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Lung Cancer FRONTIERS

The Forum for Early Diagnosis and Treatment of Lung Cancer

In Memoriam:

Thomas L. Petty, MD

December 24, 1932 – December 12, 2009

By James T. Good, Jr., MD

Born in Boulder, Colorado on Christmas Eve, 1932, Tom Petty was a special gift to his fellow man. Self made, in all respects, he embraced and encouraged those around him. We are saddened by Tom's departure but relieved that his suffering is over.

Tom's accomplishments and awards are so numerous they require a 54 page curriculum vitae to list them all. He was Head of the Division of Pulmonary Medicine at the University of Colorado School of Medicine from 1971 to 1983 and Director of the Webb-Waring Lung Institute from 1983 to 1988. For the next seven years, he was Director of Academic and Research Affairs at Health One Center for Health Sciences Education, in Denver, and was Emeritus Professor of Medicine at National Jewish Health and the University of Colorado until his death. The Aspen Lung Conference was named after him in 1991. He chaired numerous national pulmonary and critical care committees and was president of the American College of Chest Physicians (ACCP) from 1981 to 1982. He was elected Master in both the ACCP and the American College of Physicians, the highest honor that can be awarded to a member.

His roles as mentor, educator, innovator, inventor, researcher, and prolific writer all define his professional career, but it was his love and compassion for friends and patients that provided his gift of "living each day". His sense of humor, joke telling, and warmth will be greatly missed.

As a medical leader, he supported his students, residents, fellows and junior faculty and fostered an attitude of cooperation, encouragement and excellence, while never being judgmental. To Tom Petty, the opportunity to care for a patient was an honor, never a duty. His most recent books, *Adventures of an Oxy-Phile* and *From Both Ends of the Stethoscope*, detail his experience being a patient using supplemental oxygen and are enlightening for both patients and physicians.

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The purpose of ***Lung Cancer Frontiers*** is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.

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When put in perspective, one realizes that Tom's medical contributions affected the lives of not thousands, but millions of patients worldwide. His early research in the use of home oxygen, and his partnering with industry, resulted in innovations that revolutionized oxygen therapy and enhanced the lives of patients with cardio-respiratory limitations.

At the same time he was involved with home oxygen therapy, pulmonary rehabilitation and new strategies for the treatment of COPD, his contributions in critical care medicine and ventilator management for patients with acute respiratory failure were equally outstanding. Tom helped develop the current intensive care model, encouraging free-standing critical care units that were separate from post-operative recovery rooms. Because of his excellent observations and research, most of the supportive ventilator strategies used today stem from his early work.

Never one to rest on his previous accomplishments, Tom continually looked at new challenges and problems confronting patients with lung disease. In the last years of his life, he championed the concept of early detection and treatment of lung cancer. He co-authored several research studies evaluating the role of sputum cytology in diagnosing lung cancer in high-risk patients, the most recent of which appears in the November 2009 issue of *The Journal of Thoracic Oncology*. In 1996, to further the cause of lung cancer detection, he founded *Lung Cancer Frontiers*. He was actively involved in editing the publication until the time of his death.

We will miss you, Tom.

James T. Good, Jr., MD, is Professor of Medicine in the Division of Pulmonary and Critical Care at National Jewish Health and a longtime colleague and close friend of Dr. Petty. He completed his fellowship in pulmonary medicine at the University of Colorado while Dr. Petty was Division Head and Director of the fellowship training program.

Gene Expression Profiles for the Treatment of Non-small Cell Lung Cancer

The Promise of Personalized Cancer Therapy

By John Strickler, MD and Anil Potti, MD

***John Strickler, MD**, is a Hematology/Oncology Fellow at Duke University School of Medicine, Durham, NC. He is currently performing genomic research in Dr. Anil Potti's laboratory and is interested in novel therapies for thoracic malignancies.*

***Anil Potti, MD**, is Associate Professor of Medicine in the Division of Medical Oncology at Duke University School of Medicine, Durham, NC. His interests include treatment of thoracic malignancies and the use of genetic and genomic markers to assess disease severity and predict the likelihood of response to therapy.*

