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RESEARCH PERSPECTIVES

A Summary of the 2025 Lung Cancer Summit at Stanford University: Understanding Lung Cancer in Persons Who Have Never Smoked

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INTRODUCTION

In the United States, lung cancer remains the second most common cancer and leading cause of cancer mortality among both men and women.[1] Globally, lung cancer in never smokers (LCINS), defined as individuals who have smoked less than 100 cigarettes in their lifetime, makes up between one-quarter and one-third of lung cancer deaths, which if categorized as a distinct entity would represent the fifth most common cause of cancer death worldwide.[2,3] Despite this individual and societal burden, recognition of the problem among medical providers remains inadequate, standardized screening guidelines are lacking, and further therapeutic developments are needed. Therefore, further awareness of and attention to LCINS remains an area of unmet need, which this Summit aimed to address.

SUMMIT FRAMEWORK

The Center for Asian Health Research and Education (CARE) at Stanford University School of Medicine in Palo Alto, California convened a group of experts across medical and scientific disciplines of the Stanford faculty for the inaugural Stanford Lung Cancer Summit: Understanding Lung Cancer in People Who Have Never Smoked, March 11–12, 2025. As envisioned by co-chairs Bryant Lin MD, Clinical Professor of Medicine and Heather Wakelee MD, Professor of Medicine (Oncology), the intention of the Summit was to bring together Stanford University faculty to: (1) explore disease etiology and epidemiology, (2) drive consensus on screening and early disease detection, (3) discuss established and novel treatment modalities, and (4) understand patient perspectives in order to guide provider awareness and community outreach. The first day of the Summit focused on the current body of evidence including lung cancer screening, risk factors and epidemiology, and treatment of both early-stage and advanced disease. The second day shifted to a future-facing perspective, including presentations on emerging molecular and immunologic etiologies of LCINS, novel strategies for disease detection, and development of novel targeted therapies.

DAY 1: CURRENT DEVELOPMENTS – FROM SCREENING TO TREATMENT

Strategies for screening and diagnosis

Douglas Liou, MD, Clinical Associate Professor of Cardiothoracic Surgery (Thoracic Surgery), Stanford University School of Medicine (Stanford), initiated the Summit by reviewing the epidemiology of lung cancer, with an emphasis on the burden among individuals who have never smoked. Dr. Liou discussed data from the US National Lung Screening Trial (NLST), demonstrating a 20% relative reduction in lung cancer-related mortality for annual low-dose computed tomography (LDCT) compared with chest x-ray (CXR), as well as the similar European NELSON trial (Dutch-Belgian Randomized Lung Cancer Screening Trial) comparing LDCT with no

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screening (Table 1).[4,5] Based on these data, the 2021 US Preventive Services Task Force (USPSTF) recommended annual lung cancer screening with LDCT in adults aged 50 to 80 years with a 20 pack-year smoking history who either currently smoke or have quit within the last 15 years.[6] Despite such recommendations, the uptake of LDCT lung cancer screening remains low (less than 20%), compared with much higher screening rates for breast, cervical, and colorectal cancer (approximately 70%).[7,8] Natalie Lui, MD, Assistant Professor of Cardiothoracic Surgery (Thoracic Surgery) at Stanford, then discussed the TALENT study (Taiwan Lung Cancer Screening in Never-Smoker Trial), a national screening trial in Taiwan in which subjects between the ages of 55 and 75 years who were light or never smokers with one additional risk factor (most importantly family history) were screened with LDCT.[9] The invasive lung cancer detection rate was 2.1%, higher than the US NLST trial enrolling patients with heavy smoking histories (Table 1).[4,9] TALENT has now led to Taiwan's current early detection program, which thus far has demonstrated stage shift towards less advanced disease.[10]

