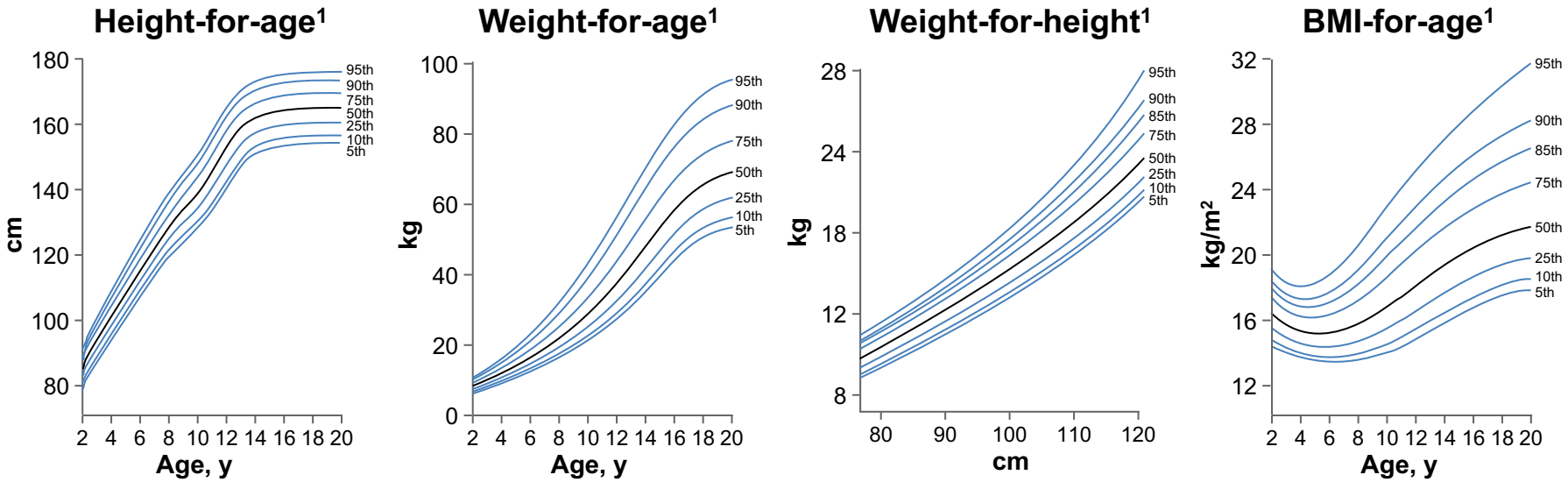
Growth in Children and Adolescents With Cystic Fibrosis

Objectives

- Discuss the relation between mutations in cystic fibrosis transmembrane conductance regulator (*CFTR*) and growth in patients with cystic fibrosis (CF)
- Explore the consequences of growth deficiency in patients with CF
- Consider factors relevant to evaluation of growth in patients with CF
- Examine the effects of improvements in care on CF growth indices

VERTEX

Growth in Children and Adolescents Is Assessed in Multiple Ways

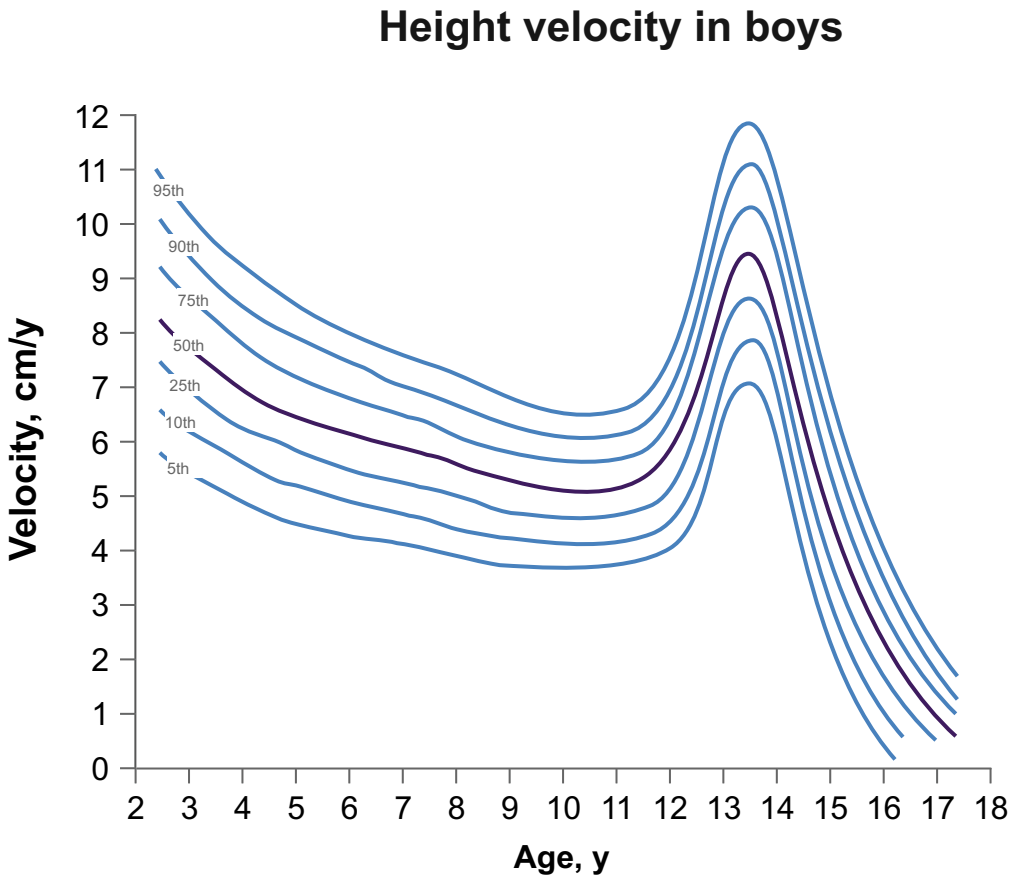


- Common methods for monitoring growth rates in children include height-for-age (HFA), weight-for-age (WFA), weight-for-height (WFH), and BMI-for-age[1]
  - Often expressed as percentiles[1]
  - Height measurements are often reported as “target height”, accounting for the child’s parents stature[2]
- Other growth and nutritional indices include percent ideal body weight[3] and lean body mass (LBM; also referred to as fat-free mass)[4]

BMI, body mass index.

1. Centers for Disease Control and Prevention. CDC Growth Charts. http://www.cdc.gov/growthcharts. Accessed April, 2020. 2. Zhang Z et al. *J Cyst Fibros.* 2010;9(2):135-142. 3. Hirche TO et al. *J Cyst Fibros.* 2009;8(4):238-244. 4. Veldhuis JD et al. *Endocr Rev*. 2005;26(1):114-146.

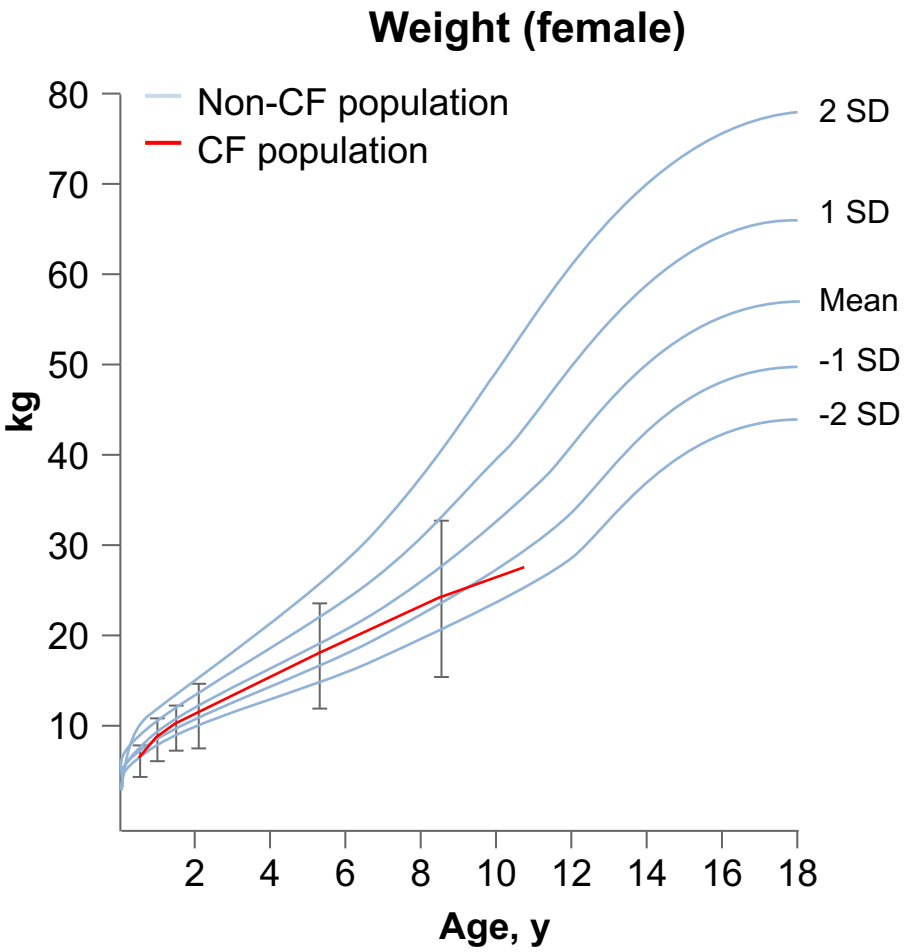
Growth Curves Help Determine Individual Growth Trajectories



- Early childhood and the stages of puberty are associated with differences in height velocity

Reprinted from *The Journal of Pediatrics*, 107(3), Tanner JM, Davies PSW, Clinical longitudinal standards for height and height velocity for North American children, 317 329, © 1985, with permission from Elsevier.
Tanner JM, Davies PSW. *J Pediatr.* 1985;107(3):317-329.

