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

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Objectives

- Review the Epidemiology of COPD Genetics
- Discuss the ATS guidelines for COPD Genetic Screening
- Understand the importance of Treatment options forAlpha 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
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  - Glaxo
  - Genetech
  - Forest
  - Astra Zeneca
  - Pearle

Uncovering Alpha-1

- 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.

1. Campbell EJ, et al. *Chest.* 2000;117(5 suppl 1):303S. 2. Brantly M. *Clin Chem.* 2006;52(12):2180-2181. 3. de Serres FJ. *Environ Health Perspect.* 2003;111(16):1851-1854. 4. de Serres FJ, et al. *Clin Genet*. 2003;64(5):382-397. 5. Campos MA, et al. *Chest.* 2005;128(3):1179-1186. 6. Silverman EK, Sandhaus RA. *N Engl J Med.* 2009;360(26):2749-2757. 7. About AAT deficiency. http://www.alpha1health.com/healthcare-professionals/about-aat-deficiency/. Accessed February 15, 2013.

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[1]

The Problem

- Up to 25 million Americans have an abnormal allele (S or Z)[2]
- An estimated 100,000 Americans have alpha-1[3]
- **90% remain undiagnosed[4,5]**
- **Early diagnosis and treatment is associated with health benefits[6]**
- Most common inherited risk factor for COPD (1 in 10 COPD patients)[6]

Alpha-1 in the US[3]

COPD, chronic obstructive pulmonary disease.

1. de Serres FJ. *Environ Health Perspect.* 2003;111(16):1851-1854. 2. de Serres FJ, et al. *Clin Genet*. 2003;64(5):382-397. 3. Campos MA, et al. *Chest.* 2005;128(3):1179-1186. 4. Silverman EK, Sandhaus RA. *N Engl J Med.* 2009;360(26):2749-2757. 5. About AAT deficiency. http://www.alpha1health.com/healthcare-professionals/about-aat-deficiency/. Accessed February 15, 2013. 6. Brantly M. *Clin Chem.* 2006;52(12):2180-2181.

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]

DNA Molecule Unwinding From a Chromosome Inside the Nucleus of a Cell

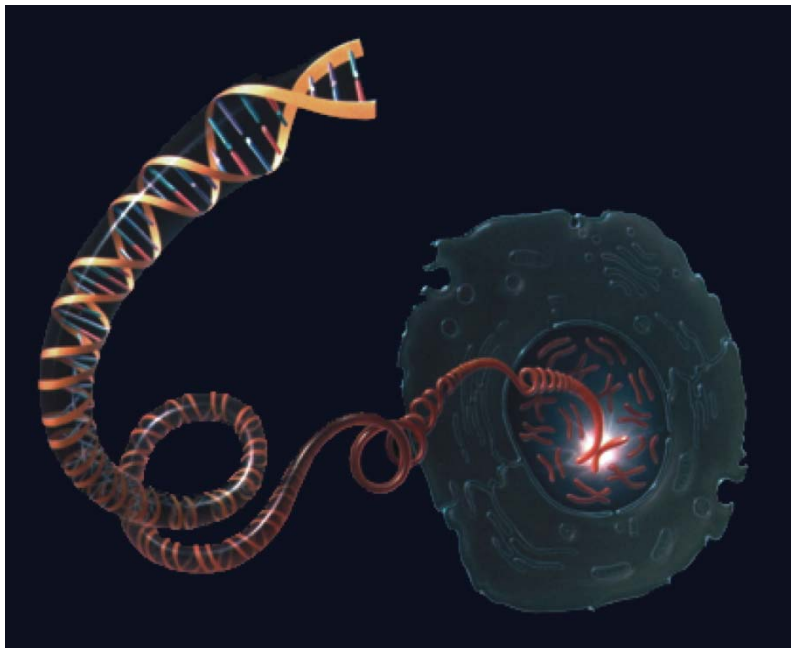
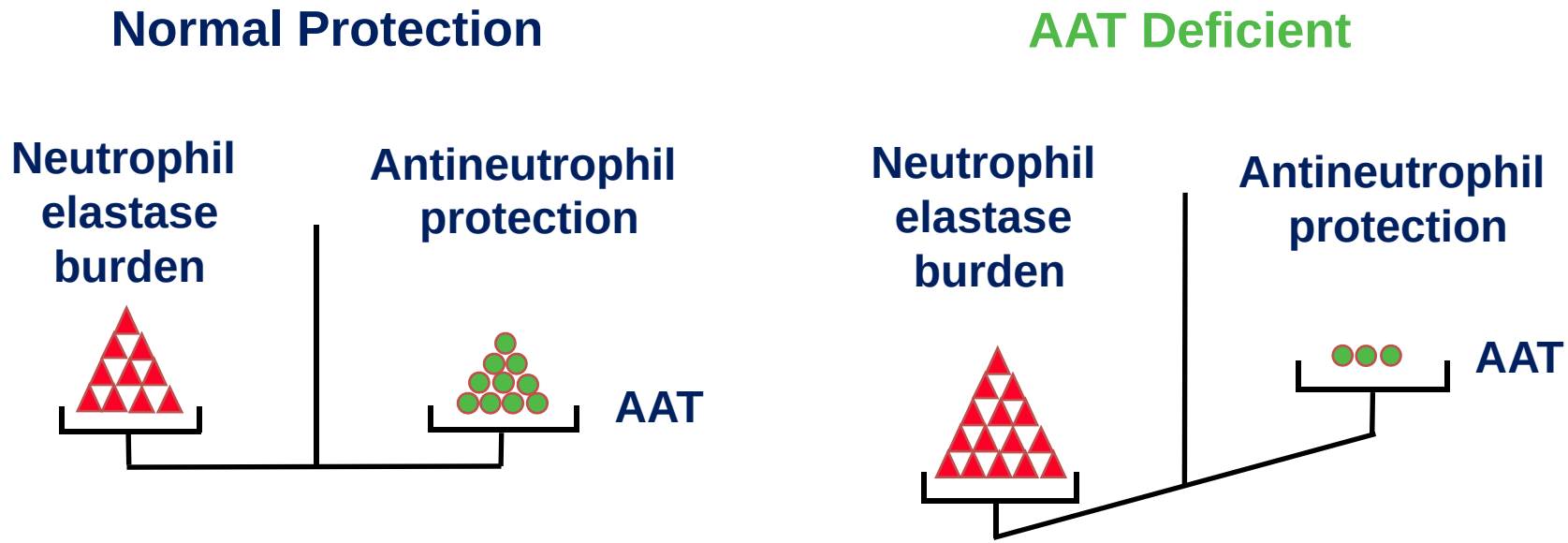


Image courtesy of the National Human Genome Research Institute (www.genome.gov).

