Ion Robotic Bronchoscopy System the Focus of a Multicenter Trial

Mayo Clinic continues to assess a variety of techniques to allow for safer bronchoscopic sampling of lung nodules and masses to allow diagnostic yields approaching that of CT-guided biopsy (90% yield) without the inherent risks of a pneumothorax associated with CT-guided lung biopsy, which is often reported at about 15%.

Specialists at Mayo Clinic’s campuses in Rochester, Minnesota, and Jacksonville, Florida, have joined teams from five other medical centers to conduct a multicenter trial, enrolling 300 patients to prospectively evaluate the use of the Intuitive Ion robotic bronchoscopy system (Figure).

“The trial will assess the ability of this novel navigation system in terms of precision and accuracy for the ability to navigate and successfully biopsy peripheral lung nodules between 1 and 3 cm in size,” says Janani S. Reisenauer, M.D., an interventional pulmonologist and thoracic surgeon at Mayo Clinic in Rochester, Minnesota, and study site principal investigator. “The slim catheter size, along with the ability to retain its articulation, has allowed us to access lesions that were previously unreachable by standard bronchoscopic techniques.”

Specialists at Mayo Clinic’s campus in Phoenix/Scottsdale, Arizona, are also using a robotic bronchoscopy system to provide patients with access to this exciting new technology.

For more information

Figure. Intuitive Ion robotic bronchoscopy system in use.
Fibrosing mediastinitis (FM) represents a fibroinflammatory disease involving the mediastinum and hilar areas. It is characterized by expansive growth of fibroinflammatory tissue within this space, resulting in narrowing and obstruction of vital vascular structures such as the superior vena cava, pulmonary arteries and veins; airways; or the esophagus. The disease primarily presents in younger patients and relentless disease progression has been associated with a high mortality.

While in most cases FM is thought to represent an idiosyncratic response to an external antigen — in North America, the antigen is most commonly histoplasmosis — idiopathic cases can also occur.

“The diagnosis of FM can be very challenging. There is no definitive diagnostic test and tissue biopsies are typically complicated and risky,” says Tobias Peikert, M.D., a critical care specialist and pulmonologist at Mayo Clinic in Rochester, Minnesota. “Histoplasmosis-associated FM classically presents as a calcified right-sided mediastinal mass. Clinical symptoms depend on the anatomic structures involved by the process.

“During the diagnostic evaluation, it is crucial to exclude mimics of the disease, including lymphoma, most commonly nodular-sclerosing Hodgkin’s disease, other metastatic malignancies, mediastinal granulomatous infections and IgG4-related disease, as noted in studies published in Medicine in 2011 and International Journal of Rheumatology in 2012. PET-CT and targeted invasive tissue biopsies are crucial in patients with nonclassic clinical presentations such as noncalcified, diffuse and bilateral mediastinal infiltration and extrathoracic disease.

**Management of Fibrosing Mediastinitis**

![Tobias Peikert, M.D.](image)

**Figure.** A. Serial CT images of a patient with progressive fibrosing mediastinitis before 2017, in 2018 and after rituximab therapy. B. Spirometry before rituximab. * The measurement is abnormal. C. PET-CT before treatment. D. Spirometry after a single cycle of rituximab.

### B. Spirometry

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
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<tr>
<td><strong>FVC (L)</strong></td>
<td>3.21</td>
<td>2.68</td>
<td>2.24</td>
<td>*2.24</td>
<td>*69</td>
</tr>
<tr>
<td><strong>FEV1 (L)</strong></td>
<td>2.53</td>
<td>2.11</td>
<td>1.64</td>
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<td>*64</td>
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<tr>
<td><strong>FEV1 (%)</strong></td>
<td>80</td>
<td>67</td>
<td>73</td>
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<td></td>
</tr>
<tr>
<td><strong>FEF 25%-75% (L/sec)</strong></td>
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<td>1.39</td>
<td>*1.10</td>
<td>*43</td>
<td></td>
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<tr>
<td><strong>FEF MAX (L/sec)</strong></td>
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<td>4.72</td>
<td>5.25</td>
<td>83</td>
<td></td>
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<tr>
<td><strong>MVV (L/min)</strong></td>
<td>98</td>
<td>82</td>
<td>*76</td>
<td>*77</td>
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</tr>
</tbody>
</table>

### C. PET-CT

![FDG-PET-CT](image)

