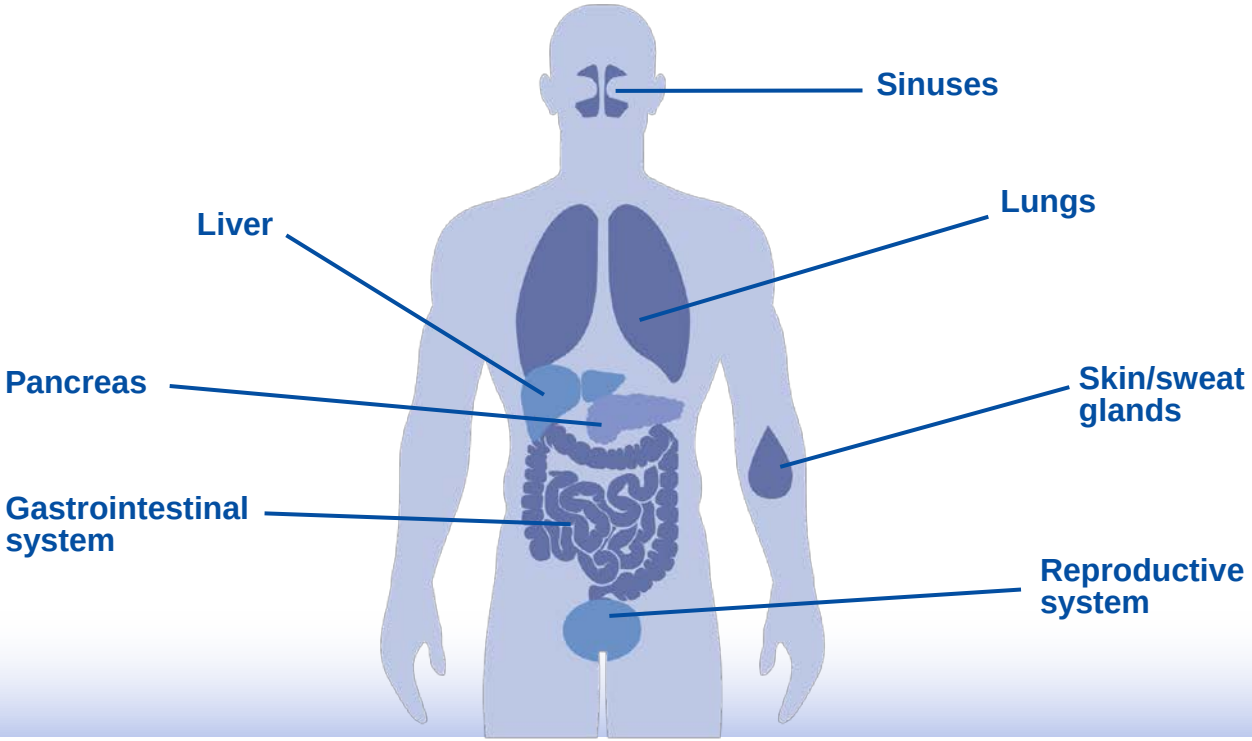
UNDERSTANDING THE EARLY, SYSTEMIC PROGRESSION OF CYSTIC FIBROSIS (CF)

A Resource for the CF Center Care Team

Overview:
CF is a progressive, multi-systemic disease[1-5]

- Many signs and symptoms appear early in life[1,4]
- Organ damage, such as in the lungs or liver, can occur before symptoms[6,7]
- Techniques to detect CF disease and monitor progression continue to evolve[8,9]



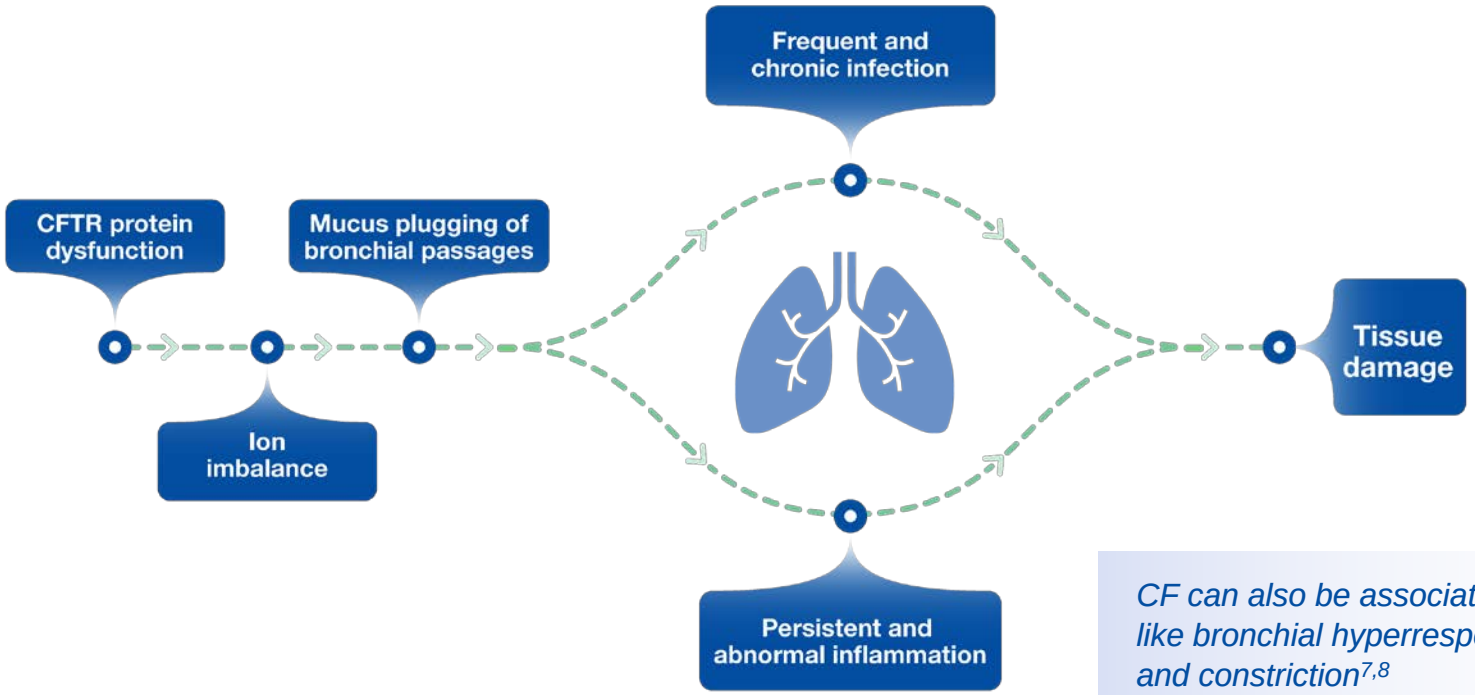
References: 1. Zielenski J. *Respiration*. 2000;67(2):117-133. **2.** Davis PB. *Am J Respir Crit Care Med*. 2006;173(5):475-482. **3.** Welsh MJ et al. Cystic fibrosis: membrane transport disorders. In: Valle D et al, eds. *The Online Metabolic & Molecular Bases of Inherited Disease*. New York, NY: The McGraw-Hill Companies Inc; 2004: part 21, chap 201. www.ommbid.com. **4.** O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. **5.** Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **6.** Kobelska-Dubiel N et al. *Prz Gastroenterol*. 2014;9(3):136-141. **7.** Ellemunter H et al. *Respir Med.* 2010;104(12):1834-1842. **8.** Marshall H et al. *Thorax*. 2017;72(8):760-762. **9.** Rybacka A, Karmelita-Katulska K. *Pol J Radiol*. 2016;81:141-145.

