Bronchiectasis Patient-Centered Research Priorities and Roadmap

November 28, 2016 (draft)

This research roadmap, developed in collaboration with patients, will provide essential direction for future bronchiectasis research.

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EXECUTIVE SUMMARY

Dear Bronchiectasis Community,

In the past few years we have seen an encouraging trend in the conduct of medical research. "Patient-centered research" has emerged, placing a high priority on incorporating the voice and thoughts of the patient into the development of medical studies. With the help of the Patient Centered Outcomes Research Institute (PCORI) and our partners, this movement has finally arrived in the area of bronchiectasis. Together with scientists and physicians, patients assist to set research priorities, help design studies that answer questions relevant to them, and collaborate in interpreting the outcomes of such studies. Patients provide perspective on living with their diagnosis of bronchiectasis and what is needed to improve their treatment and health-related quality of life. PCORI calls this new way of conducting research "research done differently", and we hope the change is lasting.

This Bronchiectasis Research Roadmap is a thoughtful, timely document that incorporates patient and clinical stakeholder input. Bronchiectasis is a rare, but not uncommon chronic lung disease that has few treatment options that have been rigorously examined. Patients endure a chronic cough and infectious exacerbations that are often difficult to manage. Evidence of risks and benefits of treatments are needed. The priority areas with specific objectives and next steps included in this roadmap provide a description of needs and a way to move the field forward in a patient-focused manner.

We thank the many patients and stakeholders who came together to participate in the discussion and complete the needs assessment survey, particularly our 7-member Patient Advisory Panel and patients who are part of the bronchandntm360social.org network supported by the COPD Foundation and NTM Info & Research.

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INTRODUCTION

BACKGROUND

Bronchiectasis is a rare, chronic, inflammatory lung disease that has a marked impact on quality of life. There are an estimated 100,000 adults over 65 living with bronchiectasis and nearly 200,000 overall in the U.S.[1,2] The disease predominantly affects females and incidence increases with age. Although bronchiectasis is common in patients with cystic fibrosis (CF), there are differences in which drugs work and how well drugs work in CF versus non-CF bronchiectasis patients. Here we focus solely on non-CF bronchiectasis, referred to as "bronchiectasis" throughout the document.

Bronchiectasis is characterized by dilated and damaged bronchi and is distinct from obstructive lung disease (COPD). Patients with bronchiectasis suffer chronic productive cough, debilitating weakness and fatigue, dyspnea, hemoptysis, and are at high risk for recurrent pneumonia and death due to lung infections. Exacerbations are a regular complication characterized by increased respiratory symptoms and decreased lung function and often result in hospitalization. In most, but not all cases, exacerbations are associated with infections. Important pathogens in this setting include nontuberculous mycobacteria (NTM) such as *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus*, as well as other bacterial organisms such as *Pseudomonas aeruginosa* and *Haemophilus influenzae*.[3] These infections can markedly affect quality of life, and chronic disability can greatly diminish individual participation in social, occupational, and recreational activities.

In the 2013 we collaborated with NTM Info & Research (NTMir, a national NTM patient advocacy organization) to conduct an electronic survey of bronchiectasis patients from among the 2000 total members. A total of 511 patients with bronchiectasis responded to questions about research priorities and impacts of bronchiectasis disease.[4] The quotes below taken directly from our pilot survey highlight patient concerns about their bronchiectasis diagnosis:

(1) "My pulmonologist doesn't seem to think it's a big deal to have this and just says to keep on the Advair."
(2) "Dismay of lack of understanding by medical practice, lack of understanding about degree of seriousness."
(3) "Greatest bronchiectasis concern is how to stop its progression"
(4) "Lack of training and info to improve symptoms and quality of life… what is best?"
(5) "My biggest concern is that it increases my risk of repeated [NTM] infection. And there is nothing I can do to reverse the damage."

