^{18}F-FDOPA PET for the Noninvasive Prediction of Glioma Molecular Parameters: A Radiomics Study

TO THE EDITOR: We have read with interest the paper by Zaragori et al. about the role of PET using 6-^{18}F-fluoro-L-DOPA (^{18}F-FDOPA) in the prediction of molecular parameters by radiomics (*1*). We agree that radiomics is a promising approach to improve the accuracy of amino acid PET (*2*). This has been demonstrated, for example, for the differentiation of recurrent tumor from treatment-related changes (*3,4*).

Zaragori et al. report that radiomics features of static and dynamic ^{18}F-FDOPA data in patients with a neuropathologic diagnosis of grade II, III, or IV glioma were able to predict IDH mutations and the 1p/19q codeletion with an area under the curve of 0.831 and 0.724, respectively. The authors conclude that ^{18}F-FDOPA PET using a full set of radiomics features is an effective tool for the noninvasive prediction of IDH mutations and for prediction of the 1p/19q codeletion in routine practice.

Although we have no doubt about the quality of the study, we would like to point out a problem with the preselection of patients. For this study, 74 patients with grade II–IV gliomas were retrospectively selected from a larger collective. The authors assume that the results of the study are valid for the noninvasive prediction of molecular parameters in patients with suspected glioma, that is, in the setting of preoperative diagnostics in which, apart from clinical and radiologic parameters, no information is available about the histology of the tumors.

Previous studies investigating the final diagnosis of patients referred for amino acid PET with suspected brain tumor, however, reported that 20%–40% had benign lesions or nonglial tumors (e.g., inflammation, ischemia, or lymphoma) (*5*–*7*). The radiomic features of these lesions were not considered in the present analysis and could significantly affect the results of the study. Therefore, the validity of the study for noninvasive prediction of molecular parameters in the setting of preoperative diagnostics is at least doubtful.

A similar issue could also be observed in another recently published study (*8*), which investigated the prediction of TERTp mutation status in IDH wild-type (IDHwt) high-grade gliomas using pretreatment dynamic *O*-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET) PET radiomics. In that study, patients with IDHwt tumors were selected from a mixed population of patients, and the authors reported that radiomics based on time-to-peak images extracted from dynamic ^{18}F-FET PET scans could predict the TERTp mutation status of IDHwt diffuse astrocytic high-grade gliomas with high accuracy preoperatively. Since the IDH mutation status in the preoperative population is not known, the analysis is considerably affected by the IDH-negative gliomas and benign lesions, and the validity of this study also—in the setting of preoperative diagnostics—has to be viewed with great caution.

Summarizing, we would like to point out that image analysis methods aiming at noninvasive prediction of molecular parameters have to be based on a representative preoperative population. Preselection of such populations based on postoperative histologic data leads to an erroneous and not clinically useful conclusion.

We conclude that the results of such studies can be considered only as hypotheses and have no relevance for clinical practice.

REFERENCES

1. Zaragori T, Oster J, Roch V, et al. ^{18}F-FDOPA PET for the noninvasive prediction of glioma molecular parameters: a radiomics study. *J Nucl Med.* 2022;63:147–157.
2. Lohmann P, Galldiks N, Kocher M, et al. Radiomics in neuro-oncology: basics, workflow, and applications. *Methods.* 2021;188:112–121.
3. Ahrari S, Zaragori T, Rozenblum L, et al. Relevance of dynamic ^{18}F-DOPA PET radiomics for differentiation of high-grade glioma progression from treatment-related changes. *Biomedicines.* 2021;9:1924.
4. Lohmann P, Elahmadawy MA, Gutsche R, et al. FET PET radiomics for differentiating pseudoprogression from early tumor progression in glioma patients post-chemoradiation. *Cancers (Basel).* 2020;12:3835.
5. Pichler R, Dunzinger A, Wurm G, et al. Is there a place for FET PET in the initial evaluation of brain lesions with unknown significance? *Eur J Nucl Med Mol Imaging.* 2010;37:1521–1528.
6. Rapp M, Heinzel A, Galldiks N, et al. Diagnostic performance of ^{18}F-FET PET in newly diagnosed cerebral lesions suggestive of glioma. *J Nucl Med.* 2013;54:229–235.
7. Hutterer M, Nowosielski M, Putzer D, et al. [F-18]-fluoro-ethyl-L-tyrosine PET: a valuable diagnostic tool in neuro-oncology, but not all that glitters is glioma. *Neuro Oncol.* 2013;15:341–351.
8. Li Z, Kaiser L, Holzgreve A, et al. Prediction of TERTp-mutation status in IDH-wild-type high-grade gliomas using pre-treatment dynamic [^{18}F]FET PET radiomics. *Eur J Nucl Med Mol Imaging.* 2021;48:4415–4425.