COPD, chronic obstructive pulmonary disease.

1. Campbell EJ, et al. *Chest.* 2000;117(5 suppl 1):303S. 2. Miniño AM, et al. *Natl Vital Stat Rep.* 2010;59(2):1-52. 3. Campos MA, et al. *Chest.* 2005;128(3):1179-1186.

Low Levels of AAT Leave Lung Tissue Vulnerable



AAT, alpha$_1$-antitrypsin.

Köhnlein T, Welte T. *Alpha-1 Antitrypsin Deficiency: Clinical Aspects and Management.* Bremen, Germany: UNI-MED Verlag AG; 2007.

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

AAT, $alpha_1$-antitrypsin.

Köhnlein T, Welte T. *Alpha-1 Antitrypsin Deficiency: Clinical Aspects and Management.* Bremen, Germany: UNI-MED Verlag AG; 2007:16-39.

Do ANY of Your Patients Present With These Complaints?

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]

1. McElvaney NG, et al. *Chest.* 1997;111(1):394-403. 2. Alpha-1 Foundation website. alpha-1foundation.org/what-is-alpha-1. Accessed March 5, 2013. 3. Alpha-1 Association website. www.alpha1.org/home/alpha-1-awareness-and-testing. Accessed March 5, 2013.4. Eden E, et al. *Respir Med.* 2006;100(8):1384-1391.

Diseases Commonly Associated With Alpha-1

- COPD
- Bronchiectasis
- Liver disease
- Necrotizing panniculitis

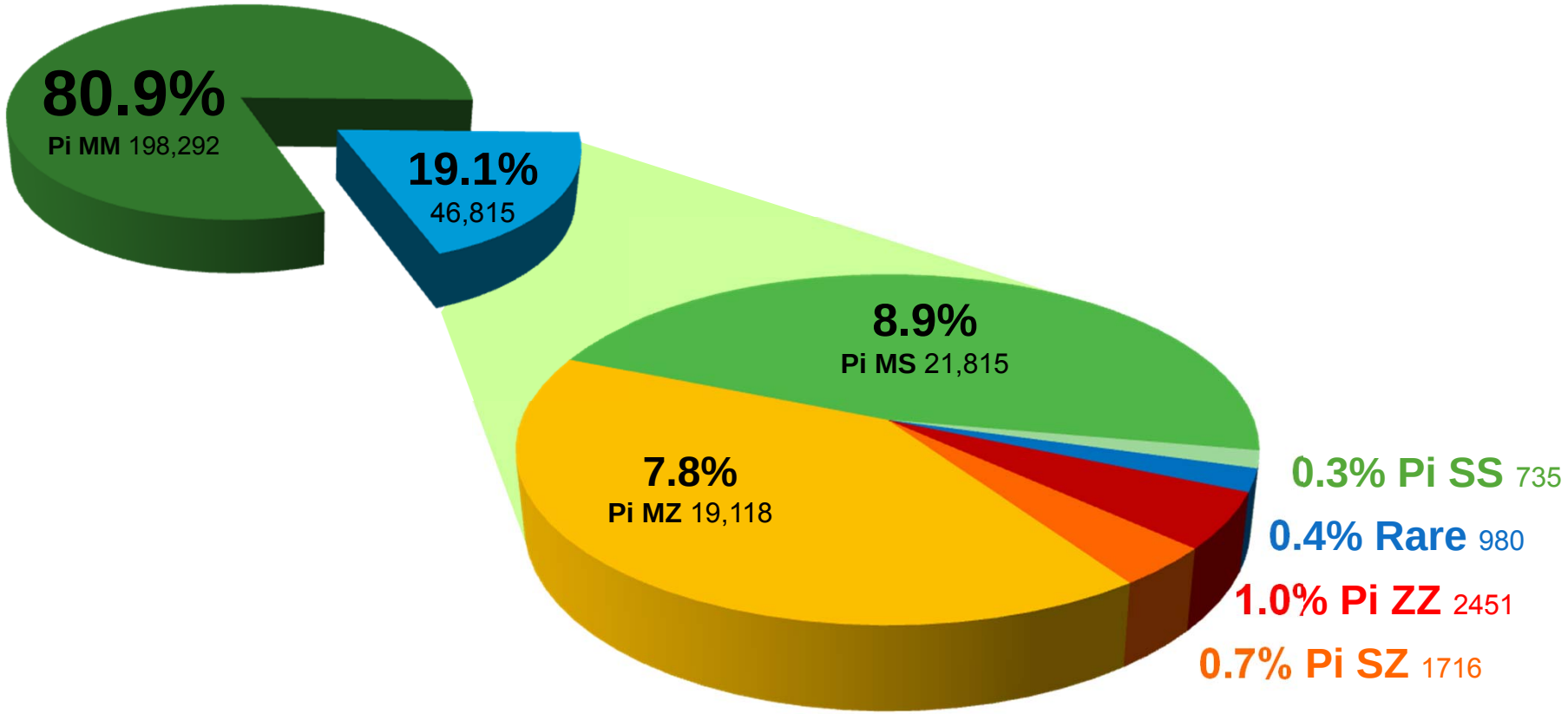
PROLASTIN®-C (alpha$_1$-proteinase inhibitor [human]) is indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe deficiency of alpha$_1$-proteinase inhibitor (alpha$_1$-antitrypsin deficiency). The effect of augmentation therapy with any alpha$_1$-proteinase inhibitor (alpha$_1$-PI), including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in alpha$_1$-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.

