2010 EXECUTIVE SUMMARY

On May 13 and 14, 2010, the Prevent Cancer Foundation convened the seventh annual workshop in Bethesda, MD, to explore strategies to advance the use of quantitative CT imaging in the process of drug development for lung cancer. The motivation for this workshop is a desire to improve clinical outcomes in lung cancer, as this cancer remains the most world’s most lethal cancer. Cancer now has the most devastating economic impact of any cause of death worldwide, with lung cancer having the highest economic impact of all. The previous six workshops have seen significant progress emerge from the deliberations of the faculty.

To open the forum, Dr. James Mulshine, chair of the workshop organizing committee, outlined the strategy for the workshop. He reviewed a number of positive accomplishments that have derived from previous meetings and discussed new challenges for participants to consider. Specifically, he noted that a growing number of new molecularly-targeted therapies are being introduced for advanced lung cancer. He mentioned, however, that there is a bottleneck in completing the trials required for FDA approval. In addition, the ability to diagnose early lung cancer continues to improve, with the additional possibility of developing new strategies to accelerate the process of regulatory review.

A recent New England Journal of Medicine report from a European randomized lung cancer screening trial concluded that a disciplined work-up strategy using a quantitative imaging tool was associated with a favorable diagnostic efficiency and Stage I detection rate of 74%. These factors provide an impetus to consider the development of new drugs that may be used in the treatment of early lung cancer, such as in the adjuvant setting where quantitative imaging of the thorax would have benefit. A number of recent papers from the Quantitative Imaging Biomarker Alliance (QIBA) underscore the growing feasibility of quantitative evaluation of small changes across time in the evaluation of primary lung cancer.

The Seventh Workshop maintained the focus on driving innovation and broad cross-disciplinary inclusion. Important models for the direction of the workshop have emerged from research in the clinical management of breast cancer and cardiovascular disease. In both fields there is a growing focus on moving to earlier disease management approaches.
The reason high-resolution imaging is so useful in finding early lung cancer is that these cancers typically develop in the periphery of the lung. This peripheral lung tissue is air filled, so that the borders of these early primary lung cancers are accentuated by contrast of the air-to-soft-tissue interface, which results in unusually favorable clinical images. The high contrast ratio with peripherally located lung cancer nodules provides an instructive model system for exploring developmental issues with quantitative imaging.

Innovations that have emerged from this forum include the impetus for the development of several image databases (e.g., National Cancer Institute RIDER Database; The Prevent Cancer Foundation-Cornell Database; the Optical Society of America’s Interactive Science Publishing Database, which now contains CT lung scans and relevant phantoms; and the Lung Cancer Alliance Patient-donated Database (Give-A-Scan). These databases include collections of different types of image files and these diverse imaging repositories are a critical validation resource in allowing the development of quantitative imaging software measurement tools.

This forum has contributed to conceptualization and completion of the first neoadjuvant-window-of-opportunity trial in lung cancer, led by Dr. Nasser Altorki and colleagues, using the GlaxoSmithKline drug pazopanib. In this trial, which was published in the Journal of Clinical Oncology (2010 Jul 1; 28(19):3131-7), 35 patients scheduled to undergo lung cancer surgery with a curative intent agreed to a 2-3 week preoperative course of pazopanib, an oral, dual kinase, VEGF inhibitor. The trial was designed to determine pazopanib’s effect on tumor growth and molecular markers. Over 80% of the cases showed a favorable volume reduction response to pazopanib along with a favorable modulation of molecular endpoints.

With this clinical trial approach, the frequency of expression of this drug target can be objectively determined in untreated lung cancers. Then the consequences of drug exposure in the resected tumor tissue can be assessed, objectively providing relevant information that is virtually impossible to obtain with conventional drug development approaches. This proof-of-concept success led the leadership of GSK to move directly to a randomized Phase II adjuvant trial in early stage lung cancer, involving patients at high risk of relapse.

This strategy of getting more information about the relevance of a target by using data from a neoadjuvant, window-of-opportunity trial is a new model for drug development in non-small cell lung cancer. It establishes an efficient path to potential regulatory approval for an adjuvant indication for early lung cancer drug therapy. The tamoxifen precedent of success in reducing new cancers during adjuvant therapy may lead to an eventual chemoprevention claim as well.
With pazopanib, the neoadjuvant clinical trial strategy provides a model pathway for accelerating the drug approval process.