Although survival rates for non-small cell lung cancer (NSCLC) have demonstrated modest improvement over the past 20 years, overall 5-year survival remains unacceptably low, and many patients are subjected to toxicity from chemotherapy with uncertain therapeutic value.[1-3] In the past decade, "personalized" approaches to cancer treatment have dramatically improved response rates to treatment for select patient subtypes.[4-7] Within the field of lung cancer, selecting patients with the epidermal growth factor receptor (EGFR) mutation improves response rates dramatically to EGFR targeted therapy, leading to improved progression free survival when compared directly to conventional chemotherapy.[8-11] Unfortunately, for the vast majority of NSCLC patients, the transition to malignancy involves the accumulation of numerous complex mutations, suggesting that the search for a single point mutation or molecular marker may not lead to effective treatment for most patients. Given the extensive heterogeneity of NSCLC, gene expression profiles may be a superior tool for understanding basic tumor biology, predicting recurrence, and guiding therapeutic options.

Gene Expression Profiles

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Gene expression profiles are based on DNA microarray technology, which is capable of measuring nearly all genes in the cancer genome simultaneously.[12] Generation of DNA microarray data requires the collection of tumor tissue, extraction of RNA from the tissue, labeling of the RNA with a detectable marker, and hybridization of RNA to complementary DNA (cDNA) probes on the array.[13] The level to which an individual gene is expressed is signified by relative color intensity on the array determined by the amount of bound RNA. Genomic data is then filtered to isolate the most relevant overexpressed and underexpressed genes in the sample population. Statistical analyses are performed to develop "signatures", or combinations of gene expression changes, to predict the desired phenotype.[14] The gene expression signatures are then applied to an unrelated patient population to validate predictive accuracy. Such an approach can thus be utilized to dissect clinically relevant phenotypes (i.e. prognosis, or response to therapy).

In the context of NSCLC, current staging techniques are unable to provide detailed information regarding an individual's risk of relapse after treatment. For example, the prognosis for early stage (IA) NSCLC patients treated with resection alone is imprecise, with nearly 30% of these patients developing disease recurrence.[15] DNA microarray analysis offers an opportunity to improve the prognostic and predictive capabilities of initial staging for NSCLC.[16-26] To develop a gene expression-based model that can be used to alter clinical decisions for early stage NSCLC, our group analyzed genomic data from 198 NSCLC tumor samples and developed a gene expression signature ("metagene") to predict recurrence. The metagene model predicted disease recurrence with greater than 90% accuracy, compared to an accuracy of 64% for pathologic and staging data alone.[14,27] The metagene model is currently being tested in a National Cancer Institute-funded prospective phase III clinical trial, in which patients with stage I NSCLC are stratified into low risk and high risk groups based on gene expression profiles. This trial will also give us the opportunity to validate several other previously published predictors of outcome in early stage NSCLC.

Just as gene expression signatures may predict risk of recurrence, the technology may also be applicable to chemotherapeutic sensitivity. Standard treatment paradigms for most solid tumors, including lung cancer, include single-agent or combination chemotherapy regimens. As there is currently no diagnostic test to predict response to specific therapeutic agents, clinicians have limited guidance to determine which of the approved regimens to select for their patients. Several signatures have been developed by matching *in vitro* chemotherapy response with gene expression data.[28] These signatures are then independently validated in separate cell lines.[28] For example, based on gene expression and sensitivity data from the NCI-60 panel of cell lines, a 50-gene expression signature for docetaxel sensitivity was developed. The gene expression signature predicted response to docetaxel among a population of 30 lung and ovarian cancer cell lines with an accuracy of 80%.[27] Using a similar approach, a genomic predictor for cisplatin sensitivity was used to enrich for patients most likely to be sensitive to cisplatin therapy.[14,29] As a result of encouraging preclinical data, prospective trials are now enrolling patients to confirm the feasibility of genomic-based predictions of chemotherapeutic drug sensitivity.

