This document provides a detailed response from the QIBA CT Small Lung Nodule Profile Task Force (TF) to the concerns raised by Mike McNitt-Gray sent on September 11, 2017.

The text in black color below provide the relevant direct quotes from the McNitt-Gray September 11, 2017 letter. The text in blue is the response from the QIBA CT Small Lung Nodule Profile TF and provided to QIBA for distribution on October 7, 2017.

Fundamentally, this is a non-standard phantom using non-standard methods and even non-standard metrics. That is ok, but to be widely accepted (and widely imposed as part of compliance) it does require two major steps: (a) some explanation and demonstration of the underlying methods and what the results are actually measuring. This could be done by comparison to existing methods or use some other form of demonstration; and (b) some evidence that these have some effect on nodule volumetric measurements.

> The QIBA CT Small Lung Nodule Profile TF determined that currently existing "standard" phantoms were not adequate to meet the needs of addressing the QIBA CT Small Lung Nodule Profile's claims since the relevant nodule size window is much smaller than the precedent imaging biomarker, i.e. the RECIST criteria. In so far as most of screening will take place away from tertiary care centers, we needed a simple, inexpensive reference tool for the task of verifying the performance of a CT scanner/protocol pair throughout the full scanner field of view. In recognition of this, the TF has developed a new phantom and methods that address the QIBA CT Small Lung Nodule Profile [1] needs. TF members have presented this work numerous times in QIBA meetings, abstracts, invited presentations, and publications over the last two years. Most recently the QIBA CT Small Lung Nodule Profile TF has published an overview of quality assurance for CT lung nodule quantitative measurement which covers many of the topics described below [2].
>
> Verifying performance from iso-center out to CT scanner periphery is a requirement for the CT Small Lung Nodule TF because many small nodules present in the periphery of the lungs and CT scanners are known to exhibit worse image quality performance out in the periphery (e.g. resolution, HU bias, image noise) [6,16]. The most widely used phantom in the US, the Gammex 464 used by ACR for CT accreditation, has a stated error of +-1.5mm when measuring slice thickness and is also not capable of measuring slice thickness and in-plane resolution in a CT scanner's periphery which is required for Profile conformance. In fact, no existing "standard" CT phantom measures the image quality metrics (edge enhancement, resolution, resolution aspect ratio, linearity, spatial warping, and image noise) determined to be needed by the CT Small Lung Nodule TF throughout the full scanner field of view. In addition, the Gammex 464 phantom costs over $4,000, requires a trained medical physicist to operate, and requires significant amounts of CT scanner time to properly set up and use. The requirement of the QIBA CT Small Lung Nodule Profile is to verify that a CT scanner and acquisition protocol achieve Profile image quality characteristics each time the scanner or protocol is changed and at least once per year and do so using less than 10 minutes of CT scanner time. The reason for this time requirement is that a short evaluation time makes the evaluation possible in between patients and minimizes the impact of conformance on scanner throughput. While many academic medical centers may have the

resources to use a “standard” phantom for this task (if such a “standard” phantom were able to measure all that is needed for the QIBA CT Small Lung Nodule Profile), there are very few community hospitals that can achieve conformance with a “standard” phantom due to lack of sufficiently skilled personnel, additional phantom costs, and loss of CT scanner time. The currently proposed conformance approach and phantom in the QIBA CT Small Lung Nodule Profile costs approximately $200, measures all of the critical image quality characteristics determined to be needed by the QIBA CT Small Lung Nodule Profile, takes around 5 minutes of scanner time to scan, and with fully automated and cloud based software that runs in under 5 minutes (for a 120 slice CT phantom scan dataset), can be effectively used by a CT technologist or medical physicist for verifying conformance with the QIBA CT Small Lung Nodule Profile image quality requirements without significant burden.

While it is easy to state that a “standard” phantom and phantom analysis methods should be used, actually achieving the goals of the QIBA CT Small Lung Nodule TF with a “standard” phantom is not known to be possible. Thus, we feel the development of a new phantom and analysis methods that have been developed and tested over many years and that leverage standard methods from the literature where they help advance the goals of the QIBA CT Small Lung Nodule Profile, is a reasonable and effective path for the QIBA CT Small Lung Nodule Profile.