The quotes above reflect the uncertainty in treatment and prognosis for bronchiectasis patients. The goals of treatment are to improve symptoms, reduce airway inflammation, limit further bronchiectasis progression, and prevent chronic lung infection and acute symptomatic infectious exacerbations. There are no published U.S. guidelines for bronchiectasis treatment, but in 2010 the British Thoracic Society (BTS) produced guidelines summarizing current therapies.[5] This guideline revealed a lack of safety and effectiveness data to guide treatment and highlighted the need for research in many aspects of this disease. It did not, however, discuss utilizing a patient-centered approach and to date, there has been little attention to patient input. One new area, in which patient input is systematically sought, is the development of patient-reported outcomes, such as measures of health-related quality of life (HRQoL). In a series of qualitative and quantitative studies, patient input was the most significant influence on the development of the Quality of Life-Bronchiectasis instrument (QOL-B).[6,7]

There are a number of new therapies being tested, including ciprofloxacin and other inhaled or oral antibiotics. We need input on which interventions are most appealing or concerning to patients and which outcome measures are most important. Given the goals of therapy involve maintaining quality of life and minimizing disease progression, and given the routine use of a number of untested therapies (e.g. antibiotics, steroids, bronchodilators, hypertonic saline, others), we believe that both prioritizing research questions and studying outcomes of interest to patients will provide the most efficient progress in caring for patients with this disease. This research roadmap, developed in collaboration with patients, will provide essential direction for future bronchiectasis research.

STAKEHOLDERS (*INDICATES PATIENT ADVISORY PANEL)

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TIMELINE

April 2016	Develop needs assessment survey with Patient Advisory Panel input.
May to November 2016	Anonymous patient needs assessment survey available.
August 2016	Webinar to discuss preliminary survey results with Stakeholders.
September 2016	Draft roadmap.
October-November 2016	Gather feedback from Stakeholders and patient on bronchandntm360social.
November 2016	Discuss objectives, next steps with Stakeholders.
December 2016	Final Stakeholder consensus survey of objectives and next steps.
December 2016	Finalize roadmap document.

NEEDS ASSESSMENT SURVEY

The Needs Assessment survey was conducted electronically and anonymously using an online SurveyMonkey™ survey. Patients were invited to visit the survey link and participate by letter for BRR patients, on bronchandntm360social.org, through emails to COPD and NTMir communities, and publication in the COPD Digest. Overall the survey patient population (N=405 with a self-reported diagnosis of bronchiectasis) reflects the general population with bronchiectasis. Most (77%) were between 50 and 79 and 89% were female; 18% had no listed underlying condition, 26% had a COPD diagnosis, 15% had a non-CF genetic condition, and a total of 58% had any current or past history of NTM. See Figures 1 to 4 below for responses by age group, sex, region, and underlying condition.

