MTV measurements using the same software was 91% for the method that uses 41% of maximum SUV and more than 95% for all other methods, and we considered this to be good agreement (*1*). The success rate of MTV measurement was unaffected by scanning conditions (whether compliant or not with the EANM Research Ltd. harmonization program) and the presence or absence of subsequent disease progression. The uptake time influenced the success rate of measurements for the method that uses 41% of maximum SUV and the method that uses majority vote 3, which were less successful with longer uptake times.

Laffon and Marthan propose that MTV cutoffs derived from PET data to guide discrimination of prognosis should be accompanied by upper and lower confidence limits based on measurement uncertainty. The main purpose of our work was not to derive cutoffs to discriminate prognosis but to take a first step to answer a methodologic question, which was to determine the optimal automatic segmentation method or methods for MTV to apply in a larger cohort. The criteria in our study focused on 2 aspects. First, did the MTV measurement methods generate plausible total tumor burden segmentations? This was prioritized over precision, as good repeatability does not necessarily provide meaningful results. Thereby, whether such (known) precision should subsequently be used to define a threshold uncertainty or gray zone is a matter of effect size in the studied population and the intended use of the biomarker. Second, to apply a method clinically or in trials, the segmentation and workflow should be fast and easy to use and have minimal observer interaction. By applying these criteria, we identified 2 candidate methods (majority vote 2 and the method based on a fixed SUV threshold of 4.0 g/mL) that can be considered for further MTV biomarker validation. For individual patient assessment to guide prognosis and when the ultimate goal is to offer personalized treatment, MTV should ideally be assessed as a continuous variable. Then, cut points and measurement errors or misclassification become less relevant.

We presented data on discriminatory power to confirm similarity for the different segmentation methods as shown previously (*2*) and to support the argument that choice of method can be based on ease of use and success rates in giving plausible volumes under various conditions. For the current study, we used a case-control design to test parameters that might influence the best segmentation method—meaning that the patient population and any derived cutoffs would not be representative of usual clinical practice. We are progressing with MTV measurement in a large warehouse of clinical and scan data in patients with non-Hodgkin lymphoma (https://petralymphoma.org/). Sufficient data are required to derive robust optimal MTV cutoffs for training, validation, and test datasets. In these studies, measurement error, confidence limits, and uncertainty will be considered.

Finally, MTV is a robust predictor of prognosis in diffuse large B-cell lymphoma but will likely need to be factored into an algorithm with baseline clinical factors, including the international prognostic index (*3*), and potentially with emerging biomarkers that reflect tumor dissemination and molecular heterogeneity (*4,5*) and dynamic response markers (*3,4*).

DISCLOSURE

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Sally F. Barrington*
Ben G.J.C. Zwezerijnen
Henrica C.W. de Vet
Martijn W. Heymans
Ronald Boellaard*
**St. Thomas Hospital,*
London SE1 7EH, U.K.
E-mail: sally.barrington@kcl.ac.uk

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Data-Driven Motion Correction in Clinical PET: A Joint Accomplishment of Creative Academia and Industry

TO THE EDITOR: I read with great interest the recent *JNM* article by Walker et al. comparing data-driven and hardware-driven motion correction technologies in PET (*1*). The former is an important innovation, and its transition into the marketplace is exciting to see. Publications such as this one play a pivotal role in the technology's acceptance and broader dissemination. However, this work is very similar to work from our group published in 2016 (*2*), and unfortunately, our publication was not properly referenced.

Like Walker et al., we compared nongated, software-gated, and hardware-gated images head-to-head in a large set of clinical PET scans, using quantitative analysis of lesion uptake and qualitative masked reviewer scoring of image quality, with similar results—a statistically significant preference for software-gated images over hardware-gated images and with similar ratios of performance metrics. There are, of course, subtle differences between the gating approaches, and Walker et al. note that their work validates newly available commercial technology. Given that this work focused on commercial product testing, it should add scientific context to note that the *key points* they presented also describe our earlier findings.

Also, in their closing discussion Walker et al. suggest that data-driven gating with quiescent-period sorting is a practical motion correction strategy but that retention of more than 50% of coincidences may be required before respiratory gated PET imaging can dependably support the clinic. We are happy to share that we have also studied this issue, finding that clinical PET data support a spectrum of ideal or optimal bin sizes throughout a given population and, ultimately, that no single bin size will ensure maximum benefit, or even any benefit, for any given patient (*3*). The implication, and what we have shown in our work, is that the legacy of *one-size-fits-all* binning strategies could be improved upon with a *data-conforming binsize* one, and make the motion correction effort better suited for routine clinical use.

The commercial technology discussed in the article of Walker et al. is GE Healthcare's MotionFree product. To the credit of the company, it recognized the potential of data-driven motion correction and developed a product to translate this potential to clinic settings. The algorithms used in GE Healthcare's product, and in our 2016 and earlier publications (*2–5*), are remarkably similar.

