Context: How does Profiling fit in to what we are trying to accomplish overall?
Step 1: What is the clinical question being addressed, i.e., what is the biomarker?

Cancer staging
The extent of lung cancer dissemination is defined at the time of initial diagnosis of a patient in a process called staging. The schema (TNM Classification of Malignant Tumors?) for staging lung cancer has been updated recently so that it more accurately clusters patients who benefit from particular therapeutic interventions with predictable outcomes {Goldstraw, 2007 #7}.

A table of how staging relates to lung cancer drug therapy approaches, the imaging approaches used in those stages and issues relative to the image requirements is summarized in Table 1.

Table 1: Summary of Image Processing Issues Relative to Stage of Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>% of Cases</th>
<th>5-year Survival</th>
<th>Imaging Focus/ Therapy Focus</th>
<th>Imaging Tool</th>
<th>Issues</th>
<th>Thoracic Segmentation</th>
<th>Hi-Res</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>16</td>
<td>49</td>
<td>Primary tumor/ Neo and adjuvant RX</td>
<td>sCT</td>
<td>Small cancers surrounded by air</td>
<td>Can be straightforward</td>
<td>Needed</td>
</tr>
<tr>
<td>II/III</td>
<td>35</td>
<td>15.2</td>
<td>Primary, hilar and mediastinal lymph nodes/ Combined modality</td>
<td>sCT, PET</td>
<td>Larger tumors and nodes abut other structures</td>
<td>Often challenging</td>
<td>Optional</td>
</tr>
<tr>
<td>IV</td>
<td>41</td>
<td>3</td>
<td>Primary/regional nodes and metastatic sites/ Chemotherapy</td>
<td>sCT, PET, Bone, Brain scans</td>
<td>Tumor response often determined outside of the chest</td>
<td>Often challenging</td>
<td>Optional</td>
</tr>
</tbody>
</table>

For this discussion, Stage I is considered separately as it is typically treated with surgery and has the highest potential for curability. Because Stage II is relatively uncommon, Stage II and III are clustered together as their clinical management can be similar involving combinations of radiation therapy and chemotherapy with or without surgery. Stage IV is the most common form of lung cancer; its treatment typical involves only the use of drug therapy approaches. There is a number of trial types listed in the fourth column.
Step 1: What is the clinical question being addressed, i.e., what is the biomarker?

Cancer staging
The extent of lung cancer dissemination is defined at the time of initial diagnosis of a patient in a process called staging. The schema (TNM Classification of Malignant Tumors?) for staging lung cancer has been updated recently so that it more accurately clusters patients who benefit from particular therapeutic interventions with predictable outcomes {Goldstraw, 2007 #7}.

A table of how staging relates to lung cancer drug therapy approaches, the imaging approaches used in those stages and issues relative to the image requirements is summarized in Table 1.

Table 1: Summary of Image Processing Issues Relative to Stage of Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>% of Cases</th>
<th>5-year Survival</th>
<th>Imaging Focus/Therapy Focus</th>
<th>Imaging Tool Issues</th>
<th>Hi-Res</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>16</td>
<td>49</td>
<td>Primary tumor/Neo and adjuvant RX</td>
<td>sCT, PET</td>
<td>Needed</td>
</tr>
<tr>
<td>II/III</td>
<td>35</td>
<td>15.2</td>
<td>Primary, hilar and mediastinal lymph nodes/Combined modality</td>
<td>sCT, PET, Bone, Brain scans</td>
<td>Optional</td>
</tr>
<tr>
<td>IV</td>
<td>41</td>
<td>3</td>
<td>Primary/regional nodes and metastatic sites/Chemotherapy</td>
<td>sCT, PET, Bone, Brain scans</td>
<td>Often</td>
</tr>
</tbody>
</table>

For this discussion, Stage I is considered separately as it is typically treated with surgery. Because Stage II is relatively uncommon, Stage II and III are clustered together involving combinations of radiation therapy and chemotherapy with or without surgery. Stage IV is the most common form of lung cancer; its treatment typical involves only the use of drug therapy approaches. There is a number of trial types listed in the fourth column.
Step 2: How does the field understand the end point involved?
Step 3: What is the performance of the currently accepted methodology?

[Diagram of RECIST criteria showing progression, stable, and partial response stages with measurement and assessment timelines.]