(a) Recently the core CT image quality modeling and simulation methods that have informed the QIBA CT Small Lung Nodule Profile were presented in February 2017 at the SPIE Medical Imaging Symposium and expanded into an SPIE Medical Imaging conference paper [3]. This paper was distributed to the QIBA volumetric CT committee during the 2017 QIBA annual meeting (May 17 to 18, 2017). As a service to the community, these methods have been made freely available through the Amazon cloud for nearly two years with over 30 international clinical sites and research groups using the methods and collaboratively discussing and helping refine the methods [4]. To our knowledge, this was the first time that such a low-cost, fully automated, and web-enabled resource has been made available to the CT imaging community. In addition, members of the QIBA CT Small Lung Nodule Profile TF have held 14 annual quantitative imaging workshops mainly focused on the measurement of lung nodules where in recent years there have been industry panels and breakout group discussions to discuss methods for evaluating conformance. The QIBA CT Small Lung Nodule Profile TF feels we have engaged in high levels of scientific dialogue with the CT imaging community on the proposed methods and have strongly encouraged scientific discourse.

The fundamental techniques and measurement results supporting the methods proposed in the Profile are found in the 2017 SPIE Medical Imaging paper [3] and the QIBA CT Small Lung Nodule Profile [1]. The SPIE paper explains how important image quality metrics are calculated and further how they are used with a modeling and simulation algorithm to estimate small lung nodule volumetric change measurement performance. This algorithm and analysis approach (using ellipsoidal virtual nodules) was used along with crowd-sourced data [5,6,7,8] to arrive at the current CT image quality specifications for the QIBA CT Small Lung Nodule Profile. From our research studies and publications the most important image quality characteristic is the

measurement of 3D resolution. The research studies within these recent abstracts are being prepared for submission to various publications.

(b) An overview and description of the QIBA CT Small Lung Nodule Profile TF approach and methods is provided below:

Edge Enhancement: Edge enhancing reconstruction kernels are applied to the 2D image plane and therefore result in non-isotropic modification of gradient edges. A major and well recognized issue with edge enhancing reconstruction kernels is that they modify HU values along and near edges, which introduce HU biases that can throw off various components of volumetric analysis algorithms. This is particularly problematic for differential geometry operators that are often used in the identification and removal of small vessels and other potentially confounding attached, adjacent, and nearby structures. An additional issue is that edge enhancing reconstruction kernels make the presentation and distribution of nodule signal more dependent on nodule orientation. Of greatest importance is that the application of edge enhancing recon kernels gives acquired CT images the appearance of having better resolution than the system truly has. For these three main reasons, the Profile discourages the use of edge enhancing recon kernels beyond a 5% edge enhancement specification. The current QIBA CT Small Lung Nodule Profile provides a proposed method for measuring edge enhancement.

3D Resolution: It is well accepted in the imaging community that resolution plays a major role in CT lung nodule volume measurement. One example of this is the dependence of CT lung nodule volume precision on the slice thickness specified for a CT acquisition where thinner slice thicknesses produce more precise volumetric measurements. The CT Small Lung Nodule Profile recognizes the importance of a CT acquisition system's resolution by placing a limit on the 3D resolution of the system, which is represented as the volume of the 3D Point Spread Function (PSF) ellipsoid. The Profile further recognizes that the CT imaging literature has traditionally expressed the 3D resolution of an acquisition system with two measurements, an in-plane MTF (a frequency domain representation) and a slice sensitivity profile (a spatial representation). The QIBA Small Lung Nodule TF found this approach to be more complicated than is needed and instead has expressed the full 3D resolution at a position as a 3D PSF ellipsoid where resolution along all dimensions of the PSF are calculated and expressed with the same exact estimation method. This is a simpler and more intuitive approach to estimating resolution with multiple benefits and no known problems or limitations. The current draft of the QIBA CT Small Lung Nodule Profile describes a method for calculating 3D resolution.

Figure 1.1 demonstrates how this resolution method and representation can easily and intuitively characterize changes in X,Y PSF, Z PSF, and full 3D PSF ellipsoid resolution across a scanner field of view when comparing scans acquired with a low dose lung cancer screening protocol with a B40f kernel and reconstructed with three different slice thicknesses (0.6mm, 1.0mm, and 2.0mm) on a Siemens SOMATOM Definition AS CT scanner. This data also demonstrates the high level of stability of the measurements methods.

