COPD AND THE ELUSIVE ALPHA-1 ANTITRYPSIN DEFICIENCY

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OBJECTIVES

- Briefly review COPDs
- Etiology and Epidemiology AATD
- Current Treatments AATD
- Future Outlook AATD

CBABE

Umbrella Acronym

C – Cystic Fibrosis

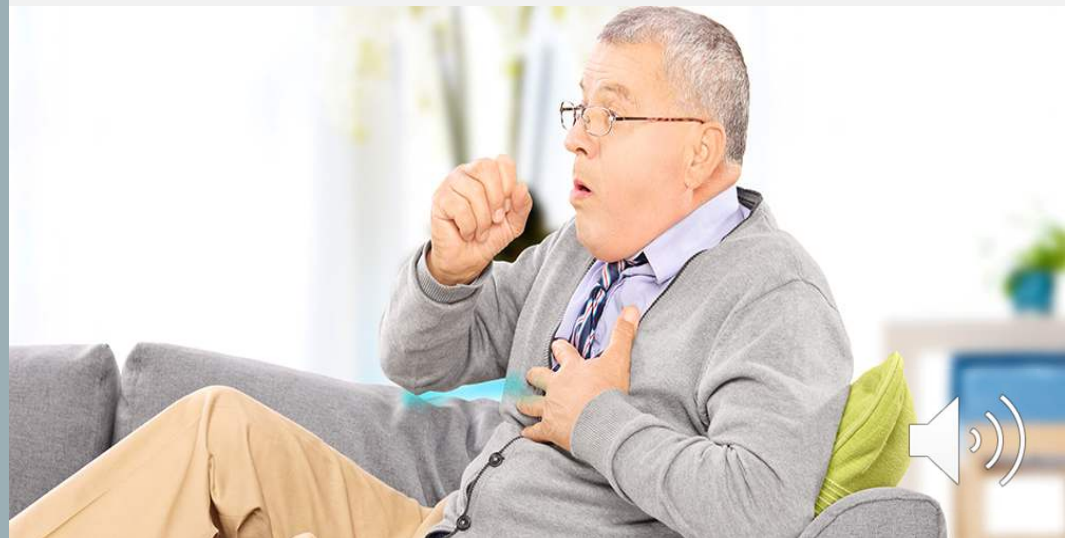
B – Bronchiectasis

A – Asthma

B – Bronchitis (Chronic)

E – Emphysema*

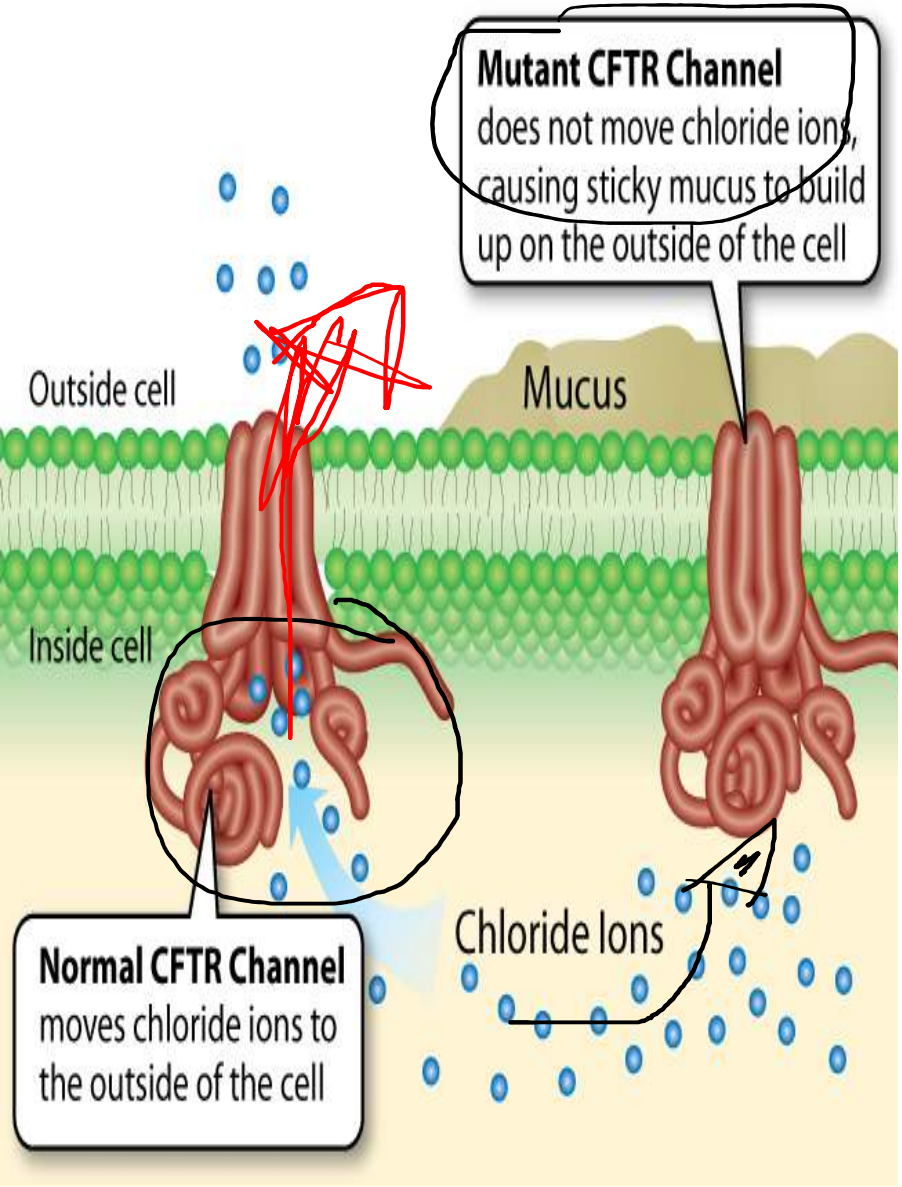
- COPD is common – preventable (sometimes) – and treatable
- Is the third leading cause of death in the US
- Can be genetic but is largely environmental
- Linked with other comorbidities (diabetes, CAD, etc.)
- Massive health burden and diminishes QOL
- Anatomical and physiological changes

