

## Long-Term Objectives

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The CT volumetry technical committee of QIBA is building evidence for the following claim:

**Radiologic measurements based on segmentation of whole tumor volume are more precise (reproducible) than unidimensional measurements of tumor diameter. Therefore, longitudinal changes in whole tumor volumes can predict health outcomes earlier and more accurately than corresponding unidimensional measurements. This may result in smaller, more efficient clinical trials. Individual patients whose diseases have become resistant to treatment will benefit from the earlier detection of futility and the opportunity to select alternative therapies.**

Results have been reported using volumetry in a number of indications, including lung, liver, head and neck, esophagus, colorectal, sarcoma, and lymphoma. However, these results are not always reproducible in multi-center settings. Methods for measuring tumor volumes as biomarkers have not yet converged to a common set of well understood performance characteristics.

## What We've Accomplished So Far

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Historically, most work was done on geometrically simple masses surrounded by air-filled tissues of the lung. This was a natural place for QIBA to start during the first contract period. By the close of the first contract period, we will have been able to complete the following experimental groundwork projects:

- Evaluation of 1D, 2D and 3D nodule size estimation for spherical and non-spherical nodules through CT thoracic phantom imaging.
- Assessing test-retest reproducibility to determine minimum detectable change under clinical workflow conditions. This Minimum detectable change project has produced initial results and has organized a follow-up project to consider how workflow affects reader performance.
- Inter-scanner/inter-clinic comparison of reader nodule sizing in CT imaging of a phantom to estimate the inter-scanner variation in measured volumes using imagery captured under a two-arm protocol on six CT scanners. One protocol arm is derived from ACRIN 6678, the other determines the imager settings by device independent measurements.
- Comparative study of algorithms for the measurement of the volume of lung lesions (a.k.a. 3A) through a public “challenge” where participants “compete” for how well they performed a volume sizing problem and using statistical techniques to define the “class” of tests available for it irrespective of any candidate that purports to be a member of the class.
- Development of assessment and predictive metrics for quantitative imaging in chest CT.
- Quantifying variability in measurement of pulmonary nodule (solid, part-Solid and ground glass) nodules.
- As we began to expand our work from synthetic objects embedded in models to clinical data sets, it became obvious that we could not apply the methodology to lung cancer without assessing its sites of metastases. Because the imaging characteristics of many metastases to the liver and lymphatic systems are similar, we started a retrospective re-analysis of clinical trial in patients with colorectal carcinoma to determine the feasibility of experts quantifying changes in tumor volumes as a means of predicting patient survival (a.k.a. 3B) The key criteria proposed to judge the utility of the new end-point primarily relate to its ability to accurately and reproducibly predict the eventual Phase III end-point for treatment effect.

The team has also written, reviewed, and begun promotion of its Profile for advanced disease. Additionally, the team has started to compose a “Small Pulmonary” nodule Profile for neoadjuvant clinical trials.

## Our Proposal on Where to Go From Here

Our goals in a second contract period will be to (1) complete our project in lung cancer by developing methods for quantifying its metastases to the liver and lymphatic system; and (2) expand these results to a broader set of indications that also produce solid metastatic lesions in the liver and the lymphatic system. These tissues are common sites of disease in colorectal, esophageal, renal, breast, stomach,, pancreatic, melanoma, etc.

## Knowledge Gaps and Development Plan

We propose to utilize the approach we have refined in the first period. The CT volumetry technical committee has established a staged analysis plan for validating volumetry as a biomarker. Success in early stages leads to progressively more and more complex clinical data sets until the process is ultimately qualified for deployment in clinical practice and in multicenter trials. Conceptually, the process-map is divided into discrete stages, which are indicated below:

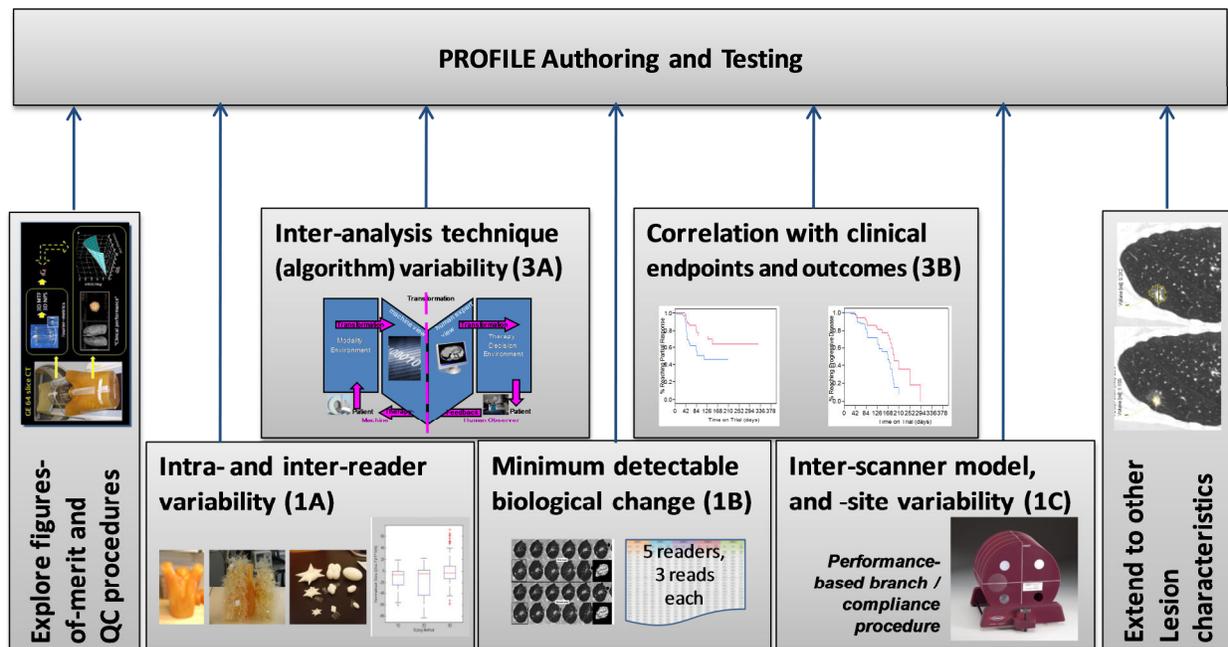


Figure: Process map for qualifying volumetric image analysis using computed tomography, showing relationship to standardization of the biomarker’s measurement and interpretation using Profiles.

## Proposed Experimental Groundwork Projects

1. Collect Data to fill gaps identified in previous work in completing the QIBA profile for advanced disease / larger tumors:
  - a. Expand evaluation of 1D, 2D and 3D nodule size estimation by radiologists for solid nodules using phantoms that mimic the contrast and setting of hepatic and lymphatic metastases using a study design drawn from the prior project that utilized phantoms for solid and part-solid lesions in the lung, but extending to different background densities.

- b. Assess test-retest reproducibility to determine minimum detectable change under clinical workflow conditions using patient data sets of the liver using a study design similar to the 1B project.
  - c. Administer additional challenges utilizing the 3A study design and logistics for patient data sets in the thorax and abdomen to characterize comparative algorithm performance. This project will result in compliance / proficiency testing methodology that can be used in successively posed challenges that build evidence capable of being registered at CDER as well as CDRH.
  - d. Apply predictive metrics for CT volumetry in a calibration and quality control program that can be used for both compliance testing and ongoing QC.
2. Collect Data to fill gaps identified by FDA for qualification of CT biomarkers:
- a. Conduct additional validation studies of volumetric CT as a biomarker for predicting patient survival in an expanded range of indications. It is not sufficient that the end-point being considered for a phase II trial be a prognostic indicator of clinical outcome, although it will usually be the case that early end-points are prognostic of clinical outcome even in the absence of a treatment effect. Within the context of a clinical trial, the early end-point must capture at least a component of treatment benefit, a concept that specifies that a change due to treatment in the early end-point predicts a change in the ultimate clinical end-point.
3. Initiate work on additional imaging biomarkers:
- a. Quantitative CT
    - i. Response assessment in drug trials
      - 1. Volumetry of smaller masses
      - 2. Morphometry (shape, angle, geometric features)
      - 3. Densitometry (heterogeneity) (see COPD/Asthma section)
    - ii. Screening (characterization of longitudinal change in screening-identified nodules)
    - iii. Individual-patient diagnostic (symptomatic)
  - b. Multi-modality transfer and harmonization
    - i. Volumes on MR, e.g., GBM
    - ii. TLG with PET lesion segmentations