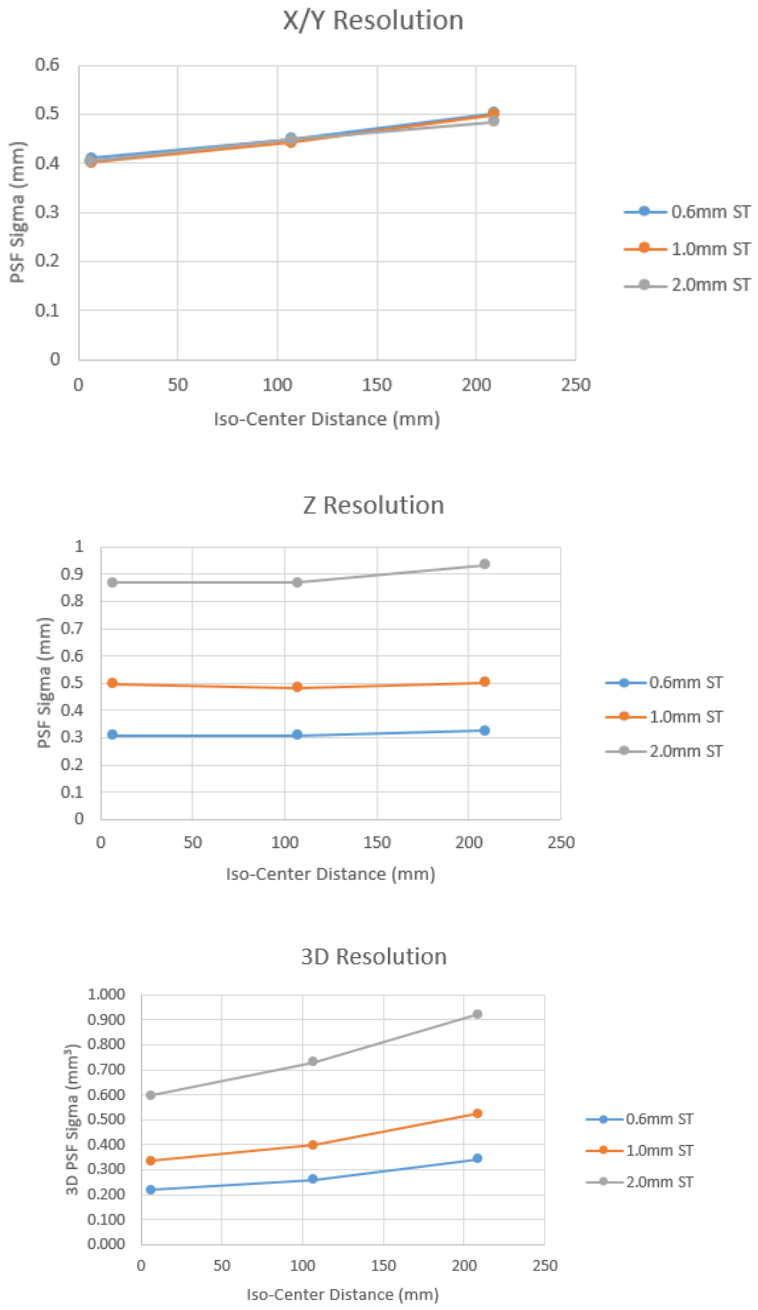

Figure 1.1: X/Y, Z, and full 3D PSF resolution measurements across the field of view of a Siemens SOMATOM Definition AS CT scanner keeping the low dose scan parameters the same except for using three different slice thicknesses.

3D Resolution Aspect Ratio: As stated above, the QIBA CT Small Lung Nodule Profile avoids image acquisition settings that make nodule measurement performance dependent on nodule orientation. The reason for this is that the orientation of the patient and the lungs during sequential CT scans introduces lung nodule orientation variability. Given that patients hold their

breath for each CT scan and the inflation of the lung and resulting deformation of the lung parenchyma can be large, the Profile establishes bounds on how anisotropic important imaging properties can be. As resolution is the most critical image quality metric for the QIBA CT Small Lung Nodule Profile, there is a specific limit on the Z to X resolution aspect ratio of the 3D PSF ellipsoid. It is axiomatic that the larger this aspect ratio, the more dependent nodule volume measurement performance will be on nodule orientation. The Profile has set a generous aspect ratio limit of 2.0 for Z/X PSF sigma resolution and have verified with a 2016 crowd sourcing study involving 54 international CT scanners that this will not negatively impact the vast majority of scanners and protocols that follow the QIBA CT Small Lung Nodule Profile acquisition setting requirements. The current QIBA CT Small Lung Nodule Profile provides a proposed method for measuring the 3D resolution aspect ratio based on the X and Z sigmas of the 3D point spread function.

HU Bias: Volume measurement of a solid lung nodule is mainly performed through segmentation of the nodule boundary across an image gradient that transitions from a background lung parenchyma attenuation value (~ -850 HU) to a human soft tissue density value (~ 0 HU). If the CT acquisition system introduces a large bias when acquiring these HU values, there is the potential for increasing lung nodule volume measurement variability. The QIBA CT Small Lung Nodule Profile thus has generous limits (+- 35 HU) on the amount of air and acrylic material bias that are allowed to maintain conformance with the Profile. CT acquisitions that exceed such a large bias limit should be evaluated by local medical physics personnel as this may indicate an issue is present with the CT scanner and protocol. The current QIBA CT Small Lung Nodule Profile provides a proposed method for measuring HU Bias in air and acrylic materials.

