

# evidence | *note*

In response to an enquiry from the Scottish Clinical Imaging Network  
PET/CT Working Group

Number 79 May 2018

## Is the use of positron emission tomography/computed tomography (PET/CT) in investigating and/or assessing patients for diagnosis and/or staging of myeloma clinically and cost-effective?

### Key points

- The quantity and quality of the evidence base was not sufficient to determine the diagnostic accuracy of 18F-fluorodeoxyglucose (FDG) PET/CT in the context of investigating patients with suspected myeloma.
- In the assessment of newly-diagnosed myeloma patients, there was evidence that FDG PET/CT is likely to detect more lesions than x-ray, but when compared to other modern imaging methods (MRI being the most commonly used comparator) there was conflicting evidence about whether FDG PET/CT can detect more lesions.
- There is evidence that FDG PET/CT is not cost-effective for the diagnosis of myeloma across a wide range of sensitivity and specificity values (60-100%).
- No relevant cost-effectiveness studies were identified to assess the cost-effectiveness of FDG PET/CT among newly-diagnosed myeloma populations.

### What is an evidence note?

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The evidence notes are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

## Definitions

**Staging:** the process of categorising patients by characteristics of their disease, for example severity.

**Re-staging:** the process of categorising the presence or absence of recurrence or spread of cancer following initial treatment. Re-staging can also be used to monitor response to cancer treatment.

**Sensitivity:** the probability that a person having a disease will be correctly identified by a clinical test, that is the number of true positive results divided by the total number with the disease<sup>1</sup>.

**Specificity:** the probability that a person not having a disease will be correctly identified by a clinical test, that is the number of true negative results divided by the total number of those without the disease<sup>1</sup>.

## Literature search

A systematic search of the literature was carried out between 22 and 29 August 2017 to identify systematic reviews, health technology assessments and other evidence-based reports. During the same time period, the primary literature was systematically searched using the following databases: Medline, Embase, Cinahl and Web of Science.

Results were limited to myeloma studies that were published in English from 2007 onwards and reported patient management outcomes.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

Concepts used in all searches included myeloma, multiple myeloma and positron emission tomography/computed tomography (PET/CT). A full list of resources searched and terms used is available on request.

## Introduction

Functional imaging with positron emission tomography (PET)/computed tomography (CT) (PET/CT) is widely used in the diagnosis and staging of a variety of cancer types. Imaging with PET/CT has primarily utilised 18F-fluorodeoxyglucose (FDG) as a radiolabelled tracer for oncological indications (FDG PET/CT). At present, guidelines note the value of FDG PET/CT as a predictive prognostic tool in the monitoring of metabolically active disease during and after treatment<sup>2,3</sup>, but its role in the initial investigation and assessment of myeloma is less clear. There have been at least four new or updated guidelines relevant to NHS clinical practice that have made recommendations on the use of FDG PET/CT for the staging and/or re-staging of myeloma within the last three years<sup>2,4-6</sup> which suggests a growing evidence base. PET technology has been recognised (as has MRI) as an imaging option in the staging of this disease according to the Durie and Salmon Plus criteria<sup>7</sup>, but it is not clear what additional clinical benefit PET/CT hybrid imaging might provide beyond PET imaging alone. This evidence note reviews both the clinical effectiveness and cost effectiveness of FDG PET/CT in the investigation and/or assessment of patients with suspected or newly diagnosed myeloma.

## Health technology description

PET/CT is a non-invasive imaging technique that combines information from two different imaging modalities: PET provides information about functional and metabolic cellular activity, while CT images

give precise anatomical localisation<sup>8</sup>. The procedure usually involves injecting a radiolabelled tracer into the body, but the tracer can also be ingested or inhaled. The radiolabelled tracer is taken up and accumulates in metabolically active cells (such as malignant cells) and emits gamma rays detected by the PET and CT technology to produce colour-coded images of the body demonstrating the cellular activity of both normal and malignant tissue. Images acquired from PET and CT devices can be combined into a single superimposed image (PET/CT) that provides important diagnostic information as well as assessing the effectiveness of treatment in cancer. The radiolabelled tracers are then passed out of the body in the urine or bowel movement. 18F-fluorodeoxyglucose (FDG) is the most common radiolabelled tracer used with PET/CT imaging.

