then be managed and, if necessary, the bone must be stabilised. Dead space management may include local myoplasty, free-tissue transfers and the use of antibiotic-impregnated beads or cement. In patients with osteomyelitis associated with a prosthetic device, the prosthesis may have to be removed, followed by surgical debridement, packing of the dead space (eg, with antibiotic-impregnated beads or myoplasty) and, if infection is cleared, prosthetic replacement.
- In more severe cases, a delay in the clinical management of a patient may require the amputation of the affected limb or extremity (eg, the diabetic foot).

Based on expert opinion, if a false-positive diagnosis is made, the patient is likely to receive unnecessary and intensive antimicrobial treatment. The antimicrobial therapy chosen for treatment of the osteomyelitis is dependent on the microbial aetiology of the infection and the *in vitro* antibiotic susceptibility profile of the pathogen detected. In general, patients in Australia are treated with a course of parenteral antibiotics while in hospital, followed by a period of 'hospital in the home' care where parenteral antibiotic therapy is completed. If necessary, the patient may then be treated with a course of oral antibiotic therapy. However, in the case of a false-positive diagnosis (eg, a patient with a soft-tissue infection but no underlying osteomyelitis), it is likely that the patient will be 'cured' earlier in this intensive treatment programme than if they had true osteomyelitic

disease. Some patients may have limited removal of healthy bone in an attempt to confirm the diagnosis.

Change in clinical outcomes

There are no head-to-head studies that report changes in clinical outcomes associated with LeukoScan® and technetium-99m stannous colloid labelled WBC scanning or gallium-67 scanning. Furthermore, it was not possible to perform an indirect comparison of LeukoScan® with technetium-99m stannous colloid labelled WBC scanning or LeukoScan® with gallium-67 scanning in patients with suspected osteomyelitis of the long bones and feet, including those with diabetic foot ulcers. Consequently, a comparison of the effect of these testing modalities on patient-relevant health outcomes could not be performed. In other words, the comparative effect of these diagnostic tests on patient-relevant clinical outcomes remains uncertain.

Data were not available to perform a direct comparison of the effect on patient-relevant health outcomes of LeukoScan® and of indium-111 and technetium-99m labelled HMPAO WBC scanning in patients with suspected osteomyelitis of the long bones and feet, including those with diabetic foot ulcers.

As noted previously, delineation of the treatment of osteomyelitis is difficult for several reasons. However, the best clinical outcomes in patients with osteomyelitis are generally achieved when there is early diagnosis and prompt initiation of antibiotic therapy, before extensive destruction of the bone (Carek et al 2001). If osteomyelitis is detected early enough and antibiotic therapy is successful, surgical debridement of the bone and surrounding tissue is not always necessary.

The implications of a false negative-diagnosis on clinical outcomes will depend on the length of delay before the disease is detected and the aggressiveness of the osteomyelitic infection. Based on expert opinion, the clinical outcomes associated with a false-negative diagnosis may include the following.

- No change in clinical outcome.
- Removal of infected bone and surrounding tissue where none would be required if the infection had been promptly detected and successfully treated, or more extensive removal of infected bone and surrounding tissue than otherwise required, with a resultant increase in morbidity and disability. In patients with osteomyelitis associated with a prosthetic device, the prosthesis may have to be removed, followed by surgical debridement, and prosthetic replacement. This process would be associated with a marked increase in morbidity and temporary or possible permanent disability.
- Amputation, with a resultant increase in morbidity and disability.
- In rare cases, a delay in the detection of osteomyelitis may have the potential to cause death (eg, due to septicaemia, especially in immunocompromised patients).

The implications of a false-positive diagnosis on patient-relevant health outcomes are likely to be less severe. They may include the following.

- Limited removal of healthy bone in an attempt to confirm the diagnosis, which may be accompanied by an increase in morbidity.

- Increased time in hospital and in 'hospital in the home' care for the administration of parenteral antibiotics.

