March 19, 2023

Meredith Loveless, M.D., FACOG
Chief Medical Officer
CGS Administrators, LLC
26 Century Boulevard Ste 610
Nashville, TN 37214

Re: Proposed LCD – Positron Emission Tomography (PET) Scan for Inflammation and Infection (DL39521)

Dear Dr. Loveless:

On behalf of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), thank you for the opportunity to comment on the proposed local coverage determination (LCD) on Positron Emission Tomography (PET) Scan for Inflammation and Infection (DL39521) issued by CGS Administrators on February 2, 2023. SNMMI and its more than 15,000 members set the standard for the practice of nuclear medicine and molecular imaging by creating guidelines, sharing information through journals and meetings, and advocating on key issues that affect molecular imaging and therapy, research, and practice.

The SNMMI is most concerned that your extremely-restrictive proposed coverage criteria will limit the delivery of highly appropriate imaging care to your beneficiaries to the detriment of their care.

SNMMI strongly believes that PET scans will not be overused in cases of suspected infection/inflammation but rather will be applied as a problem-solving tool when other diagnostic methods have come up negative or equivocal, often in critically ill patients. It may in fact result in savings of downstream costs of unresolved sources of infection and expedite care by targeting the treatment to the source of infection detected by FDG PET/CT. This position is supported by a recent publication on “Best Practices for Imaging Cardiac Device-Related Infections and Endocarditis; A JACC Cardiovascular Imaging Expert Panel Statement, which is attached to this comment letter. In particular, we draw your attention to the central illustration on page 907 which provides a schematic of approaches for integrating multimodality imaging for suspected prosthetic heart valve infection, suspected cardiac implantable electronic device infection, and suspected left ventricular assist device infection.
Furthermore, SNMMI is a strong supporter of appropriate use criteria (AUC) and has developed AUC for many imaging modalities. CGS should ensure that any LCD is aligned with the available AUC.

Under the proposed LCD, CGS would cover PET scans for certain patients with fever of unknown origin (FUO) and cardiac sources of infection and inflammation. Other uses of PET for inflammation and infection would be non-covered. SNMMI strongly recommends that substantial revisions be made to the proposed LCD to align it with the clinical evidence. SNMMI understands that for a number of inflammation/infection indications, use of PET and PET/CT may not be first-line diagnostic tools. In those cases, CGS should cover PET and PET/CT as second-line tools when the primary tools (e.g., echocardiography for suspected native cardiac valve infection) are inconclusive. As a general matter, that is a much better approach to coverage than not covering PET and PET/CT at all.

It is our view that PET imaging will not be abused and that CGS should make sure that it is available to patients who need it to make a definitive diagnosis, many of whom are critically ill and have no other diagnostic test options. Our comments focus on those indications that CGS incorrectly proposes to non-cover because they are experimental and/or investigational. Specifically, we address use of PET in patients with inflammation or infection associated with the following conditions:

- FUO in Immunocompromised Patients
- Native Endocardial Valve Infections
- Joint Arthroplasty
- Chronic Osteomyelitis
- Diabetic Foot
- Spondylodiscitis

For each of these indications, the CGS conclusion that the use of PET or PET/CT is “experimental” and/or “investigational” is incorrect. In fact, the literature cited by CGS supports coverage of PET and PET/CT for all these indications subject to certain limitations.

Our view, as described below, is that CGS has misinterpreted the literature it reviewed and come to incorrect conclusions about the state of the evidence for many indications. Therefore, SNMMI strongly recommends that CGS not finalize the LCD as proposed. If CGS finalizes an LCD on use of PET for inflammation or infection, the LCD should provide coverage for use of PET for the indications we discuss in this comment letter. At a minimum, CGS must cover all indications that the SNMMI AUC rated with a score of 7 or higher. We have attached the SNMMI AUC for the use of nuclear medicine in musculoskeletal infection imaging and in FUO for your reference.

A. **FUO in Immunocompromised Patients**
CGS proposes to cover PET scans for a patient with FUO who is not immunocompromised if the patient meets certain conditions. Use of PET in patients with FUO who are immunocompromised would be noncovered. The logic behind this proposed policy is not supported by evidence we are familiar with.

None of the literature cited by CGS supports non-coverage of PET in these patients. In fact, the paper by Kouijzer et al. (reference 3) cited in the proposed LCD to support this exclusion provides specific data indicating that PET may indeed be quite useful in such patients. The other cited paper (reference 4) does not specifically address the use of PET in immunocompromised patients. SNMMI is not aware of any literature supporting non-coverage of PET for FUO in this population and there are data that clearly support its use. In a retrospective investigation, ten patients with HIV-associated FUO underwent 18F-FDG-PET/CT after other conventional diagnostic procedures had not identified the cause of the fever. Nine of the scans were abnormal and in all nine the cause of fever was identified by further diagnostic workup based on the FDG-PET/CT results (Castaigne C, Tondeur M, de Wit S, et al. Clinical value of FDG-PET/CT for the diagnosis of human immunodeficiency virus-associated fever of unknown origin: a retrospective study. Nuclear medicine communications, 2009;30:41–47.)

