SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

Appropriate Use Criteria for the Use of Nuclear Medicine in Fever of Unknown Origin

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EXECUTIVE SUMMARY

The diagnostic workup of the patient with fever of unknown origin (FUO) begins with a thorough history and physical examination, complete blood count with differential, chest x-ray, urinalysis and culture, electrolyte panel, liver enzymes, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. Additional imaging procedures, including nuclear medicine tests, are generally used as second-line procedures (*1*).

The purpose of this document is to describe the appropriate use of nuclear medicine imaging in adults and children with FUO. It is anticipated that, based on the recommendations provided, nuclear medicine imaging tests will be appropriately applied to improve the care of these patients. These appropriate use criteria (AUC) were developed by an autonomous workgroup composed of representatives from the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the Infectious Diseases Society of America (IDSA), and the American College of Nuclear Medicine (ACNM). These criteria were developed in accordance with the Protecting Access to Medicare Act of 2014, which requires that all referring physicians consult AUC through a clinical decision support mechanism prior to ordering advanced diagnostic imaging tests, including nuclear medicine and positron emission tomography (PET) procedures (*2*). The AUC in this document are intended to assist referring health care providers in the appropriate use of nuclear medicine imaging procedures in patients with FUO.

There are several limitations to the literature regarding the value of nuclear medicine imaging for FUO. Published results consist primarily of retrospective investigations, with relatively few subjects, performed at a single institution, and using various standards of truth against which the test was judged. This is especially true for labeled leukocyte and gallium-67 (^{67}Ga) imaging in children. Well-designed prospective multicenter investigations are lacking. In the absence of substantive data, the authors of this document relied on expert opinion from nuclear medicine specialists in the United States, Europe, and Africa, as well as from the referring clinical community. The workgroup is of the opinion that the most accurate assessment of the utility of nuclear medicine imaging in FUO is obtained by combining the existing literature with the opinions of multidisciplinary experts. The recommendations provided relate only to the appropriate use of nuclear medicine imaging and do not preclude other testing, nor are they intended to replace clinical judgement. Referring health care providers should consider patient history, physical examination, and other test results when contemplating nuclear medicine imaging. This document may also be helpful by providing guidance for imaging specialists, as well as for developers of clinical decision support tools.

Inflammation of unknown origin (IUO), a recently described entity, is an illness lasting more than 3 weeks, with fever not exceeding 38.3°C (100.9°F) on several occasions, accompanied by elevated inflammatory markers (CRP ≥ 30 mg/L or increased ESR), which remains undiagnosed despite appropriate investigation after at least 3 outpatient visits or 3 days of hospitalization (*3*). Three major disease groups cause IUO: malignancies, infections, and inflammatory diseases. Early identification of the underlying cause is crucial for proper patient management (*4*). The criteria for IUO, except for fever of 38.3°C (100.9°F) or higher, are similar to those for FUO, and identifying possible causes of IUO, as with FUO, remains a clinical challenge. Data on nuclear medicine imaging in IUO have focused almost exclusively on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET and PET/computed tomography (CT) in adults. Data on ^{67}Ga and labeled leukocyte scintigraphy are nearly nonexistent. In view of the fact that the criteria for FUO and IUO are similar, except for fever of more than 38.3°C (100.9°F), and that the most

common etiologies of these 2 entities are similar, it is the expert opinion of the workgroup that the recommendations for nuclear medicine imaging of FUO are also applicable to IUO.

INTRODUCTION

FUO, in both children and adults, is one of the more challenging clinical conditions for patients and treating physicians alike. In up to 50% of cases, no definite diagnosis is established. Important subsets of the classic FUO include nosocomial, neutropenic, HIV-associated, and organ transplant-associated FUOs. Nuclear medicine imaging studies are often performed as part of the diagnostic workup of patients with FUO. In vitro labeled leukocytes and ^{67}Ga were, for many years, the mainstay of nuclear medicine imaging in this population. ^{18}F-FDG PET and PET/CT have rapidly assumed an increasingly important role in the diagnostic workup of these patients (*1*).

METHODOLOGY

The experts of this AUC workgroup were convened by the SNMMI to represent a multidisciplinary panel of health care providers with substantive knowledge in the use of nuclear medicine procedures in FUO. In addition to SNMMI members, representatives from the ACNM and the IDSA were included in the workgroup. Eleven physician members were ultimately selected to participate and contribute to the AUC. A complete list of workgroup participants and external reviewers can be found in Appendix A. Appendix B is a summary of definitions of terms and acronyms, Appendix C provides the disclosures and conflicts-of-interest statement, and Appendix D describes the solicitation of public commentary.

AUC Development

The process for AUC development was modeled after the RAND/UCLA Appropriateness Method for AUC development (*5*). It included identifying a list of relevant clinical scenarios in which nuclear medicine imaging can be used in the patient with FUO, a systematic review of evidence related to these clinical scenarios, and a systematic synthesis of available evidence. This was followed by the development of AUC for each of the clinical scenarios by using a modified Delphi process. In addition, this process strove to adhere to the Institute of Medicine's standards for developing trustworthy clinical guidance (*6*). The final document was drafted on the basis of group ratings and discussions.

Scope and Development of Clinical Scenarios

To begin this process, the workgroup discussed various potential clinical scenarios for the appropriate use of nuclear medicine imaging in the patient with FUO. For clinical scenarios, the relevant populations of interest were children and adults with FUO of all genders, ages, races, and geographic locations.

The workgroup identified 6 clinical scenarios for nuclear medicine imaging, which were evaluated and addressed in 2 sections: FUO in Adults and FUO in Children. The scenarios are intended to be as representative of the relevant patient population as possible for the development of AUC. The resulting AUC are based on evidence and expert opinion regarding diagnostic accuracy and effects on clinical outcomes and clinical decision making as applied to each scenario. Other factors affecting the AUC recommendations were potential harm, including long-term harm that may be difficult to capture; costs; availability; and patient preferences.

Systematic Review

To inform the workgroup, a systematic review of the relevant evidence was commissioned by an independent group, the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University (*7*). The primary purpose of the systematic review was to synthesize the evidence on the accuracy of nuclear medicine imaging techniques for the diagnosis of FUO and on the effects of nuclear medicine imaging on clinical outcomes and clinical decision making. The workgroup selected the following key questions to guide the review:

1. What is the accuracy of ^{67}Ga scintigraphy with or without single-photon emission computed tomography (SPECT) or SPECT/CT for the diagnosis of FUO in adults and children?
2. What is the accuracy of in vitro labeled leukocyte scintigraphy with or without SPECT or SPECT/CT for the diagnosis of FUO in adults and children?
3. What is the accuracy of PET, PET/CT, or PET/magnetic resonance imaging (MRI) with ^{18}F-FDG for the diagnosis of FUO in adults and children?
4. What are the effects of nuclear medicine imaging for FUO on clinical outcomes or clinical decision making (e.g., use of treatments, subsequent tests)?

For key questions 1 through 3, the reviewers assessed the effects of the use of various radiopharmaceuticals, different imaging methods, and demographic and clinical characteristics of the populations (e.g., immunocompetent, immunosuppressed, diabetic, prosthetic materials, pregnant patients) to the extent possible.

The inclusion and exclusion criteria for papers for this review were based on the study parameters established by the workgroup, using the PICOTS (population, intervention, comparisons, outcomes, timing, and setting) approach. Searches for relevant studies and systematic reviews were conducted on the following databases: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Ovid MEDLINE (through January 2018). These searches were supplemented by reviewing the reference lists of relevant publications and suggestions from the workgroup members.

