Alpha-1 Antitrypsin Deficiency

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Conflicts of Interest

Company	Research	Consultant	Honorarium	Grant
Biocryst	x	x		
CSL Behring	x	x	x	x
Grifols	x		x	
Takeda	x		x	x
HAE-A		Advisory Board		
Alpha-1 Foundation				PSU Center

Objectives

- **Recognize** the many ways Alpha-1 Antitrypsin Deficiency (Alpha-1) presents
- **Improve** your understanding of the disease
- **Increase** screening for alpha-1
- **Examine** the data supporting augmentation therapy and how to manage alpha-1 patients

“Chance favors
the prepared mind”

Louis Pasteur - 1854

History of AAT

- 1962: Dr. Carl-Bertil Laurell (1919-2001) at the University of Lund, Sweden discovered the absence of the alpha-1 band in 2 serum electrophoresis gels.

- Further investigation by Dr. Sten Eriksson demonstrated 4 more.

- 4 of the 6 patients had emphysema.

Laurell and Eriksson,1963

What is the normal genotype for alpha-1 protein?

- 1. SS
- 2. ZZ
- 3. Null-Null
- 4. MM
- 5. FF

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Normal AAT Protein

- Normal AAT protein phenotype “M”
- 95% is made in the liver
- Main function is to neutralize/control neutrophil elastase, a potent proteolytic enzyme able to damage the elastin matrix of the lung.
- Autosomal Co-dominant inheritance

Alpha-1-antitrypsin – Z Protein

- PiZ results from a point mutation that encodes a single Amino Acid substitution. Glutamate (+) replaces Lysine (-)
- Z protein misfolds/polymerizes & accumulates in the liver
- Low secretion results in "deficient" serum level.
- Z phenotype accounts for 95% of clinical illness.

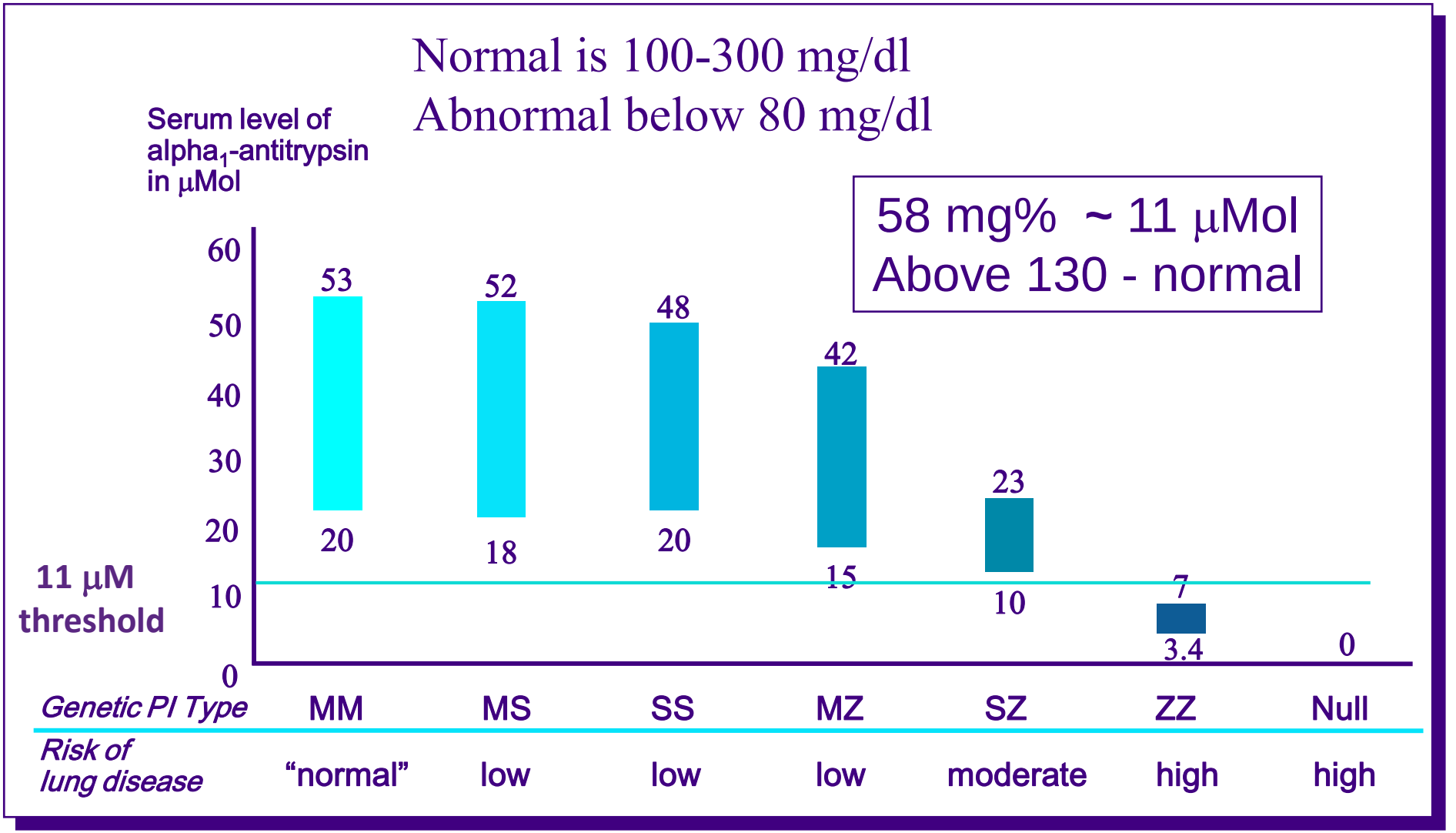
Carrell and Lomas, 2002

Other Deficient Variants

- S allele :
  - Variant is associated with milder deficiency
  - Not associated with AAT accumulation within hepatocyte
- Null allele – No AAT production
  - Zero serum level
  - Earlier lung but no liver disease
- More than 100 other rare mutations exist

De Serres, 2002 and 2007

Inheritance – Diagnostic Levels



How common is severe AATD?