Data-driven motion correction has evolved over the last two decades, and our group has been active in its development. In 2007, we recognized that, at the data level, motion in PET is captured and recorded in localized signal fluctuations. To our knowledge, we were the first to demonstrate the ability to characterize patient motion through direct constructive combination of time–activity signal fluctuations in the data acquired, an original idea that at the time improved significantly on the strategy of tracking geometric or center-of-mass–type motion (*4–7*). In recognizing the importance of practicality, our group was also the first, to our knowledge, to consider and demonstrate that processing can be accelerated to virtually real time through strategic collapsing of raw (i.e., sinogram) data (*8*). Notably, these innovations provided proof of principle and formed the basis of most data-driven gating publications since. Additionally, we believe that our group was the first to discuss and demonstrate the concept of fully automated workflows as a uniquely practical strategy for bringing robust motion management into the clinic (*9–11*). We developed innovative spinoff concepts, such as using a quality factor (defined as the ratio of signal in respiratory and nonrespiratory temporal frequencies in our collected motion trace) to determine a priori the capacity of the signal to usefully correct a patient scan (*7*) and to modulate bed acquisition times based on information from such signals for practical clinical integration (*10*). It is gratifying that the MotionFree product integrates all the foregoing innovations originally presented in our earlier publications.

The overlap between our motion characterization innovation and the principal-component analysis algorithm supporting the GE product has not yet been articulated in literature, and is presented here for context and comparison. In the years 2007–2010, our group developed the idea of strategically combining the time evolution of raw PET signal to characterize patient motion and suggested that it is likely the methods could be improved with further development of signal weighting (*5,7,8*). In 2011, for example, Thielemans et al. investigated this possibility by integrating a well-established mathematic function of principal-component analysis to calculate these weighting factors (*12*). Our recent comparisons between principal-component analysis–based weighting and our original constructive combination-based methods have not yet been published, but they show that the 2 methods perform comparably or, in many cases, virtually identically (*13*)—a likely consequence of the fact they are derived from the same deconstruction of signal. It is, therefore, no surprise that the results of Walker et al.'s clinical assessment and ours are so similar. This is an important result because it indicates that the data-driven gating technology, based on combining spatially clustered signal fluctuations, can perform comparably across different centers, vendors, and implementations.

In data-driven motion management, our field is witnessing the culmination of a physics innovation concept-to-impact cycle, with GE Healthcare providing a first-to-market product (for general PET respiratory motion correction). Many research scientists who began this journey over a decade ago have contributed original ideas to this effort (*12,14–20*). Alongside others, our group contributed to inventing the technology, enabling its practicality, advocating for its consideration, and demonstrating its clinical utility. In the process, we found researchers eager to cooperate, vendors who offered support, and an effective process for solution development that built off each other's accomplishments and ideas. We also found challenges, which illuminated prospects to expand our field's infrastructure to better support data-driven innovation. These opportunities include evolving our understanding of data as a resource; opening pathways for data innovation to reach the market/clinic; and fostering a community that embraces new concepts for innovation, which we expect to come with a rapidly advancing digital landscape (*21–23*).

Ultimately, our goal should be to transition to a field where data science innovation is only limited by our imagination and not by a legacy infrastructure, and we are presented now with a chance to build that field. The path there is best supported with allied cooperation, inclusive visions, and shared successes.

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Adam L. Kesner
1250 First Ave., Room S-1119E (Box 84)
New York, NY 10065
E-mail: kesnera@mskcc.org

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REPLY: Dr. Kesner's letter regarding our recent publication (*1*) raises several useful points. We wholeheartedly agree that data-driven gating is an important innovation. Indeed, the launch of a commercial implementation provides an opportunity for celebration of this success and for reflection on the journey. The many teams involved in both academic institutions and industry should be rightly satisfied by this achievement, and it should spur them and others to continue pushing for further improvements and innovations for the benefit of the many patients whom we humbly serve.

We are grateful to Dr. Kesner for raising awareness about some current and past developments relating to data-driven gating in PET, including his own valuable contributions and those of his coworkers. He has championed this field for many years (*2–4*). We do, however, note that although commercial developments often take inspiration from academic publications, such developments can also include specific innovations or implementation details that are kept outside the public domain. We hence take this opportunity to also acknowledge the contributions of the many exceptional scientists and developers who rarely publish in the academic literature.

In our recent work, we cited the work of Dr. Kesner in both the introduction and the discussion but made a conscious decision not to include an overview of the general development of data-driven gating techniques. Instead, we provided key references that relate to the specific commercially developed solution that our manuscript concerned. Likewise, and as noted in our discussion, we chose not to include an extensive comparison to different algorithms. Rather, we chose to keep our discussion focused on aspects of the commercial solution and to keep our manuscript within the journal's word limit. We considered that the main interest in our work would come from that part of the *JNM* readership who directly use these techniques as health-care professionals. For this subset of the readership, the performance of the clinically available software and the limitations of our testing were considered the most important topics for discussion, and these were prioritized over a comparison of the performance of different algorithms or software that is currently absent from the clinic. Although an extended discussion of the many unapproved data-driven gating algorithms (and their differences) had interest and value, it did not make the final cut. To give some justification, consider the length of the letter from Dr. Kesner, which covers just some of these points: it is one third the word limit for our entire manuscript. We also feel that a comparison of the commercial solution with other algorithms is best achieved via a dedicated study on a common dataset. We hence respectfully disagree with the assertion that we did not "properly" reference his work, or that his works have not been acknowledged. In fact, they are acknowledged through various citations and discussions in each of our recent publications on this topic (*1,5,6*). We are happy to acknowledge them once again.

Because the translation of this technology into a clinical product is an exciting landmark, we suggest that now may be an appropriate moment for others to provide an objective review of this technology and the potential for further development.

DISCLOSURE

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Matthew D. Walker*
Kevin M. Bradley
Daniel R. McGowan
**Radiation Physics & Protection,*
Churchill Hospital, Old Rd.
Oxford, OX3 7LE, U.K.
E-mail: matthew.walker@ouh.nhs.uk

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