The role of CFTR dysfunction in cumulative organ damage in CF

CFTR dysfunction begins a cascade leading to structural damage in the lungs

The cascade can result in infection, inflammation, and damage[1-5]

- Progressive lung disease is the leading cause of CF morbidity and mortality[2,6]

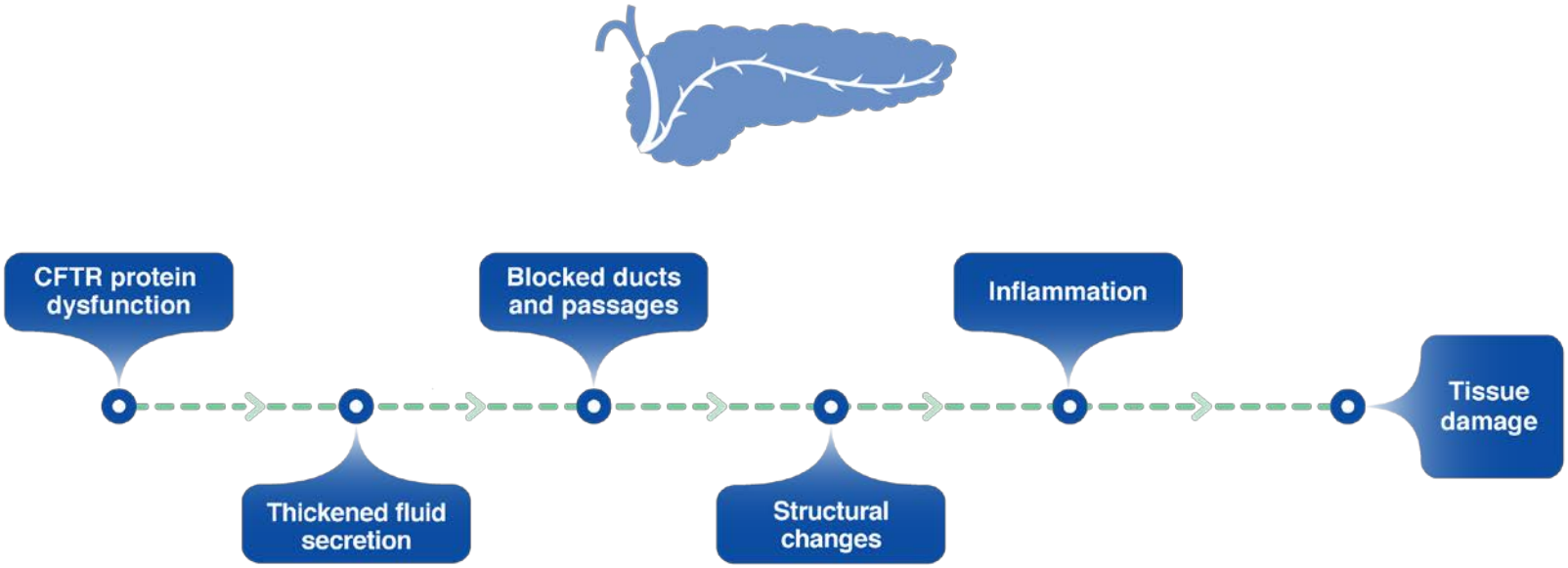


CF can also be associated with asthma-like bronchial hyperresponsiveness and constriction[7,8]

References: 1. Elborn JS. *Lancet*. 2016;388(10059):2519-2531. **2.** O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. **3.** Cantin AM et al. *J Cyst Fibros.* 2015;14(4):419-430. **4.** Lyczak JB et al. *Clin Microbiol Rev*. 2002;15(2):194-222. **5.** Levy H et al. *Pediatr Pulmonol*. 2007;42(3):256-262. **6.** Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **7.** Kent BD et al. *Pediatr Pulmonol.* 2014;49:205-213. **8.** Balfour-Lynn IM, Elborn JS. *Thorax*. 2002;57(8):742-748.