In addition to cDNA microarray expression profiling, an emerging gene expression technology involving the use of microRNAs (miRNAs) has shown promise for predicting prognosis, risk of recurrence, and response to treatment. Conserved throughout nature, miRNAs are 21-23-nucleotide single-stranded RNAs that bind complementary sequences in target mRNAs, thereby inducing RNA degradation and preventing translation.[30] MiRNAs regulate nearly one-third of all human genes, and may act either as tumor suppressors or oncogenes.[30,31] MiRNA microarray expression signatures have been used to determine prognosis and risk of recurrence in numerous malignancies, including lung cancer. For example, Yanaihara et al. demonstrated decreased survival in lung adenocarcinoma patients with high levels of *mir-155* expression and low levels of *let7a-2* expression.[25] A separate study reported a statistically significant relationship between reduced expression of *let-7* and poor outcomes in patients receiving potentially curative resection of their lung cancer.[32] Based on these studies, current efforts are on-going to determine how best to modulate miRNAs thought to be involved in the oncogenic process.

While the use of genomic profiles to predict recurrence and response to therapy is promising, the importance of prospectively testing these approaches cannot be overemphasized, as there are several limitations. In addition to cost considerations and the current limited availability of genomic technologies outside of specialized academic centers,

Gene Expression Profiles

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several barriers prevent the widespread adoption of this technology into routine clinical practice. First, the acquisition of multiple genetic alterations likely leads to significant molecular heterogeneity within a tumor class, thereby leading to multiple gene expression profiles for "poor prognosis" and drug sensitivity. Second, batch effects and gene chip platform differences in independent studies may lead to discordant results for the same sample, potentially compromising the reproducibility of results. Standardization between genomic assays must be performed without compromising true genetic differences. Finally, DNA microarray technology typically requires acquisition of mRNA from fresh frozen tissue, which poses logistical difficulties for clinicians. Given the myriad challenges, it is critical that expression signatures undergo rigorous validation, both of their predictive capabilities and the statistical methods used to construct them.[14]

If prospective clinical trials confirm the value of gene expression signatures, DNA microarray and miRNA technology could be a crucial component to clinical decision-making for patients with NSCLC. Genomic data may not only provide a more accurate prediction of prognosis, but also guide decision-making about the value of adjuvant treatment. More importantly, where uncertainty exists regarding the selection of chemotherapeutics, genomic data may help guide the selection of specific treatments, thereby minimizing exposure to potentially toxic and unnecessary therapies. Finally, genomic data may reveal insights regarding the underlying biology of a patient's tumor, providing additional avenues for novel therapies. If its promise is fulfilled, genomic data may become a critical component of "personalized" cancer care.

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Selections from the Peer-Reviewed Literature

By Patrick Nana-Sinkam, MD

***Patrick Nana-Sinkam, MD** is Assistant Professor and Research Director, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, in the College of Medicine at Ohio State University. His clinical interests include thoracic malignancies, smoking-related lung disease, and critical care. His research focuses on the role of microRNAs in lung tumor development and progression, and the role of prostaglandins in smoking-related pulmonary diseases.*

1. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial

Chlebowski RT, Schwartz AG, Wakelee H, Anderson GL, Stefanick ML, Manson JE, Rodabough RJ, Chien JW, Wactawski-Wende J, Gass M, Kotchen JM, Johnson KC, O'Sullivan MJ, Ockene JK, Chen C, Hubbell FA; Women's Health Initiative Investigators, Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, CA. *Lancet*, 2009; 374:1243-1251

BACKGROUND: In the post-intervention period of the Women's Health Initiative (WHI) trial, women assigned to treatment with oestrogen plus progestin had a higher risk of cancer than did those assigned to placebo. Results also suggested that the combined hormone therapy might increase mortality from lung cancer. To assess whether such an association exists, we undertook a post-hoc analysis of lung cancers diagnosed in the trial over the entire follow-up period.

METHODS: The WHI study was a randomised, double-blind, placebo-controlled trial undertaken in 40 centres in the USA. 16, 608 postmenopausal women aged 50-79 years with an intact uterus were randomly assigned by a computerised, stratified, permuted block algorithm to receive a once-daily tablet of 0.625 mg conjugated equine oestrogen plus 2.5 mg medroxyprogesterone acetate (n=8,506) or matching placebo (n=8,102). We assessed incidence and mortality rates for all lung cancer, small-cell lung cancer, and non-small-cell lung cancer by use of data from treatment and post-intervention follow-up periods. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00000611.