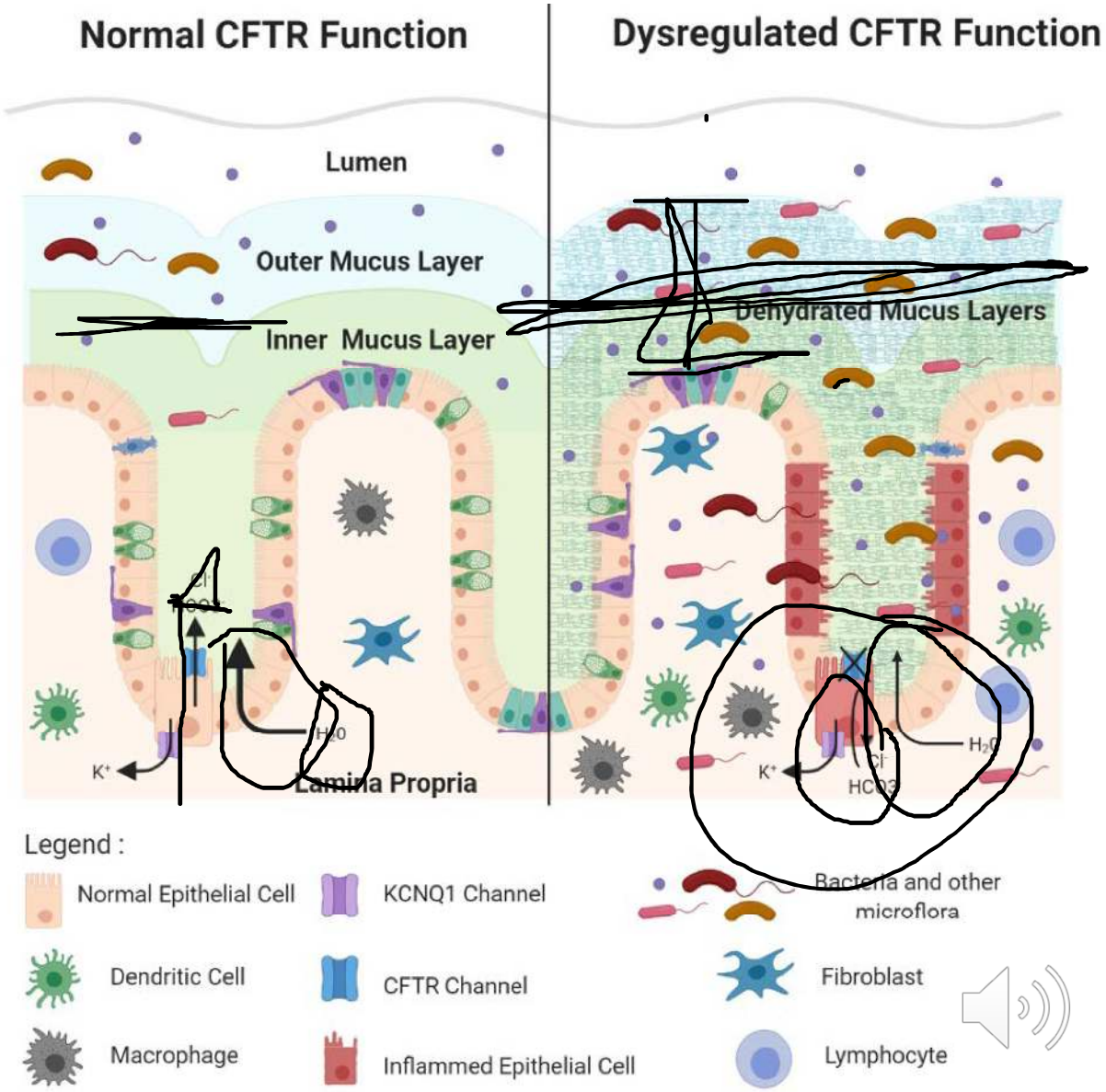


CF

- Common genetic condition characterized by 1000(s) of cystic fibrosis transmembrane conductance regulator (CFTR) gene variations
- Most common (70 -75%) variation is a phenylalanine codon – 507 on chromosome 7 (band q31)
- Abnormal movement of sodium and chloride across the epithelial surface (not just lungs)
- This equates to abnormally thick mucus everywhere

- >70% of patients diagnosed before age 2
  - Sweat Chloride Test – Gold Standard, though not the only
  - Usually performed twice - >60 mEq/L is definitive
- Whites, Hispanics, AA, Asian, respectively
- Leads to recurrent pneumonias and scar tissue coupled with a plethora of complications
- O2 therapy, bronchopulmonary hygiene, lung expansion, nebs of all kinds, xanthines, expectorants, antibiotics, gene modulators (ivacaftor, trikafta, etc.), gene therapy, lung transplant, mechanical ventilation, rehab, nutrition regimens, etc.

