Abstract

Background

Osteomyelitis is an infection of the bone which can occur in people with diabetic foot ulcers. It can be diagnosed using X-rays, ultrasound, scintigraphy, magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT) and positron emission tomography (PET).

Objectives

To review the evidence on the diagnostic accuracy of imaging tests to diagnose osteomyelitis in people with diabetic foot ulcers.

Methods

We conducted a systematic review and meta-analysis. MEDLINE, EMBASE and other databases were searched to July 2018. Risk of bias was evaluated. Diagnostic accuracy was estimated using bivariate meta-analyses.

Results

Thirty-six studies were included in the meta-analysis. Eight studies were at high risk of bias

MRI had high diagnostic accuracy (22 studies: 96.4% sensitivity (95% CI 90.7 to 98.7); 83.8% specificity (76.0 to 89.5)). PET scans also had high accuracy (6 studies: 84.3% sensitivity (52.8 to 96.3); 92.8% specificity (75.7 to 98.2)), and possibly also SPECT, but with few studies (3 studies: 95.6% sensitivity (76.0 to 99.3); 55.1% specificity (19.3 to 86.3)).

Scintigraphy (17 studies: 84.2% sensitivity (76.8 to 89.6); 67.7% specificity (56.2 to 77.4)), and X-rays (16 studies: 61.9% sensitivity (50.5 to 72.1); 78.3% specificity (62.9 to 88.5)) had generally inferior diagnostic accuracy.

Conclusions

MRI and PET both reliably diagnose osteomyelitis in diabetic foot ulcer patients. SPECT may also have good diagnostic accuracy, although evidence is limited. This review confirms most current guidelines, showing that MRI may be the preferable test in most cases, given its wider availability and the lack of potentially harmful ionising radiation.

**Key words**

Osteomyelitis, diabetic foot ulcers, diagnosis, imaging tests, systematic review, meta-analysis

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# Introduction

Osteomyelitis is an infection of the bone and bone marrow.[[1](#_ENREF_1), [2](#_ENREF_2)] It is particularly common in people with diabetes, generally as a complication of diabetic foot ulcers.[[3](#_ENREF_3)] Without adequate treatment it may, in extreme cases, require amputation of the foot, or may lead to potentially fatal septicaemia.[[4](#_ENREF_4)] The treatment for osteomyelitis is usually a course of antibiotics, and in some cases surgery may be used.[[5](#_ENREF_5)]

Blood tests are used initially to identify potential osteomyelitis, including white blood cell count, C reactive protein (CRP) and erythrocyte sedimentation rate (ESR).[[6](#_ENREF_6)] If these tests indicate infection patients are referred for further diagnostic testing. The gold standard test for osteomyelitis is histopathology or microbiology using a sample from a bone biopsy or pus aspiration from the bone. However, biopsies are invasive and generally require anaesthesia, and analysis of results may take several days.

Diagnostic imaging of the foot may improve diagnosis and reduce the need for unnecessary biopsies in people whose ulcers have not led to osteomyelitis. Several diagnostic imaging methods can be used to identify osteomyelitis: including X-rays, ultrasound, computed tomography (CT) scans, planar scintigraphy, magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans, and single-photon emission computed tomography (SPECT).[[5](#_ENREF_5), [7-9](#_ENREF_7)]

X-rays are easily available and cheap to perform, but are poor at detecting osteomyelitis in its early stages.[[8](#_ENREF_8)] MRI scans are probably most widely recommended and used; they are more accurate than X-rays, and able to detect osteomyelitis in its early stages, although they are expensive to perform.[[9](#_ENREF_9)] Current NICE guidance recommends X-ray as a first test, to either confirm advanced osteomyelitis, or to rule out other causes. If osteomyelitis is suspected but unconfirmed, the X-ray is followed by an MRI scan.

Four previous systematic reviews or meta-analyses of diagnostic imaging techniques for osteomyelitis in people with diabetic foot ulcers [[10-13](#_ENREF_10)] varied in their conclusions, mainly depending on the tests included. MRI, PET and white blood cell scintigraphy were all considered suitable imaging tests.

There is therefore no comprehensive and up-to-date systematic review of all diagnostic imaging tests for osteomyelitis in people with diabetic foot ulcers. This paper systematically reviews all the relevant literature, with the aim of identifying the imaging test or tests with the best diagnostic accuracy, and the greatest clinical utility.

# Methods

A systematic review was performed following the general principles recommended in CRD guidance and the PRISMA statement. The protocol details have been registered on PROSPERO (number CRD42017068511). This paper formed part of a larger review project reported elsewhere.[[14](#_ENREF_14)] Diagnostic accuracy findings for people who do not have diabetes are published elsewhere [reference to be added once published].

## Literature searches

A search strategy was developed in MEDLINE including search terms for osteomyelitis and relevant diagnostic imaging techniques (see Appendix A), with no language, date, geographical or study design restrictions. The MEDLINE strategy was adapted to the other databases consulted.

Searches were performed in August 2017 and updated in July 2018. The following databases were searched: MEDLINE, EMBASE, CENTRAL, Cochrane Database of Systematic Reviews (CDSR), CINAHL Plus, PubMed, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database. The reference lists of relevant systematic reviews were checked.

Titles and abstracts and full text of studies were independently assessed for inclusion by two reviewers using the inclusion criteria outlined below. Disagreements were resolved through discussion and, where necessary, consultation with a third reviewer.

### Inclusion criteria

Participants were any patient with diabetic foot ulcers with suspected osteomyelitis. All diagnostic imaging technique that could potentially identify osteomyelitis, either alone or in combination with other relevant tests, were eligible, including: X-rays, magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), planar scintigraphy, single-positron emission computed tomography (SPECT), and ultrasound.

The preferred reference standard was histopathology or microbiology from bone biopsy or pus aspiration. Surgery was also accepted as reference standard. As biopsies are invasive, clinical follow-up of at least six months was accepted as confirmation of absence of disease. Studies were excluded if a positive osteomyelitis diagnosis was made by clinical follow-up alone or by using a second imaging test.

The main review outcome was diagnostic accuracy of the imaging test compared to the reference standard expressed as sensitivity (percentage of people with osteomyelitis with a positive diagnostic test result) and specificity (percentage of people without osteomyelitis with a negative test result). Studies reporting sensitivity and specificity, or sufficient data to calculate both measures, were included.

## Data extraction

Data were extracted for patient and study characteristics, details of diagnostic tests, and reference standard tests. The numbers of patients confirmed positive or negative according to the reference standard, and the number of true positive, true negative, false positive and false negative test results were extracted. If not reported, sensitivity and specificity estimates (with their 95% confidence intervals) or other reported diagnostic accuracy data were extracted. Data were extracted by one reviewer and independently checked for accuracy by at least one other reviewer. Discrepancies were resolved by consensus, with involvement of a third reviewer when necessary. Where multiple reports were identified for a single study, the most recent or most complete report was used as principal data source.