Karl-Josef Langen*
Felix M. Mottaghy
**Forschungszentrum Jülich*
Jülich, Germany
E-mail: k.j.langen@fz-juelich.de

Published online Jan. 27, 2022.
DOI: 10.2967/jnumed.122.263837

Reply: ^{18}F-FDOPA PET for the Noninvasive Prediction of Glioma Molecular Parameters: A Radiomics Study

REPLY: We read with interest the letter to the editor by Langen and colleagues in response to our recent study published in *The Journal of Nuclear Medicine* (1). We agree with them that radiomics analysis is a promising approach for PET imaging in neurooncology, although its application in clinical practice needs to be defined more precisely on the basis of the clinical question at hand. The added value of 6-^{18}F-fluoro-L-DOPA (^{18}F-FDOPA) PET radiomics over conventional static analysis, derived from SUV parameters, appears to hold more promise for the initial diagnosis (*1*) than for detecting recurrent disease (*2*). Extensive effort is also needed to study these radiomics tools prospectively, including in a real clinical setting of nonglioma lesion, as well as to make these tools available and amenable to accurate interpretation by nuclear physicians in clinical routine practice. We would like to respond to this letter by raising 3 points.

First, and from a methodologic point of view, radiomics analysis needs to be compared with a robust benchmark (*3,4*). Immunohistologic analysis of tumor samples is still considered the gold standard for defining brain tumors at the initial diagnosis. Although these

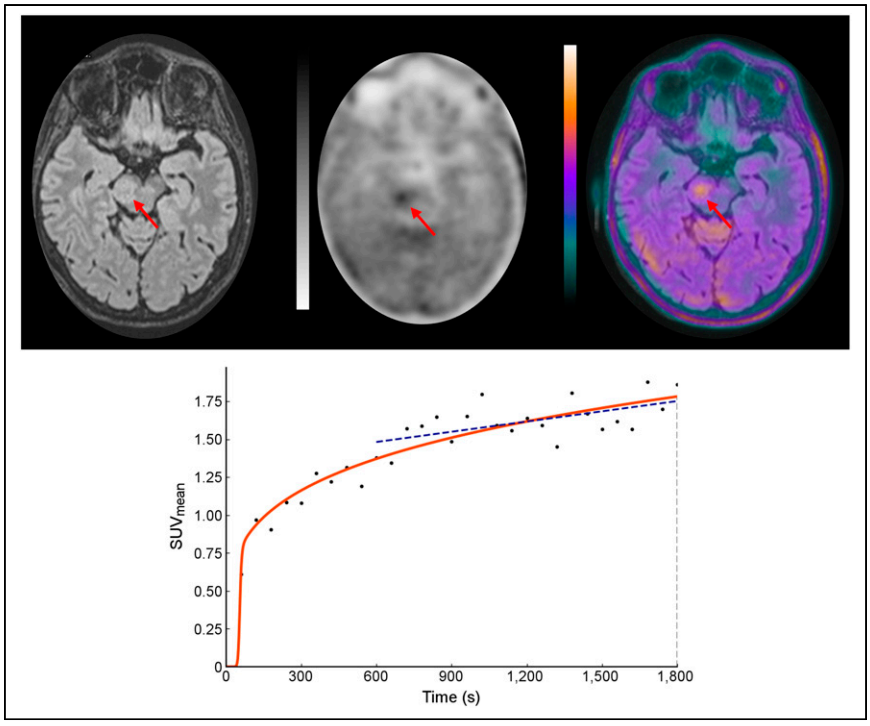

FIGURE 1. Axial slices of inflammatory lesion of midbrain (arrows) in hypersignal fluid-attenuated inversion recovery MRI (top left panel), showing moderate ^{18}F-FDOPA uptake in PET image (top middle panel) and PET/MR image (top right panel) in 68-y-old woman. Interestingly, dynamic acquisitions (bottom panel) showed constantly increasing SUV curve suggestive of nonaggressive lesion.