Participants in the Workshop from both the academic and commercial sides have extensively discussed the value of data sharing and open reporting. The donation of both raw molecular data and imaging data enables aggregation of extremely valuable information that would allow integrated analysis of the imaging and molecular response. In this fashion, the design of future trials, especially with trials that are randomized with placebo control or that include patient assignment through a Bayesian design may provide extraordinary value, as they allow for repurposing of the trial data to address a wide range of new questions.

An overview slide presented at Workshop VII summarizes the range of progress from previous Workshops:
A productive strategic partnership between the Prevent Cancer Foundation and the Optical Society of America has arisen out of previous workshops and has led to a number of positive contributions, such as the development of a dedicated open source lung cancer lesion sizing toolkit for the research community, the publication of a monograph summarizing the activities of the field, and the recent publication of a special issue of *Optics Express*, which features the use of a lesion sizing tool kit with a range of curated DICOM image files.

A goal of the Seventh Workshop was to review in depth the opportunities with image processing research, in order to integrate calibration and phantom tools in clinical trials performed in regulatory-directed studies. The purpose of this research has been to improve image quality and minimize variance of quantitative measurements across clinical trial settings where there are different vendor platforms.

Ricardo Avila of Kitware reviewed the technical issues surrounding the sources of variance in quantitative clinical imaging. He demonstrated how using phantoms with defined physical characteristics allows for evaluation of the non-homogeneity of image acquisition with CT detectors from various vendors. It is of interest that there is degradation in the performance of certain detectors as one moves from the isocenter to the imaging table. Mr. Avila presented the rationale for use of a new synthetic calibration device in allowing improved quantitative imaging. This is now being incorporated into the ongoing Abigail trial protocol being conducted by Roche Pharmaceuticals.

Dr. James Kiley, Director of the Division of Lung Diseases at the National Heart, Lung and Blood Institute (NHLBI) presented on the epidemiology and pathogenesis of chronic obstructive pulmonary disease (COPD) and described how these mechanisms overlapped with others thought to be central to the development of lung cancer. He then reviewed the research programs supported by NHLBI, such as COPD Gene, that are already attempting to integrate clinical imaging with molecular pathogenesis research. He outlined the rationale for integrating quantitative approaches to clinical imaging for both lung cancer and COPD as a synergistic opportunity.

From discussions at previous workshops, there is recognition of the major opportunity to advance the dialogue on the use of quantitative imaging tools to cross-fertilize and accelerate image processing research across lung cancer and COPD. This topic emerged as a major focus of discussion during the Workshop, i.e., to devise strategies for more adaptive collaboration across these two fields moving forward.
David Mozley next reviewed Merck’s efforts to evaluate and improve the quality of clinical imaging in their ongoing trials of new drugs for treating advanced non-small cell lung cancer. In this pragmatic experience, issues such as image analysis and slice thickness emerged as critical to the quality of the quantitative imaging. This ambitious effort underscored the importance of teamwork and communication in optimizing the quality of clinical imaging in a drug development process.

Dr. Dan Sullivan, who was representing the Radiological Society of North America (RSNA) presented an overview of efforts by a consortium developed by RSNA and other stakeholders to advance the development of quantitative imaging. The Quantitative Imaging Biomarker Alliance (QIBA) was developed with the mission of improving the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients and time. The overall goal is to develop measurement devices rather than imaging devices.

In this regard, Dr. Sullivan emphasized that from a regulatory perspective, the performance of a clinical measurement has to be undertaken within the context of a specifically defined purpose. He then outlined the partners and the process that QIBA is pursuing in order to make progress on advancing quantitative imaging applications in clinical medicine.

This presentation was followed by that of Dr. Andrew Buckler, who was also representing QIBA. Dr. Buckler outlined a range of specific activities in which QIBA was addressing particular issues related to quantitative imaging in lung cancer drug development. He reported on QIBA’s activities in applying to the FDA for qualification of quantitative imaging as biomarker. These activities were outlined especially in regard to the relevance of the contribution of QIBA participants in defining the sources of lesion-measurement variance in lung cancer drug response assessment.

