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Radiomics and Imaging Genomics: Quantitative Imaging for Precision Medicine

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Throughout the history of radiology—a medical specialty that came into being shortly after the discovery of x rays in 1895—its practice involved a skilled observer (the radiologist) looking at images and transcribing observations in relation to the indications for the imaging examination and any incidental findings. Radiologists are trained to understand how appearance on imaging correlates with underlying disease/health and strive to report it in unambiguous terms. However, there is variation in interpretation among radiologists,[1,2] and even among radiologists speaking the same language, descriptive terminology varies,[3,4] thereby making impractical the mass mining of radiological interpretations for discovery of linkages between observations and specific diseases.

Despite these limitations, radiologists continued to study and report on the linkage between specific image features and underlying disease, e.g., contrast enhancement patterns of focal liver lesions on CT and malignant/benign classifications of tumors on breast images. While radiologists were busy understanding and characterizing these "imaging phenotypes," biologists were making great strides understanding the genomic basis of intracellular processes,[5] leading to the ability to characterize the "molecular phenotype" ("-omics," e.g., genomics, proteomics, metabolomics, transcriptomics, copy number, methylation) through advanced sequencing of tissue from biopsy and/or resection samples.

In the 1980s and 1990s, quantitative imaging scientists and engineers were developing algorithms for the extraction of imaging phenotypes from radiographic images for use in computer-aided detection/diagnosis and for risk assessment and prognostic/predictive tasks.[6,7] However, it wasn't until the early part of the century when researchers began exploring links between the imaging and molecular phenotypes. For example, in 2002, Huo et al. showed the relationship between computerized texture analysis of the breast parenchyma on mammography and presence of the BRAC1/BRCA2 gene mutation.[8] In 2007, Segal et al. reported that radiological observations of tumors seen on CT "systematically correlate with the global gene expression programs of primary human liver cancer" derived using microarray analysis of the resected tumor.[9] In 2008, Diehn et al. reported linkages between the imaging phenotype of glioblastoma multiforme (GBM) on MRI to the molecular phenotype derived using DNA microarray analysis[10] and survival. And in 2010, Bhooshan et al. demonstrated relationships between computer-extracted MRI phenotypes and breast cancer subtype and aggressiveness.[11] Many papers have since expanded the literature on deriving quantitative image features, deriving and reducing the interobserver variability of semantic image features, associating image features with molecular phenotypes, genetics, and outcomes, and the results of mining these associations for discovery (e.g., see Refs. 12–18).

These and other early studies gave birth to two terms that are increasingly prevalent in the literature today. Radiomics[19,20] is a name given to the science of converting medical images into computer-accessible and -searchable data. While the term radiogenomics has previously been used to describe the study of genetic variation associated with response to radiation (radiation genomics),[21] in the present context we use radiogenomics (or imaging genomics) to describe relationships between molecular and imaging phenotypes.[22] To highlight recent ongoing work in the areas covered by these terms, and promoted through the efforts of various programs including the National Cancer Institute's Quantitative Imaging Network (QIN),[23] the Quantitative Imaging Biomarkers Alliance (QIBA),[24] and the American Association of Physicists in Medicine (AAPM),[25] this issue of the *Journal of Medical Imaging* contains a Special Section on Radiomics and Imaging Genomics.

These ten JMI articles describe advances in radiomics and imaging genomics along several fronts. Nyflot et al. and Echegaray et al. explore variations in radiomic signatures as a function of stochastic noise and region-of-interest segmentation, respectively. Nyflot concludes that radiomics studies should specify standard acquisition protocols, while Echegaray demonstrates that there may be many radiomics features (specifically some gray-value statistics and textures) that are minimally affected by differences in segmentation boundaries.

Also within this special section, the value of one-dimensional gray-value statistics, as well as multiscale and -orientation gray-level variations (i.e., image textures), are demonstrated for several purposes. For example, Lee et al.

apply these metrics to tumor habitats (regions with different intensity characteristics) in MR scans of patients with GBM, and show associations with 12-month survival. Ghosh et al. show that texture features of tumors in CT scans of patients with clear cell renal carcinoma can predict specific gene mutations. Mattonen et al. show that the image texture within automatically generated regions of interest in CT scans of patients who have had stereotactic ablative radiotherapy for lung cancer treatment can be used to separate radiation necrosis from recurrence. Tiwari et al. use texture metrics on different types of MRI scans of patients treated by laser ablation for neuropathic cancer pain that were predictive of early treatment response. Finally, while most studies of texture have been centered on the tumors themselves, Dilger et al. show that texture metrics computed from regions of interest surrounding lung nodules have value in the prediction of malignancy.

Other investigators report novel frameworks for integrating radiomic and -omics data and mining the resulting databases for associations with clinical data. For example, for breast cancer, Wu et al. integrate mammographic features and SNPs with traditional risk factors to improve risk prediction, and Guo et al. show significant correlations of DCE-MRI radiomic features to clinical and genomic characteristics. Both of these and many other studies argue for continued development and expansion of large imaging[26] and -omics[27] databases utilizing standardized protocols. Finally, lest one conclude that image features are only useful in cancer research, see Xie et al. for a report on detecting ventricular-septal defects in mouse embryos through segmentation and pixel analysis.

A word of caution, however. While radiomics and imaging genomics articles continue to populate the literature, many of them (including some in this special section) (a) involve small numbers of subjects with respect to the number of radiomics features investigated, thereby raising concerns of over fitting; or (b) do not report validations in external cohorts, thereby limiting generalizability to additional patient populations, imaging by different scanner types, etc. These articles are important landmarks and vehicles for disseminating ideas, but themselves should be seen as pilot studies, suggestive of further investigation and validation. Those of us in this research community should remain conscious that correlation does not imply causation[28] and that we need to strive to fully validate and generalize our methods and results.

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