Cystic Fibrosis in Children

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Presenter Disclosure

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The following relationship(s) exists related to this presentation:

CF Foundation, Consulting and Research Funding (Institution)
Objectives

• Describe the incidence and genetics of CF
• Understand the impact of newborn screening
• Discuss the pathophysiology of CF lung disease
• Describe approaches to treating the underlying defect in CF
CF EPIDEMIOLOGY AND GENETICS
**Incidence and Prevalence**

- Most common fatal genetic disorder in Caucasians
  - 1 in 3,600 Caucasian births
  - 1 in 17,000 African-Americans
  - 1 in 31,000 Asian-Americans
- 30,000 people in US and 70,000 worldwide
- Carrier rate 1:30
Proportion of People with CF Reaching Adulthood

Number of Children and Adults with CF, 1987–2017

- Adults 18 Years and Older
- Children Under 18 Years

Year | Adults 18 Years and Older | Children Under 18 Years
--- | --- | ---
87 | 29.8% | 70.2%
88 |  | 70.2%
89 |  | 70.2%
90 |  | 70.2%
91 |  | 70.2%
92 |  | 70.2%
93 |  | 70.2%
94 |  | 70.2%
95 |  | 70.2%
96 |  | 70.2%
97 |  | 70.2%
98 |  | 70.2%
99 |  | 70.2%
00 |  | 70.2%
01 |  | 70.2%
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03 |  | 70.2%
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06 |  | 70.2%
07 |  | 70.2%
08 |  | 70.2%
09 |  | 70.2%
10 |  | 70.2%
11 |  | 70.2%
12 |  | 70.2%
13 |  | 70.2%
14 |  | 70.2%
15 |  | 70.2%
16 |  | 70.2%
17 |  | 70.2%

53.5% | 46.5%
Genetics

- CF Transmembrane Conductance Regulator (CFTR) protein
  - Long arm of Chromosome 7
  - Controls the movement of salt and water
- Over 1,900 mutations
  - F508del most common
<table>
<thead>
<tr>
<th>Class</th>
<th>Production Mutations</th>
<th>Processing Mutations</th>
<th>Gating Mutations</th>
<th>Conduction Mutations</th>
<th>Insufficient Quantities</th>
<th>Increased Turnover at cell surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td></td>
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<tr>
<td>Class II</td>
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<td></td>
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<td></td>
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<tr>
<td>Class III</td>
<td></td>
<td></td>
<td>Reduced CFTR function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Class V</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Class VI</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

| G542X       | F508del              | G551D                | R117H            | 3849+10kbC->T        | N287Y                  |                                    |

CF Foundation Patient Registry 2016
Airway hydration

Image courtesy of R Boucher
NEWBORN SCREENING
Question 1

• Newborn screening for a healthy, full-term baby girl reveals CFTR mutations F508del and R117H
• Sweat chloride levels are 37 and 44 mmol/L, respectively
Question 1: Which of the following results would increase suspicion that this child has cystic fibrosis?

A. Sweat test = 55 mmol/L
B. Fecal elastase level of 395 mcg/g stool
C. Presence of the 5T form of the poly-T sequence of intron 8
D. Presence of the 9T form of the poly-T sequence of intron 8
E. Sputum culture with *Staphylococcus aureus*
Question 1: Which of the following results would increase suspicion that this child has cystic fibrosis?

C. Presence of the 5T form of the poly-T sequence of intron 8
R117H and poly-T sequence

- Found in intron 8 of the *CFTR* gene
- Can impact CFTR function by aberrant splicing of exon 9
- 5T alleles are considered mutations
  - Decrease the efficiency of intron 8 splicing
- 7T and 9T alleles are considered polymorphic variants
## R117H and poly-T predicted outcomes

