



Pulmonary and Thoracic Surgery **ADVANCES**

Evaluating Genetic Markers to Discover Undiagnosed Pulmonary Fibrosis

Pulmonologists and geneticists in the Lung Center at Brigham and Women's Hospital are developing a novel study incorporating genetic testing to identify patients at risk for pulmonary fibrosis with the goal of detecting and treating the disease at earlier stages.

Gary M. Hunninghake, MD, Director of the Sarcoidosis and Granulomatous Lung Disease Service, Ivan O. Rosas, MD, Director of the Interstitial Lung Disease Program, and Benjamin A. Raby, MD, MPH, Director of the Pulmonary Genetics Center, are collaborating on a new genetic study, which includes both patients with pulmonary fibrosis and their relatives. Earlier work by this team has shown that patients with IPF and those with early stages of pulmonary fibrosis share a high prevalence of specific genetic determinants (*N Engl J Med.* 2013 Jun 6; 368(23):2192-200).

"Pulmonary fibrosis appears to be one of the most genetically determined lung diseases, and may be much more common than many suspect," said Dr. Hunninghake. "Our work suggests that undetected pulmonary fibrosis can result in a high rate of mortality, even after taking into account other medical conditions. More worrisome, it is probable that the diagnosis of pulmonary fibrosis is being missed in a substantial portion of patients."

Examining First Degree Relatives of PF Patients

To address this problem, the team is embarking on a novel research study involving both the clinical assessment and genetic testing of patients with established pulmonary fibrosis, and then testing their first-degree relatives for genetic risk factors. The goal is to determine if genetic testing in these at-risk relatives helps to improve the rate of subclinical idiopathic pulmonary fibrosis (IPF) diagnosis. Testing of first-degree relatives (siblings and children) in this study will include CT scanning, pulmonary function testing, and genetic testing. Genetic counseling will be provided, and results of the genetic testing will be communicated to those first-degree relatives who are tested. As part of this study, the team is currently enrolling 200 patients with established pulmonary fibrosis and 100 of their first-degree relatives without known fibrosis. Genetic testing in patients with established pulmonary fibrosis is also being conducted to determine if certain genetic variants influence outcomes or capture different disease states.

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Raphael Bueno, MD, and Bruce Levy, MD, co-directors of the Lung Center, are pleased to provide you with this update on pulmonary and thoracic surgery at BWH.

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New BWH Surgeon-in-Chief

Advanced Technologies Expand Options for Lung Transplant Recipients

Specialists within the Lung Center at Brigham and Women's Hospital (BWH) are utilizing the latest technologies to improve the viability of donor lungs and the potential for transplantation for more patients.

"Typically, for every 10 donors, only one set of lungs is suitable for transplantation, making the lungs a highly valued organ," said Raphael Bueno, MD, Chief of Thoracic Surgery at BWH, and co-director of the Lung Center. "To better serve our patients, we need to seek out as many potential donors as possible, which means patients on the waitlist can get lungs transplanted sooner, thus reducing the mortality rate."

The Lung Center has increased the number of lung transplants performed annually by making new technologies available to patients, and increasing staffing to include four surgeons whose focus is to perform lung transplants, said Dr. Bueno.

"We also send a surgeon, perfusionist, and resident/fellow to donor hospitals to evaluate each offer, which has helped increase lung transplant volume this year. Additionally, we began evaluating ABO compatible donors for recipients, whereas in the past we only evaluated ABO identical donors," said Hari Reddy Mallidi, MD, Co-Director of Lung Transplant, ECMO and Lung Assist Devices at the Lung Center.

Advanced Technologies: ECMO and EVLP

Technologies utilized in the Lung Center are also helping to expand the number of organs available for transplantation.

Extracorporeal membrane oxygenation (ECMO) is an intensive care technology that takes over the work of the lungs temporarily for patients waiting for transplantations. Acting as a lung, it delivers oxygen to a patient's bloodstream, allowing time for damaged lungs or a stressed heart to rest and recover.



Hari Reddy Mallidi, MD, Co-director, Lung Transplant, ECMO and Lung Assist Devices, and Hilary J. Goldberg, Medical Director of the Lung and Transplant Program, are leading efforts to utilize the latest technologies to improve the viability of donor lungs and the potential for transplantation for more patients.

