

REPLY: We thank Lu et al. for their comments. We certainly agree with many and, most importantly, that “Imaging of cardiac sarcoidosis remains challenging” for us all. To answer their specific points, first, regarding the duration of dietary preparation, our patients were recommended to consume two high-fat, low-carbohydrate meals, as is consistent with recent guidelines (1). We specifically choose *not* to exclude noncompliant patients because we wanted to challenge our readers with a spectrum of real-world cases.

Second, Yu et al. make a good point about correlating the ^{18}F -FDG PET/CT results with the results of other types of imaging, such as cardiac MRI, and with clinical findings. We are looking at this in other ongoing projects and did not think it was needed for the main message of the current paper (2).

Third, regarding Figures 1 and 2, we did not screen the entire set of images but chose the first good examples identified. Also, the fact that Yu et al. do not agree with our image interpretation absolutely highlights the main message of our paper. For Figure 1B, Yu et al. correctly point out the issue of papillary muscle activity; however, the patient also clearly had basal anterior uptake and patchy right ventricular uptake consistent with the “focal on diffuse” pattern. Whether this pattern should be considered indeterminate for cardiac sarcoidosis is controversial. However, the recent SNMMI–ASNC expert consensus document (1) considered the “focal on diffuse” pattern to be consistent with possible inflammation. Further, the consensus document specifically highlights the importance of the location of the abnormal focal uptake in this situation (1). For Figure 2B, there is faint diffuse myocardial uptake; poor preparation may have contributed to this finding, but the lateral uptake intensity is in keeping with a normal variant (1,3,4).

Finally, we agree with the comment that it is possible that, with a modified patient preparation protocol (e.g., with 72 h of dietary preparation (5)), we might have achieved even greater interobserver agreement. However, the value, patient compliance with, and practicality of very prolonged diet preparation have not been tested prospectively. Our work sets a standard against which subsequent research can be measured, and we very much hope that interreader variability can be greatly improved. Further research such as this is vitally important because clinicians caring for patients with cardiac sarcoidosis base important management decisions on ^{18}F -FDG PET imaging results.

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PSMA Ligands for Imaging Prostate Cancer: Alternative Labeling by Complex Formation with $\text{Al}^{18}\text{F}^{2+}$

TO THE EDITOR: In the case of prostate cancer, prostate-specific membrane antigen (PSMA) has been shown to be a valuable target for application by various ligands in clinical diagnosis. The unique feature of PSMA is the pocket, 70 Å long, with 2 binding sites in the tip addressed by the chiral centers of *S*-amino acids such as those used by Kularatne et al. (1). In the middle, additional binding sites are highly selective for centers with high electron densities such as π -electrons. Various developments were performed such as those by Low, Pomper, and their colleagues (1–3). An important contribution was brought up by the work of Sterzing et al., who developed and proved the use of ^{68}Ga -PSMA-11 (^{68}Ga -PSMA-HBED-CC) for diagnosis of prostate cancer by PET imaging directly in patients (4). Meanwhile, there are various compounds labeled with ^{68}Ga and ^{18}F , and indeed, there now is a discussion on which radionuclide to prefer for labeling, as featured in a “Hot Topics” article of *The Journal of Nuclear Medicine* by Kesch et al. (5). Many PSMA ligands are labeled by ^{68}Ga in a complex attached to the molecule of interest. That approach exhibits the outstanding advantage of applying the same compound in therapy just by choosing the appropriate radionuclide, such as ^{90}Y or ^{177}Lu . That, however, is not possible in the case of ^{18}F -compounds in which the radionuclide is bound via a prosthetic group.

It is the aim of our letter to draw attention to a highly interesting alternative developed by McBride et al. (6). They showed the easy formation of $\text{Al}^{18}\text{F}^{2+}$ and application for labeling by complex formation, as has been well applied in the case of ^{68}Ga . The surprising observation was that $\text{Al}^{18}\text{F}^{2+}$ exhibits the chemical behavior of a radiometal and that the labeling process was through complex formation using a kit procedure as performed by Malik et al. (7) and Boschi et al. (8) and schematically described by us recently (9).

