DUKE UNIVERSITY MEDICAL CENTER
Department of Radiology

June 6, 2019

Dr. Christopher Palestro

Chairman of the Advisory Committee on the Medical Use of Isotopes

Nuclear Regulatory Commission

Dear Dr. Palestro,

I am a diagnostic radiologist at Duke University Medical Center, and I also have specialty certification in Nuclear Radiology (American Board of Radiology-Nuclear Radiology,1977, Cert. #20014). In my entire 40-year career in radiology I have been focused on means to improve the reproducibility of results that patients receive when they have clinical imaging studies done. From my earliest days in radiology (1978-present) I have repeatedly lectured and written that patients should get the same result if they go to the radiology department on a Wednesday than if they go on a Tuesday. Sadly, that is too often NOT the case. The reasons for this day-to-day variability are complex and reflect the use of different scanners, software, technologists, local operating procedures, and different radiologists. (As an example of my long-term interest and concern about this issue I list one of my early (1983) references at the bottom of this letter, pertaining to the variability in interpretation of lung ventilation-perfusion scans.)

One strategy to reduce variability, and a very important one, is to extract objective, reproducible, quantitative results from clinical imaging scans. Since all clinical imaging studies today are digital, this is very feasible. In 2007, with support from the Radiological Society of North America (RSNA), I left the National Cancer Institute (NIH) and formed the Quantitative Imaging Biomarkers Alliance (QIBA) [https://www.rsna.org/en/research/quantitative-imaging-biomarkers-alliance]. QIBA now has about 20 committees working on a variety of quantitative imaging biomarkers, and over 1000 participants representing more than 150 stakeholder entities and organizations. The FDA recently released a draft guidance for quantitative medical devices [https://www.fda.gov/media/123271/download] and they reference QIBA and some of our QIBA publications as the source for their definitions and concepts used in the guidance (Ref 2 below is in the Guidance).

One of our first QIBA committees dealt with the standardized uptake value (SUV) from FDG-PET scans [http://qibawiki.rsna.org/images/1/1f/QIBA_FDG-PET_Profile_v113.pdf]. Rigorous attention must be paid to all potential sources of variance in order to obtain reproducible, clinically meaningful SUV results. This is entirely possible in nuclear medicine departments that care about the quality of their results.

Because of my interest and expertise in the issues of imaging scan quality assurance and quantification, Ron Lattanze of Lucerno contacted me a couple of years ago to provide scientific consultation services to Lucerno, primarily involved in reviewing and editing their draft scientific publications. However, I have

no financial interest in the company or their products, and I am not being paid to write this letter. I attended the NRC meeting on April 3, 2019, and am writing this letter to add my perspective to the discussion that occurred at that meeting.

There is no question that reproducible, quantitative SUV results from FDG-PET scans are increasingly viewed as important in clinical oncology – both in routine clinical practice as well as in clinical trials. Here are some supporting points:

- In 2010 a colleague of mine, Tracy Jaffe, and I surveyed several hundred oncologists at NCI-funded cancer centers about tumor measurements (mostly about measurements on CT), and found that more than half of oncologists also expected SUV to be provided from FDG-PET scans (ref 3). My interactions with oncologists in many venues over the past decade indicates that the proportion who want to use SUV in patient management decisions is steadily increasing,
- In 2018 the ACR approved a quality performance measure entitled: Measure 4: Use of Quantitative Criteria for Oncologic FDG PET Imaging [https://www.acr.org/-/media/ACR/Files/Quality-Programs/Diagnostic-Imaging-2018-Measure-Set-Final.pdf?la=en], which says in part: "Final reports for FDG PET scans should include at a minimum: … d. At least one lesional SUV measurement OR diagnosis of "no disease-specific abnormal uptake". And it goes on to note: "Often injection-site infiltrates, such as arms, or attenuation-correction errors can significantly alter SUV values in lesions, leading to false conclusions." Thus, providing an accurate SUV result for ***every*** cancer patient is an expected performance measure by the American College of Radiology.
- The 2018 Guidelines of the EANM, referenced on the SNMMI web site [http://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=6414&navItemNumber=10790#Onc], state: "Report any problems with FDG administration and image the injection area if extravasation is suspected." This acknowledges that extravasation is a problem to be avoided, but it leaves open the question as to how an extravasation would "be suspected".
- A recent example from the oncology literature concerning the increasing interest in using SUV data comes from the Eighth Edition of the Cancer Staging Manual (Ref 4), where the chapters on lung and breast cancer staging (written by oncologist expert panels) recommend that SUV values now be recorded into all cancer registries at all cancer centers:

  P. 441 (lung) "PET should provide the following information:

  a. Presence of normal or abnormal uptake in the primary tumor and quantification by maximum standardized uptake value (SUV-max).
  b. Presence of normal or abnormal uptake in hilar and mediastinal nodes and quantification by SUV-max."

  "Although SUV-max is subject to many intra- and interinstitutional variations, it is important to record it at initial staging to assess metabolic tumor response after treatment, especially after induction treatment to evaluate the possibility of tumor resection. SUV also has shown prognostic value, at least for Stage I-III squamous cell carcinoma and adenocarcinoma."

  p. p 601 (breast) - "18F-FDG-PET reports should include standardized uptake values (SUVs) of the identified lesions."

- Manufacturers are promoting the accuracy and precision of SUV from their devices, because increasingly their customers understand the value of this and expect such precision:

  [https://www.gehealthcare.com/products/molecular-imaging/discovery-mi]

  https://www.siemens-healthineers.com/en-us/molecular-imaging/xspect/syngo-via/technical-details

  https://www.usa.philips.com/healthcare/product/HC882456/ingenuity-tf-petct-system

  https://us.medical.canon/products/computed-tomography/celesteion/technology/

  All of the PET/CT scan manufacturers strongly emphasize in their marketing materials the quantitative ability of their devices, and they would not invest the engineering resources to accomplish this if they did not believe their customers wanted this level of quantitative accuracy. But obviously these devices cannot provide accurate and reproducible SUV calculation if there has been infiltration of the injection.

My comments above have been focused on the need for accurate and reproducible quantitative results in oncologic FDG-PET scans because that is my primary area of expertise. However, the literature clearly supports the need for similar reproducible quantification in several other clinical areas, such as cardiology. You have an expert from that domain and a thought leader regarding the importance of quantification on your committee - Vasken Dilsizian, M.D (Ref 5) – and he could certainly provide more context for the cardiology arena and other clinical applications. For example, a recent joint position paper from the SNMMI and ASNC on myocardial blood flow measurements (Ref 6) includes this point:

- "Consistent tracer injection profiles improve the reproducibility of MBF measurements."

Similar publications can be found recommending rigorous image acquisition parameters for PET scanning of cardiac inflammatory conditions (Ref 7), sarcoidosis (Ref 8) and many other conditions.

As discussed at the April 3, 2019 NRC meeting, infiltrated injections of FDG can also adversely affect qualitative, visual interpretations of oncologic PET studies, and I will not elaborate on that here because my professional focus has been on the need for reproducible quantitative results. Also, as stated at the April 3 meeting, and documented in the various materials provided to the committee by Lucerno, infiltrated injections are much more common in nuclear medicine than most people realize, and this is a fixable problem. The incidence of infiltrations in other aspects of healthcare delivery is much lower, and there is clear evidence that the rate of infiltrations can be significantly reduced by the standard QA methodology of documenting the occurrence and providing feedback to those responsible.

I strongly endorse the current process of having the NRC and ACMUI re-evaluate the 1980 NRC policy that states that infiltrations are virtually impossible to avoid and therefore should not be considered a misadministration or a reportable event, even if the infiltration exposed patients to radiation levels that exceed Subpart M reportable limits.

I strongly encourage the NRC and ACMUI to modify this 1980 policy and remove the infiltration reporting exemption. Such a change in policy would lead to a significant improvement in the reproducibility of SUV measurements, and greatly improve their clinical usefulness. This will translate into a major benefit to patients in this era of precision medicine.

Thank you for the opportunity to provide these thoughts and opinions,

Sincerely,

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References:

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