### D. Spirometry

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>LLN</th>
<th>Found</th>
<th>%Predicted</th>
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<tbody>
<tr>
<td><strong>VC MAX</strong></td>
<td>3.08</td>
<td>2.38</td>
<td>3.40</td>
<td>111%</td>
</tr>
<tr>
<td><strong>FVC</strong></td>
<td>3.08</td>
<td>2.38</td>
<td>3.40</td>
<td>111%</td>
</tr>
<tr>
<td><strong>FEV1</strong></td>
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<td>1.90</td>
<td>2.43</td>
<td>99%</td>
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<tr>
<td><strong>FEV1/FVC</strong></td>
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<td>68.9</td>
<td>71.4</td>
<td>89%</td>
</tr>
<tr>
<td><strong>FEF 25%-75%</strong></td>
<td>2.41</td>
<td>1.31</td>
<td>1.68</td>
<td>70%</td>
</tr>
<tr>
<td><strong>PEF</strong></td>
<td>5.6</td>
<td>2.9</td>
<td>6.8</td>
<td>121%</td>
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<tr>
<td><strong>FET</strong></td>
<td></td>
<td></td>
<td></td>
<td>6.78</td>
</tr>
<tr>
<td><strong>MVV</strong></td>
<td>97</td>
<td>64</td>
<td>90</td>
<td>92%</td>
</tr>
</tbody>
</table>
“The management of FM is mainly focused on the relieving of vascular and airway obstructions. Surgical interventions are typically avoided and patients are managed with vascular (superior vena cava, pulmonary artery and pulmonary vein) and, less commonly, airway stents, as noted in studies published in the Annals of the American Thoracic Society in 2017 and Catheterization & Cardiovascular Interventions in 2019. These interventions should be primarily driven by patient symptoms. “Therapeutic responses to systemic therapies such as steroids and antifungal therapy have been very disappointing. However, we have recently started the successful off-label use of rituximab for patients with FM, as noted in the study published in Medicine in 2011 and research published in the American Journal of Respiratory and Critical Care Medicine in 2014.

“We have now treated almost 30 patients with metabolically active (confirmed by PET-CT), progressive FM with rituximab. Disease progression was almost universally halted, 67% of patients improved symptomatically and the noncalcified areas of FM decreased on average by 41% (Figure). This extremely exciting data was presented at the 2019 European Respiratory Society International Congress in Madrid.”

For more information


European Respiratory Society International Congress; 2019; Madrid.

Updates in Interstitial Lung Disease: Current Facets of Anti-Fibrotic Therapy

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic interstitial lung disease with a median survival of 2.5 to five years. Until 2014, lung transplantation was the only available treatment — along with supportive therapies including oxygen, pulmonary rehabilitation, and the management of comorbidities such as obstructive sleep apnea or symptomatic gastroesophageal reflux disease.

Current medical management involves two oral anti-fibrotic agents: nintedanib and pirfenidone. Nintedanib is a triple tyrosine kinase inhibitor acting at multiple sites in the fibrotic pathway, while the exact mechanism of pirfenidone remains unknown. “Both agents demonstrate comparable slowing of functional decline as measured by change in forced vital capacity (FVC) on pulmonary function testing over a 12-month study period,” says Teng Moua, M.D., a pulmonologist at Mayo Clinic’s campus in Rochester, Minnesota. “Neither has demonstrated significant influence on patient-reported outcomes such as dyspnea or respiratory-related quality of life. Both are similar in cost, with currently limited data on long-term survival or mortality improvement.”

Results vary with treatment options for IPF
While drugs are widely available, a survey study of European practices published in BMC Pulmonary Medicine in 2017 suggested up to 40% of diagnosed patients with IPF remain untreated. Barriers to drug initiation include:

• Uncertainty with atypical presentations, particularly those with earlier or inconsistent radiologic findings (Figure)
• Concern for untoward side effects in those with more stable or slowly progressive disease
• Lack of perceived clinical benefit in asymptomatic patients, or those with normal or already severely limited pulmonary function testing.

Drug effect on rate of FVC decline also appears variable as reviewed in a manuscript published in the American Journal of Respiratory and Critical Care Medicine in 2016 suggesting early stabilization of pre-treatment decline.
within three months of treatment initiation while in some there may not be appreciable change for a year or more.

Results of a large clinical trial involving pirfenidone published in the *New England Journal of Medicine* in 2014 found that close to 20% of those in the treatment arm saw a clinically important decline in FVC (greater than 10% over the 12-month study period), suggesting some patients may not have an early response to directed treatment or no response at all. In these two patients, anti-fibrotic therapy was started immediately at presentation, despite diagnostic uncertainty in the first patient.

