EARLY LUNG CANCER SCREENING WORKSHOP

National Cancer Institute / American Cancer Society March 7th and 8th, 2001 Doubletree Hotel, Rockville, MD

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Executive Summary

Recommendations

Group 1

- a Explore and develop clinical trial designs that can adapt to changing information. Draw sequential statistical methods and Bayesian methods from the existing statistical literature on adaptive designs. Plan for changing technology during the course of a trial and characterize technology in an ongoing way.
- b Observer performance may dominate technology differences and the effects of screening. Therefore, measure early and train observers appropriately.
- c Consider modest, short-term, intermediate endpoints to allow cutting losses early.
- d Modeling do for overall evaluation at variable times depending upon goal and with detailed data on lead time, length time, and survival characteristics by cell type for patients treated and not treated.
- e Costs consider measuring during trial with conditions mentioned above; cost effectiveness analysis (CEA) worthwhile if effects are present and "large."
- f Be aggressive about quality assurance.

Group 2

- a Studies should be designed and performed to answer practice-relevant questions: e.g., "What should be done with small lesions?"
- b Develop models to evaluate varying screening and treatment strategies and risk/outcome in terms of cost and effectiveness.
- c There is a need for coordinated and standardized surveillance of both screening and treatment in the community with emphasis on quality assurance.
- d All prospective studies of lung cancer screening should be organized to achieve a multi-disciplinary, state-of-the-art approach to detection, treatment, and follow-up.
- e Screening programs provide a unique opportunity to educate patients on risk factors such as smoking. There is a need to evaluate different strategies to reduce smoking.

Group 3

- a Support the development of a repository of standard data elements with an explicit data dictionary that defines key characteristics, such as: the variables to be included, the structure of the data set (field values), XML schema, and data collection methods (e.g., the format of possible questions; prompts used by interviewers; in the future, CAPI, CATI systems).
- b Support innovation in the use of information technology for data collection, transmission, management, and analysis.
- c In order to facilitate research that requires the pooling of data across diverse studies, support is needed for convening a group of experts to agree on core data elements, for managing the data system, for data analysis, and for the creation of public-use research resources.

Group 4

- a Evaluate spirometry of current and former smokers age fifty five or younger as an eligibility criterion for lung cancer screening.
- b In lung cancer screening trials, collect blood samples to evaluate genetic polymorphisms that activate and detoxify tobacco carcinogens and possibly DNA repair as part of a lung cancer screening trial. This could be undertaken within a subset of patients.
- c Collect specimens of blood, sputum and sampling of oral epithelial cells (e.g. mouthwash or buccal smears) from all screened participants.
- d At the time of resection, preserve samples of blood and tumor both to validate detection markers and to develop prognostic markers for metastasis and survival.
- e Include biomarker analysis in lung cancer screening trials.
- f Support an infrastructure, such as EDRN, for validation trials for biomarker profiles of early lung cancer.
- g Establish programs and adequate resources for relating "radiographic markers" of lung cancer to biomarkers of lung cancer.
- h Support development and validation of CAD methods for lung cancer screening.
- i Provide adequate support for personnel resources for screening trials.
- j Include collection of basic lung cancer risk data in screening trials.
- k Acquire health economics, quality of life and other outcome data as part of screening studies.
- 1 The integration of the individual components to the entire lung cancer screening process must be considered from the health care provider, clinical research and patient advocate perspectives.

Group 1: Impact of Technology Changes on Screening Studies

Purpose

How can the presumed future changes in low-dose helical computed tomography (CT) technology be most effectively managed in the clinical trials setting? How do we deal, from a scientific and research point of view, with the fact that technology is changing faster than we can study it? What are the potential issues associated with the integration of computer-aided diagnosis (CAD) into screening technologies.

Summary following Discussion

A. Reader Variability

A random sample of the performance of United States mammographers on a set of screening mammograms has shown great reader variability (Beam, Layde, Sullivan, etc., see attached Figure 1). A similar situation might hold for readings of spiral CT screening studies. A randomized controlled trial (RCT) of spiral CT screening will average over and blur out this and other effects. It could be useful to have ancillary multiple-reader studies to break out the variability of overall system performance into its multiple components: e.g., patients and technology, range of reader skill, relevant interactions or correlations, and their dependence on lesion size, etc. Methods have now been developed for separating these using multivariate receiver operating characteristic (ROC) analysis (Beiden, Wagner, Campbell, Metz, Jiang: Academic Radiology, July 2001, in press). Thus, it becomes possible with the appropriate ROC methodology to measure many of the relevant variables and to model the dependence of outcomes on lesion size, reader training (with and without computer-assisted reading), independent physical laboratory measurements, available therapy, and even the interaction of all of the above with molecular and genetic markers. These variables can either move performance along a given ROC curve or up to higher ROC curves (Figure 2). Thus, the moving-target effect can be controlled or accounted for by a combination of the appropriate measurements and refined models.