## Quality assessment

Risk of bias of the included studies was assessed using the QUADAS-2 tool.[[15](#_ENREF_15)] Critical appraisal was performed by one reviewer and independently checked by at least one other reviewer.

## Meta-analysis

For each diagnostic imaging test data was synthesised in meta-analyses using both bivariate meta-analysis of sensitivity and specificity and hierarchical summary receiver operating characteristic (HSROC) analysis.[[16](#_ENREF_16), [17](#_ENREF_17)] To do this a statistical model that regressed index test outcome (positive or negative for osteomyelitis) against whether each person did or did not have confirmed osteomyelitis, based on the reference standard, was used. [[18](#_ENREF_18)] Studies were pooled if there were three or more studies eligible for the analysis. Random effects models were used to account for potential heterogeneity in diagnostic accuracy across studies. Results were presented as summary sensitivity and specificity estimates, with 95% confidence intervals, plotted in ROC space, and as summary HSROC curves.

Where studies reported diagnostic accuracy for multiple tests data for each test were included in the analysis. Where studies reported multiple results for the same imaging test (for example, diagnosis by different clinicians, or using different definitions of a positive test result) only the data with the greatest diagnostic accuracy (i.e. having the highest diagnostic odds ratio) were included.

Positive predictive values (PPV) and negative predictive values (NPV) were also analysed using the same logistic regression approach. It should be noted that PPV and NPV depend on the incidence of osteomyelitis in each study, and so may be more heterogeneous than sensitivity and specificity.

In addition to the bivariate analyses, meta-analyses of estimated diagnostic odds ratios (DOR) and positive rates (PR, the proportion of people whose imaging test result suggests osteomyelitis, and so who would be diagnosed with osteomyelitis on the basis of the imaging test) were also performed. Univariate meta-analyses (ignoring correlation between outcomes) of sensitivity, specificity, PPV and NPV were also performed, for comparison with the bivariate analyses. In all these meta-analyses heterogeneity was assessed using I2.[[19](#_ENREF_19)]

#### Comparison of imaging tests

Diagnostic tests were compared by examining summary diagnostic odds ratios derived from the logistic regression models and by comparing summary ROC curves. Where studies reported diagnostic accuracy data for two or more imaging tests on the same patient population these tests were compared within study by comparing sensitivity, specificity and diagnostic odds ratio estimates. The bivariate regression models were extended to include all imaging tests in one model, to allow tests to be formally compared for differences in diagnostic odds ratio and specificity.

# Results

This review identified 36 studies relating imaging tests for the diagnosis of osteomyelitis in people with diabetic foot ulcers. MRI was evaluated in 21 studies[[20-40](#_ENREF_20)] X-ray in 16,[[21](#_ENREF_21), [22](#_ENREF_22), [27](#_ENREF_27), [28](#_ENREF_28), [32](#_ENREF_32), [36](#_ENREF_36), [38](#_ENREF_38), [39](#_ENREF_39), [41-49](#_ENREF_41)] PET in six [[32](#_ENREF_32), [34](#_ENREF_34), [37](#_ENREF_37), [50-52](#_ENREF_50)] and SPECT in 3 studies.[[26](#_ENREF_26), [53](#_ENREF_53), [54](#_ENREF_54)] Only one study evaluated the accuracy of ultrasound scans. There were no studies evaluating the accuracy of CT scans. Scintigraphy was evaluated in 17 studies, using a range of isotopes including primarily 99mTc (H)MDP (9 studies), [[21](#_ENREF_21), [22](#_ENREF_22), [42](#_ENREF_42), [43](#_ENREF_43)] [[39](#_ENREF_39), [45-47](#_ENREF_45), [49](#_ENREF_49)] as well as In-111 WBC (four studies), [[21](#_ENREF_21), [33](#_ENREF_33), [43](#_ENREF_43), [45](#_ENREF_45)] and 99mTC HMPAO WBC (two studies).[[42](#_ENREF_42), [50](#_ENREF_50)]

Figure 1 shows the PRISMA flow diagram outlining the screening process with reasons for exclusion of full-text papers. The literature searches identified 18,386 references. After initial screening of titles and abstracts, 597 were considered to be potentially relevant. This left the 36 studies that met the inclusion criteria and were included in the review and meta-analysis.[[20-53](#_ENREF_20), [55-58](#_ENREF_55)] Two studies were excluded from analysis: one [[55](#_ENREF_55)] did not report sufficient diagnostic accuracy data, and one [[56](#_ENREF_56)] was of a combination imaging tests not considered in any other study. The results of these studies are reported elsewhere.[[14](#_ENREF_14)]

[ Figure 1 here]

Table 1 presents a summary of design and patient characteristics of all included studies. Just under half of the studies were published in or after 2000, and just under half were conducted in the USA. The sample size of the studies ranged from 9 to 338, but most studies were small: only 10 included 50 or more participants.[[25](#_ENREF_25), [26](#_ENREF_26), [31](#_ENREF_31), [32](#_ENREF_32), [40](#_ENREF_40), [41](#_ENREF_41), [43](#_ENREF_43), [44](#_ENREF_44), [53](#_ENREF_53), [59-64](#_ENREF_59)]

## Risk of bias

Overall, most diagnostic accuracy studies were small, and poor reporting means that there is significant uncertainty about the quality of most of the studies.

Table 2 presents a summary of the results of the critical appraisal. Eight studies were at high risk of bias for at least one domain, although poor reporting of study methods, particularly regarding the selection of patients and the conduct of the index test, mean that there is significant uncertainty about risk of bias in the majority of studies.

Twenty-two studies did not provide sufficient information to assess the risk of bias associated with the selection and enrolment of patients into the study. In particular, whether all eligible patients were recruited during a defined period of time. Therefore, the risk of selection bias, for instance due to exclusion of patients who may be harder to diagnose, cannot be excluded. Three studies did not blind the interpretation of the index test to the results of other index tests or to the reference standard, and were therefore considered at high risk of bias. Another nine studies did not provide sufficient information on blinding and were therefore considered at unclear risk of bias. Nearly all studies had a low risk of bias associated with the reference standard and patient flow, and none of the included studies raised significant concerns about their applicability to the diagnostic accuracy review questions.

[Table 3 here]

## Meta-analysis

The sensitivity and specificity estimates from the included studies are presented in Figure 2. The results suggest high sensitivity (generally over 80%) for MRI and scintigraphy, but with a wide range of specificities. PET scan showed high specificity, but a range of sensitivities. X-ray generally had low sensitivity. There were too few studies of SPECT or ultrasound to draw any immediate conclusions.