FINDINGS: After a mean of 5.6 years (SD 1.3) of treatment and 2.4 years (0.4) of additional follow-up, 109 women in the combined hormone therapy group had been diagnosed with lung cancer compared with 85 in the placebo group (incidence per year 0.16% vs 0.13%; hazard ratio [HR] 1.23, 95% CI 0.92-1.63, p=0.16). 96 women assigned to combined therapy had non-small-cell lung cancer compared with 72 assigned to placebo (0.14% vs 0.11%; HR 1.28, 0.94-1.73, p=0.12). More women died from lung cancer in the combined hormone therapy group than in the placebo group (73 vs 40 deaths; 0.11% vs 0.06%; HR 1.71, 1.16-2.52, p=0.01), mainly as a result of a higher number of deaths from non-small-cell lung cancer in the combined therapy group (62 vs 31 deaths; 0.09% vs 0.05%; HR 1.87, 1.22-2.88, p=0.004). Incidence and mortality rates of small-cell lung cancer were similar between groups.

INTERPRETATION: Although treatment with oestrogen plus progestin in postmenopausal women did not increase incidence of lung cancer, it increased the number of deaths from lung cancer, in particular deaths from non-small-cell lung cancer. These findings should be incorporated into risk-benefit discussions with women considering combined hormone therapy, especially those with a high risk of lung cancer.

EDITORIAL COMMENT: This manuscript represents a landmark study that further supports the detrimental effects of hormonal therapy in postmenopausal women. The Women's Health Initiative was a randomized, double blinded, placebo–controlled trial of 16,608 women between the ages of 50 and 79 assigned to either combined hormonal

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therapy or placebo. At approximately five years of follow-up, individuals randomized to combined therapy demonstrated a higher risk for cardiovascular complications, breast and colon cancer. Given previous *in vitro* and *in vivo* data to suggest that estrogen may promote lung tumorigenesis and angiogenesis, the authors sought to determine if combined hormonal therapy increases the incidence and mortality from lung cancer in the WHI cohort. The authors observed that while there was no difference in incident cases of lung cancer between the two groups, women receiving combined hormone therapy had a higher number of deaths attributable to lung cancer (HR 1.71, p=0.01), higher number of deaths attributable to non-small cell lung cancer (HR 1.87, p=0.004), higher frequency of metastatic disease (HR 1.71, p=0.04) and poorly differentiated tumors (HR 2.0, p=0.03). Of note, there was no difference in incidence of small cell cancer cases, and smoking status did not affect the results. Previous studies have been mixed, partially based on study design, but the randomized nature of the current investigation strengthens the conclusion. Granted, there were some limitations, including incomplete information on treatment modalities for the lung cancer patients, and overall small numbers of cases. Nevertheless, the results of this study should have implications for how health care providers counsel postmenopausal women (particularly higher risk smokers) about the use of combined hormonal therapy and the risk for lung cancer.

2. Randomized controlled trials of the efficacy of lung cancer screening by sputum cytology revisited: a combined mortality analysis from the Johns Hopkins Lung Project and the Memorial Sloan-Kettering Lung Study

Doria-Rose VP, Marcus PM, Szabo E, Tockman MS, Melamed MR, Prorok PC, Biometry Research Group, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD. *Cancer* 2009; 115:5007-5017

BACKGROUND: Two randomized controlled trials of lung cancer screening initiated in the 1970s, the Johns Hopkins Lung Project and the Memorial Sloan-Kettering Lung Study, compared 1 arm that received annual chest X-ray and 4-monthly sputum cytology (dual-screen) to a second arm that received annual chest X-ray only. Previous publications from these trials reported similar lung cancer mortality between the 2 groups. However, these findings were based on incomplete follow-up, and each trial on its own was underpowered to detect a modest mortality benefit.

METHODS: The authors estimated the efficacy of lung cancer screening with sputum cytology in an intention-to-screen analysis of lung cancer mortality, using combined data from these trials (n = 20,426).

