Commercially Competitive Vendor-Agnostic Image Reconstruction Could Be a Leap Forward for PET Harmonization

TO THE EDITOR: I read with interest the recent publication in *The Journal of Nuclear Medicine* titled "A Guide to ComBat Harmonization of Imaging Biomarkers in Multicenter Studies" (*1*). The work discussed in the article presents valuable ideas and concepts to the community and continues a tradition of inspired diligence that has ushered our field toward an increasingly efficacious infrastructure for PET harmonization. Efforts to improve harmonization in PET metrology provide a significant and fundamental contribution to the field; they support our ability to work confidently with images and develop meaningful clinical assessments and innovations.

Image reconstruction is a central step in the image generation process. In recent years, significant gains have been made in PET image quality at the stage of image reconstruction, we can note that application of the technology has transitioned into the proprietary and vendor-specific domain. As we look to the future and see inevitable evolution of artificial intelligence–aided reconstruction, we can expect that in the coming years it will likely be more difficult to fully describe reconstruction algorithms because they will be partially defined by the select training datasets used to build them (*2*). It appears that we are on a trajectory that will usher in continued divergence of advanced reconstruction algorithms across vendors, increased layers of vendor specificity, and subsequently greater challenges to harmonize PET.

The field of data science is continually maturing, perhaps most notably in the areas of artificial intelligence and radiomics. Simultaneously we are learning to take on new roles as stewards of data (*2*,*3*). Our growth in this realm is relevant for harmonization efforts because the prospect of evolving the field toward greater access to raw data has many implications, including the potential to create reliable, cross-platform image reconstruction tools. Such a solution could present an ideal, alternative strategy for addressing the "scanner affect," essentially through reducing the (technically unnecessary) variability of vendor-specific image reconstruction algorithms across scanners.

The importance of homogenizing PET data is fundamental to the field. A basis for the advancement of diagnostic imaging are standards established through multicenter trials. The greater the uncertainty in the trial data, the greater the possibility a study will be underpowered, and it adds an increased possibility of the trial producing incorrect conclusions (*4*). Uncertainty stems in part from variability in the image generation processes and can be addressed through standardization or harmonization. We can recall *standardization* refers to the process of making something conform to a standard whereas *harmonization* is the action, or process, of making something consistent or compatible. The former is preferable where possible—we cannot reasonably standardize hardware, but we could create the means to standardize processing, in support of those applications of PET that may benefit from it. A recent review of multicenter use of PET/CT concluded that "standardization" of acquisition and processing "should precede any multicenter trial that uses PET SUVs quantitatively"; and that "This should be a high priority for future multicenter trials using quantitative imaging" (*5*). The priority is echoed and amplified if we consider the field's collective responsibility to ensure that our patient's data are being used for optimal benefit (*3*). It therefore becomes prudent to recognize that an infrastructure that supports optional standardized advanced image reconstruction is preferential.

We are at least several years away from having reliable third-party PET image reconstruction tools—it is possible from a technical standpoint, but we do not presently have the industrial framework to support it, and raw data formats as well as reconstruction algorithms are proprietary. But whether we are several years away from realizing this solution, or several decades, may depend on if we are willing to have the requisite discussion now. Several pathways could be considered for implementation. One method could be tuning PET systems to produce reliable, compliant raw data formats, which could enable investment in creating competitive cross-platform processing tools.

Data access across imaging is in fact a large and consequential subject. Harmonization in PET is one of many topics that are connected to this faucet on our infrastructure. Generally, opening access to raw data for third-party solution development addresses a central pivot of the PET instrumentation field and would have wide ranging implications for innovation beyond, and downstream of, improved harmonization or standardization (*6*). Radiomics, AI, and other avenues of imaging data science would directly reap the benefits—access to data and its quality (fidelity) is a new bottleneck for technologic advancement. Although the topic of data access is complex, cross-vendor reconstruction for supporting harmonization efforts would be a straightforward and logical solution for addressing the harmonization problem at its crux. Correspondingly, the clear and concise implication of unified reconstruction in the harmonization challenge lends support to the more general assertion that greater access to data should support a more efficacious modern imaging field.

In summary, practical solutions, such as those presented by the authors, provide real benefit to the field. But as we look to the future, it is time to add agnostic image reconstruction to the discussion of solutions for harmonization. The same advancements in computing technology that have enabled new advances in image reconstruction also make it prudent to reevaluate our infrastructure for accessing and using data at its source.