Figure 1 Scatterplot of sensitivity vs specificity among the 108 U.S. radiologists who participated in the study by Beam, et al. (Reprinted with permission of C. Beam.)

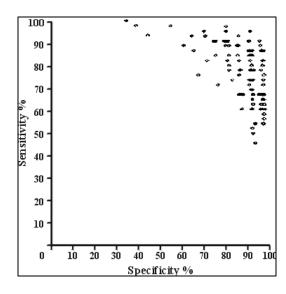
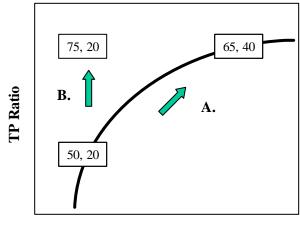


Figure 2 Changing Test Characteristics

The effect of a new technology could be either:

- A. To move the performance to a new point on the same ROC curve, or:
- B. To move the performance to a point on a different ROC curve.



FP Ratio

B. Assumptions and Ground Rules Agreed On For the Discussion

Spiral CT screening studies will have short accrual time (12-24 months); screening will occur for 3-5 years; there will be long follow-up periods

Technology changes would be considered for the time-frame of the next five years only.

The inclusion of costs for cost-effectiveness evaluation should be considered.

Investigators should plan for cost measurements during trial. But this is difficult to do (impossible, perhaps) because extra data collected as part of clinical trial probably does not reflect what would happen in the real world in the absence of trial.

If cost data are collected, then there will be potential for cost-effectiveness evaluation at the end if the effectiveness is "large."

C. What Will Change

Computed Tomography (CT) – incremental improvements in resolution with possibility to characterize lesions better; no *major* changes during accrual or screening period of next five years

Computer Assisted Diagnosis (CAD) – image processing and presentation will improve; ergonomic improvements in workstations will occur

Biomarkers will emerge for the risk assessment of the patient and the characterization of lesions, including aggressiveness

D. Measuring Technology per se (controlling for observers)

There is a need for the characterization of physical performance characteristics across trials (e.g., detection of nodules, measurement of change in nodules)

E. Other Factors Affecting Performance of a Technology

Case Mix – other diseases and co-morbidity

Reader Variability – likely to dominate changes in technology because of major differences (15 points in TP and FP) across readers. Can education help? Can CAD help?

Quality Assurance – performed during study

F. Current or Planned Clinical Studies on CT

Observational (Non-Experimental)

- 1. ELCAP, I-ELCAP, NY ELCAP
- 2. Moffitt Cancer Center
- 3. Munster
- 4. Mayo
- 5. Japan more than 20,000 patients

Randomized Controlled Trials (RCT)

- 1. Lung Special Study, NCI 3400 patients, up to 15,000 by September 2002
- 2. ACRIN, proposed start-up in late 2001 with up to 7000 patients by January 2003

G. Questions: Non-Experimental vs RCT

Does one accrue more quickly than the other? No

Do changes in technology impact one more than the other...

- ...during accrual (18-24 months)? No
- ...during screening (3-5 years)? No
- ...during follow-up? Yes, probably
- ...at dissemination? Maybe, depends on magnitude of changes

Are results of one more generalizable than the other in terms of ethnicity, geography, gender, co-morbidity, site of care, treatment elements, etc.? *No*

Does one have more potential than the other for intermediate endpoints to help with study design and maybe analysis, e.g., biomarkers or other surrogates, distribution of tumors by stage, incidence of interval cancers between screens? Yes; RCTs may have better controls

Conclusions and Recommendations:

Reimbursement considerations – generally, it is not possible or desirable to freeze technology during study.

Reimbursement considerations – modeling can be used to estimate the impact of new performance characteristics of the imaging technology with the conditions indicated below in Recommendation 1(d).

Study design – Non-Experimental and RCT are both useful	
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Recommendation I(a). Explore and develop clinical trial designs that can adapt to changing information. Draw sequential statistical methods and Bayesian methods from the existing statistical literature on adaptive designs. Plan for changing technology during the course of a trial and characterize technology in an ongoing way.