- 1. 11,000 people in the USA
- 2. 110,000 people in the USA
- 3. 1.1 million people in the USA
- 4. Very rare disease effecting about 1000 people in the USA

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Population Screening Studies

- 200,000 neonates screened in Sweden
  - Pi*ZZ in 127, or 1 in 1575
- 20,000 blood donors tested in St. Louis
  - Pi*ZZ : 1 in 2857
- 965 consecutive emphysema patients
  - 2-3% were Pi*ZZ
  - 8% were Pi*MZ

Sveger, 1976; Silverman et al, 1989; ATS/ERS AATD Standards, 2003

Prevalence of Alpha-1

- The most prevalent potentially fatal genetic disorder of adult Caucasians in the United States.
  - An estimated 25 million individuals carry deficient genes
  - Over 110,000 Americans have severe Alpha-1 deficiency
  - Less than 10% are diagnosed

Stoller et al, 2005

Comparison of PI*ZZ Prevalence

Disorder	Prevalence
AAT deficiency (PI*ZZ)	Over 100,000
Cystic Fibrosis	30,000
Huntington's Disease	30,000
Spina Bifida	166,000
Idiopathic Pulmonary Fibrosis	128,000
Testicular Cancer	196,000
Ovarian Cancer	177,000
Hodgkin's Lymphoma	164,000
Cervical Cancer	243,884

Clinical Presentation of Alpha-1

How do you identify AATD?

- 1. Xray
- 2. CT scan
- 3. History
- 4. Spirometry
- 5. Physical

How do you identify AATD?

- 1. Xray
- 2. CT scan
- 3. History
- 4. Spirometry
- 5. Physical

- None of the above

Clinical History and Spirometry

- Results from 2 patient registries regarding prior diagnosis before Alpha-1:
  - 54% had emphysema
    - The mean FEV_1 among 1129 participants in the NHLBI registry was 43% of predicted with a mean age of 45.
  - 72% had respiratory symptoms
    - Dyspnea started as early as 32 years of age
  - 42-46% with chronic bronchitis
  - 35% had a diagnosis of asthma.
    - 30% of NHLBI patients had FEV_1 reversibility when tested with spirometry.
- **Clinical presentation or spirometry does NOT ID AATD!**

NIH-AATD Registry Group, 1998; Silverman and Sandhaus, 2009, Campos et al, 2005

Radiology

- A review of chest radiographs from 165 consecutive ZZ alpha patients:
  - 15% were normal
  - Only 20% showed the "classic" finding of emphysema at the bases
- A review of 102 CTs of ZZ alpha patients
  - 64% showed basal predominance
  - 36% had predominant apical disease
- HRCT often finds bronchitis and bronchiectasis

Chest x-rays and CT scans can NOT identify AATD.

Yamashiro et al, 2009

Radiographic Presentation of Alpha-1 Is Variable

Basilar-Predominant Panacinar Emphysema

Upper Lobe–Predominant Emphysema

Bronchiectasis

Absence of Pathophysiology

Why do those with Alpha-1 deficiency get Lung Disease?

Why do those with Alpha-1 deficiency get Lung Disease?

- Uncontrolled proteolytic attack on lung tissue because of low circulating levels of AAT.
- The Z protein is less effective at inhibiting neutrophil elastase than the M protein.
- Cigarette smoke can inactivate the patient's own AAT in the lungs.
- Normal AAT levels function to suppress inflammatory chemoattraction.
- Z protein acts as a chemotactin

When does the average person who is ZZ develop lung disease?

- 1. at 20 years
- 2. at 30 years
- 3. at 40 years
- 4. at 50 years
- 5. at 60 years

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- 3. at 40 years
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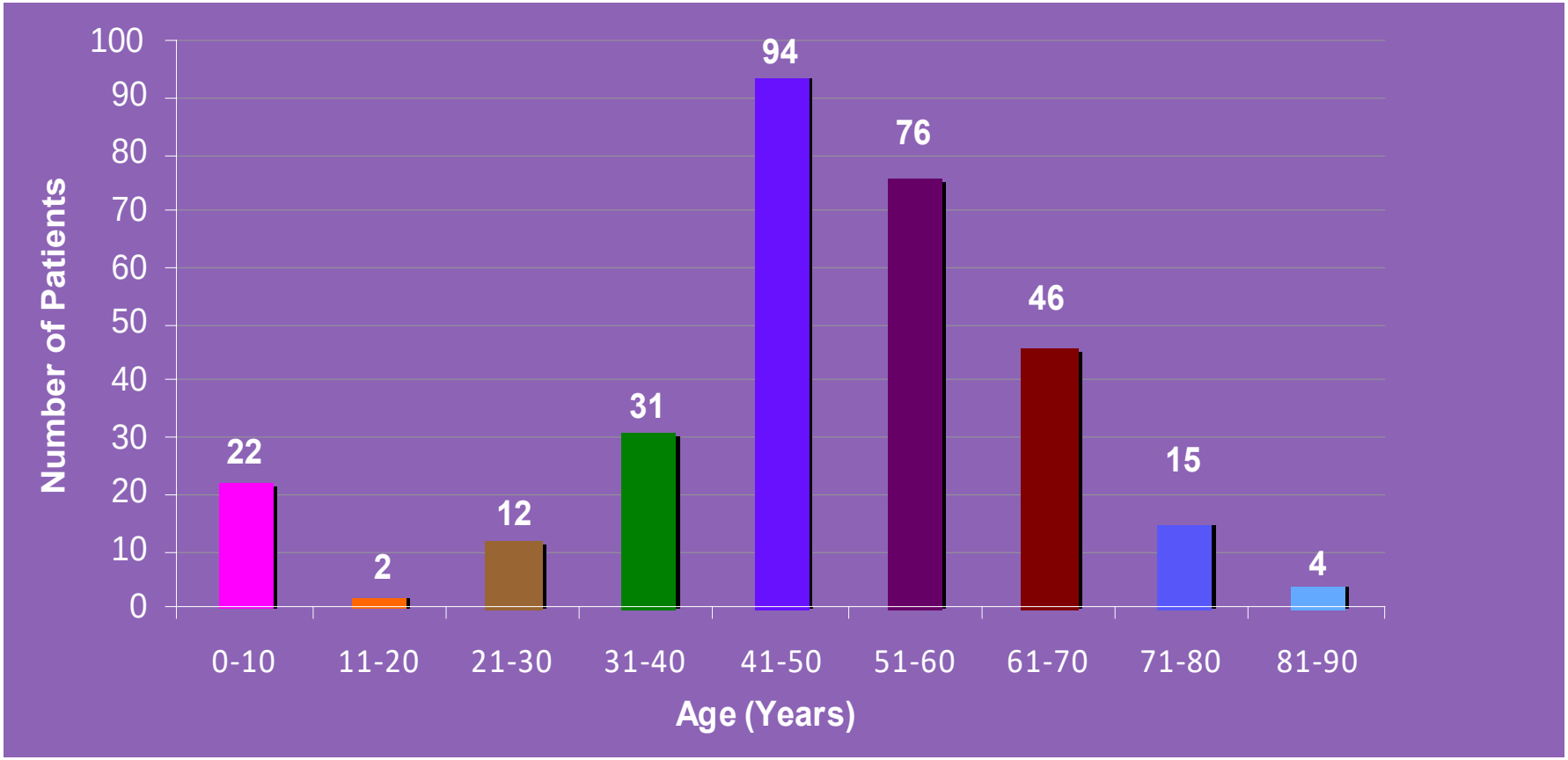
- It depends, but as young as 32 years