In a recent multicenter, open-label, phase 3, randomized, controlled trial, FDG-PET/CT was conducted in high-risk hematology patients with neutropenic fever. In this investigation, FDG-PET/CT supported decision making regarding antimicrobial therapy and was superior to conventional CT for this purpose. The investigators concluded that FDG PET/CT “can support decision making regarding antimicrobial cessation or de-escalation and should be considered in the management of patients with hematological diseases and persistent or recurrent high-risk neutropenic fever after chemotherapy or transplant conditioning.”

A recent review proposed a single, encompassing diagnostic and management algorithm that incorporates FDG-PET/CT in the workup of FUO, regardless of the category, be it classical, immunocompromised, nosocomial, etc. The authors note that “The diagnostic yield of FDG PET/CT appears to be more than 50% and the yield is at least 30% greater than that of conventional CT. The performance appears to be better in patients with infections or neoplasms than in those who have autoimmune conditions. FDG PET/CT also appears to be superior to other nuclear imaging methods, such as PET without CT and gallium or leukocyte scintigraphy.” There is no indication that PET/CT is not effective in patients with autoimmune conditions but only that performance may be better in specific other populations. In particular, immunocompromised children with fever benefit from FDG-PET/CT. Alternative tests such as gallium-67 and labeled leukocyte imaging have not performed well in children with FUO in general, although there are no data comparing these tests to use of FDG-PET/CT. The

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SNMMI’s AUC for FUO states that gallium-67 and labeled leukocyte scintigraphy are rarely appropriate (score: 3) in children with FUO, while FDG-PET is appropriate in this population (score:8). Excluding immunocompromised children would deprive them of the most valuable nuclear medicine test available while exposing them to higher radiation doses from the non FDG PET methods.\textsuperscript{3,4,5,6}

SNMMI believes that PET and PET/CT may actually be more medically necessary in an immunocompromised patient population because of the potential for unusual infectious agents and the need to make a diagnosis quickly so treatment can be initiated as soon as possible. CGS should delete this exclusion from coverage in the final LCD. We recommend that any LCD finalized by CGS include coverage of PET and PET/CT for patients with FUO, regardless of the category.

B. Cardiac Inflammation and Infection

As a threshold matter, SNMMI agrees with the comments submitted by the American Society of Nuclear Cardiology (ASNC). Specifically, SNMMI agrees with the ASNC proposed redline of the draft LCD for cardiac conditions. The recommended changes are as follows in red font:

Cardiac Section

1. Clinical exam and laboratory evaluation lead to clinical suspicion of the condition and this is documented in the medical record \textbf{AND}
2. Non-specific or inconclusive imaging from \textit{any one or more} echocardiography and/or CT and/or cardiac MRI or in selected cases where other imaging is not possible or where FDG PET may be the most sensitive test (Such as patients presenting with AV block) \textsuperscript{6} \textbf{AND}
3. PET scan is conducted with cardiac preparation protocol\textsuperscript{8,9} \textbf{AND}
4. The patient is being evaluated for one of the following conditions and the specific criteria have been met:
   a. Infective Endocarditis: the patient has a prosthetic valve-\textit{or where native valve endocarditis is suspected but not proven by TTE/TEE and blood cultures}
   b. Device Infections (pacemaker, defibrillators, LVAD) suspected.
   c. Aortitis and systemic vasculitis

d. Cardiac Sarcoidosis:
   i. The patient has risk factors for cardiac sarcoidosis (such as systemic sarcoidosis with cardiac findings),
   ii. A young patient (<70 years of age) with unexplained, new onset conduction system disease, heart failure without explanation)\textsuperscript{11}
   iii. Ventricular arrhythmia without another explanatory cause
   iv. For guiding subsequent treatment of proven cardiac sarcoidosis, if PET is the primary test used to follow the patient for the cardiac aspect of sarcoidosis (not in conjunction with cardiac MRI, CT or other nuclear imaging studies). These tests may be used for other purposes so it is confusing if they are not permitted in conjunction with FDG-PET.

In particular, CGS proposes to cover PET for patients with infective endocarditis of prosthetic valves but would non-cover PET for patients with native cardiac valves. SNMMI disagrees with this proposal. CGS should cover PET and PET/CT to aid in the diagnosis of infectious endocarditis in native cardiac valves. The literature included in the bibliography and discussion of evidence supports coverage. While PET and PET/CT may not be quite as sensitive and specific in infective endocarditis in native valves as it is in artificial valves, that is not a sufficient justification for non-coverage. Rather, it would be appropriate to cover PET and PET/CT where native valve endocarditis is suspected but not proven by echocardiography and blood cultures.

