2015 EXECUTIVE SUMMARY

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Abstract
The Prevent Cancer Foundation Lung Cancer Workshop XII: Quantitative CT Imaging: Screening and Tobacco-Induced Disease Management was held in Bethesda, Maryland on May 4 and 5, 2015. The two goals of the Workshop were to define strategies to drive innovation in pre-competitive quantitative research on the use of imaging to assess new therapies for management of early lung cancer and to discuss a process to implement a national program to provide high quality CT imaging for lung cancer and other tobacco-induced disease.
Summary
For the twelfth year, the Prevent Cancer Foundation hosted the interactive Workshop on Quantitative Imaging: Screening and Tobacco-induced Disease Management. In this forum a diverse group of biomedical professionals share perspectives on how to accelerate the application of quantitative computed tomography (QCT) of the thorax to improve outcomes for lung cancer and other tobacco-induced diseases of the chest. A key defining feature of this sustained effort is working toward integrating critical different perspectives including technical, strategic and policy, to define plans to achieve the workshop goal of accelerating progress towards more favorable patient outcomes (1). Since the previous Workshop, we have witnessed the landmark decision by the Centers for Medicare and Medicaid Services (CMS) to follow the evidence-based recommendations of the United States Preventive Services Task Force in deciding to reimburse the use of low-dose spiral CT as a screening tool for early lung cancer detection in a high risk, tobacco-exposed cohort (2).

In making this decision, CMS was obliged to ensure that federal health care resources invested with implementation of the CT-based lung cancer screening were appropriately focused on individuals who are most likely to derive health benefit with minimal avoidable harm. However, a consensus does not exist defining a single best practice for screening management. Most often, the clinical decision to begin an invasive diagnostic work-up in an individual undergoing the screening process is governed by the size of a pulmonary nodule that may be found in the course of annual screening by use of QCT. It has been reported that the “false positive” diagnosis can be significantly reduced if performing further diagnostic work-ups in the baseline round is restricted to individuals who are found to have pulmonary nodules that are greater than 6mm in diameter(3).

However, we know in routine clinical practice there could be marked variability in accuracy of measuring small pulmonary nodules (4). Developing a defined imaging process for the reliably accurate QCT to measure pulmonary nodules is an essential part of ensuring the quality of care in the lung cancer screening process. This challenge represents a critical use case to demonstrate the application of imaging as a clinical management biomarker to ensuring optimal outcomes with this new population-based cancer screening tool.

In his overview comments, Steering Committee Chair Dr. James Mulshine outlined that the focus of the Workshop was to identify gaps or bottlenecks or opportunities with strategic issues in implementing effective QCT-based management to improve lung cancer screening outcomes. Given the situation with ramping up national implementation of lung cancer screening, a major issue in this regard is how to optimize QCT in a routine clinical practice setting. This effort is also linked to the larger question of how to integrate continuous process improvement into the
national lung cancer screening process so as to enable better, cheaper, faster approaches to lung cancer screening as they emerge and then are implemented to improve the efficiency of this service. This issue is also an important consideration for CMS in seeking the optimal approach to deliver this service. The foundational experience for cancer screening for CMS has been their previous experience in managing quality issues for breast cancer screening. Much of this effort was made in collaboration with the American College of Radiology (ACR) in implementing a national quality system for breast cancer screening. This experience is being largely replicated in developing a new lung cancer screening quality approach as outlined in a process, which the American College of Radiology has called Lung-Rads (5). A core aspect of that effort is the establishment of a national lung cancer screening archive that will aggregate site specific information that ensures defined quality standards are met. With lung cancer screening however, there are new opportunities to have a greater impact with such efforts, as the information obtained with a lung CT contains three-dimensional information that is much more informative than the usual two-dimensional information obtained with standard mammography. At this year’s Workshop a key discussion topic focused on the value of creating national image archives in addition to the standard data previously obtained by the ACR. This issue presents a whole range of technical and policy issues and therefore was established as one of the two topics for the 2015 Breakout discussions. The title of the Breakout Session was “Implementing Lung Cancer Screening Registries to Accelerate Clinical Management Research: Policy Considerations.”