For example, improvement in FVC decline in those with more-consistent versus probable or suggestive radiologic findings was similar in one post-hoc analysis published in the *American Journal of Respiratory and Critical Care Medicine* in 2017. Rate of FVC decline on drug therapy appeared similar in those with severe disease (defined as FVC less than 50% of predicted) to those with mild or moderate disease. Patients with normal (more than 70% or 90%) FVC at presentation also had similar rates of decline when initiated on therapy.

“As respiratory symptoms are not alleviated by anti-fibrotic therapy, patients who are asymptomatic may find it difficult to initiate and sustain treatment due to imposed adverse effects. There is no systematic data to suggest onset of symptoms would be delayed in asymptomatic patients with or without PFT abnormality,” says Dr. Moua. “Patients with combined pulmonary fibrosis and emphysema, whose FVC decline may be difficult to follow due to false normalization, remain a challenging subgroup to treat.”

Radiologic emphysema may occur in up to 10% of patients with IPF, with the primary controlled trial, published in the *New England Journal of Medicine* in 2014, specifically excluding any patient with radiologic emphysema from trial participation and subsequently limiting the systematic evaluation of anti-fibrotic therapy in such patients.

**Figure.** Computerized tomography (CT) examples of two patients with suspected idiopathic pulmonary fibrosis. One patient has a probable usual interstitial pneumonia pattern (A). The other patient has a more consistent pattern (B). Diagnostic confidence leading to treatment is often greater in patients with more consistent radiologic patterns compared with those with probable or indeterminate findings, which may delay treatment in the latter. In these two patients, anti-fibrotic therapy was started immediately at presentation, despite diagnostic uncertainty in the first patient.

Continued research needed for anti-fibrotic therapy
Anti-fibrotics are currently being studied in other non-IPF progressive interstitial lung diseases. An international trial found nintedanib to be effective in slowing FVC decline in patients with scleroderma-related lung fibrosis. Treatment medication was overall well tolerated with only about a 16% withdrawal or discontinuation rate. The study appeared in the *New England Journal of Medicine* in 2019.

Findings from an international study looking at nintedanib for the treatment of progressive non-IPF fibrotic lung disease, published in the *New England Journal of Medicine* in 2019, noted an improved rate of overall disease decline in those patients on therapy versus placebo. Disease progression in the study was defined by specific clinical, radiologic and functional changes. The study ultimately enrolled fibrotic subtypes including chronic hypersensitivity pneumonitis, connective-tissue disease-related interstitial lung disease, and occupational and fibrotic sarcoidosis. Patients already on traditional treatments (corticosteroids, steroid-
sparing agents) were allowed to keep such therapies in addition to trial nintedanib.

Similarly, a phase II double-blind randomized controlled trial found pirfenidone to be well tolerated in progressive unclassified diseases, but did not successfully model change in its primary outcome of FVC decline as measured by daily home spirometry. Site spirometry testing did suggest decreased rate of FVC decline among those taking the trial drug. Study results were published in *Lancet Respiratory Medicine* in 2019.

An ongoing trial looking at the efficacy of pirfenidone in rheumatoid arthritis-related fibrotic lung disease, TRAIL-1, is actively recruiting across multiple sites in the United States.

While ushering in an era of medical treatment for a once-progressive and fatal disease, caveats to management in certain IPF subgroups and the expansion of indications to include other non-IPF progressive fibrotic lung disease highlight the current state of the available anti-fibrotics.

**For more information**


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**Advancing Care in Chronic Obstructive Pulmonary Disease**

Pulmonary Medicine at Mayo Clinic is advancing the care of patients with chronic obstructive pulmonary disease (COPD) by offering a home-based pulmonary rehabilitation program that provides technology that monitors patient activity and well-being in addition to health coaching. There is no cost to participate, and the program is open to any patient with significant COPD symptoms. The program can be done regardless of where the patient resides.

Funded by the National Institutes of Health, the program is based on a landmark study led by Mayo Clinic and published in *American Journal of Respiratory and Critical Care Medicine* in 2016 and *Respiratory Care* in 2017.

“Hundreds of participants have been tested and found the technology simple and easy to use. The health coaching included in the program demonstrates that the program is effective with intervention that improves quality of life and decreases emergency department visits and hospitalizations,” says Roberto P. Benzo, M.D., program director, director of the Mindful Breathing Laboratory, and a pulmonologist at Mayo Clinic’s campus in Rochester, Minnesota. “Providing patients with mindful and assertive communication supports the patients’ autonomy and expertise to increase their confidence to deal with their conditions.”