A false-positive diagnosis has implications with regards to resource use. These implications are discussed in the economic sections of this report.

Cost-effectiveness

The review of effectiveness presented in this assessment found that there was no evidence of superiority of LeukoScan® relative to the main comparator, gallium-67 scanning. Therefore a formal cost-effectiveness analysis on the basis of this conclusion would show that LeukoScan® is a dominated intervention, because it has greater costs without providing additional benefits.

An economic analysis calculated incremental cost-effectiveness ratios based on a nominally better accuracy for LeukoScan® compared with technetium-99m labelled HMPAO WBC scanning. The economic evaluation showed that LeukoScan® was most cost-effective in patients with suspected osteomyelitis of the long bones or feet. In these patients, LeukoScan® more accurately identified disease-positive patients than technetium-99m labelled HMPAO WBC scanning, leading to an incremental cost of $24,056 per additional patient free of osteomyelitis. In patients with diabetic foot ulcers and suspected osteomyelitis, the incremental cost of LeukoScan® per additional patient free of osteomyelitis was $26,348. These analyses indicate that the incremental cost of LeukoScan® per additional patient free of osteomyelitis is greater than the cost of treating a patient with osteomyelitis.

Recommendation

LeukoScan® is safe and as effective as current methods of white blood cell scanning but is more costly. MSAC recommends that additional funding is justified for patients who do not have access to ex-vivo white blood cell scanning.

- The Minister for Health and Ageing accepted this recommendation on 8 August 2003 -

Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Dr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Dr Ewa Piejko	general practice
Professor John Simes	clinical epidemiology and clinical trials
Mr Chris Sheedy	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Dr Robert Stable	Australian Health Ministers' Advisory Council representative

Professor Bryant Stokes	neurological surgery
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Supporting committee

Supporting Committee for MSAC application 1056
LeukoScan® for use in diagnostic imaging of the long bones and feet in patients with suspected osteomyelitis, including those with diabetic foot ulcers

Professor John Simes (Chair) MD, SM, FRACP Senior Principal Research Fellow and Director, NHMRC Clinical Trials Centre Professor of Clinical Epidemiology, NHMRC Clinical Trials Centre and Department of Public Health and Community Medicine, University of Sydney Medical Oncologist, Royal Prince Alfred Hospital	MSAC member
Dr Miles Beaman MBBS, FRACP, FRCPA, FACTM Infectious Diseases Physician, Freemantle Hospital Head, Department of Microbiology, Western Diagnostic Pathology	Nominated by the Australasian Society of Infectious Diseases
Dr Luke Connelly BA (Econ) MEconSt PhD Associate Professor of Health Economics and Assistant Director, National Centre of Research on Disability and Rehabilitation Medicine (CONROD), The University of Queensland	Co-opted member
Dr Barry Elison MBBCh, FRACP Director, Department of Nuclear Medicine, Wollongong Hospital	Nominated by the Australia and New Zealand Association of Physicians in Nuclear Medicine
Dr Kenneth Francis Hume MBBS, FRCS (Ed), FRACS Senior Fellow, Australian Orthopaedic Association	Nominated by the Australian Orthopaedic Association
Dr Michael Kitchener MBBS, FRACP Senior Visiting Medical Specialist, Queen Elizabeth Hospital	MSAC member

Dr Ken Miles
MBBS, MSc (Nuclear Medicine), MD, FRCR
Specialist in Nuclear Medicine & Radiology, Southernex Imaging Group, Queensland
Adjunct Professor, Centre for Medical, Health & Environmental Physics, Queensland University of Technology, Brisbane