A similar cascade occurs in the pancreas, leading to organ damage[1,2]

- Damage to the pancreas is multi-factorial, driven primarily by CFTR dysfunction[1,2]

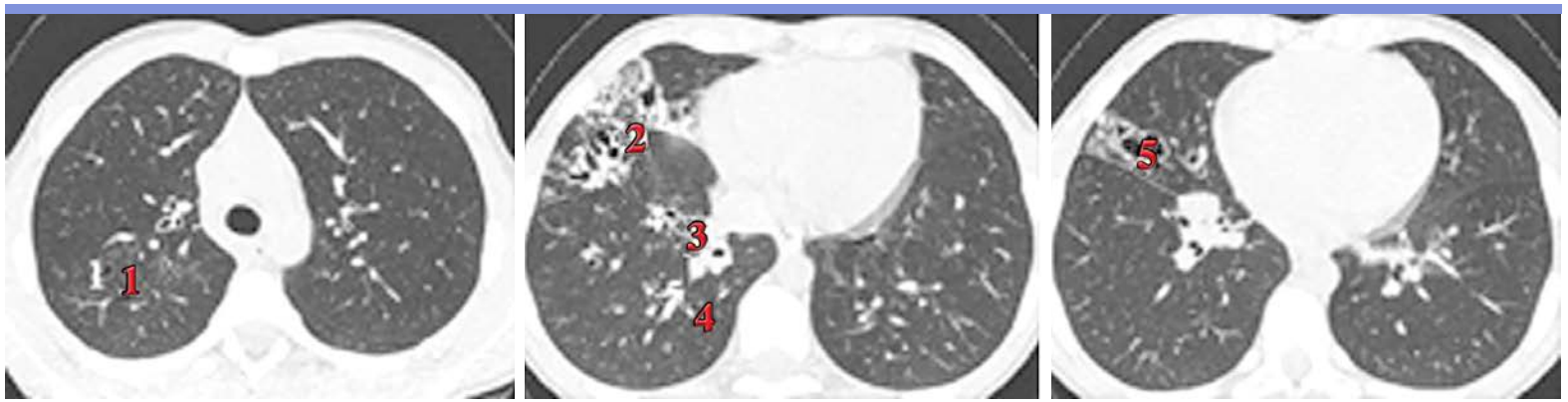


References: 1. Sathe MN et al. *Pediatr Clin North Am*. 2016;63(4):679-698. **2.** Gibson-Corley KN et al. *J Pathol*. 2016;238(2):311-320.

Lung disease begins early in CF

Patients with CF may experience structural lung damage before ppFEV$_1$ declines

HRCT scans with lung abnormalities in a 13-year-old with a ppFEV$_1$ of 99%[1]



1. Bronchiectasis

2. Peripheral cysts
3. Bronchiectasis
4. Mucus-plugged bronchus

5. Peripheral cysts

This retrospective study comprised 25 children with CF with a mean age of 10.7 years and a mean ppFEV$_1$ of 76%.[1]

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- Although ppFEV$_1$ is recommended beginning at age 3 years for training purposes and depending on child developmental level, young children frequently have difficulty performing ppFEV$_1$ reliably before the age of 6[2,3]
- Patients who can perform ppFEV$_1$ might have lung abnormalities before ppFEV$_1$ declines[4]

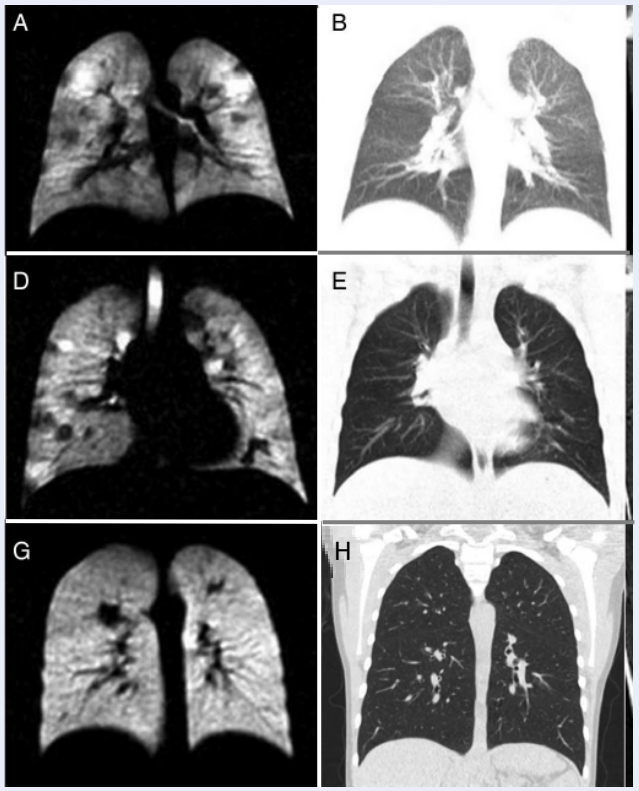
CT, computed tomography; HRCT, high-resolution computed tomography; ppFEV$_1$, percent predicted forced expiratory volume in 1 second.

References: 1. de Jong PA et al. *Radiology.* 2004;231(2):434-439. **2**. Lahiri T et al. *Pediatrics*. 2016;137(4). pii: e20151784. **3.** Beydon N et al. *Am J Respir Crit Care Med*. 2007;175(12):1304-1345**. 4.** Ellemunter H. *Respir Med.* 2010;104(12):1834-1842.

