STATEMENT OF THE AMERICAN THORACIC SOCIETY
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The Role of the NIH in Lung Health Advancements
Diseases of breathing such as lung cancer, COPD and asthma constitute the third leading cause of death in the U.S., responsible for one of every seven deaths. The NIH is the world's leader in groundbreaking biomedical health research for the prevention, treatment and cure of lung disease, but due to eroded funding, the success rate for NIH research grants has plummeted to below 13%, which means that more than 85% of meritorious research is not being funded. **The ATS asks the Committee to provide $32 billion in funding for the NIH in FY2015.**

The following three diseases, lung cancer, lymphangioleiomyomatosis (LAM) and pulmonary hypertension show how the NIH's investment in basic science discoveries, clinical and translational research has transformed outcomes for patients with these diseases and saved lives.

Lung Cancer
Lung cancer is the leading cause of cancer death in the U.S. Lung cancer kills more people than cancers of the breast, prostate, and colon combined. In 2013, 159,480 Americans died of the disease. Although the rate of smoking is declining in the U.S., 94 million current or former smokers remain at serious risk for the disease. The worldwide burden of lung cancer is also projected to rise substantially. Advances in surgical, radiotherapeutic, and chemotherapeutic treatments have been made, but the long-term survival rate for lung cancer remains low. Only about 17% of people diagnosed with lung cancer survive for 5 years after the diagnosis. Most lung cancers are only detected when they cause symptoms and have already spread outside the lung. Accordingly, researchers have focused on detecting lung cancer at an earlier stage, when people are not having symptoms and when treatments are more effective. Prior to 2010, no screening test was proven to decrease deaths from lung cancer.

Lung cancer research has historically been under-funded relative to its burden as the leading cause of cancer death. But, in 2002, the NIH decided to undertake support of a major initiative to evaluate the effects of screening patients at high risk for the disease. The National Cancer Institute's (NCI) Division of Cancer Treatment and Diagnosis sponsored a large-scale screening trial, one of the most expensive ever funded by the NIH, called the National Lung Screening Trial (NLST). The NLST compared two ways of detecting lung cancer, low-dose helical CT scanning and standard chest X-ray, for their effects on lung cancer death rates. The study enrolled 53,500 male and female current or former heavy smokers, aged 55 – 74, with no history or symptoms of lung cancer at 33 trial sites nationwide over a 20 month period. Participants were screened once a year for 3 years and were then followed for 3.5 additional years with no screening.

The NLST's results were announced in November 2010 and they were groundbreaking. The study found that CT screening reduced lung cancer deaths by 20% and reduced deaths from all

causes by 7%. The 20 percent lower lung cancer death rate translates to approximately three fewer deaths per 1,000 people screened in the CT group compared to the chest X-ray group. NCI Director Harold Varmus, M.D., heralded the NLST's findings as evidence that CT screening of high-risk populations can save lives.

The NLST's findings have contributed greatly to the development of new clinical guidelines and policy recommendations which in the long term will save even more lives. One of the most significant policy outcomes has been the U.S. Preventive Services Task Force's (USPSTF) lung cancer screening recommendations, issued in December 2013, which recommend annual screening for lung cancer with low-dose CT in people 55 – 80 years old with a heavy smoking history. As required by the Affordable Care Act, the USPSTF's recommendations for lung cancer screening will now be a free preventative service for patients with health insurance. The NLST's findings and data are still being studied by NCI researchers and may yield answers to other lung cancer discoveries including the identification of biomarkers. The NCI's investment in funding the NLST, which was assisted by the doubling in NIH funding between 1995 and 2005, yielded an enormous clinical advance in lung cancer screening that is already saving lives and will save many more over the coming years.

LAM (lymphangioleiomyomatosis)

Lymphangioleiomyomatosis (LAM), is a rare, fatal lung disease that affects women of childbearing age. People with LAM have progressive loss of lung function and many die from respiratory failure. In LAM disease, muscle cells that line the lungs' airways and blood vessels, called LAM cells, multiply abnormally and infiltrate the lungs and other organs such as the kidneys. The air sacs in the lung also swell and form cysts. The disease is often misdiagnosed as emphysema, asthma or bronchitis. About 2,000 people in the U.S. have LAM.

In the early 1990's, people diagnosed with LAM had little cause for hope as no treatments were available and very little was known about the disease. But in 1995, the mother of a young woman with LAM, Sue Byrnes, formed the LAM Foundation, an organization dedicated to raising money to fund LAM research. The LAM Foundation brought researchers and patients together at annual conferences to share information and develop a research agenda for the disease, beginning with basic science studies to determine the molecular mechanisms and genetic basis of the disease. Foundation members successfully lobbied Congress and the National Heart, Lung and Blood Institute (NHLBI) to develop a LAM registry, including a tissue bank. Following studies funded by the LAM Foundation and the NHLBI which established some of the basic biology of the disease, including identification of the LAM gene, the network of researchers and patients next worked to organize patients to participate in clinical trials.

The Foundation's Scientific Director, Francis McCormack, M.D. and other researchers in the field identified the drug sirolimus, commonly used to treat various early stage cancers as a potential treatment for LAM, because it regulated LAM cell growth. In 2007, the NIH funded the first large-scale phase 3 clinical trial of sirolimus, called the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) trial. With sites in 3 countries, the MILES trial studied patients treated with sirolimus vs. placebo over a 1 year period, followed by a year of observation without any treatment.