Nominated by the Royal Australian and New Zealand College of Radiologists

Dr Janney Wale
PhD
Consumer representative

Nominated by the Consumers' Health Forum

Appendix C Studies included in the effectiveness review

Table 33 Levels of evidence and study characteristics

Comparator	First author (year)	Level of Evidence		Quality score	Diagnostic work-up consistent with Australian setting[a]	Patient characteristics	Patient numbers			Reference standard	Comparator
		Bandolier (2002)	NHMRC				Reviewed test n(ITT) n(eval)	Reference standard n(eval)	Comparator n(ITT) n(eval)		
Technetium-99m stannous colloid	***LeukoScan®***										
Three-phase bone scan	Study 08[b]	4	III-2	8	x	Suspected osteomyelitis of the long bones	n = 130 n = 96	n = 96	n = 130 n = 88	Bone biopsy	^{111}In oxine *or* ^{99m}Tc HMPAO WBC scan
^{99m}Tc HMPAO WBC scan	Ryan (2002)	4	III-2	4	x	23 possible infected TKR 3 total THR 8 internal fixation device 4 septic arthritis 2 chronic osteomyelitis 2 infected fracture site 5 other	n = 55 n = 47	n = 47	None	Review of case notes (WBC count, ESR, indium WBC scan, culture of blood and swabs and operative findings)	None
None											
Gallium-67 scanning											
Plain radiography; ^{99m}Tc MDP; ^{111}In; ^{99m}Tc MDP/^{111}In	Devillers (2000)	4	III-2	5	x	Patients with a low or medium suspicion of bone or joint osteomyelitis	n = 23 (32 foci) n = 32 foci	n = 23 (32 foci)	HMPAO WBC n = 23 (32 foci) n = 32 foci Three-phase bone scan n = 23 (32 foci) n = 30 foci	Variable: radiography; bacterio-logical; histology; long-term clinical follow-up/ radiology	HMPAO WBC scan; three-phase bone scan
	Harwood (1999)	4	III-2	8	x	Suspected osteomyelitis in patients with diabetic foot ulcers	n = 150 n = 122	n = 123	n = 150 n = 111	Bone biopsy	^{111}In oxine *or* ^{99m}Tc HMPAO WBC scan
Gallium-67/ three-phase bone scan ratio	Becker (1996)	4	III-2	4	x	High index of suspicion of having an abscess or an inflammatory process	n = 53 n = 25 lesions (21 patients)	Variable combination of reference standards used	n = 53 n = 16 lesions	Variable: histology, cytology, imaging, surgery or follow-up	^{111}In oxine *or* ^{99m}Tc HMPAO WBC scan (results not differentiated between the two)

Reference standard	Comparator	First author (year)	Level of Evidence		Quality score	Diagnostic work-up consistent with Australian setting[a]	Patient characteristics	Patient numbers			Reference standard
			Bandolier (2002)	NHMRC				Reviewed test n(ITT) n(eval)	Reference standard n(eval)	Comparator n(ITT) n(eval)	
Biopsy and culture	Three-phase bone scan; ^{99m}Tc MDP/ ^{111}In										
		Chik (1996)	2	III-2	9	x	Painful joint prosthesis	n = 40 n = 40	n = 40	n = 40 n = 30	Operative culture or long term clinical follow-up
		Gutfilen (1994)	4	4	6	nr	Suspected osteomyelitis	n = 25 n = 25	n = 25	n = 25 n = 25	Histological studies
Surgical proff of active or inactive disease	Plain radiograph; three-phase bone scan; CT	Schroth (1981)	4	4	6	nr	Septic loosening of an endoprosthesis	n = 42 n = 42	n = 42	None	Bacteriological and histological studies
		Johnson (1996	2	III-2	9	x	Adult diabetics with suspected osteomyelitis of the foot or ankle	n = 22 n = 22	n = 22	Plain radiography n = 22 n = 22 ^{99m}Tc MDP n = 22 n = 22 ^{111}In n = 22 n = 22 ^{99m}Tc/^{111}In n = 22 n = 22	Deep culture and histology and/or long-term clinical follow-up
Bone biopsy or histological evaluation/ patient follow-up	Three-phase bone scan										
Surgery or bone biopsy and culture or clinical follow-up	Three-phase bone scan	Sorsdahl (1993	4	III-2	5	x	Patients with suspected osteomyelitis	Gallium-67 background ratio n = 110 (126 sites) n = 126 sites	n = 110 (126 sites)	Gallium-67/ three-phase bone scan ratio n = 110 n = 126 sites	Bone biopsy or histological sections or absence of clinical infection at six-month follow-up

