Cystic Fibrosis Related NTM Infections

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NTM Provider Course
National Jewish Health
Disclosures

• Funding from the Cystic Fibrosis Foundation
• Paratek Pharmaceuticals Advisory Board
Learning Objectives

- Understand the pathophysiology of typical pulmonary disease in cystic fibrosis (CF)
- Learn how to diagnose NTM pulmonary disease in a CF patient and recognize differences from non-CF patients
- Discuss differences in NTM treatment strategies for the CF population
- Identify unmet needs in the study of NTM in the CF patient and opportunities for collaboration and research
Cystic Fibrosis

• Syndrome of chronic sinopulmonary infections, malabsorption and nutritional abnormalities
• Most common lethal genetic disease in Caucasians
• CF gene encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein
Pathophysiology of Cystic Fibrosis

Abnormal CFTR protein
Defective ion transport
Airway surface liquid depletion
Delayed mucociliary clearance

Mucus Obstruction

Infection

Inflammation

Cycle of Destruction

End Stage Lung Disease

http://www.nhlbi.nih.gov/health/health-topics/topics/cf/signs.html
Lung Disease in CF

- Bronchiectasis
- Infection
  - *Staphylococcus aureus*
  - *Pseudomonas aeruginosa*
- Inflammation
- Mucous Plugging
Unique Aspects of NTM infection in CF

- Disease with the highest prevalence of pulmonary NTM
- Universal occurrence in the setting of other bacterial co-infections
- Susceptible to both slow and rapid-growing NTM
- Appears that only a subpopulation of CF patients are vulnerable
  - 19% prevalence (2010-2016 CF registry data)
- Detection often occurs in asymptomatic patients through annual screening within the CF Care Center model
What is the current estimated NTM prevalence in CF patients in the U.S.? (CFF Registry 2011-2015)

1. 4%
2. 10%
3. 19%
4. 25%
NTM Species Distribution in CF in the U.S.

Prospective
- Mycobacterium abscessus complex
  - M. abscessus
  - M. bolletii
  - M. massiliense
  Co-infection classified as M. abscessus

Colorado (2010)
Retrospective
- Mycobacterium avium complex
  - M. avium
  - M. intracellulare
  - M. chimaera

CFF Registry (2010)
Retrospective
- Other (approximately 140 species)
  - M. kansasii
  - M. fortuitum
  - M. chelonae

N=128
N=130
N=923

From Nick Symposium NACFC 2013;
Olivier AJRCCM, 2003; Roux JCM, 2009; Martiniano AATS, 2014
Patient-to-Patient Spread of NTM in CF

- Local outbreaks of *M. abscessus* subspecies *massiliense* in CF Care Centers
  - University of Washington CF Center (Aitken ML, AJRCCM, 2012)
  - Hawaii (NACFC podium talk)
  - Papworth CF Center, U.K. (Bryant JM, Lancet, 2013)
- Evidence of “dominant circulating clones” among CF patients in the U.K., Australia and North Carolina (Bryant JM, Science, 2016)
  - Associated with high mortality and treatment failure in CF (Kapnadek SG, Amer J Infect Control, 2016)
10 yo male, CF (F508del/W1282X), FEV₁ 120%
Staphylococcus aureus, Stenotrophomonas maltophilia

- 1st NTM *M. abscessus* subsp. *abscessus*, 2012, age 12
- 2nd NTM *M. intracellulare*, 2015, age 16
- Hearing loss and allergies to several meds
NTM Screening in CF

CFF/ECFS Recommendations:

• Annual NTM cultures in spontaneously expectorating individuals with a stable clinical course
  • Screen for NTM prior to starting chronic azithromycin therapy
• In the absence of clinical features suggestive of NTM pulmonary disease, individuals who are not capable of spontaneously producing sputum do not require screening cultures for NTM
• Culture and smears for acid fast bacilli from sputum should be used for NTM screening
  • Recommend against the use of oropharyngeal swabs for NTM screening

ATS/IDSA Statement: “Diagnosis, Treatment, and Prevention of NTM Disease” AJRCCM 2007;
US CFF/ECFS “Consensus recommendations for the management of NTM in individuals with CF, Thorax, 2016
Diagnostic Criteria for NTM Pulmonary Disease