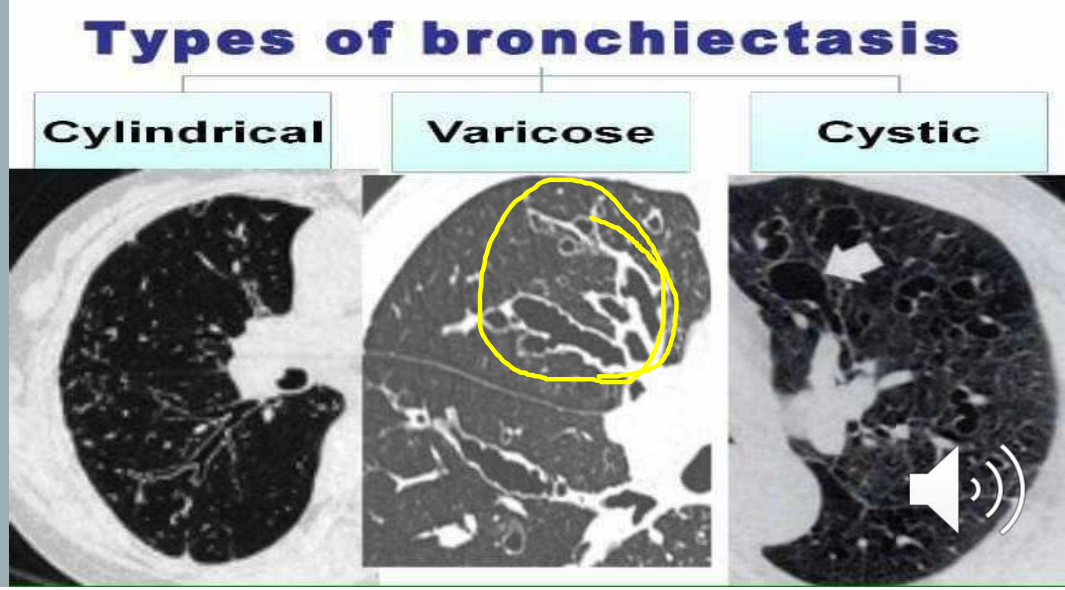

Mutant CFTR Channel
does not move chloride ions, causing sticky mucus to build up on the outside of the cell
Outside cell
Mucus
Inside cell
Chloride Ions
Normal CFTR Channel
moves chloride ions to the outside of the cell


Normal CFTR Function
Dysregulated CFTR Function
Lumen
Outer Mucus Layer
Inner Mucus Layer
Dehydrated Mucus Layers
Lamina Propria
Legend :
Normal Epithelial Cell
KCNQ1 Channel
Bacteria and other microflora
Dendritic Cell
CFTR Channel
Fibroblast
Macrophage
Inflammed Epithelial Cell
Lymphocyte

BRONCHIECTASIS

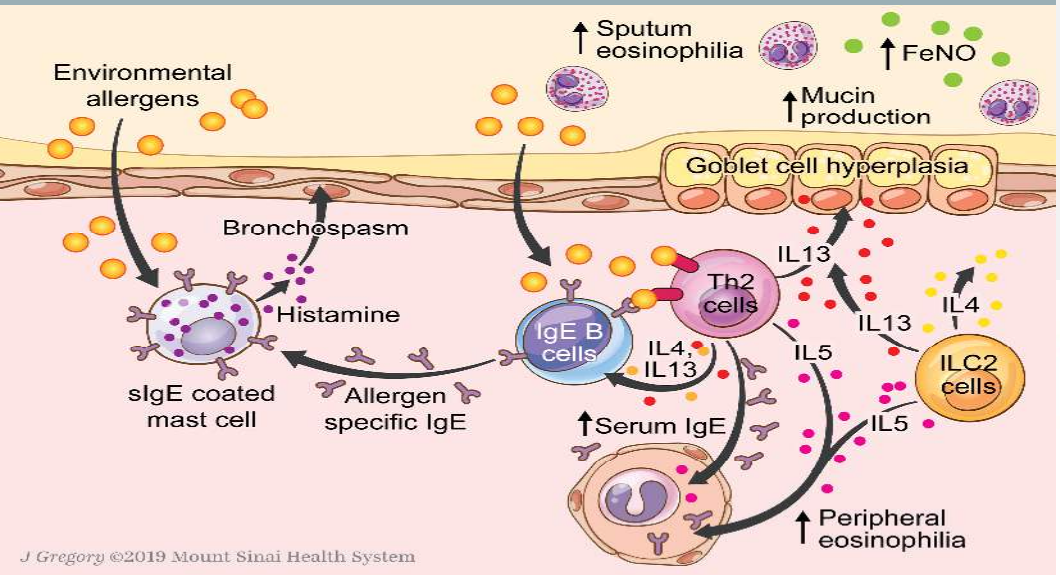
- Permanent distortion and dilation of one or more bronchi – bronchial wall destruction (common in lower, less supported airways – hence, hyperinflation, atelectasis, fibrosis, and poor mucus clearance)
- Can be *acquired* or *congenital*, and takes three anatomical variations:
  - Cylindrical
  - Cystic
  - Fusiform

- Acquired = recurrent pneumonia, bronchial obstruction, inhalation, and aspiration
- Congenital = CF, Kartageners Syndrome (dextrocardia-bronchiectasis-sinusitis)
- Treated similarly to CF
- Sputum settles into layers and is foul smelling

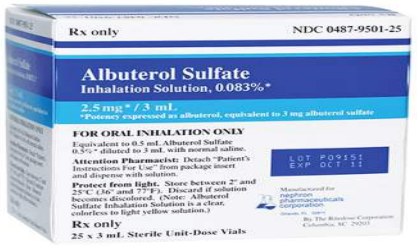


ASTHMA

- Numerous agencies involved with asthma prevention and the like
- Two major types: intrinsic (unclear why) and extrinsic (external agent)
- General immunological response:



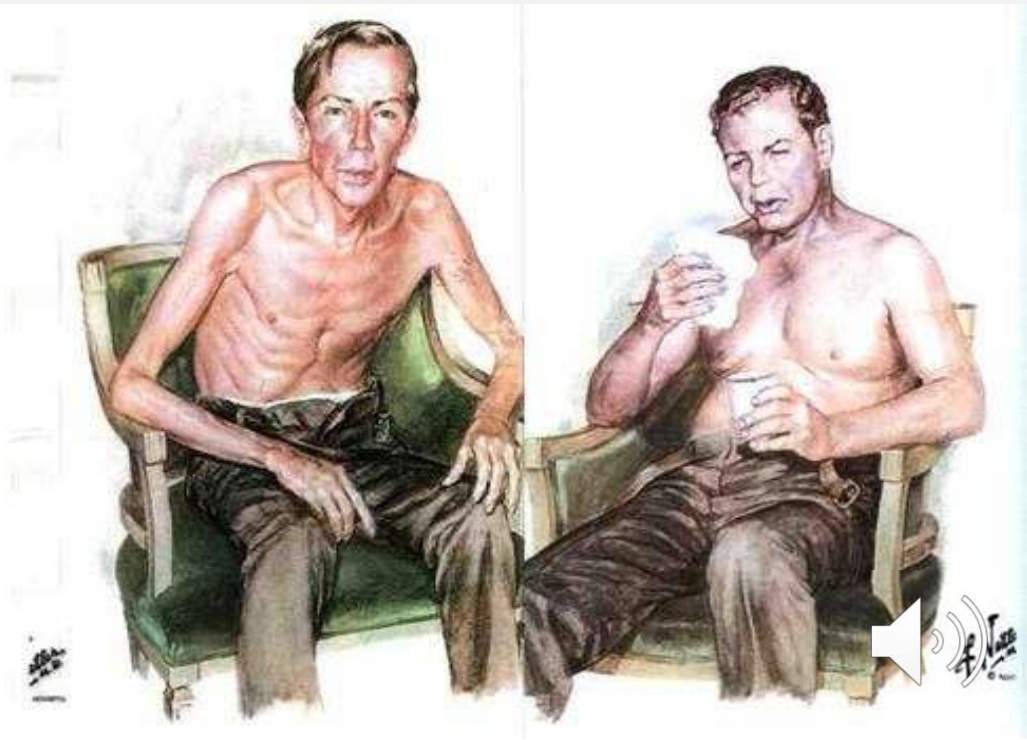
- Other risk factors: obesity, gender, infection, sleep, GERD, etc.
- Spirometry showing reversibility FEV1 >/= 12% or 200ml
- Four classifications: intermittent, mild, moderate, severe
- General management: develop p/p relationship, identify and eliminate triggers, assess, treat, monitor, manage exacerbations, other considerations
- May need O2, BP hygiene, nebs, and MV
- NUMEROUS nebs, injections, etc.



CHRONIC BRONCHITIS

- Chronic and productive cough for 3 months in each of two consecutive years
- Chronic inflammation in peripheral airways
- Bronchospasm, air trapping (late stage)
- Excessive mucous and possible plugging
- Usually in unison with emphysema w millions of diagnoses

- "Blue bloaters"
- May be "stocky" or over weight
- Hypoventilate
- Higher cardiac demand – RHF
- Polycythemia