Reference standard	Comparator	First author (year)	Level of Evidence		Quality score	Diagnostic work-up consistent with Australian setting[a]	Patient characteristics	Patient numbers		
			Bandolier (2002)	NHMRC				Reviewed test n(ITT) n(eval)	Reference standard n(eval)	Comparator n(ITT) n(eval)
Bacterial culture or long-term clinical follow-up	^{111}In WBC; ^{99m}Tc MDP bone scan; plain radiography	Seabold (1989)	4	III-2	11	x	Fracture-non-uniform	n = 54 n = 45	n = 54	Three-phase bone scan n = 54 n = 46 ^{99m}Tc MDP/ ^{111}In n = 54 n = 49
Biopsy, culture and histopathological examination	None	Tumeh (1988)[c]	4	III-2	9	x	Patients with prior bone infection	n = 27 n = 27	n = 27	Plain radiograph n = 27 n = 27 Three-phase bone scan n = 27 n = 27 CT n = 27 n = 27
Needle biopsy and culture or by open surgery (+ve patients) and clinical follow-up (– ve patients)	Three phase bone scan; ^{111}In WBC	Sugarman (1987)	4	III-2	5	x	Patients with pressure sores that had not healed after two weeks of localised care	n = 402 n = nr	n = 402	Three-phase bone scan n = 402 n = nr
Local fluid or tissue culture, blood culture + localised signs of bone pain and tenderness; biopsy, histology; clinical evaluation	None	Tumeh (1986)[c]	4	III-2	9	x	Patients with prior bone infections or old fractures (with or without infection)	n = 149 n = 136	n = 136	Three-phase bone scan n = 149 n = 136

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; eval, evaluable patients; HMRAO

First author (year)	Level of Evidence		Quality score	Diagnostic work-up consistent with Australian setting[a]	Patient characteristics	Patient numbers		
	Bandolier (2002)	NHMRC				Reviewed test n(ITT) n(eval)	Reference standard n(eval)	Comparator n(ITT) n(eval)
Al-Sheikh (1985)	4	III-2	7	✓	Patients with clinically suspected subacute or chronic bone infection with radiological abnormality	n = 21 n = 21	n = 21	^{111}In WBC n = 21 n = 21 ^{99m}Tc MDP bone scan n = 21 n = 21 Plain radiography n = 21 n = 21
Esterhai (1985)	4	III-2	8	✓	Post-traumatic fracture non-union	Gallium-67/ ^{99m}Tc MDP[d] n = 24 n = 24	n = 24	None
Schauweker (1984)	4	III-2	9	✓	Patients with suspected osteomyelitis and abnormal three-phase bone scan	n = 57 n = 29	n = 57	Three-phase bone scan n = 57 n = 57 ^{111}In WBC n = 57 n = 57
Rosenthall (1982)	4	III-2	5	x	Patients having suspected disease of the bone, joint or adjacent soft tissue	Gallium-67/ ^{99m}Tc MDP n = 500 n = 159	n = 159	None

Appendix D Literature search strategies

LeukoScan® Medline search strategy

The search strategy used to identify relevant studies of LeukoScan® in Medline is presented in **Table 34**.