"We added the ECMO program to three intensive care units to manage patients with acute heart failure, lung failure, or combined heart and lung failure. The system can be deployed rapidly and allows for immediate resuscitation of patients in extremis," said Dr. Mallidi.

Ex-vivo lung perfusion (EVLP) is a procedure used to minimize swelling in donor lungs in an effort to make them suitable for transplantation. EVLP involves keeping donor lungs 'breathing' outside of the body and providing them with nutrients and blood-substitutes. The method also removes white blood cells in the donor lungs, which minimizes the risk of rejection.

"EVLP has the potential to perfuse lungs infected with hepatitis C or pneumonia, for example, with anti-viral medications that would essentially cure the lungs and make them suitable for transplantation," said Dr. Bueno. "I expect that EVLP will enable us to perform an additional 10 to 20 transplants this year."

EVLP's uses may extend beyond transplants as well. For example, queried Dr. Bueno, could a lung with cancer be taken out of a living person, treated with extra-high doses of chemotherapy with EVLP and then be put back in the patient? Investigators in the Lung Research Center – part of the Brigham Research Institute – are exploring these questions.

"These are wonderful examples of how unmet clinical care needs guide research directions," Dr. Bueno said. "In turn, research results get rapidly translated to new, clinical opportunities for our patients."



Raphael Bueno, MD
Chief, Division of Thoracic Surgery,
Co-director, Lung Center



Hari Reddy Mallidi, MD
Co-director, Lung Transplant, ECMO and Lung Assist Devices

Access to Our Lung Center Services

At Brigham and Women's Hospital, our specialists are available for timely consultations and will work with you to develop treatment plans for your patients. Our Physician Liaison Ellen Steward can provide direct assistance with patient referrals and consultations. Ellen can be reached at (617) 582-4733 or esteward@partners.org.

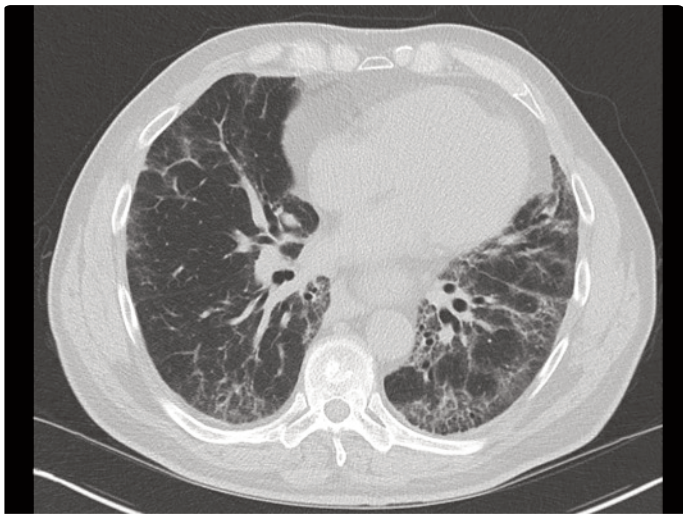
Landmark Study Evaluates Antifibrotic Therapy in Patients with Interstitial Lung Disease Associated with Rheumatoid Arthritis

Experts in the Lung Center at Brigham and Women's Hospital (BWH) are leading a groundbreaking trial to assess the use of antifibrotic therapy in patients with rheumatoid arthritis-related interstitial lung disease (RA-ILD).

"Improvement in the management of articular and cardiovascular effects of rheumatoid arthritis has reduced morbidity and mortality of RA patients, but we are challenged with addressing severe respiratory complications in many of these patients, particularly as they age," said Ivan O. Rosas, MD, Director of the Interstitial Lung Disease Program. "There are currently no effective treatments for progressive fibrotic lung disease in patients with rheumatoid arthritis."

International Study in RA-ILD

Dr. Rosas is the International Principal Investigator of the first randomized clinical trial testing medication for pulmonary fibrosis in rheumatoid arthritis patients. Scheduled to open in early 2017, this double-blinded study (*Phase II Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease*) will enroll approximately 270 adult participants (ages 18 to 85) at 16 sites in the United States, 10 sites in the United Kingdom, and four sites in Canada. Patients will be randomized to receive either pirfenidone or placebo for 52 weeks. The primary outcome of the study is to assess the efficacy of pirfenidone in RA-ILD as defined by progression-free survival over the course of the study.