analyses are considered as the reference in oncology, we know that they suffer from several limitations. Information extracted from immunohistologic analysis is representative of only the region from which the sample was taken and of only the time of collection, which means that this type of analysis is both spatially (*5–7*) and temporally limited (*8*). In this vein and for lack of a better alternative, the recently published retrospective amino acid PET radiomics studies exploring the prognostic benefits of molecular parameters of brain tumors at initial diagnosis were, similarly to ours, all based on immunohistologic analyses (*9–11*). In differential diagnoses, brain tumors, brain inflammatory lesions, ischemia, or primary central nervous system lymphomas are typically "do not touch" lesions (*12*), with correspondingly very low rates of available histologic analyses, which restricts their inclusion in these types of retrospective studies. In their study, Renard et al. (*13*) underline that less than one third of their pseudotumor patients had available histology.

Second, PET imaging in neurooncology needs be interpreted in the era of multimodal and multiparametric approaches as advocated by the current European guidelines, which recommend amino acid PET at the initial tumor diagnosis as an adjunct to MRI (*14*). High-grade gliomas may be accurately distinguished from primary central nervous system lymphomas using morphologic MRI (*15*), with recent MRI technical advances expected to further increase performance in differentiating from inflammatory brain lesions (*16*). These improvements in MRI-based brain lesion characterizations will allow more specific identification of the best candidate brain lesions to refer for amino acid PET imaging. Moreover, conventional static analysis of ^{18}F-FDOPA PET imaging is also useful in discriminating between pseudotumoral and tumoral lesions (*13*).

Finally, the 2 amino acid PET studies mentioned by Langen and colleagues (*1,11*) reported the prognostic significance of dynamic parameters, obtained from VOI-based or voxel-based extractions combined with radiomics analysis, for respectively predicting IDH and TERTp mutations. As already extensively discussed elsewhere (*17*), aggressive brain gliomas are associated with high tracer uptake within the first few minutes after injection followed by a decrease in the uptake curve, whereas less aggressive gliomas typically show a slow increase in amino acid uptake, with the highest values observed at later time frames. Amino acid PET imaging of brain inflammation is also associated with a consistently increasing SUV curve (*14*). Figure 1 provides representative ^{18}F-FDOPA PET images of a brain inflammation case. Other dynamic amino acid PET studies also suggest that lymphomas (*18*) and benign lesions (*19*) show dynamic patterns similar to the ones observed in less aggressive gliomas. Dynamic PET imaging of brain lesions at the initial diagnosis, in addition to conventional static analysis (*13*), should therefore help identify nonglioma brain lesions. This possibility will, of course, need to be further confirmed by well-designed prospective studies.

To summarize, radiomics analysis of amino acid PET imaging has the potential to emerge as a truly effective tool for the noninvasive characterization of gliomas, provided that multimodal and multiparametric imaging is used. Currently, the primary aim of radiomics analyses in neurooncology is to generate hypotheses with promising results, to consider in a next step toward prospective evaluation in the real clinical setting.

ACKNOWLEDGMENT

We thank Petra Neufing for critical review of this letter.