Table 34 LeukoScan® Medline search strategy

	Keyword/search history	Results
1	leukoscan.ti,ab.	14
2	sulesomab.ti,ab.	3
3	immu?mn3.ti,ab.	0
4	or/1–3	16
5	(anti?leu?ocyte or anti?granulocyte).tw.	249
6	(fab or (fragment adj antigen binding)).tw.	10,100
7	granulocyte antibody.tw.	53
8	or/5–7	10,384
9	exp antibodies, monoclonal/	105,825
10	hybridomas/	9447
11	or/9–10	109,334
12	or/8–11	117,126
13	12 and diabetic foot/	3
14	12 and exp fractures/	18
15	12 and bony callus/	6
16	12 and osteomyelitis/	41
17	12 and osteitis/	1
18	12 and (diabet$ adj5 (foot or feet or ulcer$)).tw.	7
19	12 and osteomyelitis.ti,ab.	38
20	12 and osteitis.ti,ab.	4
21	or/13–20	74
22	or/4,21	83
23	limit 22 to yr=1990–2002	74

LeukoScan® Embase search strategy

The search strategy used to identify relevant studies of LeukoScan® in Embase is presented in **Table 35**.

Table 35 LeukoScan® Embase search strategy (1988–2002, week 32)

	Keyword/search history	Results
1	leukoscan.mp.	27
2	sulesomab.mp.	12
3	sulesomab Tc 99m/	13
4	immu?mn3.mp.	0
5	or/1–4	32
6	(anti?leu?ocyte or anit?granuolcyte).ti,ab.	41
7	(fab or (fragment adj antigen binding)).tw.	6640
8	granulocyte antibody.tw.	49
9	or/6–8	6726
10	exp monoclonal antibody/	78,684
11	exp radiopharmaceutical agent/	38,208
12	or/10–11	115,553
13	or/9,12	120,582
14	13 and diabetic foot/	25
15	13 and exp diabetes mellitus/	1577
16	15 and exp foot disease/	39
17	15 and exp skin ulcer/	38
18	13 and (diabet$ adj5 (foot or feet or ulcer$)).tw.	48
19	13 and exp fracture/	280
20	13 and exp osteomyelitis/	413
21	13 and exp osteitis/	456
22	13 and osteomyelitis.tw.	266
23	13 and osteitis.tw.	30
24	or/19–23	762
25	24 and 9	13
26	24 and 10	92
27	or/14,16–18,25–26	149
28	limit 27 to yr=1990–2004	141
29	28 and animal/	0
30	28 and nonhuman/	14
31	28 and exp animal/	0
32	or/29–31	14
33	32 not human/	6
34	28 not 33	135
35	from 34 keep 1–135	135

Technetium-99m stannous colloid labelled WBC scanning Medline search strategy

The search strategy used to identify relevant studies of technetium-99m stannous colloid labelled WBC scanning in Medline is presented in **Table 36**.

Table 36 Technetium-99m stannous colloid labelled WBC scanning Medline search strategy

	Keyword/search history	Results
1	technetium compounds/	294
2	1 and (tin compounds/ or tin fluorides/)	62
3	technetium/	17,332
4	3 and tin/	406
5	tc-99m-sn colloid$.ti,ab.	8
6	tc-99m-tin colloid$.ti,ab.	22
7	(technetium adj5 (stannous or tin) adj3 colloid$).ti,ab.	42
8	((tc or technetium) adj3 99m adj3 (stannous or sn or tin) adj3 colloid$).ti,ab.	72
9	(colloid$ or stannous).ti,ab.	15,101
10	or/2,4–9	15,342
11	10 and diabetic foot/	1
12	10 and exp fractures/	28
13	10 and bony callus/	0
14	10 and osteomyelitis/	20
15	10 and osteitis/	1
16	10 and (diabet$ adj5 (foot or feet or ulcer$)).tw.	1
17	10 and osteomyelitis.ti,ab.	23
18	10 and osteitis.ti,ab.	1
19	or/11–18	51

Technetium-99m stannous colloid labelled WBC scanning Embase search strategy

The search strategy used to identify relevant studies of technetium-99m stannous colloid labelled WBC scanning in Embase is presented in **Table 37**.