Two investigators independently reviewed abstracts and full-text articles against prespecified eligibility criteria, as defined by PICOTS. The population comprised adults and children with FUO. The imaging modalities were as follows:

- ^{67}Ga-citrate scintigraphy, with or without SPECT or SPECT/CT
- Technetium-99m (^{99m}Tc) or indium-111 (^{111}In) in vitro labeled leukocyte scintigraphy, with or without SPECT or SPECT/CT
- ^{18}F-FDG PET, PET/CT, or PET/MRI

For questions on diagnostic accuracy, the reviewers included cross-sectional and cohort studies and systematic reviews of cross-sectional and cohort studies that reported the diagnostic accuracy of the imaging modality against a reference standard. Studies that used histopathological or microbiological findings as part of the reference standard, with or without clinical follow-up, were included. The reviewers excluded studies in which the reference standard was unclear or not reported, consisted only of clinical follow-up, or was based on alternative imaging findings only. Primary studies on diagnostic accuracy were also excluded if they used a case-control design or enrolled cases only.

For effects on clinical outcomes, reviewers included cohort studies of nuclear medicine imaging versus no nuclear medicine imaging that reported mortality, morbidity, or other clinical outcomes. For effects on clinical decision making, reviewers included cohort studies and imaging series of nuclear medicine imaging that reported effects on subsequent use of tests and treatments. In lieu of primary studies, when available, reviewers included good- and fair-quality systematic reviews and meta-analyses that were most relevant to the key questions and scope and had more recent search dates. They did not conduct updated meta-analyses to incorporate new studies. Rather, they conducted a qualitative examination of the results of new studies and the degree to which they were consistent or inconsistent with pooled or qualitative findings from prior systematic reviews and meta-analyses. Non-English language articles and studies published only as conference abstracts were excluded.

Two investigators independently assessed the quality (risk of bias) of each study as “good,” “fair,” or “poor” by using predefined criteria that were specific for each study design. AMSTAR (A MeaSurement Tool to Assess systematic Reviews) was used for systematic reviews (except diagnostic accuracy), adapted by the US Preventive Services Task Force criteria for randomized trials and cohort studies, and QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) for primary studies and systematic reviews of diagnostic accuracy (*8,9*). Discrepancies were resolved through a consensus process. The strength of the overall evidence was graded as high, moderate, low, or very low by using GRADE methods based on quality of evidence, consistency, directness, precision, and reporting bias.

Database searches, review of reference lists, and suggestions from experts resulted in 6,537 potentially relevant articles. After a dual review of abstracts and titles, 1,334 articles were selected for full-text dual review. Of these, 51 studies were determined to meet inclusion criteria and were included in this review. Twenty-four systematic reviews on diagnostic accuracy, covering a total of 255 unique studies, were also included in this review.

Rating and Scoring

In developing these AUC for nuclear medicine imaging in FUO, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: “The concept of appropriateness, as applied to health

care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics" (*10*).

At the beginning of the process, workgroup members convened via webinar/teleconference to develop the initial clinical indications. On evaluating the evidence summary of the systematic literature review, the workgroup further refined its draft clinical indications to ensure their accuracy and facilitate consistent interpretation when scoring each indication for appropriateness. Using the evidence summary, workgroup members were first asked individually to assess the appropriateness and provide a score for each of the identified indications. Workgroup members then convened in a group setting for successive webinars to discuss each indication and associated scores from the first round of individual scoring. After deliberate discussion, a consensus score was determined and then assigned to the associated appropriate use indication. For this scoring round, the expert panel was encouraged to include their clinical expertise in addition to the available evidence in determining the final scores. All members contributed to the final discussion, and no one was forced into consensus. After the rating process was completed, the final appropriate use ratings were summarized in a format similar to that outlined by the RAND/UCLA Appropriateness Method (*5*).

The workgroup scored each indication as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores 7–9 indicate that the use of the procedure is appropriate for the specific clinical indication and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific indication. This implies that more research is needed to classify the indication definitively. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific indication and generally is not considered acceptable.

As stated by other societies that develop AUC, the division of these scores into 3 general levels of appropriateness is partially arbitrary, and the numeric designations should be viewed as a continuum. In addition, if there was a difference in clinical opinion for an indication such that workgroup members could not agree on a common score, that indication was given a "may be appropriate" rating to indicate a lack of agreement on appropriateness based on the available literature and the members' collective clinical opinion, indicating the need for additional research.

FUO in ADULTS

Introduction

Persistent undiagnosed fever, now referred to as FUO, was first recognized in the early 20th century, and many investigations of FUO have been conducted over the years. It is important to be cognizant of the fact that FUO is not a biologically uniform phenomenon, but a common manifestation of many different disease processes. The core features of FUO are failure to identify a cause of the fever after reasonable inpatient or outpatient investigations, and the persistence of fever for a sufficient length of time to exclude self-limiting fevers (*11*). Petersdorf and Beeson (*12*) first defined FUO as "fever higher than 38.3°C (100.9°F) on several occasions, persisting without diagnosis for at least 3 weeks in spite of at least 1 week's investigation in hospital." Durack and Street (*13*) revised this definition to include patients who had unexplained fever for 3 outpatient visits or 3 days in the hospital. This definition was further divided into 4 categories: classic, nosocomial, neutropenic, and HIV related (Table 1).

Etiologies of FUO fall mainly into 1 of 5 groups: infection, neoplasm, inflammatory (e.g., connective tissue diseases), miscellaneous, and undiagnosed illness. The frequency of infections as a cause for classic FUO has generally ranged from 16% to 55% since the 1950s, with different types of infections based on geographic location. Among the remaining etiologies, 18%–19% were due to neoplasms, 15%–17% were caused by inflammatory diseases, 13%–19% were secondary to miscellaneous etiologies, and 9% had no diagnosis (*13-15*). Over time, this distribution changed, with the most prominent shifts being an increase in undiagnosed cases, from 16% in the 1980s to 50%–53% in the 2000s. In contrast, miscellaneous causes decreased from approximately 19% in the 1960s to 3%–12% in the 2000s (*13-17*) (Table 2). Much of the variability in presentation is related to different age groups, income levels, and geographic areas (*18*). Many patients with FUO have complex medical histories and comorbidities and may be taking various medications, all of which can complicate the interpretation of diagnostic tests.

FUO represents an estimated 1.5%–2% of hospital admissions, with mortality rates ranging from less than 10% to more than 30% (*19-21*). Several factors contribute to morbidity associated with FUO, including prolonged hospital stay, repeated invasive and noninvasive investigations, and presumptive treatment and cost implications (*19*). Despite the multitude of approaches in the literature for the workup of FUO, the cornerstone of diagnosis remains a thorough history, physical examination, and routine initial testing. Signs, symptoms, and abnormalities pointing toward a possible diagnosis are referred to

as potentially diagnostic clues (PDCs) (*22,23*). In general, first-line evaluation includes basic laboratory and imaging tests, followed by more advanced imaging if first-line evaluation is not conclusive. In virtually all cases, PDCs will be present (*22,24*). Invasive procedures have now largely been replaced by advanced diagnostic imaging, although laparoscopy and laparotomy are still useful for FUO in the setting of solid tumors, peritoneal carcinomatosis, lymphoma, and disseminated tuberculosis (*25*).

When a diagnosis is not evident from basic PDCs, radiological imaging is most often used as part of the workup. Conventional radiological techniques such as CT, MRI, and ultrasound are most often used and are generally easily accessible. A limitation of these modalities is difficulty in detecting early inflammatory or infectious lesions, as significant anatomical changes may be absent in the early phase (*26*). When PDCs are absent or misleading and first-line investigations are inconclusive, second-line investigations, including nuclear medicine imaging, may be used. Determination of the most appropriate investigation should be directed toward a diagnostic algorithm aimed at a cost-effective, noninvasive approach that ultimately expedites a diagnosis and minimizes prolonged hospitalization and unnecessary investigations.

Clinical Scenarios and AUC Scores

Clinical scenarios for the diagnosis of FUO in adults, along with final AUC scores, are presented in Table 3.

Scenario 1: Diagnosis of FUO in adults, labeled leukocyte scintigraphy (Score 4, May be Appropriate)

The role of labeled leukocyte scintigraphy in the diagnosis of FUO was addressed in 1 systematic review, the quality of which was fair (*27*). This review included 6 studies with sample sizes ranging from 19 to 32 patients (n = 153). In all 6 studies, ^{111}In-labeled leukocytes were used. Only planar imaging was performed; none of the studies included SPECT or SPECT/CT. The pooled sensitivity and specificity for diagnosing FUO with ^{111}In-labeled leukocyte scintigraphy were 0.33 (95% confidence interval [CI], 0.24–0.44) and 0.83 (95% CI, 0.61–0.94), respectively. The diagnostic yield, defined as the proportion of patients in whom the imaging results contributed to the diagnosis, of ^{111}In-labeled leukocyte scintigraphy was 0.20 (95% CI, 0.14–0.28).