Lung disease may also be detected by MRI

The use of MRI in CF continues to evolve

- Historically, MRI has been of limited use in assessing lung disease[1]
- New MRI research techniques, such as ventilation with hyperpolarized gas, can visualize the location and extent of lung abnormalities as reliably as CT scans, but without the radiation exposure[1,2]
- However, MRI techniques remain research tools requiring specialized equipment and image acquisition techniques[3]



Three patients with CF in whom ^{3}He MRI detected abnormalities that were not detected in CT scans.[2]

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Nineteen children with CF and 10 controls were assessed. Subjects attended on a single occasion when clinically stable, and were assessed with SF_6 LCI, plethysmography, spirometry, hyperpolarized ^{3}He MRI and ^{1}H MRI. Patients with CF also underwent inspiratory and expiratory chest CT. All subjects had ppFEV$_1$ *z*-score > -1.96 and were aged between 6 and 16 years old.[2]

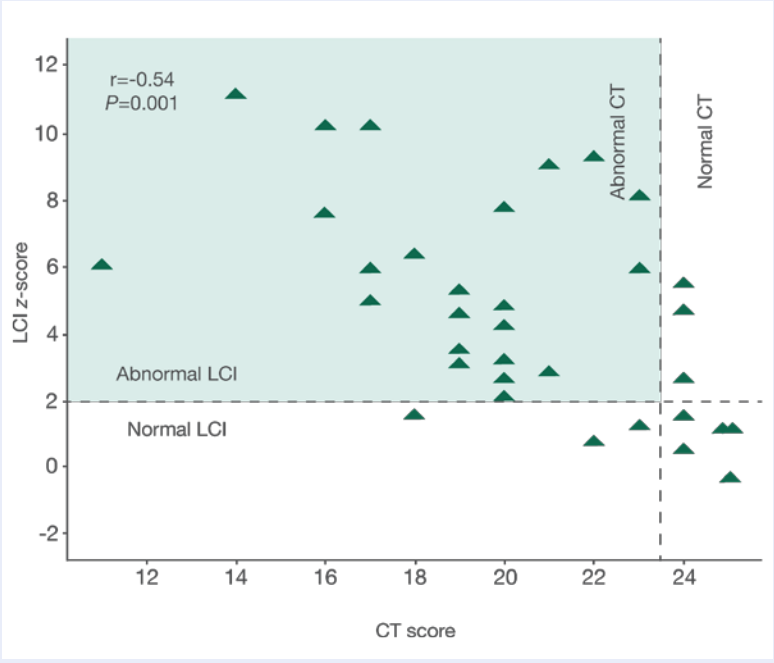
^{3}He, hyperpolarized helium-3; ^{1}H, hydrogen; LCI, lung clearance index; MRI, magnetic resonance imaging; SF_6, sulfur hexafluoride.

References: 1. Mall MA et al. *Pediatr Pulmonol*. 2016;51(S44):S49-S60. **2.** Marshall H et al. *Thorax*. 2017;72(8):760-762. **3**. Dasenbrook EC et al. *PLoS One*. 2013;8(9):e73286. doi:10.1371/journal.pone.0073286.

Lung clearance index (LCI) detects early CF airway disease

- LCI is most often used as an endpoint in research trials, especially in young patients to assess lung function. Its clinical use is evolving[1]
- LCI is more sensitive to small peripheral airway abnormalities than $ppFEV_1$[2]

LCI *z*-score vs CT score[3]



- LCI shows a significant correlation with CT scan for verification of early disease[3]
- In the same study, LCI *z*-score and CT scans revealed pulmonary disease in almost 80% of the study population with normal $ppFEV_1$[3]

Study evaluated 34 patients with CF and normal $ppFEV_1$ age 6-26 years (mean age 14 years), 26 of whom were found to have early lung disease on CT scan and LCI.[3]

Reprinted from Ellemunter H et al. *Respir Med*. 2010;104(12):1834-1842, with permission from Elsevier.

References: 1. Stanojevic S et al. *Am J Respir Crit Care Med*. 2017;195(9):1216-1225. **2.** Kent L et al. *J Cyst Fibros.* 2014;13(2):123-138. **3.** Ellemunter H et al. *Respir Med.* 2010;104(12):1834-1842.

Pancreatic insufficiency and the progression of CF pancreatic disease

CF affects both the exocrine and endocrine functions of the pancreas

- In the healthy pancreas, CFTR channels regulate chloride and bicarbonate secretion, which, in turn, affects the composition of pancreatic fluids that carry enzymes into the intestine[1]
- In CF, these processes are altered due to CFTR dysfunction[1]

Blocked pancreatic ducts

Exocrine: CFTR dysfunction causes clogged pancreatic ducts. Enzymes unable to pass into the intestines break down the pancreas itself, leading to[1,2]:

- Organ damage and scarring (fibrosis)
- Inflammation

Endocrine: Islet β cells, which regulate insulin secretion, can be lost in CF due to a variety of mechanisms[1,3]

- CF-related diabetes can occur in up to 2% of children age <10 years, 19% of adolescents age 10 to 19 years, and 40% to 50% of adults[3,4]

References: 1. Gibson-Corley KN et al. *J Pathol*. 2016;238(2):311-320. **2.** O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. **3.** Rana M et al. *Nat Rev Endocrinol*. 2010;6(7):371-378. **4.** Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017.