When compared with ^{68}Ga , ^{18}F exhibits quite a few advantages. The longer half-life (110 min vs. 68 min) allows single-batch preparation for many patients, even in 1 day. Moreover, late and longer registrations are possible, thus increasing contrast and the detection of small lesions due to the low positron energy of ^{18}F (0.65 MeV, vs. 1.9 MeV for ^{68}Ga) (10).

^{68}Ga is available as a generator radionuclide, and the fact that ^{18}F has to be produced by a cyclotron is usually thought to be a disadvantage. However, during the past 10 years, the number of cyclotrons has greatly increased, finally reaching a kind of “all around” availability. After any ^{18}F production run, just a flushing of the target systems supplies waste ^{18}F activity in a high amount, so that practically no production costs exist.

In summary, the facile and high-yielding radiosynthesis of PSMA ligands that is possible using $\text{Al}^{18}\text{F}^{2+}$ chemistry makes it worthy for clinical development in PET imaging of prostate cancer, compared with the clinically established ^{68}Ga -PSMA tracers.

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REPLY: Thank you for allowing us to respond to Drs. Hans-Jürgen Machulla and Ehab Al-Momani, who point to the recently established preclinical utility of ^{18}F - AlF^{2+} as an alternative radiometal-like moiety for low-temperature radiolabeling of radiometal-complexing agents conjugated to prostate-specific membrane antigen (PSMA) ligands for prostate cancer PET imaging. We also gratefully acknowledge their comments on our articles (1,2) questioning the need for radiofluorinated PSMA PET tracers in addition to the ^{68}Ga -labeled versions already available as a diagnostic version of theranostic ligands, and we appreciate their perspective on ^{18}F -labeled PSMA tracers. Indeed, in recent years several ^{18}F -labeled PSMA radioligands apart from the mentioned ^{18}F - AlF^{2+} -labeled variants have already been introduced both preclinically and clinically (3–5). Particularly, Szabo et al. (4) clinically introduced ^{18}F -DCFPyL, an improved second-generation ^{18}F -PSMA ligand, which was followed by the work of further optimized next-generation PET tracer ^{18}F -PSMA-1007 recently introduced by Giesel et al. (5). Both ^{18}F -labeled ligands have already entered prospective clinical trials, highlighting the obvious high potential of these radiofluorinated tracers for the primary diagnosis of prostate cancer and detection of relapse by means of PET/CT and PET/MRI. In this connection, the good manufacturing practice-compliant procedures for the production of these radiofluorinated PSMA ligands have

also already been established to cover all regulatory prerequisites. Regardless, the ^{18}F - AlF^{2+} -labeled versions of PSMA ligands originally intended for radiometal labeling (e.g., ^{68}Ga and ^{177}Lu), despite sophisticated and successful radiolabeling, again have to be carefully preclinically evaluated. This is necessary for every PSMA tracer bearing a new radiolabel moiety, and in this case especially, potential defluorination in vivo has to be considered. However, only limited preclinical results in vitro and in vivo are available for ^{18}F - AlF^{2+} -labeled PSMA ligands. The major concern is the necessary elucidation of maintained binding affinity and internalization properties after ^{18}F - AlF^{2+} labeling of the theranostic PSMA ligand of interest and, finally, examination of the pharmacokinetic properties in vivo. In this respect, we are looking forward to seeing the first-in-man data obtained with ^{18}F - AlF^{2+} -labeled versions of PSMA ligands proving their clinical impact, including acceptance as indicated by the necessary urooncologic referrals. In any case, we strongly appreciate the comments of Drs. Machulla and Al-Momani and agree with their statement that ^{18}F -labeled PSMA ligands are essential in the future not only because of the advantageous nuclear properties of ^{18}F but also to cover the clinical demand in daily patient care by offering large-scale batches of the respective ^{18}F -tracer. We are strongly convinced that, depending on the hospital and PET center environment and infrastructure in countries with reduced clinical demand, ^{68}Ga -labeled PSMA ligands will still play a clinical role in the future.

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