Table 37 Technetium-99m stannous colloid labelled WBC scanning Embase search strategy

	Keyword/search history	Results
1	technetium tin colloid tc 99m/	230
2	technetium tin fluoride tc 99m/	3
3	tc-99m-sn colloid$.ti,ab.	9
4	tc-99m-tin colloid$.ti,ab.	20
5	(technetium adj5 (stannous or tin) adj3 colloid$).ti,ab.	33
6	((tc or technetium) adj3 99m adj3 (stannous or sn or tin) adj3 colloid$).ti,ab.	77
7	(colloid$ or stannous).ti,ab.	13,655
8	or/1–7	13,743
9	8 and diabetic foot/	0
10	8 and exp diabetes mellitus/	91
11	10 and exp foot disease/	0
12	10 and exp skin ulcer/	0
13	8 and (diabet$ adj5 (foot or feet or ulcer$)).tw.	1
14	8 and exp fracture/	22
15	8 and exp osteomyelitis/	23
16	8 and exp osteitis/	23
17	8 and osteomyelitis.ti,ab.	18
18	8 and osteitis.ti,ab.	1
19	or/9,11–18	47

Gallium-67 scanning Medline search strategy

The search strategy used to identify relevant studies of gallium-67 scanning in Medline is presented in **Table 38**.

Table 38 Gallium-67 scanning Medline search strategy

	Keyword/search history	Results
1	gallium/	1334
2	exp gallium isotopes/	3636
3	gallium citrate$.ti,ab,rn.	256
4	or/1–3	4756
5	4 and diabetic foot/	3
6	4 and exp fractures/	26
7	4 and bony callus/	1
8	4 and osteomyelitis/	161
9	4 and osteitis/	7
10	4 and (diabet$ adj5 (foot or feet or ulcer$)).tw.	9
11	4 and osteomyelitis.ti,ab.	136
12	4 and osteitis.ti,ab.	8
13	or/5–12	208
14	limit 13 to (human and english language and yr=1980–2002	147
15	case report/ or letter.pt. or editorial.pt.	1,564,806
16	14 not 15	96

Gallium-67 scanning Embase search strategy

The search strategy used to identify relevant studies of gallium-67 scanning in Embase is presented in **Table 39**.

Table 39 Gallium-67 scanning Embase search strategy

	Keyword/search history	Results
1	gallium citrate/	56
2	gallium citrate ga 67/	1683
3	gallium/	868
4	gallium 67/	2261
5	gallium 68/	170
6	or/15	4639
7	6 and diabetic foot/	8
8	6 and exp diabetes mellitus/	46
9	8 and exp foot disease/	13
10	8 and exp skin ulcer/	12
11	6 and (diabet$ adj5 (foot or feet or ulcer$)).ti,ab.	12
12	6 and exp fracture/	37
13	6 and exp osteomyelitis/	208
14	6 and exp osteitis/	226
15	6 and osteomyelitis.ti,ab.	176
16	6 and osteitis.ti,ab.	11
17	or/7,9–16	286
18	limit 17 to (human and english language)	236
19	limit 18 to (editorial or erratum or letter or note)	8
20	18 and case study/	0
21	or/19–20	8
22	18 not 21	228
23	22 and sensitivity.mp.	20
24	22 and specificity.mp.	21
25	22 and reference standard.mp.	0
26	22 and gold standard.mp.	0
27	22 and accuracy.mp.	15
28	22 and positive predictive value$.mp.	0
29	22 and ppv.mp.	0
30	22 and (negative predictive value$ or npv).mp.	0
31	22 and negative.mp.	28
32	22 and (false or positive).mp.	50
33	or/23–24,25–32	76
34	22 and exp clinical trial/	9
35	35 or/33–34	81

Appendix E List of citations and reasons for exclusion

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Reason for exclusion: review.

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Appendix F Leukoscan® study characteristics

Table 40 provides a description of the reference standards used in the studies identified for review.