Pancreatic exocrine insufficiency is a common early problem in CF

CFTR activity[1] **Sweat chloride level[1]**	**100 mmol/L** **0%**	**30 mmol/L**		**<30 mmol/L** **100%**
Pancreatic function[1,2]	**90% pancreatic insufficiency by age 1**	**50% pancreatic insufficiency**		**Normal pancreatic function**
Typical mutations[1]	***F508del*** ***G542X*** ***G551D***	***R117H(5T)*** ***R334W***	**Carrier**	**Healthy**

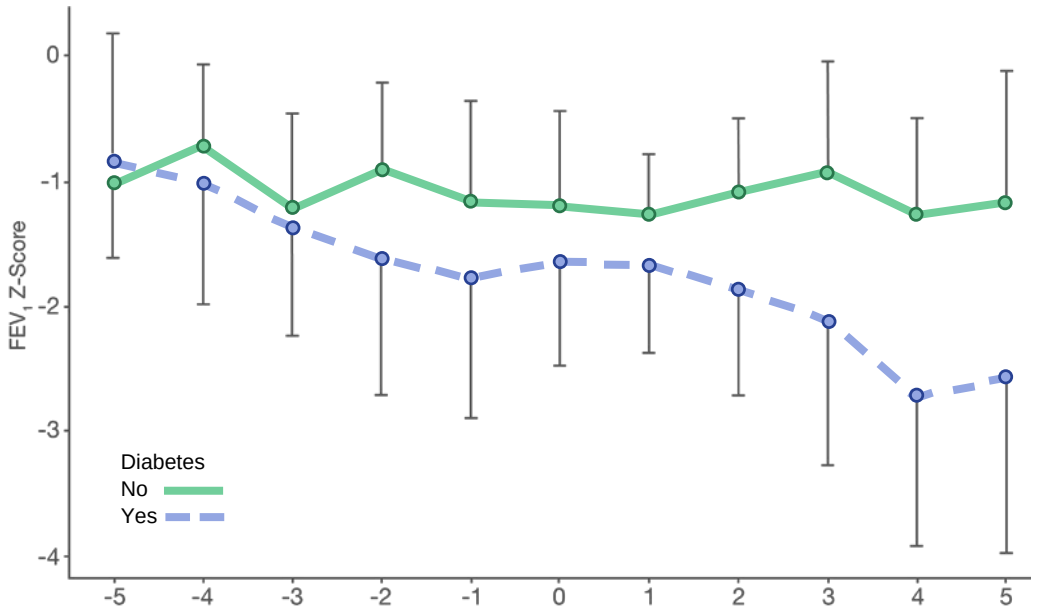
- Genotypes that result in little to no CFTR function are typically associated with pancreatic insufficiency[1,3]
  - Up to 60-90% of newborns are pancreatic insufficient at birth or shortly afterward, and structural abnormalities are often present in utero[1,2,4]
- Genotypes that result in at least some CFTR function are typically associated with pancreatic sufficiency[1]

References: 1. Elborn JS. *Lancet*. 2016;388(10059):2519-2531. **2.** O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. **3.** Gibson-Corley KN et al. *J Pathol*. 2016;238(2):311-320. **4.** Borowitz D et al. *J Pediatr*. 2009;155(6 Suppl):S73-S93.

CF-related diabetes is associated with more severe disease

- Patients with glucose intolerance and poorly controlled CF-related diabetes have lower average ppFEV$_1$[1,2]

Median FEV$_1$ *z*-scores in patients with CF with and without diabetes[3]



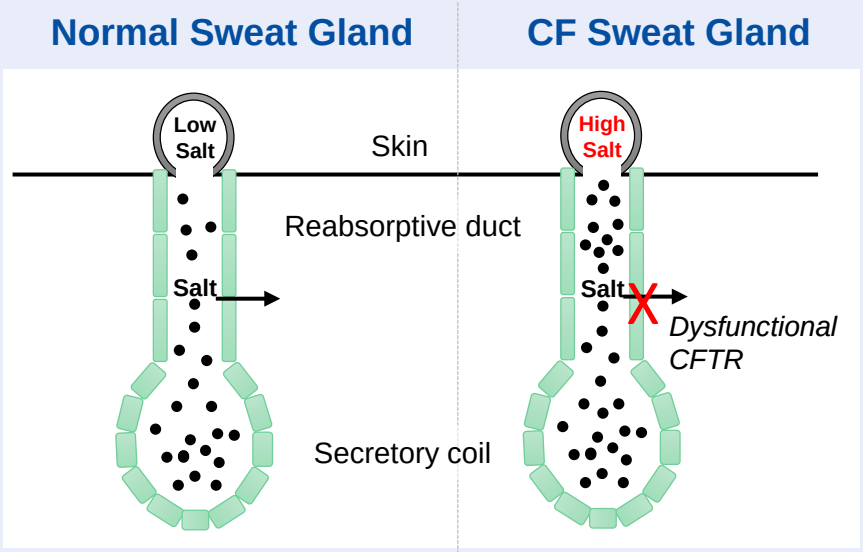
Adapted from Terliesner N et al. *J Pediatr Endocrinol Metab.* 2017;30(8):815-821. Retrospective study in 32 patients with CF diagnosed as having CF-related diabetes (n=16) vs matched patients without diabetes (n=16).[3]

References: 1. Gibson-Corley KN et al. *J Pathol*. 2016;238(2):311-320. **2.** Leclercq A et al. *J Cyst Fibros*. 2014;13(4):478-484. **3.** Terliesner N et al. *J Pediatr Endocrinol Metab*. 2017;30(8):815-821.

Elevated sweat chloride levels are diagnostic of CF

Sweat Chloride Guidelines in the Diagnosis of CF[1]	
Sweat Chloride Level (mmol/L)	Relation to CF
<30	**CF unlikely**
30 to **59**	**Warrants further diagnostic tests**
≥60	**Consistent with CF**

The sweat gland is a tube-shaped structure in the skin, and has a secretory coil and a reabsorptive duct[2]



Normal sweat contains water and salt (sodium chloride). As fluid passes through the reabsorptive duct, salt is absorbed back into the body. The remaining fluid is emitted onto the skin as sweat.

In CF, the CFTR channel is unable to reabsorb chloride back into the body, resulting in sweat with a high chloride concentration.