Recommendation I(b). Observer performance may dominate technology differences and effects of screening. Therefore, measure early and train observers appropriately.

Recommendation I(c). Consider modest, short-term, intermediate endpoints to allow cutting losses early.

Recommendation I(d). Modeling – do for overall evaluation at variable times depending upon goal and with detailed data on lead time, length time, and survival characteristics by cell type for patients treated and not treated.

Recommendation 1(e). Costs – consider measuring during trial with conditions mentioned above; cost-effectiveness analysis (CEA) – worthwhile if effects are present and "large."

Recommendation I(f). Be aggressive about quality assurance.

Group 2: Methodologies for Evaluation of Screening

Purpose

An assessment of the various methodologic approaches to evaluating screening performance, efficacy and other aspects of new screening technologies in trials and observational data.

Summary following Discussion:

To answer the question, "Is Screening Effective?" – Majority opinion was that an RCT is desirable; a feasibility study is underway by NCI

Some participants favored an alternative design

For studies of natural history – data from observational and experimental studies are contributory to understanding predictors of progression

Conclusions and Recommendations:

Recommendation 2(a). URGENT: Studies should be designed and performed to answer practice-relevant questions: e.g., "What should be done with small lesions?"

Current opportunity – randomized trial of small lesions to treatment or no-treatment groups; perform a feasibility study. Analyze accumulating data in a coordinated and standardized fashion to evaluate experience with these small lesions.

Recommendation 2(b). Develop models to evaluate varying screening and treatment strategies and risk/outcome in terms of cost and effectiveness.

Recommendation 2(c). There is a need for coordinated and standardized surveillance of both screening and treatment in the community with emphasis on quality assurance.

Recommendation 2(d). All prospective studies of lung cancer screening should be organized to achieve a multi-disciplinary, state-of-the-art approach to detection, treatment, and follow-up.

Recommendation 2(e). Screening programs provide a unique opportunity to educate patients on risk factors such as smoking. There is a need to evaluate different strategies to reduce smoking.

Group 3: Data Standardization and Informatics

Purpose

The type of comparisons to be made across studies dictate the degree of data standardization required for various factors, such as study population, criteria for entry, follow-up, and intervention. What types of comparisons are feasible across studies? What will be the influence of rapidly evolving use of computerized systems for management of data in research and in clinical practice?

Summary following Discussion:

With lung cancer screening CT studies now beginning, the potential for data standardization and informatics to facilitate combining and comparing data across diverse study designs is great.

Specifics of innovation in information technology and its influence on research were not addressed.

In the development of major collaborative initiatives, funding agencies should consider and plan for incorporating data collected in this process, such as CT images, into public-use research resources.

Conclusions and Recommendations:

Recommendation 3(a). Support the development of a repository of standard data elements with an explicit data dictionary that defines key characteristics, such as: the variables to be included, the structure of the data set (field values), XML schema, and data collection methods (e.g., the format of

possible questions; prompts used by interviewers; in the future, CAPI, CATI systems).

This process should consider identifying minimum data elements that might be shared across diverse study designs. In the area of lung cancer screening by CT, minimum data elements are likely to include patient characteristics, imaging data, and pathology data. In the future, minimum data elements may also include systems data.

Recommendation 3(b). Support innovation in the use of information technology for data collection, transmission, management, and analysis.

Recommendation 3(c). In order to facilitate research that requires the pooling of data across diverse studies, support is needed for convening a group of experts to agree on core data elements, for managing the data system, for data analysis, and for the creation of public-use research resources.

Group 4: New Frontiers of Science for Screening

Purpose

An assessment of what other "science of early detection" should be brought to bear as populations at high risk are identified and followed.

Summary following Discussion:

A. Biomarker Specimen Collection

Trials of lung cancer screening with helical CT provide a unique opportunity to define the molecular dynamics of very early lung cancer that other studies do not offer. Potential applications of biomarkers are:

- i. Identify individuals at high risk of developing radiologic and other early disease endpoints
- ii. Complement CT screening and early lung cancer detection
- iii. Refine work-up of CT positive findings (growing nodules) and thereby improve specificity
- iv. Serve as intermediate endpoints to monitor medical management of growing nodules by phenotyping the status of critical molecular pathways in the early cancer.

These are new areas for biomarker application with the potential for providing additional information at modest marginal costs and without incurring morbidity to the screening subjects. Nevertheless, if the specimens are not collected, preserved, and linked to patient demographic, exposure and outcome data by design at the beginning of a screening trial, the role of biomarkers cannot be defined.