Patients With CF May Have Weight Deficits

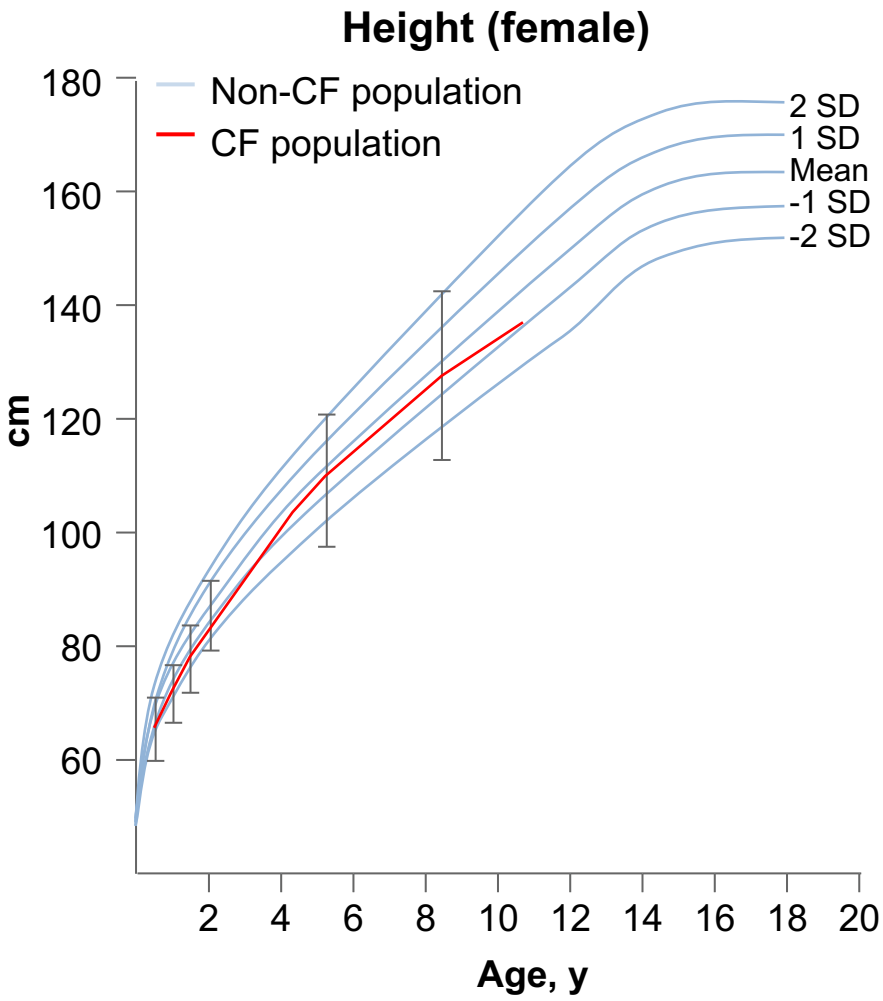


- Mean weight of CF population is lower than control population

Age, y	N	Weight Z-Score (male and female)		
		Mean	95% CI	*P* Value
1	34	-1.1	-1.5 to -0.8	<0.001
1.5	32	-0.9	-1.3 to -0.7	<0.001
2	31	-0.6	-0.93 to -0.2	0.001
5	27	-0.6	-1.03 to -0.1	0.008
8	17	-0.66	-1.13 to 0.0	0.012
11	9	-0.7	-1.3 to -0.2	0.003

SD, standard deviation.
Reprinted from *Journal of Cystic Fibrosis*, 2(2), Keller BM et al, Growth in prepubertal children with cystic fibrosis, homozygous for the Delta F508 mutation, 76-83, © 2003, with permission from Elsevier.
Keller BM et al. *J Cyst Fibros.* 2003;2(2):76-83.

Patients With CF May Have Height Deficits

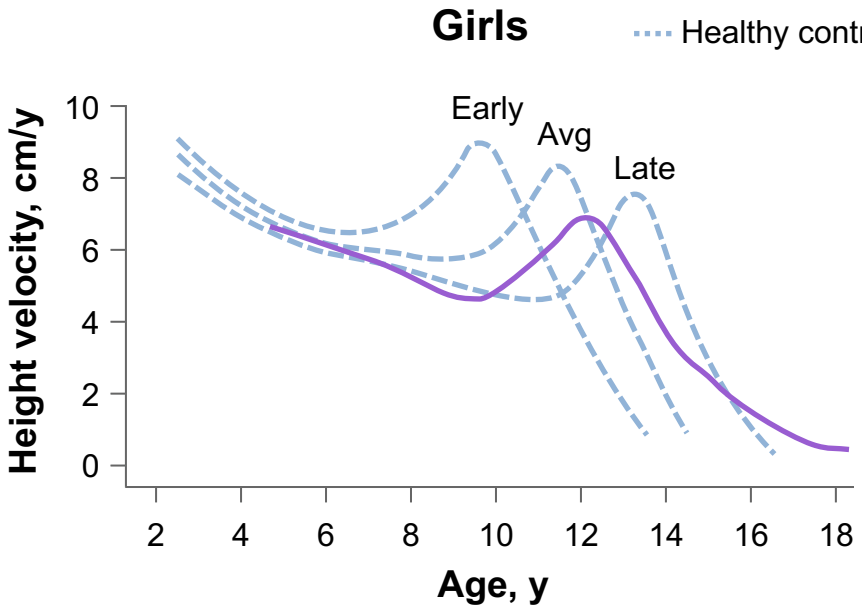


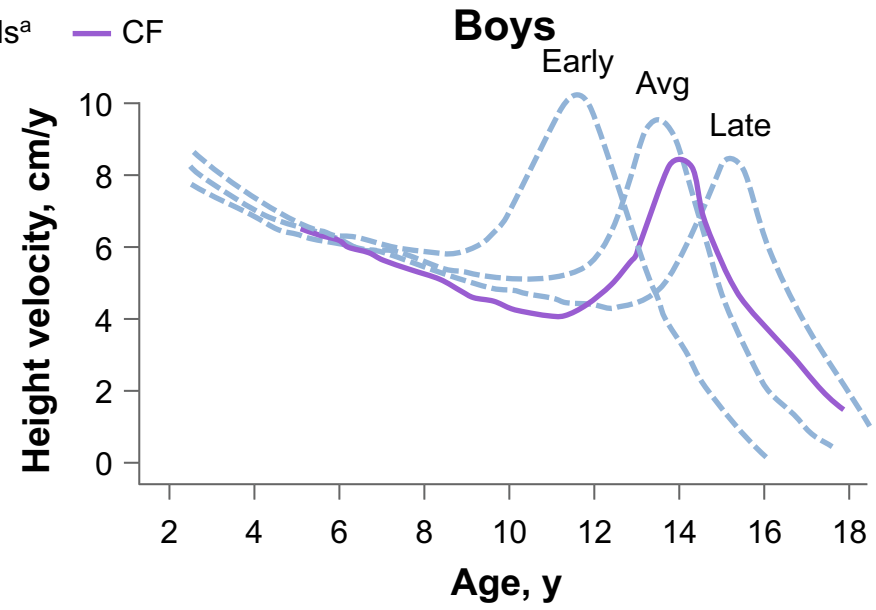
- Mean height of CF population is lower than control population

Age, y	N	Height Z-Score (male and female)		
		Mean	95% CI	*P* Value
1	34	-1.1	-1.5 to -0.7	<0.001
1.5	32	-1.3	-1.7 to -0.8	<0.001
2	31	-0.5	-0.8 to -0.1	0.007
5	27	-0.4	-0.8 to 0.0	0.028
8	17	-0.2	-0.8 to 0.4	0.251
11	9	-0.7	-1.4 to 0.0	0.028

Reprinted from *Journal of Cystic Fibrosis*, 2(2), Keller BM et al, Growth in prepubertal children with cystic fibrosis, homozygous for the Delta F508 mutation, 76-83, © 2003, with permission from Elsevier.
Keller BM et al. *J Cyst Fibros.* 2003;2(2):76-83.