Average Age at Diagnosis



Based on 302 patients with PiZZ out of 26,520 patients tested.
M Brantly, U of Florida

Missed Clinical Recognition

- Average Alpha-1 patient has symptoms for 7.2 to 8.3 years before diagnosis is made.

- 44% of Alpha-1 patients see at least 3 doctors (PCP or specialist) before a diagnosis is made.

Campos et al, 2009

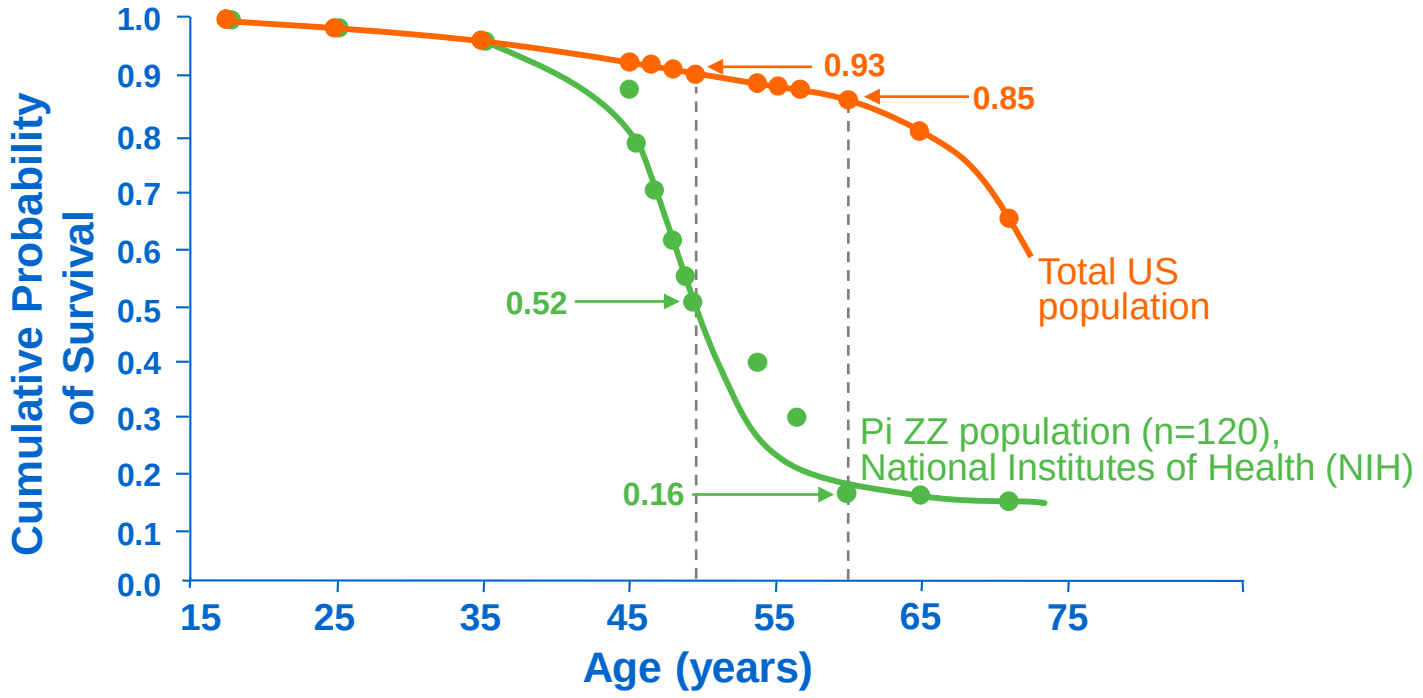
AATD and Survival

- Median survival in Danish population with AATD = 54 years (49 years for probands)
- No augmentation therapy use in Danish with AATD
- In non-smokers lung disease often develops after age 50
- ATTD plus tobacco can lead to 60 to 315 cc of FEV-1 loss per year

Seersholm et al, 1995

Patients With Alpha-1 Pi ZZ Have Significantly Shorter Life Spans

Survival Analysis of Patients With Alpha-1 Pi ZZ vs Total US Population prior to augmentation



Alpha-1 Liver Disease

When does AATD liver disease first present?