There are currently six PET/CT machines in operational use within the NHS in Scotland, although one is owned by the University of Edinburgh (Kate Henderson, Commodity Manager, National Procurement, National Services Scotland, personal communication, 22 August 2017) but is still used by the NHS.

## Epidemiology

Across Europe the incidence of multiple myeloma is six people per 100,000 population<sup>9</sup>. Myeloma is considered one of the most common haematological malignancies<sup>10, 11</sup>. It occurs more commonly in elderly patients and median age upon diagnosis is between 65 and 70 years old<sup>10, 11</sup>. It is more likely to affect men than women.<sup>11</sup>

In myeloma, abnormal plasma cells (M proteins) accumulate within the bone marrow and because plasma cells are responsible for producing antibodies for the immune system, the production of abnormal antibodies compromises this process<sup>11</sup>. Almost one-third of patients are asymptomatic, known as 'smouldering' myeloma. Plasma cells can also form a mass known as a plasmacytoma inside the bone marrow or soft tissue. When there is only one mass in the body this is known as solitary plasmacytoma, whereas more than one mass indicates multiple myeloma. In addition, patients who do not have myeloma can present with a condition called monoclonal gammopathy of undetermined significance (MGUS). In MGUS excess M proteins are detected in the body but have not formed any mass or caused any symptoms, and other myeloma criteria are absent. Among myeloma diagnosed patients, MGUS tends to be a precursor condition, but not all patients with MGUS will go on to develop myeloma<sup>12</sup>.

Bone pain is the leading reason for clinical presentation in myeloma patients<sup>11</sup>. Almost all diagnosed multiple myeloma patients will develop bone lesions during the course of their disease or have evidence of bone loss upon diagnosis<sup>10</sup>. When myeloma is described as intra-medullary it is confined to the bone marrow, whereas extra-medullary disease extends to the soft tissue around the bone. Common side effects are pathological fractures and hypercalcaemia. Other (less common) side effects include neurological disorders, renal failure, infections and fever<sup>11</sup>. In rare cases, patients can have non-secretory or oligo-secretory disease where M proteins are not revealed by serum or urine tests<sup>13</sup>.

There were 477 new cases of multiple myeloma (and malignant plasma cell neoplasms) diagnosed in Scotland in 2015 and incidence over the past twenty years has shown a general increase<sup>14</sup>. There were 231 deaths from the disease in Scotland in 2015, although the mortality rate appears stable despite the increase in the number of diagnoses in recent years. After one year, 75.5% of diagnosed patients are still alive compared with 47.7% at five years. Multiple myeloma accounted for 1.5% of all cancer diagnoses and cancer deaths in Scotland in 2015<sup>14</sup>.

## Current guidelines

Five clinical practice guidelines were identified that make recommendations on FDG PET/CT in patients with myeloma. These are the International Myeloma Working Group guidelines<sup>2</sup>, the US National Comprehensive Cancer Network clinical practice guidelines for multiple myeloma (version 2)<sup>3</sup>, the British Society for Haematology guidelines<sup>4</sup>, the Royal College of Radiologists/Royal College of Physicians' evidence-based indications for the use of PET/CT<sup>6</sup> and the NICE guideline on myeloma<sup>5</sup>. Many of these guidelines incorporate clinical expert opinion in the creation of their guideline recommendations. This Evidence Note only summarises the available published literature.

