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Computed Tomography Scanning for Early Detection of Lung Cancer

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Abstract

Parallel and often unrelated developments in health care and technology have all been necessary to bring about early detection of lung cancer and the opportunity to decrease mortality from lung cancer through early detection of the disease by computed tomography. Lung cancer screening programs provide education for patients and clinicians, support smoking cessation as primary prevention for lung cancer, and facilitate health care for tobacco-associated diseases, including cardiovascular and chronic lung diseases. Guidelines for lung cancer screening will need to continue to evolve as additional risk factors and screening tests are developed. Data collection from lung cancer screening programs is vital to the further development of fiscally responsible guidelines to increase detection of lung cancer, which may include small groups with elevated risk for reasons other than tobacco exposure.

CIGARETTES AND LUNG CANCER

The cigarette-rolling machine was invented by James Albert Bonsack in 1880. Prior to this invention, cigarettes had been rolled by hand. Bonsack sold his invention to James Duke of Durham, NC. By 1883, The W. Duke, Sons and Company were producing 250,000 cigarettes per day. Initially seen as a luxury item, machine-rolled cigarettes rapidly replaced hand-rolled cigarettes at the end of the nineteenth century. The popularity of cigarettes increased, particularly between 1910 and 1920, in large part due to the distribution of free cigarettes to soldiers during World War I.

Lung cancer was a very rare disease until 1910. The long latency between smoking cigarettes and developing lung cancer contributed to delay in identification of the strong association between the two (1–3). By 1950, cigarettes were associated with lung cancer, although the first Surgeon General's warning was not placed on cigarette packaging until 1964. The feminist movement brought advertising that promoted an increase in smoking by women (4). In 1987, the number of lung cancer deaths surpassed that of breast cancer deaths in women in the United States, reflecting increasing long-term survivorship for breast cancer while the death rate from lung cancer remained very near the rate of diagnosis, perpetuating the stigma of lung cancer (5).

The earliest surgical treatment for lung cancer was pneumonectomy, first performed by Evarts Graham in 1933 (6, 7). Surgical techniques and improvements in anesthesia over the next 20 years led to improved selection and outcomes. Debates in the 1950s led to the conclusion that a lobectomy was an equivalent oncologic operation to pneumonectomy with improved preservation of lung function. The prospective Lung Cancer Study Group trial of 1983 led to the acceptance of lobectomy as the gold standard of surgical treatment of lung cancer. The "minimally invasive" revolution of the 1990s led to the development of VATS (video-assisted thoracoscopic surgery) lobectomies and subsequently robotic lobectomies. The twenty-first century has brought targeted therapies, angiogenesis inhibitors, drugs directed at targets such as epidermal growth factor receptors, and the ability to deliver therapies as a daily pill. Multimodality therapies incorporate surgery, chemotherapy, and radiation therapy. Effective therapy is a fundamental requirement for successful screening to decrease mortality from any disease (8).

LOW-DOSE COMPUTED TOMOGRAPHY SCAN SCREENING

A decade of technological development in computed tomography (CT) allowed the introduction of a CT scan during a single breath hold in 1989 (9). During the 1990s, the ability to detect early lung cancer by low-dose CT scans was intensively studied in the United States and Japan (9–11). The publication of the Early Lung Cancer Action Program results in 1999 revealed the potential for early detection to increase survival, although the study design did not address lung cancer–specific mortality. The creation of lung cancer CT screening programs during this period continues to inspire lung cancer screening programs to provide primary prevention through smoking cessation and support of long-term smoking abstinence along with CT screening.

The National Cancer Institute and the American College of Radiology Imaging Network joined forces to perform the National Lung Screening Trial (NLST). This randomized trial of screening enrolled 53,454 subjects in order to provide 90% power to detect a 20% difference in lung cancer–specific mortality. In order to maximize the likelihood of subjects developing lung cancer before conclusion of five or more years of follow-up, enrollment criteria included (*a*) age 55–74, (*b*) smokers or former smokers who had smoked within the preceding 15 years, and (*c*) a minimum of a 30-pack-year history of cigarette smoking. Subjects were randomized to three annual CT scans or three annual chest radiographs. The trial was terminated early when >20% mortality difference was achieved in the group that received CT scans. Thus, in 2011, we had

scientific evidence that early identification of lung cancer using low-dose CT scans could decrease deaths from lung cancer (12, 13).