There are no intraindividual comparisons of labeled leukocyte scintigraphy and ^{67}Ga scintigraphy in patients with FUO, and intraindividual comparisons with ^{18}F-FDG are limited. Two prospective investigations compared planar ^{111}In-labeled leukocyte scintigraphy with ^{18}F-FDG PET (*28,29*). In an investigation of 21 patients with FUO, in which infection/inflammation was the cause in 7 cases (37%) and tumor was the cause in 1 case (5%), there was no significant difference in the sensitivity of labeled leukocyte scintigraphy, 71% (CI, 37%–85%), and ^{18}F-FDG-PET, 50% (CI, 16%–84%). The specificity of labeled leukocyte scintigraphy was 92% (CI, 71%–100%), which was significantly higher than that of ^{18}F-FDG-PET, 46% (CI, 34%–62%) (*28*).

In an investigation of 23 patients with FUO, in which infection was the cause in 6 cases (26%), inflammation in 8 cases (35%), and tumor in 1 case (5%), sensitivity was 20% for labeled leukocyte scintigraphy and 86% for ^{18}F-FDG-PET ($P < 0.01$). There was no statistically significant difference in the specificity of labeled leukocyte scintigraphy (100%) and ^{18}F-FDG-PET (78%) (*29*).

The value of a negative labeled leukocyte study for excluding infection as the cause of FUO is uncertain. Some investigators have reported that a negative result reliably excludes infection (*27,29,30*). Other investigators have found that this is not the case (*31,32*).

Few data are available on the role of ^{99m}Tc- labeled leukocytes in the workup of FUO. In an investigation of 87 patients with nosocomial FUO who underwent planar imaging with the addition of SPECT when indicated, the sensitivity and specificity of ^{99m}Tc-labeled mononuclear leukocytes were 95.8% and 92.3%, respectively. Infection was the cause of the FUO in 67.8% of the cases, inflammatory conditions in 8%, and neoplasm in 3.4% (*33*). Although the test performed very well in this study, infection was the cause of the FUO in two-thirds of cases, which is an unusually high percentage. In addition, the investigators isolated and labeled only mononuclear leukocytes, in contrast to the clinical standard of care in which a mixed population of white blood cells (WBCs) are labeled.

Scenario 2: Diagnosis of FUO in adults, ^{67}Ga scintigraphy (Score 5, May be Appropriate)

A recent meta-analysis, the quality of which was fair, included 6 studies with a total of 397 patients. The pooled sensitivity of ^{67}Ga scintigraphy was 60% (95% CI, 0.45%–0.73%), and the pooled specificity was 63% (95% CI, 0.37%–0.84%). The source of the fever was correctly localized in about one-third of patients. The diagnostic yield was 0.35 (95% CI, 0.25–0.46) (*27*).

In 3 prospective investigations, in which only planar imaging was performed, the diagnostic usefulness of ^{67}Ga scintigraphy ranged from 6% to 29% (*34-36*). In a retrospective investigation of 47 patients with FUO, the sensitivity and specificity of ^{67}Ga scintigraphy were 86% and 77%, respectively. The authors suggested using this radiopharmaceutical early on in patients with FUO to help direct further organ-specific imaging to the area of concern (*37*).

Few data are available on ^{67}Ga SPECT and SPECT/CT in patients with FUO. In an investigation of 18 patients who underwent both planar imaging and SPECT, the number of positive scans increased from 5 on planar imaging to 9 with the inclusion of SPECT. The sensitivity and specificity of planar imaging alone were 45% and 100%, respectively. With SPECT, the sensitivity was 67% and the specificity was 78%. In contrast, the sensitivity and specificity of ^{18}F-FDG PET were 81% and 86%, respectively (*38*).

In an investigation of 102 patients who underwent planar imaging and SPECT, ^{67}Ga scan results were abnormal in 41 (40%) patients. Abnormal scan results contributed to the final diagnosis in 21 (21%) patients. In only 2 patients (2%), however, were the results considered significant or critical to the final diagnosis. These investigators concluded that ^{67}Ga has limited utility in the evaluation of FUO (*39*). In a multicenter prospective study of 128 patients, the sensitivity of ^{67}Ga-SPECT was 25% (95% CI, 15.5%–37.5%), which was significantly less than the sensitivity of ^{18}F-FDG PET/CT: 45% (95% CI, 33.1%–58.2%, P = 0.0029). The clinical impact, defined as the contribution of the test to the final diagnosis, was significantly lower for ^{67}Ga SPECT than for ^{18}F-FDG PET/CT (57% vs. 91%, respectively, $P < 0.001$) (*40*).

In 27 patients with FUO (n = 17) or IUO (n = 10) who underwent whole-body ^{67}Ga SPECT/CT, the diagnostic yield of the test was 30% (95% CI, 14%–50%). The clinical efficacy of the test was 44% (95% CI, 25%–65%). The authors concluded that in patients with FUO or IUO, ^{67}Ga SPECT/CT is a first-line nuclear medicine test when ^{18}F-FDG PET/CT is not available (*41*).

^{67}Ga SPECT/CT was compared with ^{18}F-FDG PET/CT in 58 patients with FUO. The sensitivity, specificity, and accuracy of ^{67}Ga SPECT/CT were 45%, 81%, and 55%, respectively. The sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT were 79%, 56%, and 72%, respectively. The clinical contribution of ^{18}F-FDG PET/CT was significantly higher than that of ^{67}Ga SPECT/CT (72% vs. 55%, respectively, $P < 0.05$) (*42*).

Disadvantages of ^{67}Ga include a 2- to 3-day interval between administration and imaging, the relatively high patient radiation dose, and suboptimal image quality. As a result of decreasing demand, production of ^{67}Ga has decreased and this radiopharmaceutical is no longer as readily available as it has been in the past.

Scenario 3: Diagnosis of FUO, ^{18}F-FDG PET and PET/CT (Score 8, Appropriate)

The role of ^{18}F-FDG PET and PET/CT in patients with FUO was addressed in 4 systematic reviews (*27,43-45*). The quality of evidence in all 4 was fair. One systematic review evaluated ^{18}F-FDG PET/CT in FUO (n = 595) (*45*). The pooled sensitivity was 85% (95% CI, 0.81%–0.88%), with an area under the receiver operating characteristic curve of 0.88 (SE = 0.05). Specificity was not reported. Another review included 9 studies (n = 388) (*44*). ^{18}F-FDG PET was performed in 5 studies and ^{18}F-FDG PET/CT in 4. The pooled sensitivity of ^{18}F-FDG PET was 83% (95% CI, 0.73%–0.90%), and the pooled specificity was 58% (95% CI, 0.49%–0.66%), with a positive likelihood ratio of 2.40 (95% CI, 0.91–6.35) and a negative likelihood ratio of 0.30 (95% CI, 0.08–1.10). The pooled sensitivity of ^{18}F-FDG PET/CT was 98% (95% CI, 0.94%–0.998%), and the pooled specificity was 86% (95% CI, 0.75%–0.93%), with a positive likelihood ratio of 5.78 (95% CI, 3.34–10.03) and a negative likelihood ratio of 0.05 (95% CI, 0.01–0.25).