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A VISION of ALSYMPCA

TO THE EDITOR: I just read the 2 editorials written by Hofman (*1*) and by Czernin and Calais (*2*) commenting on the use of ^{177}Lu-PSMA-617 therapy in patients with metastatic castration-resistant prostate cancer (mCRPC), mainly on the results of the VISION trial (*3*). ^{177}Lu-PSMA-617 together with ^{68}Ga- or ^{18}F-labeled PSMA ligands are doubtless important theranostic technologies that provide a new perspective on mCRPC treatment, as stated in another recent editorial by Srinivas and Iagaru (*4*). However, I miss in the VISION trial a comparison with the results of another study performed a few years ago that analyzed the use of ^{223}Ra in the treatment of mCRPC patients, the ALSYMPCA trial (*5*). Although ^{223}Ra is used to treat patients with exclusive bone metastases, this group represents most patients with mCRPC. In some studies, the percentage of patients with bone metastatic disease, with or without concomitant lymph node disease but without visceral (lung and liver) disease, represents around 70% of cases (*6*), and in this group the presence of concomitant lymph node disease does not appear to change the overall survival (this high percentage was also confirmed in the VISION trial, in which 91% of patients had bone metastases, 50% had lymph node metastases, 9% had lung metastases, and 12% had liver metastases) (*6*). Therefore, ^{223}Ra could represent an adequate option to treat most patients with mCRPC. In this sense, it will be useful if the authors of the VISION study, as well as of other future studies on this issue, also present the survival results for the distinct groups of metastatic lesions or, at least, separate the results of the ones with bone metastatic disease without visceral disease from the group with visceral disease. This separation would be useful to indirectly compare the effects of ^{177}Lu-PSMA-617 with the effects of ^{223}Ra in the group without visceral metastases and also to assess the effect of ^{177}Lu-PSMA-617 in the group of patients with visceral metastases, who certainly are not candidates for ^{223}Ra therapy.

In this line of reasoning, it is interesting to note that median survival differences between groups receiving or not receiving the radionuclide therapy are similar in both trials: 4 mo (15.3 mo vs. 11.3 mo for patients receiving or not receiving the therapy, respectively) in VISION and 3.6 mo (14.9 mo vs. 11.3 mo) in ALSYMPCA. Besides, although the authors of the VISION study did not present the results of subgroups with and without visceral metastases, in the supplementary appendix of the study (*3*) the authors presented the survival results in subgroups with and without liver metastases and showed that there is no statistically significant difference in overall survival in the subgroup with liver metastases. These findings, in my opinion, are worrisome and suggest that the main effect of ^{177}Lu-PSMA-617 in overall survival could be due to its action on bone metastases and not on visceral metastases.

Therefore, presentation of the survival results by subgroups will be essential to define the patients who would most benefit from ^{177}Lu-PSMA-617 therapy and to further establish the best theranostic algorithm to treat these patients (e.g., patients with exclusive bone disease would first receive ^{223}Ra, and patients with visceral disease would first receive ^{177}Lu-PSMA-617). Last, it is important to say that ^{223}Ra therapy is already a reality in several places around the world whereas ^{177}Lu-PSMA-617 is a distant vision; thus, to move from ALSYMPCA to VISION, VISION has to show where it is really effective.

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Reply: A VISION of ALSYMPCA

REPLY: Dr. Duarte urges an analysis of the VISION trial in an effort to ascertain results in subsets of men with bone and visceral disease. He then suggests an indirect comparison between ^{177}Lu-PSMA-617 and ^{223}Ra.

I agree with the first point but disagree with the second. The VISION trial (*1*) can be analyzed in a multiplicity of new ways. Right now, just the prespecified primary analyses have been published (*1*). There are many analyses that will follow that include not only the distribution of the disease (as suggested by Duarte) but also the various biomarkers that are known to be prognostic in other settings. These biomarkers might include hemoglobin, neutrophil-to-lymphocyte ratio, prostate-specific antigen, alkaline phosphatase, lactate dehydrogenase, performance status, age, time since diagnosis, pain, and others. As it turns out, the dataset from VISION is rich and there is much more to explore.

On the second point, there is disagreement. The ALSYMPCA trial with ^{223}Ra (*2*) was conducted in a long-ago era, before the use of novel hormones such as abiraterone and enzalutamide and before the widespread use of cabazitaxel. Further, patients enrolled in ALSYMPCA were not required to progress after docetaxel (but approximately half did). All patients enrolled in VISION had progressed after either