Table 40 Description of reference standards used in studies of LeukoScan®

First author (year)	Reference standard
Study 07[a]	Bone biopsy (preferably closed percutaneous) performed on 80 patients. Specimens obtained used for histology and/or bacterial cultures. The managing physician did not recommend a bone biopsy on 21 patients on ethical grounds.
Study 08[a]	Bone biopsy (preferably closed percutaneous) performed on 95 patients. Specimens obtained used for histology and/or bacterial cultures. The managing physician considered that the clinical picture in 28 patients did not warrant a bone biopsy.
Ryan (2002)	Not stated.
Becker (1996)	Various tests used: patient data and final diagnoses were obtained by bacterial tests, biopsy, or any other standard diagnostic technique such as: CT scanning, surgery, MRI, ultrasound.
Becker (1994)	Various tests used: patient data and final diagnoses were obtained by bacterial tests, biopsy, plain radiographic studies, CT, MRI or surgery.

Abbreviations: CT, computerised tomography; MRI, magnetic resonance imaging; ^{99m}Tc MDP, technetium-99m methylene diphosphonate; WBC, white blood cell.
[a]Data also published in Harwood et al (1999), Hakki et al (1997) and Harwood et al (1994).

Table 41 provides a description of the comparator tests performed in the studies identified for review.

Table 41 Description of comparator tests performed in studies of LeukoScan®

First author (year)	Comparator
Study 07[a]	Within 10 days of the LeukoScan® procedure, patients underwent a WBC scan, with either ^{111}In or ^{99m}Tc used as a radiolabel (for a short period of time during the study indium oxine was not available; a ^{99m}Tc-labelled bone scan was performed during this time).
Study 08[a]	Within 10 days of the LeukoScan® procedure, patients underwent a WBC scan, with either ^{111}In or ^{99m}Tc used as a radiolabel (for a short period of time during the study indium oxine was not available; a ^{99m}Tc-labelled bone scan was performed during this time).
Ryan (2002)	None.
Becker (1996)	38 of the 53 patients underwent WBC imaging using ^{111}In oxine (n = 29) or ^{99m}Tc HMPAO (n = 9).
Becker (1994)	WBC imaging using ^{111}In oxine (Amersham) (n = 8) or ^{99m}Tc HMPAO (Amersham) (n = 8) performed within five days prior to or after antibody imaging, using either 20 MBq of ^{111}In or 400 MBq of ^{99m}Tc HMPAO. Gamma camera images obtained four hours and 20 hours after reinjection of the labelled WBCs.

Abbreviations: HMPAO, hexamethylpropyleneamine oxime ; ^{111}In, indium-111; ^{99m}Tc, technetium-99m; WBC, white blood cell.
[a]Data also published in Harwood et al (1999), Hakki et al (1997) and Harwood et al (1994).

Table 42 provides a description of the efficacy outcomes reported in the studies identified for review.

Table 42 Efficacy outcomes reported in studies of LeukoScan®

First author (year)	Outcomes
Study 07[a]	Diagnostic utility – defined as efficacy of LeukoScan® to detect infection/inflammation in bone (osteomyelitis). It was assessed by the standard diagnostic parameters (sensitivity, specificity, accuracy, PPV, NPV). Clinical benefit – defined as the impact of the LeukoScan® diagnostic utility results on patient management, assessed by the following: • Contribution of diagnostic information that was not available from other procedures or that permitted reductions in the need for these procedures • Changes in clinical management • Improvement in clinical outcomes • Ease of use and safety of LeukoScan® compared with other diagnostic modalities.
Study 08[a]	Diagnostic utility – defined as efficacy of LeukoScan® to detect infection/inflammation in bone (osteomyelitis). It was assessed by the standard diagnostic parameters (sensitivity, specificity, accuracy, PPV, NPV). Clinical benefit – defined as the impact of the LeukoScan® diagnostic utility results on patient management, assessed by the following: • Contribution of diagnostic information that was not available from other procedures or that permitted reductions in the need for these procedures • Changes in clinical management • Improvement in clinical outcomes • Ease of use and safety of LeukoScan® compared with other diagnostic modalities.
Ryan (2002)	Diagnostic accuracy – sensitivity, specificity, accuracy, PPV, NPV of LeukoScan® based on a retrospective review of case notes.
Becker (1996)	Diagnostic accuracy – the detection of focal inflammation in patients thought to have acute infections. Dose – the effect of different amounts of antibody, ranging from 0.1 mg to 1.0 mg.
Becker (1994)	Diagnostic accuracy– sensitivity, specificity, accuracy, PPV, NPV of LeukoScan® for the detection of soft-tissue infections *and* osteomyelitis (data not separated).