REFERENCES

1. Zaragori T, Oster J, Roch V, et al. ^{18}F-FDOPA PET for the noninvasive prediction of glioma molecular parameters: a radiomics study. *J Nucl Med.* 2022;63:147–157.
2. Ahrari S, Zaragori T, Rozenblum L, et al. Relevance of dynamic ^{18}F-DOPA PET radiomics for differentiation of high-grade glioma progression from treatment-related changes. *Biomedicines.* 2021;9:1924.
3. Lohmann P, Galldiks N, Kocher M, et al. Radiomics in neuro-oncology: basics, workflow, and applications. *Methods.* 2021;188:112–121.
4. Orlhac F, Nioche C, Klyuzhin I, Rahmim A, Buvat I. Radiomics in PET imaging. *PET Clin.* 2021;16:597–612.
5. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med.* 2012;366:883–892.
6. Bettoni F, Masotti C, Habr-Gama A, et al. Intratumoral genetic heterogeneity in rectal cancer: are single biopsies representative of the entirety of the tumor? *Ann Surg.* 2017; 265:e4–e6.
7. Zhang XC, Xu C, Mitchell RM, et al. Tumor evolution and intratumor heterogeneity of an oropharyngeal squamous cell carcinoma revealed by whole-genome sequencing. *Neoplasia.* 2013;15:1371–1378.
8. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med.* 2011;3:75ra26.
9. Lohmann P, Lerche C, Bauer EK, et al. Predicting IDH genotype in gliomas using FET PET radiomics. *Sci Rep.* 2018;8:13328.

10. Haubold J, Demircioglu A, Gratz M, et al. Non-invasive tumor decoding and phenotyping of cerebral gliomas utilizing multiparametric ^{18}F-FET PET-MRI and MR Fingerprinting. *Eur J Nucl Med Mol Imaging.* 2020;47:1435–1445.
11. Zhicong Li, Kaiser L, Holzgreve A, et al. Prediction of TERTp-mutation status in IDH-wildtype high-grade gliomas using pre-treatment dynamic ^{18}F-FET PET radiomics. *Eur J Nucl Med.* 2021;48:4415–4425.
12. Huisman TAGM. Tumor-like lesions of the brain. *Cancer Imaging.* 2009;9 Spec No A:S10–S13.
13. Renard D, Collombier L, Laurent-Chabalier S, et al. ^{18}F-FDOPA-PET in pseudotumoral brain lesions. *J Neurol.* 2021;268:1266–1275.
14. Law I, Albert NL, Arbizu J, et al. Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [^{18}F]FDG: version 1.0. *Eur J Nucl Med Mol Imaging.* 2019;46:540–557.
15. Malikova H, Koubska E, Weichet J, et al. Can morphological MRI differentiate between primary central nervous system lymphoma and glioblastoma? *Cancer Imaging.* 2016;16:40.
16. Han Y, Yang Y, Shi Z, et al. Distinguishing brain inflammation from grade II glioma in population without contrast enhancement: a radiomics analysis based on conventional MRI. *Eur J Radiol.* 2021;134:109467.
17. Verger A, Imbert L, Zaragori T. Dynamic amino-acid PET in neuro-oncology: a prognostic tool becomes essential. *Eur J Nucl Med Mol Imaging.* 2021;48:4129–4132.
18. Aki T, Nakayama N, Yonezawa S, et al. Evaluation of brain tumors using dynamic ^{11}C-methionine-PET. *J Neurooncol.* 2012;109:115–122.
19. Chan DL, Hsiao E, Schembri G, et al. FET PET in the evaluation of indeterminate brain lesions on MRI: Differentiating glioma from other non-neoplastic causes – A pilot study. *J Clin Neurosci.* 2018;58:130–135.

Timothée Zaragori
Antoine Verger*
**Université de Lorraine*
Nancy, France
E-mail: a.verger@chru-nancy.fr

Published online Mar. 17, 2022.
DOI: 10.2967/jnumed.122.264035

Single–Time-Point Tumor Dosimetry Assuming Normal Distribution of Tumor Kinetics

TO THE EDITOR: An excellent recent review by Sgouros et al. on the multifaceted complexities of tumor dose–response was highly informative (*1*). However, it did not address a practical aspect—how to routinely implement tumor dosimetry in the context of today's stifling economic mantra of "cheaper, better, faster." The fine balancing act between clinical needs and health-care economics is an everyday challenge in any busy clinic. But there is hope, in the form of single–time-point dosimetry as a compromise for resource-intensive multiple–time-point imaging.

Previous work by Hänscheid et al. on single–time-point dosimetry works well for normal organs, but its application to metastases is questionable because of widely heterogeneous tumor biology (*2*). Tumors are, by definition, inherently abnormal. Therefore, the effective half-life (T_{eff}) of any tumor type will have a wide spread of values. This means that a single average T_{eff} defined for a tumor type might not be sufficiently personalized to an individual patient.

