^{68}Ga-NODAGA-Exendin-4 PET Scanning for Focal Congenital Hyperinsulinism: Need for Replication

TO THE EDITOR: ^{18}F-6-fluoro-L-DOPA PET (^{18}F-DOPA PET) scanning has been the mainstay in the diagnosis and localization of focal lesions in patients with congenital hyperinsulinism (CHI) (*1*). Although scan-to-lesion correlation is not completely perfect, the predictive value of ^{18}F-DOPA PET as a clinical tool has been clinically meaningful and reliable, with sensitivity ranging from 75% to 100% (*1*,*2*), enabling significant transformation in the surgical management of focal CHI (*3*,*4*).

^{68}Ga-NODAGA-exendin-4 PET (^{68}Ga-exendin PET) is a new imaging modality that has potential to replace ^{18}F-DOPA PET (*5*). ^{68}Ga-exendin PET has been shown to have greater sensitivity and surgical preference in the localization of focal CHI. This exciting development has the advantage of molecular specificity in targeting glucagon-like peptide-1 receptor in pancreatic β-cells, as well as relatively low radiation (estimated at 0.77 mSV for a 1-y-old child) (*6*), although the short half-life (68 min) of ^{68}Ga requires access to a local production site.

However, our enthusiasm for this new diagnostic development in CHI is tempered by a deeper examination of the data and a review of the trial design to derive divergent conclusions from those reported prematurely and optimistically by the authors (*5*). The prospective arm of the study recruited only 8 patients, with no justification provided on the sample size needed to demonstrate clinical benefit. In comparing ^{68}Ga-exendin PET with ^{18}F-DOPA PET, the order of scanning was not made explicitly clear; considering the reporting and interpretation of nonconcurrent scans (at an interval of 4–72 d) by nonmasked observers, results were undoubtedly influenced by carry-over bias. Unusually, authors added a retrospective arm to the study, citing real-world observations to support doubtful findings from prospective study data but reinforcing observational bias in the process.

Although the authors provided clear descriptions of radiotracer production and PET imaging techniques, the article ignored the need to confirm focal CHI by correlating scan results with histopathologic results on intraoperative pancreatic frozen sections. Further, the authors did not discuss location specificity or the surgical complexity in achieving complete resection of lesions to demonstrate true benefit from shifting reliance on ^{68}Ga-exendin PET as a surgical navigational tool. Therefore, it remains unclear whether ^{68}Ga-exendin PET offered real-world benefit to patients in either prospective or retrospective arms of the study.

The combined experience of specialist CHI centers in the United Kingdom, Germany, and the United States over 14 years has established ^{18}F-DOPA PET as a proven clinical tool in the diagnosis of focal CHI. Notwithstanding this success, as a group we feel it is important to investigate improved imaging techniques that are more accessible, inexpensive, and reliable. However, the development of an alternative imaging modality away from ^{18}F-DOPA PET will require convincing strength of data, which the recently published paper (*5*) does not provide. Clearly, this paper whets the appetite with interesting preliminary information that needs to be replicated in well-designed, prospective multicentered studies with robust patient numbers to demonstrate clear clinical benefit.

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Reply: ^{68}Ga NODAGA-Exendin-4 PET Scanning for Focal Congenital Hyperinsulinism: Need for Replication

REPLY: Science needs differences in opinions to ensure that facts are presented in a truly *reproducible* way. That is why we welcome the comments by Banerjee et al. (*1*), and we have to admit that we actually agree with most of them.

Needless to say, the results of our study must be tested for replicability—as every set of novel data must be tested. Having said that, we would like to highlight that we have never claimed that this study was a registration trial. In fact, we clearly state that these are the first results of clinical imaging of congenital hyperinsulinism with ^{68}Ga NODAGA-exendin-4, and we did raise this issue in the discussion and conclusion sections (*2*).

Pertaining to the comments on retrospectively including 11 patients outside the prospective study, we do agree that there is a possibility of extending the bias. However, as the nature of the study was proof of concept and considering the expertise of the Charité Berlin Centre in treating congenital hyperinsulinism patients from all around the world, we decided to include all available patient data.