The other major topic for a Workshop Breakout was “Imaging the Extent of Tobacco Injury during Lung Cancer Screening”. This topic reflects the remarkable harvest of imaging information obtained by a low dose thoracic CT. Beyond the visualization of suspicious pulmonary nodules for potential early lung cancer, thoracic CT also permits an assessment of COPD status, coronary artery calcification as well as other major diseases. The complex question emerges as what to do with such information. Is it reliable? Is it routinely available? Does the focus on lung cancer imaging compromise the quality of the other pulmonary or cardiac imaging performance? Since lung cancer, COPD and heart disease are all related to tobacco-exposure, does this provide an impetus for organizing these three major diseases into a single care setting as part of an annual CT for lung cancer screening?

In bringing together these three diseases when the usual care patterns are to manage these entities in separate settings, there are a number of challenging health care, advocacy, reimbursement, and technical imaging issues. The most disruptive question in this regard was whether consideration should be given to reframing lung cancer screening to tobacco-injury screening, given that many major health consequences of tobacco injury can be visualized. A rationale supporting such an approach is that smoking cessation would benefit all of these same
diseases as would other dietary and exercise lifestyle changes and by integrating their management, one may optimize reducing risks of the three major causes of tobacco-related mortality (6, 7). This Breakout was intended to explore these questions and recommend how progress could be made moving forward.

The Keynote address for Workshop XII was delivered by Dr. Fred Hirsch, who outlined how new trial methodologies are being developed to accelerate the validation of molecularly targeted therapy. He reviewed the work of the National Cancer Institute and the Foundation for the National Institutes of Health Lung Master Protocol (Lung-MAP)-A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400 (8). In his presentation, Dr. Hirsch described how this protocol involves biomarker-driven drug selection in an integrated phase II Master Protocol structure. This novel trial approach employed a common analysis platform (next-generation DNA sequencing) to identify actionable molecular abnormalities, followed by randomization to the relevant targeted therapy versus standard of care. This efficient approach saves time and vastly increases patient access to potentially active drugs by leveraging the full NCI national clinical trials mechanism to implement this innovative study.

For the third year the James L Mulshine National Leadership Award was presented; this year’s honoree was Dr. Claudia Henschke. The award was presented by Dr. Andrew von Eschenbach who was the Director of the National Cancer Institute at the time that the randomized National Lung Screening Trial was launched. In his comments, Dr. von Eschenbach reviewed the contributions made by Dr. Henschke, noting the adversity often faced by innovators who bring forward ideas that challenge the status quo and observing that the essence of leadership is embodied in the ability to overcome obstacles to the acceptance of new ideas.

A key aspect of this Workshop has been the active leadership role of patient advocacy groups in advancing the application of quantitative imaging. Carolyn Aldige, President and Founder of the Prevent Cancer Foundation, host of this workshop series since its inception, chaired the session. The first presenter was Laurie Fenton Ambrose, President and CEO of the Lung Cancer Alliance; she outlined their role in advancing lung cancer screening from a policy perspective. A key aspect of this work has been to organize the institutional consortium called the National Framework for Lung Cancer Screening Excellence, to ensure the quality and equity with the national implementation of lung cancer screening. Dr. Jeff Allen next reviewed the efforts of Friends of Cancer Research, especially focusing on how their organization worked to help implement the innovative new trial structure described in Dr. Hirsch’s keynote presentation. John Walsh of the COPD Foundation outlined the catalytic role his foundation has had in working with the National Heart Lung and Blood Institute and others in implementing the
innovative studies of the COPDGene Study. This has been a multi-faceted effort to define the genetic basis for COPD progression. The COPD Foundation has been an active partner in these efforts to ensure COPD patients’ needs are met as well as ensuring that COPD patients are helping to achieve the study goals of this effort. Mr. Walsh reported how patient engagement was central to achieving very rapid and large accrual goals (9). An important part of this effort has been the progress made through patient donation of personal health information in ways that overcome bottlenecks in assembling large enough databases to validate clinical outcomes with COPD. Another major aspect of the COPDGene effort has been on thoracic CT imaging of COPD signatures, which could represent a strong bridge between the lung cancer and the COPD communities. A number of promising avenues for collaboration exist between the lung cancer and the COPD communities.