One systematic review included 34 studies on the role of ^{18}F-FDG PET and PET/CT for evaluation of FUO (N = 1,659) (*27*). Twelve studies evaluated ^{18}F-FDG PET (n = 522), and 22 studies evaluated ^{18}F-FDG PET/CT (n = 1137). ^{18}F-FDG PET had a pooled sensitivity of 76% (95% CI, 0.66%–0.83%) and a pooled specificity of 50% (95% CI, 0.30%–0.70%). The diagnostic yield was 0.44 (95% CI, 0.31–0.58). For ^{18}F-FDG PET/CT, the pooled sensitivity was 86% (95% CI, 0.81%–0.90%) and the pooled specificity was 52% (95% CI, 0.36%–0.67%). The diagnostic yield was 58% (95% CI, 0.51%–0.64%). A systematic review of ^{18}F-FDG PET/CT (n = 905) reported similar results, with a pooled diagnostic yield of 56% (95% CI, 0.50%–0.61%) (*43*).

In a recent systematic review of patients with FUO or IUO (n = 1,927), the pooled sensitivity of ^{18}F-FDG PET/CT was 84% (95% CI, 0.79%–0.89%), and the pooled specificity was 63% (95% CI, 0.49%–0.75%). The pooled positive and negative likelihood ratios were 2.3 (95% CI, 1.5–3.4) and 0.25 (95% CI, 0.16–0.38), respectively. The diagnostic odds ratio (OR) was 9 (95% CI, 4.0–20). ^{18}F-FDG PET/CT contributed to the diagnosis of FUO and IUO in 59% (1,136 of 1,927) of cases (*46*).

With the lack of a true gold standard for FUO and high frequency of undiagnosed etiology of up to 10%–60%, sensitivity and specificity calculations may be misleading because of the artificial definition of true-negative and true-positive results. In an attempt to overcome these limitations, 1 group of investigators conducted a stratification-based meta-analysis, which demonstrated an increase in the absolute final diagnostic rate from 36% to 83% when ^{18}F-FDG PET results were abnormal (*47*).

Elevated inflammatory markers (particularly CRP), anemia, and adenopathy have been suggested as predictors of high-yield ^{18}F-FDG PET/CT. Although true-positive cases are considered contributory to the diagnosis of FUO, true-negative cases, which have been reported to lead to a negative predictive value of 100%, are also contributory (*48,49*). A negative ^{18}F-FDG PET/CT result can be a predictor of favorable prognosis in patients with FUO (*11*). One systematic review studied the association of ^{18}F-FDG PET/CT results with spontaneous remission in FUO. Patients with negative scan results were significantly more likely

to have spontaneous remission of fever than were those with positive scan results, with a summary risk ratio of 5.6 (95% CI, 3.4–9.2) (*50*).

Several systematic reviews have focused on the diagnostic yield of ^{18}F-FDG PET/CT as a measure of assessing the ability of this test to help obtain a diagnosis. A recent systematic review calculated a diagnostic yield of 58% (95% CI, 0.51%–0.64%) when the test was performed following multiple other unsuccessful diagnostic tests. In this review, which compared various nuclear medicine imaging modalities in patients with FUO, the pooled sensitivity of ^{18}F-FDG PET/CT was 86% (95% CI, 0.81–0.90) and the pooled specificity was 52% (95% CI, 0.36%–0.67%) versus 60% (95% CI, 0.45%–0.73) and 63% (95% CI, 0.37%–0.84%) for ^{67}Ga, respectively, and 33% (95% CI, 0.24%–0.44%) and 83% (95% CI, 0.61%–0.94%) for ^{111}In leukocyte scintigraphy, respectively (Table 4) (*27*). In a study that compared ^{18}F-FDG PET/CT and ^{67}Ga SPECT/CT in 58 patients with FUO, the sensitivity, specificity, and clinical contribution/accuracy of ^{18}F-FDG PET/CT was 79%, 56%, and 72%, respectively, compared with 45%, 81%, and 55%, respectively, for ^{67}Ga SPECT/CT (*42*). Additional comparative studies have also demonstrated that ^{18}F-FDG PET and PET/CT are superior to ^{67}Ga and labeled leukocyte imaging in patients with FUO (*28,29,38,40,42*).

^{18}F-FDG has several advantages over ^{67}Ga and labeled leukocyte scintigraphy. Semi-quantitative analysis, which is more feasible with PET than with SPECT, could be of potential usefulness for monitoring treatment response. ^{18}F-FDG provides high-resolution, 3-dimensional images of the whole body that, especially when performed as PET/CT, facilitates precise localization of abnormalities. ^{18}F-FDG is associated with a lower effective radiation dose than that of ^{67}Ga and ^{111}In-labeled leukocytes, does not require handling of blood products or labeling of cells, is not dependent on the circulating WBC count, and has a shorter acquisition time. The interval between radiopharmaceutical injection and imaging is only about 1 hour, and so results are readily available. The impact of antibiotic use on ^{18}F-FDG uptake is unlikely to be of clinical significance (*51*).

In addition to outperforming ^{67}Ga and ^{111}In-labeled leukocytes, the diagnostic yield of ^{18}F-FDG PET/CT is at least 30% greater than that of conventional CT (*11*).

Limitations of ^{18}F-FDG include difficulty in assessing for brain, urinary tract, and occasionally gastrointestinal pathologies due to the normally high physiological uptake in these organs. The sensitivity of the test for vasculitis, a common cause of FUO, is adversely affected by empiric steroid use (*52*).

^{18}FDG-PET/CT, when performed early in the workup of the patient with FUO, can reduce, or at least limit, the cost of the evaluation. Two studies have evaluated the cost-effectiveness of ^{18}F-FDG PET/CT in patients with FUO (*53,54*). In a European investigation, integrating ^{18}F-FDG PET/CT earlier in the diagnostic workup of FUO would have saved €5,471 ($5,848 US) by facilitating an early diagnosis, decreasing length of hospitalization, and reducing the number of unnecessary tests (*53*). In another study, investigators compared 326 patients with FUO or IUO who underwent ^{18}F-FDG PET/CT to 415 patients who did not. Although costs for patients undergoing ^{18}F-FDG PET/CT were significantly higher than those for patients who did not undergo this test, the 2 groups were not comparable. The percentage of critically ill patients, proportion of rheumatological diseases, number of examinations, and hospitalization days to diagnosis were significantly higher in the group that underwent ^{18}F-FDG PET/CT than in the group that did not. The mean length of hospitalization and mean medical costs before diagnosis were significantly lower in the group of patients who underwent ^{18}F-FDG PET/CT within 1 week after hospital admission than in the group of patients who underwent the test more than 1 week after admission. The authors concluded that early use of ^{18}F-FDG PET/CT could shorten the length of hospitalization and limit medical costs (*54*).

Although most investigations have focused on ^{18}F-FDG PET or PET/CT in patients with classic FUO, a recent multicenter, open-label, phase 3, randomized, controlled trial of ^{18}F-FDG PET/CT was conducted in high-risk hematology patients with neutropenic fever. In this investigation, ^{18}F-FDG PET/CT supported decision making regarding antimicrobial therapy and was superior to conventional CT for this purpose (*55*).

TABLE 3

Clinical Scenarios for the Diagnosis of FUO in Adults

Scenario no.	Description	Appropriateness	Score
1	Labeled leukocyte scintigraphy	May be appropriate	4
2	^{67}Ga scintigraphy	May be appropriate	5

3	^{18}F-FDG PET and PET/CT	Appropriate	8

Summary of Recommendations

^{18}F-FDG PET and PET/CT are the nuclear medicine tests of choice in adults with FUO and should be included in the diagnostic algorithm for this indication. ^{67}Ga scintigraphy should be reserved for those situations in which ^{18}F-FDG PET and PET/CT are not available. Labeled leukocyte scintigraphy should be reserved for those situations in which ^{18}F-FDG PET and PET/CT are not available *and* there is a high index of suspicion for infection as the cause of the fever.