[Figure 2 here]

Table 3 presents the results of univariate meta-analyses. MRI and SPECT have high sensitivity to detect osteomyelitis of over 90%. PET and scintigraphy have sensitivity above 80%, but X-ray has lower sensitivity (68.9%). Specificity was more varied, with only PET having a specificity above 90%. Specificity for SPECT was low (55.09%) although this estimate was highly imprecise (95% CI 55.0% to 86.9%). MRI had the highest diagnostic odds ratio (51.1), suggesting best overall diagnostic performance, but PET and SPECT had similar values (33.9 and 22.9 respectively). Diagnostic odds ratios were much lower for scintigraphy, X-ray and ultrasound.

PET has a markedly lower positive rate (45.9%) than MRI, SPECT or scintigraphy, despite broadly similar prevalence of osteomyelitis across studies. This means that fewer people are considered to have osteomyelitis using PET: a consequence of its higher specificity and lower sensitivity.

[Table 3 here]

Figure 3 shows the result of a bivariate meta-analysis of sensitivity and specificity. Due to non-convergence of their respective bivariate analyses the univariate results are presented for PET and SPECT. This bivariate meta-analysis of diagnostic accuracy found that MRI scans (the most widely studied test) can detect osteomyelitis with high accuracy (96.4% sensitivity (95% CI 90.7 to 98.7); 83.8% specificity (76.0 to 89.5)). PET scans also had high diagnostic accuracy (84.3% sensitivity (52.8 to 96.3); 92.8% specificity (75.7 to 98.2)), with lower sensitivity, but higher specificity, than MRI. SPECT scans also had high accuracy (95.6% sensitivity (76.0 to 99.3); 55.1% specificity (19.3 to 86.3)), but based on only three studies. The summary HSROC curves (see Figure 4) suggest that MRI, PET (and possibly SPECT, although data are limited) have similar overall HSROC curves, and so similar diagnostic accuracy.

Scintigraphy (84.2% sensitivity (76.8 to 89.6); 67.7% specificity (56.2 to 77.4)), and X-ray (61.9% sensitivity (50.5 to 72.1); 78.3% specificity (62.9 to 88.5)) had generally inferior diagnostic accuracy when compared to MRI, PET or SPECT. This was confirmed by their lower diagnostic odds ratios and poorer HSROC curves (see Figure 4). There was evidence that the diagnostic accuracy of scintigraphy depended on the type of scintigraphy used.

[Figures 3 and 4 here]

Figure 5 gives the results of the bivariate meta-analysis of PPV and NPV, which shows that both MRI and PET have high PPV (88.9% and 88.6%) and NPV (95.4% and 85.4). Scintigraphy and X-ray have lower PPV and NPV rates. This confirms the conclusions seen in the main analyses of sensitivity and specificity.

Figure 6 shows the sensitivity and specificity of the scintigraphy studies according to test used. This shows substantial variation in diagnostic accuracy. HMDP scintigraphy has poor specificity, generally below 50%. WBC scintigraphy appears to have better specificity of around 70%. 99mTc HMPAO WBC scintigraphy appears to have the best diagnostic accuracy, with results similar to those seen for MRI although only two studies were included. Meta-analysis of the 11 99mTc MDP studies gave a sensitivity of 87.3% (95% CI 76.8 to 93.5), but a poor specificity of 29.8% (95% CI 16.4 to 47.8). Meta-analysis of the 4 In-111 WBC studies gave a sensitivity of 79.7% (95% CI 71.8 to 85.8), and specificity of 71.3% (95% CI 62.1 to 79.0). Given the limited numbers of studies, meta-analyses for other types of scintigraphy were not performed. It therefore appears that the most up-to-date forms of scintigraphy, such as 99mTc HMPAO WBC scintigraphy may have higher diagnostic accuracy, similar to that of PET or MRI.

[Figures 5 and 6 here]

We also considered studies that compared different imaging tests. Figure 7 shows the diagnostic odds ratios for all tests within studies. This suggests that MRI was generally superior to X-ray and scintigraphy, and scintigraphy was moderately superior to X-ray in most studies. Results from logistic regression models to compare the tests within and across studies are presented in Table 4. These results agree with the general findings. MRI and PET both have higher diagnostic odds ratios and higher specificity than X-ray. X-ray and scintigraphy have lower diagnostic odds ratios and lower specificity than MRI. PET scans have a similar diagnostic odds ratio to MRI, but higher specificity. There were too few studies of SPECT to draw any conclusions. It should be noted that this analysis combines all types of scintigraphy and, as discussed above, 99mTc HMPAO WBC scintigraphy may have better diagnostic accuracy.

[Figure 7 and Table 4 here]

# Discussion

MRI, PET and, possibly, SPECT scans all have broadly similar and high accuracy when diagnosing osteomyelitis. All three tests correctly diagnose most people with, and most people without, osteomyelitis. All three may therefore be suitable imaging tests for reliably diagnosing osteomyelitis, although the number of studies of SPECT is limited. No clear reason to prefer one test over the other in terms of diagnostic accuracy was identified. However, MRI also gives additional information as to the location of fluid collections and anatomical detail for surgical planning not given by SPECT or PET in such detail. PET or SPECT may be required if an MRI scan is inconclusive.

MRI generally had poorer specificity than PET, with a wide range of specificities across studies. This means that there may be substantial numbers of “false-positive” cases when using MRI PET scans had poorer sensitivity, but higher specificity, than MRI, with more consistent results across studies. However, MRI may still provide greater visual detail to guide the surgical approach than PET alone.

Scintigraphy, in general, is less accurate than MRI or PET, but current methods of scintigraphy, particularly 99mTc HMPAO WBC scintigraphy, may have comparable accuracy, and this should be the preferred approach. However, planar scintigraphy may have poorer diagnostic accuracy than 3D SPECT imaging.

X-ray on its own has poor diagnostic accuracy so should probably not be used in isolation. There was only one study of ultrasound, and none of CT scans, suggesting that these should not generally be used given the lack of evidence on their diagnostic accuracy.

## Strengths and limitations

This was the first review in the field to consider all relevant imaging tests. This was also the first meta-analysis of osteomyelitis, and, to our knowledge, the first practical diagnostic meta-analysis in any field, to use regression models to formally compare different diagnostic tests. This made it the first analysis to comprehensively and reliably compare the various imaging tests for osteomyelitis.