**Clinical Criteria:**
Pulmonary symptoms: cough, sputum production, dyspnea, hemoptysis with nodular or cavitary opacities on CXR, or an HRCT that shows multifocal bronchiectasis with multiple small nodules

**Microbiological Criteria:**
Positive culture results from at least 2 separate expectorated sputum samples  
OR  
Positive culture results from at least 1 BAL  
OR  
Transbronchial or lung biopsy with mycobacterial or histopathologic features of NTM and a positive culture for NTM

ATS/IDSA Statement: “Diagnosis, Treatment, and Prevention of NTM Disease” AJRCCM 2007
CF-Specific Considerations

Exclusion of other diagnoses:
Other CF pathogens and co-morbidities should be considered as potential contributors to a patient’s symptoms and radiological features when determining the clinical significance of NTM positive cultures.

Suboptimal CF care
Pulmonary Exacerbations
- Typical CF pathogens
- New bacterial infection

Co-morbidities:
- Allergic pulmonary aspergillosis (ABPA), asthma
- CF-related diabetes
- Sinus disease
- Gastroesophageal reflux
- Chronic aspiration
- Nutritional deficiencies

ATS/IDSA Statement: “Diagnosis, Treatment, and Prevention of NTM Disease” AJRCCM 2007;
WHO TO TREAT? 3 Patient Cohorts

Transient: Only one positive culture

Indolent infection: Multiple positive cultures over time, but no evidence of accelerated progression of CF lung disease

NTM Disease: Multiple positive cultures over time, and radiographic and clinical evidence of accelerated progression of CF lung disease

From Nick Symposium NACFC 2013; Olivier AJRCCM, 2003; Esther J Cys Fibr, 2010; Martiniano AATS 2014;
Clinical significance of a first positive NTM culture in CF

Change in ppFEV₁ before and after first positive NTM culture
Average time of follow-up 4.4 years (n=96)

Persistent/Indolent (n=37)
Transient (n=22)
Active (n=37)

Likely some patients will progress to NTM disease even after years of clinical stability

Significant decline in FEV₁ for 1 year prior to 1st culture
18 months from 1st culture to start of treatment

Martiniano AATS 2014
Unmet Needs

• Validated CF-specific diagnostic criteria
• Standardized treatment protocol for initial infections with *M. abscessus* complex or *M. avium* complex
  • Defined rates of treatment response
  • Markers of response and treatment endpoints specific to CF
  • Lifelong treatment strategies for persistent or recurrent NTM infections
• Pharmacokinetic analysis of standard antimicrobial agents in CF patients
• NTM-specific antibiotics that can be administered for prolonged treatment courses
• Definition of mechanism(s) of pathogen acquisition and apparent patient-to-patient transmission
• Better appreciation of the relative significance of various species within the *M. abscessus* complex and the MAC
• Better understanding of host and pathogen interactions impacting progression to NTM disease and treatment response
PROSPECTIVE EVALUATION OF NTM DISEASE IN CYSTIC FIBROSIS (PREDICT) Trial

• Primary Objectives
  • To test a standardized diagnostic protocol to identify pediatric and adult CF patients with NTM disease
  • To define an expected rate of disease diagnosis
• Prospective, observational study at the Colorado CF Care Center (Children’s Hospital Colorado and National Jewish Health)
  • Expanded to 10 geographically diverse locations across the U.S.
• Inclusion: CF patients, 6 years and older, with a recent positive NTM culture (last 2 years)
• Exclusion: Previous NTM treatment or history of transplant
PREDICT Disease Diagnosis Flowchart

1. Positive Culture
   - Review NTM History
   - Is patient eligible for PREDICT Study?
     - Yes
       - Notify and schedule visit
       - Consent obtained for PREDICT Study?
         - Yes
           - PREDICT Follow Up
             - CFQ-R
               - Blood/sputum/urine samples for banking and research
               - Repeat NTM culture
             - Clinical Assessment Procedures
               - Treat comorbidities as needed
               - Greater than expected clinical decline?
                 - Yes
                   - Were other respiratory pathogens aggressively treated?
                     - Yes
                       - Meet NTM Disease Diagnosis
                         - Refer to PATIENCE Study Visit Flowchart
               - At least 2 positive cultures in past 2 years?
                 - Yes
                   - Consent for PATIENCE Study
     - No
       - Treat or follow as per institutional practice
   - No
     - Negative Culture