<table>
<thead>
<tr>
<th>One mutation: CF-causing mutation, e.g., F508del</th>
<th>Second mutation: R117H + ?</th>
<th>Predicted outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>R117H + 5T</td>
<td>R117H will <strong>likely</strong> act as a disease-causing mutation</td>
<td></td>
</tr>
<tr>
<td>R117H + 7T</td>
<td>R117H is <strong>unlikely</strong> to act as a disease-causing mutation. May result in male infertility</td>
<td></td>
</tr>
<tr>
<td>R117H + 9T</td>
<td>R117H is <strong>highly unlikely</strong> to act as a disease-causing mutation. Male infertility is typically not affected</td>
<td></td>
</tr>
</tbody>
</table>
The Sweat Test

• Pilocarpine iontophoresis is the only approved method

• Ranges of Chloride Concentration
  – < 30 mM/L, normal range
  – > 60 mM/L suggestive of CF

• Minimum acceptable sweat volume
  – Filter paper: 75 mg
  – Microbore tubing: 15 microliters
Question 2

- Newborn screening results come back for a healthy, full-term baby boy
- Initial immunoreactive trypsinogen (IRT) levels are in the highest 5% of IRT values obtained that day
- DNA mutation analysis reveals one copy of G551D
- Sweat test results are 35 mmol/L and 38 mmol/L at 3 weeks
- Complete gene sequencing detects a missense mutation in cis
Which of the following is the most likely diagnosis?

A. Cystic fibrosis
B. Cystic fibrosis transmembrane conductance regulator-related metabolic syndrome (CRMS)
C. False positive NBS result
D. CFTR-related disorder
E. Atypical cystic fibrosis
Which of the following is the most likely diagnosis?

B. Cystic fibrosis transmembrane conductance regulator-related metabolic syndrome (CRMS)
## CRMS/CFSPID

### CFTR-Related Metabolic Syndrome (CRMS)

**Follow at CF Center**

<table>
<thead>
<tr>
<th>SC (mmol/L)</th>
<th>Number of CFTR Mutations</th>
<th>Group A**</th>
<th>Group B or D***</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 60</td>
<td></td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>40-59</td>
<td></td>
<td>1</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

**Unresolved: Possible CRMS**

| 40-59       | 0 | 0 |

### Group A

- “CF-Causing”
  - 1078delT
  - 1677delTA
  - 1717-1G>A
  - 1898+1G>A
  - 2184delA
  - 2184insA
  - 2789+5G>A
  - 3120+1G>A
  - 3659delC
  - 3849+10kbC>T
  - 621+1G>T
  - 711+1G>T
  - A455E
  - E822X
  - F508del
  - G542X
  - **G551D**

### Group D

- “Unknown or Uncertain Significance”
  - Many missense mutations

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Borowitz J Pediatr 2009
Cystic Fibrosis: Diagnosis

Clinical presentation of CF:
Positive NBS
Signs and/or symptoms
Family History

Sweat Chloride Testing

≥60mmol/L
CFTR Genetic Analysis
2 CF-causing CFTR mutations

30-59mmol/L
CFTR genotype undefined or known MVCC

≤29mmol/L
No CFTR mutations

CFTR Physiologic Testing
NPD/ICM

CFTR dysfunction
Testing Unavailable, Equivocal
CFTR function preserved

CF Diagnosis
CF Diagnosis Not Resolved
CF Unlikely

MVCC: Mutation of varying clinical consequence
NPD: Nasal potential difference
ICM: Intestinal current measurement

Farrell J Pediatr 2017
Cystic Fibrosis: Diagnosis

- Cystic Fibrosis: 84.2% (n=880)
- CRMS/CFSPID: 11.3% (n=118)
- CFTR-related Disorder: 4.5% (n=47)
Early diagnosis improves growth
Lung function according to mode of diagnosis

![Graph showing lung function (FEV1 % predicted) by mode of diagnosis and age (6-10 and 11-20 years)].