Spatial Warping: As stated in the open issues section of the current draft of the QIBA CT Small Lung Nodule Profile, spatial warping along the Z-dimension has been observed (and first reported by the TF members) to be quite high in the periphery of some model CT scanners, and this can significantly increase the variability of CT lung nodule change measurements [9]. Given that a nodule may appear anywhere in the scan field of view, and nodules appear more often in the lung periphery, the QIBA CT Small Lung Nodule Profile verifies that spatial warping is not excessive throughout the scanner field of view and up to 200mm from scanner isocenter. The limit on spatial warping currently required is also very generous and designed to catch only large displacements that would greatly impact small nodule volume measurement variability. This approach is aligned with QIBA's goal of enhancing accurate and enabling reliable clinical decision support. Due to the clinical management requirements for this new imaging activity, this Profile is avoiding a potentially confounding factor with a small number of scanners that had not been previously characterized. This provision protects the manufacturer and the clinical community from a threat to the reliability of quantitative imaging as a foundational tool in lung cancer screening clinical decision making. The new Profile embeds a solution for measuring 3D spatial warping at different distances from scanner iso-center that no previous CT phantom has had the capability to quantify. The current QIBA CT Small Lung Nodule Profile provides a simple proposed method for estimating 3D spatial warping.

Image Noise: Image noise represents a QIBA CT Small Lung Nodule Profile image quality metric that has a low level of influence over lung nodule measurement performance. Volume

measurement of a solid lung nodule with little attachment to surrounding structures and not compromised by confounding conditions, as is specified in the QIBA CT Small Lung Nodule Profile, is a clinical segmentation problem with a contrast-to-noise ratio (CNR) of at least 17 (a transition from approximately -850 HU to 0 HU). Noise levels can go much higher before nodule segmentation algorithms will have trouble identifying the boundary of such a nodule. Multiple publications have noted or provided clinical study evidence [10, 11, 12, 13, 14, 15] of the insensitivity of volumetric lung nodule measurement algorithms to different dose levels and iterative recon settings (both influence image noise levels), which in our view is consistent with the CNR reasoning above. Sui and colleagues directly state at the end of their conclusion [13]:

> "There was no significant difference in nodule volume or diameter measurements between ultra-low-dose CT and LDCT protocols for solid nodules."

Willemink and colleagues have extensively studied this topic area and further reinforce this view stating in conclusion of a recent publication [12]:

> "In a phantom model, no clinically relevant differences beyond reported interscan variation levels between lung nodule volumes were measured in nodules 5 mm or larger at reduced tube voltage and tube current–time product, with radiation dose reductions up to 90.6% for both FBP and iterative reconstruction, suggesting that it is safe to convert FBP protocols to iterative reconstruction and reduce tube voltage and tube current–time product for lung nodule follow-up."

Nevertheless, the current QIBA CT Small Lung Nodule Profile places wide limits (50 HU SD) since observing such high levels of image noise for a low mass phantom may indicate that (a) structural reconstruction artifacts may be influencing the acquisition and/or (b) that the CT scanner and protocol may have difficulty achieving ALARA guidelines when a medium sized patient (with higher mass) is scanned. In either case, it is recommended that a medical physicist examine the scans and the scanner for image quality issues. The current QIBA CT Small Lung Nodule Profile provides a proposed method for measuring image noise in acrylic material that is highly consistent with accepted methods for standard phantoms.

The new conformance approaches embedded within the QIBA CT Small Lung Nodule Profile largely emerged from the program requirements inherent to robustly characterize longitudinal changes in nodule volumes for the lung cancer screening setting allowing responsibly clinical decision-support. This involves precisely characterizing changes as small as 41 mm^3 for the smallest size nodule supported by the Profile. Important innovation in this regard leverages the ability of the integrated software/ phantom construct to allow for automated data acquisition/analysis of a number of potentially critical fundamental determinants of QI rigor. However, with the complexity of many types and versions of CT scanners in the field and given the multi-dimensional space related to the range of potential acquisition settings, we not only can assess the known critical determinants of Claim Conformance, but we can also monitor a range of additional image features. This provides the ability to monitor the QI process for unanticipated Conformance challenges that could be a consequence of new kernels, alternative acquisition

approaches or iterative reconstruction that had not been previously known to affect QI performance. As the FDA uses broad post marketing surveillance approaches to inform quality and safety issues with new drug approvals, the image acquisition and conformance capabilities of the new Small nodule approach could be a first step toward evolving a robust approach to a QI surveillance capability for QIBA that in the future may also be of interest to FDA, CT manufacturers as well as software developers to observe the actual granular performance of their new tools in real life settings.