In the final presentation, Clay Alspach, Chief Counsel for the Energy and Commerce Committee of the US House of Representatives, outlined the goals of the proposed legislation called “21st Century Cures Act” (10). Mr. Alspach outlined that the goal of this legislation was to help modernize the health-care innovation infrastructure, incorporate a patient perspective into the drug and device approval process, support advances in personalized medicine, streamline clinical trials, and provide more resources to support cutting-edge research and help young scientists. He noted that the spirit of the legislation and the goals of the Workshop seemed to be highly aligned. He commended efforts to link science to policy to accelerate innovation.

Dr. von Eschenbach, who uniquely served as Commissioner of the Food and Drug Administration following his directorship of the NCI then led a lively panel discussion of pharmaceutical and imaging industry leaders on how industry can collaborate to further accelerate progress in reducing the mortality burden of tobacco-related diseases. A number of successful models of pharmaceutical/academia collaboration were discussed with strong support emerging for the more combinatorial approaches to drug development represented by the Master Protocol effort. A repeated comment was that cross-industry collaborations were occurring with ever-greater fluidity, but academic institutions were not as comfortable with such complex interactions.

A specific example of this was with models for clinical trials contracting language where industry has moved to accepted template language but academic institutions often still required customized language. Dr. Greg Curt of AstraZeneca suggested that early progression mechanisms for lung cancer may be shared with late stage lung cancer and efforts should be directed to mapping shared targets to potentially identify already developed agents that may be useful in treating early stage cancers such as in the adjuvant setting. He also suggested a greater
focus on mapping shared biological mechanisms across small cell and non small cell lung cancer, as understanding the biology is the key step in developing effective therapeutic tools. The rising numbers of early stage lung cancers detected through lung cancer screening will make these studies much more feasible than in the past.

He also suggested that innovative approaches tailored for early, airway-confined lung cancer could be approached more safely and efficiently with aerosolized drug delivery. AstraZeneca had supported an NCI effort to use aerosolized budesonide as a chemopreventive approach in a pilot trial in Milan in a trial of subjects with non-solid pulmonary nodules.

Dr. Richard Frank, Chief Medical Officer at Siemens, discussed the interplay of diagnostic imaging tools such as QCT to also be used as a biomarker to measure therapeutic response. He outlined imaging industry efforts to ensure that these imaging biomarkers have the performance capabilities to reliably guide clinical management as a key shared objective of the imaging industry with the Workshop goals.

Drs. Ronit Simantov of Pfizer and Joseph Treat of Lilly both outlined how closely the pharmaceutical industry was tracking developments in lung cancer, both in regard to molecularly targeted therapy as well as with advances in lung cancer screening. Broad consensus emerged as to the need for industry and academia to expand collaborative interactions.

Dr. von Eschenbach suggested that new business models were needed for lung cancer, more like the ecosystem in the computer industry that fluidly collaborates to continuously produce cheaper, better, faster portable computers. To achieve this vision, Dr. Curt suggested use of national agencies such as NCI as a safe harbor to support such efforts and to potentially house sensitive data resources. Pragmatic issues were also discussed, such as the fragmentation in aspects of the FDA review structure that is a barrier to considering integrative diagnostic and therapeutic platforms. An opportunity for assisting FDA regulatory review was to work more strongly with patient advocacy groups to enable more robust participation of patients and subjects in diagnostic and therapeutic trials. Larger trials with rapid accrual can greatly accelerate innovation, but the key to sustained progress in such efforts is in ensuring that true patient needs are actually being met.

The next session was entitled “Establishing the Foundation of Precise Integration of Imaging in Early Lung Cancer Care” and explored the many issues related to establishing high quality and robust methods in lung cancer imaging and its expansion to other smoking-related diseases. Mr. Ricardo Avila presented on the numerous image quality issues that have been recently been
uncovered in a wide range of CT scanner systems, the impact of these issues on measurement performance, and the steps being taken to maintain high quality imaging in imaging studies. One area that has received a great deal of recent attention by the Quantitative Imaging Biomarker Alliance (QIBA) small nodule profile committee is the distribution of quantitative guidance on minimum levels of volumetric change necessary for a sub-centimeter lesion to overcome standard levels of imaging variability. Mr. Avila described the current QIBA small nodule profile guidance and gave an overview of the theoretical and experimental methods used to arrive at the guidance estimates. He then went further and gave an overview of recent data collected with CT pocket phantoms and a new CT table phantom designed to be scanned with patients as a radiological quality assurance instrument to provide verification of minimum quality standards during patient imaging. He concluded with the recommendation that continuous and individual CT scan image quality monitoring is needed to overcome the measurement issues associated with high levels of imaging variability within individual CT scans as well as across scanner models.

