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Quantitative imaging is growing in popularity and clinical utility, and this special section of the *Journal of Medical Imaging* features articles that present results of this method across medical imaging modalities and applications. Quantitative imaging is the science of extracting numeric information from medical images to measure or predict a patient's health. Larry Clarke was an early and enthusiastic champion of quantitative methods in medical imaging, and the fullness and diversity of this issue stand as a tribute to his dedication to the field. Sadly, Larry passed away in April 2016 before many aspects of his vision for quantitative imaging could be realized.

Larry Clarke was a distinguished medical physicist and chief of the Imaging Technology Development branch of the Cancer Imaging Program in NCI. In this position, he had many diverse responsibilities. Not only did he create new research funding initiatives in the form of program announcements for basic and translational imaging research, he also mentored NCI program directors in methods of government program management. He is remembered for the many invited presentations and lectures he gave, both inside and outside the NCI, as well as for his participation in various professional societies such as AAPM and SPIE, and the many publications to which he contributed. In addition, he served on many committees and workshops,¹ promoting quantitative imaging as a method to measure response to therapy during clinical trials.

Larry earned his PhD in medical physics from the National University of Ireland in 1978, and soon traveled to the United States to begin his career. Academic interests in medical imaging led him to the University of South Florida and the H. Lee Moffitt Cancer Center and then to the University of Miami. More recently, he held a position as adjunct professor at George Washington University. In 1999 he opted for a change in career by accepting a government position with the National Cancer Institute (NCI) as branch chief in the newly formed Cancer Imaging Program. This decision set him on a career path that benefitted not only him, but also the many scientists, clinicians, and others who have had the opportunity to interact with him.

Larry's passion for quantitative imaging led him to champion the idea of creating public databases of images and patient outcomes that would be of use by scientists interested in developing software for measuring or predicting patient response to cancer therapy by processing the information contained in the archived medical images. The Lung Imaging Database Consortium (LIDC)² and the Reference Image Database for Evaluation of Response (RIDER)³

were the result. Today, The Cancer Imaging Archive (TCIA) can trace its origins to these early database activities.

The value of public databases and quantitative imaging methods can be realized only if standards for medical imaging are created and used. These standards include protocols for data collection, image feature extraction, analysis of the information, and uniform methods for data archiving. The reduction of bias and variance through standardization of data collection and processing can reduce the cost and size of clinical trials. Precision algorithms that extract quantitative information from the resulting images can then provide clinicians with reproducible information on tumor progression or regression without qualitative guesswork. In addition, the use of standards as a part of quantitative imaging methods permits the collection and consolidation of data from multisite clinical trials that use different scanner platforms. These advantages of quantitative imaging were obvious to Larry, and he eagerly confronted the challenges of establishing the many standards needed to realize these quantitative advantages.⁴

In 2007, after two successful experiences with research network organizations and executions,⁵ Larry and I sat at lunch and planned for a network emphasizing quantitative imaging in the clinical environment. The concept for the new network was written, and by early 2008, after approval by NCI management, the first teams joined the Quantitative Imaging Network (QIN) through the NCI peer review process to begin collaborative research.⁶ Over the next few years, the network grew steadily with Larry as the science officer while I served as the program director. Our activities in the QIN were similar to characters in a wagon train working its way westward in the nineteenth century. I was the wagon master, staying close to the trail and the wagons, solving the day-to-day issues, while Larry was the scout, riding over the hills to explore new paths and directions that would lead the wagon train to its destination. This level of teamwork was highly beneficial for the network, and the number of participants grew to 28 by 2013.

When organizing a collaborative network of research teams, there is always the concern that participants might prefer to act alone rather than collaborate in the group. To minimize this "siloing," we chose to operate the QIN under an executive committee consisting of the principal investigators from each research team. This committee meets once each month by teleconference to discuss direction of the network, to plan interaction with professional societies such as RSNA, SPIE and others, and to set policies and procedures for the network in areas such as joint publications, sharing of data, and the conduct of algorithm challenges. This oversight structure is an important component to the collaborative success of

the network. In addition, several working groups were created, focusing on issues that were of concern to the entire network. The use of informatics, for example, is important to each research team, so a working group was formed to deal with informatics issues on behalf of the entire network. Other working groups include clinical trial design and development, PET/CT, MRI, and image analysis and performance metrics. These working groups remain active today.