NLST stands as a valuable milestone in the effort to change the previously dismal outcome of lung cancer. Cigarette smoking provided a large enough risk to allow this one very large trial to detect a sufficiently high mortality difference to establish CT in lung cancer screening in clinical practice. Lung cancer is not limited to smokers and former smokers, however, and smaller, more variable risk factors need to be better understood in order to establish population-level screening guidelines to cover other high-risk populations.

LUNG CANCER SCREENING GUIDELINES

The current guidelines of the US Preventive Services Task Force and Centers for Medicare and Medicaid Services are based on NLST criteria, as adjusted through intersociety professional dialogue. NLST succeeded in proving benefit with three annual screens despite both increasing risk due to increasing age and greater enrollment of younger and therefore comparatively lower-risk individuals. Lung cancer screening CT has been in clinical use since the NLST safety and monitoring committee terminated the study because the decrease in lung cancer–specific mortality crossed the 20% boundary defined by the 90% power of the study. Lung cancer screening CT infrastructure benefited from following the long-established mammography screening model, including creation of a standardized lexicon for communication of results. The American College of Radiology (ACR) Lung CT Screening Reporting and Data System, Lung-RADS™, provides a classification system with a standardized lexicon for description of findings and communication of results. It follows the model of the Breast Imaging Reporting and Data System, Bi-RADS, providing annual follow-up recommendations for continuing screening of patients through primary care providers. Category 3 suggests benign behavior with a request for six-month follow-up to confirm baseline. Category 4 is reserved for screens requiring clinical interaction. This would include following up an ambiguous lesion that is actually due to pneumonia and resolves on three-month follow-up, but it also includes the patient who receives immediate consideration for lung cancer staging and treatment. Significant incidental findings requiring additional work-up are also part of the Lung-RADS™ reporting system. The lexicon can be expected to change over time to improve correlation between recommendations and outcomes, as has been the case for mammography. The evolution of the lexicon and guidelines for screening will be crucial to maintaining the benefit identified by NLST as lung cancer screening CT is implemented in clinical practice (14–16). The dramatic reduction in lung cancer–specific mortality seen in the NLST was partly due to the extensive use of low-risk re-imaging with repeat CT scans and partly due to the low risk of diagnostic interventions. Specifically, the operative risk for positive screened participants in the NLST was only 1%. As lung cancer screening expands to all communities, the success or failure of the screening program depends on access to thoracic surgery centers that can provide low operative mortality (12, 17). Expanding treatment options to include stereotactic body radiation therapy and other new therapies within the guidelines will also depend on intersociety dialogue (18).

LUNG CANCER RISK CALCULATION

Evaluation of lung cancer risk in selecting patients for screening is based on patient characteristics. This type of pretest probability assessment must be reconciled with cultural and geographical considerations and may vary widely between populations. Endemic fungal infections and culture-specific cooking and housing are examples of the potential sources for differences in pretest probability of lung cancer in different regions (19).

The widespread adoption of lung cancer screening CT has greatly increased the number of lung nodules requiring continuing surveillance that may also have specific identifiable levels of risk (20–25). The risk of lung cancer in any particular small nodule is not uniform. Features such as development of solid components within ground-glass nodules and development of spiculated margins increase the probability of an individual nodule representing lung cancer. Diffuse features of lung parenchyma that characterize emphysema and pulmonary interstitial fibrosis also increase the probability of an individual nodule representing lung cancer.

Specific lung nodule risk also varies with location within the lung parenchyma. The most frequent site of lung cancer is the right upper lobe owing to the flow dynamics for warm air, and consequently cigarette smoke, within airways when cigarettes are smoked in a generally erect posture. A very short fine linear opacity representing an interlobular septum with the right relationship to a small ovoid peripheral lung nodule is highly associated with an intrapulmonary lymph node. A longer fine line extending to a distant pleural surface from an equally small lung nodule is highly associated with adenocarcinoma of the lung (26).