FIGURE 1: SURVEY RESPONDENTS BY AGE GROUP

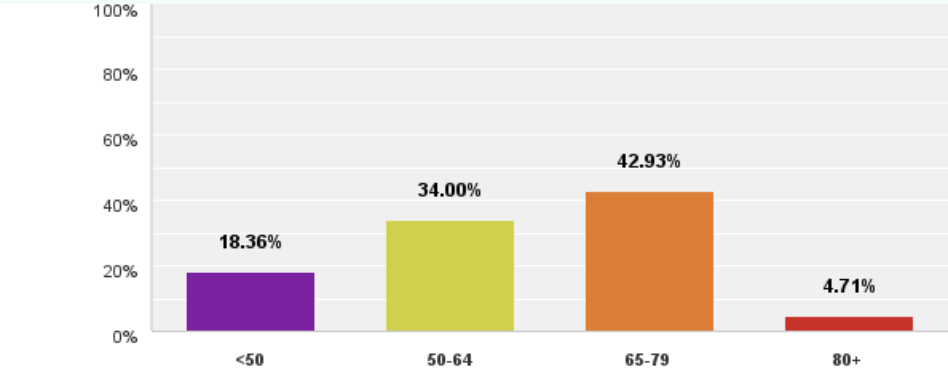


FIGURE 2: SURVEY RESPONDENTS BY SEX

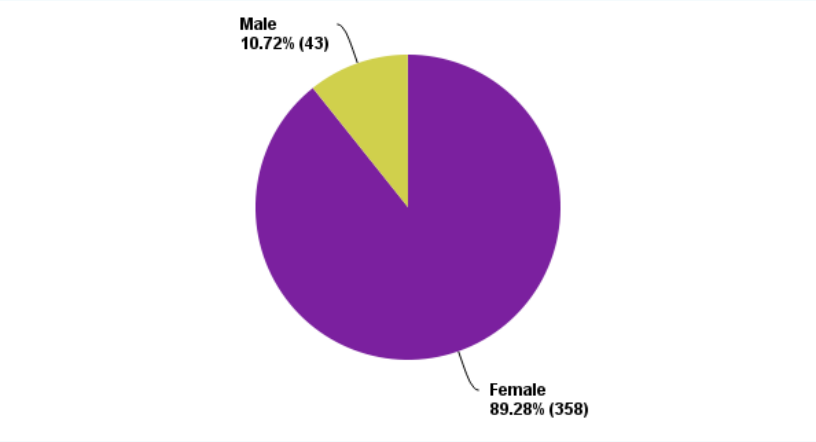


FIGURE 3: SURVEY RESPONDENTS BY GEOGRAPHIC LOCATION

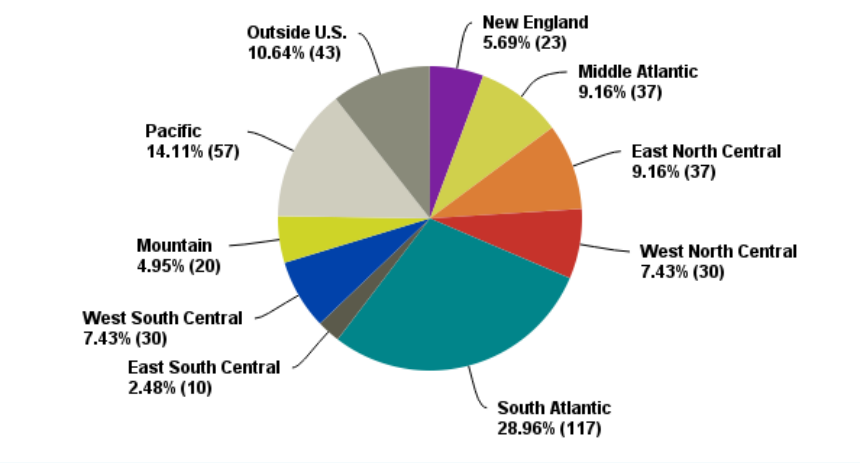
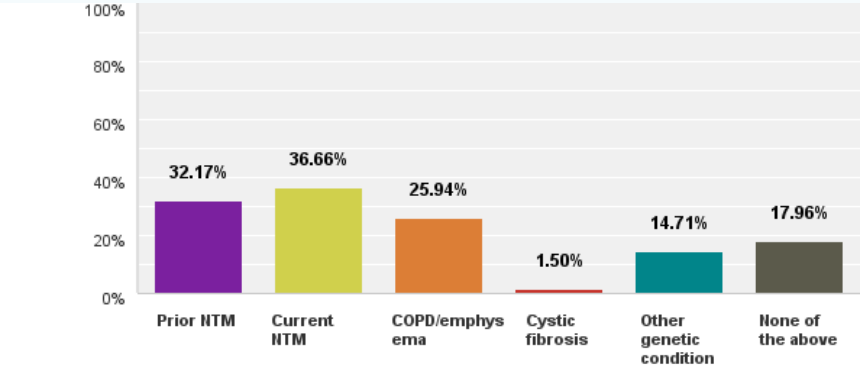


FIGURE 4: UNDERLYING CONDITIONS IN SURVEY RESPONDENTS


100%
80%
60%
40%
20%
0%
32.17%
36.66%
25.94%
1.50%
14.71%
17.96%
Prior NTM
Current NTM
COPD/emphysema
Cystic fibrosis
Other genetic condition
None of the above

