

Standardization of Quantitative Imaging: The Time Is Right, and ^{18}F -FDG PET/CT Is a Good Place to Start

Enhanced techniques have made quantitative medical imaging increasingly important to clinical research (1,2). Performance expectations, and particularly the rigor with which performance is statistically characterized, are high in the research context. Even though individual factors may have a relatively small (5%–30%) effect on quantification by themselves, the overall cumulative effect on quantitative outcome and its precision can be large (50%–100%) (3). A great deal of work is needed to achieve effective implementation, not just in individual laboratories but ultimately in general use (4,5). Success will be achieved when quantitative imaging results are broadly comparable and are widely

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disseminated rather than being possible only in highly selective and controlled environments.

Two important articles on this topic are included in this issue of *The Journal of Nuclear Medicine*. Graham et al. (6) survey the imaging procedure and analysis protocols across 15 leading institutions, including the 8 Imaging Response Assessment Teams. Meanwhile, Beyer et al. (7) cast a wider net inclusive of a large range of centers drawn from the Academy of Molecular Imaging databases with responses back from 128 institutions. Despite the very different approaches taken in selecting

institutions for their respective surveys, the results are remarkably concordant with respect to how differently sites conduct scans. For example, sites vary across all experience levels with regard to such issues as uptake period, dietary requirements, handling of diabetic patients, weight-based activity injection, handling of extravasations, use of contrast in CT, relationship between diagnostic CT and CT performed for attenuation correction, application of glucose corrections, and ultimately the ability to compare numbers across scanner models and makes, which involves such issues as acquisition timing and reconstruction methods. Differences in how studies are reported, formats used for image data and metadata, level and type of training, and reading practice (e.g., site vs. central reads) add to the issues. It would seem that standardization is a long way off, if judged from the results of these critical reports.

Concern about these topics is by no means new. An often-cited article by Hoffman et al. addressed the issue in 1984 (8). By 1999, key articles had been published by Weber et al. (9) declaring that reproducibility was possible and by Young et al. (10) articulating guidelines to improve consistency. However, several articles in the 2003–2004 time frame, such as by Bourguet et al. (11), Hallett (12), Feuardent et al. (13), and Marsden (14), suggested the need for more work to develop, refine, and promulgate consistent protocols if we were to achieve quantitative accuracy. By 2006–2007, new protocol recommendations were published, including articles by Shankar et al. (15), Delbeke et al. (16), Hallett et al. (17), and Westerterp et al. (18). These studies showed that strict standardization of all aspects of imaging is required to obtain

quantitative, accurate, reliable, and precise results. Moreover, it was becoming increasingly evident that the need to align guidelines across groups was as important as the need for individual groups to make recommendations on what those guidelines could be.

Achieving standardization to minimize variation in multicenter studies and allow comparability of results from different trials necessitates a cooperative structure. Although many stakeholders are interested in this goal, none can accomplish it alone. For example, cooperative groups such as the American College of Radiology Imaging Network, the European Organization for Research and Treatment of Cancer, Cancer and Leukemia Group B, and the Southwest Oncology Group have been established to pursue collaborative clinical studies, as has the SNM Clinical Trials Network. However, industry engagement both by the users of biopharmaceuticals and by suppliers of medical devices and software is also necessary. A unifying platform is critically needed to facilitate cooperation among all the stakeholders.

The process of convergence has quickened in recent years. Wahl has published a proposal for response assessment that incorporates protocol guidance (19). Based on work initiated in The Netherlands but with cooperation from other countries such as Germany and the United Kingdom (20), the European Association of Nuclear Medicine has arrived at consistent protocol guidance across Europe (21). Fukukita has reported on similar efforts in Japan (22). Meanwhile, the Food and Drug Administration garnered a high degree of interest at an April 2010 meeting jointly hosted by the SNM and the Radiological Society of North America dealing with stand-

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ardization to control variability and inconsistency in methods of acquisition, interpretation, and analysis of images in clinical trials and specific ways to address the Food and Drug Administration regulatory expectations for PET (23). The Quantitative Imaging Biomarkers Alliance (24), using the Uniform Protocols in Clinical Trials process, has extracted content from various guidelines into a consolidated document to aid in the consensus process (25), and this document was used as the base material for a consensus protocol built by leaders from the United States, Europe, and Asia at the World-Wide Standardization of FDG PET Protocols for Multicenter Clinical Trials, convened by the SNM at its June 2010 meeting in Salt Lake City.

The articles by Graham et al. (6) and Beyer et al. (7) are important because they establish the scope of work before us in education and communication. They identify areas in which standardization has been easier versus areas in which it has been more difficult. These findings allow focus to be placed on what it will take for the collective efforts to make a practical impact.

Although there is a quickening sense of progress toward the desired state of having comparable quantitative imaging results across suppliers and across centers, it is equally true that there is still the daunting challenge ahead of how to promulgate standardization across our varied centers. We believe that the field is ready for this stage as it has never been before, with visible steps that indicate researchers are both willing and capable of organizing to realize the potential. Standardization is a prerequisite to establishing ^{18}F -FDG PET/CT as an accepted quantitative imaging biomarker and will pave the way for definition of metabolic response criteria, both for use in clinical trials and for patient care. Efforts such as those by

Graham and Beyer enable us to focus on the right issues, whereas the convergence and consensus-building work inform us of where we wish to arrive. What remains is for each of us to stay involved and play a part as we recognize the common good these efforts help us to do together.

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