Deep analytical techniques and machine learning offer the promise of improved assessment of nodule risk. Nodule risk calculators have not yet replaced clinical expertise that also incorporates pretest probability derived from patient-specific risk factors and additional data such as pulmonary function and genetic tests. Computer-assisted detection can provide both types of input to radiologists with variable levels of integration in clinical radiology practice. The ability of deep analytics to identify the specific combination of risk factors will change the way risk assessment is performed and how guidelines are developed and administered.

Until the automated collection and analysis of all nodule risk data are available in real time, we will continue to use guidelines with periodic updating based on professional dialogue across specialties. This is how we moved from NLST research data with three annual lung cancer screening CT scans to clinical practice with annual lung cancer screening CT scans while the risk of lung cancer continues to rise. Professional dialogue also extends between screening and clinical patient care. This has allowed the Fleischner Society to issue guidelines for follow-up of incidental pulmonary nodules (27–29).

In 2004, the Fleischner Society addressed follow-up of incidentally detected indeterminate solid nodules. The size ranges recognized both technological practicality and lung cancer screening CT research activities. The selection of 4 mm as the minimum size for follow-up adhered to the minimum size selected by NLST that had been specifically chosen to be more conservative than the Early Lung Cancer Action Program's selection of 5 mm. This recognized improvement in CT resolution between the 1990s and early 2000s. The guidelines also provided for 8-mm nodules that could be reliably evaluated by positron emission tomography (PET)/CT to have that test considered as well as follow-up, biopsy, and resection. At that time, the Fleischner Society guidelines recognized high risk and low risk without defining either. The decision of when to refer the patient to a specialist was not part of the guidelines, but as a practical matter, primary care physicians were encouraged to refer patients for subspecialty consultation and possible surgery when nodules grew from 6 mm to 8 mm. The expectation that primary care physician manage 4-mm nodules by report is analogous to Lung-RADS Categories 1 and 2. The selection of two years of stability for benign designation honored practice predating the development of CT.

The 2013 Fleischner Society guidelines addressed ground-glass and part-solid nodules that are worrisome for lung cancer, particularly adenocarcinoma of the lung, and require significantly longer follow-up. Radiologists who had seen long periods of stability in ground-glass nodules that years later developed into clinical lung cancers were not enthusiastic about the recommendation to perform no follow-up imaging for nodules of 5 mm or less. The establishment of clinical lung cancer screening programs provided the security of annual follow-up.

The give and take between clinical guidelines for incidental pulmonary nodules using screening and other research literature resulted in a single set of Fleischner Society guidelines for all incidental pulmonary nodules in 2017. These guidelines provide the level of evidence and have also reintroduced common sense in allowing different approaches to be considered appropriate in various situations. Few nodules measuring <6 mm in diameter warrant follow-up. This represents the type of step forward that we can expect to be followed by improvements in risk assessment for nodules and further development of Lung-RADS standardized reporting for lung cancer CT that follows the pattern long established by mammography rather than the Fleischner Society guidelines for incidental pulmonary nodules.

FOCUSING ON THE INDIVIDUAL

Analyses of NLST data have shown development of lung cancer in women and minorities at younger ages and with lower-intensity smoking history (30–38). Independent risk factors for lung cancer include age, family history of early-onset lung cancer (defined as diagnosis before age 60), and chronic lung diseases such as emphysema and interstitial pulmonary fibrosis. Additional risk factors with variable contributions to the specific risk profile of any individual include occupational exposures such as asbestos, prior radiation therapy, and genetically linked tumors. Increasing the understanding of shared tumor biomarkers and genetics will improve selection criteria for women and minorities.

Lung cancer is unlikely to become rare again even if cigarette smoking is eliminated in our society. We now know it as a family of diseases that have evolved over time and can continue to evolve. We are beginning to diagnose lung cancer in younger adults whose disease may have specific although incompletely understood causes in terms of genetics and exposures. As lung cancer falls in line with other cancers and has more identified causes beyond cigarette smoking, it is imperative to eliminate the stigma long associated with lung cancer.

