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In Reply

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We thank Perera and colleagues for their comments on our article.¹ Indeed, the current state of histologic confirmation of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scans is less than ideal, as they point out in their meta-analysis² in which only 5 of the 16 studies that were evaluated had histologic confirmation. All were retrospective, relatively small single-institution studies (12–130 patients). The majority were based on preoperative staging studies of intermediate-or high-risk primary cancers prior to radical prostatectomy, a bias by itself because these tumors tend to be large and represent the more aggressive side of the clinical spectrum. Only 1 study (n = 28) described lymph node metastases in the biochemical recurrent setting. The retrospective, single-institution nature of these studies enables unforeseen biases to creep in, typically creating more favorable outcomes than might be seen with unselected prospective populations. Notably absent from the current literature are large studies involving PSMA PET with histologic confirmation of local recurrences or bony metastases and even lymph nodes in both treatment-naïve and treated patients. Prostate cancer is a complex and diverse disease that evolves over its course. One cannot assume that PSMA performs equally throughout all of prostate cancer's "clinical states" as we do when we base our conclusions on only one initial clinical state of the disease. We need prospective studies nested within multi-institutional treatment trials that include the whole range of disease locations and clinical states of prostate cancer before we can declare PSMA PET a "validated" PET imaging biomarker.³

We apologize for our US-centric view of the current commercial availability of PSMA agents. Admittedly, we have an incomplete understanding of the approval process for PET agents outside the United States and we are happy to learn of the broad availability of the agent across several continents. The US approval system must appear equally opaque to outsiders. As for the United States, a commercial product is several years down the road, awaiting the results of several industry-sponsored multi-institutional prospective trials that include biopsy confirmation. We agree, PSMA radiotracers are revolutionizing the field and we are hopeful for their sustained impact on patient care.

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