At Last, ^{18}F-FDG for Inflammation and Infection!

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Several decades after ^{18}F-FDG was first used as a radiotracer, the time has now come for the United States to embrace ^{18}F-FDG as the molecular imaging test of choice for many inflammatory and infectious indications (including sarcoidosis, fever of unknown origin, and musculoskeletal infection) as the Centers for Medicare and Medicaid Services (CMS) retired its National Coverage Decision (NCD) on ^{18}F-FDG PET effective January 1, 2021. Our European colleagues, in what could be a prequel to this editorial, made a similar argument regarding ^{18}F-FDG, particularly for fever of unknown origin (*1*), and argued that efforts should be made to secure reimbursement for ^{18}F-FDG imaging to minimize human suffering and avoid unnecessary and costly procedures (*1*). Indeed, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and European Association of Nuclear Medicine provided joint guidance for the use of ^{18}F-FDG in inflammation and infection nearly a decade ago (*2*).

^{18}F-FDG was first introduced as a radiotracer in 1976 for measuring glucose metabolism in determining regional brain function (*3*,*4*,*5*). The ability of ^{18}F-FDG to localize in the myocardium and in tumors led to its clinical deployment in myocardial viability and in tumor imaging (*5*,*6*). As whole-body PET imaging and fusion with CT became available a decade later, it became apparent that ^{18}F-FDG rapidly detects inflammation and infection in humans, with a performance comparable to that of in vitro labeled leukocytes and ^{67}Ga (*7*, *8*). Many studies have subsequently demonstrated the ability of ^{18}F-FDG to identify sites of inflammation and infection (*1*,*9*,*10*). Fast-forwarding decades after its introduction as a tracer, ^{18}F-FDG has been used as a tool to detect active inflammatory disorders and monitor response to therapeutic interventions (*1*,*11*,*12*).

Though ^{18}F-FDG had shown a great deal of promise in detecting infectious disorders, due in part to the high expression of glucose transporters in inflammatory cells and uptake by infectious organisms (*1*,*13*,*14*), CMS was measured in accepting the plethora of scientific data in this area. In 2004, CMS agreed to cover use of ^{18}F-FDG for differential diagnosis of frontotemporal dementia from Alzheimer disease under specific requirements for its use in a CMS-approved practical clinical trial focused on the utility of ^{18}F-FDG for diagnosis of dementing neurodegenerative diseases (*15*). In 2008, CMS received a formal, complete request to reconsider its de facto national noncoverage of ^{18}F-FDG in lieu of bone, in vitro labeled leukocyte, and ^{67}Ga scintigraphy for chronic osteomyelitis, periprosthetic hip infection, and fever of unknown origin (*16*). CMS determined, however, that at the time, they viewed the evidence as inadequate to conclude that ^{18}F-FDG for the requested indications improves health outcomes in the Medicare populations and therefore determined that ^{18}F-FDG was not reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act (*16*).

The scientific evidence supporting the utility of ^{18}F-FDG in inflammation and infection has increased dramatically since 2008. On the basis of these now overwhelmingly compelling data, SNMMI leadership again approached CMS with a request for coverage of ^{18}F-FDG in inflammation and infection. In the 2021 Medicare Physician Fee Schedule Final Rule, CMS finally retired the NCD for the noncoverage of FDG PET for inflammation and infection (*NCD Manual,* §220.6.16) (*17*). This was a herculean effort led by the content experts and leaders from SNMMI and supported by the American Society of Nuclear Cardiology and was the culmination of multiple meetings, phone calls, letters, and e-mails over the last several years. Using the systematic review commissioned by the SNMMI for the development of appropriate-use criteria for nuclear medicine in musculoskeletal infection imaging, and other recent multidisciplinary guidelines and consensus statements on the role of ^{18}F-FDG in cardiac sarcoidosis developed collaboratively between European and American medical societies and other relevant guidelines, the content experts convinced the Coverage and Analysis Group at CMS that the existing policy of not covering ^{18}F-FDG for inflammation and infection was untenable. As a result, CMS removed the national noncoverage policy and directed that coverage determinations for ^{18}F-FDG for inflammation and infection would be made locally by the Medicare administrative contractors (MACs) (*17*).

Now that MACs are required to cover ^{18}F-FDG for inflammation and infection according to reasonable and necessary guidelines, we have endeavored to ensure that they are aware of the retirement of the old NCD and to gauge their willingness to monitor and process claims for a period of 1 to 2 y or to create a local coverage determination. Only 1 of the 5 MACs that we have communicated with thus far had a strong inclination to start working on a local coverage determination immediately. Two MACs requested additional information, and 2 stated that before discussing a local coverage determination they were going to take an approach of waiting, watching, and monitoring as they gather additional information about the clinical indications for which these claims will be submitted. Effectively, this means that ^{18}F-FDG will be covered as reasonable and necessary for these inflammation and infection indications.

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Notably, 2 MACs were specifically interested in the cost effectiveness of ^{18}F-FDG. In an era favoring cost transparency, this type of request was not at all surprising to us. Fortunately, the data are in our favor. ^{18}F-FDG PET is a cost-effective imaging modality, avoiding unnecessary investigations and reducing the duration of hospitalization. In a Spanish study of fever of unknown origin, the mean cost per patient of the diagnostic procedures preceding ^{18}F-FDG PET/CT was €11,167 ($13,636), including an average of 11 d of hospitalization and outpatient visits. If ^{18}F-FDG PET/CT had been performed earlier in the diagnostic process, €5,471 ($6,681) per patient would have been saved on diagnostic tests and hospitalization days (*18*, *19*).

Regardless of the different approaches taken by the MACs, the SNMMI has vowed to work closely with these groups, ensuring that new guidelines, appropriate-use criteria, and other relevant data constitute the basis of their decision-making process. As additional evidence is collected, the society will endeavor to work with CMS to expand coverage for other nononcologic PET indications as well. We are pleased that through the work of many over several decades, ^{18}F-FDG for inflammation and infection is now increasingly available for patients covered by Medicare. Many private insurance payers follow Medicare guidance, suggesting ^{18}F-FDG may soon be available to even more patients with possible infections or inflammation.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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