In the next presentation, Dr. David Yankelevitz reviewed his group’s quantitative imaging work, with several ongoing or completed clinical trials. A key concept emerging from this experience relates to the interface between the tumor nodule and the lung as seen through high-resolution imaging.

The current approach to defining this interface is to have one or more expert radiologists draw a line around the edge of the nodule or alternatively to have the computer choose the boundary based on pre-defined criteria. Dr. Yankelevitz showed a series of high-resolution tumor cases in which the infiltrative and extremely irregular edge of the tumor were evident. It was clear from these images that boundaries drawn using the traditional approaches described above were at best an approximation of the boundary of the tumor.
Reconciling the reality of the complex irregular geometry of tumor volumes known to be a cardinal feature of malignancies, Dr. Yankelevitz proposed the term “zone of transition” to describe the interface or boundary between the tumor nodule and the surrounding normal structures. This observation is relevant, given the intense debate about “ground truth” in determining tumor volume changes and associated measurement variance in the setting of therapeutic response assessment. In essence, it represents an area of inherent uncertainty when measuring tumor volumes and needs to be considered as a separate component when considering potential measurement error.

Dr. Thomas Baer is the immediate past president of the Optical Society of America (OSA) and has been OSA’s chief liaison in the increasing number of joint efforts between the Prevent Cancer Foundation and the OSA. A key development in this regard is advancing the acceptance of open publication of primary imaging data as an integral part of the publication process.

To increase the productivity of this process, Dr. Baer outlined OSA’s efforts to advance quantitative imaging through the strategic development of a lesion-sizing toolkit. This resource is a hosted image processing environment with libraries of published clinical images in DICOM format. Through the Web, researchers can access hosted cases to download, visualize or interact with the stored images. He then discussed a variety of tools, such as AzureBlast, that demonstrate the capabilities of cloud-based hosted computational environments, seen as a possible platform for the next generation of shared analysis and visualization tools linked to the OSA’s open scientific publishing initiative.

Jonathan Silverstein then discussed the relevance of distributed grid computing resources to support and expand quantitative imaging research. He subsequently described examples of the infrastructural development with grid computing resources, such as the NIH-supported Biomedical Imaging Research Network (BIRN), that can facilitate the process of quantitative research. A critical aspect of this approach is related to the culture of case-driven application of technology to support the activities of self-assembled groups of researchers (or virtual organizations) rather than a heavy emphasis on specialized technology.

Dr. Lawrence Rothenberg then discussed issues with the use of ionizing radiation for medical imaging. This included an overview of measures to minimize the dose required to acquire a high quality clinical image. He then described the medical risks associated with these processes and related this exposure to other known types of risks.

A panel reviewed the activities of QIBA in their systematic effort to define sources of variance in precise quantitative imaging. A focus of the QIBA effort was to define the extent of variance in
measuring volume under ideal conditions. This also included an exhaustive series of phantom images that have been acquired under a variety of conditions to look at variations in measurement precision across vendor platforms. The goal is to determine what variables contribute most to the precision or lack of precision of quantitation. Aspects of this work have been published to serve as a reference source for the quantitative imaging community.

In the next presentation, Dr. Venice Archer reviewed the pragmatic process of integrating provisions for high quality quantitative imaging into regulatory-directed clinical trials. This experience was part of the Abigail clinical trial sponsored by Roche Pharmaceuticals. Dr. Archer also presented the experience of integrating directly into the trial a calibration device that was scanned with the patient on each imaging cycle.

Dr. Raúl San José Estépar then reviewed the use of image processing strategies in COPD clinical research, both to characterize airspace and airway disease. In his overview, Dr. San José outlined how the invariant properties of CT, like mass preservation, may provide metrics for COPD disease progression that do not vary with scanning technologies across vendors and platforms. He then outlined the challenges in controlling the variances associated with the imaging process in this setting and demonstrating the challenges in developing quantitative measures for evaluating the clinical course of COPD parallel to the relevant issues already discussed with lung cancer imaging.