- **Newborn Screening**
- **Symptoms**
- **Meconium ileus**

For each age group:
- **6-10 years**
  - Newborn Screening: p < 0.01
  - Symptoms: p < 0.01
  - Meconium ileus: p < 0.01
- **11-20 years**
  - Newborn Screening: p < 0.01
  - Symptoms: p < 0.01
  - Meconium ileus: p < 0.01

**Accurso J Pediatr 2005**
FEV$_1$ vs Age by Birth Cohort
Complications from Late Diagnosis

• Electrolyte abnormalities
  – Hypochloremia
  – Hyponatremia

• Growth
  – Failure to thrive
  – Hypoproteinemia
  – Kwashiorkor

• Rectal prolapse

• Vitamin deficiencies
  – E: Hemolytic anemia
  – K: Bleeding diathesis
  – Zinc: Acrodermatitis

• Hepatobiliary
  – Focal biliary cirrhosis
  • Cirrhosis occurs in ~5% of patients

• Portal hypertension
  – Hypersplenism and esophageal varices
  • Bleeding can be life-threatening
CF LUNG DISEASE
Etiology of CF lung disease

• Lungs appear grossly normal at birth
• Begins with small airways

• Decreased mucociliary clearance
  – Dehydration of mucus
  – Altered mucins

Defective CF Gene
  ↓
Defective/Deficient CFTR
  ↓
Decreased Chloride Secretion
  ↓
Increased Sodium Absorption
  ↓

Obstruction
  ↓
Infection
  ↓
Inflammation
  ↓
Lung Destruction

Konstan Pediatr Pulmonol 2008
Normal

Cystic Fibrosis

Courtesy of Jim Chmiel
Detecting Lung Disease

• Functional
  – Spirometry
  – Multiple breath washout (MBW)
  – MRI scan (perfusion and ventilation, active inflammation)

• Structural
  – Chest radiograph
  – CT scan
  – MRI Scan
CT imaging of CF lungs

10 year old, FEV$_1$ = 86% predicted

13 year old, FEV$_1$ = 96% predicted

De Jong Eur Respir J 2004
Multiple breath washout

- Measure of ventilation inhomogeneity
- Lung clearance index = ventilation required to clear inert gas
- ↑LCI indicates inefficient gas mixing
- Sensitive to changes in lung disease
- Tracks with later lung function
- Several limitations
MBW Read out

![Graph showing MBW Readout](image-url)
MBW can be used to detect early lung disease

Inflammation in CF

- Occurs early in life
- Excessive relative to the burden of bacteria
- Persistent even in the absence of detectable organisms
- Contributes to lung damage
- Neutrophils release
  - Oxidants and proteases $\rightarrow$ damage the lung
  - DNA $\rightarrow$ increases secretion viscoelasticity
- May be directly linked to the basic defect in CF
Inflammation in CF (Continued)

- Lung inflammation leads to bronchiectasis
- Other complications follow:
  - Hypoxemia
  - Hemoptysis, pneumothorax
  - Chronic hypoxemia and pulmonary vasoconstriction
  - Pulmonary hypertension and right ventricular hypertrophy (cor pulmonale)
- Respiratory insufficiency eventually leads to death
Lung infections

![Graph showing the percentage of individuals with lung infections by age and bacterial species.](image)
*Pseudomonas aeruginosa (Pa)* is associated with poor outcomes

- Acquisition is associated with
  - Proinflammatory response
  - Lower lung function
  - Increased cost of care
  - Decreased survival
- Biofilm protects from host defenses and antibiotics

![Graph showing FEV1 (% Predicted) over years pre/post mucoid Pa acquisition](image)
Eradication of *Pa*

- 72-90% of eradication attempts are successful
- *Pa* recurs in ~33% within 18–27 months
- *Pa* recurrence is associated with the risk of IV-treated pulmonary exacerbations
- No clear evidence for treatment of *Pa* recurrence
MEDICATIONS AND THEIR IMPACT ON DISEASE PROGRESSION
Extrapolating Relative Benefit

*Improvement in FEV₁ vs. Slowing the Rate of Decline*

![Graph showing FEV₁ percentage predicted over age](image)

- Increase FEV₁ without change in rate of decline
- The “Cure”
- Slow FEV₁ rate of decline (slope)