2. CFQ-R:
   - Obtain quarterly per protocol

3. Clinical Assessment Procedures:
   - Height/Weight
   - Spirometry
   - Acute Antibiotics For Respiratory Disease
   - NTM Radiologic Assessment
   - NTM Clinical Syndrome
   - CF Pathogen Assessment and Management Comorbidity Assessment

Property of Presenter
Not for Reproduction
Definitive treatment of other airway co-pathogens

Strongly consider a two week-course of IV antibiotics focused on known (non-NTM) infections in patients with a clinical syndrome, even in the absence of clear evidence of a pulmonary exacerbation.
What do the CFF/ECFS consensus guidelines recommend for first-line treatment for macrolide-susceptible, non-cavitary MAC?

1. Thrice weekly oral azithromycin, ethambutol, rifampin
2. Daily oral clarithromycin, ethambutol, rifampin
3. Daily oral azithromycin, ethambutol, rifampin
4. Daily inhaled amikacin and oral azithromycin
What do the CFF/ECFS consensus guidelines recommend for initial, “intensive” phase treatment for MABSC?

1. IV amikacin, IV cefoxitin, oral azithromycin, oral linezolid x 12 weeks
2. IV amikacin, IV imipenem, IV tigecycline, oral azithromycin x 4 weeks
3. IV amikacin, oral clarithromycin x 12 weeks
4. 1 or 2
5. 1, 2 or 3
Treatment Considerations in CF

• MAC treatment should be daily
  • Abnormal intestinal absorption and altered pharmacokinetics in CF
CF subjects (fasting or fed) and Healthy Controls with Sub-therapeutic MAC Drug Levels

Conclusions: Although medians values were within therapeutic ranges, up to 20% of CF subjects in the fasting state, and 25% of subjects in the fed state, had sub-therapeutic drug levels.

Implications:
1. Sub-therapeutic drug levels may be a contributor to MAC treatment failure in some CF patients.
2. Drug levels should be obtained in CF patients experiencing treatment failure.

Martiniano, SL, et al. Peds Pulm
Treatment Considerations in CF

• MABSC treatment should include an intensive phase followed by continuation/chronic suppressive phase
  • Intensive: IV 2 IVs, plus oral azithromycin, plus 1-2 additional drugs
  • Continuation: inhaled amikacin, plus 2-3 oral antibiotics

• Macrolide-resistant MAC or MABSC, consider consultant with experts in the NTM in CF
Potential treatment schedule for MABSC and MAC

From US CFF/ECFS Consensus Recommendations for the Management of NTM in CF, Thorax 2016
PROSPECTIVE ALGORITHM FOR TREATMENT OF NTM IN CYSTIC FIBROSIS (PATIENCE) Trial

• **Primary Objectives**
  • To test a standardized initial treatment protocol for pulmonary disease caused by *M. avium* complex (MAC) and *M. abscessus* complex (MABSC) in CF patients
  • To determine an expected rate of treatment response
• Prospective, observational study at the Colorado CF Care Center (Children’s Hospital Colorado and National Jewish Health)
  • Expansion to 10 geographically diverse locations across the U.S.
• **Inclusion:** All patients with CF determined to have NTM pulmonary disease from PREDICT due to *M. avium* complex (MAC) or *M. abscessus* complex (MABSC)
• **Exclusion:** Pregnant or breastfeeding

CFF #NICK13A0
PATIENCE Treatment Algorithm

- **M. avium complex**
  - Yes: Macrolide sensitive
    - Yes: Severe?
      - Yes: 
        - **Azithromycin**
        - **Rifampin**
        - **Ethambutol**
      - No: 
        - **Azithromycin**
        - **Rifampin**
        - **Ethambutol**
    - No: 
      - **Azithromycin**
      - **Rifampin**
      - **Ethambutol**