- 1. age 6 to 10 yo
- 2. during adolescences
- 3. Not until adulthood
- 4. Rarely affects people with AATD
- 5. In early childhood

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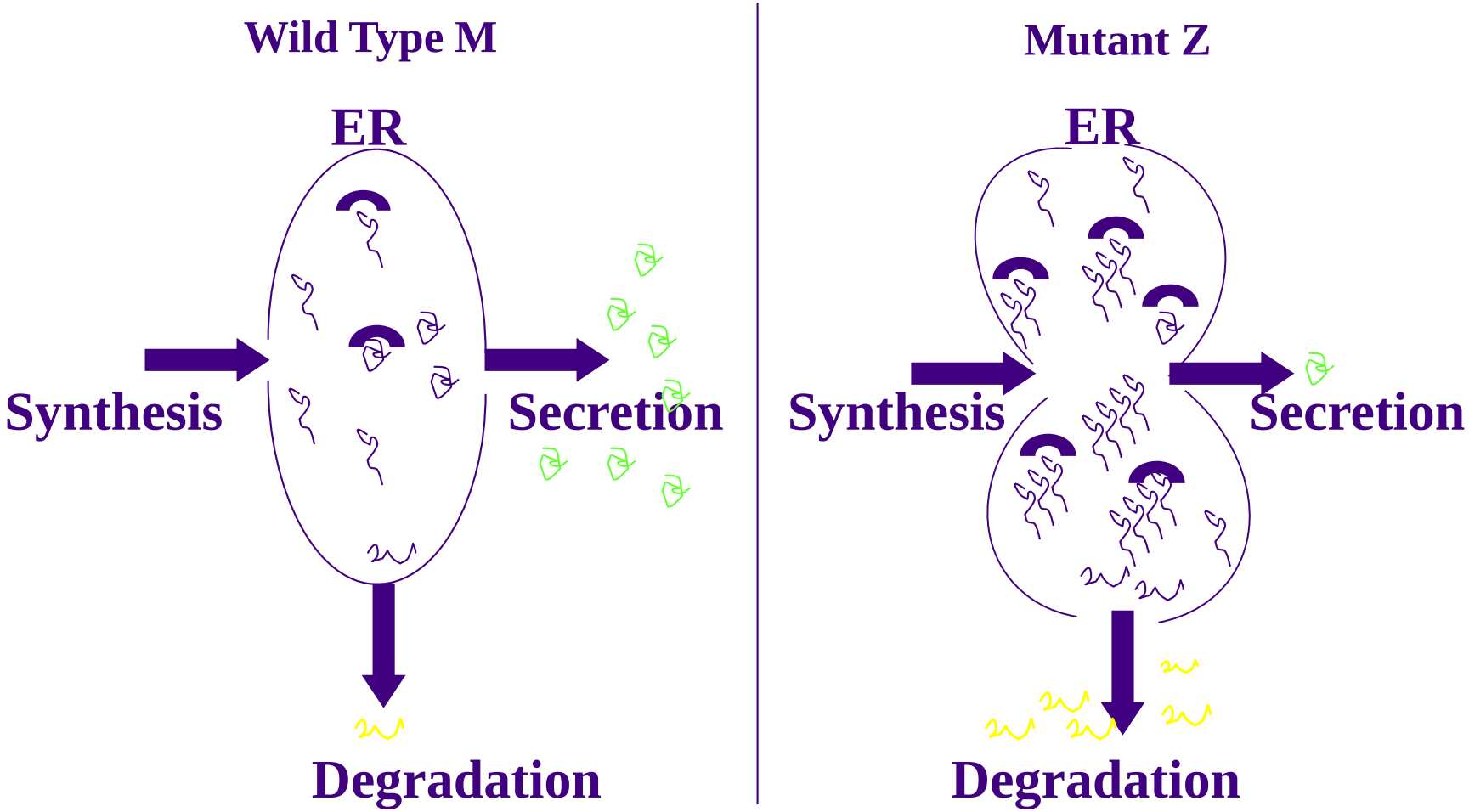
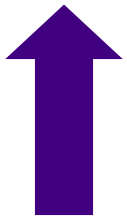
AAT Protein Processing



Proteasomal and autophagic degradative pathways may govern hepatic risk

Human ZZ Liver



PAS + intracellular inclusions are polymerized AAT ‘Z’

Highly Variable Hepatic Risk

- Risk of *life threatening* liver disease in childhood is about 5%.
  - 2nd most common reason for liver transplant
- Risk of *any* liver disease or dysfunction in childhood is 15-50% (depends on testing).
- The *majority* of ZZ infants with problems at birth are well by age 18y.
- Significant, but possibly silent liver disease in older adults likely over 50%.

Eriksson, 1985 and 1987

Liver Management

- Regular contact with a doctor who is familiar with alpha-1 liver disease.

- A combination of asking about new symptoms, physical examination monitoring, blood tests, education on obesity, alcohol and liver toxic medications, x-ray/ultrasound exams

- vaccines (hep A and B).

Nelson et al, 2012

Treatment

- There are no specific treatments to prevent alpha-1 liver damage.
- There are effective treatments used for liver disease in general.
- Liver transplantation : trading one disease for another?
- Augmentation therapy has no effect on liver disease.

Liver Management

- Avoid or limit alcohol:
  Controversially means less than one drink per day.
- Avoid obesity (fatty liver disease).
- Occasional Tylenol in ordinary doses.
- NSAIDS may have potential to increase hepatic injury. (experimental data)
- Consider hepatitis vaccination

Evolving therapies

(Mitchell EL, Curr Pathobiol Rep. 2017;5;243-252)

- Caperones: phenylbutyrate
- Autophagy-Enchancing Agents: rapamycin, carbamazepine, tamoxifen, fluphenazine
- Bile Acids: ursodeoxycholic acid
- Polymerization Inhibitors: monoclonal antibodies
- Gene Transfer: knockdown of the Z protein and express the “wild type” protein
- Somatic Stem Cells: mesenchymal or bone-marrow derived

Pearls

- Liver biopsy not required for *diagnosis.*
- Patients with cirrhosis may remain stable *without* transplantation for 10y or more.
- The majority of ZZ children will do well with minimal intervention.
- Genetic and environmental disease modifiers are likely important, but poorly understood.
- Typical liver disease supportive care or transplant are the only recommended therapies at this time.

Time to Test

Who should be tested for AATD?

Who Should Be Tested?