In clinical practice, many lung nodules are detected incidentally. Weijia Chua, MD, Clinical Assistant Professor of Medicine (Pulmonary, Allergy, and Critical Care Medicine) at Stanford, reviewed the DELUGE (Detecting Early Lung Cancer in the Mississippi Delta) study, a prospective study from a community-based health care system in which incidental lung nodules accounted for more than four times the number of lung cancer diagnoses compared with a lung cancer screening program. Despite this finding, only 49% of those diagnosed with lung cancer through the incidental lung nodule program would have been eligible for screening by traditional criteria.[11] Henry Guo, MD, PhD, Clinical Professor of Radiology at Stanford, emphasized that technologic advances have allowed iterative decreases in radiation doses associated with LDCT screening, from approximately 5 mSv in 2013 to as low as 0.4 mSv in 2024.[12] During the discussion panel, Leah Backhus, MD, Professor of Cardiovascular Surgery at Stanford, offered the perspective that while the shared-decision making encounter required by the Centers for Medicare and Medicaid Services (CMS) offers patients information and context, it is in contrast to other forms of cancer screening and may serve as a barrier to LDCT uptake.[13]

Risk factors and epidemiology

Ann Hsing, PhD, Professor of Medicine and of Epidemiology and Population Health at Stanford began this session by emphasizing the gaps in population-level data when studying LCINS. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database does not capture smoking data, and only certain state-level registries do so. Within these limitations, the rates of LCINS appear stable across most groups over time; however, incidence among Asian women who have never smoked may be increasing by approximately 2% per year.[14–16] Specifically among this population, Dr. Hsing highlighted the ongoing Female Asian Never Smokers (FANS) study, which is a collaboration among the University of California, San Francisco (UCSF), the University of California, Davis (UC Davis), Stanford, and more recently other centers in Southern California. The study, led by Scarlett Gomez, PhD, Professor of Epidemiology and Biostatistics (UCSF), Iona Cheng, PhD, Professor of Epidemiology and Biostatistics (UCSF), and Moon Chen, Jr., Professor of Internal Medicine (Hematology/Oncology) (UC Davis), aims to recruit 400 lung cancer cases and 600 matched controls in California.[17] In general for LCINS, risk factors are both endogenous (e.g., genetics or family history) and exogenous (e.g., pollution or cooking fumes). Linda Kachuri, PhD, Assistant Professor of Epidemiology and Population Health at Stanford, discussed the genetic epidemiology of LCINS, particularly several associated chromosomal loci established through genome-wide association studies (GWAS), including 5p15.33 (*TERT-CLPTM1L*) and 3q28 (*TP63*).[18,19] Beyond GWAS, polygenic risk scores have the potential to refine risk trajectories in people who have never smoked, so far shown in a European population with ongoing expansion to a multiancestry cohort.[20]

Julie Wu, MD, Staff Physician and Medical Oncologist at the Palo Alto (California) Veterans Institute for Research, further expanded on risk prediction models, emphasizing that almost all existing models for lung cancer include smoking as a major driving factor.[21] While several models have been developed to predict lung cancer risk in never smokers, these have been developed in varied populations with only modest predictive capabilities.[22–25] Even with existing risk prediction models, electronic health record (EHR)-embedded tools and large language models (LLMs) are needed to bridge the implementation gap to lung cancer screening. Summer Han, PhD, Associate Professor of Neurosurgery and of Medicine at Stanford, discussed that current prospective studies of lung cancer screening in never smokers are single-arm studies, which cannot demonstrate a mortality benefit (Table 1).[9,26] Additional challenges limiting population-level intervention include understanding the optimal screening strategy, generalizability to broader target populations, and cost effectiveness. Dr. Han has proposed a research initiative called INSIGHT to address these questions, utilizing a simulation modeling-based approach and a cross-institutional EHR-based database for LDCT screening.

