EXECUTIVE SUMMARY

Lung Cancer Workshop IX "Application of Quantitative CT Imaging to Early Lung Cancer Management: Accelerating Progress"

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"Application of Quantitative CT Imaging to Early Lung Cancer Management: Accelerating Progress"

The Ninth Prevent Cancer Foundation Workshop entitled "Application of Quantitative CT Imaging to Early Lung Cancer Management: Accelerating Progress" was held in Hyattsville, MD on May 3 and 4, 2012. A wide range of stakeholders attended the Workshop in an effort to build on the momentum established by earlier Workshops in this productive series. A second goal of Workshop IX was to discuss the development of policies surrounding implementation of population-based screening of high-risk individuals.

In his introductory overview, Dr. James Mulshine, Rush University, reported that this workshop series was established to catalyze the use of quantitative imaging techniques in clinical applications of CT. The initial focus of the Workshops was on better quantification techniques that will add value for improving patient care, as well as improving efficiency of clinical trials exploring new drug targets to reverse the course of lung cancer. The hypothesis was that more precise imaging would decrease the number of subjects per trial and shorten time-on-study per subject, which would reduce drug development times and speed development of new lung cancer treatments. This breakthrough would overcome the problems created by current lung cancer research approaches, which are difficult, slow and costly.

The keynote address was delivered by Dr. Andrew von Eschenbach, former Director of the National Cancer Institute (NCI) and former Commissioner of the Food and Drug Administration (FDA). He set the tone for addressing such a major public health challenge in an effort to stem the tide in the War on Cancer. Dr. von Eschenbach envisions using a population-based early detection strategy centered on the use of low-dose computed tomography (LDCT) scans, validated by a large and costly study of a high risk population of current and former smokers. This study, the National Lung Screening Trial, was launched during his tenure as Director of the NCI and he outlined the confluence of issues that influenced the decision to begin the study.

Next, Dr. Daniel Sullivan, Duke University, and Science Director of the Radiological Society of North America, reviewed the work he has led with the Quantitative Imaging Biomarker Alliance (QIBA) in evaluating the many aspects of achieving robust measurements of clinical images. This work has led to numerous publications and an extended dialogue with the FDA about the approach to responsible regulatory approval

of specific applications of quantitative imaging used as a biomarker in a formal clinical setting, such as in the process of new drug approval.

The third speaker of the opening plenary, Dr. Kyle Myers of FDA, reviewed the complex regulatory issues embedded in moving image quantification into a regulatory environment. The Food and Drug Administration has been working with a number of partners, but the quantity of images, the range of settings acquiring clinical images and the array of uses in which such imaging tools are being applied comprise an enormous review challenge.

The subsequent presentations surveyed progress across a number of areas. Dr. Larry Clarke of the NCI outlined the progress made by the Quantitative Imaging Network in more rigorously integrating quantitative imaging approaches into early stage clinical trials. Dr. Gary Kelloff, also of the NCI, outlined how the strategic partnership with the Foundation of the National Institutes of Health is supporting a number of trials in which quantitative Positron Emission Tomography (PET) is being evaluated as a tool to more effectively gauge drug response.

Additional presentations reviewed the quantitative imaging process to define and then minimize measurement variance so as to improve imaging performance. These included work on quality control, integration of phantoms, and software development. It is emerging that variance on quantitative approaches is less problematic if one determines the volume of the change between two time points rather than attempting to characterize the volumes of the two individual lesions and then subtracting one from the other to determine the difference. In this regard, negative information is still quite valuable, emphasizing the need to study cases not only with significant documented changes, but other cases in which no meaningful change in volume occurred.

Rick Avila of Kitware outlined a range of new and growing high resolution image collections (associated with clinical outcomes), including a growing resource of lung CT images donated by patients who are motivated by their earnest desire to accelerate the progress of software development to assist in early lung cancer management. Presentations by Drs. Claudia Henschke, Russell Bowler and John Newell touched on the convergence of imaging approaches across lung cancer and COPD to allow better understanding of the relationships and shared pathogenesis between these two smoking-related diseases. The ongoing activities of the COPDGene program were presented and in these efforts there are over ten thousand subjects with GWAS, CT, spirometry and other characterizations which are now the subject of intensive research scrutiny.

Of interest was the cross analysis of parallel work in COPD to allow optimal image acquisition parameters - which shared many similarities with lung cancer acquisition requirements, but had more demanding requirements for characterization of quantitative aspects of anatomic components in the periphery of the lung. One of the more promising areas of potential action following the workshop was the opportunity to obtain the necessary resources to continue to do follow-up of the COPDgene study population.

In Breakout Sessions, Workshop participants addressed two key topics related to the development of policy surrounding lung cancer screening programs: the status of "Implementing Quantitative Imaging Processes in Screening and Treatment Clinical Settings" and "Progress with Quantitative Imaging from a Technical Issues and Opportunity Perspective".

In the Screening Implementation Breakout Session, the group discussed the question of how to broaden the dialogue nationally about the opportunity presented by lung cancer screening to save lives. The transition in management of lung cancer from late stage disease to early stage disease mirrors the trend that occurred over the last decade for breast cancer. This dialogue is important not only for developing effective national screening programs but also has profound relevance to lung cancer drug development, as finding many more early stage patients provides the opportunity to develop less costly, safe, and more effective adjuvant therapy for treating resectable, early stage lung cancer.

The group reviewed progress with patient-donated image collections and outlined approaches to broaden participation in this very interesting new approach to image collection that provides unrestricted use of clinical follow up information. Discussion also centered on defining steps to accelerate responsible dissemination of lung cancer screening services.

