

# Potential future consideration for imaging and blood-based biomarkers for precision medicine in lung cancer

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In this issue, we have reviewed the current status of imaging and blood-based biomarkers in translational lung cancer research. Clearly, some small but important initial steps have been made toward realizing precision medicine approaches for this disease, and research in this area has revealed significant opportunities to address unmet needs and validate imaging and blood-based biomarkers in clinical trials.

We are pleased to note that the NCI-funded National Clinical Trials Network NCTN has recognized the role of functional imaging in clinical trials and precision medicine. RTOG (now NRG Oncology) began functional imaging work in 2003. The Alliance (which was created from the merger of CALGB, ACOSOG and the NCCTG) and SWOG introduced imaging committees upon their formation in 2012. Most notably, the formation of ECOG-ACRIN elevated the importance of imaging to one of its two primary missions in that new Group.

To further provide integrated imaging and radiation quality control programs in support of the NCTN program, the NCI funded a quality assurance core facility known as Imaging and Radiation Oncology Core (IROC) in 2014. As detailed by Xiao and Rosen in this issue (1), IROC has been tasked with providing standardizing radiotherapy and imaging quality, data management services to enforce consistent quality among innovative technical developments in imaging, and new therapeutic modalities for multi-institutional clinical trials. This core service organization provides scientific and technical expertise in both imaging and radiotherapy quality assurance to the entire clinical network. A number of QA Centers in the

past NCI Cooperative Group Programs have joined their collective strengths to form this new IROC group. IROC assures high-quality data for clinical trials designed to improve clinical outcomes for cancer patients worldwide. IROC provides five quality assurance core functions: site qualification, protocol development support, credentialing, data management (pre- and post-review), and case review. The continuous success of IROC has established the very first step for implementing imaging for precision medicine in clinical trials.

Looking into the future, we envision even greater opportunities to apply novel imaging techniques within national cooperative group trials. Built on the foundational role of IROC, and early phase work from cancer centers and the Cooperative Groups, imaging for consistent outcome assessment and as integrated biomarkers have become feasible. We can now apply standardized imaging procedures set by the Quantitative Imaging Biomarker Alliance (QIBA) and tools developed by the Quantitative Imaging Network (QIN) to perform correlative studies for multicenter cooperative trials to maximize the information gained via imaging for guidance of precision medicine.

Specific areas of focus in lung cancer imaging-based biomarkers that will push this field forward can be multidimensional. CT and positron emission tomography (PET) imaging biomarkers provide complementary knowledge to analyses from tissue biospecimens. CT scans, widely available for all clinical trial patients, can now be assessed with greater sophistication, using radiomic techniques, at for prognosis and treatment response prediction. FDG-PET and other molecular imaging tests

as robust predictors of tumor control and patient survival would support the use of molecular imaging as an accepted endpoint in some therapy trials. MRI may also provide another dimension of assessment for lung and mediastinal tissue analyses.

To advance the role of imaging in precision medicine for clinical trials, specific tasks that can be implemented, particularly in cooperative groups include (but are not limited to):

- (I) Identify imaging resources available in the group archive system led by IROC, and develop strategies to maximize what can be learned from imaging outcome correlates from the completed clinical trials.
- (II) Mandate submission of high-quality imaging data for ongoing trials. Such imaging data should include all scans associated with pre-treatment staging, target delineation and treatment planning, and follow-up imaging used for assessment of treatment response and tumor progression.
- (III) Validate CT, FDG-PET, and other imaging tests as robust predictors of patient survival, to support the use of imaging as an accepted ‘surrogate’ endpoint in later-stage therapy trials.
- (IV) Standardize the modern imaging tests needed for clinical trial eligibility for each disease site and each clinical trial.
- (V) Implement prospective imaging biomarker correlative studies in future trials.
- (VI) Develop clinical trials to test new imaging tools and/or new applications of conventional imaging to direct treatment interventions, like personalized adaptive treatment as described in RTOG1106.
- (VII) Develop new predictive and early-response molecular imaging biomarkers, using probes designed to quantify specific therapeutic targets or specific pharmacodynamics or radiation therapy responses, to assess the efficacy treatment in near-real-time.

