INTERVIEW

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CD 2, Tracks 25-31

Track 25 Modest historic improvements in lung cancer survival

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Track 31 Prognostic value of the multigene assay in nonsquamous NSCLC

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CD 2, Track 26

DR LOVE: Would you discuss the National Lung Screening Trial, which aimed to determine whether screening with low-dose CT could reduce mortality from lung cancer?

DR JABLONS: We can make significant strides if we can identify patients at the early stages of disease. The predominant risk factor for the development of lung cancer is smoking. We can identify this risk factor, and we should be able to screen these patients. CT scans are an effective tool for finding nodules in the lung.

The National Lung Screening Trial accrued about 53,000 patients, half of whom were randomly assigned to undergo screening with the standard, which is a chest x-ray. The other half underwent screening with low-dose CT. Eligible participants were patients at high risk who were older than age 55 and had a history of smoking of at least 30 pack-years. These patients were monitored and if a suspicious nodule was found, the CT scan was repeated. Lung tumors, with the exception of low-grade adenocarcinoma in situ, will grow in time. If growth was observed, it was biopsied. If cancer was detected, it was resected.

Early analysis reported a dramatic 20% survival benefit in patients who were screened with low-dose, noncontrast CT (National Lung Screening Trial Research Team 2011; [4.1]). This was the first time a prospective, randomized trial indicating the benefit of

cancer screening was conducted. This was a brilliantly conducted multicenter trial that should yield a wealth of useful information over the next few years.

4.1

National Lung Screening Trial: Reduced Lung Cancer Mortality with Low-Dose CT Screening

	Low-dose CT group (n = 26,722)	Radiography group (n = 26,732)	Relative reduction in mortality
Rate of positive screening results	24.2%	6.9%	—
Incidence of lung cancer (cases per 100,000 person-years)	645	572	—
Deaths from lung cancer (No. per 100,000 person-years)	247	309	20.0% $p = 0.004$
Deaths from any cause	1,877	2,000	6.7% $p = 0.02$

"The cost-effectiveness of low-dose CT screening must also be considered in the context of competing interventions, particularly smoking cessation. NLST investigators are currently analyzing the quality-of-life effects, costs, and cost-effectiveness of screening in the NLST and are planning collaborations with the Cancer Intervention and Surveillance Modeling Network to investigate the potential effect of low-dose CT screening in a wide range of scenarios."

National Lung Screening Trial Research Team et al. *N Engl J Med* 2011;365(5):395–409.

CD 2, Tracks 28-31

DR LOVE: Would you discuss your recently published paper describing a genomic assay to predict survival in patients with resected NSCLC?

DR JABLONS: The technology for the study came from our laboratory at UCSF. The idea was to try to find a molecular biomarker or a collection of genes that could provide a signature to identify high-risk early-stage lung cancer. About 50,000 patients with Stage I and II disease would be eligible to benefit from this analysis in the United States.

The overall survival for patients with Stage I disease after resection in the United States is approximately 60% to 65%. That means 35% to 50% of patients fail to survive as a result of occult micrometastasis. The biology of the tumor can inform us whether a lesion is truly localized or if occult micrometastatic disease may be present, which we cannot image. The purpose of this study was to be able to identify the group of patients at high risk for mortality.

The current test is a 14-gene test based on an algorithm. The assay was developed in a cohort of about 360 patients with early-stage nonsquamous NSCLC at UCSF. It was then independently validated in 433 patients with Stage I lung cancer at the Kaiser Permanente Northern California hospitals and 1,006 patients with Stage I to III lung cancer resected in several Chinese cancer centers.

The results showed that in about 1,000 patients in the United States with Stage I nonsquamous NSCLC, the survival was 71% for the group of patients at low risk versus 49% for those at high risk, with a *p*-value of 0.0003. In China the results were similar with 74% for the patients at low risk versus 44% for the patients at high risk, with a

p-value less than 0.0001 (Kratz 2012; [4.2]). The fact that similar results were obtained on 2 continents is one of the remarkable aspects of this study.

The test currently is purely prognostic, but we are about to embark on a large-scale, international, prospective, randomized trial that will enroll 1,500 patients with nonsquamous NSCLC that has been completely resected and has adequate surgical and clinical staging. The 14-gene assay will be performed, and patients in the high-risk category will be randomly assigned to systemic chemotherapy with a platinum doublet or pemetrexed/cisplatin. The patients will be followed for time to progression and survival.

We hope to accrue quickly and within the next 3 to 4 years be able to not only validate the prognostic value, but also establish whether a predictive benefit can be observed for administering chemotherapy in patients at high risk for mortality after surgical resection. ■

4.2

Practical Molecular Assay to Predict Survival for Patients with Resected Nonsquamous Non-Small Cell Lung Cancer

	5-year overall survival	*p*-value
Kaiser validation cohort (n = 433)		
Low risk	71.4%	
Intermediate risk	58.3%	0.0003
High risk	49.2%	
Chinese validation cohort (n = 1,006)		
Low risk	74.1%	
Intermediate risk	57.4%	<0.0001
High risk	44.6%	

Methods: A 14-gene expression assay that uses quantitative PCR, runs on formalin-fixed, paraffin-embedded tissue samples and differentiates patients with heterogeneous statistical prognoses was developed in a cohort of 361 patients with nonsquamous NSCLC resected at UCSF. The assay was then independently validated by 2 separate cohorts.

Conclusion: This practical, quantitative PCR-based assay reliably identified patients with early-stage non-squamous non-small cell lung cancer at high risk for mortality after surgical resection.

Kratz JR et al. *Lancet* 2012;379(9818):823-32.

SELECT PUBLICATIONS

Chen DT et al. **Prognostic and predictive value of a malignancy-risk gene signature in early-stage non-small cell lung cancer.** *J Natl Cancer Inst* 2011;103(24):1859-70.

Ding L et al. **Somatic mutations affect key pathways in lung adenocarcinoma.** *Nature* 2008;455(7216):1069-75.

Hou J et al. **Expression profiling-based subtyping identifies novel non-small cell lung cancer subgroups and implicates putative resistance to pemetrexed therapy.** *J Thorac Oncol* 2012;7(1):105-14.

Hutchinson L. **Lung cancer: Practical assay to predict survival.** *Nat Rev Clin Oncol* 2012;9(3):127.

Kratz JR et al. **A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: Development and international validation studies.** *Lancet* 2012;379(9818):823-32.

National Lung Screening Trial Research Team et al. **Reduced lung-cancer mortality with low-dose computed tomographic screening.** *N Engl J Med* 2011;365(5):395-409.

Siegel R et al. **Cancer statistics, 2012.** *CA Cancer J Clin* 2012;62(1):10-29.

Sox HC. **Better evidence about screening for lung cancer.** *N Engl J Med* 2011;365(5):455-7.

Xie Y, Minna JD. **A lung cancer molecular prognostic test ready for prime time.** *Lancet* 2012;379(9818):785-7.