THE RESEARCH ROADMAP

During the past year, Stakeholders and patients have identified the following six broad priorities for bronchiectasis research:

1. Improve treatment of bronchiectasis and prevent exacerbations
2. Improve treatment of exacerbations and associated infections
3. Improve health-related quality of life
4. Predictors of poor prognosis
5. Understand impact of underlying conditions
6. Patient-centered clinical trial outcomes

We discuss each of these in more detail as well as describing ways to strengthen or expand current research efforts. Where applicable, specific research objectives are provided.

PRIORITY 1: IMPROVE TREATMENT OF BRONCHIECTASIS AND PREVENT EXACERBATIONS

The goals of bronchiectasis therapy are to improve symptoms, maintain quality of life, reduce exacerbations, and prevent disease progression. Over 75% of survey responders selected treatment of bronchiectasis as one of their top 3 research priorities. When limited to a single therapeutic priority, 51% selected bronchiectasis treatment, 23% selected treatment of associated infections, and 13% selected complementary or alternative therapy.

We know that a number of untested therapies (e.g. antibiotics, steroids, bronchodilators, hypertonic saline, others) are routinely used to treat patients with bronchiectasis (Table 1). During the prior year, 60% of survey responders reported taking ICS and 22% reported taking oral steroids for at least 30 days in a row. Clinicians recommend airway clearance devices, presenting patients with the various options and allowing patients to select whichever works best for them without evidence of comparative effectiveness. Airway clearance is a daily, time-intensive therapy for patients who typically spend 30 to 60 minutes per day to clear their lungs. Despite this, 54% of survey respondents reported using positive expiratory pressure (PEP) therapy, 24% reported using the vest/chest oscillation, and 8% reported using the Lung Flute.

TABLE 1. PHARMACOTHERAPIES AND AIRWAY CLEARANCE DEVICES USED IN BRONCHIECTASIS

Anti-inflammatory		**Bronchodilators**		**Mucous/ airway clearance**
Inhaled steroids	beclomethasone budesonide flunisolide fluticasone mometasone triamcinolone	**Short acting**	albuterol levabuterol pirbuterol	inhaled hypertonic saline vibratory positive expiratory pressure chest physiotherapy/ percussive therapy
		Long acting	formoterol tiotropium salmeterol	
Combined steroid/ bronchodilator	ipratratropium/albuterol Budesonide/formoterol fluticasone/salmeterol			
Oral steroids	prednisone			
Macrolide antibiotics	azithromycin, erythromycin*			

*tested in randomized clinical trials for bronchiectasis

Exacerbations are characterized by increasing symptoms and decreased lung function, typically but not exclusively associated with respiratory infections. This worsening of symptoms may occur 3-6 times per year or more. Prevention of exacerbations was the second most commonly selected research priority, selected as one of the top 3 priority by 56% of survey respondents.

To prevent infectious exacerbations, antibiotics may be given to eradicate bacteria (e.g. *Pseudomonas)* or as suppressive therapy to reduce bacterial burden. Suppressive antibiotics, including inhaled tobramycin, gentamicin, and colistin are used "off-label" for patients with bronchiectasis. However, evidence of a benefit of inhaled antibiotics in patients with bronchiectasis is lacking. Two Phase 3 randomized placebo-controlled trials of inhaled aztreonam did not provide clinical benefits in bronchiectasis patients.[8] Results from two Phase 3 RCTs of inhaled ciprofloxacin are expected in the near future.

There are several important areas that need further research including the role of rotating antibiotics and optimal duration and dosing schedule for suppressive antibiotics.