FUO in CHILDREN

Introduction

In 1965, Brewis (*56*) defined FUO in children as a temperature > 38.3°C (100.9°F) persisting for > 5 days with no localizing signs on physical examination. Three years later, Dechovitz and Moffet (*57*) included children with fever persisting for > 2 weeks. In the 1970s, retrospective case series from academic medical centers further defined FUO as follows:

- rectal temperature > 38.9°C (102.1°F) on multiple occasions for > 3 weeks (outpatients) or > 1 week (inpatients) (*58*)
- rectal temperature > 38.5°C (101.4°F) on at least 5 occasions for > 2 weeks (*59*)
- temperature > 38.4°C (101.1°F) (method not specified) on multiple occasions for > 3 weeks (outpatients) or > 1 week (inpatients) (*60*)

The definition of FUO in children has continued to evolve over time. In 2011, Chow and Robinson (*61*) performed a systematic review in which they concluded that most case series required persistence of fever for > 1 week with negative initial workups. This definition takes into consideration that most common viral infections (e.g., upper respiratory infections, acute gastroenteritis) and uncomplicated bacterial infections (e.g., otitis media, pharyngitis) have fevers of < 7 days' duration (*61,62*).

Early investigations (*58-60,63,64*) of pediatric FUO established 4 major causes: infectious diseases, inflammatory conditions, neoplasms, and miscellaneous/undiagnosed causes. Infectious diseases, especially bacterial infections, and osteomyelitis made up 29%–52% of cases. Inflammatory disorders (e.g., juvenile idiopathic arthritis and systemic lupus erythematous) accounted for 10%–20% of cases, and malignancies (e.g., leukemia, lymphoma, and neuroblastoma) accounted for 4%–13% (*58-60*). In about 12%–20% of children, fevers resolved without a specific diagnosis being established (*65*).

The first step in the evaluation of FUO in children is to confirm the fevers by repeated measurements of temperature, both in the health care setting and at home (*62*). The patient and the patient's parents/caregivers are often asked to keep a fever diary. Next, a thorough history and a comprehensive physical examination are performed to assess for signs and symptoms that may be indicative of specific clinical syndromes (*65*). Initial laboratory workup often includes a complete blood cell count with differential, inflammatory markers (e.g., CRP, ESR), liver and renal function tests, urinalysis, and urine and blood cultures (*64,66*). Initial imaging studies are frequently guided by signs and symptoms (e.g., chest radiograph for tachypnea and cough). If a specific anatomical region is identified, more detailed imaging, such as ultrasound, CT, and MRI may be performed (*67*). In contrast to CT, MRI does not use radiation, but it is more time-consuming and young children often require sedation. When fever persists and its etiology cannot be identified by these evaluations, nuclear medicine imaging is often performed.

Clinical Scenarios and AUC Scores

Clinical scenarios for the diagnosis of FUO in children, along with final AUC scores, are presented in Table 5.

Scenario 4: Diagnosis of FUO in children, labeled leukocyte scintigraphy (Score 3, Rarely Appropriate)

Labeling leukocytes in infants and young children is challenging and often impractical, given the large volume of blood that needs to be withdrawn for the labeling procedure (*68*). The high radiation dose is another significant disadvantage to the use of labeled leukocyte scintigraphy in children.

There were no data in the systematic reviews on the role of labeled leukocyte scintigraphy for the diagnosis of FUO in children. In 1 investigation, 30 children between 15 months and 18 years of age, including 16 with a final diagnosis of infection, underwent planar ^{111}In-labeled leukocyte scintigraphy. The test correctly identified 15 children with acute infection, but there were 6 false-positive scans as well. The test was 94% sensitive, but only 57% specific, which is in contrast to most investigations in which the specificity of the test is high (*69*).

In an investigation of 15 children with suspected occult infection, there were 4 true-positive and 5 false-negative scans (45% sensitivity). There were no false-positive results (*70*). As part of a larger investigation, 11 children with FUO underwent

planar ^{111}In-labeled leukocyte scintigraphy. The test results were abnormal in 5 children, all of whom had diffuse cardiac activity. Myocarditis, however, was suspected in only 1 of the 5 (*63*).

Scenario 5: Diagnosis of FUO in children, ^{67}Ga scintigraphy (Score 3, Rarely Appropriate)

There were no data on the role of ^{67}Ga scintigraphy in children with FUO in the systematic reviews. As part of a larger series, 4 children underwent ^{67}Ga scintigraphy, with 1 positive result: osteomyelitis with an associated soft tissue abscess (*63*). In another investigation, only 4 of 30 children with FUO had positive ^{67}Ga scan results. Only 1 of 25 children who presented with systemic signs and symptoms in addition to fever had positive scan results. Three of 5 children with focal complaints in addition to fever had positive scan results. All 3 had localized infections that had not been identified with other imaging modalities. The authors concluded that although ^{67}Ga scintigraphy is rarely useful in children with FUO who present with only systemic complaints, this test may be helpful when there is a suspicion of localized infection, even when other imaging tests have negative results (*71*).

In addition to the 2- to 3-day interval between administration and imaging, suboptimal image quality, and decreasing availability, the relatively high radiation dose is a significant disadvantage to the use of ^{67}Ga in children.

Scenario 6: Diagnosis of FUO in children, ^{18}F-FDG PET and PET/CT (Score 8, Appropriate)

Evidence on the role of ^{18}F-FDG PET and PET/CT in pediatric FUO is limited (*72*). Few systematic reviews are available. The published experience consists primarily of retrospective investigations with variable definitions of FUO and variable criteria for establishing the final diagnosis. Despite these limitations, published data support the use of ^{18}F-FDG PET and PET/CT in children with FUO (*67*).

In 1 investigation, ^{18}F-FDG PET (n = 3) or PET/CT (n = 28) scans were performed in 31 children with FUO (*73*). A final diagnosis was established in 16 (52%) cases. The sensitivity and specificity were 80% and 78%, respectively. One-third of the scans were considered clinically helpful. In another investigation, 69 children underwent 77 ^{18}F-FDG PET (n = 47) or PET/CT scans (n = 30) (*74*). Forty-seven scans were performed for FUO and 30 for IUO. A final diagnosis was established in 54% of the patients. Forty-five percent of all scans were clinically helpful; of these, 43% were helpful when the test was performed for FUO and 48% were helpful when it was performed for IUO. There was no correlation between laboratory, demographic, and clinical parameters and usefulness of the scans. The authors concluded that ^{18}F-FDG PET and PET/CT are valuable because invasive procedures are avoided and the time to diagnosis may be shortened, allowing prompt institution of appropriate therapy.

In one of the largest investigations to date, the results of ^{18}F-FDG PET/CT performed in 110 children with FUO were reviewed (*75*). The final diagnosis at hospital discharge was used as the reference standard. A definite cause of fever was established in 62% of children, which included endocarditis (n = 12), systemic juvenile idiopathic arthritis (n = 5), inflammatory bowel disorder (n = 5), and cholangitis (n = 4). The test results were positive in 78% (53 of 68) of children and negative in 22%; positive results indicated endocarditis (n = 5; 4 had an artificial valve), systemic juvenile idiopathic arthritis (n =2), monoarticular arthritis (n = 1), drug-induced fever (n = 2), Kawasaki arteritis (n = 2), systemic lupus erythematosus (n = 1), urinary tract infection (n = 1), and familial Mediterranean fever (n = 1). False-positive test results occurred in 9% (10 of 110), suggesting lymphoma (n = 3), pulmonary infection (n = 3), inflammatory bowel disorder (n = 2), soft tissue infection (n = 1), and vasculitis (n = 1). Treatment modifications were made in 53% of the patients after the ^{18}F-FDG PET/CT, although the significance of these modifications is unclear. Finally, multivariate logistic regression demonstrated that CRP level was positively associated with finding a true-positive focus of fever (OR = 1.01 per mg/L increase in CRP level), suggesting that ^{18}F-FDG PET/CT is likely to be more useful in patients with an elevated CRP level.

In a recent systematic review that included 6 studies (n = 191) of children younger than 18 years of age with FUO, the authors found that patients with abnormal ^{18}F-FDG PET or PET/CT results were approximately 17 times more likely to have definite diagnoses than were those with normal results (OR 16.75, 95% CI, 8.0-35, $P < 0.00001$) (*76*).

The management of children who are waiting for liver transplantation can be complicated by FUO. Infections outside the liver may preclude transplantation, and hepatic infections may necessitate liver resection for cure. In an investigation of 11 children with FUO who were candidates for liver transplantation ^{18}F-FDG PET identified intrahepatic infection in 5, all of whom underwent transplantation. Liver transplantation in the 6 children with normal hepatic FDG uptake was performed only after they defervesced. Of note is the fact that conventional imaging studies were not contributory in any of the children (*77*).

