Dear NLST Participant:

We are pleased to inform you that we will finish our final lung screening tests by the end of this year and are well into the next important phase of the National Lung Screening Trial (NLST). Again, we thank you for your ongoing commitment to NLST which is one of the largest and most comprehensive lung cancer screening trials ever sponsored by the National Cancer Institute (NCI).

You may have heard recent news reports about other medical studies on the use of spiral computed tomography (CT) scans. One study followed patients with lung cancer for several years and estimated a 10-year survival rate of 85%. Because the study didn't include a control arm of patients who received CT scans to compare with x-rays, the investigators could only estimate survival rates. They also could *not* report decreases in lung cancers deaths (mortality rates or death rates) in the study. While a number of important observations have come from this study, its limitations confirm the critical the need for NLST to find a conclusive answer to screening benefit.

The confusion surrounding this recent medical study is due to the problems that arise when looking at **survival rates rather than the number of lung cancer deaths** (mortality rates) as the key measure of effectiveness for CT scans, or other methods, as a cancer screening tool. Survival and mortality rates are very different measurements and unfortunately, survival cannot be used to determine if overall lives are saved by early cancer screening. Only the effects on mortality rates have been shown to give an accurate measure of the benefit of screening and it takes a controlled trial, like the NLST, to be able to measure mortality rates.

The NLST was thoughtfully designed to allow us to answer several important questions about lung cancer screening. Although the recent news reports are interesting, at this time:

- We DO know that CT detects more lung nodules than chest x-ray (CXR), but that the majority of those nodules are benign (non-cancerous)
- We DON'T know if CT screening actually detects more cancers that will be lethal (deadly) if not detected
- We DON'T know if CT screening will reduce the number of advanced, more lethal cancers that occur
- We DON'T know what additional harms result from the excess nodules seen on CT screens because of follow-up tests, surgeries, and possibly unnecessary treatments
- We DON'T know if any potential *benefits* of lung cancer screening outweigh the *risks* of screening

The answers to these questions will determine which screening test – CT or CXR – is more effective in lung cancer screening. Finding the answers requires a controlled trial like the NLST in which the two groups being screened by each method can be compared with one another. We need to remain in contact with you and other NLST participants in order to understand all of the health consequences of screening, good and bad.

We will continue to inform you of any new information about screening that becomes available from the NLST and other medical studies. For right now, the experts on our independent Data and Safety Monitoring Board have just completed their review of all of our current data. They are a group of medical experts *outside of the NLST* whose first responsibility is to ensure the safety of the NLST participants and to make certain that there is no group of participants in NLST who are at greater risk because of the assigned screening method. After reviewing the current data, members of the Data and Safety Monitoring Board strongly encouraged all of us, NLST investigators and participants, to continue the important work of the this study.

We are always in the process of evaluating the data emerging from the study. Our Data and Safety Monitoring Board will meet next in six months to conduct what is called an interim analysis. If there are any findings to report we will inform you and all of our participants. In addition, there are many questions the NLST is addressing, some of which will not be answered until the study ends in 2009. Until then, we ask that you continue to complete your questionnaires and contact us with <u>any</u> questions you have about lung cancer screening. The NLST remains the most important and definitive study of lung cancer screening benefit worldwide, and the information we gain from you and other participants will be used to determine public health policy for years to come.

In case you are interested in learning more about the important differences between survival and mortality measurements in evaluating the value of early cancer screening methods, we are enclosing a brief discussion outline of the issues involved.

Again, thank you for your participation in the NLST. Your individual role is key to understanding the potential value of early screening in reducing the burden of lung cancer. We will not know if either CT or CXR screening can save lives without your continued support and involvement in the NLST.

Sincerely,

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NLST Co-Director, National Cancer Institute

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NLST Co-Director, American College of Radiology Imaging

Understanding the Limitations of Survival Measurements When Evaluating Screening Benefit

Survival refers to the number of people who are alive at a certain point relative to when they were diagnosed. A screening test that detects cancers before signs or symptoms develop improves "survival" times, simply because the cancer is found earlier – even if the patient still dies on the very same day had they not been tested. This phenomenon is called **lead-time bias (Figure 1)**. This is one of the reasons why survival is not an acceptable way to measure how good a screening test is.