Extending the discussion of imaging in pulmonary disease, Dr. George Washko discussed the quantitative imaging issues associated with evaluation of pulmonary artery hypertension, which occurs in 26-90% of the cases of established COPD. Vessel remodeling, inflammation and endothelial dysfunction are cardinal features of COPD and the mechanisms driving these processes have analogues in cancer pathogenesis. Algorithms and vasculature disease metrics developed for large multi-center COPD trials may have relevance to lung cancer image processing.

Dr. John Reilly reviewed the application of lung imaging in NIH-sponsored multi-center trials. An opportunity with more robust quantitative imaging is the potential reduction of surgical evaluations of individuals suspected to have lung cancer (so-called “futile thoracotomy rate”). This is a novel but powerful metric of imaging utility in the diagnostic setting and a fertile area for ongoing image processing research.

Another CT imaging application is the assessment of “lung injury” which is presumed to reflect host response to tobacco or other lung toxins. With CT, areas of lung destruction, manifesting as emphysema, can be measured. Thus, Dr. Claudia Henschke discussed her group’s analysis of the
correlation of lung injury and the actual likelihood of eventually developing lung cancer. The ground truth for these analyses is the outcomes of over 50,000 cases with follow-up that have been studied under the International Early Lung Cancer Action Project (I-ELCAP). Dr. Hensechke also provided information as to how imaging findings can be used to improve risk estimates for lung cancer since those estimates are traditionally based solely on clinical features of age and smoking history.

This session concluded with a panel discussion of potential areas for collaboration between the two fields and a number of constructive options were offered.

To begin the next session, Dr. Robert Nordstrom described the range of image processing research activities of the National Cancer Institute. This includes efforts such as the Reference Image Database for Evaluation of Response (RIDER). There are several issues motivating the development of quantitative imaging in clinical drug development: 1) to enable more rapid go-no go decisions for lung cancer drug development candidates, 2) to allow for smaller study sizes to evaluate new candidate drugs, and 3) to allow faster regulatory approval times to validate the benefit of new targeted therapies.

A new grant mechanism for the Cancer Imaging Program was revealed in a recent program announcement (PA-10-067). This is an RO1 mechanism that is intended to support investigator-initiated quantitative imaging applications. The full announcement is hosted at www.http://grants.nih.gov/grants/guides/pa-files/PA-10-067.html.

Dr. Nicholas Petrick then gave a detailed review of the FDA Center for Devices and Radiological Health (CDRH)'s investigation of quantitative CT through anthropomorphic phantoms. This presentation summarized the status of FDA efforts in regards to studies of simulation, physical phantoms and actual clinical imaging measurement. The ongoing progress of this work, which focuses on defining and then minimizing sources of variance in quantitative imaging can be found at Public Access (https://imaging.nci.nih.gov). To date, the FDA efforts have resulted in an FDA data collection of over 5,000 data sets that now comprise a reference standard. Research in lung CT today suggests that imaging bias, mainly affected by nodule size and variance, is small under standardized conditions.

In the next presentation, Dr. Gudrun Zahlmann of Roche Pharmaceuticals discussed the topic, “Tumor Volume and Clinical Outcome - A role for the Re-use of High Quality Quantitative Image Databases?” In this superb synthesis, Dr. Zahlmann reviewed the presentations and discussions at the Workshop in relation to the process of qualification of quantitative CT as a biomarker of drug response for use in FDA- regulated clinical trials. Dr. Zahlmann had discussed three
qualification options, including: 1) to develop volumetric measurement as a novel biomarker for clinical outcome and qualify it as a novel approach on its own, 2) to develop volumetric measurements as replacement for uni-dimensional measurements in RECIST and 3) to develop a combination of 2D – 3D measurements as biomarkers.

Dr. Zahlmann concluded with the question, “Can we encourage a process with the pharmaceutical industry to routinely donate clinical trials data to a shared database allowing repurposing of data to support a FDA-directed qualification process for imaging biomarkers?”

In this regard, since so many drug approvals involve internationally-acquired clinical trial results, it is critical to elucidate the legal requirements needed to allow international cooperation on this effort. In addition, to accelerate progress in this effort, a clearly-identifiable benefit must be articulated for trial sponsors to join in and contribute to such an activity.

To facilitate cooperation across clinical trial accrual sites, there needs to be a standardized procedure to generate images across all studies. We need to have an understanding of the essential meta-data that make a database suitable to address the intended regulatory requirements. This unprecedented effort will require ongoing guidance from regulatory bodies such as the FDA, to ensure that the process results in an outcome acceptable to the regulatory agencies.