An alternative framework for single–time-point tumor dosimetry is proposed here to complement that by Hänscheid et al. (*2*). It assumes a normal distribution of tumor T_{eff} around its mean and uses ± 1 SD to rationalize tumor T_{eff} values for faint (poor), mild (weak), moderate (good), and intense (excellent) tumor avidity. Whichever method of single–time-point tumor dosimetry the user eventually chooses will depend on whether each method's assumptions are reasonably valid for the patient at hand.

To illustrate this alternative method, let us consider ^{131}I-avid bone metastases from differentiated thyroid cancer. For this exercise, it is necessary to quote preliminary data. From a very small dataset of 8 bone metastases by 2 studies (6 lesions) and 2 lesions from our own data, the mean tumor T_{eff} in ^{131}I-avid bone metastasis prepared by thyroid hormone withdrawal was approximately 4.07 $\pm$ 2.52 d (*3,4*). Its wide SD reflects the highly heterogeneous biology of metastases.

Next, we invoke the central-limit theorem to assume a normal distribution of tumor T_{eff} around its mean. This assumption is obviously false in the current example of only 8 lesions but will eventually trend closer to the truth with future additional data. Within this normal distribution framework, bone metastases that are visually assessed to have faint ^{131}I avidity will be to the left of -1 SD (T_{eff}, $<$1.55 d), mild avidity will be at -1 SD (T_{eff}, 1.55 d), moderate avidity will be at the mean (T_{eff}, 4.07 d), and intense avidity will be at $+1$ SD (T_{eff}, 6.59 d). The visual classification of ^{131}I avidity may be referenced to the liver, analogous to the Krenning score (*5*).

Lesion mass is measured by sectional volumetry. Lesion activity at time t (d) after administration of ^{131}I is measured by calibrated scintigraphy. Finally, the tumor-absorbed dose (Gy) may be calculated by the method described by Jentzen et al., which assumes a linear initial time–activity concentration rate and a time to peak tumor uptake of 8 h, followed by monoexponential clearance in accordance with tumor T_{eff} (*6*). This alternative method of single–time-point dosimetry could also be applied to ^{131}I-avid soft-tissue metastases, with preliminary data suggesting that the mean tumor T_{eff} prepared by thyroid hormone withdrawal could be approximately 2.55 $\pm$ 0.35 d (*7,8*).

REFERENCES

1. Sgouros G, Dewaraja YK, Escorcia F, et al. Tumor response to radiopharmaceutical therapies: the knowns and the unknowns. *J Nucl Med.* 2021;62(suppl 3):12S–22S.
2. Hänscheid H, Lapa C, Buck AK, Lassmann M, Werner RA. Dose mapping after endoradiotherapy with ^{177}Lu-DOTATATE/DOTATOC by a single measurement after 4 days. *J Nucl Med.* 2018;59:75–81.
3. Eschmann SM, Reischl G, Bilger K, et al. Evaluation of dosimetry of radioiodine therapy in benign and malignant thyroid disorders by means of iodine-124 and PET. *Eur J Nucl Med Mol Imaging.* 2002;29:760–767.
4. Pötzi C, Moameni A, Karanikas G, et al. Comparison of iodine uptake in tumour and nontumour tissue under thyroid hormone deprivation and with recombinant human thyrotropin in thyroid cancer patients. *Clin Endocrinol (Oxf).* 2006;65:519–523.
5. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with ^{68}Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. *Radiographics.* 2015;35:500–516.
6. Jentzen W, Freudenberg L, Eising EG, Sonnenschein W, Knust J, Bockisch A. Optimized ^{124}I PET dosimetry protocol for radioiodine therapy of differentiated thyroid cancer. *J Nucl Med.* 2008;49:1017–1023.
7. Maxon HR, Thomas SR, Hertzberg VS, et al. Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. *N Engl J Med.* 1983;309:937–941.
8. Kumar P, Bal C, Damle NA, Ballal S, Dwivedi SN, Agarwala S. Lesion-wise comparison of pre-therapy and post-therapy effective half-life of iodine-131 in pediatric and young adult patients with differentiated thyroid cancer undergoing radioiodine therapy. *Nucl Med Mol Imaging.* 2019;53:199–207.

