

DEVELOPING A NEW COST- EFFECTIVE BLOOD-BASED SCREENING TEST FOR LUNG CANCER

Lung cancer: The #1 cancer killer

The American Cancer Society estimates there will be 221,200 new cases of lung cancer in 2015, representing 13% of all cancer diagnoses. An estimated 158,040 deaths are expected to occur in the U.S. from lung cancer this year, more than those of breast, prostate and colon cancers combined.

Worldwide, there were an estimated 1.8 million new cases of lung cancer, accounting for 12.9% of all cancers. There were also 1.59 million deaths—19.4% of all cancer deaths—in 2012.

Eighty to ninety percent of lung cancers are associated with smoking. Other risk factors include exposure to substances such as radon, asbestos and silica, as well as second-hand smoke.

The risks and rewards of cancer screening.

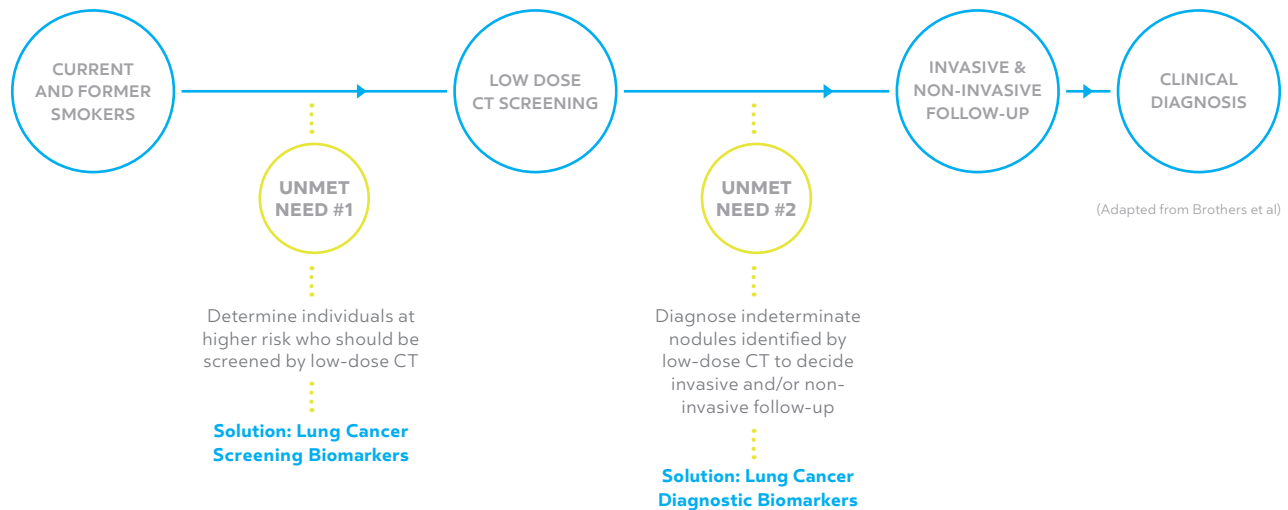
Less than 20% of lung cancers are diagnosed at an early stage at which the five-year survival rate could be as high as 80% (stage 1A). But since lung cancer has historically been detected as the result of symptoms that present themselves at later stages of the disease, 57% of lung cancer cases are diagnosed at an advanced stage. These patients face a five-year survival rate of only four percent.

With the advent of improved CT technology, it's possible to detect potential malignant nodules in high-risk populations. The large U.S. National Lung Screening Trial (NLST) Research Team demonstrated that screening high-risk subjects decreases mortality

CANCER DEATHS		
WORLDWIDE		UNITED STATES
1,590,000	LUNG	160,000
745,000	LIVER	25,000
723,000	STOMACH	11,000
694,000	COLORECTAL	50,000
521,000	BREAST	41,000
400,000	ESOPHAGEAL	16,000

(World Cancer Report 2014, Cancer Facts & Figures 2015)

BLOOD-BASED BIOMARKERS MAY ADDRESS UNMET SCREENING NEEDS



from lung cancer by 20%. However, there are some major limitations to CT screening:

- Although CT is sensitive (about 94%), it has a low specificity, especially for the initial screen (about 73%) with a high number of false positives. This results in unnecessary follow-up investigations, including invasive needle biopsies and surgery, leading to higher costs, mortality and morbidity.
- Though studies are not definitive, the cumulative effect of radiation from multiple scans may be harmful.
- The interpretation of CT scans depends on the experience of the reader and can vary from one center to another.

Another significant challenge is the increasing identification of incidental nodules discovered upon imaging for reasons unrelated to lung cancer screening. It's estimated that in the U.S. there are about three million patients

with such nodules detected annually. The clinical challenge is how to manage subjects with these incidental nodules. Options include follow-up imaging ("watchful waiting") or more aggressive investigations. Both entail risk.

How a simple blood test could improve detection.

A simple blood test to complement CT could significantly improve the detection of early-stage lung cancers. This requires only a blood draw that could be done at a physician's office as part of a routine physical that already checks blood for other parameters (e.g., cholesterol, glucose). The test could be performed in any setting—urban, rural, academic or community.

A small reduction of false positives could significantly affect costs.

A recent review (Brothers, et al) indicates that although the NLST showed that LDCT demonstrated a reduction in mortality, two major needs remain unmet. First, screening the

general population via CT scan is not an option, there's a need to limit CT screening to those with the highest risk. Second, there's a need to reduce the high number of nodules identified by CT that are false positives. Blood-based biomarkers may address both these issues.