The limitations of this review are largely a consequence of the limitations in the identified studies. There were numerous concerns about the potential for bias in the included studies. Most studies were small, with fewer than 50 participants, and were conducted retrospectively. Risk of bias assessment suggested potential bias due to unclear methods of patient selection and lack of blinding between index tests and references standards. However, sensitivity statistical analyses (not reported here) found no evidence that these concerns led to actual biases in the results. Some imaging tests were reported in few studies, particularly ultrasound and SPECT scans, so we were not able to fully assess their diagnostic accuracy.

# Conclusions

This review has found that MRI has high accuracy to diagnose osteomyelitis in people with diabetic foot ulcers. As MRI machines are generally more widely available, and MRI does not expose patients to harmful ionising radiation, this review concludes that MRI will generally the most appropriate imaging test, after initial X-ray. This confirms current guidance such as that of NICE in the UK and ACR guidance for the US (where MRI is classed as “usually appropriate”). This review therefore provides the rigorous statistical assessment of all diagnostic evidence required to properly confirm this guidance, so that the guidance is not based on literature review and expert opinion alone.

This review has identified a potential problem of overdiagnosis of osteomyelitis when using MRI scans (because studies of MRI scans had varying, and often poor, specificity). Clinicians and radiographers should be made aware of this potential for overdiagnosis. MRI may therefore be best suited to cases where patients will be treated with antibiotics, so overdiagnosis is not likely to cause harm.

X-ray was found to have poor diagnostic accuracy in isolation, and so should probably not be used without confirmation from another test. It remains unclear whether the common practice of using X-ray as a first test and proceeding to an MRI if the X-ray is inconclusive maximises diagnostic accuracy. It is, however, likely that X-ray can be used to rule out osteomyelitis in more obvious cases (e.g. when symptoms are the result of bone fracture).

PET scans have high diagnostic accuracy, and better specificity than MRI. PET therefore appears to be the most suitable test in cases where MRI is not appropriate. PET may also be better suited than MRI to situations where avoiding false-positive diagnoses is important; for example, when the test would be followed by surgery or other invasive procedures. Current guidance may need to be modified to reflect this evidence. While SPECT appears to have similar diagnostic accuracy to PET there are, perhaps, too few studies so far to recommend its general use.

Scintigraphy was found to have poor diagnostic accuracy in general, and, for most recent forms of scintigraphy such as WBC, accuracy no better than PET or SPECT. This suggests that planar scintigraphy is unlikely to be a preferred diagnostic test, and perhaps current ACR guidance should be amended to remove any recommendation in favour of planar scintigraphy.

# References

1. National Institute for Clinical, E., *Diabetic foot problems: prevention and management*. 2015, National Institute for Health and Care Excellence London.

2. Malhotra, R., C.S. Chan, and A. Nather, *Osteomyelitis in the diabetic foot.* Diabetic Foot & Ankle, 2014. **5**.

3. Berendt, A.R., et al., *Diabetic foot osteomyelitis: A progress report on diagnosis and a systematic review of treatment.* Diabetes/Metabolism Research and Reviews, 2008. **24**(SUPPL. 1): p. S145-S161.

4. Josse, J., F. Velard, and S.C. Gangloff, *Staphylococcus aureus vs. osteoblast: relationship and consequences in osteomyelitis.* Frontiers in cellular and infection microbiology, 2015. **5**: p. 85.

5. Carek, P.J., L.M. Dickerson, and J.L. Sack, *Diagnosis and management of osteomyelitis.* American Family Physician, 2001. **63**(12): p. 2413-20.

6. Lima, A.L., et al., *Recommendations for the treatment of osteomyelitis.* Brazilian Journal of Infectious Diseases, 2014. **18**(5): p. 526-34.

7. Gold, R., *Diagnosis of osteomyelitis.* Pediatrics in Review, 1991. **12**(10): p. 292-7.

8. Karmazyn, B., *Imaging approach to acute hematogenous osteomyelitis in children: an update.* Seminars in Ultrasound, CT & MR, 2010. **31**(2): p. 100-6.

9. Pineda, C., R. Espinosa, and A. Pena, *Radiographic imaging in osteomyelitis: the role of plain radiography, computed tomography, ultrasonography, magnetic resonance imaging, and scintigraphy.* Seminars in Plastic Surgery, 2009. **23**(2): p. 80-9.

10. Dinh, M.T., C.L. Abad, and N. Safdar, *Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis.* Clinical Infectious Diseases, 2008. **47**(4): p. 519-27.

11. Kapoor, A., et al., *Magnetic resonance imaging for diagnosing foot osteomyelitis: a meta-analysis.* Archives of Internal Medicine, 2007. **167**: p. 125-132.

12. Lauri, C., et al., *Detection of Osteomyelitis in the Diabetic Foot by Imaging Techniques: A Systematic Review and Meta-analysis Comparing MRI, White Blood Cell Scintigraphy, and FDG-PET.* Diabetes Care, 2017. **40**(8): p. 1111-1120.

13. Treglia, G., et al., *Diagnostic performance of Fluorine-18-Fluorodeoxyglucose positron emission tomography for the diagnosis of osteomyelitis related to diabetic foot: a systematic review and a meta-analysis.* Foot, 2013. **23**(4): p. 140-8.

14. Llewellyn, A., et al., *Imaging tests for the detection of osteomyelitis: a systematic review.* Health technology assessment, 2019: p. 1-128.

15. Whiting, P.F., et al., *QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies.* Annals of internal medicine, 2011. **155**(8): p. 529-536.

16. Reitsma, J.B., et al., *Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews.* Journal of clinical epidemiology, 2005. **58**(10): p. 982-990.

17. Rutter, C.M. and C.A. Gatsonis, *A hierarchical regression approach to meta‐analysis of diagnostic test accuracy evaluations.* Statistics in medicine, 2001. **20**(19): p. 2865-2884.

18. Simmonds, M.C. and J.P.T. Higgins, *A general framework for the use of logistic regression models in meta-analysis.* Statistical methods in medical research, 2016. **25**(6): p. 2858-2877.

19. Higgins, J.P.T., et al., *Measuring inconsistency in meta-analyses.* BMJ: British Medical Journal, 2003. **327**(7414): p. 557.

20. Al-Khawari, H.A., et al., *Evaluating diabetic foot infection with magnetic resonance imaging: Kuwait experience.* Medical Principles & Practice, 2005. **14**(3): p. 165-72.

21. Croll, S.D., et al., *Role of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections.* Journal of Vascular Surgery, 1996. **24**(2): p. 266-70.

22. Enderle, M.D., et al., *Correlation of imaging techniques to histopathology in patients with diabetic foot syndrome and clinical suspicion of chronic osteomyelitis. The role of high-resolution ultrasound.* Diabetes Care, 1999. **22**(2): p. 294-9.