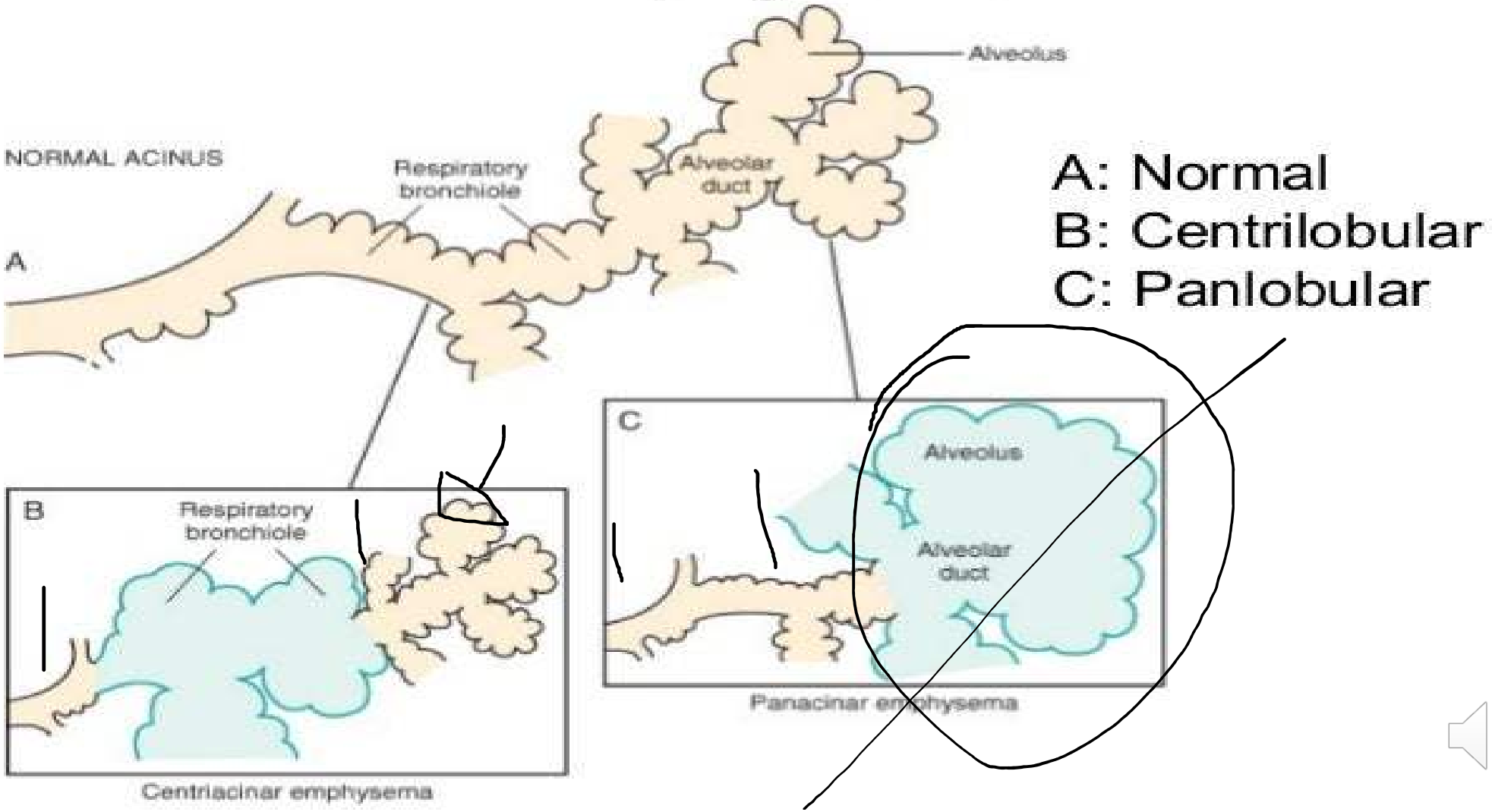


EMPHYSEMA (CENTRILOBAR)

- Dilation and destruction of the airways distal to the terminal bronchi
- Centrilobar is mostly caused by *tobacco smoke*
- Gold Mild >/= 80%
- Gold Moderate >50% but <80%
- Gold Severe >30% but <50%
- Gold Very Severe <30%
- Decreased DLCO <25ml/min/mmHg

- "pink puffer"
- Typical cachexic COPD pt.
- Tripoding, accessory muscle use, and pursed lip breathing
- Malnourished due to the "cycle"

Emphysema


Alveolus
NORMAL ACINUS
Respiratory bronchiole
Alveolar duct
A
A: Normal
B: Centrilobular
C: Panlobular
C
Alveolus
Alveolar duct
B
Respiratory bronchiole
Panacinar emphysema
Centriacinar emphysema

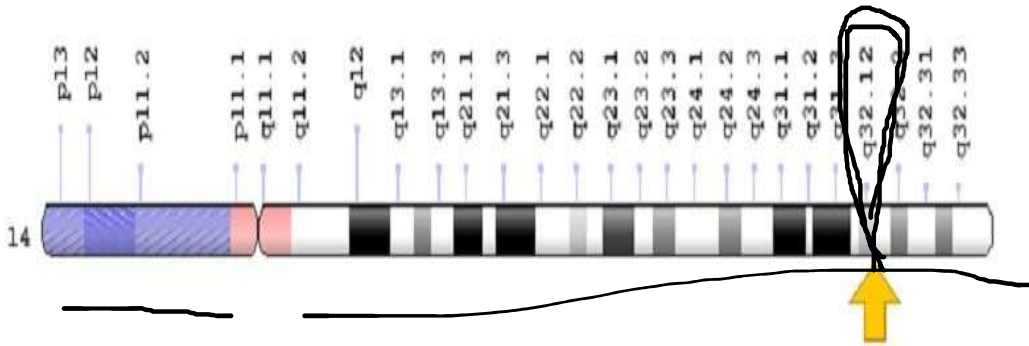
EMPHYSEMA (PANLOBAR)

- Proximal to terminal bronchioles
- Known as the most severe form of emphysema
- Progression of COPD in the smoking and occupational pool is irrelevant
- Commonly associated with Alpha-1 Antitrypsin Deficiency
- Genetic
- 1 of every 50 emphysema cases

WHAT AND HOW - AATD

- Initially described in 1963
- AAT is a protein produced in the liver (mainly), that maintains protease-antiprotease homeostasis.
- The protease, neutrophil elastase, specifically, when in large amounts, destroys the lung and alveolar structure and matrix. NE can degrade elastin, collagen, etc.
- Smoking has also shown to decrease the amount of AAT in circulation

- So a deficiency of Alpha 1 Antitrypsin creates a situation in which there are too many elastin destroying proteases and not enough inhibitors.
- Emphysema, even centrilobar, has a tendency to have increased compliance.