Growth Velocity Is Reduced and Delayed in Patients With CF





Population	PHV, cm/y	Age at PHV, y
CF	7.0	12.1
Control early bloomers	9.0	9.7
Control average bloomers	8.3	11.5
Control late bloomers	7.5	13.3

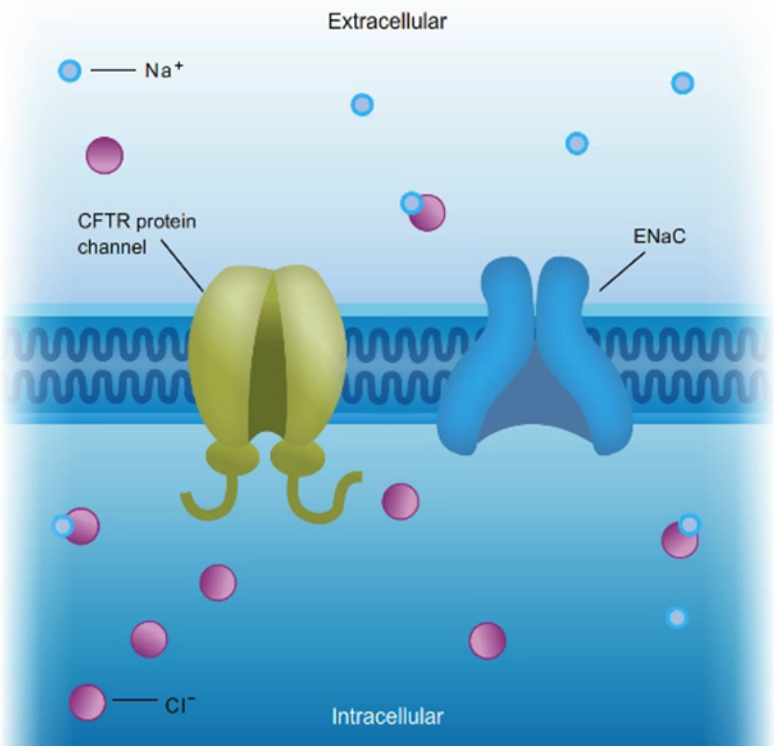
Population	PHV, cm/y	Age at PHV, y
CF	8.4	14.0
Control early bloomers	10.3	11.7
Control average bloomers	9.5	13.5
Control late bloomers	8.5	15.3

PHV, peak height velocity.
[a]50th percentile curves for early, average, and late bloomers.
Reprinted from *The Journal of Pediatrics*, 163(2), Zhang Z et al, Pubertal height velocity and associations with prepubertal and adult heights in cystic fibrosis, 376-382, © 2013, with permission from Elsevier.
Zhang Z et al. *J Pediatr.* 2013;163(2):376-382.

Growth in CF: The Role of CFTR

CFTR Channels Regulate Fluid and Electrolyte Balance in Epithelial Tissues

CFTR channels act in tandem with ENaC to regulate fluid and electrolyte balance[1,2]



CFTR gene mutations can result in CFTR protein channel abnormalities – the underlying defect of CF disease[3]

CFTR, Cystic Fibrosis Transmembrane conductance Regulator; ENaC, epithelial sodium channels.

1. MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10; 2. Goralski JL et al. *Curr Opin Pharmacol* 2010;10:294–9; 3. Rowe SM et al. *N Engl J Med* 2005;352:1992–2001

CFTR Gene Mutations Give Rise to CFTR Protein Channel Defects That Reduce Cl- and Other Ion Transport

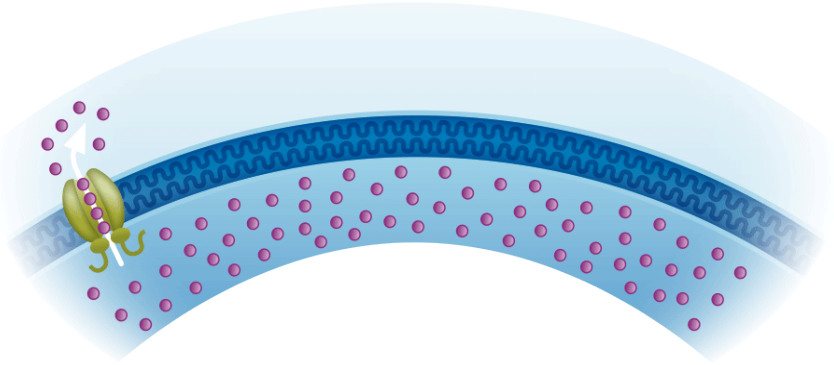
CFTR Quantity

Number of CFTR Channels in the Apical Surface

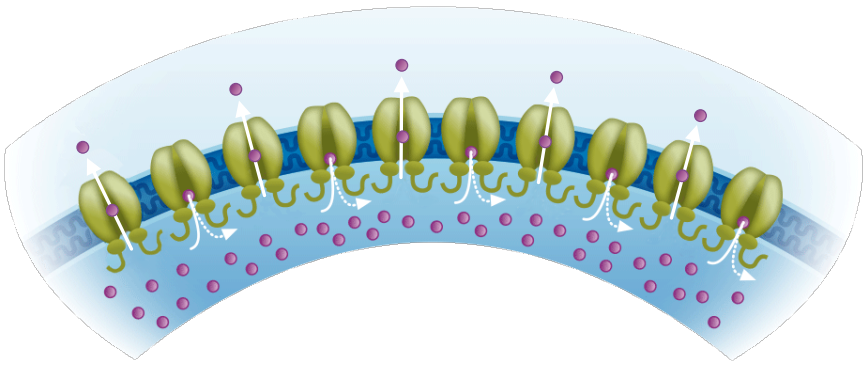
CFTR Function

Channel Open Probability ✖ Channel Conductance

Mutations that reduce the **QUANTITY** of functional CFTR proteins that reach the apical cell surface



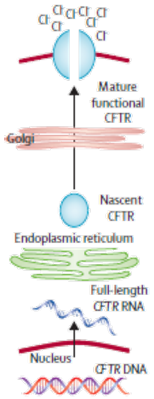
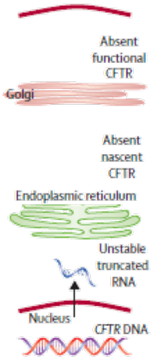
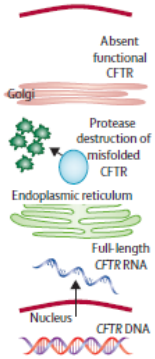
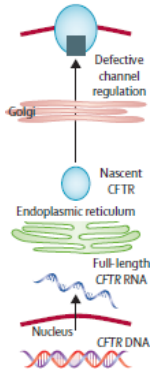
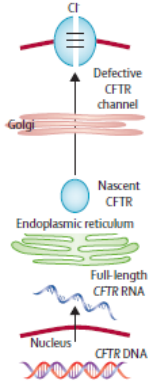
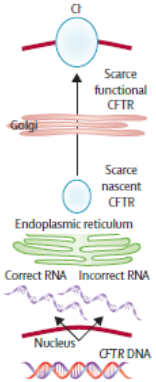
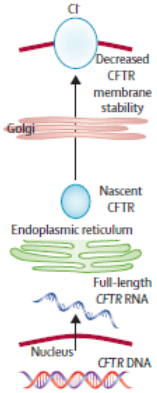
Mutations that reduce the **FUNCTION** of CFTR proteins at the apical cell surface



- CFTR channels conduct bicarbonate in addition to chloride ions.

MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10

CFTR Mutations Have Traditionally Been Classified I-VI Based on the Types of Molecular Defects

Normal	I	II	III	IV	V	VI
						
CFTR defect	No synthesis	Processing/ trafficking defect	Gating defect	Conductance defect	Reduced synthesis	Surface stability defect
Type of mutations	Nonsense, frameshift, canonical splice	Missense, amino acid deletion	Missense, amino acid change	Missense, amino acid change	Missense, non-canonical splice	Missense, amino acid change

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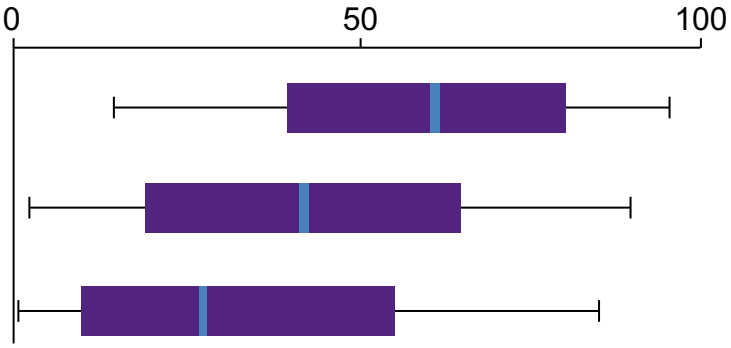
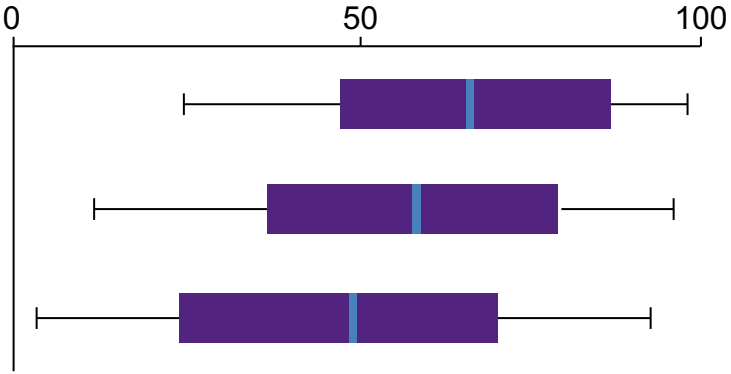
CFTR Class I-III Mutations Influence Growth More Than Those Associated With Residual Protein Function (Class IV-V) (US data)

Mutation Class I-III Group, WHO Nutritional Outcomes for Individuals Under 24 Months



	Median	5th Percentile	95th Percentile
Weight-for-length N=1225	61.4	14.7	95.2
Weight percentile N=1258	42.3	2.3	89.5
Length percentile N=1255	27.9	0.7	85.3

Mutation Class IV-V Group, WHO Nutritional Outcomes for Individuals Under 24 Months

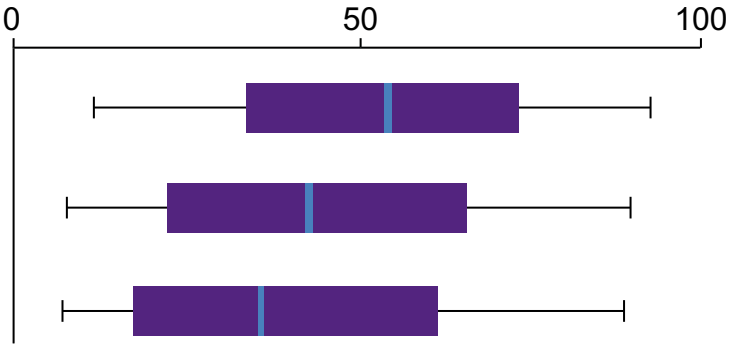


	Median	5th Percentile	95th Percentile
Weight-for-length N=187	66.1	24.2	97.8
Weight percentile N=188	58.7	11.3	95.7
Length percentile N=187	49.3	3.2	92.6

WHO, World Health Organization.
Cystic Fibrosis Foundation Patient Registry 2014 Annual Data Report Bethesda, Maryland ©2015 Cystic Fibrosis Foundation

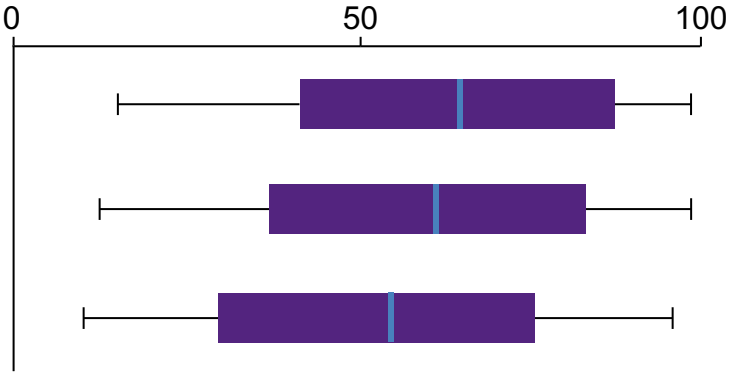
CFTR Mutation Class Influences Growth Throughout Adolescence (US data)

Mutation Class I-III Group, CDC Nutritional Outcomes for Individuals 2 to 19 Years



	Median	5th Percentile	95th Percentile
BMI percentile N=1245	51.9	7.0	92.1
Weight percentile N=1374	40.2	2.8	89.0
Height percentile N=1373	32.8	1.8	87.9

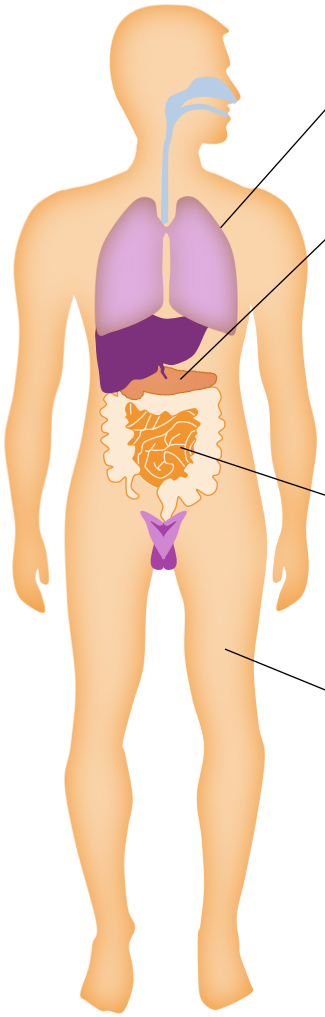
Mutation Class IV-V Group, CDC Nutritional Outcomes for Individuals 2 to 19 Years



	Median	5th Percentile	95th Percentile
BMI percentile N=14,401	63.2	10.4	98.1
Weight percentile N=15,651	59.4	7.7	98.0
Height percentile N=15,697	52.6	5.5	95.1

CDC, Centers for Disease Control and Prevention.
Cystic Fibrosis Foundation Patient Registry 2014 Annual Data Report Bethesda, Maryland ©2015 Cystic Fibrosis Foundation

CFTR Deficits Affect Organs That Influence Growth



Lung

- Lung inflammation increases resting metabolic rate[1]

Pancreas

- Exocrine pancreatic insufficiency results in lack of bicarbonate and digestive enzyme secretion[1]
- Endocrine pancreatic insufficiency may lead to CF-related diabetes (CFRD) and energy loss via glycosuria[1]
- CFRD at puberty delays growth spurt and reduces final height[4]

Gastrointestinal tract

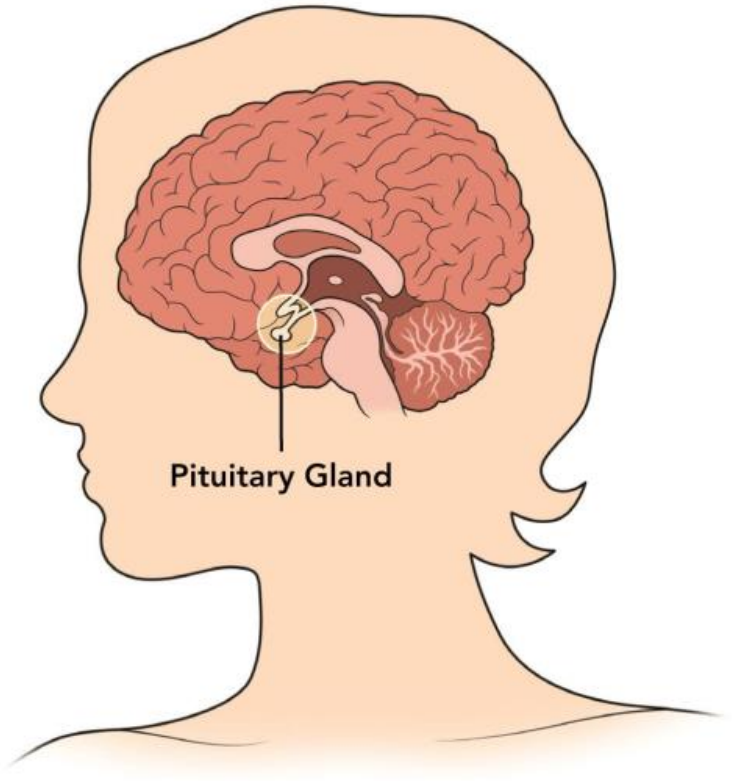
- Acidic pH and thick, sticky mucus impede digestive enzyme activity and absorption of nutrients leading to energy loss[1]

Bone

- Increased bone turnover (↑resorption ↓formation) is a characteristic of CF-related bone disease[2]
- Low bone mineral content (BMC) is related to altered body size[3]

1. Pencharz PB, Durie PR. *Clin Nutr.* 2000;19(6):387-394. 2. Stalvey MS, Clines GA. *Curr Opin Endocrinol Diabetes Obes.* 2013;20(6):547-552. 3. Kelly A et al. *J Clin Densitom.* 2008;11(4):581-589. 4. Bizzarri C et al. *Pediatr Pulmonol.* 2015;50(2):144-149.