- **M. abscessus complex**
  - Yes: M. abscessus or M. Bolletii
    - **Azithromycin**
    - **Imipenem**
    - **Amikacin (iv)**
    - **Linezolid**
  - No: M. massiliense
    - **Azithromycin**
    - **Imipenem**
    - **Amikacin**

**Severe disease** which may include:
- Smear positive and/or
- Cavity infection radiographically positive and/or
- Systemically ill

**M. avium complex Alternative Antibiotics:**
- Moxifloxacin
- Clofazimine – treatment IND
- Amikacin (neb)

**M. abscessus Alternative IV Medications:**
- Cefoxitin
- Tigecycline

**Antiinfective route key:**
- Oral
- IV
- Neb

If lack of efficacy on clinical picture (such as growing multiple species, or treatment requires additional antibiotics) consult with study PI’s before prescribing.

The Intensive Phase start treatment sequentially on successive days (start 1, if tolerated start 2, if tolerated start 3).
# Example Toxicity Monitoring Table for CF

<table>
<thead>
<tr>
<th>Medication</th>
<th>CBC</th>
<th>LFTs</th>
<th>Cr</th>
<th>Audiograms</th>
<th>Visual</th>
<th>Serum Peak Levels</th>
<th>Exam for neuropathy</th>
<th>EKG (long Qtc)</th>
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<tr>
<td><strong>Amikacin (IV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>After 1wk &amp; prn</td>
<td></td>
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<tr>
<td><strong>Amikacin (inh)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(goal 30-60)</td>
<td></td>
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</tr>
<tr>
<td><strong>Azithromycin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Every 3 mos</td>
<td></td>
<td></td>
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<tr>
<td><strong>Cefoxitin</strong></td>
<td>Monthly</td>
<td></td>
<td></td>
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<tr>
<td><strong>Clofazimine</strong></td>
<td>Monthly</td>
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<tr>
<td><strong>Ethambutol</strong></td>
<td>Monthly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily or every 3 mos</td>
<td>Every 3 months</td>
<td></td>
</tr>
<tr>
<td><strong>Imipenem</strong></td>
<td>Monthly</td>
<td></td>
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<tr>
<td><strong>Linezolid</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily or every 3 mos</td>
<td>Every 3 months</td>
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</tr>
<tr>
<td><strong>Moxifloxacin</strong></td>
<td></td>
<td>Monthly</td>
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<tr>
<td><strong>Rifampin</strong></td>
<td>Monthly</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Monthly</td>
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<tr>
<td><strong>Tigecycline</strong></td>
<td>Monthly</td>
<td>(+alb, bili)</td>
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</tbody>
</table>
Treatment goals in CF and non-CF are similar

- **Treatment Goals:**
  - Microbiological improvement
    - Colorado CF Center historic treatment “success” rates:
      » *M. abscessus* complex = 30%
      » *M. avium* complex = 71%
  - Symptomatic improvement
  - Radiographic improvement

- **Suppression:**
  - Clearing sputum of NTM likely not realistic for many patients
  - Significant and sustained benefit can still be achieved with antibiotic therapy even with + cultures
  - Must balance patient quality of life and limit toxicities

Martiniano et al, AATS, 2014
Risk for Second NTM Infection

Product-Limit Survival Estimates (with number of subjects at risk)

Probability of Single Positive NTM Species

Years Until Second Positive NTM Species

Martiniano et al., AATS, 2014
Longitudinal NTM co-infections are common in the PREDICT cohort

- **Mean 26.7 cultures** (SD 19.0, range 5-75 cultures)
- **Mean duration of 7.9 years** (SD 4.0, range 1.6-18.6 years)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Complex</th>
<th>Species</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-02CAS</td>
<td>MAC</td>
<td>M. avium</td>
<td>M. avium linage 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M. avium linage 2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M. avium linage 3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M. avium other</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>monoclonal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M. chimaera</td>
<td>M. avium other</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M. intracellulare</td>
<td>monoclonal</td>
</tr>
<tr>
<td></td>
<td>MABSC</td>
<td>M. abscessus</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- **53% (29/55) of all subjects** enrolled in PREDICT demonstrated the presence of NTM co-infection with 2 or more NTM at the complex, species, subspecies, or strain level
NTM Disease:
73% with NTM co-infections (species or strain) ($p=0.02$)
Mean of 2.3±0.2 species or strains ($p=0.01$)

