Genetic COPD: Understanding what we know, who we test, how we treat

M. Douglas Lee, MD FCCP
Wilmington Health Associates
Wilmington North Carolina
Objectives

- Review the Epidemiology of COPD Genetics
- Discuss the ATS guidelines for COPD Genetic Screening
- Understand the importance of Treatment options for Alpha One Anti-Trypsin Deficiency
- Review Treatment Options for patients with COPD and alph One Anti-trypsin deficiency
- Discuss Future research involving COPD
Financial Disclosures

- **Speaker Bureau**
  - Glaxo
  - Forest Pharmaceuticals
  - Opsuka

- **Principal Investigator Research AT PMG/Wilmington Health**
  - Glaxo
  - Genetech
  - Forest
  - Astra Zeneca
  - Pearle
AAT deficiency, commonly called alpha-1, is a potentially fatal, genetic form of COPD\(^1\)
- Alpha-1 is the major known genetic risk factor for COPD\(^2\)

Alpha-1 is not a rare disease but one that is rarely diagnosed\(^3\)
- Up to 25 million Americans have an abnormal allele (S or Z)\(^4\)
- An estimated 100,000 Americans have alpha-1\(^5\)
- 90% remain undiagnosed\(^6,7\)
- Lengthy delay in diagnosis\(^5\)
  - 8.3 ± 6.9 years between onset of symptoms and diagnosis\(^5\)

Laboratory testing is the only way to diagnose—it’s fast, easy, and FREE

Once you identify an alpha-1 patient through testing, there is a specific treatment

AAT, alpha-1-antitrypsin; COPD, chronic obstructive pulmonary disease.
Current Myths of COPD

- All COPD (especially emphysema) is caused by smoking
- Alpha-1 is rare, so I don’t need to test my patients
- Alpha-1 results exclusively in emphysema
- I don’t need to test for alpha-1 since there are no treatments
- If I test, I only have to consider homozygous patients (Pi ZZ)
- There is no need to test a smoker for alpha-1
- I do not need to test older patients for alpha-1
- A complete diagnosis of alpha-1 can be made on serum levels alone
- I know an alpha-1 patient when I see one

COPD, chronic obstructive pulmonary disease.
The View From Above—What are we missing
Alpha-1 Is Not a Rare Disease but One That Is Rarely Diagnosed

The Problem

- Up to 25 million Americans have an abnormal allele (S or Z)
- An estimated 100,000 Americans have alpha-1
- 90% remain undiagnosed
- Early diagnosis and treatment is associated with health benefits
- Most common inherited risk factor for COPD (1 in 10 COPD patients)

Alpha-1 in the US

COPD, chronic obstructive pulmonary disease.
Alpha-1: A Major Risk Factor for COPD

- Alpha-1 is a potentially fatal, genetic form of COPD\(^1\)
  - COPD is now the third leading cause of death in the US\(^2\)
  - Alpha-1 may be a contributor in up to 3% of all COPD cases in the US\(^3\)

COPD, chronic obstructive pulmonary disease.
Low Levels of AAT Leave Lung Tissue Vulnerable

AAT, alpha1-antitrypsin.
AAT Is Critical to Safeguarding Lungs

- Lung damage results from an excess burden of neutrophil elastase AND lack of AAT

- Smoking, secondary smoke, dust, and exposure to fumes accelerate lung disease in alpha-1 patients

- Infections are additional risk factors in AAT-deficient individuals

AAT inhibits excess amounts of enzymes, such as neutrophil elastase, released in response to infection, injury, inflammation

Alpha-1–related lung disease presents with common respiratory symptoms:

- Dyspnea (84%)\(^1\)
- Decreased exercise tolerance\(^2,3\)
- Wheezing (76%)\(^1\)
- Cough (42%)\(^1\)
- Excess sputum production (50%)\(^1\)
- Frequent lower respiratory tract infections\(^2,3\)
- History of suspected allergies and/or asthma\(^4\)

Diseases Commonly Associated With Alpha-1

- COPD
- Bronchiectasis
- Liver disease
- Necrotizing panniculitis

PROLASTIN®-C (alpha1-proteinase inhibitor [human]) is indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe deficiency of alpha1-proteinase inhibitor (alpha1-antitrypsin deficiency). The effect of augmentation therapy with any alpha1-proteinase inhibitor (alpha1-PI), including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in alpha1-antitrypsin deficiency has not been conclusively demonstrated in randomized, controlled clinical trials. Clinical data demonstrating the long-term effects of chronic augmentation or maintenance therapy with PROLASTIN-C are not available.