In the home-based pulmonary rehabilitation program (Figure, see page 6), Mayo Clinic provides each patient with an activity monitor and a computer tablet on which they watch and follow simple flexibility and balance exercises while oxygen and heart rate are monitored. The activity monitor also tracks daily steps. All information gathered, including physical activity, symptoms and general messages, is available to the patient’s Mayo Clinic health coach and discussed in a weekly phone call with the patient. Patients can message their health coach at any time through the computer tablet.

Research indicates that pulmonary rehabilitation completed at medical centers is a proven effective intervention for patients with COPD. Pulmonary rehabilitation improves symptoms, exercise capacity, quality of life and health care utilization.

“Unfortunately, much of current pulmonary rehabilitation is delivered in a center-based environment that has limited participation due to transportation limitations, distances traveled and often patient frailty,” says Dr. Benzo. “The home-based pulmonary rehabilitation program is a valid and equally effective alternative achieved by technology that permits clinicians to assess adherence and safety.”

A study of the development and feasibility of
A home-based pulmonary rehabilitation program was published in *Respiratory Care* in 2018.

**For more information**


Mindful Breathing Laboratory: Roberto P. Benzo. Mayo Clinic. [www.mayo.edu/research/labs/mindful-breathing/overview](http://www.mayo.edu/research/labs/mindful-breathing/overview).


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**Pediatric Sleep Medicine Integrates With Multidisciplinary Clinics To Facilitate Communication and Treatment**

Sleep concerns are common in all children, but often more so in those children who are part of special populations or those with medically complex needs. As confirmed by a study published in *Pediatrics* in 2012, obstructive sleep apnea (OSA) is present in up to 5% of children. Up to 50% of children will have a sleep complaint at some point in their lives. Up to 10% of children will have difficulty with insomnia, as confirmed in 2006 in a study published in *Sleep* and 2014 in a study published in the *Journal of Pediatric Psychology*.

“OSA and other forms of sleep-disordered breathing are even more prevalent in certain special populations, and other comorbid sleep difficulties can also be present,” says Julie M. Baughn, M.D., a pediatric pulmonologist at Mayo Clinic’s campus in Rochester, Minnesota. “Most children with OSA will benefit and their OSA may often be resolved by undergoing adenotonsillectomy. Many special populations may need additional surgeries or require the use of positive airway pressure.”

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Mayo Clinic’s Center for Sleep Medicine team recognizes the need for multidisciplinary care in these children, to treat a multitude of sleep concerns.”

Children with genetic disorders such as Down syndrome (trisomy 21), Prader-Willi syndrome, Angelman syndrome and achondroplasia; neuromuscular disorders such as muscular dystrophy, myotonic dystrophy and spinal muscular atrophy; cerebral palsy; and spina bifida are all at increased risk of OSA as well as other forms of sleep-disordered breathing. As noted in a study published in Sleep in 2011, these children require polysomnography to diagnose and treat the sleep-disordered breathing.

“Children with autism, Angelman syndrome or neurodevelopmental delay can have difficulty going to sleep and staying asleep. When children have sleep difficulties it significantly impacts their caregivers and families. Sleep concerns impact the mental health, cognition and well-being of children,” says Dr. Baughn.

**Children’s sleep disorders impact caregivers and families, too**

Mayo Clinic sleep medicine specialists recognize the multidisciplinary nature of sleep issues in children and the significant impact these issues have on the child’s caregiver or family. Knowing the importance of communication, team members collaborate with physicians in multidisciplinary clinics at Mayo Clinic Children’s Center, including the multidisciplinary Aerodigestive Clinic and neuromuscular clinic.

“The team recognizes the high risk of sleep-disordered breathing in children with spina bifida and cerebral palsy,” says Dr. Baughn. “When treatment for OSA is considered, the best therapy for the child can be discussed, as there is open communication between the sleep specialist and the child’s other providers. The ability of the sleep specialist to not only provide diagnostic interpretation of a polysomnography, but to provide a comprehensive sleep consultation is an asset that allows patient- and family-centered treatment of patients and their families.

“Our sleep medicine team works closely with endocrinologists in children with Prader-Willi syndrome who require polysomnography before and after initiation of growth hormone. We work with neurologists and pulmonologists in children with spinal muscular atrophy who are receiving nusinersen, a new genetic modifying treatment. Treatment for OSA in children is typically multidisciplinary and involves the expertise of an otolaryngologist.

The multidisciplinary model facilitates timely communication about treatment options. In the multidisciplinary Aerodigestive Clinic, the input of gastroenterologists, otolaryngologists, pulmonologists and sleep medicine specialists are all considered in the treatment plan given to a family.