SERPINA1 Geni

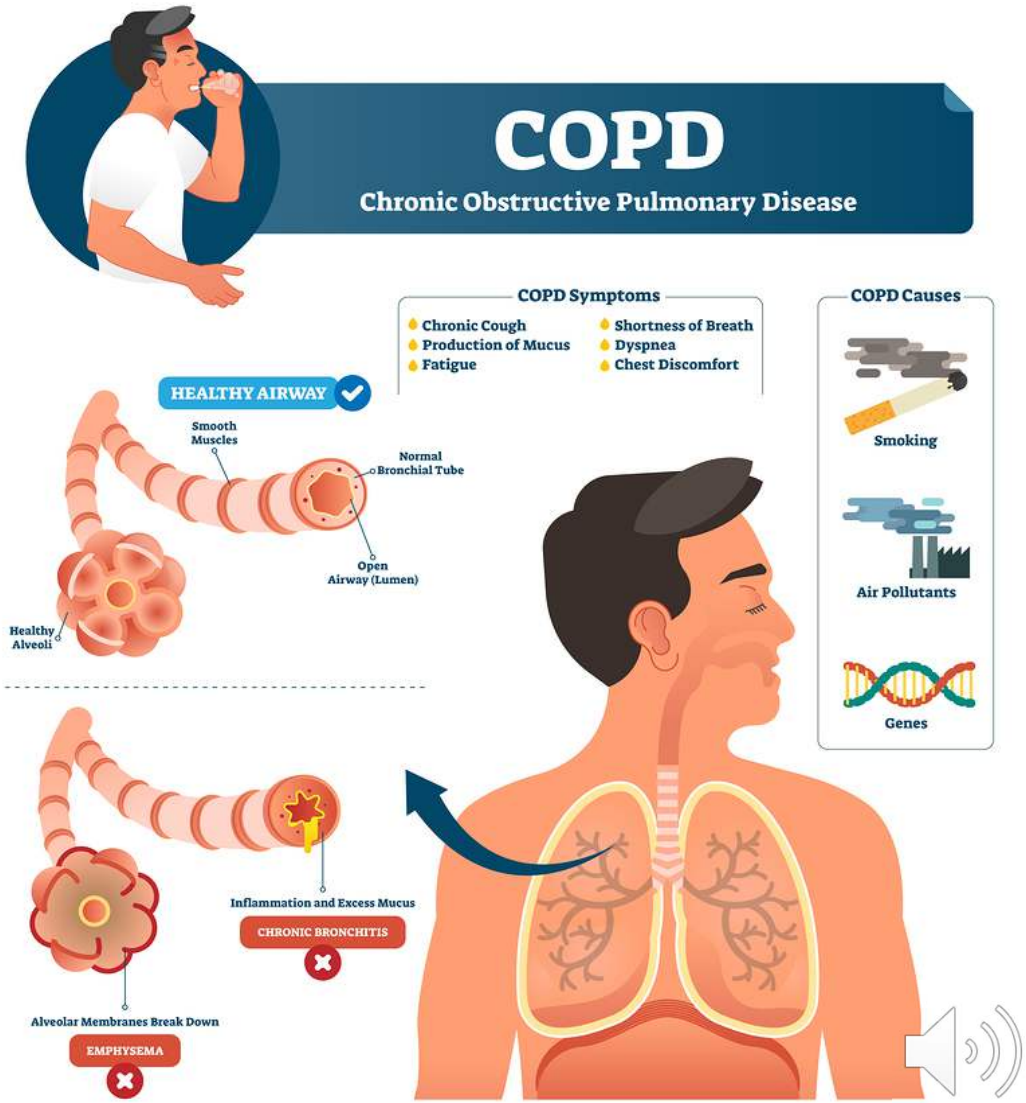
EPIDEMIOLOGY AND TESTING

- Most common in Whites, Hispanics, Blacks, Mexican Americans, and Asians (no risk), respectively
- 100,000 Americans under represented due to testing – estimated 3-5 million world wide
- Ranges: 1 in 1600 – 1 in 5000 peoples (2500)
- Estimates state 90% undiagnosed
- Severity is dependent on phenotype
- Smoking certainly increases risk
- Roughly equal men and women

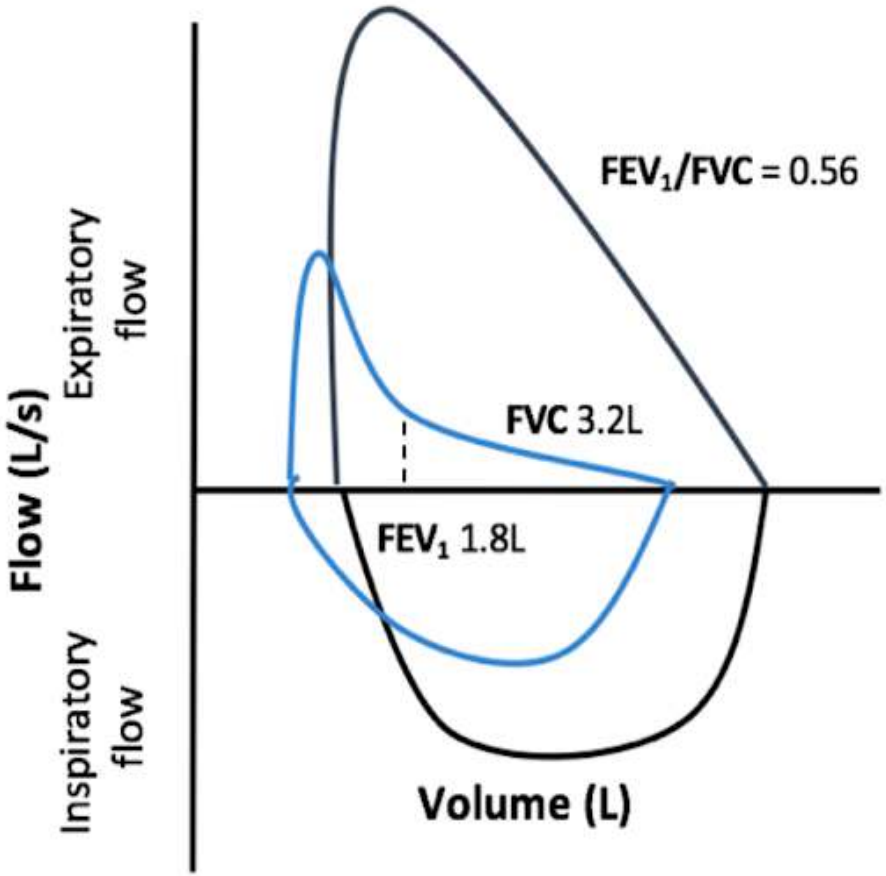
- A blood sample can be drawn for testing.
- Diagnosis is confirmed by identifying serum alpha-1 antitrypsin levels < 80 mg/dL (< 15 micromol/L) if measured by the radial immunodiffusion method or levels < 50 mg/dL (< 9 micromol/L) if measured by nephelometry.
- A nephelometer is used **to measure light scattering (light reflected off the particles in a sample), not the attenuation of light (absorbance) caused by turbidity**. Nephelometer microplate readers measure insoluble particles present in liquid solutions in the well of a microplate.
- Recommended that genotypeing and blood samples be drawn.
- Ranges vary from 75-150, 100 – 300, and the mentioned above.