OBJECTIVES

1.1 Rigorously evaluate the efficacy and safety of long term use of inhaled corticosteroids in bronchiectasis.

1.2 Compare the effectiveness of physical airway clearance techniques, accounting for patient preference and adherence.

Vibratory positive expiratory pressure

Percussion therapy/ chest physiotherapy

1.3 Evaluate the efficacy of mucolytics and hypertonic saline in bronchiectasis.

1.4 Evaluate the efficacy of bronchodilators in bronchiectasis.

1.5 Evaluate inhaled antibiotics to prevent exacerbations.

1.6 Evaluate naturopathic and alternative therapies to reduce inflammation.

1.7 Establish a consensus definition of exacerbation that can be consistently applied across studies.

PRIORITY 2: IMPROVE TREATMENT OF EXACERBATIONS AND ASSOCIATED INFECTIONS

During an exacerbation, sputum culture should be collected so an infectious cause can be established and appropriate therapy initiated.

NTM treatment guidelines have been published and are currently being updated.

There is effective treatment for *Pseudomonas* infection, *Aspergillus* and other fungal infections, and gram negative infections (i.e. xxx). However, questions remain about the optimal duration of treatment.

Commented [EH1]: Tim, please expand and update.

OBJECTIVES

2.1 Rigorously evaluate the efficacy and safety of long term use of inhaled corticosteroids in bronchiectasis.

2.2 Compare the effectiveness of physical airway clearance techniques, accounting for patient preference and adherence.

2.3 Evaluate the utility of in vitro/in vivo antibiotic susceptibility testing for guiding antibiotic treatment regimens.

PRIORITY 3: IMPROVE HEALTH-RELATED QUALITY OF LIFE

Bronchiectasis has a major impact on patient's health-related quality of life. It is a chronic, progressive disease that can be managed, but is rarely cured with surgery. The symptom burden associated with bronchiectasis is significant and can interfere with daily activities and physical, social and emotional functioning. Chronic respiratory symptoms, such as cough and sputum production, can be hard to manage in social situations, and can cause fatigue and difficulties with sleep. Most individuals will have to do treatments, such as airway clearance and inhaled medications, which take between 60 and 120 minutes a day. The top two priorities for survey respondents in relation to health-related quality of life were: 1) improving the impact of the disease on daily life (53%) and 2) reducing treatment burden (28%). Although not ranked as highly, other priorities included how bronchiectasis affects social interactions (13%) and risks for development of depression or anxiety (6%).

There are several ways to reduce treatment burden. One is to develop devices that shorten treatment time. A good example of that is the new tobramycin inhalation powder device, which decreases treatment time from 40 minutes a day to about five minutes. Another way to reduce burden is to simplify administration of the medication. The tobramycin inhalation powder device consists of disposable capsules with no need to clean or sanitize equipment. This device is also portable so that people can travel more easily.

Based on results of the survey, the HRQoL objectives are to reduce treatment burden and identify effective traditional and complementary therapies. The QOL-B has a Treatment Burden scale which can be used to measure whether a new mode of administration reduces burden. Another purpose of the QOL-B is to serve as a primary or secondary outcome measure in clinical trials of new medications or treatments. The FDA and EMA now accept patient-reported outcomes as evidence of efficacy, particularly scales that measure key symptoms (e.g., improvement in respiratory symptoms).

OBJECTIVES

3.1 Consider time and ease of administration in the development of new drugs.

3.2 Measure the efficacy of new pharmaceutical and complementary treatments including acupuncture, exercise, diet, massage, relaxation training, and yoga/mindfulness.

PRIORITY 4: IDENTIFY PREDICTORS OF POOR PROGNOSIS

Bronchiectasis is diagnosed by findings on a high resolution CT scan. Although we know that diagnosis may be delayed, the impact of this delay on prognosis is not known. However, survey respondents did not identify improved screening as a top priority. With regards to diagnosis of bronchiectasis, survey respondents were most interested in measuring disease severity and improving clinician education about bronchiectasis. Clinician education about bronchiectasis applies across all priorities, and will be addressed in the "Moving Forward" section. With regards to prognosis, 45% of survey respondents selected biomarkers as the top priority and 25% prioritized severity measures. Biomarkers and severity measures are combined as predictors of poor prognosis in this section.