Other multidisciplinary clinics at Mayo Clinic Children’s Center may not see children at risk of OSA, but do see children with other sleep disorders. Mayo Clinic Children’s Center has an active Angelman Syndrome Clinic, where children with Angelman syndrome will receive a sleep consult.

Children evaluated through the pediatric diagnostic and referral clinic who are diagnosed with postural orthostatic tachycardia syndrome can have comorbid insomnia, delayed sleep phase syndrome and hypersomnia. Children seen in developmental pediatrics, particularly those with attention-deficit/hyperactivity disorder and autism, have difficulty with insomnia and restless sleep.

“Mayo Clinic’s team of sleep medicine specialists is committed and passionate about the team approach to sleep concerns in children,” says Dr. Baughn. “That concern is never more important than in children with medically complex needs.”

**For more information**


Current Studies and Clinical Trials


- **A Clinical Study To Test How Effective and Safe GLPG1690 is for Subjects With Idiopathic Pulmonary Fibrosis (IPF) When Used Together With Standard of Care (ISABELA1)**
  - Principal investigator: Teng Moua, M.D.
  - Primary outcome measure: Rate of decline of forced vital capacity
  - Time frame: 52 weeks
  - Contact study coordinator: Shannon L. Daley at 507-293-0637 or daley.shannon@mayo.edu
  - NCT03711162

- **Impulse Oscillometry in Idiopathic Subglottic Stenosis**
  - Principal investigator: Dante N. Schiavo, M.D.
  - Primary outcome measure: Impulse oscillometry in patients with symptomatic idiopathic subglottic stenosis compared with findings in patients with small airways obstruction and healthy controls
  - Time frame: Six months to 52 weeks
  - Contact study coordinator: Hope E. Marlow at 507-284-2122 or marlow.hope@mayo.edu
  - IRB16-003960

- **A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase II Study To Investigate the Safety and Efficacy of Two Different Dose Regimens of IFX-1 as Add-On to Standard of Care in Subjects With Granulomatosis With Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)**
  - Principal investigator: Ulrich Specks, M.D.
  - Primary outcome measure: Safety and tolerability of two dose regimens of IFX-1 as add-on to standard of care in subjects with GPA and MPA compared with placebo
  - Time frame: 24 weeks
  - Contact study coordinator: Samantha (Sam) R. Hughes at 507-266-1026 or hughes.samantha@mayo.edu
  - IRB18-008714

- **Mechanistic Effects of Health Coaching To Reduce COPD Hospitalizations**
  - Principal investigator: Roberto P. Benzo, M.D.
  - Primary outcome measure: Health-related quality of life at month three via chronic respiratory questionnaire
  - Time frame: Three months
  - Contact study coordinator: Johanna P. Hoult at 507-293-1989 or hoult.johanna@mayo.edu
  - NCT03837847

- **Home Pulmonary Rehabilitation for COPD**
  - Principal investigator: Roberto P. Benzo, M.D.
  - Primary outcome measure: Higher quality of life than control group after randomization
  - Time frame: Three months
  - Contact study coordinator: Johanna P. Hoult at 507-293-1989 or hoult.johanna@mayo.edu
  - NCT03480386

- **Midodrine in Hepatopulmonary Syndrome**
  - Principal investigator: Hilary M. DuBrock, M.D.
  - Primary outcome measure: Safety and tolerability (adverse events)
  - Time frame: Six months
  - Contact study coordinator: Adam R. Miller at 507-266-8147 or miller.adam@mayo.edu
  - NCT03600870

- **PRECiSE — A Prospective Evaluation of the Clinical Utility for the ION Endoluminal System**
  - Principal investigator: Janani S. Reisenauer, M.D.
  - Primary outcome measure: Early performance outcomes of the Ion Endoluminal System, including sensitivity of system-obtained sample for malignancy
  - Time frame: Six months
  - Contact study coordinator: Hope E. Marlow at 507-284-2122 or marlow.hope@mayo.edu
  - IRB18-011348

Education Opportunities

For more information or to register for courses, visit https://ce.mayo.edu/pulmonary-medicine/node/1664, call 800-323-2688 (toll-free) or email cme@mayo.edu.

**Multidisciplinary Update in Pulmonary & Critical Care Medicine 2020**


Topics include clinical advances in pulmonary, critical care and sleep medicine; evaluation and management of various respiratory diseases; preventive and therapeutic techniques for optimal patient experiences; and medical practice guidelines.