A report released in 2020 by the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines recognizes the value of PET/CT in this population. CGS cites this report in its evidence summary and explicitly notes the recommendation related to native valve endocarditis:

“It is recommended that the Modified Duke Criteria are to be utilized as the current standard for diagnosis. This criterion incorporates the use of clinical imaging, and bacteriological criteria. Recommendation 12.2 states “In patients classified by Modified Duke Criteria as having “possible IE,” \textsuperscript{18}F-PET/CT is reasonable as adjunct diagnostic imaging.” They go further to state “\textsuperscript{18}F-PET/CT may also be considered a complementary diagnostic tool for some patients with suspected native valve endocarditis.” This recommendation is supported at the CCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines at level of 2A which is a moderate strength of recommendation and considered reasonable.” (p. 12)

SNMMI believes that CGS has reached the wrong conclusion regarding coverage of PET and PET/CT with respect to this indication. We recommend that any LCD finalized by CGS include coverage of PET and PET/CT for patients with prosthetic or native valves and otherwise adopt the refinements recommended by ASNC.

C. Joint Arthroplasty
CGS should cover PET and PET/CT for the diagnosis of infection in artificial joints. Every article reviewed by CGS supports the clinical utility of PET and PET/CT for these indications. All the professional society guidelines reviewed by CGS support coverage and the substance matter experts who participated in the CAC meeting identified situations in which FDG-PET is the preferred approach. For example, the SNMMI AUC includes the following recommendation: Diagnosis of periprosthetic joint infections (PJI) of the hip, $^{18}$F-PET/PET-CT (Score 7 – Appropriate).

SNMMI does not understand how CGS could have concluded that PET and PET/CT are experimental for this indication. If CGS wants to limit coverage to use of PET and PET/CT after other imaging procedures, such as combined In-111 WBC and Tc-99m sulfur colloid imaging are performed or after joint aspiration, that might be appropriate. But non-coverage flies in the face of the literature that CGS reviewed and the discussion of the CAC members.

**D. Chronic Osteomyelitis**

CGS should cover PET and PET/CT for chronic osteomyelitis. As with joint infections, it is SNMMI’s view that CGS has misinterpreted the data and professional society guidelines and has come to the wrong conclusion. The European consensus statement, the Wang publication, the Kulkarni publication, and the Termaat review all concluded that PET and PET/CT have high diagnostic sensitivity and specificity – better than other imaging modalities. In fact, Termaat concluded (in CGS own words) that “$^{18}$F-PET exhibited the highest diagnostic accuracy for confirming or excluding the diagnosis of chronic osteomyelitis.”

The SNMMI AUC also supports use of PET and PET/CT for osteomyelitis.

- Diagnosis of uncomplicated peripheral bone osteomyelitis, $^{18}$F-PET/PET/CT (Score 9 – Appropriate) based on fair evidence (from 2 SRs) and expert opinion.
- Diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, $^{18}$F[1]PET/PET/CT (Score 8 – Appropriate).
- Diagnosis of foot osteomyelitis in diabetic patients, $^{18}$F-PET/PET/CT (Score 8 – Appropriate).

The evidence clearly supports coverage of PET and PET/CT for osteomyelitis. Any LCD finalized by CGS should include coverage for this indication.

**E. Spondylodiscitis**

CGS quotes the SNMMI guidance for use of PET for spondylodiscitis. The Summary of Evidence states:

Spondylodiscitis (SD) Guidance was published by the Society of Nuclear Medicine and Molecular Imaging and the American College of Nuclear Medicine (SNMMI) to describe
appropriate use of nuclear medicine imaging in patients suspected of having various musculoskeletal infections. (Palestro, Clark et al. 2021) Appropriate use was based on expert panel consensus and evidence review from existing systematic reviews. In all the scenarios reviewed below evidence was rated fair unless there was no evidence to review.

- Diagnosis of spondylodiscitis in patients without spinal hardware, $^{18}$F-PET/PET/CT (Score 9 – Appropriate) based on fair evidence and expert opinion.
- Diagnosis of spondylodiscitis in patients with spinal hardware, $^{18}$F-PET/PET/CT (Score 8 – Appropriate) based on fair evidence and expert opinion and there were higher false positive rates in the present of spinal hardware than without (12.8% vs. 7%) based on fair evidence and expert opinion.

The CGS analysis supports limited coverage for all musculoskeletal indications (e.g., in some cases after other imaging has been performed). As CGS recognizes in its analysis of the evidence, the results of PET and PET/CT can be affected by taking certain medicines or the presence of certain conditions. However, those are not reasons to deny all coverage nor is the fact that the clinical trials do not show superiority of PET to MRI. These factors may support limiting performance of PET for some musculoskeletal indications as a follow-up test to non-diagnostic MRI or when MRI cannot be performed, but it certainly does not support non-coverage.

CGS should cover PET and PET/CT for spondylodiscitis and could, when appropriate, limit its use to certain patient populations.

F. Conclusion

SNMMI appreciates the opportunity to comment on the proposed LCD. As noted above, we have significant concerns with the proposed restrictions on coverage for specific patients and believe that such restrictions will be detrimental to patient care. Because of our conviction that FDG-PET is a valuable problem-solving tool and will not be overused in patients with suspected inflammation/infection, SNMMI strongly recommends that CGS either not finalize the LCD as proposed and provide coverage for use of FDG-PET and PET/CT in patients with inflammation/infection as described above.

Respectfully Submitted,

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