Table 1. Comparison of Prospective Lung Cancer Screening Trials

	NLST[a]	NELSON[b]	TALENT[c]	FANSS[d]
Full trial name	National Lung Screening Trial	Nederlands-Leuvens Longkanker Screenings Onderzoek	Taiwan Lung Cancer Screening in Never-Smoker Trial	Female Asian Nonsmoker Screening Study
Location	United States	The Netherlands and Belgium	Taiwan	New York, Massachusetts, California
Time frame	2002–2009	2004–2012	2015–2019	2021-ongoing
Enrollment	53,454	15,789	12,011	201 (ongoing)
Male/Female	59%/41%	83%/17%	26%/74%	0%/100%
Key eligibility criteria	Age 55–74; 30 pack-year smoking history and, if former smokers, had quit within 15 years	Age 50–74, current or former smoking history (quit within last 10 years) who had smoked >15 cig/day for >25 years or >10 cig/day for >30 years	Age 55–75, negative CXR, never smoked, or smoked <10 pack-years and stopped for >15 years, ≥1 risk factor (family history of lung cancer, history of pulmonary TB or COPD, cooking index ≥110, or cooking without ventilation)	Age 40–74, never smoked, Asian descent
Screening procedure(s)	Randomized to either LDCT or CXR annually for 3 years	Randomized to either LDCT × 4 (with intervals of 1, 2, and 2.5 years) or no screening	LDCT at baseline, then annually for 2 years, then every 2 years for up to 6 years	LDCT annually for 3 years
Invasive lung cancer detection rate	1.1%	0.9%	2.1%	1.5%
Survival benefit	20% relative reduction in death from lung cancer with LDCT (95% CI, 7–27%)	24% relative reduction in death from lung cancer with LDCT (95% CI, 6–39%)	No comparator arm	No comparator arm

Abbreviations: cig/day = cigarettes/day; COPD = chronic obstructive pulmonary disease; CXR = chest x-ray; LDCT = low dose computed tomography; TB = tuberculosis.

[a]National Lung Screening Trial Research T, Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365:395–409. doi: 10.1056/NEJMoa1102873

[b]De Koning HJ, Van der Aalst CM, De Jong PA, Scholten ET, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med.* 2020;382:503–13. doi: 10.1056/NEJMoa1911793

[c] Chang GC, Chiu CH, Yu CJ, et al. Low-dose CT screening among never-smokers with or without a family history of lung cancer in Taiwan: a prospective cohort study. Lancet Respir Med 2024;12(2):141–152. doi: 10.1016/S2213-2600(23)00338-7

[d]Shum E, Li W, Sequist LV, Ou SH, Goldberg JD, Chachoua A, Wong KK. Preliminary results from the Female Asian Nonsmoker Screening Study (FANSS). *J Clin Oncol.* 2023;41(16 Suppl):8510.

Advances in diagnosis and early-stage treatment

Jiwoon Chang, MD, Clinical Assistant Professor of Medicine (Pulmonary, Allergy and Critical Care Medicine) at Stanford, provided an overview of novel technologies in Interventional Pulmonology allowing for safer and more accurate tissue biopsy, including robotic-assisted bronchoscopy, cone beam CT guidance, and cryobiopsy.[27–29] Lucas Vitzthum, MD, Clinical Associate Professor of Radiation Oncology at Stanford, discussed the general principles of radiation therapy for treatment of early-stage lung cancer, emphasizing goals of reducing toxicity, improving tumor control, decreasing need for invasive procedures, and reducing time toxicity of cancer treatment. Dr. Vitzthum then reviewed modern dosimetry techniques, strategies for managing respiratory motion, and also discussed emerging technologies such as positron emission tomography (PET)-guided radiation therapy.[30,31] To close the session, Mark Berry, MD, Professor of Cardiothoracic Surgery at Stanford, discussed surgical advances in the treatment of early-stage lung cancer. Over the past decade, there has been an increase in minimally invasive surgical techniques such as robotic surgery and video-assisted thoracoscopic surgery (VATS). While lobectomy was the historical standard for early-stage lung cancer, contemporary data demonstrate that sublobar resection (segmentectomy, wedge resection) is the preferred approach for peripheral Stage IA lung cancers.[32–34] With that in mind, all surgeries for early-stage lung cancer should continue to include some degree of lymph node assessment.

Updates in targeted systemic therapy

Actionable genomic alterations, also termed driver oncogenes, are particularly enriched in LCINS. There are over 10 molecular alterations in non-small cell lung cancer (NSCLC) for which targeted therapies are approved in the advanced or metastatic setting. Joel Neal, MD, PhD, Professor of Medicine (Oncology) at

Stanford, discussed that many, but not all, of these driver oncogenes are identified more frequently in LCINS, for example classical *EGFR* mutations, *EGFR* and *HER2* exon 20 insertions, *KRAS* G12D, and many of the activating rearrangements including *ALK*, *ROS1*, and *RET*.[2] Utilizing appropriate testing modalities to identify these driver oncogenes is important, as different alterations can be missed by various testing methods, for example rearrangements on DNA-based next-generation sequencing (NGS).[35,36]