Dr. Claudia Henschke followed with an overview of the I-ELCAP global lung cancer screening experience, including numerous insights being uncovered through the analysis of this large, high quality database. Dr. Henschke continued to place an emphasis on maintaining a well-defined and monitored screening regimen during clinical management. Numerous advances in understanding of early lung cancer management were reviewed, including identification and measurement of cardiac diseases and COPD. Recent results on the utilization of radiation treatment alone vs. surgery alone and the impact of mediastinal lymph node resection were reviewed. Overall Dr. Henschke showed the importance of constant refinement and monitoring of data collection and an overview of the more than 200 publications that resulted from more than two decades following this approach.

Dr. Nicholas Petrick then gave a presentation on the steps being taken by FDA and the RSNA’s QIBA initiative to validate imaging biomarkers. Dr. Petrick covered the main analyses being performed to establish imaging biomarker performance including analyses of bias/linearity, repeatability, and reproducibility.

Dr. Raul San José Estépar addressed the technical feasibility for an integral imaging set-up to quantify smoking related diseases based on thoracic CT. Dr. San José described novel imaging approaches to perform high-throughput detection to produce a unified report that could cover status checks for COPD, coronary vascular disease, atherosclerosis, pulmonary arterial hypertension, cachexia, osteopenia, scoliosis, steatosis, and anemia. On-going validation studies can offer the needed reassurance to integrate these tools within the screening workflow.
The need for large image-based registries for algorithm development and validation was further underscored.

Dr. David Yankelevitz followed with a presentation on “Lung Cancer Registries as a Transformation Resource for Rapid Learning Across Tobacco-related Diseases.” Dr. Yankelevitz further expanded on the multi-disease opportunities associated with collecting a high quality and image-based lung cancer registry. Dr. Yankelevitz concluded with a description of the newly launched “Early Lung Cancer Research on Treatment” (ELCART) project and the focus it will have on enabling rapid learning for early lung cancer and associated diseases.

Dr. Paula Jacobs then concluded the session with a presentation on the NCI’s recently launched initiative on Algorithm Challenges. Dr. Jacobs announced that a challenge was planned that would ask algorithm developer participants to distinguish cancer patients from those without cancer. The winners of the challenges would potentially receive a substantial monetary prize. Dr. Jacobs further announced that the algorithm challenges would likely be made open to participation in 2016.

The following morning, Dr. Cheryl Healton opened the session, addressing the issues of integrating tobacco cessation with lung cancer screening and spoke about its financial benefits, as well as the critical health policy dimension. These are issues that will be important to address internationally as other nations commit to providing lung cancer screening services.