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.
[a]Data also published in Harwood et al (1999), Hakki et al (1997) and Harwood et al (1994).

Appendix G Quality scoring

Table 43 Quality scoring scale for LeukoScan® and comparator studies

Evaluation criteria	Quality score
Criteria for study validity	
A. Did the study use a consecutive sample of participants?	
No (not reported)	0
Yes	1
B. Were clinical outcomes subsequent to test results reported?	
No	0
Partially (eg, only reported for selected tests)	1
Yes	2
C. Was the test being evaluated compared with a valid reference standard?	
No (not reported)	0
Variable	1
Yes	2
D. Were the test and the reference standard measured independently (blind) of each other?	
No (or not reported)	0
The reference standard was measured independently of the test but not *vice versa*	1
The test was measured independently of the reference standard but not *vice versa*	2
The test was measured independently of the reference standard and the reference standard independently of the test	3
E. Was the choice of patients who were assessed by the reference standard independent of the test results (avoidance of verification bias)?	
No (not reported)	0
Yes	1
F. Was the reference standard measured before any interventions were started with knowledge of test results (avoidance of treatment paradox)?	
No (not reported)	0
Yes	1
Additional validity criteria for studies comparing tests	
G. Were tests (test, reference standard) compared in a valid design?	
Different tests done on different individuals, not randomly allocated (case-control)	0
Different tests done on randomly allocated individuals (parallel randomised or quasi-randomised)	1
Tests performed on each individual (single group with sequential tests)	2
Criteria relevant to the applicability of the results	
H. Was the diagnostic work-up consistent with Australian setting?	
No (not reported)	0
Yes	1
I. Did the patient population have similar disease characteristics to the TGA-listed indication?	
No	0
Partially	1
Yes	2

Abbreviations

AHMAC	Australian Health Ministers' Advisory Council
AIHW	Australian Institute of Health and Welfare
AMA	Australian Medical Association
AR-DRG	Australian-refined diagnosis-related groups
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CT	Computed tomography
DOR	Diagnostic odds ratio
EMEA	European Agency for the Evaluation of Medical Products
Fab	Antibody fragment
HAMA	Human anti-mouse antibodies
HBV	Hepatitis B virus
HCFA	Health Care Financing Administration (US)
HCV	Hepatitis C virus
HIC	Health Insurance Commission
HIRU	Health Information Research Unit (Canada)
HIV	Human immunodeficiency virus
HMPAO	Hexamethylpropyleneamine oxime
HSTAT	Health Services Technology Assessment Texts (US)
ICD-10-AM	ICD-10-AM, International Statistical Classification of Disease and Related Health Problems, 10th revision, Australian Modification
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin G
^{111}In	Indium-111
INAHTA	International Network of Agencies for Health Technology Assessment
ITT	Intention-to-treat
MBS	Medical Benefits Scheme
MDP	Methylene diphosphonate
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
M-TAG	Medical Technology Assessment Group
NCA-90	Normal cross-reacting antigen
NHMRC	National Health and Medical Research Council
NPV	Negative predictive values
PPV	Positive predictive values

QALY	Quality adjusted life years
SBU	Swedish Council on Technology Assessment in Health Care
SPECT	Single photon emission computed tomography
^{99m}Tc	Technetium-99m
TGA	Therapeutic Goods Administration
THR	Total hip replacement
TKR	Total knee replacement
WBC	White blood cell
X-ray	Plain radiography

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