Non-CFTR-Related Complications May Also Influence Growth in Patients With CF



Loss of appetite due to medications,[1] anxiety, depression,[2] and stress[3] related to chronic disease*

- Loss of appetite compounds growth problems
- Health-related quality of life is significantly associated with growth[4]

Discordant growth hormone/IGF-1 axis[5]

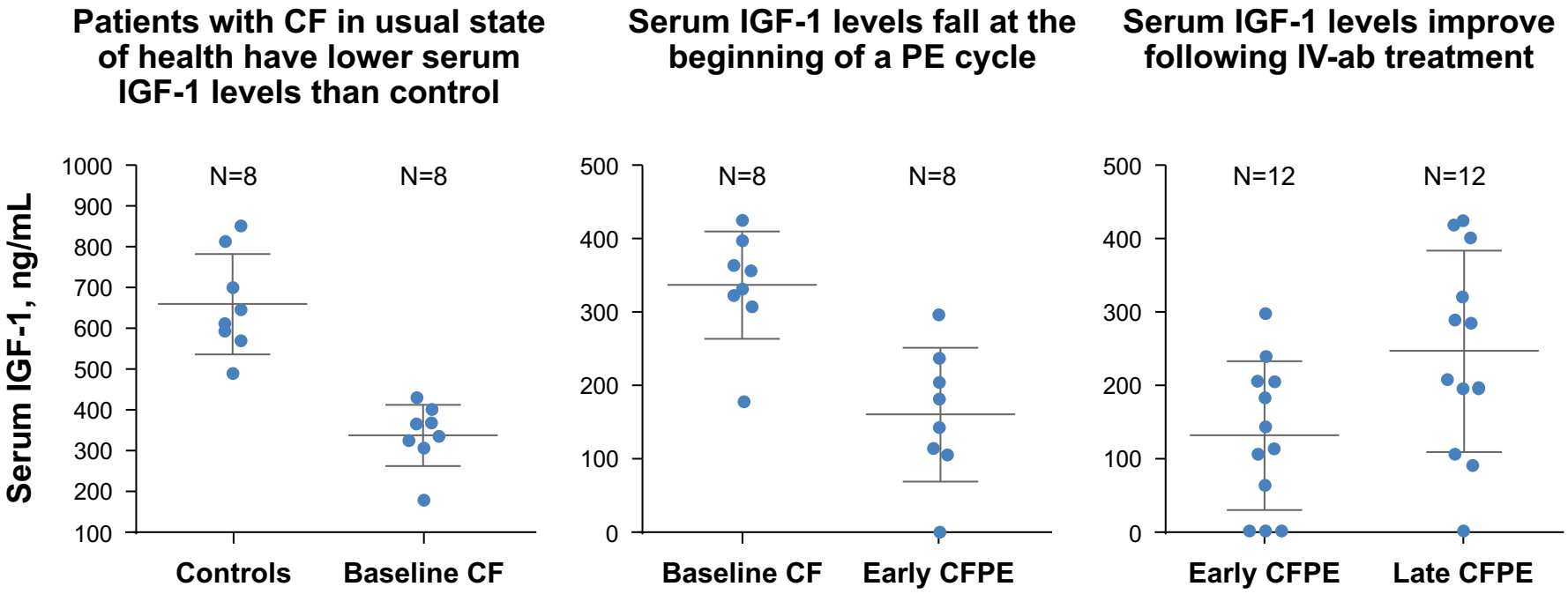
- Normal growth hormone levels, but low levels of effector proteins (eg, IGF-1)

*CFTR is expressed in the hypothalamus (involved in food intake, energy utilization, sexual development), so may also contribute to appetite and other aspects of energy regulation[6,7]

IGF-1, insulin like growth factor-1.

1. Patel L et al. *J R Soc Med.* 2003;96(43):35-41. 2. Snell C et al. *Pediatr Pulmonol.* 2014;49(12):1177-1181. 3. Culhane S et al. *Nutr Clin Pract.* 2013;28(6):676-683. 4. Sawicki GS et al. *Pediatr Pulmonol.* 2011;46(1):36-44. 5. Thaker V et al. *Cochrane Database Syst Rev.* 2013;5(6):CD008901. 6. Mulberg AE, et al. *Neuroreport.* 1998;9(1):141-144. 7. Lahousse SA, et al. *J Alzheimers Dis.* 2003;5(6):455-462.

IGF-1 Levels Are Low in CF and Decrease During Pulmonary Exacerbations



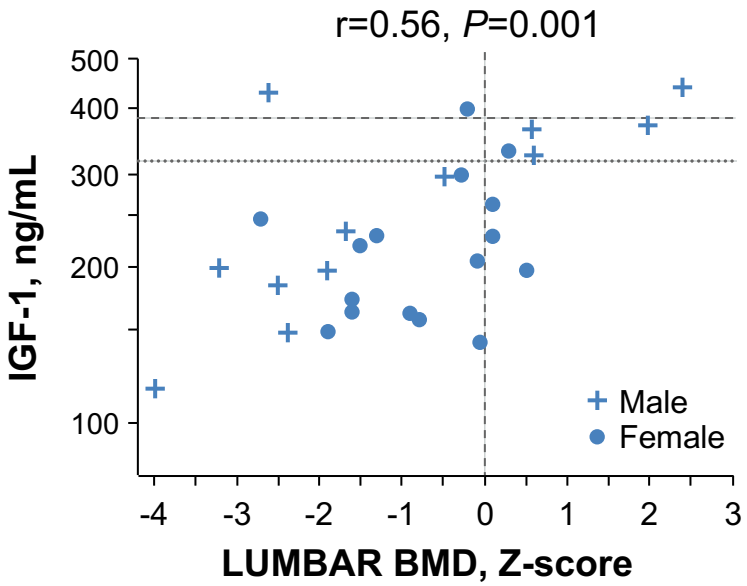
Lines denote mean and SD

CFPE, cystic fibrosis pulmonary exacerbation; IV-ab, intravenous antibiotic; PE, pulmonary exacerbation.

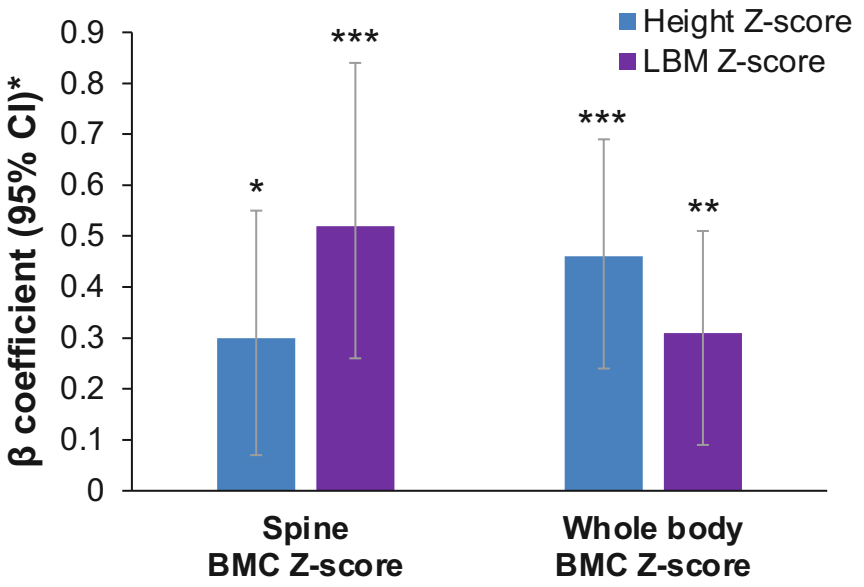
Gifford AH et al. *Pediatr Pulmonol.* 2014;49(4):335-341.