Millie Das, MD, Clinical Professor of Medicine (Oncology) at Stanford, explained that advances in targeted therapy for advanced NSCLC have been an exemplar for modern precision medicine. For example, the ALK tyrosine kinase inhibitor (TKI) lorlatinib demonstrated a standard-setting progression-free survival (PFS) of greater than five years in patients with advanced or metastatic NSCLC harboring an *ALK* rearrangement.[37] *KRAS* mutations, which were previously not felt to be targetable, now have two approved oral therapies available in the subsequent-line setting (*KRAS* G12C-specific), with KRAS G12C 'on' and pan-RAS inhibitors in development.[38–42] As acquired resistance remains an unmet need in advanced NSCLC, further emerging TKIs aim to address resistance mechanisms to existing targeted therapy and minimize off-target side effects.[43,44] Nathaniel Myall, MD, Clinical Assistant Professor of Medicine (Oncology) at Stanford, addressed the issue of central nervous system (CNS) metastases in NSCLC, which are enriched in many subtypes of LCINS and associated with an inferior prognosis. Many newer-generation targeted therapies have improved CNS penetration, leading to the question of whether radiation therapy should be used in the front-line setting.[45] In terms of emerging therapies beyond TKIs, several novel antibody-drug conjugates (ADCs) have demonstrated intracranial activity in previously treated NSCLC with driver oncogenes.[46]

Mohana Roy, MD, Clinical Assistant Professor of Medicine (Oncology) at Stanford, shifted the discussion to the early-stage setting, reviewing consensus recommendations that all patients being considered for neoadjuvant or adjuvant systemic therapy should be tested for *EGFR* and *ALK* alterations at minimum.[47] Furthermore, patients in whom *EGFR* or *ALK* alterations are identified should not receive immunotherapy but rather be offered adjuvant or consolidation TKI if meeting the criteria for ADAURA (*EGFR*-mutated NSCLC, Stage IB-IIIA after resection), LAURA (*EGFR*-mutated NSCLC, Stage III after chemoradiation) or ALINA (*ALK*-rearranged NSCLC, Stage IB-IIIA after resection).[47–50] Finally, Kavitha Ramchandran, MD, Clinical Professor of Medicine (Oncology) at Stanford, led a discussion centered around the multidisciplinary team needed to manage side effects of therapy, with particular attention towards the multifaceted parts of a patient's experience with cancer treatment.

DAY 2: PAVING THE FUTURE – FROM NOVEL DISCOVERIES TO PATIENT PERSPECTIVES

Hereditary, immune, and intrinsic determinants of lung cancer risk

Christina Curtis, PhD, Professor of Medicine (Oncology), of Genetics, and of Biomedical Data Science at Stanford, began the second day of the Summit by describing the use of integrative clusters, involving complex genomic and transcriptomic architecture to subtype various solid tumors and identify new therapeutic targets.[51] In breast cancer, her group has demonstrated that subjects with the ability to present peptides from key oncogenes are less likely to develop that subtype of cancer.[52] Analogous findings have been demonstrated in lung cancer; for example, the ability to present EGFR peptides is negatively associated with the development of *EGFR*-mutated lung cancer, especially in women. Steve Artandi, MD, PhD, Professor of Medicine (Hematology) and of Biochemistry at Stanford and Director of the Stanford Cancer Institute, reviewed evidence that telomerase is upregulated in lung cancer, supporting the previously presented GWAS data implicating the *TERT* gene as discussed by Dr. Kachuri.[19,53] In particular, Dr. Artandi highlighted two large cohort studies in which longer leukocyte telomere length was associated with increased risk of lung cancer, particularly adenocarcinoma histology.[54,55] Tushar Desai, MD, Professor of Medicine (Pulmonary, Allergy and Critical Care Medicine) at Stanford, focused on the lepidic pattern of lung adenocarcinoma, characterized by a growth pattern along intact alveolar walls. The lepidic growth pattern appears to be enriched among LCINS, and while associated with driver alterations in *EGFR* and *KRAS*, is not exclusive to these.[56,57] Dr. Desai demonstrated that pulmonary alveolar type I (AT1) cells may be the cell of origin for some lepidic adenocarcinomas via stem cell reprogramming, prompting the question of whether such knowledge can be harnessed for clinical application.[58]