Change in FEV$_1$ % predicted with dornase alfa

Change in FEV$_1$ % predicted with dornase alfa

- Mean Change from Baseline ± SE

- Dornase

- Placebo

- Week

- 3.2±1.2

- P=0.006

Quan J Pediatr 2001
Dornase alfa slows the decline of FEV$_1$
Annualized Rate of Decline of $\text{FEV}_1$ % predicted

**Ibuprofen Clinical Trial 5 to 13 y/o**

- **Ibuprofen (n=17)**
  - slope = -0.4% predicted/yr
  - 89% reduction in rate of decline, $P<0.005$

- **Placebo (n=19)**
  - slope = -3.8% predicted/yr

Median Predicted Survival Age

Median Predicted Survival Age, 1986–2017 In Five Year Increments

CF Foundation Patient Registry 2017
Advances in survival in the US and in CF care

Courtesy of Tom Ferkol
# Chronic Medication Guidelines (≥6 y/o)

<table>
<thead>
<tr>
<th>Strongly Recommend</th>
<th>Recommend</th>
<th>Case-by-Case basis</th>
<th>Recommend against</th>
<th>Insufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH tobramycin</td>
<td>INH tobramycin</td>
<td>AZM (no <em>Pa</em>)</td>
<td>Inhaled steroids</td>
<td>Other INH ABX</td>
</tr>
<tr>
<td>Dornase alfa</td>
<td>Dornase alfa</td>
<td>In mild disease</td>
<td>Oral steroids</td>
<td>Leukotriene modifiers</td>
</tr>
<tr>
<td>INH aztreonam</td>
<td>INH aztreonam</td>
<td>Prophylactic anti-Staph antibiotics</td>
<td>Chronic anti-Staph antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ivacaftor</td>
<td>Hypertonic saline</td>
<td></td>
<td>PO or INH N-acetylcysteine</td>
</tr>
<tr>
<td></td>
<td>AZM (with <em>Pa</em>)</td>
<td></td>
<td>PO or INH glutathione</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ibuprofen (&lt;18 y/o)</td>
<td></td>
<td>Ibuprofen (&gt;18 y/o)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β-agonists</td>
<td></td>
<td>INH anticholinergics</td>
<td></td>
</tr>
</tbody>
</table>
Question 3: Which of the following reduces pulmonary exacerbations in infants and toddlers with CF?

A. Hypertonic saline
B. Dornase alpha
C. Ivacaftor
D. Azithromycin
E. Inhaled tobramycin
Question 3: Which of the following reduces pulmonary exacerbations in infants and toddlers with CF?

D. Azithromycin
Decreased risk of pulmonary exacerbations

<table>
<thead>
<tr>
<th>Participants</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.6</td>
<td>0.4, 0.8</td>
</tr>
<tr>
<td>6 months – 3 years</td>
<td>0.4</td>
<td>0.2, 0.7</td>
</tr>
<tr>
<td>&gt;3-6 years</td>
<td>0.6</td>
<td>0.3, 1.5</td>
</tr>
<tr>
<td>&gt;6-12 years</td>
<td>0.8</td>
<td>0.4, 1.8</td>
</tr>
<tr>
<td>&gt;12-18 years</td>
<td>0.6</td>
<td>0.2, 1.8</td>
</tr>
</tbody>
</table>

Mayer-Hamblett *Am J Respir Crit Care Med* 2018
Pulmonary exacerbations

Marked by changes in
- Cough
- Sputum production
- Weight
- Physical exam
- Energy level
- Appetite
- Lung function

Treatment
- Antibiotics
- Chest physiotherapy
- Attention to nutrition

Associated with
- Poor quality of life
- Lower FEV$_1$
- Higher healthcare costs
- Mortality

Ferkol J Pediatr 2006
Pulmonary exacerbation frequency

~33% of patients are treated annually with IV antibiotics for an exacerbation

Figure 64: Pulmonary Exacerbations vs. Age
Outcomes after pulmonary exacerbation treatment

- Poor improvement in spirometry
- Prolonged courses of IV antibiotics
- Accelerated decline in pulmonary function
- Re-treatment
Treatment decisions are associated with FEV$_1$ recovery