COPD, chronic obstructive pulmonary disease.

What is alpha-1? Alpha-1 Foundation website. Available at: www.alphaone.org/healthcare/?c=01-What-is-Alpha-1-Healthcare. Accessed April 13, 2008.

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.

Are You Overlooking Alpha-1?

- 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

Koura F. Poster presented at: American Thoracic Society International Conference; May 18-23, 2012; San Francisco, CA.

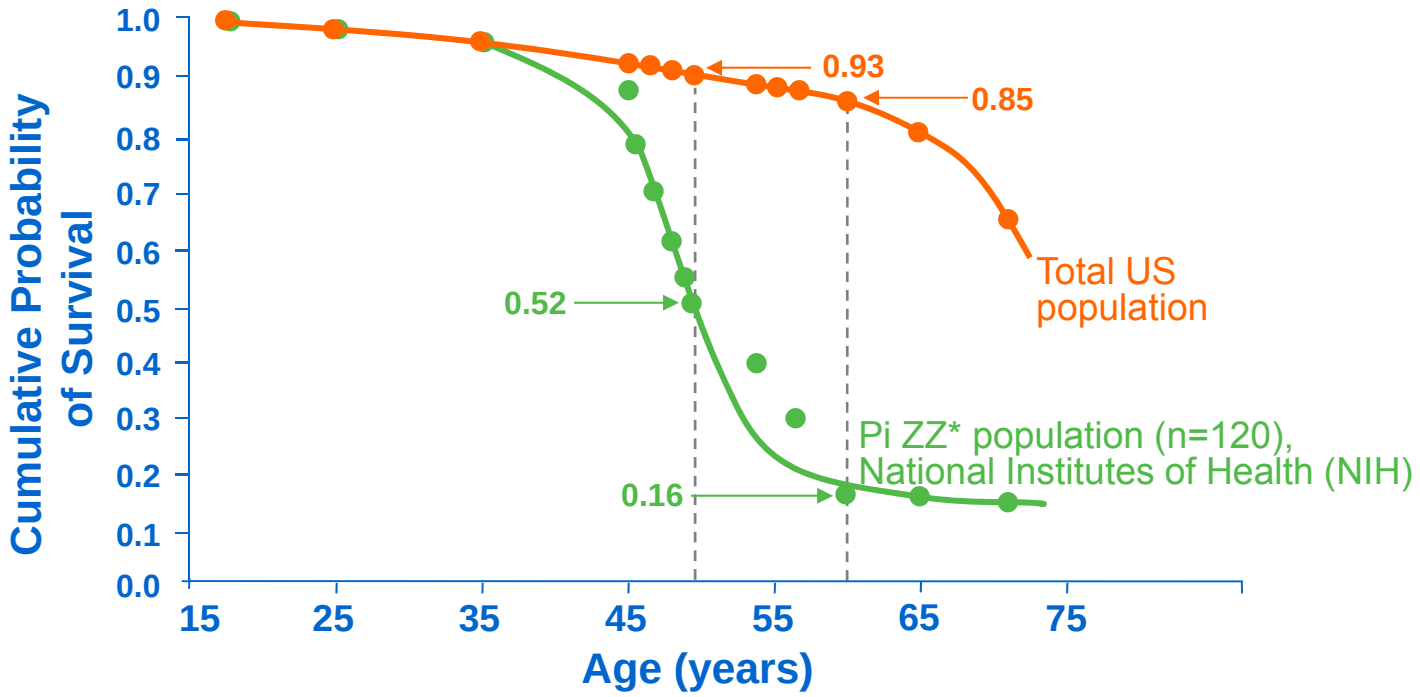
Results: Higher Regional Prevalence of Non-MM Genotypes vs US Population

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

Koura F. Poster presented at: American Thoracic Society International Conference; May 18-23, 2012; San Francisco, CA.

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.

Brantly ML, et al. *Am Rev Respir Dis*. 1988; 138(2):327-336. Official Journal of the American Thoracic Society. Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society.

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.

Campos MA, et al. *Chest*. 2005;128(3):1179-1186.

American Thoracic Society Guidelines Recommend Testing ALL Symptomatic COPD Patients

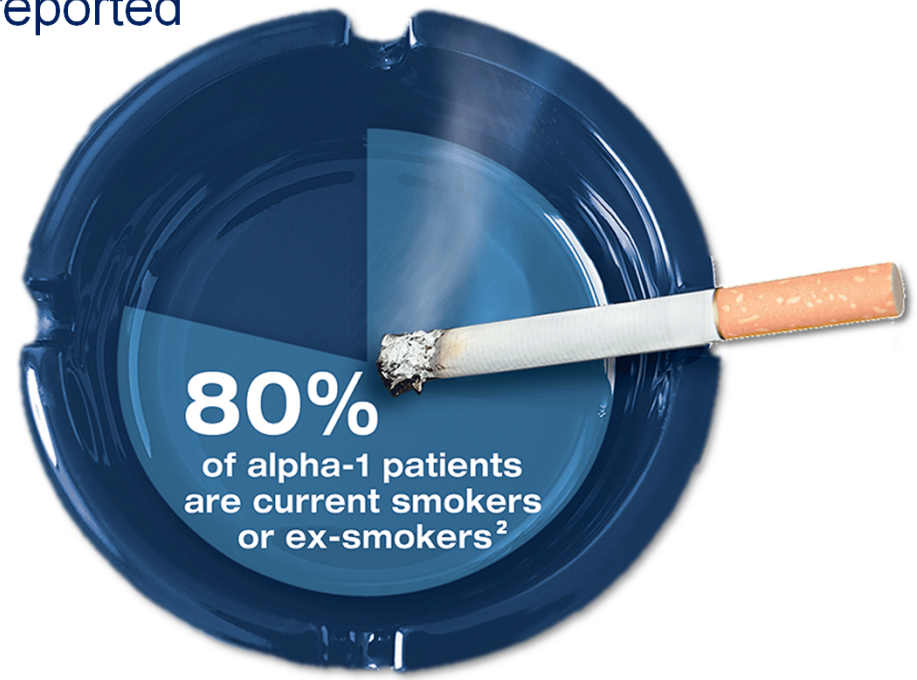
The American Thoracic Society Guidelines
• Test all adults with symptomatic COPD, **regardless of smoking history**
• Test all adults with symptomatic emphysema, **regardless of smoking history**
• Test all adults with symptomatic asthma whose airflow obstruction is incompletely reversible after bronchodilator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