The formation of working groups to which each team provides members has been very successful. The true nature of collaboration is realized in the individual working groups because each group is a microcosm of the entire network, focused on the specific issues of that working group rather than on the scientific activities facing each research team. Many of the joint publications coming from the QIN have originated in the working groups.⁷⁻¹⁰

Larry recognized that quantitative imaging methods and protocols could lead directly to computer-aided diagnosis in the clinical setting. Significant validation, however, would be required before computerized decision results could be trusted. This would require careful testing of computer results using images with known patient outcome. Larry emphasized the importance of the exercise called Grand Challenges. Here, developers of software algorithms created to diagnose some aspect of disease from patient images compete to determine which algorithm has the best performance characteristics as determined from desired outcome. The diagnosis could be as straightforward as a decision of which suspicious nodules are benign and which are malignant, or it could be as complex as a prognosis of which patients will respond to a chosen therapy and which will not.

An example of the use of a Grand Challenge was the LUNGx challenge reported between 2015 and 2016.¹¹⁻¹³ Here, the purpose was to test computerized classification of lung nodules seen on diagnostic CT scans as benign or malignant. The results from six radiologists reading the same data set were also included in the study. The results of the challenge are reported in Ref. 11, and have led to the generation of other challenge activities where computer diagnostic results are compared.

In his professional activities, Larry was a team player. This can be seen from the variety of coauthors on selected publications.^{14,15} He had a focused interest in quantitative imaging, but he shared it with a wide range of people. In addition, he carried his interest in quantitative imaging to the United Kingdom, South Korea, and other countries where the value of quantitative imaging could be discussed. Today, the QIN has associate members from over 7 foreign countries collaborating on methods and protocols.

The activities in the QIN are varied, as the articles from QIN members in this special section indicate. Not only are different imaging modalities being applied to different organ sites to validate cancer response measurement biomarkers, but an increased emphasis on informatics methods is being pursued. Larry recognized the value of artificial intelligence and deep learning methods as they apply to quantitative imaging and worked to initiate the Informatics Technology for Cancer Research (ITCR) program. While the emphasis of this program includes more than imaging research, a significant number of successful applications focus on imaging informatics.

Larry's work has led to many accolades and awards. He was a long-standing Fellow of the American Association of Physicists in Medicine (AAPM) and was inducted as a Fellow of SPIE shortly before his death. In addition, the American Institute for Medical and Biological Engineering (AIMBE) inducted Larry into its College of Fellows for outstanding contributions to the advancement of biomedical imaging, especially in the realm of cancer diagnosis and treatment. He published numerous peer-reviewed papers and served as associate editor for *Medical Physics*. His impact on the advancements in the field of cancer imaging cannot be underestimated, and the legacy of his work continues today.

The articles from QIN member teams in this special section of the *Journal of Medical Imaging* serve as testimony to the extent of Larry's influence in the quantitative imaging community. He was conversant on issues of magnetic resonance imaging, nuclear imaging, the use of imaging agents, and the subtleties involved in each. When making presentations before scientific groups, Larry chose to combine as much information on each slide as possible, thus reducing the total number of slides. For each highly-concentrated slide, he would carefully tour his audience around the images and bullet points, making important comments on each facet.

Despite the loss of leadership in quantitative imaging from Larry's untimely departure, advancements are being made steadily. The area of radiomics is a good example of how quantitative information from features undetectable in a qualitative reading of a clinical image can be extracted and analyzed for parameters of clinical significance. Combining information from images with other biomarker information such as from genomics or proteomics can expand the knowledge base and improve diagnostic capabilities. Larry Clarke understood this and his vision of quantitative imaging is becoming a key component in today's precision medicine.

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