RESULTS: Over 1/2 of squamous cell lung cancers diagnosed in the dual-screen group were identified by cytology; these cancers tended to be more localized than squamous cancers diagnosed in the X-ray only arm. After 9 years of follow-up, lung cancer mortality was slightly lower in the dual-screen than in the X-ray only arm (rate ratio [RR], 0.88; 95% confidence interval [CI], 0.74-1.05). Reductions were seen for squamous cell cancer deaths (RR, 0.79; 95% CI, 0.54-1.14) and in the heaviest smokers (RR, 0.81; 95% CI, 0.67-1.00). There were also fewer deaths from large cell carcinoma in the dual-screen group, although the reason for this is unclear.

CONCLUSIONS: These data are suggestive of a modest benefit of sputum cytology screening, although we cannot rule out chance as an explanation for these findings.

EDITORIAL COMMENT: This is an interesting study that seeks to examine the potential role for sputum cytology as a screening modality in lung cancer. In the last issue of *Lung Cancer Frontiers*, Dr. Gerard Silvestri elegantly summarized the current state of lung cancer screening and it was "clear" that lung cancer screening remains "unclear." Given its non-invasive nature, sputum cytology is an attractive approach to screening and diagnosis, particularly in patients at high risk for complications from other procedures. Unfortunately, for several reasons, sputum cytology has not become mainstream for either screening or diagnosis. In this study, the authors reexamined two large screening trials conducted in the 1970's (John Hopkins Lung Project and Memorial Sloan-Kettering Lung Study). Both trials evaluated the role of screening for lung cancer by sputum cytology and chest radiography compared to chest radiography alone. Both studies failed to demonstrate a benefit in mortality with the addition of sputum screening. In this new study, the authors propose that by examining additional follow-up information and combining data from

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both previous trials, they may identify potential benefit in sputum screening. In nine years of follow-up, the authors were unable to detect a mortality benefit with sputum cytology screening. They did detect more cases of squamous cell lung cancer of earlier stage in the chest radiography/sputum group. The authors correctly conclude that, given improved technologies for examining sputum, as well modalities for assessing potential precancerous states, mutational analyses and methylation status, perhaps another well-designed trial utilizing such technologies may be beneficial. However, until that time, sputum cytology as a method of lung cancer screening will remain out of the mainstream.

3. The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer

Vallières E, Shepherd FA, Crowley J, Van Houtte P, Postmus PE, Carney D, Chansky K, Shaikh Z, Goldstraw P, International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. *J Thorac Oncol* 2009 4:1049-1059

INTRODUCTION: For more than 50 years, small cell lung cancer (SCLC) has been staged mainly as either limited or extensive stage disease. Small published series of resected SCLC have suggested that the tumor, node, metastases (TNM) pathologic staging correlates with the survival of resected patients. Recent analysis of the 8,088 cases of SCLC in the International Association for the Study of Lung Cancer (IASLC) database demonstrated the usefulness of clinical TNM staging in this malignancy. The IASLC data bank contains an unprecedented number of resected SCLC cases with pathologic staging information. This analysis was undertaken to examine the impact of the TNM system on the pathologic staging of SCLC and to assess the new IASLC proposals in this subtype of lung cancer.

METHODS: Using the IASLC database, survival analyses were performed for resected patients with SCLC. Prognostic groups were compared, and the new IASLC TNM proposals were applied to this population and to the Surveillance, Epidemiology, and End Results (SEER) database.

RESULTS: The IASLC database contained 349 cases of resected SCLC where pathologic TNM staging was available. Survival after resection correlated with both T and N category with nodal status having a stronger influence on survival. Stage groupings using the 6th edition of TNM clearly identify patient subgroups with different prognoses. The IASLC proposals for the 7th edition of TNM classification also apply to this population and to the SEER database.

CONCLUSION: This analysis further strengthens our previous recommendation to use TNM staging for all SCLC cases.