COPD, chronic obstructive pulmonary disease.

American Thoracic Society/European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168(7):818-900.

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]

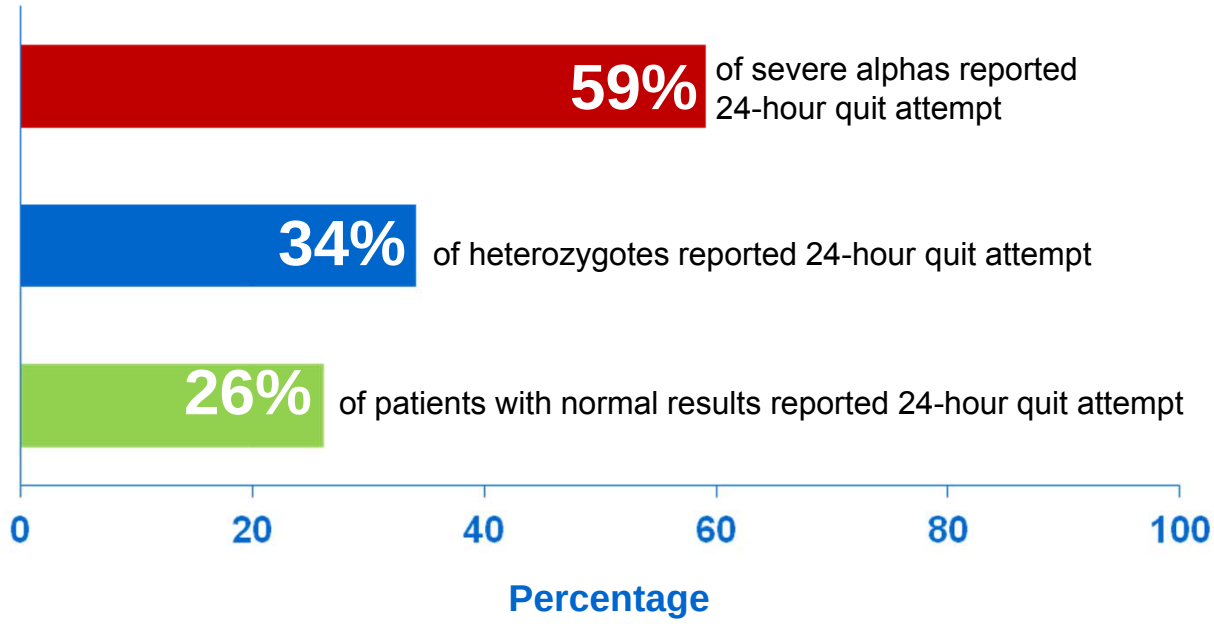


COPD, chronic obstructive pulmonary disease.

1. Løkke A, et al. *Thorax.* 2006:61(11):935-939. 2. The Alpha-1-Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med.* 1998;158(1):49-59.
3. Campos MA, et al. *COPD.* 2009;6(1):31-40.

Testing Improved Quit-Attempt Rates

Follow-up Study of Patients 3 Months After Test Results and Minimal Counseling (n=199)



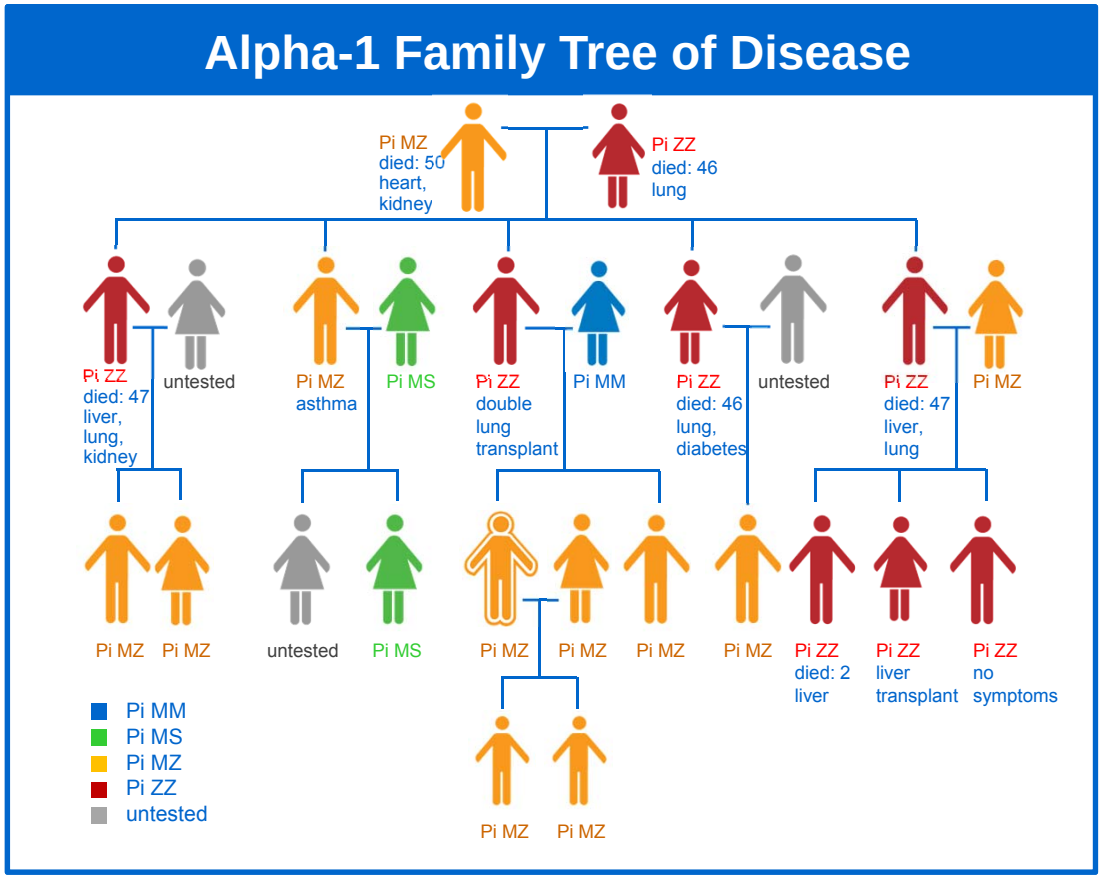
Carpenter MJ, et al. *Ann Behav Med.* 2007;33(1):22-28.