Low IGF-1 Levels Correlate With Low Bone Mass Which in Turn Correlates With Reduced Height

IGF-1 levels correlate with BMD[1]



Correlation of BMC levels with height and LBM Z-scores[2]

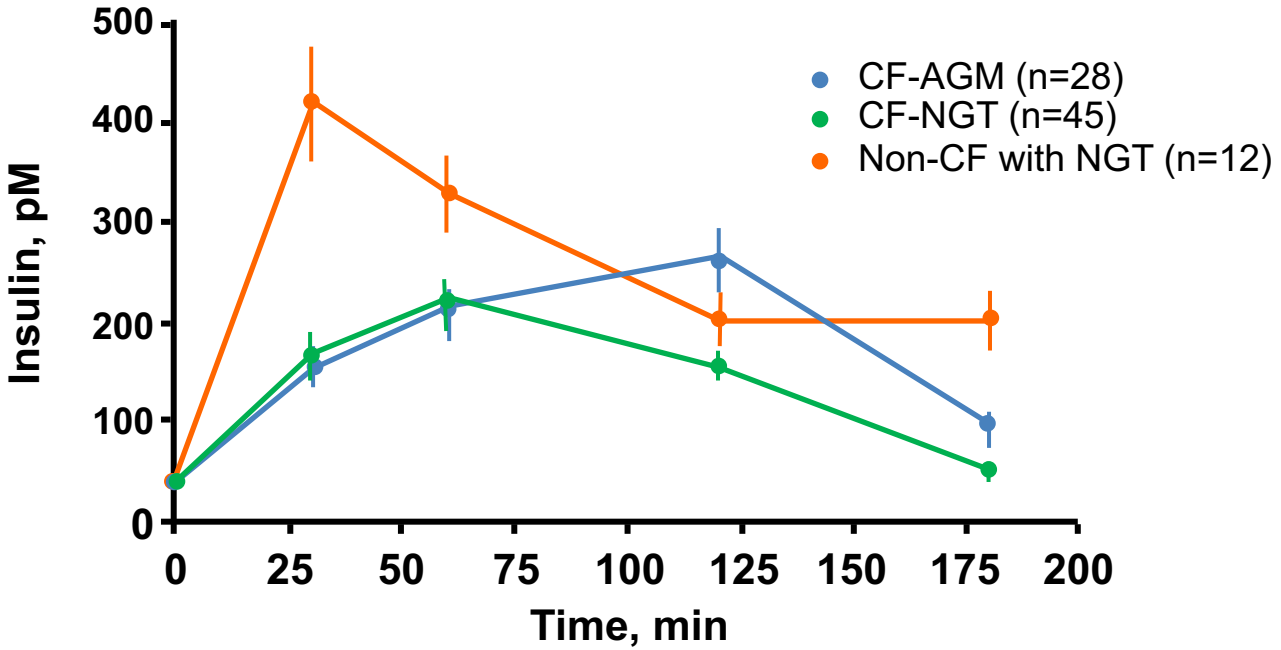


- Low IGF-1 levels correlate with low BMD Z-scores and low BMC levels (not shown)[1]
- Patients with low BMC were more likely to have lower LBM and/or lower height Z-scores[2]

BMD, bone mineral density.
*P=0.02.
**P=0.04.
***P<0.001.
Dashed line = normal male IGF-1 concentration; dotted line = normal female IGF-1 concentration.
Figure on left: Reprinted from *Osteoporosis International*, Relationship between insulin-like growth factor I, dehydroepiandrosterone sulfate and proresorptive cytokines and bone density in cystic fibrosis, 17, © 2006, 783-790, Gordon CM et al, with permission of Springer.
1. Gordon CM et al. *Osteoporos Int.* 2006;17(5):783-790.
2. Kelly A et al. *J Clin Densitom.* 2008;11(4):581-589.

Effect of Insulin Deficiency on Growth

Insulin Secretion in Response to Glucose Is Impaired in Patients With CF With or Without CFRD



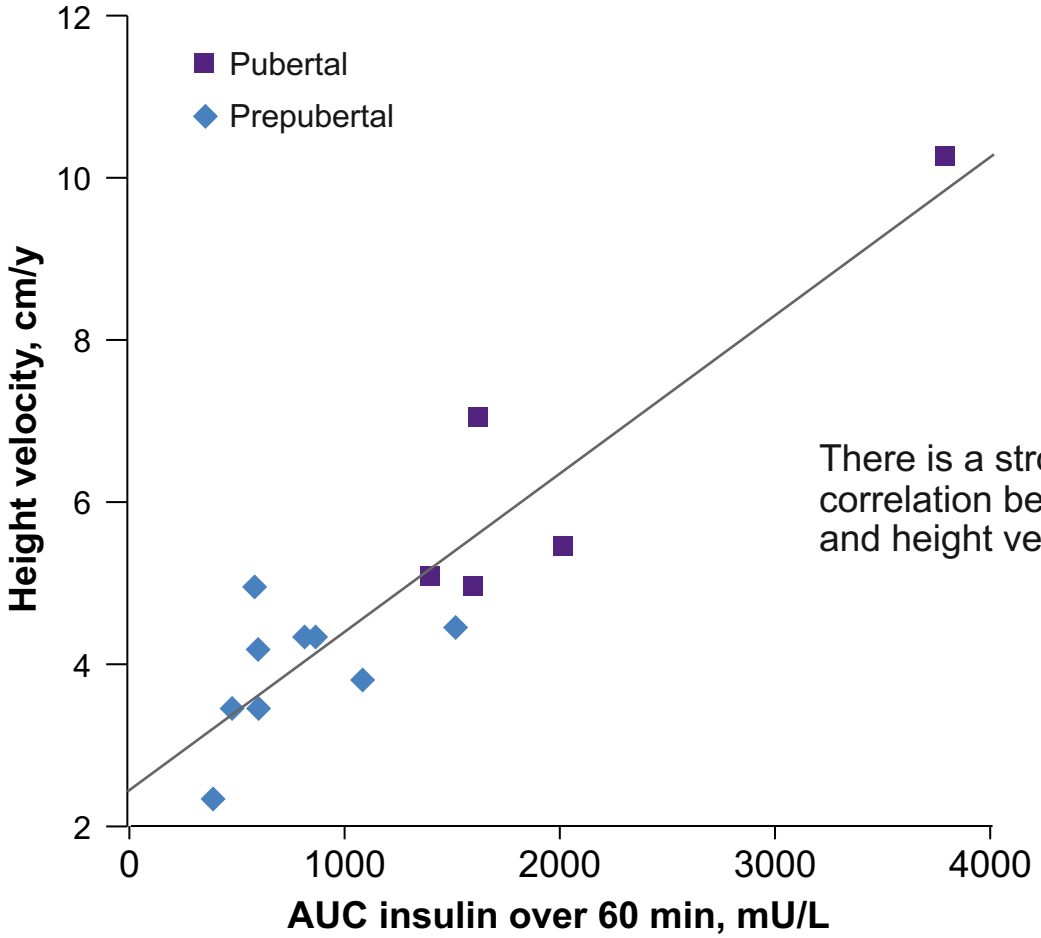
- Shown are insulin levels following glucose load in children and adolescents with CF at a single center[1]
- Lack of early-phase insulin secretion and lower overall insulin in patients with CF vs healthy controls[1,2]
- Abnormalities more pronounced with worsening glycemic status[2]
- Insulin clearance may also be increased[3,4]

CFRD, cystic fibrosis-related diabetes; AGM, abnormal glucose metabolism, including IFG, IGT, IGT/IFG, and diabetes; NGT, normal glucose tolerance.
Reprinted from *The Journal of Pediatrics*, 151(6), Elder DA et al, Glucose tolerance, insulin secretion, and insulin sensitivity in children and adolescents with cystic fibrosis and no prior history of diabetes, 653-658, © 2007, with permission from Elsevier.

1. Elder DA et al. *J Pediatr*. 2007;151(6):653-658. 2. Kelly A, Moran A. *J Cyst Fibros*. 2013;12(4):318-331. 3. Battezzati A et al. *J Clin Endocrinol Metab*. 2015;100(8):2963-2971. 4. Lanng S et al. *Clin Endocrinol (Oxf)*. 1994;41(2):217-223.