- All subjects with COPD or unexplained bronchiectasis regardless of smoking Hx
- All adults with asthma characterized by incompletely reversible airflow
- Subjects with unexplained chronic liver disease
- Necrotizing panniculitis (1 in 1000 ZZ)
- Anti-proteinase 3-positive vasculitis (C-ANCA-positive vasculitis)
  - 5.6 to 17.6% of c-ANCA+ individuals are ZZ

ATS/ERS AATD Standards, 2003

Lab Testing

- Serum blood test that measures the concentration of circulating AAT- 'levels'
  - An acute phase reactant
  - Heterozygous/normal overlap but
  - Not between ZZ and normal levels
- "Phenotyping" or Pi-typing of the protein
  - Determine whether the patient is a carrier of the deficiency or homozygous
  - Done by isoelectric focus gel analysis
- Genotyping
  - DNA testing that determines the Pi genes from extracted DNA

Stoller and Brantly, 2013

Testing for Alpha-1

- Testing for AAT levels and genotype via a single finger-stick of blood was done in the past, but uptake was poor

- Now genotyping is done by only 1 company via mouth sponge

- Can be mailed into a central lab

So you found an Alpha.

Now What ?!?!?

How would you treat AATD?

Treatment Options

- Standard Therapies in COPD Treatment
  - Smoking cessation
  - Pulmonary Rehab
  - Bronchodilators (rescue/LABA/LAMA)
  - Inhaled steroids
  - Oxygen
  - Lung/Liver transplant
- Management/Evaluation of Liver disease
- Augmentation Therapy
- Vaccines (flu, Pneumococcal, Prevnar, Hep A and B)

Quit Smoking!

Augmentation Therapy

- Augmentation therapy is
  used to increase serum
  and lung epithelial lining
  fluid levels of AAT

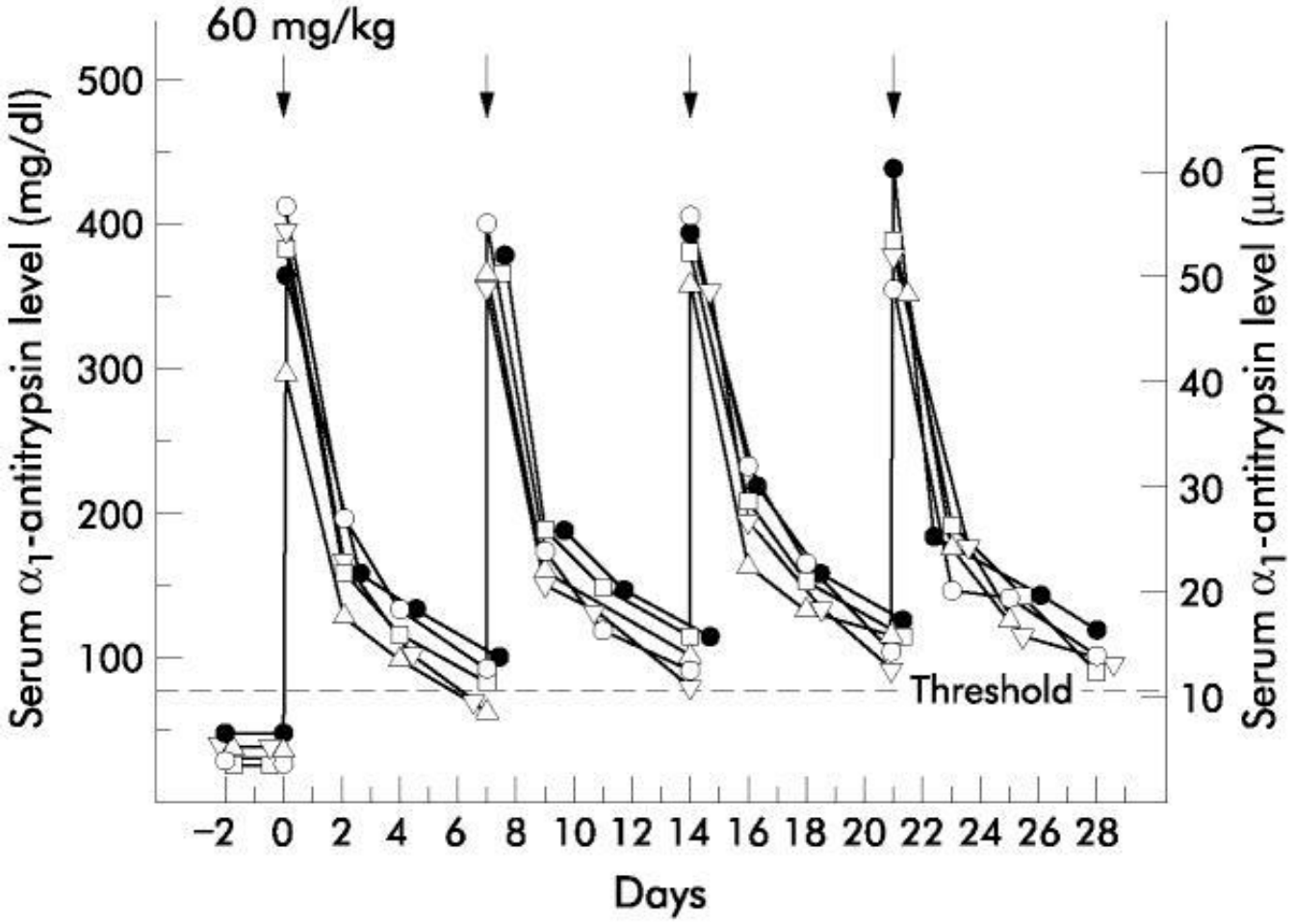
- Plasma derived treatment for adults with severe AATD and emphysema

- Cost is over 100,000 USD a year

Augmentation Therapy

- Augmentation therapy was first approved 30 years ago.
- Five approved drugs – Aralast, Glassia, Prolastin, Prolastin- C, Zemaira
- Original approval based on pharmacokinetic and biochemical data.
- Subsequent approval same criteria.
- None based on therapeutic efficacy.