We have gained some insight into secondary risk factors for lung cancer through a combination of NLST data analyses and studies such as the Multi-Ethnic Study of Atherosclerosis (MESA) and COPDGene cohort studies (39–41). The risk conferred by these additional factors can be quantified by comparison with the risk of smoking alone. In the case of tobacco-associated diseases such as chronic obstructive pulmonary disease, this incremental increase in risk does not matter when individuals already meet guidelines for screening based on cigarette smoking alone. How non-tobacco-associated risks can provide equivalent high risk for lung cancer is much less obvious. Genetic predisposition can be asserted for individuals with a family history of early-onset lung cancer. This may be a very important risk factor for women and minorities, who develop lung cancer at an earlier age and with lower smoking intensity. As riddles regarding cancer genetics are unraveled, we learn more specific causes of associations between very different cancers.

The current challenge in lung cancer screening is to find ways to translate research on populations to personalized care for patients. The value of continuing to collect data warrants the ongoing reporting of screening activity and results mandated by the Centers for Medicare and Medicaid Services in the United States. Setting aside for the moment financial considerations regarding reimbursement, insurance, and lack of insurance coverage, individualized decisions can be made best within a lung cancer screening program, as such programs provide more than a low-dose CT scan. Risk assessment and risk reduction for lung cancer and all tobacco-associated diseases are facilitated by participation in a program. Lung cancer screening programs vary widely, although most have arisen from preexisting resources and championship by interested clinicians across a variety of specialties including radiology, pulmonology, thoracic surgery, medical oncology,

and radiation oncology. Primary care providers have been asked to perform "shared decision making" with each patient prior to enrollment in a lung cancer screening program. Whether performed by the primary care physician or other provider, this process provides an important teachable moment for health improvement through understanding the risks and benefits of joining a lung cancer screening program designed to address possible lung cancers. This indoctrination is important to maintain patient compliance with recommendations and limit healthcare spending on false-positive results. For some patients, the visual demonstration of risk within a population is most helpful and can be offered readily using the online resource **http://www.shouldiscreen.com**. The AATS Lung Cancer Risk Assessment Tool (**http://aats.org/aatsimis/AATS/Applications/Lung_Screening_Calculator.aspx?WebsiteKey=81f79f5f-4a27-4146-913d-cffea0ac81f7**) provides comparisons of risk using a variety of models.

In approaching program participation that may last more than two decades with 20 or more CT scans, the radiation risk is appropriate for patients at very high risk of developing lung cancer but not warranted for patients at low risk of lung cancer. Hence, clearer definition of risk is the most important task before the healthcare system in 2017 and 2018.

The National Comprehensive Cancer Network and professional societies are keen on addressing combinations of risk that may equal or even exceed the risk of 30-pack-year smoking intensity for the purpose of offering appropriate care for individual patients. This may also be important for limiting the number of CT scans required for patients with a 30-pack-year history of smoking. Although increasing age is an independent risk factor for lung cancer, the importance of non-tobacco risk factors may decrease for patients as they approach the peak incidence of lung cancer after age 70. The collection of data regarding risks besides tobacco remains valuable for understanding non-tobacco risk factors to be considered for risk assessment in younger patients, including those less than 55 years of age.

Analyses of NLST data have already revealed greater benefit from lung cancer screening CT for the oldest group, which had increased enrollment, and greater incidence of lung cancer in younger women and minorities. Some factors affecting these differences are tobacco related, including differences in cigarette preferences. Comorbidities and genetic factors are also likely more important in these groups. The biological behavior of lung cancer exhibits gender differences: Women experience longer survival times at all stages and can have a higher likelihood of response to specific therapies. Genes such as *HER2*, long known for association with breast cancer, also now have a recognized association with a higher risk of developing lung cancer. The opportunity for lung cancer CT screening to identify lung cancer during the preclinical window associated with the earliest stage and greatest decrease in lung cancer mortality is greatest for indolent cancers, which may allow appropriate benefit from lung cancer screening CT at longer intervals, particularly once CT can be paired with biomarker surveillance. This may be most important for premenopausal women, in whom breast irradiation should remain an important consideration in balancing risks and benefits of lung cancer screening CT.