23. Ertugrul, M.B., et al., *The diagnosis of osteomyelitis of the foot in diabetes: microbiological examination vs. magnetic resonance imaging and labelled leucocyte scanning.* Diabetic Medicine, 2006. **23**(6): p. 649-53.

24. Hazenberg, C., et al., *Prediction of outcome of treatment of osteomyelitis in diabetic foot after minor amputation: the role of MR imaging.* Journal of Vascular Surgery, 2011. **53**: p. 78S-79S.

25. Johnson, P.W., M.S. Collins, and D.E. Wenger, *Diagnostic utility of T1-weighted MRI characteristics in evaluation of osteomyelitis of the foot.* AJR. American Journal of Roentgenology, 2009. **192**(1): p. 96-100.

26. La Fontaine, J., et al., *Comparison between Tc-99m WBC SPECT/CT and MRI for the diagnosis of biopsy-proven diabetic foot osteomyelitis.* Wounds, 2016. **28**(8): p. 271-8.

27. Levine, S.E., et al., *Magnetic resonance imaging for the diagnosis of osteomyelitis in the diabetic patient with a foot ulcer.* Foot & Ankle International, 1994. **15**(3): p. 151-6.

28. Lipman, B.T., et al., *Detection of osteomyelitis in the neuropathic foot: nuclear medicine, MRI and conventional radiography.* Clinical Nuclear Medicine, 1998. **23**(2): p. 77-82.

29. Mahendra, M. and R. Singh, *Diagnostic accuracy and surgical utility of MRI in complicated diabetic foot.* Journal of Clinical and Diagnostic Research, 2017. **11**(7): p. RC01-RC04.

30. Miki, F., D.G. Armstrong, and T. Hiroto, *Efficacy of magnetic resonance imaging in deciding the appropriate surgical margin in diabetic foot osteomyelitis.* EWMA Journal, 2015. **15**(1): p. 8-12.

31. Morrison, W.B., et al., *Osteomyelitis of the foot: relative importance of primary and secondary MR imaging signs.* Radiology, 1998. **207**(3): p. 625-32.

32. Nawaz, A., et al., *Diagnostic performance of FDG-PET, MRI, and Plain Film Radiography (PFR) for the diagnosis of osteomyelitis in the diabetic foot.* Molecular Imaging and Biology, 2010. **12**(3): p. 335-42.

33. Newman, L.G., et al., *Leukocyte scanning with 111In is superior to magnetic resonance imaging in diagnosis of clinically unsuspected osteomyelitis in diabetic foot ulcers.* Diabetes Care, 1992. **15**(11): p. 1527-30.

34. Rastogi, A., et al., *Utility of PET/CT with fluorine-18-fluorodeoxyglucose-labeled autologous leukocytes for diagnosing diabetic foot osteomyelitis in patients with Charcot's neuroarthropathy.* Nuclear Medicine Communications, 2016. **37**(12): p. 1253-1259.

35. Remedios, D., et al., *99mTc-nanocolloid scintigraphy for assessing osteomyelitis in diabetic neuropathic feet.* Clinical Radiology, 1998. **53**(2): p. 120-5.

36. Rozzanigo, U., et al., *Role of magnetic resonance imaging in the evaluation of diabetic foot with suspected osteomyelitis.* Radiologia Medica, 2009. **114**(1): p. 121-32.

37. Schwegler, B., et al., *Unsuspected osteomyelitis is frequent in persistent diabetic foot ulcer and better diagnosed by MRI than by 18F-FDG PET or 99mTc-MOAB.* Journal of Internal Medicine, 2008. **263**(1): p. 99-106.

38. Weinstein, D., et al., *Evaluation of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections.* Foot & Ankle, 1993. **14**(1): p. 18-22.

39. Yuh, W.T., et al., *Osteomyelitis of the foot in diabetic patients: evaluation with plain film, 99mTc-MDP bone scintigraphy, and MR imaging.* AJR. American Journal of Roentgenology, 1989. **152**(4): p. 795-800.

40. Zaiton, F., et al., *Evaluation of diabetic foot osteomyelitis using probe to bone test and magnetic resonance imaging and their impact on surgical intervention.* Egyptian Journal of Radiology and Nuclear Medicine, 2014. **45**(3): p. 795-802.

41. Aragon-Sanchez, J., B.A. Lipsky, and J.L. Lazaro-Martinez, *Diagnosing diabetic foot osteomyelitis: is the combination of probe-to-bone test and plain radiography sufficient for high-risk inpatients?* Diabetic Medicine, 2011. **28**(2): p. 191-4.

42. Blume, P.A., et al., *Diagnosis of pedal osteomyelitis with Tc-99m HMPAO labeled leukocytes.* Journal of Foot and Ankle Surgery, 1997. **36**(2): p. 120-6.

43. Larcos, G., M.L. Brown, and R.T. Sutton, *Diagnosis of osteomyelitis of the foot in diabetic patients: value of 111In-leukocyte scintigraphy.* AJR. American Journal of Roentgenology, 1991. **157**(3): p. 527-31.

44. Morales Lozano, R., et al., *Validating the probe-to-bone test and other tests for diagnosing chronic osteomyelitis in the diabetic foot.* Diabetes Care, 2010. **33**(10): p. 2140-5.

45. Newman, L.G., et al., *Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline.* JAMA, 1991. **266**(9): p. 1246-51.

46. Nigro, N.D., et al., *Clinical impact of magnetic resonance imaging in foot osteomyelitis.* Journal of the American Podiatric Medical Association, 1992. **82**(12): p. 603-15. Erratum in: J Am Podiatr Med Assoc 1993 Feb;83(2):86.

47. Park, H.M., et al., *Scintigraphic evaluation of diabetic osteomyelitis: concise communication.* Journal of Nuclear Medicine, 1982. **23**(7): p. 569-73.

48. Sarikaya, A., A.C. Aygit, and G. Pekindil, *Utility of 99mTc dextran scintigraphy in diabetic patients with suspected osteomyelitis of the foot.* Annals of Nuclear Medicine, 2003. **17**(8): p. 669-76.

49. Segall, G.M., et al., *The role of bone scan and radiography in the diagnostic evaluation of suspected pedal osteomyelitis.* Clinical Nuclear Medicine, 1989. **14**(4): p. 255-60.

50. Familiari, D., et al., *Can sequential 18F-FDG PET/CT replace WBC imaging in the diabetic foot?* Journal of Nuclear Medicine, 2011. **52**(7): p. 1012-9.

51. Franceschi, D., et al., *FDG PET/CT imaging in diabetic foot infections.* European Journal of Nuclear Medicine and Molecular Imaging, 2013. **40**: p. S36.

52. Yang, H., et al., *Mild-to-moderate hyperglycemia will not decrease the sensitivity of 18F-FDG PET imaging in the detection of pedal osteomyelitis in diabetic patients.* Nuclear Medicine Communications, 2016. **37**(3): p. 259-62.