We acknowledge the concern of Banerjee et al. (*1*), as it becomes clear from our respective remarks concerning this limitation in the introduction and discussion sections. In fact, we have concluded that exendin PET has the potential to be an improvement over ^{18}F-DOPA PET, but that more work is needed to validate these preliminary results (*2*).

To allay the concerns of bias spilling into the results of our study, we would like to stress that our group did realize that PET readings could be positively biased if the reporting was left only to the inventors of the technique. That is why we chose 2 methods of reading—that is, clinical reading at the respective site where imaging had been performed and an independent, masked reading. Thereafter, to overcome any discordant results, a joint reading was performed. Although we took the joint reading as reference, knowing that the gold standard for imaging findings can only be histopathology, specifically for new tracers and new indications, we did perform histopathologic confirmation in all specimens operated on (Supplemental Table 2 in (*2*)). Even the surgeons, trained on using ^{18}F-DOPA PET–directed surgical planning, clearly stated more confidence in exendin PET in interpretation of the image results than in ^{18}F-DOPA PET. These results are presented in the supplemental materials using the validated Likert scale (*2*).

We are grateful for the comments from Banerjee et al. supporting the conclusions we have drawn, as the points they raised are in line with the arguments we have put forward in our paper. Also, we are grateful that Banerjee et al. raise the issues for which the answers can be found in the supplemental material, thus putting emphasis on this part of the paper as well. In addition, we hope that our remarks with respect to a potential bias have helped to allay such concerns.

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Adding Nontumor Radiomic Features to the Prognostic Model Is Bothersome but Useful

TO THE EDITOR: We read with great interest the article by Dr. Yusufaly and colleagues (*1*), who developed a radiomic model incorporating tumor radiomic features, nontumor radiomic features, and clinical variables to predict disease recurrence in patients with cervical cancer. To the best of our knowledge, this was the first study to suggest that nontumor radiomic biomarkers derived from the whole body (including bone, fat, and muscle) could improve prognostic modeling of cancer. Previous studies have proven that peritumoral radiomic features could improve the performance of radiomic models (*2–4*). This study provides more comprehensive insights into the tumor and the immune state of the human body.

Despite the encouraging results, several methodologic issues should be noted. First, we are concerned about the workflow of the radiomic analysis. Although this study evaluated its radiomic quality score of 18 points (total points of 36), 2 domains were not truly conducted, that is, detection and discussion of biologic correlates and potential clinical utility. Although this study hypothesized that whole-body radiomic features may be associated with immune system function and could reflect variation in patients' global inflammatory state, it did not investigate the biologic meaning behind radiomic features by correlation with computational pathology features, radiology–pathology coregistration, or analysis of biologic pathways or genomic correlations (*5*). In addition, an assessment of potential clinical utility through statistical methods such as decision curve analysis was not performed. Second, the current feature selection is not enough despite the fact that the authors manually excluded several highly correlated features; more sophisticated and rigorous dimensionality reduction methods (such as intraclass correlation analysis and Pearson correlation coefficient analysis) must be implemented to ensure the reproducibility and independence of the identified radiomic features (*6*). Third, this study applied only C-index as a discrimination metric for evaluating the predictive performance of radiomic models, but this metric is not enough, as calibration is not fully captured by C-index. Calibration statistics such as calibration plots, which reflect the consistency between the true probability and the predicted probability, are needed (*7*). Both discrimination and calibration statistics are recommended when evaluating the performance of models. Fourth, use of the cindex.comp package and net reclassification improvement is recommended for pairwise comparisons of model performance. Fifth, given the distinct prognosis between early-stage and advanced-stage tumors, the risk stratification determined by radiomics may be confounded by tumor stage; a subgroup analysis by stage can be considered to identify the true effect of radiomics. In addition, Figure 6 showed the same hazard ratios in the models based on stage plus tumor-related biomarkers and the model based on all biomarkers, suggesting that whole-body biomarkers failed to provide additional information for risk stratification. Finally, as the authors acknowledged in the limitations, the radiomic model was developed and validated at a single small center; multiple external validations would be beneficial for more generalizability to heterogeneous groups of patients regardless of the clinical setting.

Despite the above-mentioned limitations, we still appreciate Yusufaly and colleagues for their outstanding work on nontumor radiomic biomarker analysis, which provides a more holistic model. We look forward to further works to improve the validity and generalizability of their radiomic models.

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