Dr. Harvey Hecht then provided an update on the status of coronary calcium analysis with low dose CT. The correlation with calcium analysis performed as part of lung cancer screening compared to dedicated coronary calcium studies has shown close correlation (11). This is important since dedicated coronary calcium has been shown by many studies to be the most reliable test for predicting future heart attacks. With lung cancer screening being recommended on an annual basis, the opportunity to image the coronary arteries annually also exists and there is emerging evidence that measuring rate of change in coronary calcium may be the most important indicator of an impending event. In addition, diet and lifestyle changes are being shown to effectively manage many of the changes documented by coronary artery imaging studies. If such measures are integrated into thoracic CT screening for tobacco related injury, there would be a potential to mitigate concerns regarding excess cost and overdiagnosis since invasive surgical methods would not be the primary management focus. Dr. Hecht also showed data stating the accuracy of new reconstruction algorithms for the joint quantification of coronary arteries and nodules in low-dose screening. This further reflected that CT technology advancements are providing a common imaging set-up for tobacco-induced disease screening.
The use of imaging as a biomarker in lung cancer screening is one of the most advanced applications of quantitative imaging and this carries with it many complicated statistical and methodology issues. What is the level of performance required to reliably determine if a tumor volume really changed or did some aspect of the imaging technique change in a way that affects volume quantitation as a measurement artifact? Dr. Nancy Obuchowski, the lead statistician for the Quantitative Imaging Biomarker Alliance, reviewed the emerging progress in developing a new approach to defining medical quantitative imaging. Quantitative imaging requires characterization beyond the simple notions of sensitivity, specificity and accuracy to give a more granular picture of imaging performance. The fundamental need is to allow the results of the clinical quantitative imaging relative to “ground truth” in a reproducibly definable fashion. This is a multi-parameter task and a working approach has required creating a specifically defined vocabulary of terms to define imaging performance along with the creation of new descriptors such as the concept of “Total Deviation Index” or TDI to numerically score the definable complexity in the performance of quantitative imaging biomarkers.

Breakout Discussion Summaries

Breakout A
Implementing Lung Cancer Screening Registries to Accelerate Clinical Management Research: Policy Considerations

This year’s Workshop Policy breakout session allowed for a robust discussion of the ramifications of the recent CMS final coverage determination for lung cancer screening and the role registries will be play in improving our knowledge of early lung cancer, precancerous conditions, advancing new research strategies and collaborating with those investigating other tobacco-related diseases in mutually beneficial ways. Participants acknowledged that the critical first step was to embed lung cancer screening within the public health infrastructure in the most efficient, safe, equitable, and responsible way at the community level. Several of the breakout participants were nurse navigators from community hospitals who had already begun to build-out screening programs at their respective medical centers. Each shared examples of best practices in care and offered perspectives on the types of educational tools needed to better assist them during shared decision making sessions as required by CMS. The Lung Cancer Alliance’s National Framework of Screening Excellence in the Continuum of Care, which includes to date over 350 medical centers nationwide, was considered a key blueprint and strategy to advance expeditiously and systematically this new preventive service within our health care system. Also acknowledged and discussed was the opportunity presented by the National Framework network to facilitate the collection of data through the various proposed
registries as well as the potential to collect biomedical samples – which would help contribute to outcomes research and ultimately revolutionize cancer research and patient care.

A major topic of discussion related to the challenges with the implementation of widespread screening. Here there were a variety of perspectives and they differed, depending on the role of those involved in the screening process. There were specific operational issues that related to the ability to easily identify those who were eligible for screening and difficulties in accessing healthcare information systems. Another challenge related to lack of awareness both on the part of potential referrers as well as potential participants. In addition, the amount of time necessary to register patients and engage in shared decision making was a concern, given uncertainties in terms of resources and amount of reimbursement that would be necessary to properly support those activities.

Related to this issue, a number of participants were troubled by the consistent over emphasis on harms, which misrepresented the evidence relative to a discussion about the balances between potential benefits and harms with lung cancer screening. In particular, there was a consensus that the potential benefit of screening was being understated and that this bias was evident even within recommendations from certain major societies. An important concern was the relationship between the core result from NLST which entailed a baseline and two annual rounds of screening resulting in a 20% mortality reduction and how that relates to the full potential benefit with ongoing annual lung cancer screening. Since lung cancer after heavy smoking is associated with a continuous, sustained lung cancer risk, the potential misunderstanding/misrepresentation of this benefit can have a large impact both on a person’s willingness to be screened as well as the healthcare provider’s inclination to recommend screening. Potential solutions to these misrepresentations were to develop online patient oriented information and also to organize a joint society statement that clearly defines what is known about potential benefits and harms.

A second major topic of discussion related directly to the role that registries can play in terms of enhancing the entire screening process. As a first consideration, it was necessary to define the differences between registries and management systems. Currently, entering data into a CMS certified registry will be required for CMS reimbursement and CMS has defined core data elements that need to be collected. However, there is no requirement that the registry track participants and provide assistance in terms of ease of follow-up. Management systems are available that perform this task but are independent from the CMS type registry.