53. Aslangul, E., et al., *Diagnosing diabetic foot osteomyelitis in patients without signs of soft tissue infection by coupling hybrid 67Ga SPECT/CT with bedside percutaneous bone puncture.* Diabetes Care, 2013. **36**(8): p. 2203-10.

54. Filippi, L. and O. Schillaci, *Usefulness of hybrid SPECT/CT in 99mTc-HMPAO-labeled leukocyte scintigraphy for bone and joint infections.* Journal of Nuclear Medicine, 2006. **47**(12): p. 1908-13.

55. Abdel Razek, A.A. and S. Samir, *Diagnostic performance of diffusion-weighted MR imaging in differentiation of diabetic osteoarthropathy and osteomyelitis in diabetic foot.* European Journal of Radiology, 2017. **89**: p. 221-225.

56. Bohchelian, H.A., A.D. Klisarova, and L.A. Koeva, *Single photon emission tomography in radioimmune imaging of diabetic foot infection.* Diabetologia Polska, 2002. **9**(1): p. 39-44.

57. Filippi, L., et al., *Diabetic foot infection: usefulness of SPECT/CT for 99mTc-HMPAO-labeled leukocyte imaging.* Journal of Nuclear Medicine, 2009. **50**(7): p. 1042-6.

58. Harwood, S.J., et al., *Use of Sulesomab, a radiolabeled antibody fragment, to detect osteomyelitis in diabetic patients with foot ulcers by leukoscintigraphy.* Clinical Infectious Diseases, 1999. **28**(6): p. 1200-5.

59. Chacko, T.K., et al., *Applications of fluorodeoxyglucose positron emission tomography in the diagnosis of infection.* Nuclear Medicine Communications, 2003. **24**(6): p. 615-24.

60. Erdman, W.A., et al., *Osteomyelitis: characteristics and pitfalls of diagnosis with MR imaging.* Radiology, 1991. **180**(2): p. 533-9.

61. Lewis, V.L., et al., *The diagnosis of osteomyelitis in patients with pressure sores.* Plastic & Reconstructive Surgery, 1988. **81**(2): p. 229-32.

62. Malcius, D., et al., *The accuracy of different imaging techniques in diagnosis of acute hematogenous osteomyelitis.* Medicina (Kaunas, Lithuania), 2009. **45**(8): p. 624-31.

63. Schlung, J.E., et al., *Femoral neck aspiration aids in the diagnosis of osteomyelitis in children with septic hip [published online ahead of print Sep 3 2016].* Journal of Pediatric Orthopedics, 2016.

64. Wenter, V., et al., *The diagnostic value of [(18)F]FDG PET for the detection of chronic osteomyelitis and implant-associated infection.* European Journal of Nuclear Medicine and Molecular Imaging, 2016. **43**(4): p. 749-61.

**Figure legends**

Figure 1 Study selection PRISMA flow diagram

Figure 2 Sensitivity and specificity by imaging test used

Figure 3 Bivariate analysis of sensitivity and specificity

Figure 4 HSROC curves

Figure 5 Summary PPV and NPV

Figure 6 Sensitivity and specificity of scintigraphy studies

Figure 7 Difference in DOR between imaging tests

###

Table 1 Study design and participant characteristics

| **Study** | **N** | **Imaging tests** | **Country** | **Design** | **Mean Age** **(SD) [range]** | **% Male** | **Acute or chronic OM** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Al-Khawari (2005) [[20](#_ENREF_20)] | 19 | MRI | Kuwait | Retrospective | 61[41-81] | 59% | AOM & COM |
| Aragon-Sanchez (2011) [[41](#_ENREF_41)] | 338 | X-ray | Spain | Retrospective | NR | NR | NR |
| Aslangul(2013) [[53](#_ENREF_53)] | 53 | SPECT | France, UK, Switzerland | Prospective | 63 (10) | 93% | NR |
| Blume (1997)[[42](#_ENREF_42)] | 27 | ScintigraphyX-ray | USA | Prospective | 64.7 (1) | 96% | AOM & COM |
| Croll (1996) [[21](#_ENREF_21)] | 27 | MRIScintigraphyX-ray | Canada | Prospective | 66[34-82] | 70% | NR |
| Enderle (1999) [[22](#_ENREF_22)] | 19 | MRIScintigraphyUltrasoundX-ray | Germany | Prospective | 61(10) | 90% | COM |
| Ertugrul (2006) [[23](#_ENREF_23)] | 26 | MRIScintigraphy | Turkey | Prospective | 62 (9)[40-77] | 74% | AOM |
| Familiari (2011) [[50](#_ENREF_50)] | 13 | PETScintigraphy | Italy | NR | 62[50-89] | 92% | NR |
| Filippi (2009) [[54](#_ENREF_54)] | 17 | SPECT | Italy | Prospective | 55 (4) | 59% | NR |
| Franceschi (2013) [[51](#_ENREF_51)] | 17 | PET | USA | NR | NR[21-84] | 62% | NR |
| Harwood (1999) [[58](#_ENREF_58)] | 122 | Scintigraphy | USA | Prospective | 58 [NR] | 82% | NR |
| Hazenberg (2011) [[24](#_ENREF_24)] | 21 | MRI | Netherlands | Prospective | NR | NR | NR |
| Johnson (2009) [[25](#_ENREF_25)] | 73 | MRI | USA | Retrospective | 65[26-92] | 66% | NR |
| La Fontaine (2016) [[26](#_ENREF_26)] | 52 | MRISPECT | USA | Retrospective | 50 (10)[26-74] | 73% | NR |
| Larcos (1991)[[43](#_ENREF_43)] | 51 | ScintigraphyX-ray | USA | Retrospective | 62[30-88] | 61% | AOM & COM |
| Levine (1994) [[27](#_ENREF_27)] | 27 | MRIX-ray | USA | Retrospective | 52[33-72] | 44% | AOM |
| Lipman (1998)[[28](#_ENREF_28)] | 20 | MRI | USA | Prospective | 46[28-72] | 65% | NR |
| Mahendra (2017) [[29](#_ENREF_29)] | 34 | MRI | India | Prospective | 52 (9) | 65% | NR |
| Miki (2015)[[30](#_ENREF_30)] | 26 | MRI | Japan, USA | Retrospective | 67[42-85] | 77% | NR |
| Morales (2010) [[44](#_ENREF_44)] | 132 | X-ray | Spain | Prospective | NR | NR | NR |
| Morrison (1998) [[31](#_ENREF_31)] | 68 | MRI | USA | Retrospective | 56[24-85] | NR | NR |
| Nawaz (2010) [[32](#_ENREF_32)] | 106 | MRIPETX-ray | USA | Prospective | 59[29-85] | 69% | NR |
| Newman (1991) [[45](#_ENREF_45)] | 35 | ScintigraphyX-ray | USA | Prospective | NR | NR | NR |
| Newman (1992) [[33](#_ENREF_33)] | 12 | MRIScintigraphy | USA | Prospective | NR | NR | AOM |
| Nigro (1992) [[46](#_ENREF_46)] | 44 | ScintigraphyX-ray | USA | Prospective | 55[23-84] | 57% | AOM |
| Park (1982)[[47](#_ENREF_47)] | 36 | ScintigraphyX-ray | USA | Retrospective | NR | NR | AOM & COM |
| Rastogi (2016)[[34](#_ENREF_34)] | 23 | MRIPET | India | Prospective | 58 (8) | 96% | COM |
| Remedios (1998)[[35](#_ENREF_35)] | 9 | MRIScintigraphy | UK | Prospective | 57[25-70] | 45% | COM |
| Rozzanigo (2009) [[36](#_ENREF_36)] | 16 | MRIX-ray | Italy | Retrospective | 58[42-78] | 69% | NR |
| Sarikaya (2003) [[48](#_ENREF_48)] | 26 | ScintigraphyX-ray | Turkey | NR | 59[18-80] | 77% | NR |
| Schwegler (2008) [[37](#_ENREF_37)] | 20 | MRIPETScintigraphy | Switzerland | Prospective | 66[53-89] | 60% | AOM |
| Segall (1989)[[49](#_ENREF_49)] | 23 | ScintigraphyX-ray | USA | Retrospective | 58 (13)[25-79] | 95% | NR |
| Weinstein (1993) [[38](#_ENREF_38)] | 32 | MRIScintigraphyX-ray | USA | Prospective | 49[23-81] | 68% | AOM & COM |
| Yang (2016)[[52](#_ENREF_52)] | 48 | PET | USA | Prospective | 60 (15)[36-83] | 67% | COM |
| Yuh (1989)[[39](#_ENREF_39)] | 24 | MRIScintigraphyX-ray | USA | Prospective | 58[32-74] | NR | COM |
| Zaiton (2014)[[40](#_ENREF_40)] | 102 | MRI | Egypt | Prospective | 52 (6) | 41% | COM |