The risk of lung cancer attributable to family history of lung cancer is most significant when the diagnosis has been made before age 60 in a first-degree relative. Family history, combined with personal history of certain other lung diseases, points toward a pathway for selecting younger patients for screening. Some associations in this regard are long-standing, including diffuse interstitial lung disease such as UIP-IPF (usual interstitial pneumonia–idiopathic pulmonary fibrosis). Emphysema, although associated with smoking, is an independent predictor of risk for lung cancer in the future. We may be able to focus on the lack of development of emphysema in order to understand which patients may have significantly lower risk of lung cancer despite having the highest intensity of smoking history. Pneumonia in early life may cause flow alterations within the lungs, increasing local vulnerability to damage from smoking. Prior pneumonia can also be a

confounder in our understanding of risk due to the overlap in visual appearance between incomplete resolution of the prior pneumonia and adenocarcinoma of the lung.

The incidence of lung cancer is higher in those who have had a prior cancer. Genetic associations within families suggest genetic predispositions to combinations of cancers including breast, ovarian, and pancreatic. Tobacco-associated cancers include head and neck and bladder cancers; individuals who have had these cancers are also at high risk for lung cancer. Treatment for non-lung cancer increases risk for development of lung cancer. This is particularly true for patients who have received radiation therapy for breast cancer, head/neck cancer, and intrathoracic lymphoma.

Environmental and occupational exposures vary significantly between populations. Increased risk of lung cancer has long been established in individuals with occupational exposure to asbestos, although groups with this exposure also have very significant rates of cigarette smoking. Understanding of secondhand smoke exposure may be critical in understanding development of lung cancer in lifetime nonsmokers. Caregiver smoking during childhood and employment in crowded quarters in which smoking is allowed, such as casinos and, in past years, smoking lounges, may be more important for women and minorities in the likelihood of developing lung cancer. It is unclear whether exposure during adolescence should be separately considered.

Shared decision making is important for patients outside of current guidelines, who need to understand their own responsibility for the decision. Risk assessment calculators have been developed in multiple populations and may be considered as a group in order to make decisions about enrolling in a lung cancer screening program. In the future, similar comparisons of risk calculators will become more helpful in reassessing risk after CT screening. Specific lesion features may increase or decrease the probability of cancer in an individual lesion. Endemic diseases and patient travel history may also increase or decrease suspicion of cancer in a particular nodule.

Lung cancer screening programs vary in the services they provide. CT scanner and program certifications such as those of the American College of Radiology and the Lung Cancer Alliance provide one measure for evaluation. Programs that interact directly with each participant can support smoking cessation and provide annual risk assessment as understanding of smaller risk factors increases. The potential for lung cancer screening CT to improve health extends beyond lung cancer, especially when combined with smoking cessation counseling. Rapid improvement in cardiovascular health can provide powerful motivation for smoking cessation, with value to health for each and every time an individual quits smoking. The improvements in health achievable through a lung cancer screening program extend beyond identification of occult cancer and can be most valuable to individuals with chronic obstructive pulmonary disease and coronary heart disease. Participation in a lung cancer screening program also supports adoption of lifestyle improvements for overall health. A lung cancer screening program places the patient and health promotion in the center and provides interfaces between primary and specialty care.

MILESTONES IN 2017

The dialogue between lung cancer screening CT and diagnostic CT with regard to follow-up of indeterminate pulmonary nodules has reached maturity in 2017 with publication of new, more comprehensive recommendations for management of lung nodules (ranging from nonsolid to part solid and solid tumors) along with more nuanced assessment of risk (**Table 1**). These guidelines are not identical to the Lung-RADS standardized reporting for lung cancer screening CT (**Table 2**).