Based on results from the NLST, Black et al showed that the incremental cost effectiveness ratio of LDCT screening, as compared to no screening, was \$81,000 per quality-adjusted life years. Over the next five years, an estimated 10.7 million LDCTs will be performed for lung cancer screening, resulting in the detection of 52,000 new cancers. However, this will also result in 2.9 million false positives (Roth, et al), driving up the overall costs of screening. So even a modest reduction of the false positive rate could dramatically affect costs. While detailed studies have not yet been done on the cost effectiveness of adding a blood test to CT, preliminary health economic models suggest potential improvements in cost effectiveness.

What has changed to make screening more effective?

Because of the incidence and high mortality of lung cancer, many academic centers and diagnostic companies have been searching for biomarkers for screening but with limited success. However, we now understand more thoroughly the biology of lung cancer and can identify candidate biomarkers in blood. The potential contribution of methylated DNA, miRNA, gene mutations, exosomes, protein and autoantibody signatures to the development of a diagnostic biomarker panel has become apparent and analytical procedures have made it possible to measure small amounts of these potential markers in blood. Hundreds of publications report on

on only one technology. The result has been a limitation in sensitivity and/or specificity that would not justify the cost of a trial and the number of patients that need to be tested to meet regulatory requirements. So most companies are pursuing lab-developed tests rather than hurdling rigorous regulations.

In the U.S. alone, the Medicare population has nine to eleven million smokers and ex-smokers with greater than 30 pack years of smoking history (equivalent to smoking one pack a day for 30 years) that would satisfy the CMS criteria for screening. This high-risk population should be screened yearly. Additionally, doctors discover

monitoring. Without including the casual smoker population, the potential number of annual tests would exceed 10 million.

According to Ella Kazerooni, M.D., Professor of Radiology, University of Michigan Health System, and Chair of the American College of Radiology (ACR) Committee on Lung Cancer Screening, "We are hopeful that new biomarkers validated through the FDA process, coupled with Lung-RADS* for structured reporting and management of nodules, will further significantly reduce the false positives found with low dose CT screening for lung cancer. In doing so, this may encourage more of the high risk population to come forward for screening, so that we can detect lung cancer early and make more accurate diagnoses. In the future, an algorithm that combines the Lung-RADS category with biomarkers to improve the specificity for early diagnosis of lung cancer may be possible, further reducing the additional imaging and tissue sampling required after a positive screen, and further improving the cost effectiveness of lung cancer CT screening."

A BLOOD BASED TEST IMPROVING ON THE SPECIFICITY OF CT-BASED DETECTION MAY REDUCE FALSE POSITIVES AND MAKE LUNG CANCER SCREENING MORE COST EFFECTIVE

potential blood-based lung cancer biomarkers and several companies have diagnostic products in their pipelines. However, most of these studies and companies have focused primarily

about three million incidental nodules annually, primarily through various imaging techniques. Patients with these nodules would potentially benefit from biomarker testing for initial diagnosis or

*Lung-RADS™ (Lung Imaging Reporting and Data System) is a quality assurance tool designed to standardize lung cancer screening CT reporting and management recommendations, reduce confusion in lung cancer screening CT interpretations and facilitate outcome monitoring.

Exact Sciences and MD Anderson collaboration.

Exact Sciences Corp. (NASDAQ: EXAS) is a Madison-based molecular diagnostics company that is committed to playing a role in the eradication of cancer. As part of this mission, Exact Sciences developed and received FDA approval for Cologuard, the first noninvasive screening test for colorectal cancer that analyzes both stool DNA and blood biomarkers. Exact Sciences also received a proposed coverage memorandum from the Centers for Medicare and Medicaid Services (CMS). Cologuard was the first product to take part in the joint FDA and CMS parallel review pilot program in which both agencies simultaneously reviewed medical devices.

In addition to having its own biomarker discovery engine, Exact Sciences has the experience to identify early the requirements for a clinical trial, with clearly defined metrics. The company has also worked with CMS and other payers to understand the reimbursement approach and carry out appropriate studies to validate the economic value. Exact Sciences has established a strong sales force focused on primary care physicians and Integrated Delivery Networks for the launch of Cologuard, as well as a support infrastructure to improve compliance.

The University of Texas MD Anderson Cancer Center is the world's biggest hospital focused on the detection and treatment of cancer. Its Moon Shots Program is designed to speed the conversion of scientific discoveries into clinical advances that reduce cancer deaths. The program's innovative approaches to cancer prevention, early detection and treatment focus initially on eight cancers: lung, breast, ovarian, prostate, melanoma, chronic lymphocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia.

The scientists at MD Anderson are already exploring lung cancer screening and have developed a panel that includes markers from three platforms with a combined sensitivity of >60% at a specificity of 95% in samples from cohort studies. These samples were collected before onset of symptoms and lung cancer diagnoses.

MD Anderson continues to improve on its unprecedented performance with careful selection and validation of additional markers based on ongoing studies at both MD Anderson and Exact Sciences. The goal is to develop a blood-based test that equals or exceeds the performance of CT for lung cancer screening. Although not as yet fully validated in a screening trial, the results to date are promising.

What's more, MD Anderson has already established a global network of centers eager to participate in a large national and international clinical trial making patient accrual and validation for a lung cancer screening faster and easier.

Both organizations are committed to developing and commercializing a lung-screening test with the power to improve patient outcomes and experience in a cost-effective manner.

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