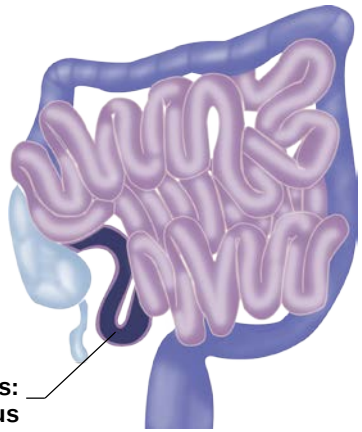
References: 1. Farrell PM et al. *J Pediatr*. 2017;181S:S4-S15.e1. **2.** Mishra A et al. *Clin Biochem Rev*. 2005;26(4):135-153.

Signs of early CF progression may be seen in other organs

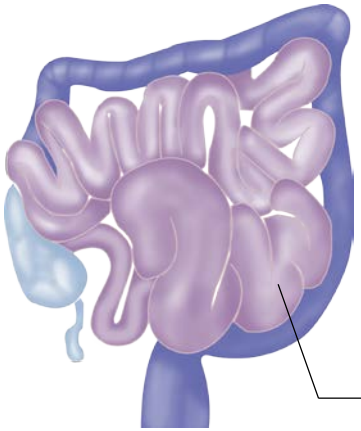
Gastrointestinal function and nutritional status can be affected by CF

Signs may be apparent in the first days of life

- CFTR dysfunction alters intestinal secretions, which, along with pancreatic dysfunction, can reduce intestinal motility and contribute to reduced nutrient absorption[1-3]
- Common symptoms include constipation and abdominal pain[3]



- 1% to 21% of newborns with CF have gastrointestinal problems, such as meconium ileus, within the first days of life[1,4]



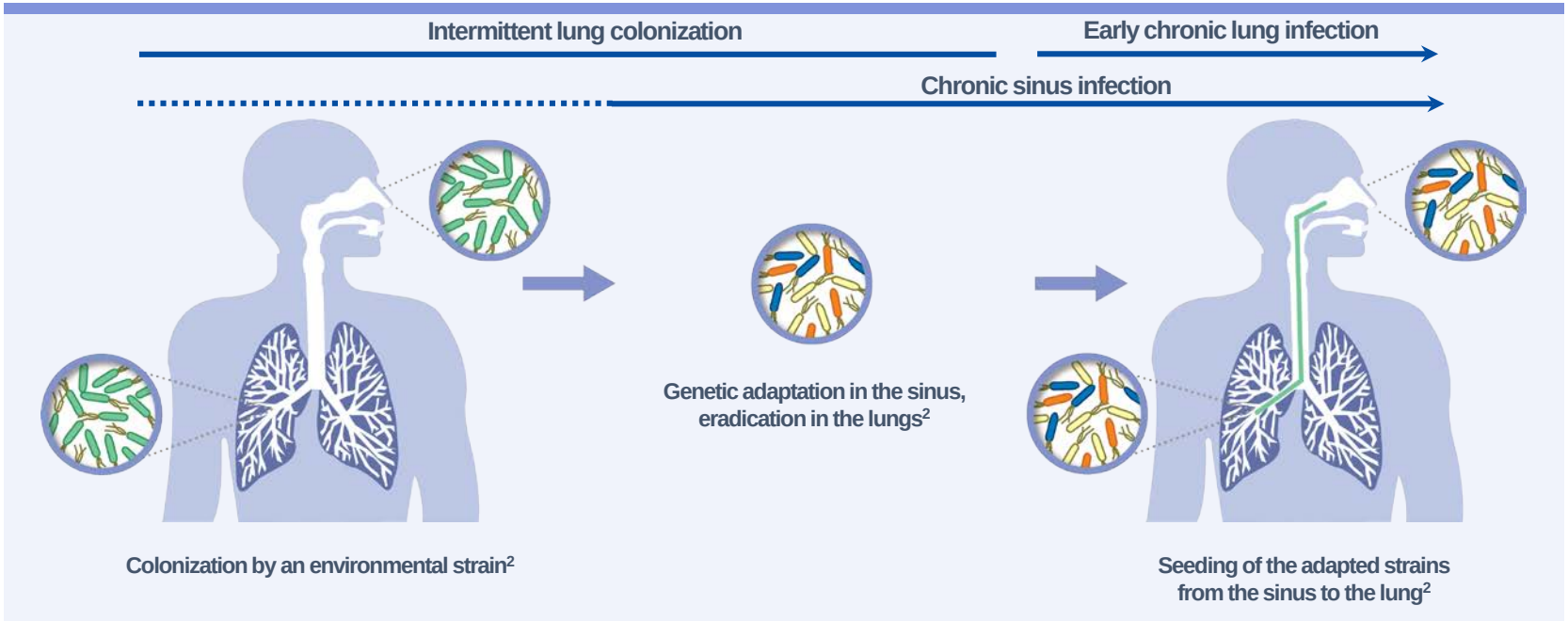
- Distal intestinal obstructive syndrome (DIOS) in older children and adults presents with clinical overlap to meconium ileus seen in newborns[5]

- DIOS may occur in **15% of all patients** with CF[4,6]
- One study found that **65% of adults with DIOS had meconium ileus** as newborns[1]

References: 1. Lavie M et al. *World J Gastroenterol*. 2015;21(1):318-325. **2.** O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. **3.** Haller W et al. *J Gastroenterol Hepatol.* 2014;29(7):1344-1355. **4.** Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **5.** Abraham JM, Taylor CJ. *J Cyst Fibros*. 2017;16 Suppl 2:S40-S49. **6.** Averill S et al. *AJR Am J Roentgenol*. 2017;209(1):3-18.