Comparison of criteria and outcomes will move the dialogue forward regarding smoking and other risk factors for lung cancer (42). The quit rule, providing lung cancer screening CT for 15 years following smoking cessation, may be on the way to falling, due to known continuing increase in risk with age. The population over age 80 is heterogeneous. Screening is not appropriate

Table 1 Fleischner Society 2017 guidelines for management of incidentally detected pulmonary nodules in adults (from Reference 29 with permission)

A: Solid nodules[a]				
Nodule type	Size			Comments
	<6 mm (<100 mm^3)	6-8 mm (100-250 mm^3)	>8 mm (>250 mm^3)	
Single				
Low risk	No routine follow-up	CT at 6–12 months, then consider CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	Nodules <6 mm do not require routine follow-up, but certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A)
High risk	Optional CT at 12 months	CT at 6–12 months, then CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	Nodules <6 mm do not require routine follow-up, but certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A)
Multiple				
Low risk	No routine follow-up	CT at 3–6 months, then consider CT at 18–24 months	CT at 3–6 months, then consider CT at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A)
High risk	Optional CT at 12 months	CT at 3–6 months, then at 18–24 months	CT at 3–6 months, then at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A)

B: Subsolid nodules[a]			
Nodule type	Size		Comments
	<6 mm (<100 mm^3)	>6 mm (>100 mm^3)	
Single			
Ground glass	No routine follow-up	CT at 6–12 months to confirm persistence, then CT every 2 years until 5 years	In certain suspicious nodules <6 mm, consider follow-up at 2 and 4 years. If solid component(s) or growth develops, consider resection (recommendations 3A and 4A)
Part solid	No routine follow-up	CT at 3–6 months to confirm persistence. If unchanged and solid component remains <6 mm, annual CT should be performed for 5 years	In practice, part-solid nodules cannot be defined as such until ≥6 mm, and nodules <6 mm do not usually require follow-up. Persistent part-solid nodules with solid components ≥6 mm should be considered highly suspicious (recommendations 4A–4C)
Multiple	CT at 3–6 months. If stable, consider CT at 2 and 4 years	CT at 3–6 months. Subsequent management based on the most suspicious nodule(s)	Multiple <6 mm pure ground-glass nodules are usually benign, but consider follow-up in selected patients at high risk at 2 and 4 years (recommendation 5A)

[a]These recommendations do not apply to lung cancer screening, patients with immunosuppression, or patients with known primary cancer. Dimensions are average of long and short axes, rounded to the nearest millimeter.

Table 2 Lung-RADS™ Version 1.0 assessment categories, release date April 28, 2014[a]

Category	Descriptor	Primary category	Management
Incomplete	NA	0	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed
Negative	No nodules and definitely benign nodules	1	Continue annual screening with LDCT in 12 months
Benign appearance or behavior	Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	
Probably benign	Probably benign finding(s)—short-term follow-up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	6-month LDCT
Suspicious	Findings for which additional diagnostic testing and/or tissue sampling is recommended	4A	3-month LDCT; PET/CT may be used when there is a ≥8-mm solid component
		4B	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on the probability of malignancy and comorbidities. PET/CT may be used when there is a ≥8-mm solid component

[a]Modified from **https://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/LungRADS/Summary.pdf** with permission from the American College of Radiology. Abbreviations: LDCT, low-dose chest computed tomography; NA, not available (examination needing additional/repeat scan or needed comparisons not yet available); PET/CT, positron emission tomography/computed tomography.

if life expectancy is less than one year. For a physically robust octogenarian with life expectancy of >7 years, screening may make sense.

Dialogue across specialties will continue the processes that allow translation from clinical trial results to individual patient care in the absence of data that are difficult or impossible to collect. Mindfulness regarding use of limited resources and maintaining cost-effective care for lung cancer are mandatory to maintain recommendations for lung cancer screening.

European lung cancer screening trials including DANTE ITALUNG and NELSON (43) have provided models for economical delivery of care and evaluated volumetric measurement not in widespread use in lung cancer screening programs. Despite the attention to small differences in nodule size, lax enrollment criteria in multiple, comparatively small European trials have not provided adequate power to detect any lung cancer–specific mortality benefit. Although it is highly unlikely that another randomized trial on the scale of NLST will be attempted, with the continuing collection of data through clinical registries, the potential for lung cancer screening CT to decrease lung cancer–specific mortality and all-cause mortality can be increased from that achieved by the NLST.

