

STATEMENT CONCERNING THE NATIONAL LUNG SCREENING TRIAL

October 28, 2010

On October 20, 2010, the Data and Safety Monitoring Board (DSMB) of the National Lung Screening Trial (NLST) conducted by the National Cancer Institute (NCI) voted unanimously, with one member absent, to stop the trial. This decision was based on two observations: first, the data necessary for inference on the primary endpoint of lung-cancer-specific mortality had been collected, and, second, there was no evidence of unforeseen screening effects that warranted acting contrary to the trial's prespecified monitoring plan. (After a briefing by the Chair, the absent member concurred with the action of the DSMB.)

In accordance with its charter, after reaching a decision, the DSMB met in closed session with the senior NCI staff members who have been responsible for oversight of the trial. It was agreed that the data supporting the DSMB's decision should be released to the investigators associated with the trial, with the intention that they would notify the subjects enrolled in the NLST.

BASIS FOR THE DECISION OF THE NLST DSMB

The primary scientific goal of the NLST was to determine whether three annual screenings with low-dose helical computerized tomography (LDCT) reduces mortality from lung cancer relative to screening with chest x-ray (CXR). The trial was designed to have 90% statistical power for detecting a 20% reduction in such mortality. A total of 53,454 participants were enrolled in the trial at 33 sites across the country.

Table 1 defines the major eligibility criteria regarding age and smoking history for entry of subjects into the NLST.

Table 1: Major NLST Eligibility Criteria Regarding Age and Smoking History

<ul style="list-style-type: none">• Age 55 to 74 years at the time of randomization• Current cigarette smokers and former smokers who quit within 15 years of randomization• A cigarette smoking history of at least 30 pack-years
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The results that formed the basis for the DSMB's decision are given below.

As shown in Table 2, for the period of screening in the NLST (September, 2002, through July, 2007), LDCT had a 24.2% positivity rate for 75,136 screens. In contrast, CXR yielded a rate of 6.9% for 73,499 screens. The higher positivity rate of screening for the LDCT arm was expected on the basis of previous uncontrolled studies.

Table 2: Screen Positivity* Rate by Annual Screening Round and Trial Arm

	LDCT			CXR		
	Number screened	Number positive	Percent Positive	Number screened	Number positive	Percent Positive
Screening round 1	26,314	7,193	27.3	26,049	2,387	9.2
Screening round 2	24,718	6,902	27.9	24,097	1,482	6.2
Screening round 3	24,104	4,054	16.8**	23,353	1,175	5.0**
All screening rounds	75,136	18,149	24.2	73,499	5,044	6.9

*A positive screen is one that may be suspicious for lung cancer.

**A suspicious abnormality that has been stable for 3 rounds of annual screening may be called negative according to protocol.

These findings were then evaluated in accordance with additional clinical assessment, as outlined in the NLST protocol. This process resulted in the diagnosis of 649 cancers (3.6% of the positive screens) detected by LDCT screening and the diagnosis of 279 cancers (5.5% of positive screens) detected by CXR. (As is evident from a comparison of the numbers of lung cancers detected by screening and of deaths from lung cancer presented below in Table 3, not all lung cancers were detected by the screening process.)

An interim analysis of the study's primary endpoint, reported to the DSMB on October 20, 2010, revealed a deficit of lung cancer deaths in the LDCT arm, and the deficit exceeded that expected by chance, even allowing for the multiple analyses conducted during the course of the trial (Table 3). Data presented at previous meetings of the DSMB did not meet the requirements for statistical significance with respect to the primary endpoint.

Table 3: Interim Analysis of Primary Endpoint Reported on October 20, 2010

Trial Arm	Person years (py)	Lung cancer deaths	Lung cancer mortality per 100,000 py	Reduction in lung cancer mortality (%)	Value of test statistic	Efficacy boundary
LDCT	144,097.6	354	245.7	20.3	-3.21	-2.02
CXR	143,363.5	442	308.3			

The secondary endpoint of the NLST is all-cause mortality. An analysis of data bearing on this endpoint was also reported to the DSMB on October 20, 2010; it revealed a deficit

of deaths due to all causes exceeding that expected by chance in the LDCT arm, compared to the CXR arm, although the effect was modest (Table 4).

Table 4: Interim Analysis of All-cause Mortality (Secondary Endpoint) Reported on October 20, 2010

Trial Arm	Person years (py)	Deaths	All-cause mortality per 100,000 py	Reduction in all-cause mortality (%)	Value of test statistic	Value for significance
LDCT	167,389.9	1870	1117.2	6.9	-2.27	-1.96
CXR	166,328.2	1996	1200.0			

The NLST DSMB also reviewed analyses of participant safety on October 20, in addition to the analyses of the primary and secondary efficacy endpoints. Based on all of these reviews, the DSMB concluded that the primary scientific goal of the NLST had been achieved, resulting in the Statement provided above.

ADDITIONAL COMMENTS FROM THE DSMB

The DSMB advises the NCI to provide the above information to all NLST investigators, and through those investigators to all subjects participating in the research, without delay, recognizing the potential importance of the information to health-related decisions that the subjects may wish to make in conjunction with their physicians.

The DSMB recognizes that further refinement of the conclusions engendered by this study will require additional analysis of the data and vigorous discussion with the biomedical community. It urges the NCI and the NLST investigators to prepare a detailed manuscript expeditiously for publication and dissemination to the public after appropriate peer review. That manuscript should more completely delineate the many important aspects of the NLST that are not, by design, addressed in this Statement. Furthermore, the DSMB wishes to emphasize that the data were derived from the study of individuals at high risk for developing lung cancer (i.e. present or past heavy smokers), and do not necessarily apply to the general population.

The current Statement completes the role of the DSMB in assuring scientific and ethical integrity and subject safety during the NLST. The Board appreciates the opportunity to have fulfilled these responsibilities for the subjects who volunteered in this crucial clinical trial to promote the health of the nation.

NLST DSMB

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