Please see Important Safety Information within this presentation and accompanying PROLASTIN-C full Prescribing Information for complete prescribing details.

COPD, chronic obstructive pulmonary disease.
Genetic Testing Found 1 in 5 Patients With Deficient Alleles*

MM (normal), MS (not deficient), SS (mildly deficient), MZ (mildly deficient), SZ (moderately to severely deficient), ZZ (severely deficient)

* Data represent patients tested for alpha-1 at the University of Florida Alpha-1 Antitrypsin Genetics Laboratory.

Data on file, Alpha-1 Antitrypsin Genetics Laboratory, University of Florida.
Regional study in Kentucky reveals higher alpha-1 prevalence vs US national data

- Regional study looked at prevalence of non-MM genotypes in a private pulmonary practice in Kentucky
- Used retrospective chart review
- Genotype data collected for 4308 patients screened for alpha-1 from October 2003 to October 2011
- Data analyzed in aggregate and compared with previously published US national prevalence data
### Results: Higher Regional Prevalence of Non-MM Genotypes vs US Population

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Observed Genotype (N)</th>
<th>Prevalence in KY Cohort (%)</th>
<th>Prevalence in Caucasian US Population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>3948</td>
<td>91.64</td>
<td>94.0 to 96.0</td>
</tr>
<tr>
<td>MZ</td>
<td>113</td>
<td>2.62</td>
<td>2.0</td>
</tr>
<tr>
<td>MS</td>
<td>174</td>
<td>4.04</td>
<td>5.0</td>
</tr>
<tr>
<td>SZ</td>
<td>12</td>
<td>0.28</td>
<td>0.05</td>
</tr>
<tr>
<td>ZZ</td>
<td>12</td>
<td>0.28</td>
<td>0.01</td>
</tr>
<tr>
<td>SS</td>
<td>5</td>
<td>0.12</td>
<td>0.05</td>
</tr>
<tr>
<td>Rare M subtypes</td>
<td>32</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Rare, deficiency-related</td>
<td>12</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4308</strong></td>
<td><strong>100.00</strong></td>
<td></td>
</tr>
</tbody>
</table>

Patients With Severe Alpha-1 Have Significantly Shorter Life Spans

Survival Analysis of Patients With Severe Alpha-1 (Pi ZZ) vs Total US Population

* Pi ZZ = severely deficient alpha-1 patient.

There Is a Lengthy Delay in Diagnosis

In a survey of 1020 members of AlphaNet,* on average

- **2 to 3 physicians seen** before correct diagnosis
- **8.3 ± 6.9 years** between onset of symptoms and diagnosis
- Patients were **45.5 ± 9.5 years of age** when identified as AAT deficient
- **Steady increase in age at diagnosis** ($P<0.05$) was observed between 1968 and 2003

* AlphaNet: Not-for-profit organization providing health management services for PROLASTIN DIRECT® led by alpha-1 experts and patients.