The guidelines recommend the use of FDG PET/CT, typically as an imaging option, at five points in the care pathway:

- As an alternative to magnetic resonance imaging (MRI) to diagnose solitary plasmacytoma<sup>4-6</sup> or in patients with MGUS-associated neuropathies to identify plasmacytomas potentially amenable to radiotherapy<sup>6</sup>.
- As an imaging option in newly diagnosed myeloma<sup>5</sup> or as an alternative to MRI when x-ray is negative in symptomatic areas of the body<sup>3</sup>. However, it is not recommended routinely for all newly-diagnosed cases<sup>4, 6</sup>.
- “As clinically indicated”, with MRI and CT as alternatives in smouldering myeloma<sup>3</sup> or to identify high-risk smouldering disease patients who require treatment<sup>6</sup>. However, it has been argued that it should only be used when whole-body x-ray is negative and MRI cannot be used<sup>2</sup>.
- As an alternative to MRI<sup>4</sup> and/or other imaging methods<sup>5, 6</sup> in the baseline assessment of non-secretory or oligo-secretory disease, or for evaluating extra-medullary disease.
- As an alternative to MRI or as an option in its own right for the subsequent serial monitoring of non-secretory disease (including after stem-cell transplant)<sup>6</sup> or evaluating extra-medullary disease,<sup>4, 6</sup> for detecting minimal residual disease more generally alongside bone marrow-based assays<sup>2</sup> or for monitoring solitary plasmacytoma<sup>6</sup>.

It should also be noted that not all these care pathway points fall within the inclusion criteria for this review, serial monitoring after stem-cell transplant would apply to a post-treatment population rather than a newly-diagnosed one.

## Clinical effectiveness

The initial screening of the literature prioritised systematic reviews. These had to include a myeloma population (sub-populations with solitary plasmacytoma or MGUS were acceptable as long as multiple myeloma patients were also included) and have at least one other imaging comparator.

Initially, five systematic reviews were identified<sup>5, 15-18</sup>. Each review contained a unique subset of primary studies; with a total of fifteen primary studies included in at least one of the reviews. Only one study (Zamagni et al, 2007) was common to all five reviews.<sup>19</sup> The overlap in the included primary studies identified in each review is shown in Table 1.

**Table 1: overlap in the inclusion of primary studies across systematic reviews**

Included Primary Study	Systematic Review Source				
	Lu 2012	NICE 2016	Regelink 2013	Van Lammeren-Venema 2012	Weng 2014
Cascini (2013)		✓			
Sager (2011)		✓			✓
Zamagni (2007)	✓	✓	✓	✓	✓
Nanni (2006)		✓	✓		✓
Fonti (2008)		✓		✓	
Lin (2014)		✓			
Spinato (2012)		✓			
Breyer (2006)	✓		✓	✓	
Nanni (2007)	✓				
Nanni (2008)	✓		✓		
Salaun (2008)	✓			✓	
Short (2009)	✓			✓	
Elliot (2011)	✓				
Bartel (2009)				✓	

The systematic reviews were of variable quality. Across all reviews there was clarity surrounding the methods used to identify studies, and the inclusion and exclusion criteria. All had used multiple reviewers to independently select and extract data, and all reported clear and appropriate methods for assessing risk of bias.

All the reviews conducted some form of quality assessment to evaluate the risk of bias and applicability of primary diagnosis studies; most of which were based on the QUADAS tool<sup>20</sup> or QUADAS 2<sup>21</sup> used by NICE. However, in many cases, details of the primary studies and their results were not well described and account had often not been given to the potential heterogeneity between patients and/or patient subgroups being assessed, particularly when results were pooled.

Owing to uncertainty surrounding review quality, each of the primary studies included in the reviews was considered in more detail. Only then was it possible to exclude the reviews by Lu et al (2012)<sup>15</sup> and Van Lammeren-Venema et al (2012)<sup>17</sup> because, upon inspection of their included primary studies, most would not have met our inclusion criteria, primarily owing to these reviews including populations that were no longer newly-diagnosed. The excluded primary studies were those by Breyer et al (2006), two by Nanni et al (2007), Nanni et al (2008), Salaun et al (2008), Short et al (2009), Elliot et al (2011), and Bartel et al (2009). These are shown in the last seven rows of Table 1 above.