The cooperative leadership and NCI funding mechanisms must promote and support correlative studies to discover and validate imaging biomarkers, and the molecular imaging community must continue to support research and development of new molecular imaging techniques. The molecular imaging community must also come together, working with cooperative clinical trial groups and the pharmaceutical industry, to support well-designed prospective trials validating molecular imaging biomarkers

as integrated markers in therapeutic trials, which will lead to their eventual use as integral biomarkers in therapeutic clinical trials and clinical practice. Ultimately, validated imaging biomarkers for outcome prediction and early imaging as a surrogate endpoint could reduce sample size and study duration, resulting in significant reductions in cost for new clinical trials. Most importantly, the development of imaging biomarkers can advance precision medicine to a new horizon for improving treatment outcome in each individual patient.

For blood-based biomarkers, we have reviewed the roles of these biomarkers for precision treatment with an emphasis on the methodology for identifying and utilizing the biomarkers in an integrated approach for future clinical trials and practice. Circulating tumor cells and/or circulating tumor DNA have shed some light on strategies for selected molecular targeted systematic therapies. Some genomic, cytokine, and/or proteomic markers have furthermore shown potential in predicting treatment toxicity. We must note that the field of blood-based markers is still in its infancy for guiding precision medicine. Blood biomarker studies—either for discovery or validation—are still mostly lacking in cooperative group lung cancer studies. While all of the cooperative groups have long since started blood, serum, or plasma biospecimen banking for “future use”, sample quality assurance and infrastructure for such an important effort are still needed in all the collaborative groups.

To advance the role of blood-based biomarkers in precision medicine, specific tasks that will increase the efficiency of this work include (but are not limited to):

- (I) Sort banked blood samples for appropriateness in biomarker testing for validity. Proteomic or cytokine tests using samples collected without appropriate temperature control or duration of blood setting may generate artificial results, as these samples are most likely degraded. Genomic testing may be the only possibility for samples collected and stored without rigorous quality control.
- (II) Follow NCI’s best practice guidelines (<https://biospecimens.cancer.gov/bestpractices/to/>) for future trials and establish standard of procedures (SOP) to ensure sample quality, and implement these SOP’s in each protocol.
- (III) Discontinue traditional blood handling procedures which do not control the blood sitting temperature before processing and the interval between blood drawing and plasma preparation. Implement the

optimal procedure validated by the multicenter international study (2).

- (IV) Provide training sessions and/or detailed written materials to research associates who are responsible for blood sampling, processing, storage, and delivery.
- (V) Focus on validating the reported promising biomarkers to design truly biomarker-guided personalized precision treatment regimens in future trials.

Blood-based markers should be viewed in the context of the patient, tumor biopsy results, local tumor presentation from imaging based assessment, and treatment factors. Both imaging and blood-based biomarkers play a crucial role on the current level of precision medicine in non-small cell lung cancer. For surgery, blood- and imaging-based biomarkers can be important for assessing the risk of distant disease and the need for a radically invasive, detrimental procedure. For systemic therapy, molecular testing of circulating tumor cells or free DNA are important for molecular targeted therapy based precision therapy (3,4). For radiation therapy, precision medicine is not only an imaging-guided treatment decision, but also depends on imaging based particularly on the anatomical deposition of the radiation dose in specific tissues, the blood-based radiosensitivity assessment of a specific organ (5), and the imaging based regional characteristics of the organ (6).

In summary, great advances in imaging and blood-based biomarkers will undoubtedly continue throughout this decade and beyond. Data from these sources clearly complement physical tissue-derived information, and do so with potential advantages such as minimum invasiveness of sampling, providing comprehensive and “eternal” information (imaging does not have ‘used up’ issue as the biopsy specimen) and avoidance of sampling errors. At the present time, imaging and blood-based biomarkers are complementary to tissue markers. We envision that in the future, imaging and blood biomarkers may replace

tissue in some settings, and that serial samples will be increasingly useful in directing meaningful treatment decisions including aggressiveness of treatment and modifications in treatment plan.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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