NR: Not reported; AOM: acute osteomyelitis; COM: chronic osteomyelitis

#

Table 2 Summary of critical appraisal of diagnostic accuracy studies

|  |  |  |
| --- | --- | --- |
|  | **Risk of bias** | **Applicability** |
| **Study** | **Patient selection** | **Index test**  | **Reference standard** | **Patient flow**  | **Patient selection** | **Index test**  | **Reference standard**  |
| Al-Khawari (2005)[[20](#_ENREF_20)] | ? | + | + | + | + | + | + |
| Aragon-Sanchez (2011)[[41](#_ENREF_41)] | + | + | + | + | + | + | + |
| Aslangul(2013)[[53](#_ENREF_53)] | + | + | + | + | + | + | + |
| Blume (1997)[[42](#_ENREF_42)] | ? | + | + | + | + | + | + |
| Croll (1996)[[21](#_ENREF_21)] | ? | - | + | + | + | + | + |
| Enderle (1999)[[22](#_ENREF_22)] | + | + | + | + | + | + | + |
| Ertugrul (2006)[[23](#_ENREF_23)] | ? | ? | + | + | + | + | + |
| Familiari (2011)[[50](#_ENREF_50)] | ? | + | + | + | + | + | + |
| Filippi (2009)[[57](#_ENREF_57)] | + | + | + | + | + | + | + |
| Franceschi (2013)[[51](#_ENREF_51)] | ? | + | + | - | ? | + | + |
| Harwood (1999)[[58](#_ENREF_58)] | + | ? | + | + | + | + | + |
| Hazenberg (2011)[[24](#_ENREF_24)] | ? | ? | + | + | + | + | + |
| Johnson (2009)[[25](#_ENREF_25)] | ? | + | + | + | + | + | + |
| La Fontaine (2016)[[26](#_ENREF_26)] | ? | + | + | + | + | + | + |
| Larcos (1991)[[43](#_ENREF_43)] | ? | ? | + | + | + | + | + |
| Levine (1994)[[27](#_ENREF_27)] | ? | ? | + | + | + | + | + |
| Lipman (1998)[[28](#_ENREF_28)] | + | + | + | ? | + | + | + |
| Mahendra (2017)[[29](#_ENREF_29)] | + | + | + | + | + | ? | + |
| Miki (2015)[[30](#_ENREF_30)] | ? | ? | + | + | + | + | + |
| Morales (2010)[[44](#_ENREF_44)] | ? | ? | + | + | + | + | + |
| Morrison (1998)[[31](#_ENREF_31)] | ? | + | + | + | + | + | + |
| Nawaz (2010)[[32](#_ENREF_32)] | + | ? | + | + | + | + | + |
| Newman (1991)[[45](#_ENREF_45)] | + | ? | + | + | + | + | + |
| Newman (1992)[[33](#_ENREF_33)] | ? | + | + | + | + | + | + |
| Nigro (1992)[[46](#_ENREF_46)] | + | - | ? | + | + | + | + |
| Park (1982)[[47](#_ENREF_47)] | - | + | + | + | + | + | + |
| Rastogi (2016)[[34](#_ENREF_34)] | + | ? | + | + | + | + | + |
| Remedios (1998)[[35](#_ENREF_35)] | ? | + | + | + | + | + | + |
| Rozzanigo (2009)[[36](#_ENREF_36)] | ? | - | ? | ? | + | + | + |
| Sarikaya (2003)[[48](#_ENREF_48)] | ? | + | + | + | + | + | + |
| Schwegler (2008)[[37](#_ENREF_37)] | + | + | + | + | + | + | + |
| Segall (1989)[[49](#_ENREF_49)] | - | + | + | + | + | + | + |
| Weinstein (1993)[[38](#_ENREF_38)] | + | + | + | - | + | + | + |
| Yang (2016)[[52](#_ENREF_52)] | + | + | - | - | + | + | + |
| Yuh (1989)[[39](#_ENREF_39)] | + | + | + | + | + | + | + |
| Zaiton (2014)[[40](#_ENREF_40)] | + | + | + | + | + | + | + |