AAT, alpha-1-antitrypsin.
American Thoracic Society Guidelines Recommend Testing ALL Symptomatic COPD Patients

<table>
<thead>
<tr>
<th>The American Thoracic Society Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Test all adults with symptomatic COPD, <strong>regardless of smoking history</strong></td>
</tr>
<tr>
<td>• Test all adults with symptomatic emphysema, <strong>regardless of smoking history</strong></td>
</tr>
<tr>
<td>• Test all adults with symptomatic asthma whose airflow obstruction is incompletely reversible after bronchodilator therapy</td>
</tr>
<tr>
<td>• Test asymptomatic patients with persistent obstruction on pulmonary function tests with identifiable risk factors (eg, smoking, occupational exposure)</td>
</tr>
<tr>
<td>• Test siblings of individuals with alpha-1</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease.
Test ALL Patients With COPD Regardless of Smoking History

- At least 25% of long-term smokers develop COPD\(^1\)
- In a National Registry study (N=1129 patients with alpha-1), 80% were either current smokers (8%) or ex-smokers (72\%)\(^2\)
- In a separate study (N=878), 82.3% reported tobacco use with a pack-year history of 23.2 ± 14.5 years\(^3\)

COPD, chronic obstructive pulmonary disease.
Follow-up Study of Patients 3 Months After Test Results and Minimal Counseling (n=199)

- 59% of severe alphas reported 24-hour quit attempt
- 34% of heterozygotes reported 24-hour quit attempt
- 26% of patients with normal results reported 24-hour quit attempt

Finding Deficient Alleles Matters

- Promotes smoking prevention and cessation and other healthy lifestyle modifications
  - Patients who are tested may be more likely to attempt to quit smoking
- Increases potential for family testing and genetic counseling
- Raises awareness to avoid hazards of occupational respiratory pollutants

Alpha-1 Is a Genetic Disorder: Test the Entire Family

You’re not just identifying a patient, you’re discovering an entire family at risk for lung disease

Data on file, Grifols.
Serum Level Alone Is NOT a Complete Diagnostic Tool

Range of Serum AAT Levels by Phenotype (µM)

- **Normal Range**
  - Pi MM
  - Pi MS
  - Pi SS

- **Increased risk of disease**
  - Pi MZ
  - Pi SZ
  - Pi ZZ

AAT, alpha1-antitrypsin.
Data on file, Grifols.
Who Do You Test and Who Are You Missing?

FEV1 Percentage Predicted by Age for 378 Pi ZZ Patients Stratified by Smoking Status

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second.


Remember, only a laboratory test can confirm the presence of alpha-1.
Now That You’ve Tested, What Next?

Common questions after testing

1. What if I find a deficient allele?
2. What if I find a ZZ?
3. What do I tell my patients?
4. Whom should I treat, and are there differences in augmentation therapy providers?
5. Are there “centers of excellence” to which I can refer?
6. What resources are available to help me?
What patients often hear:

- “You have a fatal genetic disease”
- “You have 2 years to live”
- “Get your affairs in order”

Better (and truer):

- “Now we know a reason for your symptoms”
- “A disease management program is available to help you manage your alpha-1”
- “There is specific therapy available for alpha-1–related lung disease”
Connie: Would You Test a 76-Year-Old?

- **Ethnicity, age, and sex:**
  - 76-year-old white female

- **Profession:**
  - Retired administrative assistant

- **Personal history:**
  - 40 pack-year smoker

- **Medical history:**
  - Diagnosed with advanced COPD 20 years ago; stable lung function
  - Current COPD medications
    - LAMA
    - SABA
    - ICS/LABA

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta₂-agonist.
Family medical history:
- 2 brothers diagnosed with COPD

Pulmonary function testing results:
- FEV$_1$ 45% of predicted

Intervention/Testing:
- Tested for alpha-1 by her primary care doctor after educational lecture
  - AAT serum levels confirmed at 14 µM
  - MZ allele combination identified through genotype testing
  - Confirmed through Pi testing (phenotyping)

Diagnosis:
- COPD confirmed
- Heterozygote for alpha-1 with MZ genotype ("carrier")

AAT, alpha$_1$-antitrypsin; COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second.
Connie: Case Resolution

- **Actions taken for Connie:**
  - Maintain current COPD medications
    - Maximize bronchodilators
  - Treat lung infections aggressively
  - Avoid all tobacco and environmental hazards

COPD, chronic obstructive pulmonary disease.
Actions taken for Connie’s family:
  - Family testing/genetic counseling offered
  - **Family testing results:**
    1 MZ (Connie) yielded 3 ZZ
    - Son (50 years old): ZZ with normal lung function
    - Granddaughter (26 years old): ZZ; new diagnosis of COPD
    - Great-granddaughter (14 years old): ZZ with normal lung function
    - Daughter (53 years old): MZ; Daughter’s husband (not pictured): MZ
  - All counseled to avoid tobacco and environmental hazards
  - Routine follow-up for all to monitor PFTs

PFT, pulmonary function test.
Robert: Would You Test If Lung Function Stable?