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[1]**
- Increases potential for family testing and genetic counseling
- Raises awareness to avoid hazards of occupational respiratory pollutants

1. Carpenter MJ, et al. *Ann Behav Med.* 2007;33(1):22-28.

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

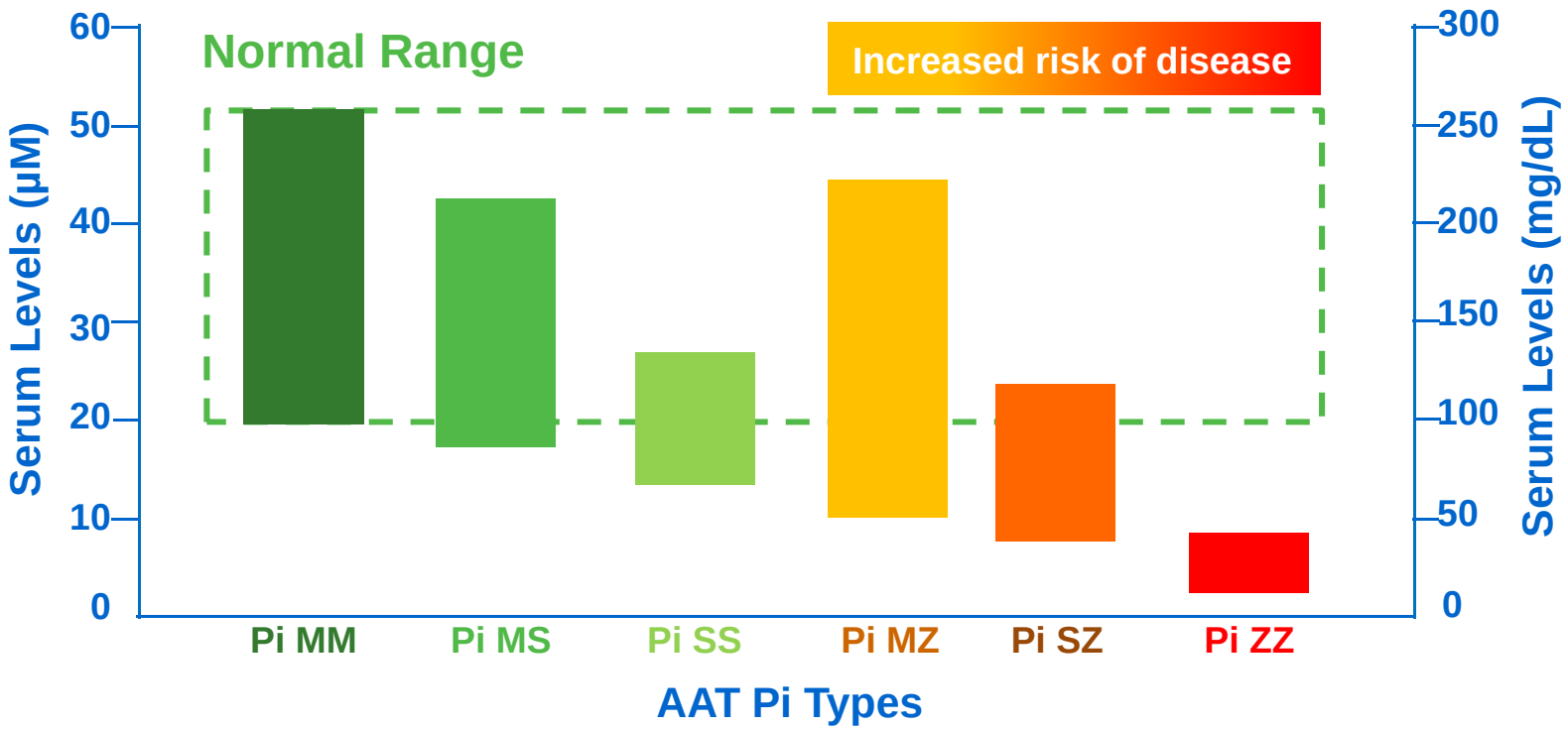


You're not just identifying a patient, you're discovering an entire family at risk for lung disease

Data on file, Grifols.