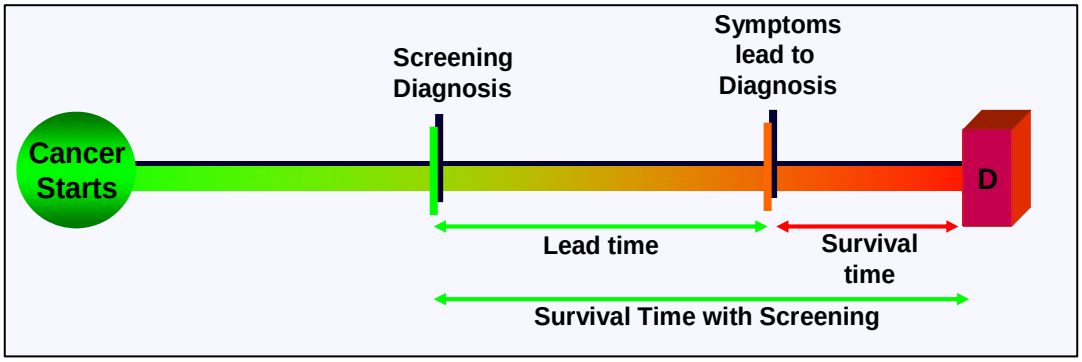

Figure 1: Survival time = time of diagnosis to time of death. With screening, diagnosis occurs sooner than diagnosis by symptoms. Survival time with screening will increase **even if the time of death is the same**.

To provide an example, a physician might detect a tumor on a screening scan that is one centimeter today and the patient lives 9 years from diagnosis. Or the same tumor could be detected 4 years later at a larger, more advanced stage and the patient lives for only 5 years from diagnosis. The patient's survival may appear to be better with early detection, but the end result is the same in terms of the patient dying at the same time either way.

In order to understand this more clearly, consider exactly how a 5-year survival rate is determined. For example, imagine 10 people were diagnosed with lung cancer 5 years ago. If 5 are alive 5 years from diagnosis, the 5-year survival rate is 50%. Suppose that with a screening test, all of these 10 people were found to have cancer 3 years earlier. Just by the fact of earlier diagnosis, the 5-year survival can increase to 100% (10 living/10 with cancer), yet it is possible that *none of the patients* with early-detected lung cancer will live even an extra day. This is illustrated in Figure 2.