EDITORIAL COMMENT: To date, the majority of proposed changes to the current lung cancer staging system have focused on non-small cell lung cancer while the staging system for small lung cancer has remained stagnant. Traditional practice continues to support small cell staging as "limited" versus "extensive" disease. Previous studies have drawn mixed conclusions as to whether TNM staging for small cell lung cancer is of clinical utility. One major limitation has been the relatively low number of surgically resected small cell cases. As part of the IASLC Lung Cancer Project, the authors identified 349 cases of surgically resected small cell lung cancers that had current pathologic TNM staging information. Of these, 262 were appropriate for the proposed 7th edition of TNM staging. By applying both staging criteria to these cohorts, the authors were able to assess survival and compare clinical to pathological staging. There were two important findings: 1) the authors identified distinct subgroups of resected small cell patients with differing prognoses using either the 6th or 7th edition staging system, suggesting that TNM staging may be appropriate for small cell lung cancer, and 2) similar to previous studies, they identified a high discordance between clinical and pathologic staging. Therefore, appropriate staging of the mediastinum and use of non-invasive modalities such as PET scanning should be integrated into clinical decision-making. There were two important limitations to this study, namely the highly selective population of patients, the majority of whom had T1 or T2 disease, and the lack of reliable data on the chemotherapy regimen received by this cohort. Nevertheless, the IASLC International Staging Committee's findings suggest that our current reductionist approach of limited versus extensive small cell may be inaccurate and that TNM staging should be applied to small cell patients for the purposes of clinical trials and to better assess treatment response.

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4. A small-cell lung cancer genome with complex signatures of tobacco exposure

Pleasance ED, Stephens PJ, O'Meara S, McBride DJ, Meynert A, Jones D, Lin ML, Beare D, Lau KW, Greenman C, Varela I, Nik-Zainal S, Davies HR, Ordoñez GR, Mudie LJ, Latimer C, Edkins S, Stebbings L, Chen L, Jia M, Leroy C, Marshall J, Menzies A, Butler A, Teague JW, Mangion J, Sun YA, McLaughlin SF, Peckham HE, Tsung EF, Costa GL, Lee CC, Minna JD, Gazdar A, Birney E, Rhodes MD, McKernan KJ, Stratton MR, Futreal PA, Campbell PJ, Wellcome Trust Sanger Institute, Hinxton, UK. *Nature* 2009 Dec 16 [Epub ahead of print]

ABSTRACT: Cancer is driven by mutation. Worldwide, tobacco smoking is the principal lifestyle exposure that causes cancer, exerting carcinogenicity through >60 chemicals that bind and mutate DNA. Using massively parallel sequencing technology, we sequenced a small-cell lung cancer cell line, NCI-H209, to explore the mutational burden associated with tobacco smoking. A total of 22,910 somatic substitutions were identified, including 134 in coding exons. Multiple mutation signatures testify to the cocktail of carcinogens in tobacco smoke and their proclivities for particular bases and surrounding sequence context. Effects of transcription-coupled repair and a second, more general, expression-linked repair pathway were evident. We identified a tandem duplication that duplicates exons 3-8 of *CHD7* in frame, and another two lines carrying *PVT1-CHD7* fusion genes, indicating that *CHD7* may be recurrently rearranged in this disease. These findings illustrate the potential for next-generation sequencing to provide unprecedented insights into mutational processes, cellular repair pathways and gene networks associated with cancer.

EDITORIAL COMMENT: This important manuscript highlights the relatively new technology of massive parallel sequencing (SOLiD or Supported Oligo Ligation Detection) as a platform for providing a more global view of mutational status in human malignancy beyond recognized mutations in candidates such as *KRAS*, *RB1* and *TP53*. This represents the first such detailed analysis of a human malignancy associated with tobacco use. The authors conducted massive parallel sequencing on the NCI-H209 small cell lung cancer cell line and detected 22,910 somatically acquired mutations. Of note, they identified at least two separate DNA repair pathways, 58 somatically acquired genomic rearrangements and recurrent rearrangements in the *CHD7* gene, a chromatin remodeler that promotes transcription. While it is still early, the application of such technologies may allow us to identify previously unrecognized mutations that could serve as the basis for further investigation and targeted therapies.

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