DISCLOSURE STATEMENT

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TABLE OF CONTENTS FOR VOLUME 1:

- ***How Tumor Virology Evolved into Cancer Biology and Transformed Oncology***, Harold Varmus
- ***The Role of Autophagy in Cancer***, Naiara Santana-Codina, Joseph D. Mancias, Alec C. Kimmelman
- ***Cell Cycle–Targeted Cancer Therapies***, Charles J. Sherr, Jiri Bartek
- ***Ubiquitin in Cell-Cycle Regulation and Dysregulation in Cancer***, Natalie A. Borg, Vishva M. Dixit
- ***The Two Faces of Reactive Oxygen Species in Cancer***, Colleen R. Reczek, Navdeep S. Chandel
- ***Analyzing Tumor Metabolism In Vivo***, Brandon Faubert, Ralph J. DeBerardinis
- ***Stress-Induced Mutagenesis: Implications in Cancer and Drug Resistance***, Devon M. Fitzgerald, P.J. Hastings, Susan M. Rosenberg
- ***Synthetic Lethality in Cancer Therapeutics***, Roderick L. Beijersbergen, Lodewyk F.A. Wessels, René Bernards
- ***Noncoding RNAs in Cancer Development***, Chao-Po Lin, Lin He
- ***p53: Multiple Facets of a Rubik's Cube***, Yun Zhang, Guillermina Lozano
- ***Resisting Resistance***, Ivana Bozic, Martin A. Nowak
- ***Deciphering Genetic Intratumor Heterogeneity and Its Impact on Cancer Evolution***, Rachel Rosenthal, Nicholas McGranahan, Javier Herrero, Charles Swanton
- ***Immune-Suppressing Cellular Elements of the Tumor Microenvironment***, Douglas T. Fearon
- ***Overcoming On-Target Resistance to Tyrosine Kinase Inhibitors in Lung Cancer***, Ibiayi Dagogo-Jack, Jeffrey A. Engelman, Alice T. Shaw
- ***Apoptosis and Cancer***, Anthony Letai
- ***Chemical Carcinogenesis Models of Cancer: Back to the Future***, Melissa Q. McCreery, Allan Balmain
- ***Extracellular Matrix Remodeling and Stiffening Modulate Tumor Phenotype and Treatment Response***, Jennifer L. Leight, Allison P. Drain, Valerie M. Weaver
- ***Aneuploidy in Cancer: Seq-ing Answers to Old Questions***, Kristin A. Knouse, Teresa Davoli, Stephen J. Elledge, Angelika Amon
- ***The Role of Chromatin-Associated Proteins in Cancer***, Kristian Helin, Saverio Minucci
- ***Targeted Differentiation Therapy with Mutant IDH Inhibitors: Early Experiences and Parallels with Other Differentiation Agents***, Eytan Stein, Katharine Yen
- ***Determinants of Organotropic Metastasis***, Heath A. Smith, Yibin Kang
- ***Multiple Roles for the MLL/COMPASS Family in the Epigenetic Regulation of Gene Expression and in Cancer***, Joshua J. Meeks, Ali Shilatifard
- ***Chimeric Antigen Receptors: A Paradigm Shift in Immunotherapy***, Michel Sadelain

Annual Review of Medicine

Volume 69, 2018

Contents

Precision Medicine: Functional Advancements
Thomas Caskey 1

Refinement of the Affordable Care Act
Vivian Ho 19

Refinement of the Affordable Care Act: A Progressive Perspective
Olveen Carrasquillo and Michael Mueller 29

The Affordable Care Act: What's Next?
Mark McClellan and Mark Japinga 41

Atrial Fibrillation Ablation
Rakesh Latchamsetty and Fred Morady 53

Heart Failure with Preserved Ejection Fraction
James D. Gladden, Antoine H. Chaanine, and Margaret M. Redfield 65

Impact of the SPRINT Trial on Hypertension Management
Lama Ghazi and Suzanne Oparil 81

Common Cardiovascular Complications of Cancer Therapy: Epidemiology, Risk Prediction, and Prevention
Vivek Narayan and Bonnie Ky 97