After removing these studies it can be seen that for the review by Regelink et al (2013), half the included studies in this review met the inclusion criteria for this evidence note and half did not meet the inclusion

criteria, so while this review was retained, the results must be treated with caution<sup>16</sup>. The review by Weng et al (2014)<sup>18</sup> was also retained.

Once the decision had been taken to consider each of the primary studies included in the systematic reviews, in order to reduce the risk of selection bias, it was also necessary to consider all other primary studies that had been identified during the initial literature search - particularly those that were too recently published to have been eligible for inclusion in the systematic reviews. From this, an additional three primary studies of relevance were identified, all of which were published after the end of the search date that informed the NICE review<sup>22-24</sup>. Table 2 provides key details about each of the relevant studies.

**Table 2: Details of populations included in each review.**

Study (Year)	Review	Study Design	Sample Size	Population	Comparator
Cascini (2013)	NICE (2016)	Prospective	22	Myeloma (not further specified)	Whole body MRI
Sager (2011)	NICE (2016), Weng (2014),	Retrospective	42	Multiple myeloma/ SPC	Whole body CT/ MRI follow up
Zamagni (2007)	NICE (2016), Regelink (2013), Weng (2014)	Prospective	46	Multiple myeloma	Spine & pelvis MRI and whole-body x-ray (WBXR)
Nanni (2006)	NICE (2016), Regelink (2013), Weng (2014)	Retrospective	14	Multiple myeloma	Spine & pelvis MRI/WBXR
Fonti (2008)	NICE (2016)	Prospective	33	Multiple myeloma	Spine & pelvis MRI/whole body 99mTc-MIBI
Lin (2014)	NICE (2016)	Prospective	15	Myeloma (not further specified)	Whole body MRI
Spinato (2012)	NICE (2016)	Retrospective	191	Multiple myeloma	Spine & pelvis MRI
<b><i>Studies below are from additional literature searching</i></b>					
Bhutani (2016)	Primary study	Prospective	46	Myeloma (including smouldering disease) or MGUS	Whole body NaF PET/CT, spine & pelvis MRI, whole body x-ray ("skeletal survey")
Fonti (2015)	Primary study	Retrospective	27	Multiple myeloma	Spine & pelvis MRI/ whole body 99mTc-MIBI scintigraphy
Li (2017)	Primary study	Prospective	98	Multiple myeloma	Whole body x-ray

The NICE review first explored the clinical effectiveness of imaging investigations (including FDG PET/CT) for people with suspected myeloma and then explored imaging for people with newly diagnosed myeloma, in order to guide treatment decisions<sup>5</sup>. Seven studies were included in total, three for patients with suspected myeloma<sup>19, 25, 26</sup> and four for patients with newly diagnosed myeloma<sup>27-30</sup>.

In the diagnosis of patients with suspected myeloma, where biopsy was used as the reference standard, two studies in the review for the NICE Guideline on myeloma reported FDG PET/CT sensitivity of 0.82 and 0.90 respectively. Specificity results were not reported. Where x-ray was the reference standard, one study reported sensitivity and specificity results of 0.75 and 0.30 respectively.

For newly diagnosed myeloma, the study by Nanni et al (2006)<sup>29</sup> found that FDG PET/CT identified more lesions than radiography and was equivalent to MRI in terms of its ability to detect lesions. Three other studies showed that FDG PET/CT detects a different pattern of disease than MRI<sup>27, 28, 30</sup>; these results are reported in Table 3. The NICE review<sup>5</sup> also reported data from the study of 62 patients by Spinnato et al (2012) which was the only study to report the effect on staging of discordant results in lesion detection by FDG PET/CT and MRI. Of the twelve patients with discordant results, staging was down-graded in eleven cases due to the FDG PET/CT result, and in one case due to the MRI result. However, the quantity of the evidence for this outcome is insufficient to determine whether the effect would be likely seen in clinical practice in Scotland.

