Methods and Challenges in Quantitative Imaging Biomarker Development

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Academic radiology is poised to play an important role in the development and implementation of quantitative imaging (QI) tools. This article, drafted by the Association of University Radiologists Radiology Research Alliance Quantitative Imaging Task Force, reviews current issues in QI biomarker research. We discuss motivations for advancing QI, define key terms, present a framework for QI biomarker research, and outline challenges in QI biomarker development. We conclude by describing where QI research and development is currently taking place and discussing the paramount role of academic radiology in this rapidly evolving field.

Key Words: Radiology; quantitative imaging; biomarker development.

Medical imaging has evolved dramatically since the first roentgenogram nearly 125 years ago (1). Modern techniques including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) now provide an unprecedented level of spatial detail and functional information (2).

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As medical imaging has progressed, older analog techniques have been steadily replaced with newer digital methods of image acquisition, processing, archiving, and display. This evolution has occurred in parallel with advancements in our understanding of the molecular underpinnings of disease and the rise of a more statistical and evidence-based approach to diagnosis and treatment. Medical imaging is now poised to leverage quantitative techniques in support of a wide range of clinical and research goals (3,4).

In a broad sense, quantitative imaging (QI) refers to the extraction and use of numerical/statistical features from medical images (see Box 1 for definitions of key terms). As a research field, QI includes the development, standardization, optimization, and application of anatomic, functional, and molecular imaging acquisition protocols, data analyses, display methods, and reporting structures, as well as the validation of QI results against relevant biological and clinical data (5,6). The QI concept is closely tied to that of a biomarker, defined as a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, pathologic process, or response to a therapeutic intervention (7). A QI biomarker is therefore an objectively measured characteristic, derived from a medical image, that can be correlated with anatomically and physiologically relevant parameters including disease presence, disease severity, disease characterization (particularly at a molecular level), predicted disease course (both with and without treatment), and treatment response. The Quantitative Imaging Biomarkers Alliance (QIBA), organized by the Radiological Society of North America, has formally defined a QI biomarker as "an objective characteristic derived from an *in vivo* image

Box 1: Definitions related to quantitative imaging biomarker development

Analytical validation—Demonstration of the accuracy, precision, and feasibility of biomarker measurement
Biomarker—A characteristic that is objectively measured and evaluated as an indicator of a normal biological process, a pathogenic process, or a response to a therapeutic intervention
Predictive biomarker—A biomarker intended to forecast disease course in the presence of a specific treatment
Prognostic biomarker—A biomarker intended to forecast disease course in the absence of treatment
Qualification—Demonstration that a biomarker is associated with a clinical endpoint
Quantitative imaging—The extraction and use of numerical/statistical features from medical images
Quantitative imaging biomarker (modified Quantitative Imaging Biomarkers Alliance definition)—An objective characteristic derived from an *in vivo* image measured on a ratio or interval scale as an indicator of a normal biological process, a pathogenic process, or a response to a therapeutic intervention (8)
Repeatability—The agreement between successive measurements made under the same conditions
Reproducibility—The agreement between successive measurements made with varying conditions, such as location or operator
Surrogate endpoint—A biomarker intended to substitute for a clinical endpoint
Utilization—Assessment of biomarker performance in the specific context of its proposed use

measured on a ratio or interval scale as indicators [*sic*] of normal biological processes, pathogenic processes, or a response to a therapeutic intervention." The emphasis of this definition on a ratio or interval variables would imply that tumor volumes or PET standardized uptake values would be considered QI biomarkers, because the difference or ratio between two values is meaningful, whereas ordinal variables such as Breast Imaging Reporting and Data System assessment categories would not. This strict definition is meant to guide QI research toward biomarkers that may be assessed and compared using robust statistical calculations including frequency distributions, medians, means, standard deviations, and standard errors of the mean (8).

This article, drafted by the Association of University Radiologists Radiology Research Alliance Quantitative Imaging Task Force, addresses issues related to QI biomarker research and development. A separate article from our Task Force outlines current clinical applications of QI (9). In this article, we describe motivations for QI biomarker development and discuss challenges for QI research using a three-part framework. We then provide an overview of where QI research and development is currently taking place. We conclude by discussing the particular role of academic radiology in advancing QI. Sections of this article were derived from individual miniscoping studies based on focused research questions (10).

MOTIVATIONS FOR QI BIOMARKER DEVELOPMENT

The promise of QI lies in the potential for increased precision and standardization of image interpretation, in both the research and clinical settings. Potential gains from the growth of QI include increased diagnostic accuracy; decreased variability and subjectivity of image analysis; increased automation of data reporting; more robust association of imaging findings with other biological and clinical parameters, including rigorous statistical correlations between quantitative datasets; and the opportunity for large-scale attempts to link phenotypic imaging patterns with genomic profiles (11). The development of QI is being driven in large part by the environment of evidence-based medicine in which diagnoses across the clinical spectrum are reinforced with quantitative data (12,13).

Perhaps the greatest demand for QI at present is from cancer clinical trials, where quantitative measurements of tumor response are used to determine the efficacy of investigational treatments. Imaging-based response assessment guidelines such as the Response Evaluation Criteria in Solid Tumors (14) have been used for decades and have been successfully validated against long-term patient outcomes in certain settings (15,16). However, in the era of targeted agents that may promote tumor stability rather than tumor regression (17–21), the oncologic imaging community has embarked on developing novel imaging biomarkers to identify and interrogate underlying molecular and functional changes in tissue, with the premise that these measurements will provide earlier and/or more accurate response assessment than tumor size changes (Fig 1) (22). Validated QI biomarkers reporting on different elements of tumor status may enhance drug development by establishing proof of concept for investigational agents, by facilitating selection of candidate agents for promotion to later stage testing, and by determining patient subgroups in which the likelihood of drug response is higher (23,24). QI biomarkers may also be useful for clinical care by offering the ability to stratify patients to the most appropriate treatments and by promoting earlier identification of patients with a poor response to a particular regimen (25).

Imaging researchers are responding to the demand for QI biomarkers by advancing a broad array of quantitative techniques across a wide spectrum of clinical and research indications (24,26–35). The common denominator linking all these efforts is the drive toward producing standardized, unbiased, and precise imaging data in support of the larger medical research and clinical enterprise. This endeavor involves particular research challenges, as presented in the next section.