8mm ΔD, 13 pixels
73% ΔVolume

Unaided Interpretation

Baseline & Treat

Assess Response

Complete Response

Partial Response

Progressive Disease

Target Lesion Measurement
RECIST: Sum of LD

4cm lesion

Time

weeks

Erasmus et al., JCO 2003
Intra-observer error
PD: 9.5% of tumors
PR: 3% of tumors
Inter-observer error
PD: 30% of tumors
PR: 14% of tumors
Step 4: What is the claim for the new biomarker, in statistically rigorous terms?
Step 5: What is the roadmap for groundwork, retrospective, prospective, and analytical?

Groundwork (“precursor questions”)... 

...Profiling (“profile details”)... 

Diagnostic Accuracy and Reproducibility 

Clinical Efficacy and Real-world Effectiveness 

Primary/region nodes and metastatic sites 

Primary, hilar and mediastinal lymph nodes 

Primary tumor/Neo and adjuvant RX
Step 5a: Technology Groundwork

Technical Characteristics and Standards

- Prospective Single-Center Phantom
- Retrospective Clinical, including “No Change” Condition
- Prospective Multi-center Phantom
Step 5b: Statistical Groundwork

1. Determine performance with respect to statistical power needed
2. Set acquisition standards necessary
3. Determine what type of evaluations are necessary to qualify
Step 5c: Clinical Groundwork

Clinical Efficacy and Real-world Effectiveness

1. Determine intra- and inter-reader sensitivity and specificity using new biomarker

2. Correlate performance of new method with currently accepted method
Step 6: How are the Profile’s clinical Claims represented statistically?

Profile Claims (what users will be able to achieve)

Claim #1: Can create, store, retrieve images of lung tumors
Claim #2: Can create, store, retrieve linear, area and volume measurements made on lung tumor images
Claim #3: Can create, store, and retrieve mark ups of lung tumors, i.e., region of interest (ROI) boundaries

Precursor: Need Sample Implementation

Chest CAD polylines or New DICOM Segmentation objects (by pixel) are likely sufficient, but should try out a sample implementation to confirm (and identify key Details to require in the Profile). Possibilities for data storage include polylines, voxels, and polygons/triangles. See also Segmentation and Markup Formats

Claim #4: Can measure lung tumor volume with repeatability of 18% for tumors greater than 10mm in Longest Diameter. Rationale: For uniformly expanding cubes and solid spheres, an increase in the RECIST defined uni-dimensional Longest Diameter of a Measurable Lesion corresponds to an increase in volume of about 72%. To diagnose Progressive Disease at a change of about one half that volume, 36%, the noise needs to be less than about 18%. The claim is thus set to be “twice as sensitive as RECIST”.  

<What do we mean by repeatability> How should the repeatability be expressed? It’s easier to meet % targets for larger tumors. Should we use mm3 instead? Or should we state % for a certain sized tumor? There is a description in Jim Mulshines work that we can copy here? Precursor: Demonstrate this accuracy and repeatability is easily achievable

Groundwork: Test-Retest measurements of FDA phantoms i.e., very-best-case-scenario, with variability one order of magnitude less than variability in "real life", i.e., algorithm returns variability of less than 1.5% <Relevant Groundwork Link 2: Test-Retest measurements of small sample of NIST cases, i.e., nearly-best-case-clinical-scenario, with variability for measurement of isolated, simple lung tumors of less than 3% (up to 4 times the noise in phantoms and less than one fifth the noise expected in real life scenarios). <Relevant Groundwork Link 3: Test-Retest measurements of a few well behaved masses in the MSKCC coffee break study of less than 10% between Image Set 1 and Image Set 2 of each patient studied twice in succession. This 10% threshold is somewhat capriciously based on the assumption that the precision of measurement in selected MSKCC coffee break tumors will be twice as good as that which can be achieved in most clinical trial scenarios. Precursor: Should thought be given to revising the RECIST definitions?

Claim #5: Can retrieve and/or contribute images, measurements and markups from/to caBIG. Are we and caBIG ready to get into this now or is it OK to leave this until our next profile, e.g. volume change, when our ideas and caBIGs infrastructure are more mature/stable?
Step 7: What Details must be specified to meet the Claim, based on the groundwork?

Profile Details (what equipment and users must do to achieve it)
The Profile defines the following roles and several transactions and activities they participate in:
- Acquisition System
- Measurement System
- Measurer

Activity: Acquisition System Calibration

Activity: Patient Preparation

Activity: Image Acquisition

Activity: Image Reconstruction

Activity: Measurement

Transaction: Transfer Measurements

Note some earlier stage NSCLC trials done with radiofrequency ablation (RAPTURE, R. Lencioni, PI) included some stage I cancers, with all lesions < 3.5 cm. Some parameters need ranges to "normalize" results across different patient sizes.
Approach: Start using it immediately, even while it is still under development.
IIBE realizing the power of imaging in medicine