All four of these studies for newly diagnosed myeloma are considered to be of poor quality, an issue noted by the NICE guideline committee who based their recommendations for the relevant section of the guideline on clinical expert experience. They also made a recommendation for further research comparing the effectiveness of MRI, FDG-PET/CT and CT<sup>5</sup>.

**Table 3: Reported detection rates for FDG PET/CT compared with MRI and/or x-ray.**

Comparator	Study	Sample size	N (%) cases where a higher number of lesions detected with FDG PET/CT	N (%) cases where an equal number of lesions detected with FDG PET/CT	N (%) cases where a lower number of lesions detected with FDG PET/CT
X-ray	Zamagni 2007	46	21 (46%)	21 (46%)	4 (9%)
	Nanni 2006	28	16 (57%)	12 (43%)	0 (0%)
MRI	Zamagni 2007	46	0 (0%)	32 (70%)	14 (30%)
	Nanni 2006	28	7 (25%)	14 (50%)	7 (25%)
	Spinnato 2012	62	23 (37%)	32 (assumed) (52%)	8 (13%)

The review by Regelink et al (2013) systematically reviewed the diagnostic accuracy of FDG PET/CT compared with either CT or whole body x-ray for the identification of bone disease in multiple myeloma<sup>16</sup>. Four studies were included and in all four cases the reference test was whole-body x-ray<sup>19, 29, 31, 32</sup>. Results were not formally pooled and instead the range of sensitivities and specificities found in each of the FDG PET/CT studies was reported; 0.67–1.00 and 0.29–0.50 respectively. The review notes that specificities for all newer imaging modalities was shown to be poor compared to x-ray<sup>16</sup>. The review also noted that FDG PET/CT may have had a higher detection rate than whole body x-ray, but detects fewer lesions in the skull and ribs. No recommendation was made with regard to FDG PET/CT, whereas CT and MRI were both advocated for lesion detection purposes. The review findings should be treated with caution given that only two of the four FDG PET/CT studies included met our inclusion criteria.

The review by Weng et al (2014) also compared FDG PET and/or FDG PET/CT, and MRI, along with scintigraphy, for multiple myeloma related bone disease<sup>18</sup>. The reference standard was either x-ray or CT alone. Three studies evaluated FDG PET/CT against the available reference standards of whole-body x-ray or CT and clinical follow up<sup>19, 26, 29</sup>, two compared FDG PET/CT against whole body x-ray<sup>19, 29</sup> and one looked at CT<sup>26</sup>. The methodology sections in the studies reported that data were pooled but that there were problems in interpreting the pooled results<sup>a</sup>. The authors concluded that FDG PET/CT (as with FDG PET, MRI and scintigraphy) is associated with a “high detection rate of bone disease” in patients with multiple myeloma and could therefore be used.

Of the three additional primary studies identified from the literature search, the study by Bhutani et al (2016) noted the added value of FDG PET/CT compared with skeletal survey x-rays but could not conclude whether or not FDG PET/CT provided additional value to MRI scans for newly-diagnosed patients<sup>22</sup>. This is in line with the findings from the NICE review. The study by Fonti et al (2015) found both FDG PET/CT and scintigraphy to be superior to MRI among newly-diagnosed patients, but concluded this was likely due to the wider field of vision available since the MRI scans conducted in the study were restricted to spine and pelvis only<sup>23</sup>. This is contradictory to the rest of the evidence base, but the field of vision for the MRI scans varied from study to study (see Table 2 ‘Comparator’ column). The study by Li et al (2017) found FDG PET/CT to be superior to whole body x-ray in detecting bone lesions among newly-diagnosed myeloma patients<sup>24</sup>, again in line with the findings from the NICE review.

## Patient and social aspects

The evidence informing the NICE Guideline on myeloma found no evidence on the patient acceptability of PET/CT for patients at either the diagnosis or newly-diagnosed stage of disease<sup>5</sup>. None of the other identified studies had reported any patient or social aspects, nor had reported whether or not they looked for these outcomes.