As these rare specimens of early lesions will represent a national resource, optimal protocols for collecting, preserving, storing, shipping and labeling for long term storage of such specimens should be developed. To realize synergies from existing NCI research investments, this validation work should be done in collaboration with expert groups such as the Lung Cancer SPORES, the Early Detection Research Network (EDRN) and the cohorts (e.g. Framingham, PLCO, EPIC). These protocols could be developed at national workshops and the result made available on webbased forums.

The careful collection and handling of specimens at the screening institutions is critical to maintain the value of the specimens for future investigation. In its planning for lung cancer screening trials, NCI should fund the support staff and data managers charged with obtaining and processing, as well as the infrastructure required for storage and information management of, these most valuable specimens.

These specimens must be made available for sharing through a central repository that includes best practices for specimen management, safety and security, maintaining confidentiality and administrative procedures for specimen sharing.

Additionally, specimens should be collected to address specific hypothese.

B. Potential Applications of Biomarkers

i. To identify individuals at high risk of developing radiologic and other early disease endpoints Evidence exists for testing the hypothesis that the enhanced lung cancer risk among obstructed (FEV $_1$ / FVC <70%), current and former smokers (i.e., between ages 45-54) justifies their inclusion in a lung cancer screening trial.

Evidence also exists for testing the hypothesis that a valid lung cancer risk profile may be determined by genetic polymorphisms for enzymes that activate and detoxify tobacco carcinogens and possibly DNA repair.

Recommendation 4(a). Evaluate spirometry of current and former smokers age fifty five or younger as an eligibility criterion for lung cancer screening.

Recommendation 4(b). In lung cancer screening trials, collect blood samples to evaluate genetic polymorphisms that activate and detoxify tobacco carcinogens and possibly DNA repair as part of a lung cancer screening trial. This could be undertaken within a subset of patients.

ii. To complement CT screening and early lung cancer detection

Biomarkers of lung cancer have the potential to enhance helical CT screening by identifying lung cancers at complementary stages (clonal, pre-invasive vs. invasive), at complementary locations (central vs. peripheral) and complementary cell type (epidermoid emphasis vs. adenocarcinoma emphasis). Biomarkers may validate which CT-detected lesions may progress and which may remain dormant.

Recommendation 4(c). Collect specimens of blood, sputum and sampling of oral epithelial cells (e.g. mouthwash or buccal smears) from all screened participants. The serial acquisition of sputum or oral epithelial specimens should be extended to at least detected cases and comparable controls and a sampling of the false-positive cases. This is an opportunity of paramount importance to define the critical molecular events of early lung cancer. A portion of the epithelial cells should be acquired and stored in a fashion to ensure regular recovery of high quality RNA.

iii. To refine work-up of positive CT findings (growing nodules)

The appropriate work-up and management of patients with very early lung cancer is not yet established. During the workup, specimens should be collected to test biomarkers of prognosis and staging ultimately to enhance clinical decision-making. If clinical management entails bronchoscopy, it is recommended that specimens be collected of bronchial lavage/brushings, and bronchial biopsies. Similarly specimens of clinically indicated needle biopsy should be preserved.

The scope and span of specimen collection should be subject to careful statistical design with the view of maximizing opportunity while minimizing costs. It will not be necessary or desirable to collect specimens from all subjects enrolled in a CT study. It must be borne in mind that the *unique* opportunity presented by a lung cancer screening study is that of obtaining specimens representing the very earliest phases of lung cancer development. Specimen collection must be focussed on exploiting this opportunity.

Recommendation 4(d). At the time of resection, preserve samples of blood and tumor both to validate detection markers and to develop prognostic markers for metastasis and survival. This may only be feasible at SPORE Sites and Cancer Centers with strong molecular diagnostic infrastructure but at least this opportunity should be included.

iv. To serve as intermediate endpoints to monitor medical management of growing nodules

Randomized trials of medical vs. surgical management of growing nodules should be developed as a separate activity. Nevertheless, during the course of such trials, the collection of biomarkers to assess relevant molecular targets for pharmacologic intervention, treatment response and outcome should be added to the archive of the proposed lung cancer screening trial to maintain the integrity of the specimen resource.

Recommendation 4(e). Include biomarker analysis in lung cancer screening trials. A biomarkers infrastructure is urgently needed to collect specimens from these earliest lung cancer lesions to characterize the molecular structure of early cancer recognized by CT.