It should be further noted that each of the Profile image quality metrics should not be solely studied and evaluated in isolation. The combination of influences from resolution (the primary driving factor), HU bias, image noise, spatial warping, and other properties can result in a poorly performing lung nodule volume measurement system. The QIBA CT Small Lung Nodule Profile TF has sought to better understand these interactions with phantom studies and by analyzing crowd sourcing study data.

Regarding evidence that these metrics influence volumetric measurements, namely the variability of volumetric change measurements, we provide data on this in the Figures and text below.

This is what led to several of the questions that were presented regarding the noise and resolution measurements that resulted from that meeting.

The second aspect of the questions that resulted from that meeting were regarding the relationship of these parameters to the performance of the task - nodule volumetrics. Does this assessment of noise affect the measurement of volume? Do these measurements of resolution? Does the 3D PSF? Does asymetry through the reconstructed scan field of view? If so, how does volume vary with each of these? And are there corrections/settings within the scanner that can mitigate these effects (if they are substantial?)

As mentioned above, 3D resolution (when informed with nodule size) is the main factor that influences volumetric change measurement performance. As it is impossible to measure all possible combinations of CT scanners and QIBA compliant acquisition protocols, the TF has taken the approach to acquire fundamental image quality performance measures of a CT scanner and image acquisition protocol and then use modeling and simulation to determine the predicted performance of a system with these image quality characteristics. As presented in recent abstracts the TF has found good levels of agreement between the proposed measurement methods (using low-cost reference objects) and standard phantom results [7] and when comparing predicted results with observed clinical volumetric error [8], with the clinical performance underlying the latter abstract reported in [15]. Further studies are underway that will provide additional data on the relationship between the QIBA CT Small Lung Nodule Profile image quality metrics and lung nodule measurement performance.

And because our scanners have available both linear (FBP-based) and non-linear (iterative) reconstruction methods, which can behave very differently depending on which algorithm is used and the local attenuation environment (e.g. resolution measurements in iterative reconstruction methods have been shown to be substantially influenced by the magnitude of the attenuation difference

between the object and background), this makes assessing performance extremely difficult over a broad set of conditions.

> The challenge of understanding the performance of a quantitative imaging measurement across a wide range of scanners and image acquisition settings is faced by all QIBA Profiles. In fact, no QIBA Profile can provide 100% assurance that a conformant acquisition protocol will result in performance in excess of stated claims. However, the QIBA CT Small Lung Nodule Profile has addressed this issue by performing studies for specific scenarios and most notably, by engaging in large crowd sourcing studies to collect fundamental image quality data at numerous real-world clinical sites (over 30), CT scanners (over 50), and protocols. This approach is not only useful for helping set initial Profile specifications, but also has the potential to provide continuous surveillance of image quality issues relevant to CT lung nodule volume measurement. The TF considers this to be an innovative new approach for economically and continuously assessing image quality performance across a wide range of international scanners and protocols. Others in QIBA have proposed this as a generalizable strategy to get feedback from the "field" as to how Profiles are performing in "real world settings".