- **Ethnicity, age, and sex:**
  - 62-year-old white male

- **Profession:**
  - Plumbing contractor

- **Personal history:**
  - 30 pack-year smoker; quit 5 years ago
  - Routinely consumes up to 4 beers/day

- **Medical history:**
  - Diagnosed with COPD 5 years ago
  - Current COPD medications
    - LAMA
    - SABA
  - Lab results from recent yearly physical showed elevated LFTs (negative hepatitis virus panel)

COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; LFT, liver function test; SABA, short-acting beta₂-agonist.
Robert: Would You Test If Lung Function Stable? (cont.)

- **Family medical history:**
  - Father died of emphysema
  - Sister diagnosed with COPD and heterozygous alpha-1 MZ genotype
  - 7 brothers in the family

- **Pulmonary function testing results:**
  - FEV<sub>1</sub> 70% of predicted
  - FEV<sub>1</sub>/FVC ratio 62% of predicted
Robert: Would You Test If Lung Function Stable? (cont.)

- **Intervention/Testing:**
  - Tested for alpha-1 based on COPD diagnosis and elevated LFTs
    - AAT serum levels confirmed at 5 µM
    - ZZ allele combination identified through genotype testing
    - Confirmed through Pi testing (phenotyping)

- **Diagnosis:**
  - COPD confirmed
  - Alpha-1

AAT, alpha-1-antitrypsin; COPD, chronic obstructive pulmonary disease; LFT, liver function test.
**Actions taken:**

- Genetic counseling and family testing recommended
- Lifestyle changes
  - Limit alcohol intake
  - Continue liver function monitoring
- Influenza, hepatitis A, hepatitis B, pneumococcal vaccinations
- Treat lung infections aggressively
- Maximize bronchodilators
- Follow up with pulmonologist in 6 months to review PFTs and determine need for augmentation therapy

PFT, pulmonary function test.
What’s Next for Patients With a Deficient Allele?

- Family testing and counseling
- Lifestyle changes
  - Smoking cessation
  - Exercise
  - Avoidance of environmental pollutants
  - Limit alcohol consumption
- Vaccinations
  - Influenza/pneumococcal
  - Hepatitis A/B
- Drug therapy for lung disorders
  - Bronchodilators
  - Inhaled steroids
  - Antibiotics
  - Oxygen
- Pulmonary rehabilitation

How Does Pulmonary Rehabilitation Help in COPD?

- Reduces dyspnea\(^1\)\(^-\)\(^3\)
- Improves endurance\(^2\)
- Reduces number of hospitalizations\(^2\)\(^,\)\(^3\)
- Improves exercise capacity\(^1\)\(^,\)\(^3\)
- Improves HRQOL\(^3\)
- Improves survival\(^3\)
- Reduces anxiety and depression associated with COPD\(^3\)

COPD, chronic obstructive pulmonary disease; HRQOL, health-related quality of life.