Serum Level Alone Is NOT a Complete Diagnostic Tool

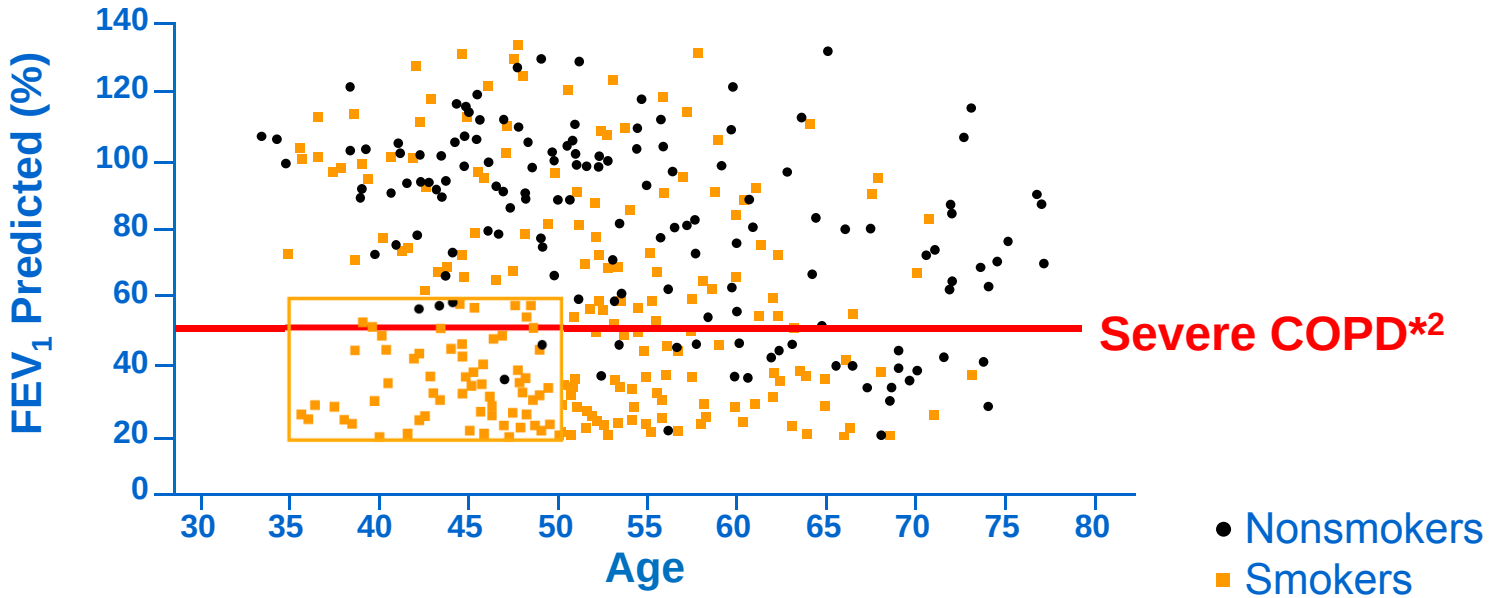
Range of Serum AAT Levels by Phenotype (µM)



AAT, alpha$_1$-antitrypsin.
Data on file, Grifols.

Who Do You Test and Who Are You Missing?

FEV_1 Percentage Predicted by Age for 378 Pi ZZ Patients Stratified by Smoking Status[1]



* Stage III severe COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

Remember, only a laboratory test can confirm the presence of alpha-1

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second.

1. DeMeo DL, et al. *Thorax.* 2007;62(9):806-813. Image copyright 2007, BMJ Publishing Group Ltd. Reproduced with permission from BMJ Publishing Group Ltd.
2. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease—Updated 2014.* Available at: www.goldcopd.org. Accessed July 7, 2014.

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?

After the Diagnosis: Breaking the News

- 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 beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta$_2$-agonist.

Connie: Would You Test a 76-Year-Old? (cont.)

- 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.

Connie: Case Resolution (cont.)

- 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 beta$_2$-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_1 70% of predicted
  - FEV_1/FVC ratio 62% of predicted

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

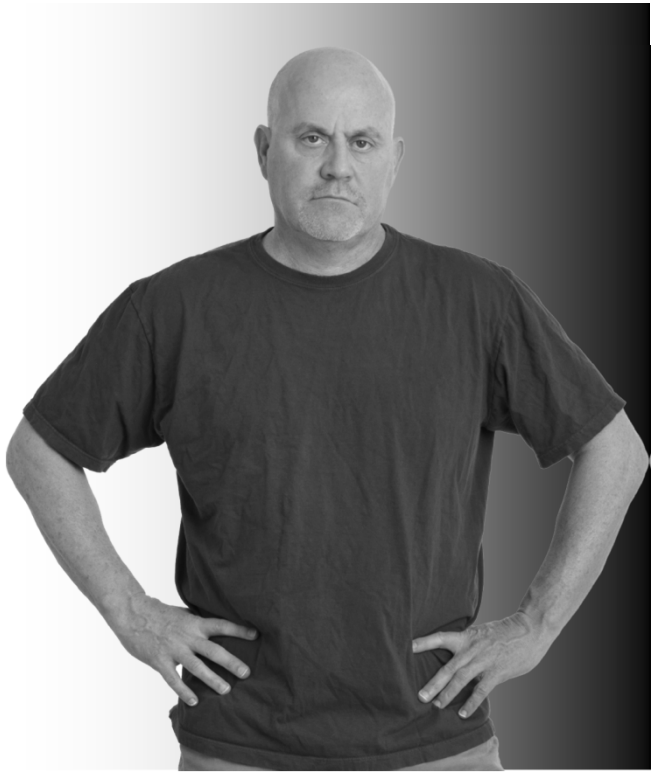
Robert:
Would You Test If Lung Function Stable? (cont.)

- 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.

Robert: Case Resolution

- 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

American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168(7):818-900.

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.

1. British Thoracic Society. *Thorax.* 2001;56(11):827-834. 2. American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168(7):818-900. 3. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease—Updated 2014.* Available at: www.goldcopd.org. Accessed July 7, 2014.