 +: Low risk of bias; -: High risk of bias; ?: Unclear risk of bias

Table 3 Univariate meta-analyses

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Test** | **Studies** | **Outcome** | **Estimate (%)** | **95% confidence interval** | **I2 (%)** |
| MRI | 21 | Sensitivity | 95.76 | 91.83 | 97.85 | 0 |
|  |  | Specificity | 81.79 | 69.35 | 89.91 | 0 |
|  |  | DOR | 51.08 | 21.3 | 122.53 | 60 |
|  |  | Positive rate | 70.43 | 64.03 | 77.47 | 1 |
| PET | 6 | Sensitivity | 84.34 | 52.77 | 96.29 | 0 |
|  |  | Specificity | 92.8 | 75.67 | 98.16 | 0 |
|  |  | DOR | 33.91 | 11.75 | 97.92 | 12 |
|  |  | Positive rate | 45.88 | 27.81 | 75.69 | 36 |
| Scintigraphy  | 17 | Sensitivity | 84.69 | 65.86 | 94.07 | 0 |
|  |  | Specificity | 73.99 | 54.96 | 86.89 | 0 |
|  |  | DOR | 8.66 | 4.74 | 15.83 | 16 |
|  |  | Positive rate | 73.57 | 64.29 | 84.2 | 9 |
| SPECT | 3 | Sensitivity | 95.53 | 75.95 | 99.31 | 0 |
|  |  | Specificity | 55.09 | 19.26 | 86.32 | 36 |
|  |  | DOR | 22.91 | 1.91 | 274.73 | 62 |
|  |  | Positive rate | 76.7 | 62.79 | 93.69 | 0 |
| Ultrasound | 1 | Sensitivity | 78.57 | 2.39 | 99.82 | -- |
|  |  | Specificity | 80 | 1.61 | 99.9 | -- |
|  |  | DOR | 14.67 | 1.16 | 185.23 | -- |
|  |  | Positive rate | 63.16 | 30.87 | 129.23 | -- |
| X-ray | 16 | Sensitivity | 68.91 | 57.55 | 78.38 | 11 |
|  |  | Specificity | 77.99 | 63.67 | 87.76 | 0 |
|  |  | DOR | 5.97 | 3.09 | 11.51 | 62 |
|  |  | Positive rate | 51.95 | 41.08 | 65.68 | 62 |

Table 4 Results of logistic regression to compare tests

|  |  |  |
| --- | --- | --- |
|  | **Difference in log odds of specificity** | **Difference in log diagnostic odds ratio** |
|  | **Estimate** | **Standard error** | **P-value** | **Estimate** | **Standard error** | **P-value** |
| **Comparison with X-ray** |
| **MRI** | 0.175 | 0.255 | 0.493 | 2.188 | 0.366 | 0 |
| **Scintigraphy** | -0.727 | 0.244 | 0.003 | 0.731 | 0.344 | 0.034 |
| **SPECT** | -0.792 | 0.728 | 0.277 | 0.43 | 1.043 | 0.68 |
| **PET** | 1.121 | 0.424 | 0.008 | 1.991 | 0.541 | 0 |
| **Comparison with MRI** |
| **Scintigraphy** | -0.902 | 0.281 | 0.001 | -1.458 | 0.389 | 0 |
| **X-ray** | -0.175 | 0.255 | 0.493 | -2.188 | 0.366 | 0 |
| **SPECT** | -0.968 | 0.682 | 0.156 | -1.758 | 0.992 | 0.076 |
| **PET** | 0.946 | 0.429 | 0.028 | -0.197 | 0.588 | 0.738 |

## Appendix: MEDLINE search strategy

1 Osteomyelitis/ (19486)

2 Petrositis/ (74)

3 (osteomyelitis or osteomyelitides).ti,ab. (20136)

4 ((bone$ or osseous or osteo) adj3 infect$).ti,ab. (6234)

5 ((spine or spines or spinal or vertebra$ or skeleton$ or skeletal or musculoskeletal) adj3 infect$).ti,ab. (4066)

6 ((tibia or tibial or femur or humerus or humeral) adj3 infect$).ti,ab. (405)

7 majeed syndrome$.ti,ab. (32)

8 (petrositis or petrositides or Gradenigo$ or petrous apiciti$).ti,ab. (251)

9 or/1-8 (34520)

10 exp Diagnostic Imaging/ (2430931)

11 (imag$ adj3 (diagnos$ or test$ or tool$ or procedure$ or method$ or technique$ or technolog$ or modalit$)).ti,ab. (168689)

12 radiograph$.ti,ab. (191546)

13 (x-ray$ or xray$ or roentgen$).ti,ab. (337423)

14 (bone$ adj2 (scan$ or imag$)).ti,ab. (12239)

15 (radionuclide adj2 (imag$ or scan$ or diagnos$)).ti,ab. (4856)

16 radioisotope$ scan$.ti,ab. (683)

17 (nuclear adj2 (medicine or imag$ or scan$)).ti,ab. (14606)

18 ((magnetic resonance adj (imag$ or scan$ or tomograph$)) or MRI or MR imag$ or MR scan$ or MR tomograph$ or MRT or NMR or NMRI or fMRI or chemical shift imag$).ti,ab. (510943)

19 ((compute$ adj2 tomograph$) or tomodensitometry or cine-CT).ti,ab. (253513)

20 ((CT or CAT) adj (scan$ or imag$)).ti,ab. (105989)

21 ((emission or positron or proton) adj2 tomograph$).ti,ab. (64652)

22 (PET or PET-CT$ or PET?CT$ or CT-PET$ or CT?PET$).ti,ab. (79016)

23 (SPECT or SPECT-CT$ or SPECT?CT$ or CT-SPECT$ or CT?SPECT$).ti,ab. (25475)

24 (SPET or SPET-CT$ or SPET?CT$ or CT-SPET$ or CT?SPET$).ti,ab. (1321)

25 (PET-MRI$ or PET?MRI$).ti,ab. (1227)

26 Fluorodeoxyglucose F18/ (25483)

27 ((FDG or fluorodeoxyglucose) adj4 (imag$ or scan$)).ti,ab. (9778)

28 (FDG-PET$ or FDG?PET$).ti,ab. (20415)

29 (ultrasound$ or ultrasonograph$ or echograph$ or ultrasonic or sonograph$ or echotomograph$ or echogram$ or echoscop$ or echosound$).ti,ab. (351485)

30 (scintigraph$ or scintiphotograph$ or scintigram$).ti,ab. (47128)

31 (scintiscan$ or immunoscintigra$ or leu#oscintigra$).ti,ab. (2486)

32 ((leu#ocyte$ adj2 (scan$ or imag$)) or leu#oscan$).ti,ab. (697)

33 (white blood cell$ adj2 (scan$ or imag$)).ti,ab. (195)

34 (WBC scan$ or WBCS).ti,ab. (2034)

35 or/10-34 (3217417)

36 9 and 35 (10908)

37 exp animals/ not humans/ (4448945)

38 36 not 37 (10184)