strategy is now used by several groups. A major advantage of this strategy is that PET-negative patients (>80% of the total population) can be spared from the adverse effects of BEACOPP.

Interim PET/CT has been also successfully evaluated to reduce long-term toxicity with treatment deescalation of advanced-stage HL (BEACOPP to ABVD) in the case of metabolic complete response after 2 cycles (*9*). In young high-risk patients with DLBCL, it has been shown that, when using the quantitative ΔSUV approach, interim PET was a good predictor of outcome and if the result was negative thus decreased the need for intensive treatment such as autologous stem-cell transplantation (ASCT) (*10*).

Beyond the first line of treatment, ^{18}F-FDG PET/CT has also a strong predictive value for relapsed or refractory HL and DLBCL patients. Especially, ^{18}F-FDG PET/CT positivity before ASCT is strongly predictive of treatment failure and allows patient selection for ASCT or other alternative therapy (*4*). Regarding classic MRI, it is not part of international recommendations, and diffusion-weighted MRI suffers from the lack of intercenter reproducibility.

If personalized medicine based on ^{18}F-FDG PET/CT performed early in the course of therapy is becoming a reality, it is mainly due to the amazing work done by the various national lymphoma groups and international meetings addressing specifically these topics (http://www.lymphomapet.com). This work has led to a significant improvement of disease control or toxicity reduction in several clinical situations.

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REPLY: We appreciate the letter to the editor written by Kanoun et al. from France. They address 2 important issues related to ^{18}F-FDG PET/CT in lymphoma, one is initial staging and the other is interim ^{18}F-FDG PET/CT for early evaluation of response to therapy. Regarding the first point, our review was solely focused on the utility of ^{18}F-FDG PET/CT in restaging and treatment response assessment (*1*). For initial staging, ^{18}F-FDG PET/CT has demonstrated high efficacy in many cancers including lymphoma (*2*). However, this will be a topic for another appropriate use criteria document. Kanoun et al. summarize some of the diagnostic value that ^{18}F-FDG PET/CT can offer in initial staging of lymphomas.

With regards to the role of ^{18}F-FDG PET/CT in the interim evaluation of response to therapy before completion of therapy, we did not include it in our analysis, as there is still no consensus based on the relatively limited available evidence (*3–7*), even if some groups have incorporated interim ^{18}F-FDG PET/CT in their clinical practice. However, we do agree that there is increasing literature on this specific topic (*8–15*). We feel that at this point the use of interim ^{18}F-FDG PET/CT for the early assessment of response to therapy in lymphoma should probably remain limited to clinical trials and not as routine clinical procedure; the only exception could be for those expert groups with experience in this setting within controlled environments (e.g., standardized protocols, homogeneous population, and double-blind reading) (*16*).

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Molecular Imaging of Bacteria in Patients Is an Attractive Fata Morgana, Not a Realistic Option

TO THE EDITOR: We read with great interest the review article entitled "Metabolic Imaging of Infection" by Lawal et al. (*1*). This communication and several others over the years have advocated imaging bacteria as a potential for further exploration (*2–5*). Indeed, it would be wonderful if PET could tell if there was an ongoing bacterial infection in the body, how aggressive it was, and whether antibiotics were effective or not. Interesting studies on bacterial imaging with candidate probes were made in bacterial cultures or with bacterial inoculates in small animals (*2–5*). The researchers knew exactly where to look and what they were looking for, and some of them made optimistic predictions about the clinical significance of their laboratory results. We feel an obligation to contest too optimistic or misleading statements, because experimental circumstances differ vastly from the conditions in the human body, where similarly high concentrations of pathogenic bacteria are rarely seen in the same spot and therefore seldom visible by PET.

We have in recent editorial commentaries expressed our views on the limitations of PET imaging in several settings including detection and characterization of bacterial infections (*6–8*). Even with modern digital detectors, time-of-flight acquisition, and iterative reconstruction, the spatial or the volume resolution with PET has difficulty in getting better than 5 mm or 65 mm^3, respectively. Thus, PET remains a gross imaging modality that faces substantial challenges in visualizing structures at the cellular and subcellular levels, particularly when the intended tracer is not taken up by a mass of cells or other structures with a volume of considerable size. To visualize biologic phenomena in both normal and disease states, a large volume of cells (or other targets) needs to be clumped together in a volume that is larger than several mm^3 or perhaps 1 cm^3 to be detectable by PET imaging, and the degree of tracer uptake in such volumes must substantially exceed that of the background activity by at least 2–3 times to attain an adequate contrast (*9*). As a result, attempts to detect and visualize targets that are smaller than a few mm^3 and with lower levels of activity will fail based on these known physical limitations of PET and may lead to studies that generate uncertain results. With a medium-sized spheric bacteria of a diameter of 2 μm equal to a volume of about 4.2 μm^3, it would require approximately 3.5×10^9 of these bacteria to create a target volume of about 65 mm^3 corresponding to a 5-diameter spheric lesion barely detectable by PET. This enormous concentration of bacteria is about the maximal obtainable in the microbiology laboratory and will hardly ever be present in the body. Bacteria in the tissues lie more scattered and are almost instantaneously attacked by the immune system and macrophages that ingest and remove them, and thus, bacterial concentrates in the body that are visible with bacterial PET tracers are more a rarity than a commonplace event.

Several tracers are very specific by targeting characteristics of living bacteria (*3,4*) or being labeled antimicrobial agents (*2,5*); however, the value of specificity depends on the purpose of imaging. Ironically, a very high specificity may imply a low clinical usefulness because we cannot image all patients with a large panel of tracers, such as one for staphylococci, another for pneumococci, and a third for *E. coli*. Specific tracers may be the crux for the future of PET, but very specific tracers are not always as representative of what we want to detect or as specific as initially assumed. For instance, abnormal uptake of amyloid probes for the study of Alzheimer disease is frequently seen in patients without this disease, and anti–prostate-specific membrane antigen tracers appear to target cancers other than prostate cancer (*10*). Therefore, it is gratifying that some of the authors of bacteria imaging express caveats. Neumann et al. highlight the competition from the huge numbers of nonpathogenic bacteria in the body (*2*), whereas Sellmeyer et al. modestly state that "noninvasive identification of sites of bacterial infection could increase our understanding of the natural history of bacterial infection in patients" and "be used to support clinical decision making" (*3*).

The problems with PET imaging of bacteria mimic the challenges of PET in general. We call for more specific tracers, but at the same time they should not always be too specific. PET may have few limits, since in principle most biologic molecules can be labeled, but we have to consider when it is worth the effort and the cost. Like it or not, for the time being ^{18}F-FDG remains the most important clinical tracer for imaging inflammation in the body, whether it is sterile or bacterial.

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