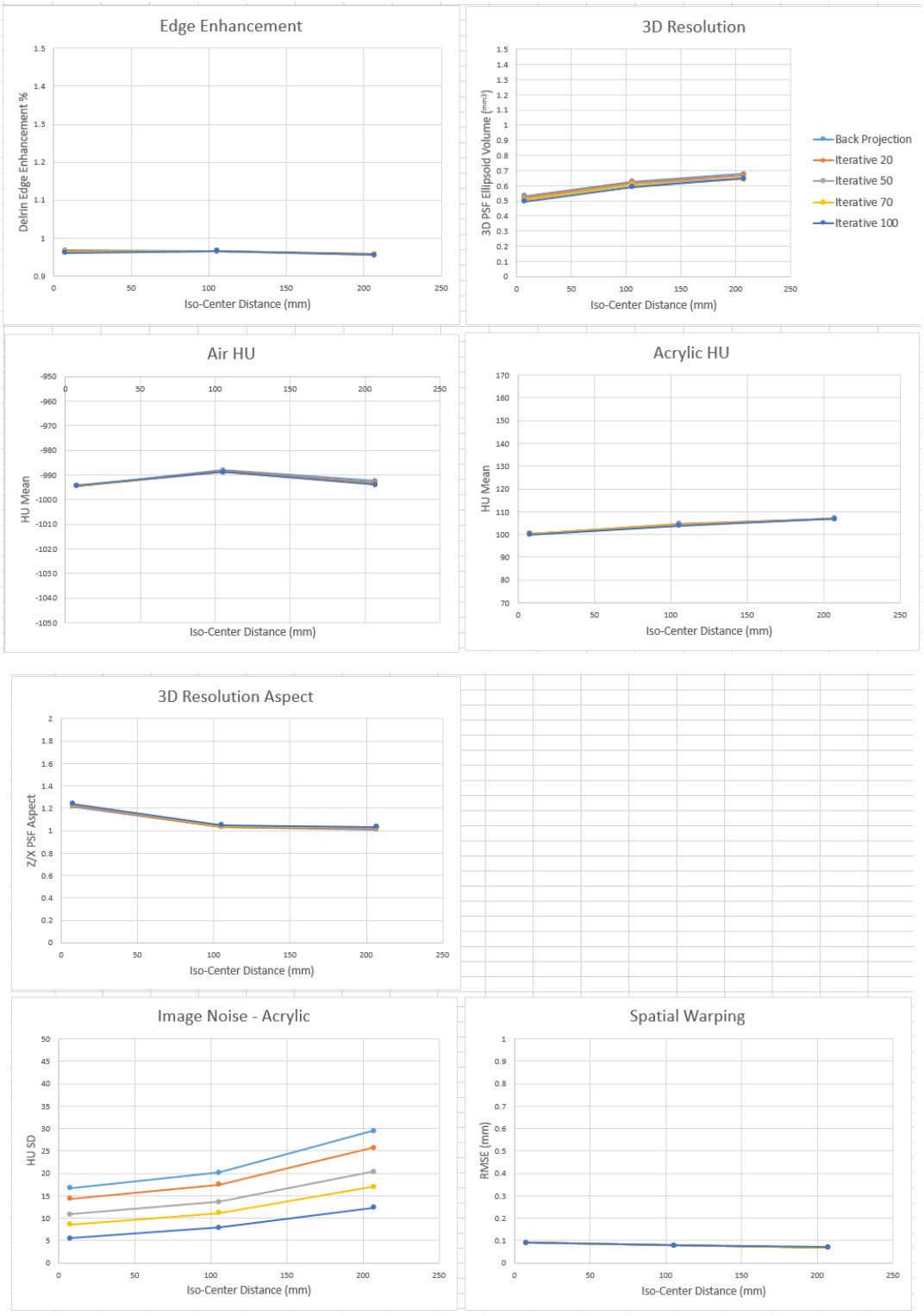

Figure 1.2: Fundamental image quality performance measures when acquiring CT data of the CTLX1 phantom with a low dose CT lung cancer screening protocol using filtered back projection and multiple iterative reconstructions. This data shows a substantial reduction in measured image noise with increasing levels of iterative reconstruction while other important CT image quality characteristics for solid lung nodules remain relatively stable.

It should also be noted that the QIBA CT Small Lung Nodule Profile is for solid lung nodules where the background to foreground contrast level is large, as mentioned above in the discussion about the influence of image noise. While we appreciate the concerns that iterative algorithms may behave differently with different attenuation difference presentations, that is outside the scope of the QIBA CT Small Lung Nodule Profile.

Our understanding of iterative reconstruction methods is that they tend to significantly decrease noise levels with small improvements to resolution. We have done initial tests of the CTLX1 phantom with varying iterative reconstruction settings on a GE Revolution CT scanner using a low dose CT lung cancer screening protocol (0.625mm slice thickness, .625mm slice spacing, 19mA, 0.5 second exposure time, 120 kVp, 1.0 pitch, and a STANDARD kernel). **Figure 1.2** shows the measurements obtained when scanning with this base protocol and modifying the reconstruction kernel to include reconstructions with different iterative reconstruction levels. As expected, noise levels dropped with higher iterative reconstruction values and 3D resolution changed slightly better. All other metrics important to the QIBA CT Small Lung Nodule Profile remained stable.

Thus, while this phantom work being shown may be a step in the right direction, it seems to me to be too early to adopt these tests into the profile and certainly too early to ask users to perform these as part of any compliance exercise, without pretty clear proof that these parameters have a demonstrable effect on nodule volumetrics. As we mentioned back in June, supporting experimental data would be helpful here.

A strength of the QIBA CT Small Lung Nodule Profile approach in using an automated, cloud-based conformance process is that it will provide a high volume, transparent mechanisms to greatly enhance the scrutiny of nodule volumetric performance. All phantom analysis data will be aggregated in the cloud and will be available for QIBA to analyze relative to downstream performance.

The modeling and simulation approach published in [3] provides evidence that the main conformance metrics in the QIBA CT Small Lung Nodule Profile is useful in predicting CT lung nodule measurement bias and precision. **Figure 2** shows the predicted vs observed mean of volume measurements results of this system within repeat low dose CT scans of different diameter spheres and three different slice thicknesses. **Figure 3** shows the predicted vs observed coefficient of variation of volume measurement results within the same repeat low dose CT scans for different diameter spheres and three different slice thicknesses.