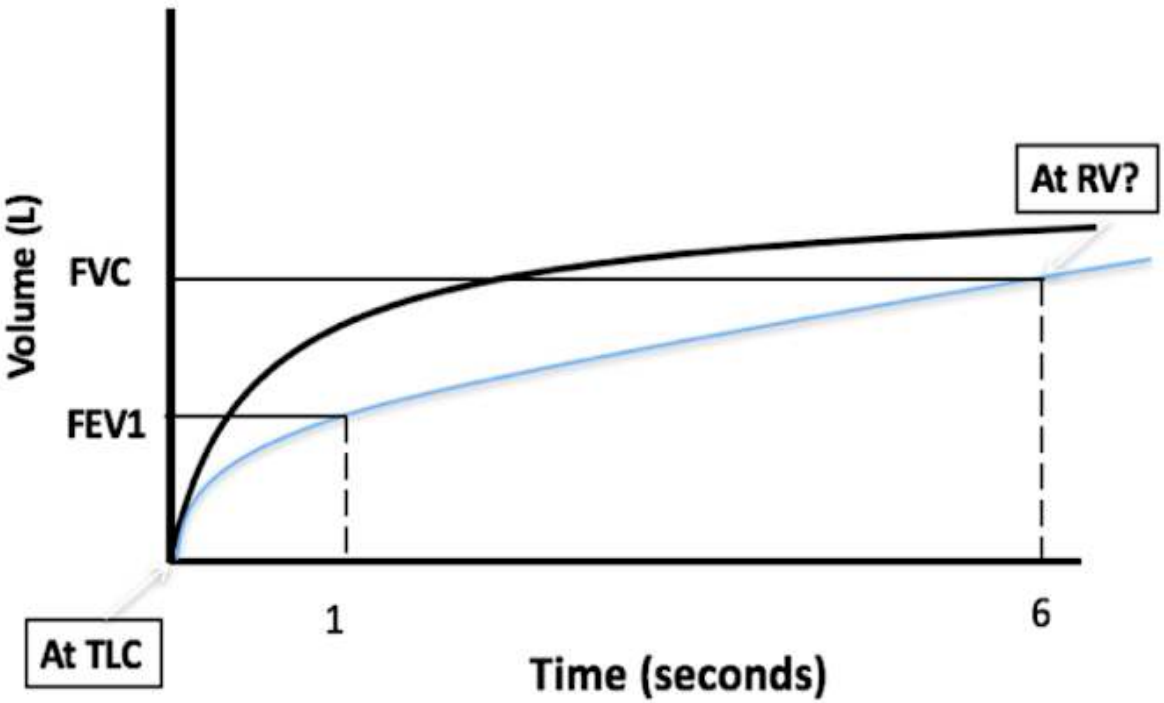
PATHOLOGIC CHANGES – BRIEF

- AAT generally manifests in the lower, more gravity impacted lobes
- Manifests as pink puffer pt.
- Airway remodeling: wound healing, i.e. cigs
- Mucous plugging
- Hyper inflation
- ECM changes
- Polycythemia
- Chemoreceptor failure
- Air trapping
- Diaphragmatic insufficiency



Obstructive Lung Disease





CURRENT TREATMENT/MANAGEMENT

- One of the most popular treatments for AATD is augmentation, or replacement therapy – healthy, AAT full blood, is admin
- More preventative than curative
- Small molecular corrector
- Certain inhaled medications
- Recombinant protein therapy

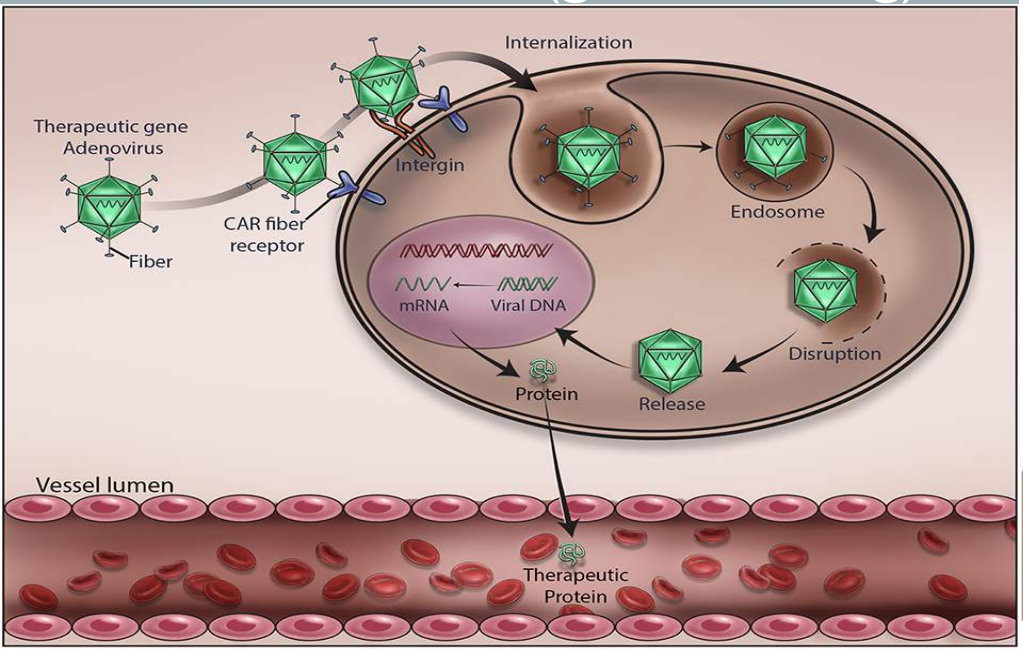
- General COPD maintenance
  - Bronchodilators (direct and indirect), steroids, airway clearance, O2
  - Pulmonary rehabilitation, nutritional support, palliative care consults, COPD action plans
  - Smoking cessation
  - Home care
  - Bronchial stents or lung volume reduction
  - NIV