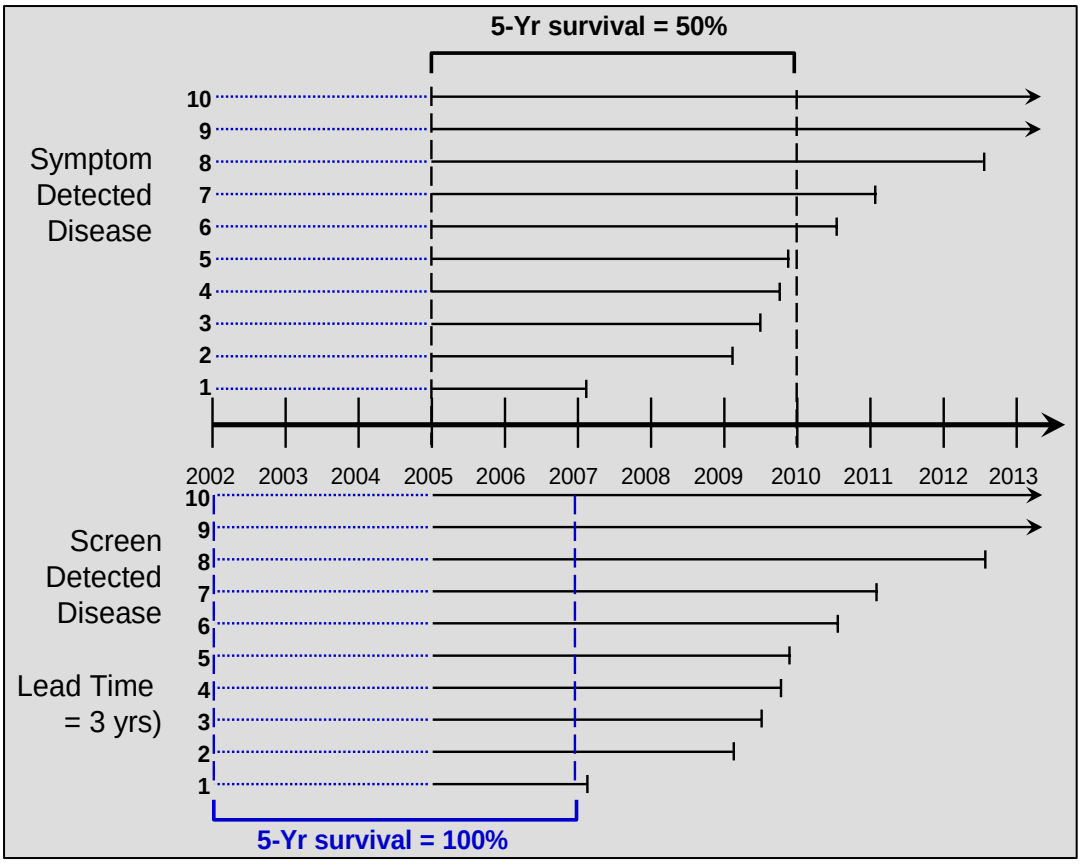

Figure 2: Effect of Lead-time on survival rates.

Symptom-detected disease: 10 patients have cancer and are diagnosed because of symptoms in 2005. In 2010, the 5-year survival is 50% (5 patients living / 10 patients with cancer).

Screen-detected disease: If the same 10 patients are found to have cancer 3 years earlier based on screening, the 5-year survival for the group is 100% (10 patients living / 10 patients with cancer) even if the time of death does not change.

In fact, it is possible that with early detection, treatment can change the course of the lung cancer, but it is *not possible* to separate out the true benefit of early treatment from the false increase in survival due to lead-time when we look only at survival measures. That is why we look at differences in mortality between groups who have been given different screening tests to know whether one screening test offers a benefit over another.

There is another problem with using survival to measure screening benefit. Studies strongly suggest that CT screening can detect lesions that look like cancer under the microscope, but that behave like benign lesions. This phenomenon is called **overdiagnosis**[1]**.** Cancers such as these do not grow over time and pose no risk of death. They are lesions that we die *with*, but not *from*. When detected by screening, they look like cancer under the microscope, they are classified as lung cancer, and are considered to be "cured" by early treatment – even when they would never have caused symptoms or death. This also causes survival measurements to be falsely elevated, and to give the impression of benefit when there is none. In fact, the surgery and other therapies that patients with these benign-behaving lesions will undergo may result in greater harm than the effects from their non-deadly cancers.

The deceptiveness of survival as a means to determine screening benefit is not hypothetical. The same thing occurred in the 1970's in a lung cancer screening trial in which picking up small cancers earlier (lead-time) and finding cancers that were not clinically relevant (overdiagnosis) provided initial reports of benefit from improved survival, but did not ultimately show a reduction in death rates. The NLST will provide conclusive answers about whether chest X-rays or CT scans is the more effective lung cancer screening test, and *whether those benefits outweigh the harms associated with screening*.

[1] It has been reported in some CT screening trials in which equal numbers of cancers are detected in non-smokers as in smokers. The cancer rates being seen with CT are higher than what would normally be expected based on medical data collected in these regions. Using CT to follow the lesions, some of the lesions that look like cancers do not grow over time, and some centers are now not resecting all of these cancers because they believe them to be benign behaving.