New Therapeutic Approaches for Familial Hypercholesterolemia
Ezim Ajufo and Daniel J. Rader 113

PCSK9 Inhibitors: Mechanisms of Action, Metabolic Effects, and Clinical Outcomes
Connie N. Hess, Cecilia C. Low Wang, and William R. Hiatt 133

Risk Stratification for Sudden Cardiac Death After Myocardial Infarction
Jonathan W. Waks and Alfred E. Buxton 147

Understanding Peripartum Cardiomyopathy
Zoltan Arany 165

Updated Recommendations for Athletes with Heart Disease
Rachel Lampert and Douglas P. Zipes 177

Antibody–Drug Conjugates for Cancer Treatment
John M. Lambert and Anna Berkenblit 191

Modern Systemic Therapy for Metastatic Renal Cell Carcinoma of the Clear Cell Type
Mamta Parikh and Primo N. Lara Jr. 209

Circulating Tumor DNA: Measurement and Clinical Utility
Joshua Donaldson and Ben Ho Park 223

Computed Tomography Scanning for Early Detection of Lung Cancer
Francine L. Jacobson and Michael T. Jaklitsch 235

Evidence for Genetic Risk Contributing to Long-Term Adverse Treatment Effects in Childhood Cancer Survivors
Maria Monica Gramatges and Smita Bhatia 247

Lymphedema: Pathogenesis and Novel Therapies
Joseph H. Dayan, Catherine L. Ly, Raghu P. Kataru, and Babak J. Mehrara 263

Novel Radiotherapy Techniques for Breast Cancer
Julie A. Bradley and Nancy P. Mendenhall 277

Recombinant Poliovirus for Cancer Immunotherapy
Matthias Gromeier and Smita K. Nair 289

CD8 T Cell Exhaustion in Chronic Infection and Cancer: Opportunities for Interventions
Masao Hashimoto, Alice O. Kamphorst, Se Jin Im, Haydn T. Kissick, Rathi N. Pillai, Suresh S. Ramalingam, Koichi Araki, and Rafi Ahmed 301

Basket Studies: Redefining Clinical Trials in the Era of Genome-Driven Oncology
Jessica J. Tao, Alison M. Schram, and David M. Hyman 319

Molecular and Genomic Determinants of Response to Immune Checkpoint Inhibition in Cancer
Russell W. Jenkins, Rohit Thummalapalli, Jacob Carter, Israel Cañadas, and David A. Barbie 333

Targeting RAGE Signaling in Inflammatory Disease
Barry I. Hudson and Marc E. Lippman 349

New Concepts in the Treatment of Malignant Pleural Mesothelioma
Ori Wald and David J. Sugarbaker 365

New Molecular Diagnostic Approaches to Bacterial Infections and Antibacterial Resistance
Ephraim L. Tsalik, Robert A. Bonomo, and Vance G. Fowler Jr. 379

Zika, Chikungunya, and Other Emerging Vector-Borne Viral Diseases
Scott C. Weaver, Caroline Charlier, Nikos Vasilakis, and Marc Lecuit 395

New-Generation High-Potency and Designer Antibodies: Role in HIV-1 Treatment
Lucio Gama and Richard A. Koup 409

Novel Latency Reversal Agents for HIV-1 Cure
Adam M. Spivak and Vicente Planelles 421

Innate Immunity and Neurodegeneration
Larisa I. Labzin, Michael T. Heneka, and Eicke Latz 437

Use and Misuse of Opioids in Chronic Pain
Nora Volkow, Helene Benveniste, and A. Thomas McLellan 451

Measuring Patient-Reported Outcomes: Key Metrics in Reconstructive Surgery
Sophocles H. Voineskos, Jonas A. Nelson, Anne F. Klassen, and Andrea L. Pusic 467

What Metrics Accurately Reflect Surgical Quality?
Andrew M. Ibrahim and Justin B. Dimick 481

Indexes

Cumulative Index of Contributing Authors, Volumes 65–69 493

Cumulative Index of Article Titles, Volumes 65–69 497

Errata

An online log of corrections to *Annual Review of Medicine* articles may be found at http://www.annualreviews.org/errata/med