Potentially both functions could be combined into a single system which would have obvious advantages over the current CMS process and this enhanced system could play a vital role in
allowing continuous process improvement with lung cancer screening. Acquiring such granular follow-up data will allow for updating of protocols based on large amounts of data with follow-up. This type of process has occurred in the I-ELCAP research and has been the primary evidentiary basis for many of the current I-ELCAP recommendations for screening management. The opportunity now exists to dramatically enhance the data collection, including the image data, and to compare different protocols and outcomes. In addition, comprehensive registry data will offer opportunities to compare outcomes between institutions both regionally as well as nationally and allow for standards to be set. There also exists the opportunity to move into the realm of actual clinical research in the context of clinical care. This can go well beyond that of the tracking of positive and “false positive” rates and actually move into areas of quality assurance, especially if actual images are collected as well.

An additional topic that was briefly discussed was the opportunity to collect not only the diagnostic information that comes from the screening but to also move into the realm of therapeutics as there should now be a shift towards a greater proportion of early stage cancers that are diagnosed. Information about these cancers should also be collected in the context of a clinical care registry. Opportunities to enhance research on treatment are vital especially given the well-known difficulties in performing randomized treatment trials for early stage disease. Finally, the additional imaging information that is available from the review of the thoracic cavities of heavily tobacco-exposed populations is of interest. The measurement of coronary artery calcium is an informative biomarker for risk of significant coronary disease and this information is generally available on the screening CT scan done for lung cancer (11, 12).

**Breakout B**

**Imaging the Extent of Tobacco Injury during Lung Cancer Screening**

In this discussion the group focused on technical issues associated with performing quantitative lung lesion measurements. It was recognized by the breakout group that the measurement of change in sub-centimeter lung nodules requires significantly better CT image quality performance as lesion size decreases. With the imminent global rollout of lung cancer screening services, the breakout group focused on establishing minimum CT image quality requirements. Three main types of image quality properties were considered important to characterize. First, it is important to understand and set limits on fundamental properties of the imaging system including: resolution which involves both 3D point-spread function and 3D sampling rates; linearity; noise and finally spatial warping.

A second type of image quality performance measure provides detection and volumetric measurement performance statistics for simple geometric objects such as spheres, ellipsoids, and platonic solids. The third type of image quality performance measure involves estimation.
of performance measures for clinical tasks (such as nodule detection/measurement and COPD detection/measurement) given the image quality of the obtained CT image.

It was further recognized that setting minimum limits on these image quality measurements would be advisable for each combination of CT scanner and acquisition protocol at an institution. However, differences in patients (e.g., patient size, calcifications, and implanted devices) and final scanner settings (e.g., changes in mA, kVp and reconstruction settings) can introduce additional performance variability. It was therefore determined that monitoring such image quality measures for each patient scan would provide the most thorough check for image quality suitability and is ultimately where the field should head. There is a great deal of variation in imaging platforms and there is also variability in how scans are acquired in different settings. The ongoing efforts in collaboration with QIBA have been to define robust procedures to consistently achieve high quality quantitative results for individuals given real world imaging realities (4).

In closing, the field of quantitative CT imaging of the lung is rapidly emerging related to the national implementation of lung cancer screening. In this Workshop, there was considerable discussion about the complex, interdependent technical challenge of implementing optimal conditions to allow a high quality CT study for early detection of lung cancer under the newly approved National Coverage for lung cancer screening. To ensure consistency in the imaging measurement tasks, such as with the process of pulmonary nodule volume determination, new provisions such as the use of a small, table top phantom may be needed to help minimize measurement variance. Monitoring such issues with Data registries set up to capture comprehensive lung cancer screening data including the full DICOM image files could be a powerful tool in allowing continuous quality improvement with the implementation of this screening service.

In addition, other complementary opportunities are also emerging. One such factor is the ability to measure other thoracic findings such as with coronary calcium. This is important since heavy smokers also have an elevated rate of coronary artery disease and coronary calcium analysis is an informative marker of risk for subsequent myocardial events (12). This may represent a unique public health opportunity for further benefit with the annual screening encounter in quantitating the extent of coronary calcium formation, as this information may be useful to enable economical interventions such as diet and exercise modifications in this high-risk screening cohort.
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