We have also evaluated the predictive capability of these methods when scanning and analyzing three rolls of scotch tape with real-world clinical nodule measurements. We

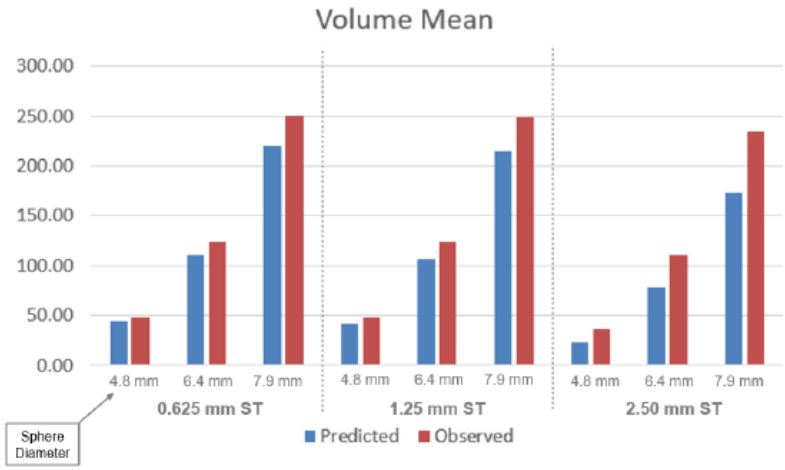

Figure 2: Comparison of predicted (blue) and observed (red) mean volumetric measurements of Teflon spheres repeat CT scanned 10 times within an anthropomorphic chest phantom. Three different sphere diameters and three different slice thicknesses were used.

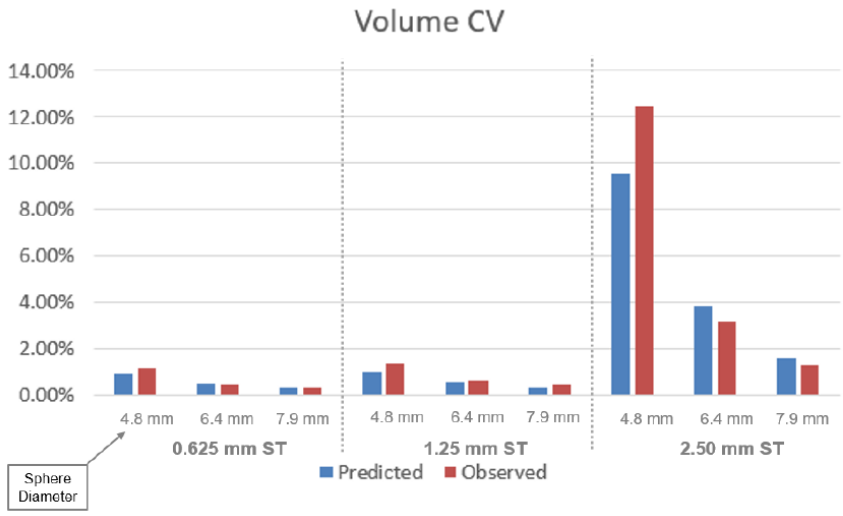

Figure 3: Comparison of predicted (blue) and observed (red) volumetric measurement Coefficient of Variation (CV) of Teflon spheres repeat CT scanned 10 times within an anthropomorphic chest phantom. Three different sphere diameters and three different slice thicknesses were used. Note that predicted vs observed remained similar despite the large range in requested slice thickness (0.625mm to 1.25mm to 2.5mm).