Management Approaches for Patients With Severe Alpha-1

- Family testing and counseling
- Lifestyle changes
  - Smoking cessation
  - Exercise
  - Avoidance of environmental pollutants
  - Limit alcohol consumption
- Vaccinations
  - Influenza/pneumococcal
  - Hepatitis A/B
- Drug therapy for lung disorders
  - Bronchodilators
  - Inhaled steroids
  - Antibiotics
  - Oxygen
- Pulmonary rehabilitation
- Surgical procedures
  - Lung transplantation in end-stage lung disease
  - Lung volume reduction surgery
- Augmentation therapy
Once You’ve Identified an Alpha-1 Patient, There Is a Specific Treatment

Treatment of Alpha-1

AAT Deficient

Neutrophil elastase burden

Antineutrophil imbalance

With Augmentation Therapy

Neutrophil elastase burden

Antineutrophil in balance

Reduce the burden of neutrophil products

Augment the lung concentration

AAT, alpha-1-antitrypsin.
Role of Augmentation Therapy in Patients With Severe Alpha-1

- Specific treatment by infusion of alpha\textsubscript{1}-antitrypsin purified from pooled human plasma\textsuperscript{1}

- When given at 60 mg/kg body weight once weekly
  - Antineutrophil elastase capacity in lung epithelial lining fluid obtained by bronchoalveolar lavage increased to 60% to 70% of normal in alpha\textsubscript{1}-deficient individuals\textsuperscript{2}
  - AAT serum trough levels remained >11 \( \mu \text{M} \textsuperscript{3} \)

- Goal of therapy:
  - Elevate levels of alpha\textsubscript{1}-antitrypsin in plasma and lung interstitium\textsuperscript{1,2}

PROLASTIN\textsuperscript{®}-C (alpha\textsubscript{1}-proteinase inhibitor [human]) is indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe deficiency of alpha\textsubscript{1}-proteinase inhibitor (alpha\textsubscript{1}-antitrypsin deficiency). The effect of augmentation therapy with any alpha\textsubscript{1}-proteinase inhibitor (alpha\textsubscript{1}-PI), including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in alpha\textsubscript{1}-antitrypsin deficiency has not been conclusively demonstrated in randomized, controlled clinical trials. Clinical data demonstrating the long-term effects of chronic augmentation or maintenance therapy with PROLASTIN-C are not available.

Please see Important Safety Information within this presentation and accompanying PROLASTIN-C full Prescribing Information for complete prescribing details.

AAT, alpha\textsubscript{1}-antitrypsin.
Mean Plasma AAT Concentration vs Time Following Treatment With PROLASTIN®-C

The effect of augmentation therapy with any alpha₁-proteinase inhibitor (alpha₁-PI), including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in alpha₁-antitrypsin deficiency has not been conclusively demonstrated in randomized, controlled clinical trials. Clinical data demonstrating the long-term effects of chronic augmentation or maintenance therapy with PROLASTIN-C are not available.

Please see Important Safety Information within this presentation and accompanying PROLASTIN-C full Prescribing Information for complete prescribing details.

AAT, alpha₁-antitrypsin; PK, pharmacokinetic.
Data on file, Grifols.
Byron:
Would You Test After Cardiac Work-up?

- **Ethnicity, age, and sex:**
  - 55-year-old white male

- **Profession:**
  - Welder/forklift driver in a gate shop

- **Personal history:**
  - 81 pack-year smoker (3 ppd x 27 years); quit 4 years ago
  - Lives with smoker of 1 ppd

- **Medical history:**
  - HTN; mild
  - Diagnosed with COPD 4 years ago; moderate obstruction
  - Current COPD medications
    - LAMA
    - SABA
    - ICS/LABA

COPD, chronic obstructive pulmonary disease; HTN, hypertension; ICS, inhaled corticosteroid; LABA, long-acting beta_2_-agonist; LAMA, long-acting muscarinic antagonist; ppd, pack per day; SABA, short-acting beta_2_-agonist.
Byron: Would You Test After Cardiac Work-up? (cont.)

- **Family medical history:**
  - Father died from MI at age 62
  - Mother had moderate asthma

- **Pulmonary function testing results:**
  - $\text{FEV}_1$ 43% of predicted
  - $\text{FEV}_1/\text{FVC}$ ratio 62% of predicted

*FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; MI, myocardial infarction.*
Byron: Would You Test After Cardiac Work-up? (cont.)