As defined by the Biomarker Definitions Working Group[9], "a biological marker or biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention." A biomarker may be measured using a radiologic exam, quantification of a substance in the blood, urine, sweat, saliva, or cerebral spinal fluid, or identification of a genetic variation.[10] A biomarker that predicts poor prognosis can be used in the clinical setting to identify patients who may benefit from therapy or those who will not, or those who are at low risk from progression and do not need therapy at that time. In addition to predictors of poor prognosis, biomarkers may be used to measure drug toxicity or as surrogate endpoint in clinical trials.

Biomarkers must undergo rigorous examination prior to use in clinical and clinical trial settings. A good biomarker is sensitive, specific, and easily reproduced (See Table for definitions). Biomarkers must correlate with clinical measures of disease progression or severity. Last, the technology used to measure the biomarker must be relatively easy to implement in routine practice.

TABLE: BIOMARKER CHARACTERISTIC DEFINITIONS

Characteristic	Definition
Sensitive	Proportion who test "positive" given that they have disease/abnormal pathology
Specific	Proportion who test "negative" given no disease/normal pathology
Reproducible	Stable measurements within an individual across short periods of time

Describe candidate biomarkers?

Commented [EH2]: Chuck, or any clinical stakeholders please weigh in.

Several tools have been developed in Europe to measure disease severity: the Bronchiectasis Severity Index (BSI) and FACED score.[11,12] The two scores, which group patients into mild, moderate, and severe categories were recently compared in a multicenter pooled analysis.[13] The BSI was consistently a good predictor of death, objective clinical outcomes (i.e. hospital admissions, exacerbations, lung function decline) and health-related quality of life measured by the QOL-B. The BSI, which takes into account more factors than the FACED score, incorporates age, predicted FEV1%, presence of chronic *Pseudomonas aeruginosa* colonization, radiologic characterization of bronchiectasis (number of lobes and type), degree of dyspnea, body mass index, exacerbation frequency, prior hospitalization for exacerbations, and chronic colonization of other bacteria. Further evaluation of the BSI tool is needed in a U.S. population, which is more diverse racially and with regards to underlying and associated conditions including nontuberculous mycobacterial (NTM) disease.

OBJECTIVES

4.1 Identify biomarker candidates.

4.2 Develop and evaluate biomarkers that can be used as predictors of poor prognosis.

4.3 Validate the BSI in the U.S. in a more diverse bronchiectasis population including Asian patients and those with NTM disease.

4.4 Validate the BSI as a predictor of exacerbations.

4.5 Evaluate the utility of BSI as a clinical tool to guide therapeutic choice.

4.6 Develop a disease activity score that takes into account subjective patient-reported outcomes.

PRIORITY 5: UNDERSTAND IMPACT OF UNDERLYING CONDITIONS

We already distinguish patients with bronchiectasis associated with cystic fibrosis with those who do not. In fact bronchiectasis is associated with a number of underlying conditions that cause the development of bronchiectasis, though in many cases it is considered idiopathic with no detected underlying diagnosis or infectious cause. Just over 22% of survey respondents selected a better understanding of the impact of underlying diagnoses as the top priority for the general category of prognosis. Common conditions that impact bronchiectasis diagnosis and treatment include chronic obstructive pulmonary disease (COPD) and asthma. The following are some of the most important rare causes of bronchiectasis:

- Allergic bronchopulmonary aspergillosis (ABPA)
- Pulmonary ciliary dyskinesia
- Cystic fibrosis CFTR mutations
- Immune deficiency (e.g. common variable immune deficiency)
- Rheumatoid arthritis
- Marfan's disease

Diagnosis and treatment of these and other underlying conditions is part of standard of care for patients with bronchiectasis. What is unclear is whether there are differences in treatment and prognosis, and how to prevent bronchiectasis development and progression.