^{18}F-FDG PET/CT potentially contributes useful information in critically ill children with FUO (*78*). In an investigation of 19 children with complicated underlying diseases requiring intensive care support, ^{18}F-FDG PET/CT results were positive in 15 patients, accurately localizing the source of fever in 14. There was 1 false-positive result. The test results were negative in 4 patients, including 2 false negatives: 1 in a patient with a *Candida tropicalis* renal abscess and the other in a patient with leukemia. Two patients with negative scan results did well clinically with spontaneous remission of their fever.

^{18}F-FDG PET/CT contributes useful information in immunocompromised children with FUO. In 1 investigation, 12 immunosuppressed children with fever underwent ^{18}F-FDG PET (n = 1) or PET/CT (n = 11) (*74*). A final diagnosis was established in 9 (75%) and 58% of the scans were clinically helpful. The sensitivity and specificity of ^{18}F-FDG PET/CT were 78% and 67%, respectively. As part of a larger investigation, 5 children with FUO following organ transplantation underwent ^{18}F-FDG PET/CT, which was performed because first-line diagnostic methods failed to yield a diagnosis. Two scan results were positive: a soft tissue abscess in the thigh and another in the liver. Two scan results were negative and no source of fever was ever identified. One scan, in which there was increased ^{18}F-FDG accumulation in a renal transplant, had false-positive results (*79*).

The clinical impact of ^{18}F-FDG PET/CT in children with malignancy or following hematopoietic stem cell transplantation with prolonged or recurrent fever has also been studied (*80*). The majority of the children in this investigation were neutropenic. The test results were abnormal in 8 of 14 (57%) children, with 1 false-negative result in a patient with invasive pulmonary aspergillosis who had undergone 15 days of treatment with voriconazole. ^{18}F-FDG PET/CT contributed to the final diagnosis in 6 of 10 (60%) patients in whom the cause of fever was identified. The clinical impact of ^{18}F-FDG PET/CT was "high" in 11 (79%) children, leading to additional investigations or procedures (including referral to specialists) that resulted in a final diagnosis. Inflammation was detected that was suggestive of infection not identified by conventional imaging or microbiological investigations and that affected antimicrobial treatment (continuing in 3 and discontinuing in 5) in 11 of 14 (79%) children.

TABLE 5

Clinical Scenarios for the Diagnosis of FUO in Children

Scenario no.	Description	Appropriateness	Score
4	Labeled leukocyte scintigraphy	Rarely appropriate	3
5	^{67}Ga scintigraphy	Rarely appropriate	3
6	^{18}F-FDG PET and PET/CT	Appropriate	8

Summary of Recommendations

^{18}F-FDG PET and PET/CT are the nuclear medicine tests of choice in children with FUO. From the results that have been reported for both ^{67}Ga and labeled leukocyte scintigraphy, neither test is recommended for children with FUO.

BENEFITS AND HARMS OF IMPLEMENTING THE AUC GUIDANCE

As with any appropriate use or appropriateness criteria, this document provides guidance on the potential role of testing for specific scenarios or patient presentations. Although it is meant to outline the workgroup's distillation and expert opinion regarding the use of nuclear medicine in these scenarios, it cannot address all patients or all clinical scenarios. Rather, it may provide support for considered clinical judgment on the basis of the available or prevailing evidence related to the use of nuclear medicine techniques in the evaluation of FUO.

The workgroup also notes that this particular topic, FUO, encompasses a variety of nuclear medicine techniques and radiopharmaceuticals: ^{67}Ga, labeled leukocytes, and ^{18}F-FDG, as well as single-photon versus positron-based detection with and without anatomical correlation. This document is not confined to a single target or technique, and so the workgroup hopes that it may provide clinicians with scientifically based flexibility in their approach to a clinical question. At the same time, the workgroup notes that the integration and complementary use of nuclear and morphological techniques may indeed provide the most appropriate strategy for what are often complex questions of extent and severity of disease.

QUALIFYING STATEMENTS

Study/Evidence Limitations

Although the medical community has, for several decades, relied on nuclear medicine imaging to evaluate FUO, the workgroup found that when rigorous inclusion criteria were applied to the systematic literature reviews, all of which were of fair quality, the body of medical literature supporting the use of these procedures was limited and the interpretation of these studies not straightforward.

Classic FUO has a broad differential diagnosis, and the causes vary with geography, type of hospital (community vs. tertiary), and patient demographics (*11*). Differences in patient populations and diagnostic workup algorithms, as well as variability in reference standards, can also affect test performance. Nuclear medicine imaging tests are often evaluated by using routinely collected clinical data without a standardized post-imaging diagnostic algorithm. In such cases, the imaging results influence the selection of subsequent tests. The few available intraindividual comparisons among nuclear medicine procedures make direct comparisons difficult.

Investigations that originally validated these techniques do not meet the methodological standards that have been developed as the medical literature has evolved. It is difficult to assess the current value of a rapidly evolving technology, such as ^{18}F-FDG PET/CT, on the basis of data acquired several years previously. Advances in technology and imaging protocols lead to improved image quality and presumably better outcomes. For example, a significant advantage of SPECT/CT over both planar and planar plus SPECT imaging is more precise localization and characterization of foci of radiopharmaceutical uptake. This in turn results in improved diagnostic accuracy and greater diagnostic confidence, as well as better inter-specialty communication. Unfortunately, there were no labeled leukocyte studies of FUO in which SPECT/CT was performed and only 2 investigations in which ^{67}Ga SPECT/CT was performed (*40,42*).

In the absence of available data in the systematic reviews, the workgroup conducted its own literature searches, combining the results of these searches with expert opinion when necessary in order to make recommendations about procedure appropriateness.

PET/MRI combines the exquisite structural and functional characterization of tissue provided by MRI with the quantitative physiological information that is provided by PET. Furthermore, performing ^{18}F-FDG PET/MRI instead of PET/CT decreases radiation exposure, which is an especially important consideration in children. At the present time, however, data on the efficacy of ^{18}F-FDG PET/MRI in the workup of the patient with FUO are not sufficient to make definitive recommendations about its use for this indication.

In addition to diagnostic accuracy, an important measure of the value of a test is its effect on clinical outcomes or clinical decision making. such as type of therapy and subsequent tests. Few data are available on the effects of ^{67}Ga and labeled leukocyte scintigraphy on clinical outcomes or clinical decision making in patients with FUO. ^{18}FDG PET or PET/CT, especially when performed early in the workup of the patient with FUO, can shorten the time to diagnosis, guide patient management, decrease the number of diagnostic procedures performed, shorten the length of hospitalization, and reduce the number of undiagnosed cases. This is true for both adults and children (*53,54,75*)

Radiation Dose Considerations

All of the imaging procedures included in this document have been approved by the U.S. Food and Drug Administration and are therefore deemed safe and effective. Nonetheless, it is worth pointing out that there are some differences in radiation dose among these procedures. Radiation exposure from the CT component of SPECT/CT and PET/CT varies with the type of CT and whether it is used for anatomical localization and attenuation correction or for diagnostic purposes. Technological advancements and the design of customized protocols, including dose modulation, tube voltage, and iterative reconstruction, have significantly lowered radiation exposure for pediatric patients (*81,82*). The guiding principle of radiation safety, the ALARA principle (as low as reasonably achievable), may be helpful in selecting imaging protocols to answer the clinical question. Tables 6 and 7 show the relative effective dose for recommended administered activities for adults and children.