- Response to $\geq 10\%$ acute decline in FEV$_1$
- 64% of acute declines in FEV$_1$ were treated

Treatment

- Hospitalization vs. None
- Home IV Antibiotics vs. None
- New Inhaled Antibiotics vs. None
- New Oral Quinolone vs. None
- New Other Oral Antibiotic vs. None

Odds Ratios with 95% CI
When all else fails: Lung Transplant

Who to refer

• Psychosocial stability
• Demonstrated adherence to therapy
• Trading one disease for another

When to refer

• FEV$_1$ vs clinical status
Lung transplantation and survival

• ~250 people with CF receive lung transplantation annually
  – 9% in pediatric patients
• Median survival = 6.6 years with FEV$_1$ <30% predicted without a lung transplant
  – Risk factors: oxygen, frequent pulmonary exacerbations, FEV$_1$, pulmonary hypertension, abnormal 6 minute walk test, massive hemoptysis, recurrent pneumothorax
• Median survival following lung transplant:
  – Adults = 9.5 years
  – Pediatrics = 5.4 years

CF Foundation Patient Registry 2017, Ramos Chest 2017, Yusen J Heart Lung Transplant 2016, Khush J Heart Lung Transplant 2018
Lung Transplantation


- Seen in 2017
- Death Date Recorded in the Registry
- Not Seen in 2017 (Lost to Follow-up)
- Retransplants

Number of Individuals

Year
CFTR MODULATORS
Modulator therapy

• Potentiators
  – Increases the open probability of the CFTR chloride channel

• Correctors
  – Helps misshaped CFTR to fold into the correct 3-D conformation

• Amplifiers
  – Increase the amount of CFTR protein produced

• Stabilizers
  – Decreases CFTR protein channel turnover at the cell surface
Ivacaftor in People with CF and G551D

A

Absolute Change in Percent of Predicted FEV1

B

Proportion of Event-free Subjects

C

Change in CFQ-R Respiratory Domain Score (points)

D

Change in Weight (kg)

A

Change in Sweat Chloride (mmol/liter)

B

Sweat Chloride (mmol/liter)

CFTR Modulators and slowing of FEV$_1$ decline

**FEV$_1$ Rate of Decline (% pred/yr ± SE)**

- **G551D + Ivacaftor**
  - Mean: 1.1
  - SD: 0.2
  - P-value: 0.03

- **Registry Controls**
  - Mean: 1.5
  - SD: 0.3

**FEV$_1$ Rate of Decline (% pred/yr ± SE)**

- **Lumacator Ivacaftor**
  - Mean: 1.8
  - SD: 0.4
  - P-value: 0.001

- **Registry Controls**
  - Mean: 2.1
  - SD: 0.5

*Sawicki Am J Respir Crit Care Med 2015, Konstan Lancet Resp Med 2017*
Question 4: What is the mechanism of action of “triple combination” CFTR modulators?

A. Potentiator/Potentiator/Corrector
B. Potentiator/Corrector/Amplifier
C. Potentiator/Corrector/Corrector
D. Potentiator/Corrector/Stabilizer
E. Potentiator/Corrector/Read through suppressor
Question 4: What is the mechanism of action of “triple combination” CFTR modulators?

C. Potentiator/Corrector/Corrector
Triple-combination therapy phase 3 clinical trials

- People with CF ≥12 years of age treated with elexacaftor-tezacaftor-ivacaftor
  - 113 patients with 2 F508del mutations
    - 10% increase in FEV$_1$ vs tezacaftor/ivacaftor alone
  - 403 patients with 1 F508del mutation + 1 minimal function
    - 14% increase in FEV$_1$ vs placebo
    - 63% decrease in rate of pulmonary exacerbations

Goal is to restore CFTR function in all people with CF

Gene (DNA) Replication

RNA Transcription

Protein Translation

Symptoms

Gene editing
Gene delivery
Stem cell biology

Transcription Translation RNA repair RNA replacement

Protein repair (CFTR modulators)