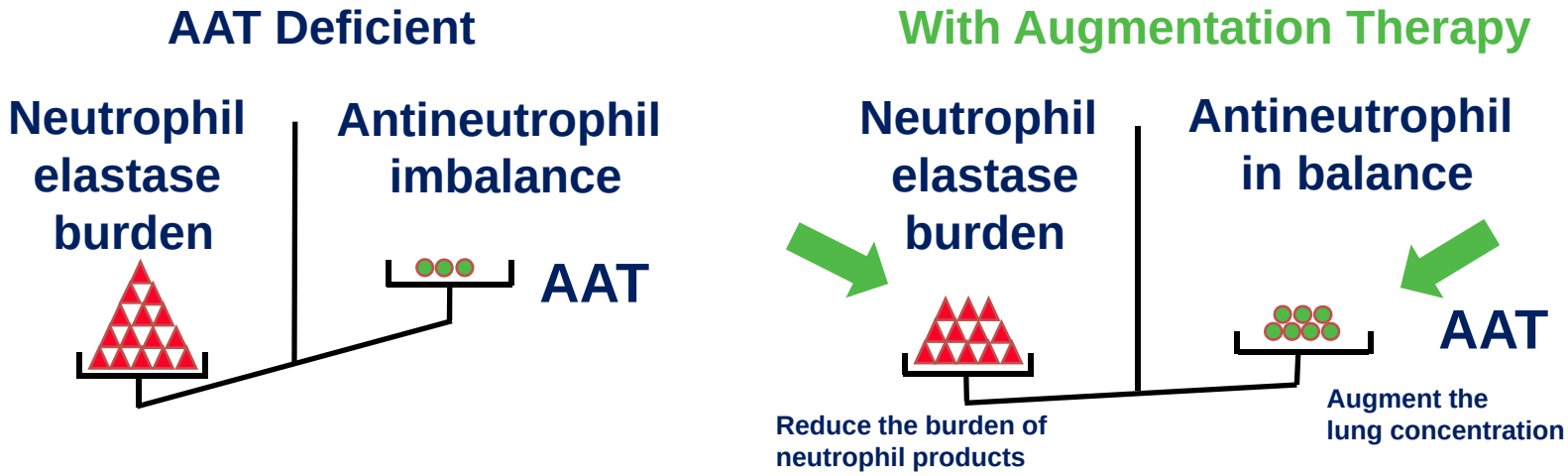
Management Approaches for Patients With Severe Alpha-1

- 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

American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168(7):818-900.

Once You've Identified an Alpha-1 Patient, There Is a Specific Treatment

Treatment of Alpha-1



AAT, alpha$_1$-antitrypsin.

Role of Augmentation Therapy in Patients With Severe Alpha-1

- Specific treatment by infusion of alpha$_1$-antitrypsin purified from pooled human plasma[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$_1$-deficient individuals[2]
  - AAT serum trough levels remained >11 μM[3]
- Goal of therapy:
  - Elevate levels of alpha$_1$-antitrypsin in plasma and lung interstium[1,2]

PROLASTIN®-C (alpha$_1$-proteinase inhibitor [human]) is indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe deficiency of alpha$_1$-proteinase inhibitor (alpha$_1$-antitrypsin deficiency). The effect of augmentation therapy with any alpha$_1$-proteinase inhibitor (alpha$_1$-PI), including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in alpha$_1$-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.

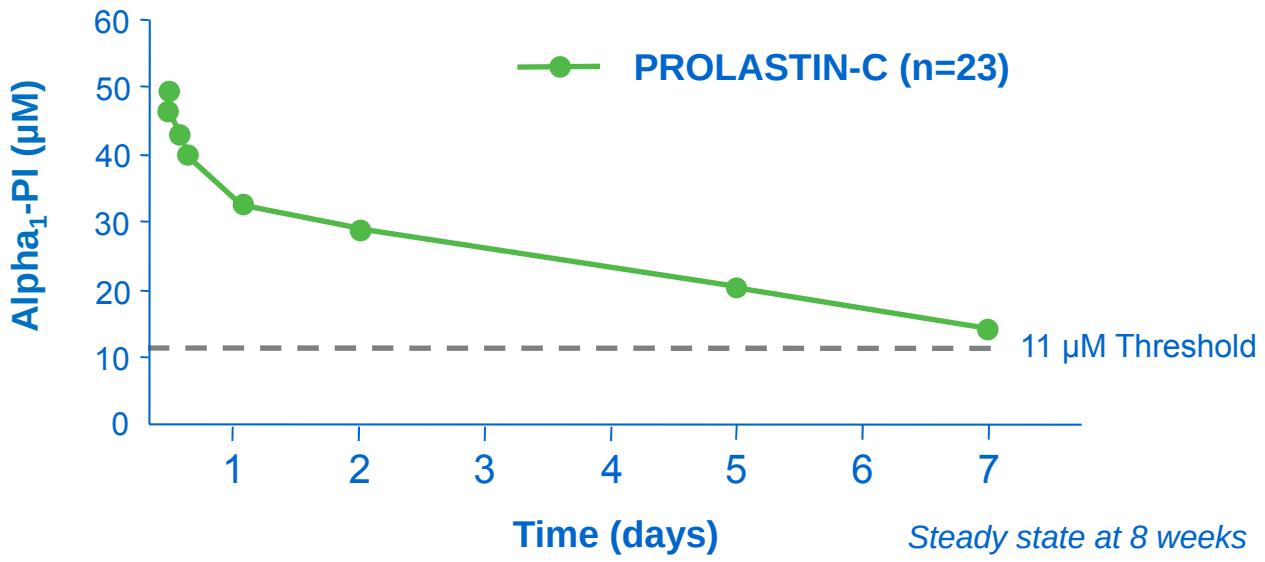
Please see Important Safety Information within this presentation and accompanying PROLASTIN-C full Prescribing Information for complete prescribing details.

AAT, alpha$_1$-antitrypsin.

1. Stoller JK, Aboussouan LS. *Lancet.* 2005;365(9478):2225-2236. 2. American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168(7):818-900. 2. Wewers MD, et al. *N Engl J Med.* 1987;316(17):1055-1062.