- **Intervention/Testing:**
  - Symptoms were more severe than expected based on PFT results; sent for cardiac work-up (negative)
  - Tested for alpha-1 by practitioner after attending medical conference
    - AAT serum levels confirmed at 5 µM
    - ZZ allele combination identified through genotype testing
    - Confirmed through Pi testing (phenotyping)

- **Diagnosis:**
  - Emphysema
  - Severe alpha-1

AAT, alpha-1-antitrypsin; COPD, chronic obstructive pulmonary disease; PFT, pulmonary function test.
**Byron: Case Resolution**

- **Actions taken:**
  - Genetic and lifestyle counseling provided
  - Recommended instituting weekly intravenous augmentation therapy with PROLASTIN®-C (alpha,1-proteinase inhibitor [human]) for severe alpha-1
  - Enrolled patient in PROLASTIN DIRECT®
    - AlphaNet* coordinator assigned

* AlphaNet: Not-for-profit organization providing health management services for PROLASTIN DIRECT led by alpha-1 experts and patients.

Please see Important Safety Information within this presentation and accompanying PROLASTIN-C full Prescribing Information for complete prescribing details.
The Only Proven Approach to Alpha-1 Health Management: ADMAPP* Study Design

Recruited and completed initial baseline survey 1028

Completed 1-year follow-up 978

Completed 2-year follow-up 905

Completed at least 22 of the 24 monthly surveys 878

10 withdrew from study
6 lost to follow-up
19 died
15 had new transplant

12 withdrew from study
4 lost to follow-up
31 died
26 had new transplant

* The ADMAPP Health Outcomes Study: Two-year study comparing outcomes in a 12-month observation period with augmentation therapy alone and 12-month intervention period with augmentation therapy plus PROLASTIN DIRECT®.

### Significant Improvements in Health Outcomes After Intervention Year (n=878)*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage Reduction</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% reduction in COPD exacerbations</td>
<td></td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>12% reduction in unscheduled physician visits</td>
<td></td>
<td>P=0.03</td>
</tr>
<tr>
<td>21% reduction in emergency room visits</td>
<td></td>
<td>P=0.02</td>
</tr>
</tbody>
</table>

- Significant (10%) increase in the use of long-acting bronchodilators (P<0.001)
  - Translates into more optimal medication use

---

* The ADMAPP Health Outcomes Study: Two-year study comparing outcomes in a 12-month observation period with augmentation therapy alone and 12-month intervention period with augmentation therapy plus PROLASTIN DIRECT®.

Summary: Uncovering Alpha-1

- Alpha-1 is not a rare disease but one that is rarely diagnosed
  - Up to 25 million Americans have an abnormal allele (S or Z)
  - An estimated 100,000 in the US are AAT deficient
  - 90% remain undiagnosed
  - Lengthy delay in diagnosis
    - 8.3 ± 6.9 years between onset of symptoms and diagnosis

- Laboratory diagnosis required
  - Use Grifols AlphaKit™ tests—fast, easy, and FREE
  - Test all adults with symptomatic COPD regardless of smoking history
  - Test all family members when a deficient allele is found

- When you do find an alpha-1 patient, there is treatment and support

AAT, alpha-1-antitrypsin; COPD, chronic obstructive pulmonary disease.
Resources to Help You Manage Alpha-1

Resources for healthcare professionals and patients

- AlphaNet
  1-800-577-2638
  www.alphanet.org

- Alpha-1 Foundation
  1-877-228-7321
  www.alpha-1foundation.org

- Alpha-1 Association Genetic Counseling Center
  1-800-785-3177
  www.alpha1.org/support/genetic-counseling-program

- Clinical Resource Centers
  alpha-1foundation.org/
  clinical-resource-centers
Upcoming Studies in COPD

- Reducing Exacerbations in COPD
  - Antibodies to Interlekin-5

- Proper Use of Inhaled Steroids in COPD
  - Bone Fracture Risk
  - Use in stable COPD

- Appropriate Stepwise Approach to COPD Management
  - LABA/LAMA Combinations
  - Triple Therapy
  - Injectable SQ Therapy
Kilimanjaro—19,341 Feet