Chest scan of a patient with rheumatoid arthritis and interstitial lung disease.

"Patients with rheumatoid arthritis-associated interstitial lung disease have clinical features that closely resemble idiopathic pulmonary fibrosis, so we anticipate that the results of previous trials can be quickly translated to the RA-ILD patient population," said Dr. Rosas. "In addition, we expect that this trial will provide us with a tremendous amount of information about the natural history of RA-ILD and help us better understand this vastly understudied patient population."

Eligible participants must meet 2010 ACR/EULAR criteria for RA, as well as ILD, determined by imaging as well as lung biopsy (when available). Participants also are required to have a percent predicted FVC > 40 and < 80 and percent predicted DLCO > 30 and < 80 at screening. The trial is inclusive of patients receiving stable doses of currently available treatments for RA. Specialists in the Lung Center also are participating in a second study of antifibrotic agents for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD) and other connective tissue diseases. (For more information regarding the RA-ILD trial, please contact Dr. Rosas at (617) 732-7821 or irosas@partners.org.)

Changing the Standard of Care for Pulmonary Fibrosis

Researchers at BWH were key contributors in the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet) studies that established that steroids or other forms of immunosuppression should no longer be used to treat idiopathic pulmonary fibrosis (*N Engl J Med*. 2012 May 24;366(21):1968-77.). Additional multicenter clinical trials that have led to the groundbreaking approval of two new antifibrotic drugs, pirfenidone and nintedanib, have been shown to slow progression of idiopathic pulmonary fibrosis (*N Engl J Med* 2014;370:2071-2082 and *N Engl J Med* 2014;370:2083-2092).

"Collectively, these studies have revised the management of patients with IPF and have opened opportunities, such as our new study in RA-ILD, to evaluate the use of these recently approved antifibrotic therapies in additional patient populations impacted by pulmonary fibrosis," said Dr. Rosas.



Ivan O. Rosas, MD
Director,
Interstitial Lung Disease Program

BWH NEWS

Gerard M. Doherty, MD, Named Surgeon-in-Chief



An acclaimed endocrine surgeon and transformative leader, Gerard M. Doherty, MD, recently joined Brigham and Women's as Hospital as Chair of the Department of Surgery and Surgeon-in-Chief, from Boston Medical Center, where he served as Surgeon-in-Chief, and Boston University School of Medicine, where he served as Chair of the Department of Surgery and James Utley Professor of Surgery. Dr. Doherty has dedicated his career to advancing the care of patients with endocrine tumors and conditions and his research interests include regeneration of parathyroid cells in hypoparathyroid patients. Dr. Doherty is a member of the Complex General Surgical Oncology Board for the American Board of Surgery and is the developer of the AccessSurgery platform for disseminating surgical information including books, images and videos for training. Additionally, he has written more than 250 peer-reviewed articles.

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"In addition to exploring whether genetic testing can help in the earlier diagnosis of pulmonary fibrosis, an important part of this study is to understand whether or not providing otherwise-healthy family members with the results of their genetic tests causes more harm than good," said Dr. Raby. "Questionnaires developed here will help us to assess the psychosocial impact of the disclosure of genetic test results." Patient enrollment recently began and is expected to continue for two years. The researchers anticipate being able to provide initial results of the study in the next three to four years.

(For more information regarding this clinical trial, please contact Ivan O. Rosas at (617) 525-7821 or irosas@partners.org.)

Clinical Care for Patients with Early Idiopathic Pulmonary Fibrosis

Those family members found to have early stages of IPF will be offered clinic visits and care for their disease. Treatment may include several antifibrotic medications recently approved by the FDA for the treatment of IPF.

"We are hopeful that relatives who we find to have early forms of pulmonary fibrosis, who are yet to develop significant symptoms, would be the most likely to benefit from the antifibrotic medications currently used to treat patients with advanced IPF, and in whom the early initiation of therapy may help to reduce the rate of decline of lung function before severe disease develops."

Preventing Pulmonary Fibrosis

Part of the core goal of the team's research is to demonstrate that primary and secondary prevention of pulmonary fibrosis is feasible. These strategies may prove to be beneficial among those who are genetically susceptible to developing pulmonary fibrosis.

"This study represents a huge opportunity for us to do early detection and prevention work in patient populations where we know it is likely that pulmonary fibrosis will develop," said Dr. Rosas.



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