A significant opportunity to optimize this process relates to using prior experience with the development of RECIST, to ensure that previous mistakes with that effort are not repeated. To accomplish this, there may be a need for an independent group that is driving this activity, one that is accepted by regulatory bodies.

Dr. Marietta Anthony of the Critical Path Institute (C-Path) followed up by outlining the work of C-Path in securing FDA approval of the use of renal biomarkers to monitor drug toxicity in a recent successful qualification process. Given C-Path’s mission and previous experience with FDA approval of a qualified biomarker, this group may possess the type of expertise to guide the qualification process for quantitative imaging as a biomarker.

One mechanism to help the field access the level of competence in volume determination with clinical images is a comparative assessment of different image-analysis algorithms. Dr. Anthony Reeves outlined how he had sponsored such an algorithm assessment process. This involved development of a benchmark set of image pairs for characterizing the performance of change-in-size lung nodule measurements: 1) establishing benchmark results for the change in size measurements using a variety of CAD methods, 2) establishing benchmark results for manual measurements, 3) exploring metrics to evaluate new measurement methods, 4) making the
DICOM dataset of carefully characterized cases available to the public and then 5) using the responses to the evaluation to improve benchmarks on the basis of the results and new understanding.

In the final presentation, Dr. Nasser Altorki reviewed the status of the completed neoadjuvant window of opportunity trial which has just been published in the *Journal of Clinical Oncology* (described on page two of this summary report). The conduct of this trial has been a major focus of many previous image processing workshops, but it is a new approach. The methodology of this proof-of-concept trial is to do a baseline biopsy to determine in what percentage of patients the relevant signaling pathway is present and at what level of functioning. Using quantitative imaging along with molecular diagnostics, the consequences of brief clinical exposure to the drug can be studied by volumetric CT and evaluation of serially acquired tumor tissues. In the pazopanib trial discussed by Dr. Altorki, 35 Stage I/II non-small cell lung cancer patients were exposed to the drug for an average of three weeks prior to the resection of the primary tumor.

From the Workshop perspective, there is hope that all raw data from the imaging and molecular analysis from these neoadjuvant, window trials will eventually be made available to aggregate with other similar datasets and then re-analyzed to determine in greater detail than ever before, what are the critical molecular mechanisms driving the progression of early operable non-small cell lung cancer.

The Breakout sessions that occurred in two groups during the course of the workshop were then presented to the assembled faculty. Extensive discussions focused on strategies to extend acceptance of data sharing of clinical trials results. A useful proposal was to encourage the practice of releasing only a partial amount of the trial data to overcome the theoretical concern of identification of trial participants.

**Workshop VII Outcomes**

The major conclusion from this Workshop in regard to a strategy for accelerating progress with quantitative imaging for lung cancer drug development involves focusing efforts of all stakeholders in working jointly towards a “rolling” qualification of volumetric imaging of lung lesions as a biomarker of drug effect in lung cancer. The “rolling” term describes an ongoing and escalating level of qualification claims as the science and available data support expansion of the FDA approval of how the imaging biomarker can be reliably applied.
Further, there is recognition by the Workshop participants that the process used for this qualification of volumetric imaging in lung cancer will serve as a precedent for qualification of other imaging tools, both in cancer and in other drug development efforts. Timely development and approval of this imaging qualification approach will require new understanding of the measurement science of quantitative imaging.

Capturing the image data with associated meta data will also require new infrastructure to support the storage and distribution of these high-content modalities. In turn, new image processing tools will be required to translate these quantitative processes into routine clinical practice. This is a major challenge for the foreseeable future. Cooperation among diverse collaborators will be essential to enable the rapid organic evolution of this field, so that improved outcomes with lung cancer and COPD can occur.
Appendix 1. **Summary of Workshop-related Publications:**

- James L. Mulshine, Thomas M. Baer, and Ricardo S. Avila, **Workshop VI:** Optics Express Special Interactive Scientific Publishing Supplement "Introduction: Imaging in diagnosis and treatment of lung cancer," Optics Express (suppl) 18, 15242-15243 (2010)