Antimicrobials Mycolytics Anti-inflammatories Nutrition

Courtesy of Jim Chmiel
OTHER DISEASE FEATURES
Organ Dysfunction in CF

Liver
- Focal cirrhosis

Intestine
- Meconium ileus
- Constipation
- DIOS

Pancreas
- Exocrine insufficiency
- CF Related Diabetes

Respiratory
- Sinusitis
- Nasal polyps
- Endobronchitis
- bronchiectasis

Sweat gland
- Salt-losing dehydration

Vas deferens
- Failure to develop

CFTR Genotype
Modifier Genes
Environmental
Therapeutic
Iatrogenic
Meconium ileus and DIOS

• Meconium ileus
  – ~15% of infants with CF
  – Inspissated fecal material and mucus, mostly in the small bowel

• Distal intestinal obstruction syndrome (DIOS)
  – Annual prevalence of 2-3%
  – Thick intestinal secretions, malabsorption, and decreased gut motility
Pancreatic insufficiency

• ~85-90% of patients with CF, usually within the first year of life

• Signs and symptoms
  – Large and greasy stools, flatulence, abdominal bloating
  – Poor weight gain and malnutrition

• Leads to vitamin (A, D, E, and K) deficiencies
  – Acrodermatitis, anemia, neuropathy, night blindness, osteoporosis, and bleeding disorders
Diagnosing pancreatic insufficiency

- 72 hour stool collections for fat absorption determination
- Recommended laboratory test is fecal elastase
  - Levels < 100 μg/g stool have an excellent predictive value
  - Enzyme replacement recommended for levels <200 μg/g stool
Pancreatic enzyme replacement therapy

• CF Foundation guidelines
  – 500-2,500 lipase units/kg/meal, titrated based on symptoms and growth
  – Infants enrolled in BONUS: 1,880 lipase units/kg/meal

• Fibrosing colonopathy
  – Limit to <2500 lipase units/kg/meal and <10,000 units lipase/kg/day
  – Infants enrolled in BONUS: up to 12,400 lipase units/kg/day

• Supplemental fat soluble vitamins
  – A, D, E, K

• High-calorie diet
  – May be >120% of recommended intake
Nose and sinus disease

• Nasal polyposis and pansinusitis
• Associated with poor quality of life
• Polyps may indicate a sweat test for non-CF patients

http://curesinusproblems.com/chronic-sinusitis-treatment/
CF-related diabetes mellitus (CFRD)

- Insulin insufficiency/resistance leads to carb intolerance
- Different from type I or type II diabetes mellitus
  - DKA is rare
  - Do not restrict diet
- Pancreas becomes replaced by fat
  - Autodigestion of the pancreas by pancreatic enzymes
  - Islet cells eventually disappear
- A yearly oral glucose tolerance test for ≥10 years of age
Prevalence of CFRD

CFRD and Impaired Glucose Tolerance by Age in Years, 2015

Cystic Fibrosis-Related Diabetes (CFRD)

Impaired Glucose Tolerance

CF Foundation Patient Registry 2015
CF osteoporosis

• Common in CF
• Secondary to vitamin D deficiency, medications
• Vertebral and rib fractures are increasingly being seen as more CF patients survive into adulthood
Prevalence of Depression and Anxiety

Depression and Anxiety by Age in Years, 2015

- Depression
- Anxiety Disorder
- Both Depression and Anxiety

CF Foundation Patient Registry 2015
CF reproductive abnormalities

- Virtually all males with classic CF are infertile
  - Congenital bilateral absence of the vas deferens
- 1-2% of infertile men have CFTR dysfunction
  - Most men with obstructive azoospermia carry 1-2 CFTR mutations
- Most women with CF are fertile
  - Thickened cervical mucus may be present
Take home points

• Newborn screening has changed CF care
• Frequent monitoring and early detection of disease progression is key
• Inflammation and pulmonary exacerbations will still occur
• CFTR modulators and other “next-gen” therapies offer significant benefits