Novel liquid biopsy technologies

Liquid biopsy refers to a noninvasive test, most commonly of the blood, used to detect circulating tumor cells, molecular alterations, or other metabolites associated with cancer.[59] Maximilian Diehn, MD, PhD, Professor of Radiation Oncology (Radiation Therapy) at Stanford, reviewed the range of liquid biopsy methods and analytic techniques, emphasizing that the appropriate application varies between assays. Focusing further on the detection of minimal residual disease (MRD) in lung cancer using circulating tumor DNA (ctDNA), a key limitation of first-generation ctDNA assays is the high false-negative rate, missing approximately two-thirds of recurrences.[60]

Phased variant enrichment and detection sequencing (PhasED-Seq) is a next-generation assay estimated to be two orders of magnitude more sensitive than first-generation assays and may be a better tool to predict clinical recurrence.[61] Mohammad Esfahani, PhD, Assistant Professor of Radiation Oncology (Radiation and Cancer Biology) at Stanford, discussed fragmentation patterns derived from cell-free DNA, which can be used to infer epigenetic expression via a method called EPIC-Seq. This technology has thus far been applied toward lung cancer detection as well as histology classification, with further applications in development.[62]

Novel therapeutic targets and drug discovery

Nathanael Gray, PhD, Professor of Chemical and Systems Biology at Stanford, presented several novel strategies for targeting *EGFR*-mutated NSCLC in preclinical development, with a focus on osimertinib-induced resistance. Dr. Gray described a novel allosteric EGFR inhibitor designed to bind away from the ATP binding site, thus circumventing resistance mutations at the osimertinib-binding pocket.[63] Also in early development are small molecule degraders of EGFR, harnessing proteolysis targeting chimera (PROTAC) technology.[64] Finally, Dr. Gray discussed novel chemical approaches (molecular bidents and proximity induction), which may help circumvent single cysteine mutation-based resistance mechanisms such as C797S. Many of the molecular targeting strategies discussed by Dr. Gray depend on protein-based screens for novel drug discovery, which requires knowledge of the target as well as the desired mechanism of action. Steven Corsello, MD, Assistant Professor of Medicine (Oncology) at Stanford, described cell-based (phenotypic) screens, which utilize CRISPR/Cas9 base editing technology to induce mutagenesis and better understand potentially targetable sensitivities.[65] Existing base editor mutagenesis screens are limited by scalability, which Dr. Corsello's ongoing work aims to address, focusing on functional evaluation of the entire EGFR signaling pathway.[66,67]

The patient and caregiver perspective

To close the Summit, the patient and caregiver advocacy panel, led by Bryant Lin, MD, Clinical Professor of Medicine at Stanford, raised a number of unmet needs to serve as a launching point for further action. Despite what is known about LCINS, there remains a knowledge gap among many in frontline primary care about lung cancer in this population, which has implications for timely diagnosis. After a lung cancer diagnosis, patients find it challenging to identify and access clinical trial opportunities, of which their treating physician may or may not have current information. And finally, patients and their families seek guidance on how to live life to the fullest on, and for some, after treatment.

SUMMIT CONCLUSIONS AND FUTURE DIRECTIONS

The 2025 Stanford Lung Cancer Summit highlighted the burden of LCINS, particularly among women and individuals of Asian descent. While the understanding of lung cancer risk among this population continues to improve, existing risk stratification tools and screening guidelines do not adequately address the US population. Based on these data, a consensus emerged among Summit participants that extended community outreach and direct engagement of frontline primary care providers should be implemented to bring further awareness to this disease. The Summit participants also proposed additional efforts, including:

1. Improved multi-institution collaboration to build high-quality datasets and biobanks capturing LCINS, harnessing existing EHR data and artificial intelligence (AI) technologies
2. A need to lower the barrier to screening by engaging payors to support reimbursement and harnessing new imaging and biopsy technologies to decrease harms
3. A need for further data, particularly prospective clinical trials, to support expert guidance or screening recommendations applicable to a US population
4. Increased funding and multidisciplinary collaboration to support the next generation of novel discoveries in academic medicine, as they apply to LCINS

ARTICLE INFORMATION

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