TABLE 6

Radiation Doses for Nuclear Medicine Imaging Procedures in FUO (Adults)[a]

	Administered activity		**Critical organ[b] absorbed dose coefficient**		**Effective dose equivalent coefficient**		**Reference**
Radiopharmaceutical	MBq	mCi	mGy/MBq	rad/mCi	mSv/MBq	rem/mCi	
^{18}F-FDG	370–740	10–20	0.13 urinary bladder[c]	0.48	0.019	0.070	*83*
^{67}Ga-citrate	150–220	4.1–5.9	0.20 lower large intestine	0.74	0.12	0.44	*84*
^{111}In-oxine white blood cells (WBCs)	10–19	0.27–0.50	5.5 spleen	20	0.59	2.2	*85*
^{99m}Tc-HMPAO WBCs	185–370	5.0–10	0.15 spleen	0.56	0.017	0.063	*86*

Abbreviation: HMPAO, ^{99m}Tc-hexamethylpropylene amine oxime.

[a]The CT dose contribution for adult PET/CT or SPECT/CT studies using low-dose CT protocols corresponds to an effective dose of 5.0 mSv (500 mrem) (*87*).
[b]Organ receiving the highest absorbed dose.
[c]Assuming a voiding interval of 3.5 h.

TABLE 7

Radiation Doses for Nuclear Medicine Imaging Procedures in FUO in Children (5 Years Old)[a]

	Administered activity		Critical organ[b] absorbed dose coefficient		Effective dose equivalent coefficient		Reference
Radiopharmaceutical	MBq/Kg	mCi/Kg	mGy/MBq	Rad/mCi	mSv/MBq	rem/mCi	
^{18}F-FDG	3.7–5.2	0.10–0.14	0.34 Urinary bladder	1.3	0.056	0.21	*88, 89*
^{67}Ga-citrate	1.5–2.6	0.041–0.071	0.72 Lower large intestine	2.7	0.40	1.5	*84*
^{111}In-oxine white blood cells (WBCs)	0.15–0.25	0.004–0.007	17 Spleen	63	1.8	6.7	*85*
^{99m}Tc-HMPAO WBCs	3.7–7.4	0.10–0.20	0.48 Spleen	1.8	0.054	0.2	*86*

Abbreviation: HMPAO, hexamethylpropylene amine oxime.

[a] The CT dose contribution for pediatric PET/CT or SPECT/CT studies using low-dose CT protocols corresponds to an effective dose of 5.0 mSv (500 mrem) (*90*).
[b]Organ receiving the highest absorbed dose.

Considerations for Pregnant and Breastfeeding Patients

In the case of a diagnostic procedure in a patient who is known or suspected to be pregnant, a clinical decision is necessary to consider the benefits against the possible harm of performing the procedure. A variety of nuclear medicine imaging studies are discussed in this guidance, some of which may have a greater radiation dose than others. Attention to procedure standards is important, including best practices in the recommendations about breastfeeding in the guidelines of the Advisory Committee on Medical Uses of Isotopes (*91*).

IMPLEMENTATION OF THE AUC GUIDANCE

To develop broad-based multidisciplinary clinical guidance documents, the SNMMI has been working with several other medical specialty societies. It is hoped that this collaboration will foster the acceptance and adoption of this guidance by other specialties. SNMMI has developed a multipronged approach to disseminate the AUC for FUO to all relevant stakeholders, including referring physicians, nuclear medicine physicians, and patients. The dissemination and implementation tactics will include a mix of outreach and educational activities targeted to each of these audiences. The SNMMI will create case studies for its members, as well as for referring physicians, and make them available via online modules and webinars. These cases will cover the appropriate clinical scenarios for the use of imaging studies in patients with FUO. Related resources such as the systematic review supporting the development of these AUC, a list of upcoming education events on the AUC, factsheets, and

other didactic materials will be made available on the SNMMI website. Live sessions will be held at the SNMMI midwinter and annual meetings, as well as at other relevant professional society meetings of referring physicians, to highlight the importance and application of these AUC. SNMMI also aims to create a mobile application for these AUC for both Apple and Android platforms.

ACKNOWLEDGMENTS (Staff)

The workgroup acknowledges staff support from the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University (Roger Chou, MD, FACP – Principal Investigator; Rebecca Jungbauer, DrPH - Research Associate; Tamara P. Cheney, MD – Research Associate; Chandler Weeks, BS – Research Assistant; Miranda Pappas, MA – Research Associate and Project Manager; Tracy Dana, MLS – Research Librarian; Elaine Graham, MLS – EPC Operations Manager, provided project oversight).

APPENDIX A: WORKGROUP MEMBERS AND EXTERNAL REVIEWERS (Staff)

Workgroup

The members of the workgroup are Christopher J. Palestro, MD (chair), FSNMMI, FACNM, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY (SNMMI); Gad Abikhzer, MD, Jewish General Hospital, Montreal, Quebec Canada (SNMMI); Zvi Bar-Sever, MD, Schneider Children's Medical Center, Tel Aviv University, Tikva, Israel (EANM, ISNM); Twyla Bartel, DO, MBA, FACNM, FSNMMI, Global Advanced Imaging, PLLC, Tulsa, OK (ACR, SNMMI); Rebecca Brady, MD, Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, OH (IDSA); Erin E. Grady, MD, FACNM, Stanford University, Stanford, CA (ACNM, SNMMI); Ora Israel, MD, FSNMMI, Technion Rappaport School of Medicine, Haifa, Israel (SNMMI); Sanjay K. Jain, MD, Johns Hopkins Hospitals, Baltimore, MD (SNMMI, WMIS); Sheetal Kandiah, MD, Emory University Hospital, Atlanta, GA (IDSA); Machaba M. Sathekge, MD, PhD, University of Pretoria, Pretoria, South Africa (SNMMI, WARMTH); and Barry L. Shulkin, MD, St. Jude Children's Research Hospital, Memphis, TN (SNMMI).

External Reviewers (Staff)

The external (peer) reviewers are John Buscombe, MD, FRCP, Addenbrookes Hospital, London EC1, United Kingdom; Francois Jamar, MD, PhD, Universite Catholique De Louvain Nuclear Medicine, Brussels, Belgium; Helen Nadel, MD, Lucile Packard Children's Hospital at Stanford, Stanford, CA; Pat Zanzonico, PhD, Memorial Sloan Kettering Cancer Center, New York, NY; and Lionel S. Zuckier, MD, MBA, FRCPC, Montefiore Medical Center, Bronx, NY.

SNMMI (Staff)

The supporting staff from SNMMI include Doug Burrichter, Program Manager, and Bonnie Clarke, Senior Director for Quality and Evidence.

APPENDIX B: DEFINITIONS OF TERMS AND ACRONYMS

ACNM: American College of Nuclear Medicine
ACR: American College of Radiology
ALARA: as low as reasonably achievable: the guiding principle of radiation safety, which is to avoid exposure to radiation that does not directly benefit the person being exposed to it
AMSTAR: A MeaSurement Tool to Assess systematic Reviews
AUC: appropriate use criteria
CI: confidence interval
COI: conflict of interest