OBJECTIVES

5.1 Describe the natural history of bronchiectasis in patients with different underlying and concomitant diagnoses.

5.2 Conduct subgroup analyses where possible to identify differences in treatment response or risks.

PRIORITY 6: CONDUCT PATIENT-CENTERED CLINICAL TRIALS

Modern research is increasingly being conducted with patient partners. The Food and Drug Administration "Patient-Focused Drug Development" initiative that is gathering input from patients and clinical experts on 20 diseases. Funding agencies including the Patient-Centered Outcomes Research Institute increasingly require patients to be involved in study development and clinical trial recruitment as stakeholders. The purpose is to conduct meaningful clinical research in order to answer questions most relevant to patients.

The QOL-Bronchiectasis (QOL-B) survey is a validated, modern tool to measure health-related quality of life in patients with bronchiectasis. The CFQ-R, a similar tool which measures health-related quality of life in patients with cystic fibrosis, is a standard endpoint in clinical trials for cystic fibrosis. In the two Phase 2 randomized trials that used the QOL-B as a primary outcome, patients scored the lowest on Respiratory Symptoms, Physical Functioning, Vitality, Health Perceptions, and Social Functioning.[7] Relatively higher scores were reported on Role Functioning, Emotional Functioning, and Treatment Burden. The Physical Functioning score was highly associated with lung function (FEV_1) at baseline. Slower 6-minute walk tests were associated with lower scores for Physical Functioning, Vitality, Role Functioning, Health Perceptions in both studies, and Respiratory Symptoms and Emotional Functioning in one. Given the impact of bronchiectasis on health-related quality of life, we support the expanded use of QOL-B as a key patient-reported outcome for clinical trials. For patients with both bronchiectasis and NTM a complementary NTM symptom module has been developed and final validation early next year.[14]

OBJECTIVES

6.1 Involve patients in the design of clinical trials for bronchiectasis.
6.2 Include the QOL-B as a primary or secondary outcome on all bronchiectasis clinical trials.
6.3 Include the NTM module for those with bronchiectasis and NTM.

MOVING FORWARD

Bronchiectasis remains a rare disease, though the prevalence is difficult to estimate. There is a growing interest internationally to better understand bronchiectasis and develop registries. In the U.S., the Bronchiectasis and NTM Research Registry (BRR) has enrolled over 2,000 bronchiectasis and NTM patients since 2007. More recently, the European Bronchiectasis Registry (www.bronchiectasis.eu/registry) was started and seeks to enroll 10,000 bronchiectasis patients and follow them longitudinally. Efforts are also underway in China, Australia, and South America. Below are specific steps that the Stakeholder panel agreed will ensure that progress is made on the objectives outlined in this document.

1) Expand data sources and analysis to better understand natural history of bronchiectasis and research priorities.

- Expand the BRR.
    - Add sites (in progress) and increase funding
    - Standardize evaluations
    - Centralize registry and modify consent to facilitate linkage to electronic health record, vital status, and Center for Medicare and Medicaid Services data
    - Add patient-reported outcomes, biorepository
- Develop a "PPRN", patient-powered research network to collect patient-reported outcomes.

2) Tools and evidence are needed to make informed treatment decisions.

- Increase the number of bronchiectasis clinical trials.
    - Use the BRR Consortium to plan and initiate clinical trials
    - Work with pharmaceutical companies to develop and test new drugs and formulations
- Improve understanding of lung microbiome, or patterns of good/bad bacteria in lungs.
- Blood, tissue, and other samples should be collected alongside a registry to allow biomarker identification and validation.

3) Increase awareness of bronchiectasis among general practitioners and patients. In our needs assessment survey, 36% of respondents selected need for patient information as top priority for communication about bronchiectasis.

- Increase patient access to recently established bronchandntm360social.org website.
    - Patients can share information, access vetted information about bronchiectasis
    - Survey patients also expressed need for in-person, local support groups

- The COPD Foundation is working on a patient booklet “Bronchiectasis 1-2-3 similar to “COPD 1-2-3” that can be distributed in doctor’s offices.

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