C. Selection and Validation of Early Lung Cancer Markers in a Lung Cancer Screening Trial

Numerous lung cancer biomarkers have been extensively reported and are at various stages of inquiry and validation. It is anticipated that during the lifetime of this trial, several of these will be validated by existing NCI mechanisms (SPORE, EDRN) and become appropriate for testing on the archived specimens collected here.

An array of relevant markers will require a matrix of specimens. This will become the first opportunity to apply extraordinary groundbreaking molecular technology (i.e. high throughput microarray, genomics, proteomics) to the earliest lesions of lung cancer as detected by CT.

Recommendation 4(f). Support an infrastructure, such as EDRN, for validation trials for biomarker profiles of early lung cancer.

D. Computer-Aided Diagnosis

Computer-aided diagnosis (CAD) will be an essential part of CT lung cancer screening and should be included within a screening trial.

Background

Computer analysis of breast images has yielded extremely promising results.

CAD is being developed for the detection and diagnosis of breast cancer as well as for breast cancer risk assessment. Use of computer analysis of screening mammography has one FDA-approved system and has been in routine clinical use for two years. Also, the use of computer analysis of diagnostic mammograms has been shown to be beneficial in observer performance studies and is currently being translated to the clinical environment.

However, computer-aided diagnosis research is still in its infancy relative to the potential gains achievable by:

- Expanding CAD research to multi-modality images (x-ray, ultrasound, MRI)
- Expanding CAD research to other diseases
- Expanding CAD research to other medical tasks, such as predicting prognosis
- Optimizing training and evaluation based on specific patient populations
- Incorporation of clinical information

Why the interest in CAD now?

- Quality of digital images is extremely good now
- Computers are faster
- Large databases of images are feasible now
- There are new computer vision techniques
- There is a recognized real medical need e.g., in screening mammography
- Investigators are sensitive to constraints imposed by the end user, e.g., the radiologist
- The public wants CAD
- CAD is accepted and valued by the radiologist/clinician
- There is a shortage of radiologists

Is there a potential synergy for imaging and biomarkers?

Use of computer analysis in the assessment of "normal" mammograms is being investigated for estimating breast cancer risk. Results from the computerized analysis of mammographic parenchymal patterns show that women at high risk for breast cancer have dense breasts and the pattern of the density tends to be coarse and low in contrast. Such computer analyses yield "radiographic markers" and these methods have been shown to be promising in 1) correlation studies with Gail and Claus "clinical markers," 2) ROC analysis between women at low risk for breast cancer and those women who have tested positive for the BRCA1/BRCA2 gene mutation biomarkers, and 3) ROC analysis between women at low risk for breast cancer and those women who have breast cancer. Identification and close follow-up of high-risk women may provide an opportunity for earlier detection of breast cancer as well as a means for monitoring prevention and treatment regimes.

Computer analysis of lesions found on spiral CT can undergo computerized classification analysis to assess the likelihood that the lesion is cancerous and such radiographic markers could be related to biomarkers.

Recommendation 4(g). Establish programs and adequate resources for relating "radiographic markers" of lung cancer to biomarkers of lung cancer.

How soon will CAD influence lung cancer screening with spiral CT?

Computer detection is already a reality in breast cancer screening. Integration with CT image acquisition systems is expected to be easier than with mammography since CT is already "digital". Various investigators are developing computer methods for "nodules" in CT, although at this early stage, performance levels vary. Databases are essential in that sufficient numbers of cases need to be collected in order to develop, train, and validate computerized methods. Lung nodule detection CT has not yet undergone any observer studies but it is expected that CAD will only help since (1) the oversight error is similar to that in screening mammography and (2) the amount of image data is becoming overwhelming for human vision.

Computerized methods for the detection of "nodules" on CT may be ready within one year from various groups. Note that it will be necessary to incorporate computer results into any modeling that is being performed for clinical trial design and extrapolation.

Besides aiding in lung cancer screening with spiral CT, computer analysis of CT images is expected to also help in the assessment of tumor response – e.g., objective measure of tumor volume.

Thus, appropriate data format and archiving are important for the inclusion of CAD in lung cancer screening trials. Depending on when trials begin, CAD may be included from the start.

Recommendation 4(h). Support development and validation of CAD methods for lung cancer screening. This would include database and algorithm development, validation with observer studies, and incorporation into clinical trials.