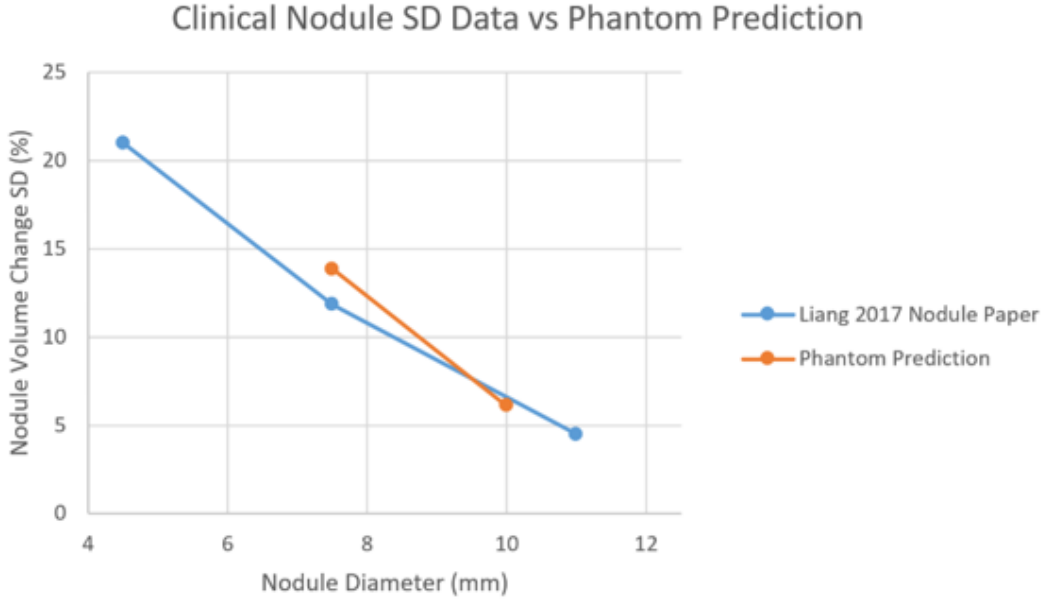

Figure 4: Predicted versus observed nodule volume change SD (%) for 117 screen detected stable nodules.

compared the prediction data from the approach outlined in [3] to results obtained from a database of 117 screen-detected stable nodules ranging in size from 2.2 to 18.7 mm that were CT scanned twice on the same CT scanner using the same protocol and published in [15]. The automated volumetric analysis was performed using two widely available commercial software packages. As **Figure 4** shows, the predicted performance matched closely with the mean performance observed for the two software packages.

The main QIBA CT Small Lung Nodule Profile image quality metrics and predictive modeling approach were used to generate the results in **Figures 2, 3, and 4**. These results demonstrate that the metrics and methods underlying the QIBA CT Small Lung Nodule Profile are effective and meaningful. Further studies are underway that will provide additional data with which to refine these methods.

This document has outlined numerous studies and methods that provide strong justification for the methods that are proposed in the QIBA CT Small Lung Nodule Profile. While there is always the need to acquire more data and perform more studies, the need to provide the clinical community with basic quantitative imaging guidance for lung nodules must also be considered. The position of the QIBA CT Small Lung Nodule Profile Task Force after hundreds of hours of discussion, numerous presentations, and multiple layers of review is that we have studied the methods sufficiently to bring this initial Profile to a vote. As more data comes in there will be ample opportunity to refine these initial methods.

I will close by re-stating the questions that our group posed back in June:

Explanation of how the noise requirements in the three additional materials would be expected to improve overall volume quantification performance (e.g. segmentation performance and beyond) compared to protocols constrained by only a single material noise requirement. In addition, an explanation of how the noise measured in essentially a non-attenuating environment (current phantom) would be expected to be representative of noise in a patient attenuation environment.

Supporting experimental data would be helpful

> The QIBA CT Small Lung Nodule Profile was recently modified to limit the noise requirement to the acrylic material only. The TF has addressed the role of noise for CT solid lung nodule volume measurement above with a theoretical justification and numerous references supporting the QIBA CT Small Lung Nodule Profile position. We greatly appreciate the comments of all the participants in the year since the QIBA CT Small Lung Nodule Profile underwent its external review. The QIBA CT Small Lung Nodule Profile is timely as national implementation of lung cancer screening is underway in the United States and gaining momentum in other countries as well. Our assumption is that the Profile will continue to undergo refinement after feedback from actual experience with utilization in the screening community. Based on a remarkably extensive dialogue on this document, we strongly endorse the Profiles urgent implementation so we contribute to a compelling new cancer screening service.

Justification for reflecting resolution in terms of PSF as opposed to the MTF50, and for use of a 3D metric and an in-plane-vs-z-axis ratio

> The QIBA CT Small Lung Nodule Profile TF has addressed this area above. It should also be noted that we have provided equations for translating between MTF and PSF. In addition, the use of a PSF representation is common for computed tomography research publications, as catalogued by pubmed.gov.

Explanation of how requirements on each of voxel bias, edge enhancement, and spatial warping would be expected to improve volume quantification (e.g. segmentation performance and beyond) compared to protocols where only noise and resolution were constrained.

Supporting experimental data would be helpful

> The QIBA CT Small Lung Nodule Profile TF has addressed these areas above. For example, we have collected fundamental image quality data on the image quality metrics stated from over 54 international CT scanners and have used this information to estimate volumetric change performance as reported in [6].

Demonstration of the effects of these parameters on volume quantification under a variety of acquisition and reconstruction conditions (eg, pitch, recon filters, slice thickness, dose) using current state-of-the-art scanners.

> The QIBA CT Small Lung Nodule Profile TF has addressed this area above. In addition, the example given in the previous response applies here as well.

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