Insulin Levels Correlate With Height Velocity

Plasma insulin AUC and height velocity in children with CF without CFRD

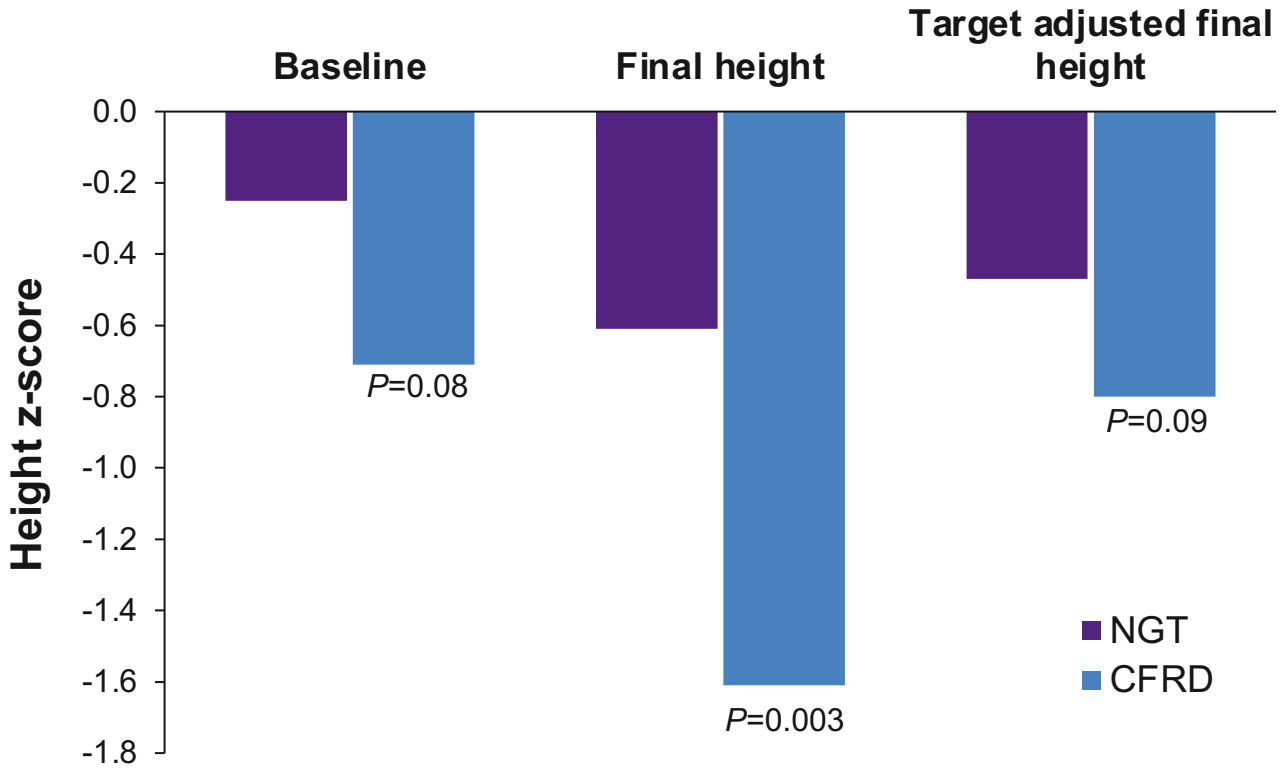


There is a strong positive correlation between insulin AUC and height velocity (*P*<0.001)

AUC, area under the curve.

Ripa P et al. *Clin Endocrinol (Oxf).* 2002;56(3):383-389.

Children With CFRD Have Lower Height Z-Scores



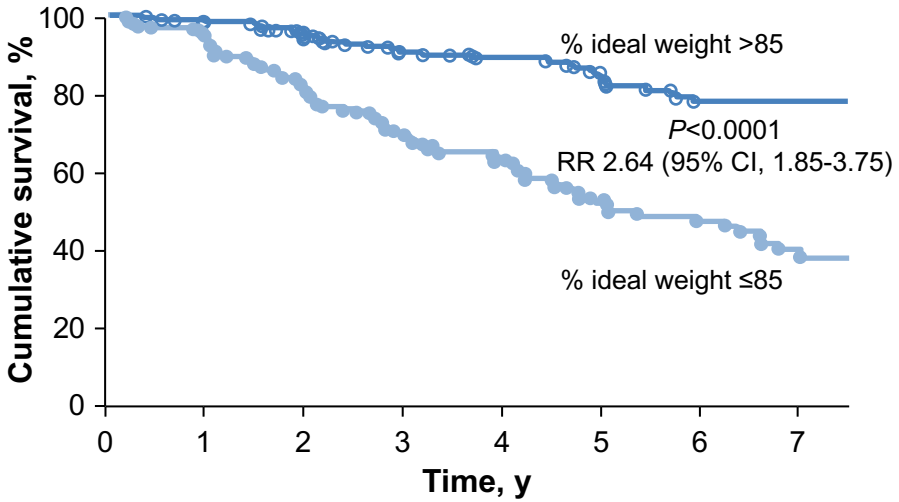
- Patients diagnosed with CFRD during puberty have lower height both at baseline (at diagnosis of CFRD) and after completion of puberty versus children with CF and NGT
- Height remained lower in children with CFRD even after adjusting for parental height

NGT, normal glucose tolerance.
Bizzarri C et al. *Pediatr Pulmonol.* 2015;50(2):144-149.

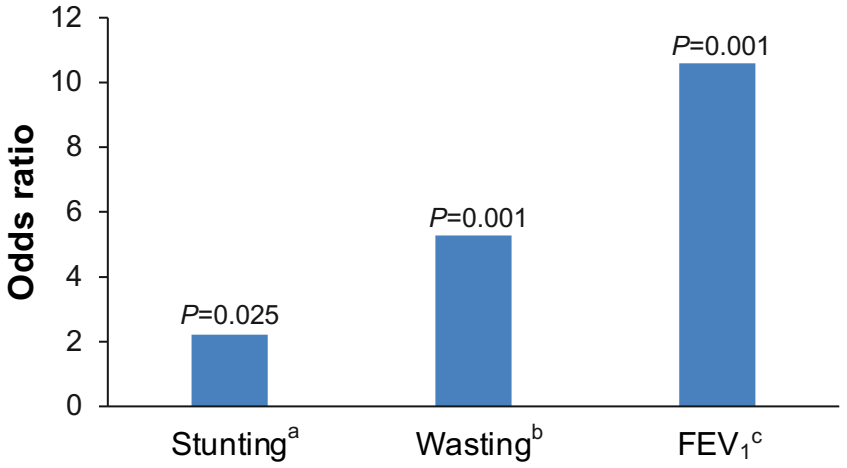
Consequences of Growth Deficiency in CF

Reduced Growth Is a Significant and Independent Risk Factor for Mortality in Patients With CF

Survival by percentage of ideal weight[1]



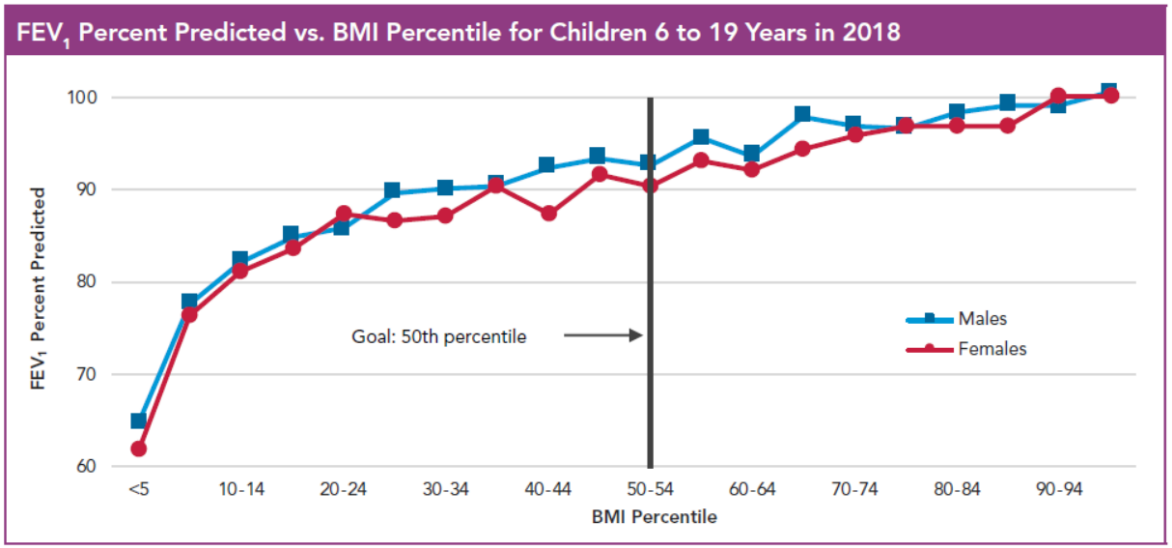
Factors associated with increased risk for mortality[2]

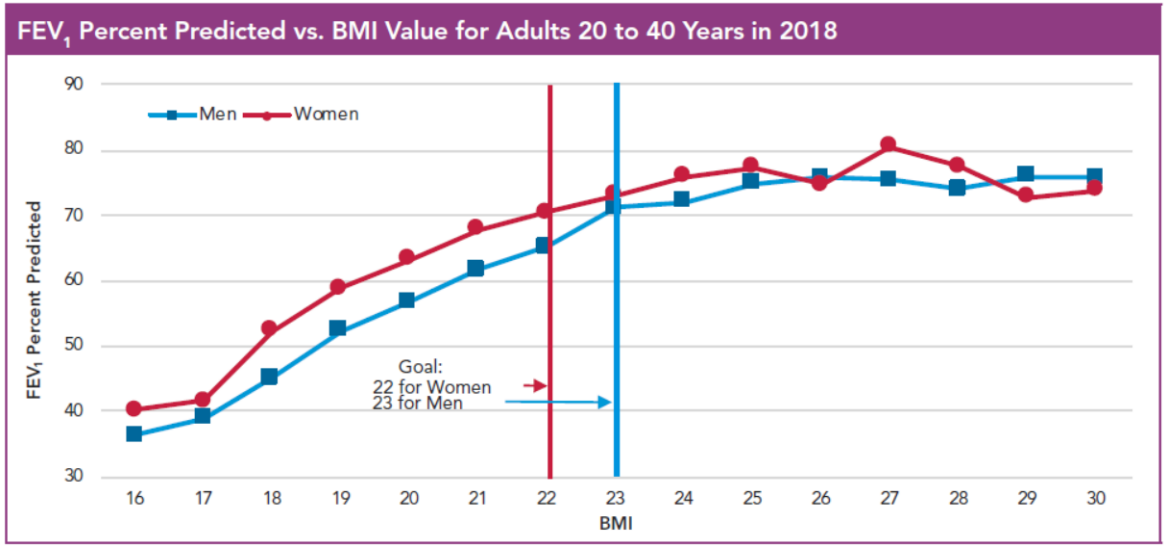


ppFEV$_1$, percent predicted forced expiratory volume in one second; RR, relative risk.
[a]Height percentile <5th.
[b]BMI <10th percentile in pediatric patients and <18.5 kg/m^2 in adult patients.
[c]ppFEV$_1$ <40%.
Figure on left: Reproduced from *Thorax*, Sharma R et al, 56, 746-750, © 2001 with permission from BMJ Publishing Group Ltd.
1. Sharma R et al. *Thorax.* 2001;56(10):746-750. 2. Vieni G et al. *Clin Nutr.* 2013;32(3):382-385.