PROLASTIN®-C (alpha$_1$-proteinase inhibitor [human]) Effectively Raises Alpha-1 Levels

Mean Plasma AAT Concentration vs Time Following Treatment With PROLASTIN®-C



The effect of augmentation therapy with any alpha$_1$-proteinase inhibitor (alpha$_1$-PI), including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in alpha$_1$-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$_1$-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:
  - FEV_1 43% of predicted
  - FEV_1/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.

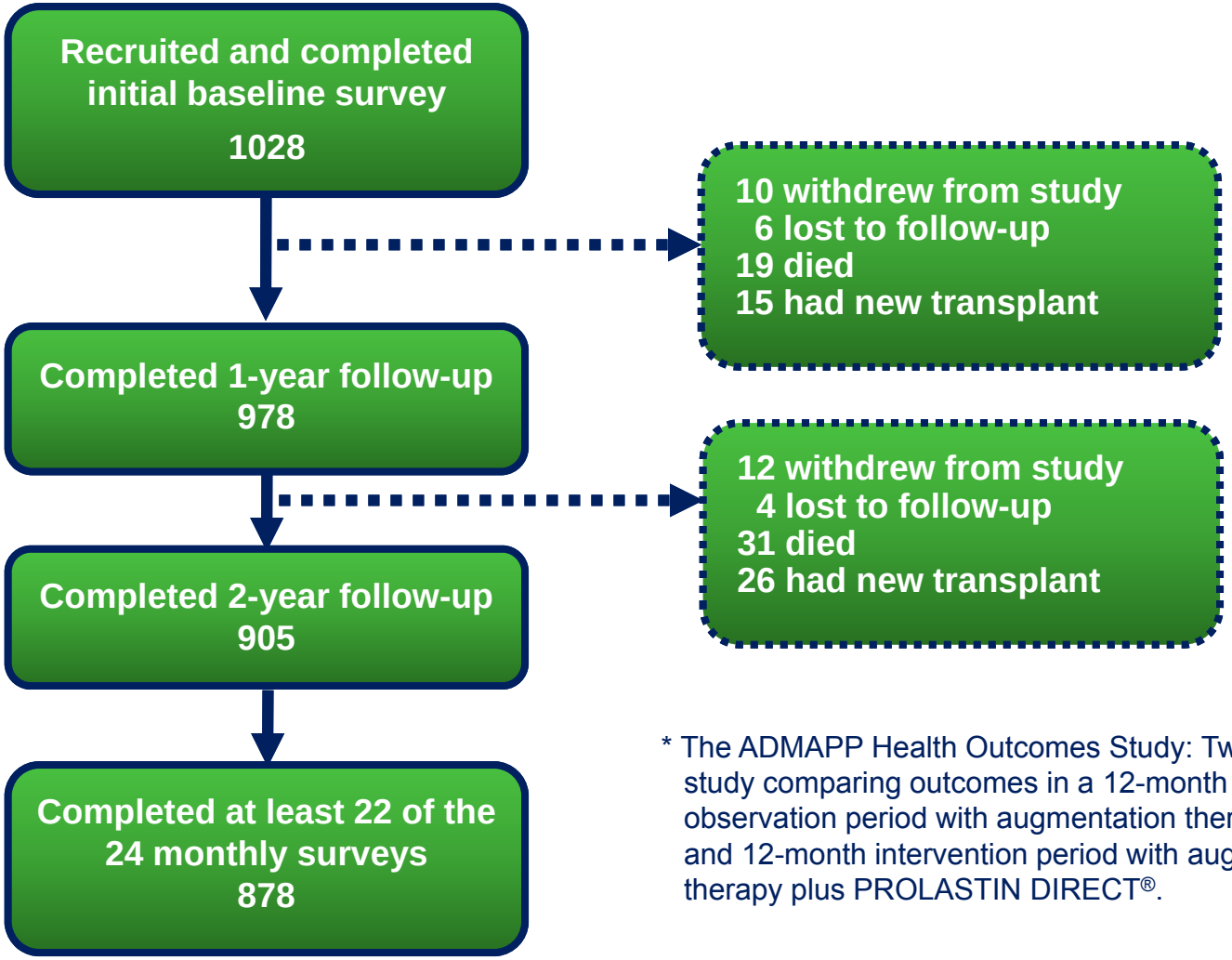
Byron: Case Resolution

- 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



* 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®.

ADMAPP, Alpha-1 Disease Management and Prevention Program.

ADMAPP* Results: PROVEN
Alpha-1 Health Management Benefits

Significant Improvements in Health Outcomes After Intervention Year (n=878)*		
↓	**10%** reduction in COPD exacerbations	*P*<0.001
↓	**12%** reduction in unscheduled physician visits	*P*=0.03
↓	**21%** reduction in emergency room visits	*P*=0.02

- 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®.

ADMAPP, Alpha-1 Disease Management and Prevention Program.
Campos MA, et al. *COPD.* 2009;6(1):31-40.

Summary: Uncovering Alpha-1

- Alpha-1 is not a rare disease but one that is rarely diagnosed[1]
  - Up to 25 million Americans have an abnormal allele (S or Z)[2]
  - An estimated 100,000 in the US are AAT deficient[3]
  - 90% remain undiagnosed[4,5]
  - Lengthy delay in diagnosis[3]
    - 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.

1. de Serres FJ. *Environ Health Perspect.* 2003;111(16):1851-1854. 2. de Serres FJ, et al. *Clin Genet*. 2003;64(5):382-397. 3. Campos MA, et al. *Chest.* 2005;128(3):1179-1186. 4. Silverman EK, Sandhaus RA. *N Engl J Med.* 2009;360(26):2749-2757. 5. About AAT deficiency. http://www.alpha1health.com/healthcare-professionals/about-aat-deficiency/. Accessed February 15, 2013.

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