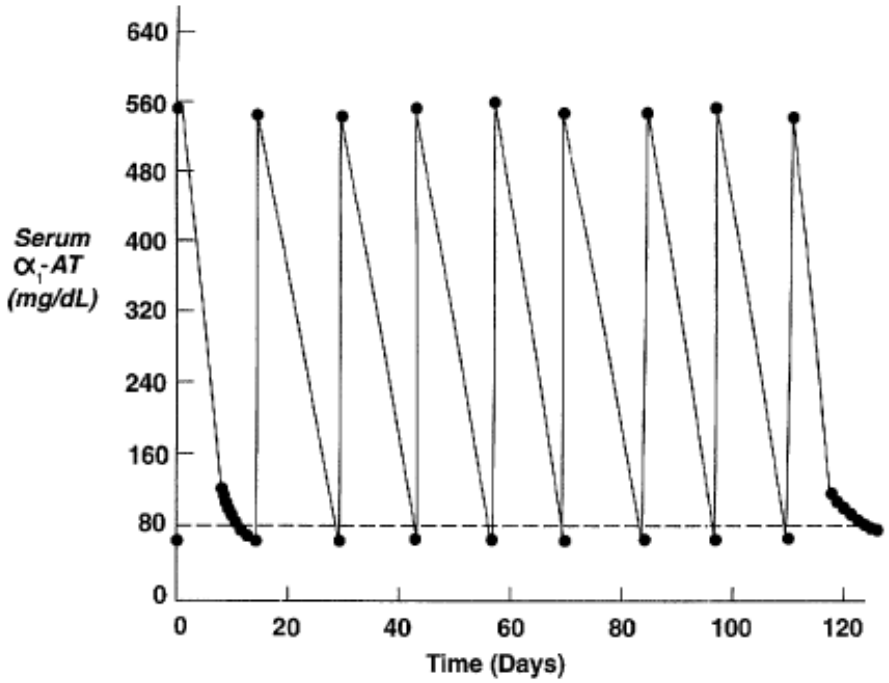
Why Augmentation Therapy?



Wewers, 1987

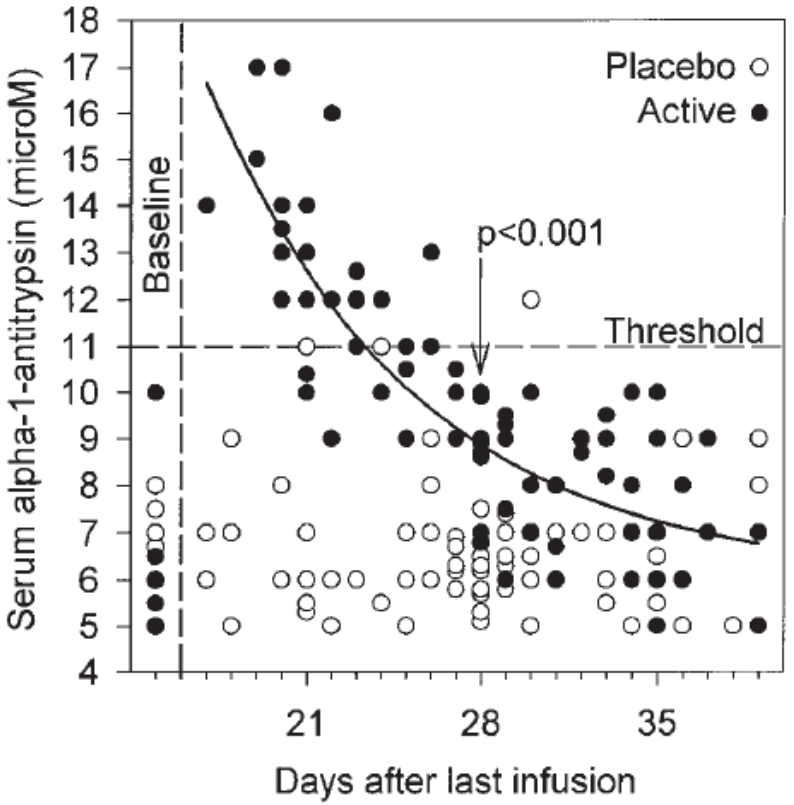
Importance of Weekly Dosing

AAT Serum Levels During Biweekly Infusions



*N=22 Day 1-28; N=21 Day 29-end

AAT Serum Levels During Monthly Infusions



Soy at al, 2006

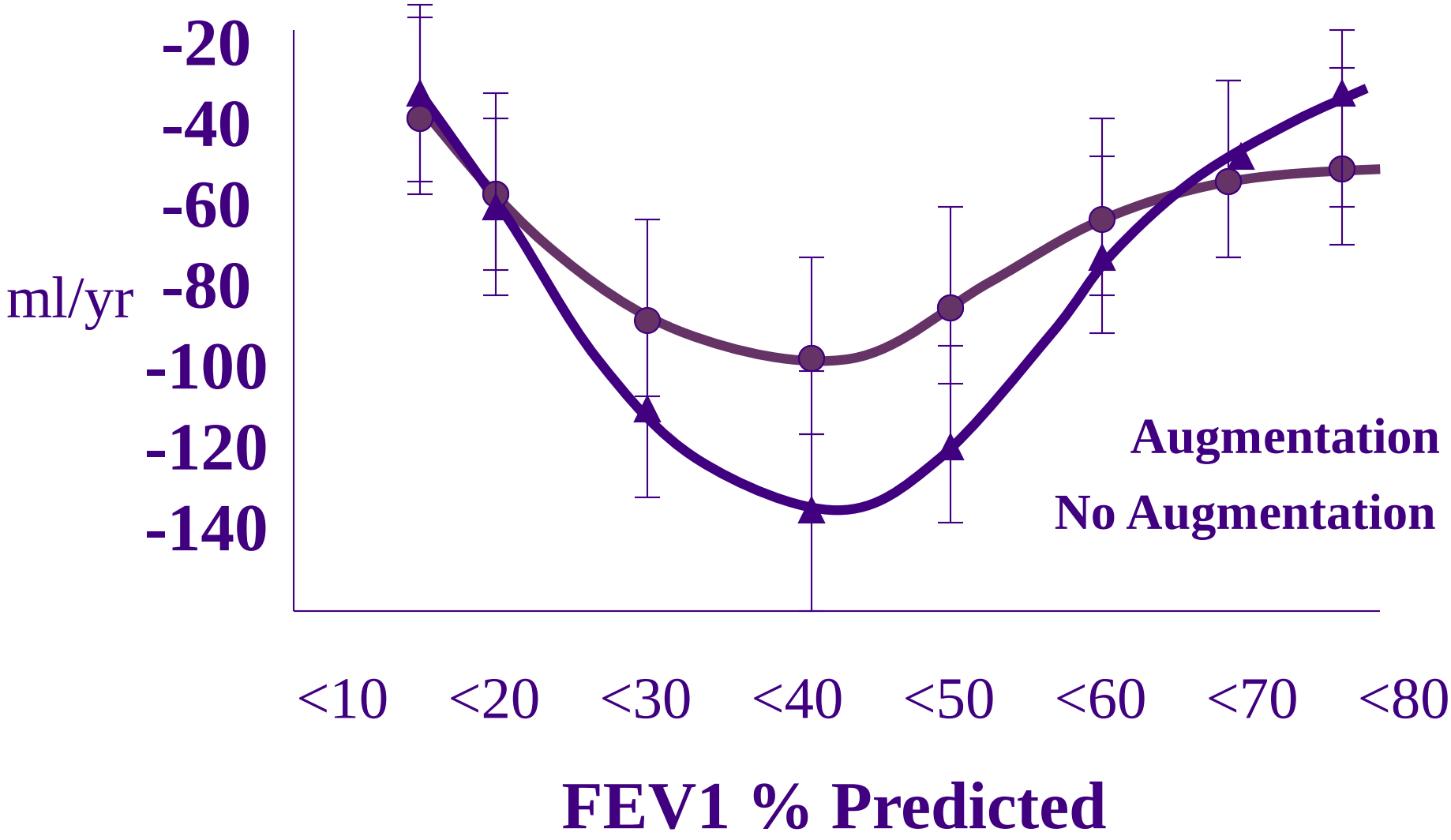
Does Augmentation Clinically Work?