<table>
<thead>
<tr>
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<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-02CAS</td>
<td>MAC</td>
<td>M. avium</td>
<td>M. avium line 1</td>
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<td>M. avium line 2</td>
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<td>M. avium line 3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M. avium other</td>
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<tr>
<td></td>
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<td>M. avium other</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M. chimaera monocalonal</td>
</tr>
<tr>
<td></td>
<td>MABSC</td>
<td>M. intracellulare</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M. abscessus monocalonal</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M. abscessus clone</td>
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</table>

Indolent Infection (No NTM Disease):
39% with NTM co-infections (species or strain)
Mean of 1.5±0.2 species or strains

<table>
<thead>
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<td>P-077LR</td>
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<td></td>
<td>M. avium other</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M. avium line 5</td>
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<tr>
<td></td>
<td>MABSC</td>
<td>M. massilense</td>
<td>M. massilense N/A</td>
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<td>M. avium line 1</td>
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<tr>
<td>A-08JMS</td>
<td>MABSC</td>
<td>M. massilense</td>
<td>M. massilense N/A</td>
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<td>M. abscessus</td>
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<td>A-11SJK</td>
<td>MABSC</td>
<td>M. abscessus clone 2</td>
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<td>A-22VNL</td>
<td>MAC</td>
<td>M. abscessus</td>
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<td>M. intracellular</td>
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<tr>
<td>A-25NMA</td>
<td>MAC</td>
<td>M. intracellular</td>
<td>M. intracellular N/A</td>
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<td>M. intracellular</td>
<td>M. intracellular N/A</td>
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<td>M. chimaera</td>
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<td>A-35RCC</td>
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<td>M. abscessus</td>
<td>M. abscessus clone 1</td>
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<td>M. intracellular N/A</td>
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<td>A-07HCL</td>
<td>MAC</td>
<td>M. intracellular</td>
<td>M. intracellular N/A</td>
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<td>A-10HPW</td>
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<td>A-26TLS</td>
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<td>A-27DRH</td>
<td>MABSC</td>
<td>M. abscessus</td>
<td>M. abscessus clone 1</td>
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<td>M. avium line 3</td>
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<td>A-13BHW</td>
<td>MABSC</td>
<td>M. abscessus</td>
<td>M. abscessus not clustered</td>
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<td>M. kansasii</td>
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<td>A-24CWE</td>
<td>MAC</td>
<td>M. avium</td>
<td>M. avium</td>
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Colorado RDP Core Flow of NTM Isolates and Data

**Molecular Core**
- 1020 isolates analyzed by whole genome sequencing (WGS)

**Culture and Biorepository Core**
- Genomic DNA
- Cluster Analysis

**Clinical Research Core**

**National Jewish Health Clinical Mycobacteriology Reference Laboratory**
- NTM isolates from:
  - CF Centers in P&P
  - Other CF Centers
  - NJH Lab
  - Centralized Labs

- >2400 isolates
- 120 CF Centers
- 46 States

**Genotyping Reports**

**Surveillance**

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Phylogenetic analysis for surveillance of *M. abscessus* transmission or shared environmental exposure in U.S. CF patients

- 79% of patients are unclustered
- 21% of patients within 10 clusters
- 70 patients meet genetic criteria for transmission
- 23 instances of 2 or more patients with highly similar strains identified in the same CF Center

Michael Strong, Colorado RDP (unpublished data)
MAC isolates are non-clustered and there is no evidence of transmission or shared environmental exposure.
Conclusions

- NTM is common in the sputum of children and adults with CF
- NTM pulmonary disease develops in about 40% of infected patients
- The role of NTM in lung disease can only be assessed following aggressive care of all other aspects of CF
- There are many unmet needs still in the study of the diagnosis and treatment of NTM in CF
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Disclosures:
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Questions?