Sinusitis is common in children and may contribute to lung infections

- Chronic rhinosinusitis is common in children with CF and incidence increases with age[1]
- Overall, sinus disease is found in up to 22% of children with CF[1]



Adapted from Folkesson A et al. *Nat Rev Microbiol*. 2012;10(12):841-851, with permission from Springer Nature.

- Sinus infections are difficult to eradicate and can serve as a reservoir for pathogens to repeatedly infect the lungs, although the role of sinuses in the development of chronic lung infection needs further elucidation[2,3]

References: 1. Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **2.** Folkesson A et al. *Nat Rev Microbiol*. 2012;10(12):841-851. **3.** Hansen SK et al. *ISME J*. 2012;6(1):31-45.

CF results in a variable but progressive disease course

- Organ damage in CF is the result of CFTR protein dysfunction, and affects the lungs, pancreas, and other organs[1-4]
- Patients may experience lung damage before a decline in lung function is detected by spirometry[5]
- CT, MRI, and LCI may detect lung abnormalities before ppFEV$_1$ declines[5-7]
- CF affects both the exocrine and endocrine functions of the pancreas[3,8]
  - Loss of either function is a common problem in CF associated with more severe lung disease
- CF also affects sweat gland function, with sweat chloride levels being diagnostic of CF[1,9]
- Gastrointestinal function and BMI are affected by CF, with signs apparent in the first days of life[2,3,10]
- Sinusitis is common in children with CF and may contribute to lung infections[11,12]

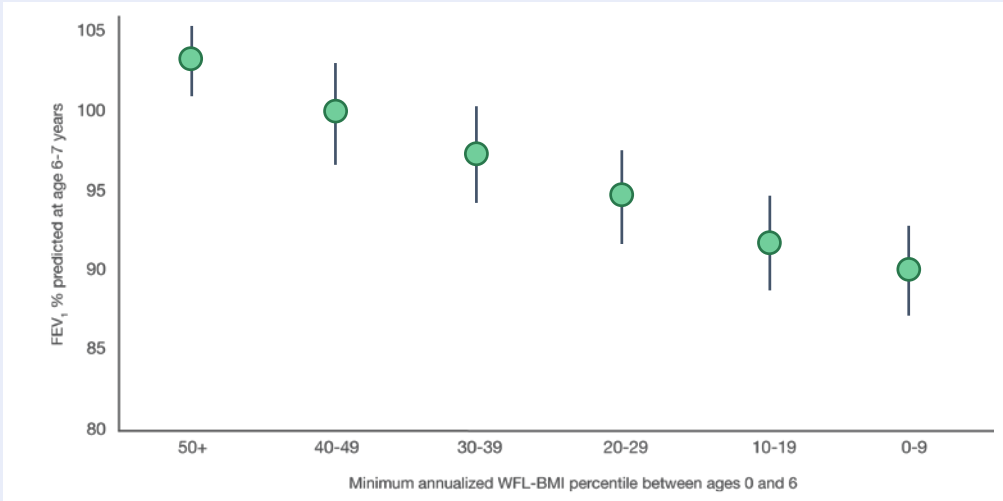
References: 1. Elborn JS. *Lancet*. 2016;388(10059):2519-2531. **2.** O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. **3.** Gibson-Corley KN et al. *J Pathol*. 2016;238(2):311-320. **4.** Abraham JM, Taylor CJ. *J Cyst Fibros*. 2017;16 Suppl 2:S40-S49. **5.** Ellemunter H. *Respir Med.* 2010;104(12):1834-1842. **6.** de Jong PA et al. *Radiology.* 2004;231(2):434-439. **7.** Marshall H et al. *Thorax*. 2017;72(8):760-762. **8.** Leclercq A et al. *J Cyst Fibros*. 2014;13(4):478-484. **9.** Farrell PM et al. *J Pediatr.* 2017;181S:S4-S15.e1. **10.** Lavie M et al. *World J Gastroenterol*. 2015;21(1):318-325. **11.** Hansen SK et al. *ISME J*. 2012;6(1):31-45. **12.** Folkesson A et al. *Nat Rev Microbiol*. 2012;10(12):841-851.

Methods to detect and monitor early CF progression

Patient growth and nutrition

Assessments	Considerations
Physical examination, signs, symptoms	• Useful for all systems: Respiratory, gastrointestinal, liver, etc[1-3]
Growth and nutrition, e.g.: • **Body mass index (BMI)** • **Weight-for-length (WFL)**	• Nutritional status is correlated with other clinical parameters, such as lung function[3]

Low WFL-BMI percentile before age 6 and ppFEV$_1$ at ages 6 to 7 years[4]



Reprinted from Sanders DB et al. *J Pediatr*. 2015;167(5):1081-1088, with permission from Elsevier.
BMI, body mass index.

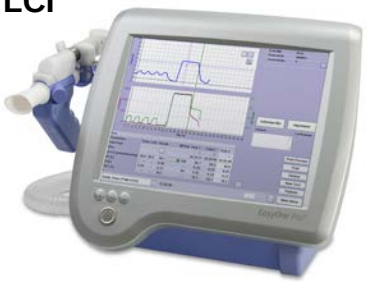
References: 1. Abraham JM, Taylor CJ. *J Cyst Fibros*. 2017;16 Suppl 2:S40-S49. **2.** Debray D et al. *J Cyst Fibros*. 2011;10(Suppl 2):S29-S36. **3.** O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. **4.** Sanders DB et al. *J Pediatr*. 2015;167(5):1081-1088.