US NHLBI Registry ‘87-95

- Prospective, non-controlled, non-randomized
- Comparison of lung function and mortality in treated versus untreated patients
- Inclusion criteria - AAT level $\leq 11\mu M$
- n : 277 treated vs 650 untreated

NIH-AATD Registry Group, 1998

Mean FEV1 Decline



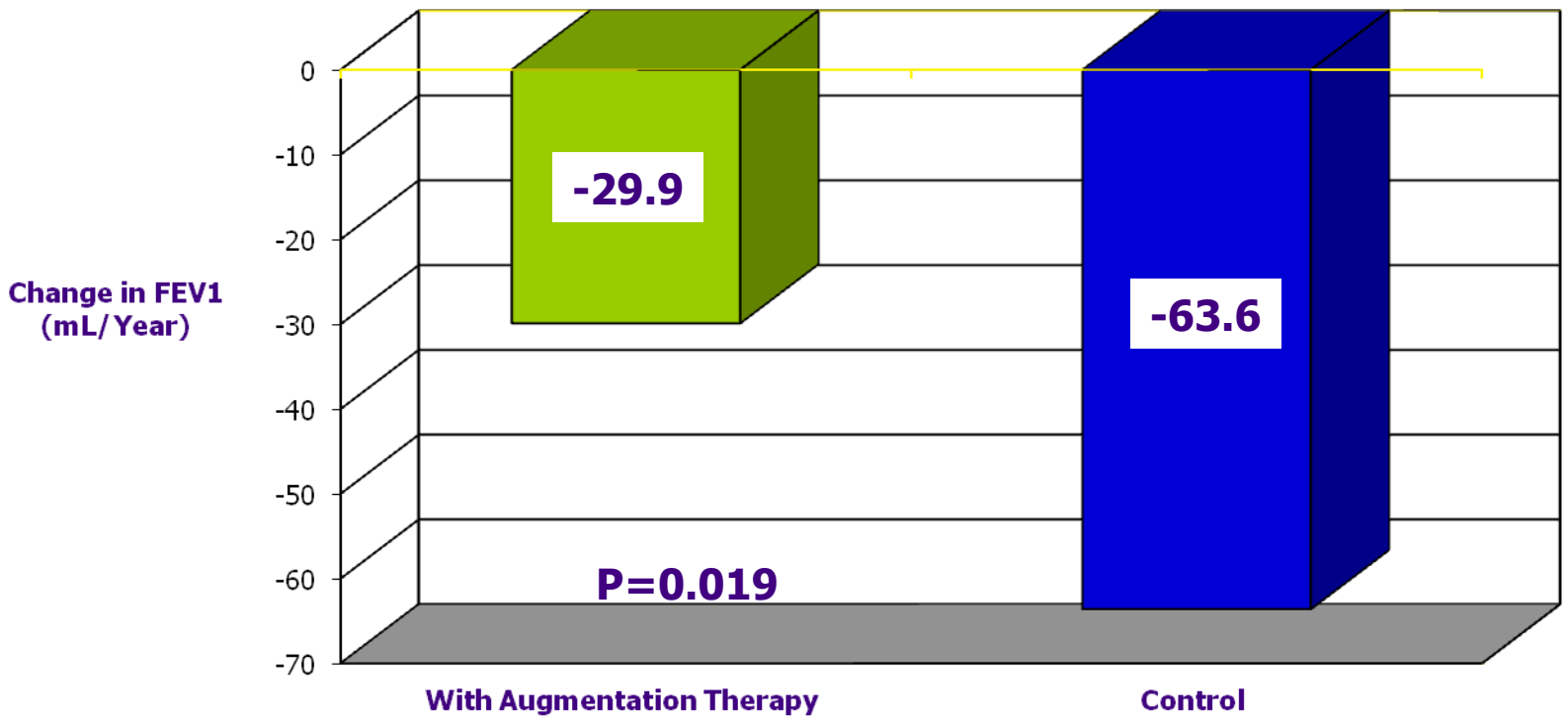
NHLBI Registry - Mortality

Canadian Registry 2005

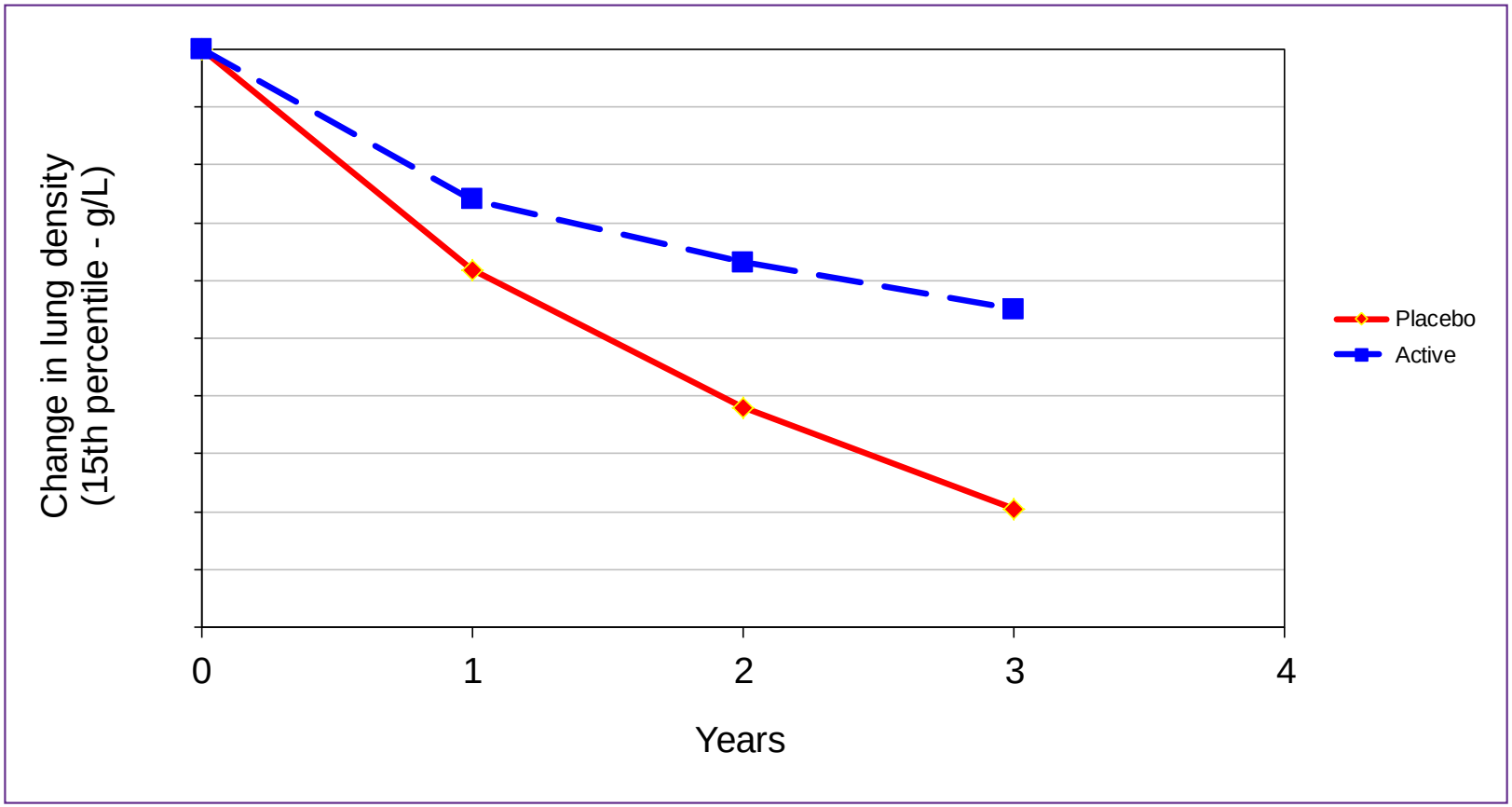
- Patients receiving Alpha-1 vs untreated matched control patients
- N: 21 patients receiving Alpha-1,
  42 controls
- Median observation was 5.6 years.
- Median duration of augmentation
  was 4.4 years.

Chapman et al, 2005

Canadian Registry



Changes in Lung CT Density



The RAPID Trial – Newly Reported

Presented at the 2013 ATS International Conference

- Placebo controlled – 2 year CT densitometry follow-up
  - Zemaira (60 mg/Kg)
  - Placebo group crossed over to Rx – followed + 2 years.
- Prespecified (in 2003) primary end point of combined CT densitometry score at TLC and FRC was not significantly different (p=0.027) between treated and placebo.
- CT densitometry at TLC was significantly different (p=0.007)
- None of the other secondary endpoints were different between groups (FEV1, exacerbations, quality of life)
- Placebo patients crossed over to treatment and followed for an additional 2 years showed slowing of decline in CT densitometry at TLC