CRP: C-reactive protein is produced by the liver and released into the bloodstream in response to inflammation.
CT: computed tomography radiography, in which a 3-dimensional image of a body structure is constructed by computer from a series of cross-sectional images acquired along an axis
EANM: European Association of Nuclear Medicine
ESR: Erythrocyte sedimentation rate is the rate at which red blood cells in anticoagulated whole blood descend in a standardized tube over a period of 1 hour. It is a nonspecific measure of inflammation.
^{18}F-FDG: ^{18}F-fluorodeoxyglucose, also referred to as fluorine-18 FDG or F-18 FDG, is a frequently used radiopharmaceutical in positron emission tomography (PET) scanning. ^{18}F-FDG is a compound in which the radioactive isotope ^{18}F is attached to a molecule of glucose. Once in the body, ^{18}F-FDG is actively taken up by various tissues and can be detected by a PET scanner. The resulting images show how the radiopharmaceutical is distributed within the body, helping physicians diagnose various medical conditions and assess how well the body is functioning.
FUO: fever of unknown origin
^{67}Ga scintigraphy: Gallium-67 scintigraphy is a diagnostic imaging test in which ^{67}Ga-citrate accumulates in infectious, inflammatory, and malignant lesions and is imaged with a gamma camera. Images can be acquired in 2 (planar) or 3 (tomographic) dimensions.
HMPAO: hexamethylpropylene amine oxime
IDSA: Infectious Disease Society of America
^{111}In: indium-111
ISNM: Israeli Society of Nuclear Medicine
IUO: inflammation of unknown origin
Labeled leukocyte scintigraphy: a diagnostic imaging test in which autologous leukocytes or white blood cells are radiolabeled with either ^{99m}Tc-HMPAO or ^{111}In-oxine. The labeled leukocytes are then reinfused into the patient from whom they were withdrawn, where they accumulate in infectious or inflammatory processes and emit activity that is detected by a gamma camera. Imaging can be acquired in 2 or 3 dimensions.
MRI: magnetic resonance imaging
OR: odds ratio
PDCs: potentially diagnostic clues
PET: positron emission tomography, a method of imaging positron-emitting radiopharmaceuticals in a patient's body by using a specialized detection device known as a PET camera. A frequently used PET radiopharmaceutical is ^{18}F-FDG, which the body treats in a manner similar to glucose.
PET/CT: a combination, or hybrid, device that provides detail on both function and anatomy by superimposing the precise location of metabolic activity from PET on a detailed anatomical image from CT.
PET/MRI: a combination, or hybrid, device that provides detail on both function and anatomy by superimposing the precise location of metabolic activity from PET on a detailed anatomical image from MRI.
PICOTS: population, intervention, comparisons, outcomes, timing, and setting. The PICOTS format is a helpful approach to summarizing research questions that explore the effects of therapy. Population refers to the sample of subjects to be recruited for a study. There may be a fine balance between defining the sample that is most likely to respond to an intervention (e.g., no comorbidity) and the sample that can be generalized to patients likely to be seen in actual practice. Intervention refers to the treatment to be provided. Comparisons refer to a reference group. The outcomes of the reference group (no intervention applied) are compared with the outcomes of the population to which the intervention was applied. Outcomes refer to a measurement that will determine the effectiveness of the intervention. Familiar and validated outcome measurement tools relevant to common patient populations include the Neck Disability Index and the Roland-Morris Disability Questionnaire. There are typically a multitude of outcome tools available for different clinical populations, each having strengths and weaknesses. Timing describes the duration of data collection, and setting describes the study location and its characteristics.
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies, version 2. The QUADAS tool was first developed in 2003. Experience, anecdotal reports, and feedback suggested areas for improvement, leading to QUADAS-2. The tool comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of concern about applicability. Signaling questions are included to help judge risk of bias. The tool is applied in 4 phases: summarize the review question, tailor the tool and produce review-specific guidance, construct a flow diagram for the primary study, and judge bias and applicability. The tool allows for a more transparent rating of bias and of the applicability of primary diagnostic accuracy studies.
SNMMI: Society of Nuclear Medicine and Molecular Imaging

SPECT: Single-photon emission computed tomography is a method of imaging single-photon-emitting radiopharmaceuticals within a patient's body by using a specialized gamma camera. The camera rotates around the patient, acquiring angular data that are reconstructed into 3-dimensional images.
SPECT/CT: a combination, or hybrid, device that provides both functional and anatomical detail by acquiring co-registered SPECT and CT images that can be fused or otherwise displayed together
^{99m}Tc: technetium-99m
WARMTH: World Association of Radiopharmaceutical and Molecular Therapy
WBC: white blood cell
WMIS: World Molecular Imaging Society

APPENDIX C: DISCLOSURES AND CONFLICTS OF INTEREST (COIs)

The SNMMI rigorously attempted to avoid any actual, perceived, or potential COIs that might have arisen as a result of an outside relationship or personal interest on the part of the workgroup members or external reviewers. Workgroup members were required to provide disclosure statements of all relationships that might be perceived as real or potential COIs. These statements were reviewed and discussed by the workgroup chair and SNMMI staff and were updated and reviewed by an objective third party at the beginning of every workgroup meeting or teleconference. The disclosures of the workgroup members can be found in Table 8. A COI was defined as a relationship with industry—including consulting, speaking, research, and nonresearch activities—that exceeds $5,000 in funding over the previous or upcoming 12-month period. In addition, if an external reviewer was either the principal investigator of a study or another key member of the study personnel, that person's participation in the review was considered likely to present a COI. All reviewers were asked about any potential COI. A COI was also considered likely if an external reviewer or workgroup member was either the principal investigator or a key member of a study directly related to the content of this AUC document. All external reviewers were asked about any potential COI.

TABLE 8

Relationships with Industry and Other Entities

Workgroup member	Reported relationships
Abikhzer, Gad	• None
Bar-Sever, Zvi	• None
Bartel, Twyla	• None
Brady, Rebecca	• None
Grady, Erin E.	• None
Israel, Ora	• GE HealthCare
Jain, Sanjay K.	• Novobiotic LLC • T3 Pharma • Fujirebio Diagnostics, Inc.
Kandiah, Sheetal	• None
Palestro, Christopher J.	• None
Sathekge, Machaba M.	• Adcock Ingram • NTP
Shulkin, Barry L.	• None

APPENDIX D: PUBLIC COMMENTARY (Staff)

The workgroup solicited information from all communities through the SNMMI website and through direct solicitation of SNMMI members. The comments and input helped to shape the development of these AUC on the use of nuclear medicine in patients with FUO.

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TABLE 1

Fever of Unknown Origin

Type	Definition
Classic	Temperature > 38.3°C (100.9°F) recorded on several occasions occurring for > 3 weeks despite investigations on 3 outpatient visits or 3 days of stay in the hospital or 1 week of invasive ambulatory investigations.
Nosocomial	Temperature > 38.3°C (100.9°F) recorded on several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifest or incubating on admission. Three days of investigations including at least 2 days of incubation of cultures is the minimum requirement for this diagnosis.
Neutropenic	Temperature > 38.3°C (100.9°F) on several occasions observed in a patient whose neutrophil count is <500/µL or expected to fall to that level in 1–2 days. This diagnosis should be considered for investigations including at least 2 days of incubation of cultures. This is also called immunodeficient FUO.
HIV-associated	Temperature > 38.3°C (100.9°F) on several occasions found over > 4 weeks or > 3 days for hospitalized patients with HIV infection. This diagnosis is considered if appropriate investigations over 3 days, including 2 days of incubation of cultures, reveal no source.

TABLE 2
Causes of FUO in Adults

Infection (16%–55%)	Neoplasm (18%–19%)	Inflammatory (15%–17%)	Miscellaneous (3%–19%)	Undiagnosed (9%–50%)
Common Complicated urinary tract infection Sinusitis Culture-negative infective endocarditis Occult abscess – dental, abdominopelvic Tuberculosis Cytomegalovirus Epstein-Barr virus **Uncommon** Acute HIV Anaplasmosis Babesiosis Bartonellosis Blastomycosis Bone and joint infections Brucellosis Coccidioidomycosis Ehrlichiosis Hepatitis A, B, E Histoplasmosis Human herpes virus 6 and 7 Leptospirosis Malaria Visceral leishmaniasis Psittacosis Q-fever Rat-bite fever Relapsing fever Salmonellosis Tick-borne diseases Tularemia Tuberculosis Whipple's disease	**Common** Leukemia Lymphoma **Uncommon** Multiple myeloma Myelodysplastic syndrome Colorectal cancer Gastric cancer Castleman disease Mesothelioma	**Common** Giant cell arteritis Adult Still disease Systemic lupus erythematosus Polymyositis rheumatica/Temporal arteritis Inflammatory bowel disease **Uncommon** Rheumatoid arthritis Sarcoidosis Granulomatosis with poly-angiitis Polyarteritis nodosa	**Common** Drug induced Hyperthyroidism Thromboembolism Hematoma **Uncommon** Factitious fever Necrotizing lymphadenitis Familial Mediterranean fever Thyroiditis Hypoadrenalism	

TABLE 4

Diagnostic Yields*

Test	Diagnostic yield	95% confidence interval
^{111}In-WBC scintigraphy	0.20	0.14–0.28
^{67}Ga scintigraphy	0.35	0.25–0.46
^{18}F-FDG PET	0.44	0.31–0.58
^{18}F-FDG PET/CT	0.58	0.51–0.64

*Reference 26