Role of the Quantitative Imaging Biomarker Alliance in Optimizing CT for the Evaluation of Lung Cancer Screen–Detected Nodules

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Abstract

The Quantitative Imaging Biomarker Alliance (QIBA) is a multidisciplinary consortium sponsored by the RSNA to define processes that enable the implementation and advancement of quantitative imaging methods described in a QIBA profile document that outlines the process to reliably and accurately measure imaging features. A QIBA profile includes factors such as technical (product-specific) standards, user activities, and relationship to a clinically meaningful metric, such as with nodule measurement in the course of CT screening for lung cancer. In this report, the authors describe how the QIBA approach is being applied to the measurement of small pulmonary nodules such as those found during low-dose CT-based lung cancer screening. All sources of variance with imaging measurement were defined for this process. Through a process of experimentation, literature review, and assembly of expert opinion, the strongest evidence was used to define how to best implement each step in the imaging acquisition and evaluation process. This systematic approach to implementing a quantitative imaging biomarker with standardized specifications for image acquisition and postprocessing for a specific quantitative measurement of a pulmonary nodule results in consistent performance characteristics of the measurement (eg, bias and variance). Implementation of the QIBA small nodule profile may allow more efficient and effective clinical management of the diagnostic workup of individuals found to have suspicious pulmonary nodules in the course of lung cancer screening evaluation.

Key Words: Lung cancer screening, pulmonary nodules, quantitative imaging biomarker, low-dose CT scans, metrology

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INTRODUCTION

With the recent endorsement of low-dose CT screening for lung cancer in high-risk individuals by the United States Preventive Services Task Force [1], multiple medical societies and the medical community are poised to implement screening in the general population [2-5]. As screening disseminates beyond the clinical trial setting and into clinical practice, care must be taken to ensure that its effectiveness and safety are optimized. Effectiveness depends on diagnosing and treating lung cancer as early as possible, while safety relates primarily to avoiding the potential harms of unnecessary diagnostic procedures. In practice, this requires the early detection of small, noncalcified lung nodules and prompt differentiation of the few that are malignant from the many that are benign, through predominantly noninvasive means.

The risk stratification of noncalcified lung nodules detected at screening is currently based primarily on their size:

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Note: The Lung Cancer Screening Protocols described in this document are a set of reasonable protocols developed by the AAPM's Working Group on Standardization of CT Nomenclature and Protocols that are to be used in the specific context of Lung Cancer Screening. These protocols were based in part on manufacturers' Low Dose Chest protocols, but were adapted based on the Working Group's experience with the National Lung Screening Trial and other screening studies.

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solid and part-solid nodules <6 mm are rarely malignant [6-8]. Nodule size may be reevaluated with the next annual screen, which forms the basis for the ACR's Lung CT Screening Reporting and Data System (Lung-RADS™) [9]. The use of imaging to assess lung nodule size is a clear example of how using quantitative imaging in a precise, reproducible fashion to guide the clinical management of lung cancer screening is a biomarker. CT-based lung cancer screening provides a demonstration of the rationale for as well as the process by which the Quantitative Imaging Biomarker Alliance (QIBA) is working to responsibly integrate the use of quantitative imaging approaches into clinical care.

Lung nodules >10 mm in diameter are much more frequently malignant than smaller nodules and are amenable to diagnostic characterization by PET/CT and tissue sampling either percutaneously or by bronchoscopy [6-8]. In the 6- to 10-mm range, the frequency of malignancy is low but gradually increases. Needle biopsy and PET/CT often are not options because of poor sensitivity in evaluating nodules of this size, while surgical resection would be invasive and of little benefit for most nodules <10 mm because the overwhelming majority of these nodules are not cancers [6-8]. Even when malignant, nodules of this size may remain at an early stage in the short term. Thus, nodules <10 mm typically are managed by performing serial CT examinations to assess for growth rate. For nonsolid or ground-glass nodules, that size threshold may be even larger, as nodules of this type rarely exhibit malignant behavior even when as large as 20 mm [6-9].

To optimally implement an approach to screening and surveillance in clinical practice, the size classification of screen-detected indeterminate lung nodules and recommendations for their management should be consistent across clinicians. In clinical practice, size is frequently determined from linear measurements of transverse nodule diameter made manually by electronic cursor placement on a single 2-D CT section. Unfortunately, such measurements are prone to substantial variation among radiologists due to factors such as differences in the subjective identification of the CT slice to be measured, variation in the perceived boundary of the nodule, and variability in the orientation of the linear measurement [10-13]. These factors contribute to variability in the classification of screening scans with small nodules as positive (with recommendation for further diagnostic evaluation before the next annual screen) or negative (no further evaluation before the next annual screen), as well as variability in the assessment of whether growth has occurred since a prior screening scan, with resultant potential for inconsistency in recommendations for diagnostic evaluation [14].

Reducing measurement variability across screening sites could help optimize the benefits of screening, minimize the harms, and improve the assessment of screening outcomes. In addition, clinicians and patients expect and deserve objective, quantitative, and reproducible results as the basis for clinical management where possible. Quantitative methods exist for lung nodule size measurement that are automated and reproducible and have great potential for accomplishing these goals. Advances in CT technology have made it possible to obtain high-resolution images of the subcentimeter nodules most frequently encountered in screening, enabling 3-D, automated, quantitative measurements of nodule volume. Because nodules frequently are asymmetric in 3 dimensions and can grow asymmetrically, automated volumetric quantification should allow improved assessment of nodule size and growth. In addition, automated volumetric assessment presents the capability of direct volume doubling time determination, which typically ranges between 30 and 400 days for malignant lesions [15].

In the lung screening setting, the change in lung nodule size may be considered a *biomarker*, which is generally defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or a response to a therapeutic intervention" [16]. The term biomarker is often assumed to imply a laboratory test, but it can also refer to a clinical measurement such as blood pressure or the output of a clinical imaging scan. Precision in providing the necessary information to reliably inform clinical management is a requirement of any contemporary biomarker application. For laboratory (biologic specimen) assays, standard terminology and methods for evaluation and validation of measurements have become established [16]. The same concepts and approaches could and should be applied to imaging assays, but this has only begun to occur in an organized way over the past few years [17,18]. The term *quantitative imaging* has recently been formally defined by QIBA [19] as

> the extraction of quantifiable features from medical images for the assessment of normal or the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal and this process includes the development, standardization, and optimization of anatomical, functional, and molecular image acquisition protocols, data analyses, display methods, and reporting structures.