- **N.B.: significance is p of 0.025 or better because this was analyzed as a one-sided test**

So what about the future?

- Higher doses of augmentation
- Biomarkers
- Other biologics
- Gene therapy

Is More Better?

Irina Petrache, AJRCCM 2019 page 270

- 10 patient pilot study, switched from 60 mg/kg to 120 mg/kg for a month
- Higher dose let to reduced levels of IL-17, TNF-alpha, leukocyte migration and activation.
- Lower dose demonstrated more elastin degradation and protease activity
- This questions the 11MM as the critical protective level since levels of 25 MM (130 mg/dl) with double dose weekly was more effective at immune control.

Evolving therapies

(Mitchell EL, Curr Pathobiol Rep. 2017;5;243-252)

- Caperones: phenylbutyrate
- Autophagy-Enchancing Agents: rapamycin, carbamazepine, tamoxifen, fluphenazine
- Bile Acids: ursodeoxycholic acid
- Polymerization Inhibitors: monoclonal antibodies
- Gene Transfer: knockdown of the Z protein and express the “wild type” protein
- Somatic Stem Cells: mesenchymal or bone-marrow derived

Summary

- Alpha-1 Antitrypsin Deficiency is more common than previously taught and still perceived.
- It causes more than just emphysema.
- Testing for Alpha-1 is quick and easy.
- Augmentation therapy is available and effective.

Nota Bene

Sometimes “Generic” COPD is actually “Genetic” COPD

Questions or concerns?
Thank you!