Yung Hsiang Kao
The Royal Melbourne Hospital
Melbourne, Australia
E-mail: yung.kao@mh.org.au

Published online Dec. 21, 2021.
DOI: 10.2967/jnumed.121.263669

Reply: Single–Time-Point Tumor Dosimetry Assuming Normal Distribution of Tumor Kinetics

REPLY: We thank Dr. Kao for carefully reading our article (*1*) and for illustrating the value of single–time-point imaging in the practical implementation of patient-specific dosimetry for radiopharmaceutical therapy. We chose to focus on fundamental knowns and unknowns, particularly tumor dose–response relationships, rather than addressing the admittedly challenging logistics of patient-specific dosimetry. As noted in Dr. Kao's letter, single–time-point formulations exist that may be applied to normal-organ and tumor-absorbed doses, although due to the potentially larger variability in tumor kinetics there may be larger error associated with application to tumor. However, the error in the tumor activity quantification step, depending on tumor size, likely dominates the uncertainty in the dose calculations. Overall, the uncertainty associated with single–time-point methods is unlikely to be clinically impactful. Clinical experience suggests that a severalfold difference in tumor-absorbed dose is needed to overcome the impact of differences in tumor radiosensitivity, dose distribution within the tumor, dose-rate differences, and other biologic effects that impact tumor response to therapy in patients.

Recognizing the imperative of achieving the right balance, we would promote an approach that enables the treating physician—in establishing treatment doses—to consider the multifaceted trade-offs among absorbed dose accuracy, health economics, the challenges of a busy clinic, and the clinical aspects of the disease. By defining a level of certainty or uncertainty in all calculated absorbed dose values, including those obtained by reduced–time-point or single–time-point methods, the treating physician is provided the information needed to make what is ultimately a clinical decision for a specific patient. If, on the basis of the disease extent and endpoints to be achieved, the physician seeks greater precision in the normal-organ and tumor-absorbed dose estimates, an extended multiple–time-point imaging protocol may be devised in conjunction with the medical physicist.

It is encouraging that in addition to the work described in the letter, the loss of accuracy associated with using a single imaging time point compared with using multiple time points has been recently investigated. Among the ever-growing list of papers in this area, we note the early work on peptide receptor radionuclide therapy by Madsen et al. (*2*) and Hänscheid et al. (*3*) and the more recent extension of this approach to other RPTs by Hou et al. (*4*) and Jackson et al. (*5*).

We thank Dr. Kao and *The Journal of Nuclear Medicine* editor-in-chief for giving us the opportunity to address this important topic.

REFERENCES

1. Sgouros G, Dewaraja YK, Escorcia F, et al. Tumor response to radiopharmaceutical therapies: the knowns and the unknowns. *J Nucl Med.* 2021;62(suppl 3):12S–22S.
2. Madsen MT, Menda Y, O'Dorisio TM, O'Dorisio MS. Technical note: single time point dose estimate for exponential clearance. *Med Phys.* 2018;45:2318–2324.
3. Hänscheid H, Lapa C, Buck AK, Lassmann M, Werner RA. Dose mapping after endoradiotherapy with ^{177}Lu-DOTATATE/DOTATOC by a single measurement after 4 days. *J Nucl Med.* 2018;59:75–81.
4. Hou X, Brosch J, Uribe C, et al. Feasibility of single-time-point dosimetry for radiopharmaceutical therapies. *J Nucl Med.* 2021;62:1006–1011.
5. Jackson PA, Hofman MS, Hicks RJ, Scalzo M, Violet J. Radiation dosimetry in ^{177}Lu-PSMA-617 therapy using a single posttreatment SPECT/CT scan: a novel methodology to generate time- and tissue-specific dose factors. *J Nucl Med.* 2020;61:1030–1036.

George Sgouros*
Yuni K. Dewaraja
Freddy Escorcia
Stephen A. Graves
Thomas A. Hope
Amir Iravani
Neeta Pandit-Taskar
Babak Saboury
Sara St. James
Pat B. Zanzonico
**Johns Hopkins University*
Baltimore, Maryland
E-mail: gsgouros@jhmi.edu

Published online Mar. 10, 2022.
DOI: 10.2967/jnumed.121.263717