E. Support Personnel

The role of support personnel (e.g., research nurses, clinical research coordinators, data entry personnel) should not be underestimated for successful completion of trials. For example, for the epidemiological data collection, a full-time research nurse coordinator is needed in addition to an effective and efficient questionnaire. Such a person would be involved in explaining and obtaining consent, assuring that the questionnaire is correctly completed, and in accurate data entry. These areas are under-funded.

Recommendation 4(i). Provide adequate support for personnel resources for screening trials. In fact, submitted proposals should be examined to insure that sufficient funding is requested to actually perform the clinical trial and collect all the necessary data.

F. Epidemiological Data

The minimum standard for any screening trial must include planning for the collection of critical lung cancer covariates data as well as factors that might influence other markers, disease or radiologic endpoints. Questionnaire instruments and collection methods should be compatible with other studies. These data are essential for study results to be interpretable. For example, recent smoking data is crucial to distinguish image findings that are closely related to smoking from those that are due to early disease. Broadly, virtually every category of biomarker and other study question requires covariate data for proper interpretation. Core categories of information include basic demographics, detailed smoking history, history of respiratory illness, key occupational exposures, and family history of lung cancer. Other tobacco use, residential and reproductive history, environmental exposure, diet and other data might be desirable but may not be practical for collection. Proper procedures for maintaining confidentiality, coding, keying, storing and linking data, applying innovative technologies (i.e. CAPI) should be part of the basic design. Generally, some information collection (i.e. current smoking, weight change, treatment, etc) should accompany any subsequent bio-specimen collection or imaging.

Recommendation 4(j). Include collection of basic lung cancer risk data in screening trials.

G. Other Screening Issues

Research into CT, biomarker and other potential lung cancer screening modalities should first characterize the performance (sensitivity and specificity) of the test when applied to particular target populations (predictive values).

It is particularly useful to design trials that apply different screening tests to the same subjects at the same time, because it is the correlations of test errors that determine whether the tests are complementary and work well together or whether one is superior to the other.

The performance criteria for each screening test, including CT, biomarker and other tests, are model dependent. That is, they depend not only on the performance characteristics of all other tests in the screening process, but also on the morbidity and efficacy of the available therapeutic options.

The screening model must include an estimation of cost effectiveness, accounting not only for dollar costs but also iatrogenic morbidity (i.e. quality of life).

Recommendation 4(k). Acquire health economics, quality of life and other outcome data as part of screening studies.

H. Clinical Management of Early Lesions

The eventual reduction of lung cancer mortality will be most completely realized in a setting where the lessons from other cancers are integrated into the design of the screening process. This entails defining all of the elements involved in the screening and optimizing each component. For example, the diagnostic evaluation of an individual with an "indeterminate finding" on spiral CT needs to be standardized based on some validated clinical management algorithm.

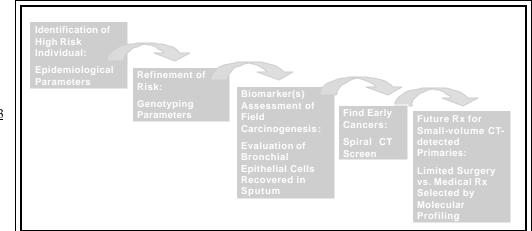
Another area of strategic importance is the issue of how a person with a "positive" CT finding is going to be definitively treated. Initial management is likely to entail surgical resection of the involved lobe and mediastinal evaluation. Thoracic surgery community is already evaluating whether less invasive procedures would be sufficient to routinely permit effective control of the small volume primary lung cancer and to conserve lung tissue to enable management of metachronous primaries.

Other innovative approaches may also emerge as particularly useful in the effective management of these small volume primary cancers and fostering research in this area should be an urgent priority. Examples of candidate managements in this regard include endoscopic surgical approaches, photodynamic laser therapy, conformal radiation therapy, brachytherapy as well as medical managements using direct drug delivery approaches (aerosols).

Recommendation 4(l). The integration of the individual components to the entire lung cancer screening process must be considered from the health care provider, clinical research and patient advocate perspectives. In particular, urgent funding is required for clinical research into management of early lesions.

I. The Future Lung Cancer Screening Journey Cascade

Group 4 considered the long-term aim of developing an early lung cancer detection cascade based on the integration of spiral CT with genotyping and biomarkers. This model (Figure 3) provides a scenario that could be considered for identifying individuals at risk of developing lung cancer, by undertaking subgroup analysis prior to using imaging techniques. This approach may be feasible within the health economics of the nation.



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