The results of the MILES trial revealed sirolimus as an effective suppressive treatment for LAM. Patients that received the drug had stabilized lung function over the year of treatment, as

compared to patients in the placebo group, who lost 10% or more of their lung function. During the one year observation period when no therapy was given, lung function in the patients who had received sirolimus resumed a decline, indicating the benefit of the treatment. Although not a cure for LAM, sirolimus is now used as a long-term therapy for LAM and has greatly improved outcomes and quality of life for most LAM patients, who no longer have to rely on oxygen to function day to day.

The LAM story shows what can be achieved with a relatively modest research investment, in LAM's case, about $20 million in NIH funding over a relatively short time frame and in conjunction with effective partnerships between researchers and patients. Within twenty years, LAM went from being a little-understood disease with no treatments and no hope for patients, to major scientific breakthroughs, including identification of the LAM gene to confirmation of an effective long-term treatment.

Pulmonary Hypertension

Pulmonary hypertension (PH) is a disease in which pressure rises in the arteries that carry blood from the heart to the lungs. Symptoms include shortness of breath during light physical activity, chest pain, and a racing heartbeat. As the disease worsens, it can make any physical activity difficult or impossible. Up to 100,000 Americans may have PH and it affects more than 2.5 million people worldwide.

Prior to FDA approval of the first drug to treat PH in 1995, people with PH lived an average of less than three years after their diagnosis. But basic and clinical research on the epidemiology, pathogenesis, and pathophysiology of PH supported by the NHLBI over the last 20 years has extended life expectancy and quality of life for people with the disease. These discoveries in the 1990's paved the way for the surge of new drugs approved to treat PH over the last decade. The PH patient community mobilized and worked with NHLBI and private pharmaceutical companies to develop a clinical research agenda to identify promising treatments for clinical trials. Registries of patients begun in the 1980's provided the patient base for participation in trials.

The NHLBI responded to congressional direction and patient advocacy by significantly increasing its investment in PH, beginning in 2005, when it created a new Vascular Medicine Branch in the Intramural Division and additionally, supported several pulmonary vascular disease research centers through extramural support. The institute’s funding on PH research further increased significantly, from $27 million in 2006 to $45 million in 2007.

The research investment from the NHLBI and private pharmaceutical companies began yielding new treatments for PH rapidly between 2004 and 2013, with nine new drugs becoming available. The key scientific discoveries were in the following 3 areas:

1.**Prostacyclin production** - NHLBI studies showed that one potential therapeutic area lay with prostacyclin, a naturally occurring body substance which dilates pulmonary arteries (a process known as vasodilation) and inhibits blood platelet clumping. This finding gave rise to development of the synthetic form of prostacyclin, epoprostenol (Flolan®), approved by the FDA in 1995 and additional vasodilators treprostinil sodium (Remodulin®, Tyvaso®) and iloprost (Ventavis®), approved between 2002 and 2004.

2. **Nitric Oxide Synthesis** - Other studies identified impaired nitric oxide and related disruption of enzyme signaling in the pathogenesis of PH. Clinical trials found that Sildenafil (Revatio®) and tadalafil (Adcirca®) relaxed pulmonary smooth muscle cells, which permitted dilation of the pulmonary arteries. A new class of vasodilating agents called soluble guanylate cyclase (sGC) stimulators were identified in later studies and the drug, Riociguat, was approved by the FDA for PH treatment in 2013.

3. **Endothelin Production** - Studies in the 1990's revealed that endothelin, a powerful substance that causes narrowing of lung blood vessels can be blocked. This finding gave rise to development of the endothelin blocking drugs Bosentan (Tracleer®) and ambrisentan (Letairis®). Bosentan has since become the most widely prescribed therapy for PH.

Thanks to the efforts of researchers and patient advocates and the support of Congress, PH has moved from being a disease once considered untreatable to one for which patients can now have a better quality of life.

Centers for Disease Control and Prevention
Tuberculosis Clinical Trials Consortium

The ATS would also like to illustrate how Centers for Disease Control and Prevention (CDC) research is impacting global health through the Division of TB Elimination's the Tuberculosis Clinical Trials Consortium (TBTC).

Tuberculosis (TB) is the second leading infectious disease killer in the world. The continued spread of drug resistant TB is a serious global health problem. TB remains a public health issue in the U.S., with every state reporting cases each year. But because TB is a disease of the poor, the private sector research investment is very minimal, which means that government-funded research, including U.S.-government funded research through the NIH and the Centers for Disease Control and Prevention (CDC), is vital to halting the TB pandemic. CDC has been conducting epidemiological, clinical and operational TB research for decades due to expertise and an available patient network in the public health system.

Funded by the Division of TB Elimination, the Tuberculosis Clinical Trials Consortium (TBTC) is conducted groundbreaking trials to produce new TB treatment regimens. In 2011, TBTC studies produced the first new treatment regimen in decades for preventing latent TB infection from developing into active disease. The new therapy reduces the current regimen from a 9 month daily course to a 3 month weekly course. This new regimen has the potential to significantly improve treatment success rates of latent and active TB, as latent TB cases are the reservoir for future active TB cases, particularly in the U.S. The TBTC is poised to launch a phase 3 trial of a new regimen for active TB, which would be transformative to global health and would save many lives worldwide.

The ATS thanks the committee for this opportunity to submit testimony.

Founded in 1905, the American Thoracic Society is the world's leading medical association dedicated to advancing pulmonary, critical care and sleep medicine. The Society's 15,000 members prevent and fight respiratory disease around the globe through research, education, patient care and advocacy.