## Safety

The evidence used to inform the NICE Guideline found no evidence on radiation exposure from imaging tests for patients at either the diagnosis or newly-diagnosed stages of disease<sup>5</sup>.

<sup>a</sup> There is a section of the report that describes pooled results for FDG PET/CT and FDG PET, but cites studies that are not listed in the references and have not been reported in any of the other reviews. It is unclear to what these results refer as they differ to diagnostic accuracy results for PET/CT reported earlier in the paper.



## Cost effectiveness

The NICE guideline conducted an economic evaluation to explore the cost-effectiveness of four imaging techniques (PET/CT, whole-body CT, whole-body and spinal MRI) with skeletal survey for the diagnosis of myeloma. The analysis took the form of a decision tree whereby each imaging technique either diagnosed patients correctly or incorrectly. Those with an incorrect diagnosis enter an additional Markov model to determine the longer term effects (costs and quality-adjusted life years [QALYs]) of the delay in their correct diagnosis. QALYs were derived from a study by Proskorovsky et al (2014)<sup>33</sup> using utilities associated with a myeloma diagnosis. Sensitivity and specificity values were taken from studies included in the NICE review of clinical effectiveness, with costs of the imaging procedures taken from NHS Reference Costs (price year 2014).

Results showed that at a willingness-to-pay threshold of £20,000 per QALY gained, PET/CT was unlikely to be cost-effective for the diagnosis of myeloma. Although the parameter inputs for sensitivity and specificity were relatively low for PET/CT compared with the other imaging modalities being evaluated against skeletal survey, a sensitivity analysis that varied these parameters from 60% to 100% found that PET/CT was never the preferred option to skeletal survey (or any of the other imaging modalities).

In considering the cost-effectiveness of imaging investigations for people with newly diagnosed myeloma, the NICE evidence review found no relevant studies on this topic and so no further modelling work was undertaken for the guideline.<sup>5</sup>

None of the other included systematic reviews or primary studies in this review of clinical effectiveness reported cost-effectiveness information and, although one cost-effectiveness study was identified from the literature search, it was not relevant to an NHS perspective and was therefore excluded.

## Conclusion

The evidence base for the clinical effectiveness of FDG PET/CT in multiple myeloma includes data from three systematic reviews and three more recently published primary studies.

In newly-diagnosed patients, although FDG PET/CT is likely to be superior in terms of detecting lesions in multiple myeloma compared with traditional imaging modalities such as whole body x-ray, there is still insufficient evidence regarding its accuracy compared with other modern imaging techniques, particularly MRI.

Where imaging results were discordant between FDG PET/CT and MRI, the FDG PET/CT result led to the down-staging of disease in more instances than MRI but this evidence comes from one study of 62 newly-diagnosed patients.

There is evidence that FDG PET/CT is not cost-effective for the diagnosis of myeloma. No relevant cost-effectiveness studies were identified to assess the cost-effectiveness of FDG PET/CT among newly-diagnosed myeloma populations.

## Identified research gaps

- Current evidence on FDG PET/CT in patients with myeloma appears to be at stage three (experimental design) or four (using registry data for long-term follow up) of the [IDEAL-D](#) framework. Therefore, future studies should be controlled, blinded, diagnostic studies or economic evaluations.
- Diagnostic studies should evaluate the impact of FDG PET/CT imaging on treatment decisions and subsequent oncological outcomes in patients with suspected or newly diagnosed myeloma.

## Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on [www.healthcareimprovementscotland.org](http://www.healthcareimprovementscotland.org)

## About evidence notes

Evidence Notes are produced to inform a decision at a particular point in time and are therefore not routinely updated. They will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the evidence note process see:

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References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network [www.knowledge.scot.nhs.uk](http://www.knowledge.scot.nhs.uk), or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from [htaglossary.net](http://htaglossary.net).

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Declarations of interest were sought from all peer reviewers. All contributions from peer reviewers were considered by the group. However the peer reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

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