An area of discussion focused on the apparent resistance of portions of the medical community to endorse screening, despite the positive results of the NLST. Part of the discussion focused on the need to expand the supply of high quality data that demonstrate how concerns about radiation exposure and unnecessary interventions can be alleviated. Moving forward there is a great opportunity to collect data in an ongoing fashion from the many institutions now performing CT screening. This will provide input for the important process of continuing evaluation of data collected in the clinical setting which can be used to continuously update protocols. Dr. von Eschenbach, co-facilitator of the Breakout Session, made the observation that the community should

consider working with large corporate partners in order to gain acceptance for screening and cited as an example the group from IBM who developed Watson.

Laurie Fenton of the Lung Cancer Alliance was one of this breakout group's facilitators; she outlined the important effort of the Lung Cancer Alliance, working with a broad consortium of institutions on a "Framework" to responsibly guide the development of low dose CT lung cancer screening programs. So far, close to 200 institutions - including many NCI-designated Cancer Centers - have opened lung cancer screening programs dedicated to providing high-quality, multi-disciplinary screening services committed to principles of transparency, quality control and incorporation of national best practices. When institutions make a commitment to honor these principles, the quality of delivered screening services will be greatly improved. This will lead to fewer unnecessary invasive procedures being performed, with fewer treatment complications, especially in regard to complications of surgery.

Further measures to improve outcomes with lung cancer screening were discussed, as were policies to ensure integration of lung cancer screening with tobacco cessation measures. In addition, issues with cost effectiveness of lung cancer screening were discussed and it was noted that high quality screening management was associated with an improved cost profile for the delivered care. Thus, there are two motivations for optimizing screening programs: First, it leads to better outcomes with fewer complications and second, it reduces the cost of screening deployment.

As previously discussed during this Workshop series, quantitative CT enables the conduct of innovative trial structures, such as neoadjuvant, window-of-opportunity studies that provide a powerful way to define how and in whom new molecularly-targeted drugs may work. This is a promising new space for innovative drug development. For example, scientists at GlaxoSmithKline, working with faculty from this Workshop, designed and completed the neoadjuvant window-of-opportunity trial of pazopanib. Dr. Nasser Altorki of Weill Cornell Medical College and colleagues published the study in the *Journal of Clinical Oncology*.

During the "Progress with Quantitative Imaging from a Technical Issues and Opportunity Perspective" Breakout Group's discussions, there were a number of areas of consensus. These included the large opportunity to distill the number of imaging parameters to the ones that really matter, which would enable buy-in from imaging vendors to make compliance with these approaches simpler. The group also agreed that the CIBR program of FDA may be an important venue to advance these discussions. In

addition, the goal was endorsed to have phantoms used to specify machine performance in terms of fundamental imaging properties.

If software is developed to automatically validate phantom performance, it would again make it simpler for sites to comply with such measures. More work is required to define a given level of resolution and accuracy for each potential parameter, but progress has been made. Another area where further progress is urgently needed is with improvements of workflow in performing lung cancer screening.

There was considerable discussion on the need to better define and standardize the specification of a CT acquisition. It was well recognized by the participants that CT scanners have added too many vendor-specific parameters for defining a CT scan acquisition. Lack of standardization in defining an image acquisition request across vendors has significantly degraded our ability to do reproducible research in multi-center trials and potentially adds substantial bias to individual imaging studies. The main area of consensus and recommendation in the technical breakout group was that a new approach, based on fundamental image quality metrics, is needed to define and define and characterize the performance of a CT acquisition. In addition, CT phantoms are needed that are capable of verifying the performance acquired image acquisitions.

The group also agreed upon the need to ensure open participation of all potential stakeholders in pre-competitive image processing collaboration. For this reason, it would be important to ensure participation of all vendors in ongoing major COPD trials. Moreover, many technical issues are unresolved. For example, scatter correction is important and further support of collaborative forums such as this Workshop is critical to sustaining rapid progress in this promising new field.

The group discussed issues with assessing the impact of medical radiation during CT screening and determining the trade-off between lower dosage for reduced radiation exposure versus image quality. Medical radiation exposure has been frequently cited as an area of concern regarding potential harm for low-dose CT. However, lung cancer screening is currently restricted to older, heavily tobacco-exposed populations. The current dose per scan now averages less than 1.0 mSv.

Careful quality control to minimize radiation exposure is prudent. However, the dose required for optimal image quality for a CT study for both lung cancer and COPD should be determined to ensure that optimal diagnostic information is acquired. While the optimal required radiation dose has not yet been defined, most meeting participants felt progress on this issue was being made since the medical radiation exposure required for a high quality screening study continues to decrease.

Finally, the group spent considerable time discussing approaches to developing image analysis algorithms. A major issue was the QIBA approach in which a Profile (defined quantitative imaging process for lung lesion sizing) will be definitive use of a 30% cutoff. This discriminant was determined looking only at the volumetric growth technical questions and there was a concern about the variance contributed by clinical and biological factors. The group discussed the remaining need to establish response criteria for volumetrics within the specific context of a defined use case.

Further discussion focused on the QIBA goal of "Clinical Acceptance," attempting to define exactly what characteristics would be inherent in that goal, but more work in this area is needed. The group also assessed the state of qualified imaging collections in that area available to support progress in quantitative imaging research. Clearly more data are urgently needed, especially for randomized clinical trials with molecular and genetic metadata. Further work is needed to communicate to clinical trial sponsors about the importance of such resources in enabling foundational quantitative imaging research to proceed.

The Workshop adjourned with a sense of good progress having been made but aware of many more challenges remaining.