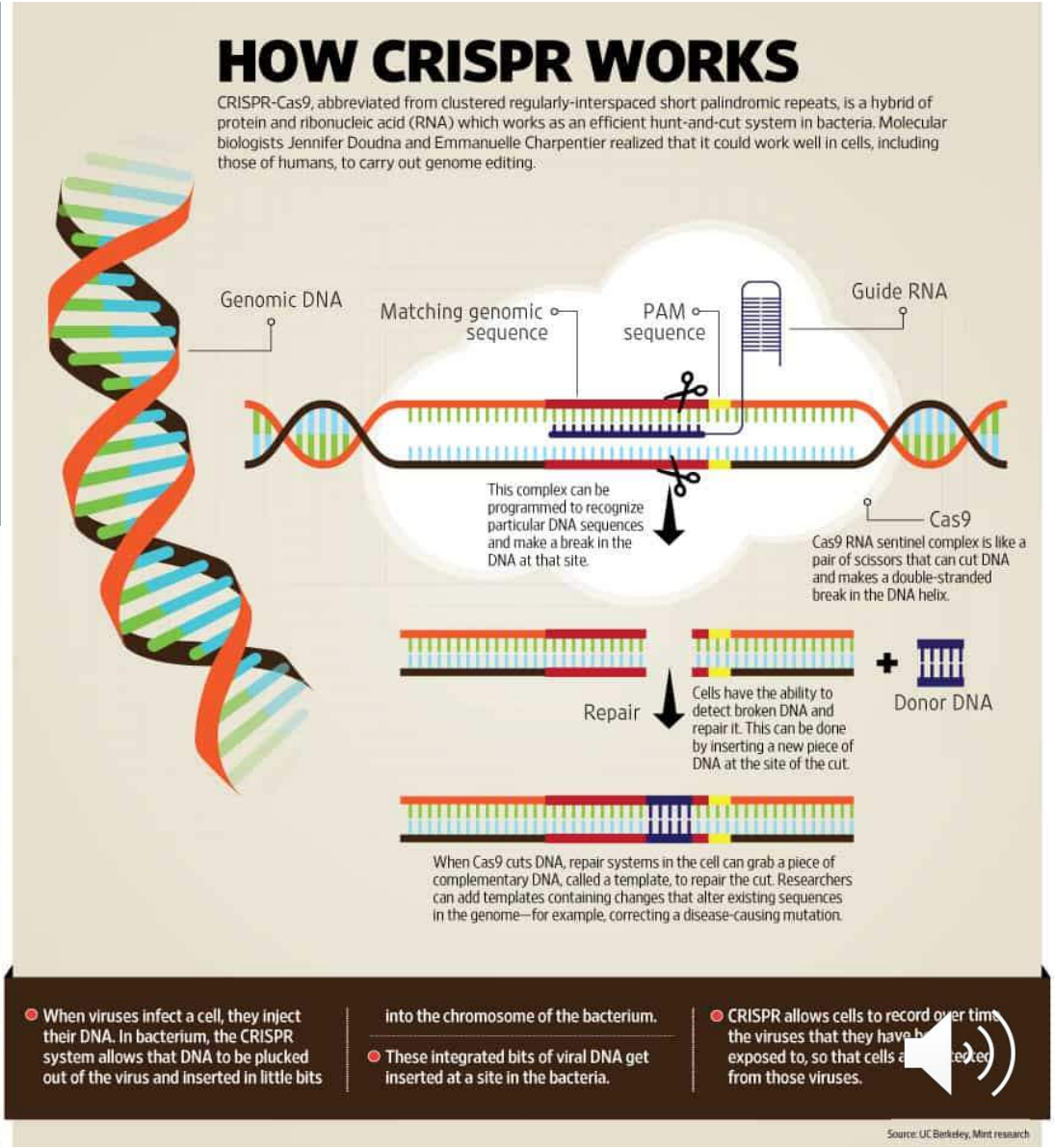
FUTURE

Gene therapy

Gene modulation

CRISPR-Cas9 (gene editing)





THE RTS ROLE

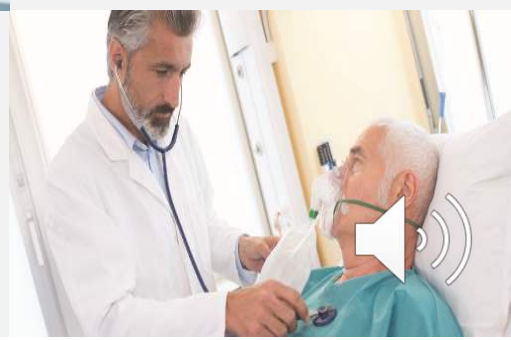
- Plethora of knowledge surrounding obstructive diseases
- Are able to decipher needed care
- Are the experts regarding COPD and other cardiopulmonary complications
- Are in the perfect position for patient advocacy

- COPD Navigators
- Pulmonary Navigators
- Case Managers
- Community Health
- Ethics
- Academics

Educators

Mentors

- Researchers
- Public Health
- Specialists



RECAP

COPD is complex and ever evolving

Emphysema is NOT the only obstructive condition

Emphysema specifically can manifest genetically

AATD is hereditary and under represented diagnostically

There are certain and specific therapies for AATD

Science is leaning more towards curative mechanics vs therapeutic

YOU are the expert

YOU are the advocate

YOU can make the difference