Lung function tests

Assessments	Considerations
Spirometry (e.g., ppFEV$_1$)	• Athough ppFEV$_1$ is recommended beginning at age 3 years, young children frequently have difficulty performing ppFEV$_1$ reliably[1,2] • ppFEV$_1$ may not show a decline in lung function despite underlying disease in the lungs[3]
Lung Clearance Index (LCI)	• Correlates to lung abnormalities detected by imaging more accurately than ppFEV$_1$ in early stages of disease in young children[3,4] • May be easier to perform in younger patients[5] • Has been used as an endpoint in research trials of young pediatric patients to assess lung function[5] • Clinical use of LCI is evolving[4]

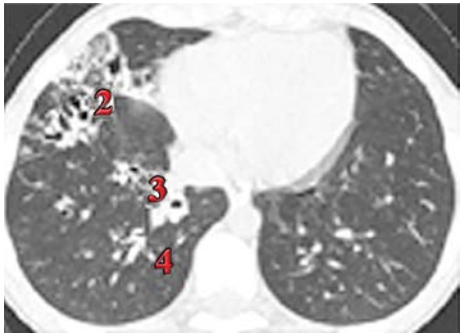
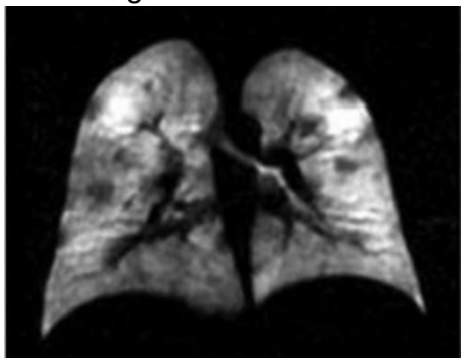
Spirometry

LCI



References: 1. Lahiri T et al. *Pediatrics*. 2016;137(4). pii: e20151784 **2.** Beydon N et al. *Am J Respir Crit Care Med*. 2007;175(12):1304-1345**. 3.** Ellemunter H. *Respir Med.* 2010;104(12):1834-1842. **4.** Davies G et al. *Expert Rev Respir Med.* 2017;11(1):21-28. **5.** Kent L et al. *J Cyst Fibros*. 2014;13(2):123-138.

Lung imaging

Assessments	Considerations
Computed Tomography (CT) Scan	• Visualizes structure and abnormalities of the lungs[1] • More sensitive than ppFEV$_1$ in detecting early lung disease and monitoring progression[1] • Radiation burden with frequent imaging may be a concern[1] CT scan image of lung damage[2,a]  2. Peripheral cysts 3. Bronchiectasis 4. Mucus-plugged bronchus
Magnetic Resonance Imaging (MRI)	• Can visualize structure and function of the lungs and other organs[3] • Does not use radiation[3,4] • Emerging MRI techniques used in research include: − Ventilation MRI of the lungs with hyperpolarized gas[4] − Ultra-short echo time (UTE) sequences[3,5] MRI image of lung abnormalities[4,b] 

[a]Image adapted from de Jong PA et al. *Radiology*. 2004;231(2):434-439, with permission from RSNA Rights. [b]Image adapted from Marshall H et al. *Thorax*. 2017;72(8):760-762, with permission from BdeMJ Publishing Group Limited.

References: 1. Gustafsson PM et al. *Thorax*. 2008;63(2):129-134. **2.** de Jong PA et al. *Radiology.* 2004;231(2):434-439. **3.** Roach DJ et al. *Ann Am Thorac Soc*. 2016;13(11):1923-1931. **4.** Marshall H et al. *Thorax*. 2017;72(8):760-762. **5.** Mall MA et al. *Pediatr Pulmonol.* 2016;51(S44):S49-S60.

Lab assessments

Assessments	Considerations
Liver Function Tests (including ALT, AST, AP, GGT)	• Up to 85% of patients with CF may have 2 or more abnormal liver function tests (particularly ALT) by age 21 years[1] • CF-related liver disease should be considered if any 2 of the following are present[2]: - Elevated transaminases (AST and ALT) and GGT levels >ULN on at least 3 consecutive assessments in 1 year, after excluding other causes - Physical exam, ultrasound, or biopsy suggest liver disease
Exploratory Assessments	**Considerations**
Fecal Elastase-1 (FE-1)	• Measures pancreatic exocrine function[3,4] • Low FE-1 after 2 weeks of age signifies pancreatic insufficiency and can help identify pancreatic insufficient patients with inconclusive sweat chloride levels[5,6] • Use in clinical trials is currently limited to an exploratory endpoint[7] • Assessed from stool samples that are easily obtained from patients of all ages[4]
Immunoreactive Trypsinogen (IRT)	• Elevations indicate pancreatic damage[8] • IRT levels in blood may be raised in infants with CF[8,9] • Used in neonatal screening for CF, along with other diagnostic tests, to verify the diagnosis of CF[8,9]

ALT, alanine transaminase; AST, aspartate transaminase; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

References: 1. Woodruff SA et al. *J Cyst Fibros*. 2017;16(1):139-145. **2.** Debray D et al. *J Cyst Fibros*. 2011;10(Suppl 2):S29-S36. **3.** Sathe MN et al. *Pediatr Clin North Am*. 2016;63(4):679-698. **4.** Walkowiak J et al. *J Cyst Fibros*. 2016;15(5):664-668. **5.** Daftary A et al. *J Cyst Fibros*. 2006;5(2):71-76. **6.** Barben J et al. *J Cyst Fibros*. 2016;15(3):313-317. **7.** Bodewes FA et al. *Pediatr Pulmonol*. 2016;51(S44):S18-S22. **8.** O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. **9.** Paracchini V et al. *JIMD Rep*. 2012;4:17-23.

CF is a progressive, multi-systemic disease

Signs and symptoms appear early in life

Lung damage begins early—and can go undetected[1-3]

Pancreatic complications often begin at birth, affecting exocrine function; loss of endocrine function can occur in adulthood[4,5]

Gastrointestinal function can be affected by CF[6]

Sinusitis is common even in children and may contribute to lung infections[7,8]

Signs of CF progression can be detected early with established and emerging techniques[4,9-11]

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