VERTEX

Growth and Nutritional Status Are Associated With Pulmonary Function in Patients With CF

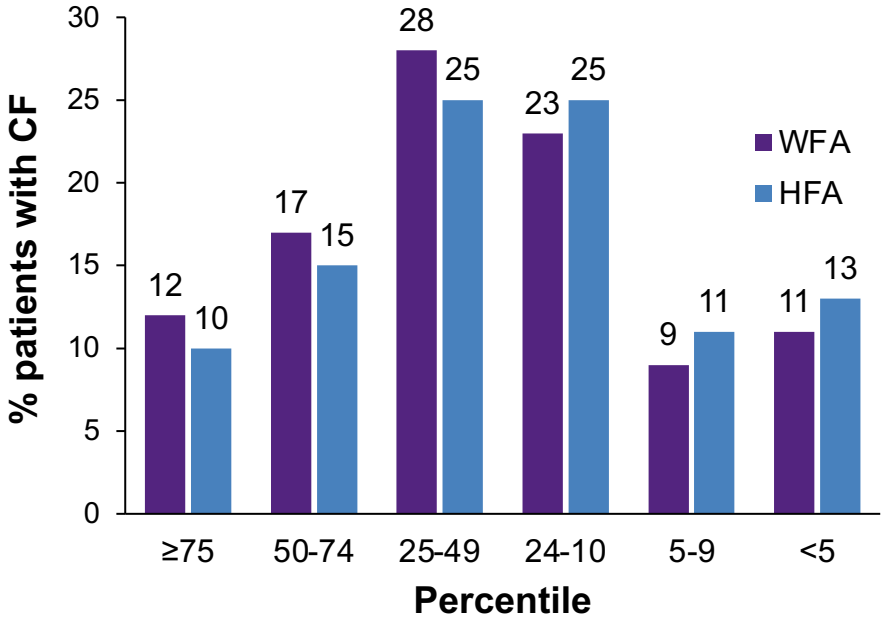




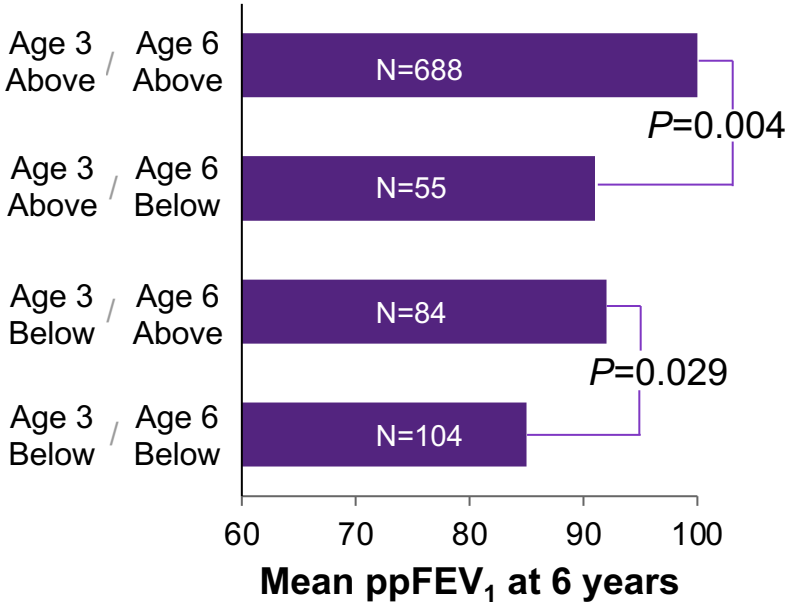
Cystic Fibrosis Foundation (CFF) Registry. 2018 Annual Data Report Bethesda, MD: CFF 2019

Growth, Nutritional Status and Pulmonary Function in Patients With CF

Growth indices below the 50th percentile in most children with CF at age 3 (N=931)[1]



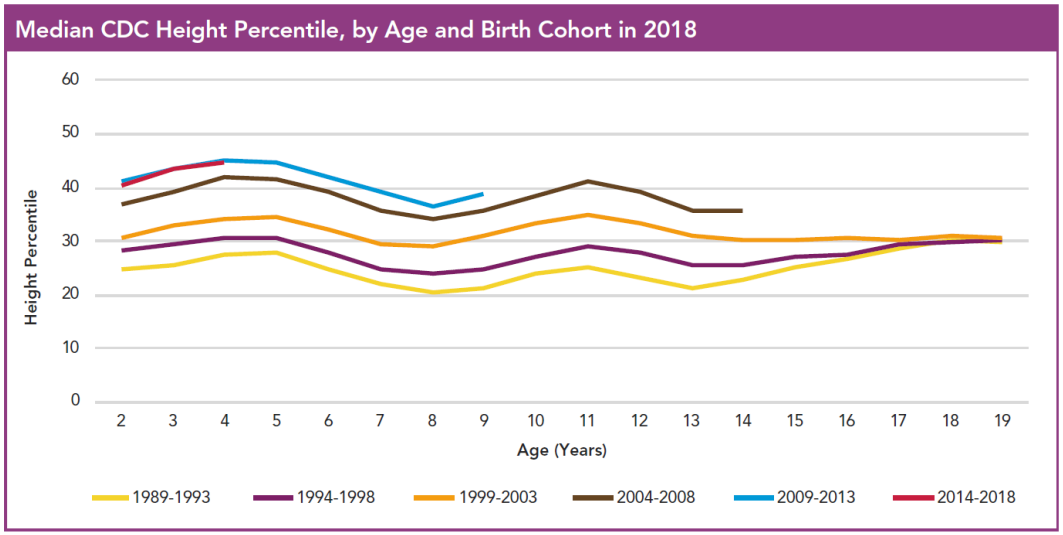
WFA >10th percentile at age 3 years and 6 years associated with better $ppFEV_1$ at age 6 years in CF[1]

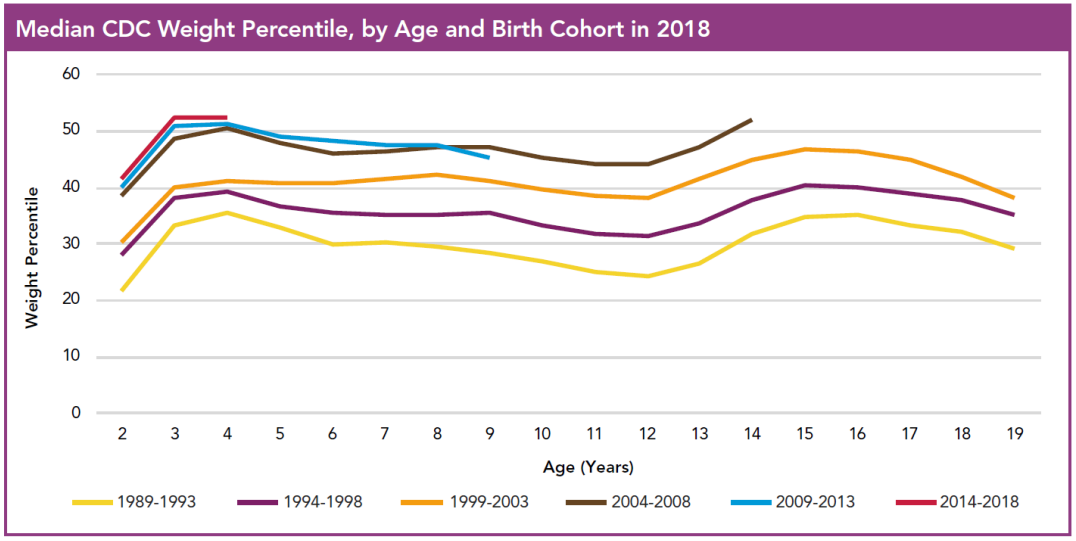


$ppFEV_1$, percent predicted FEV_1; WFA, weight-for-age.
Konstan M et all. *J Pediatr.* 2003;142(6):624-630.

Improvements in CF Care and Growth Trajectories

Growth Rates in Children With CF Have Improved Over Time (US data)

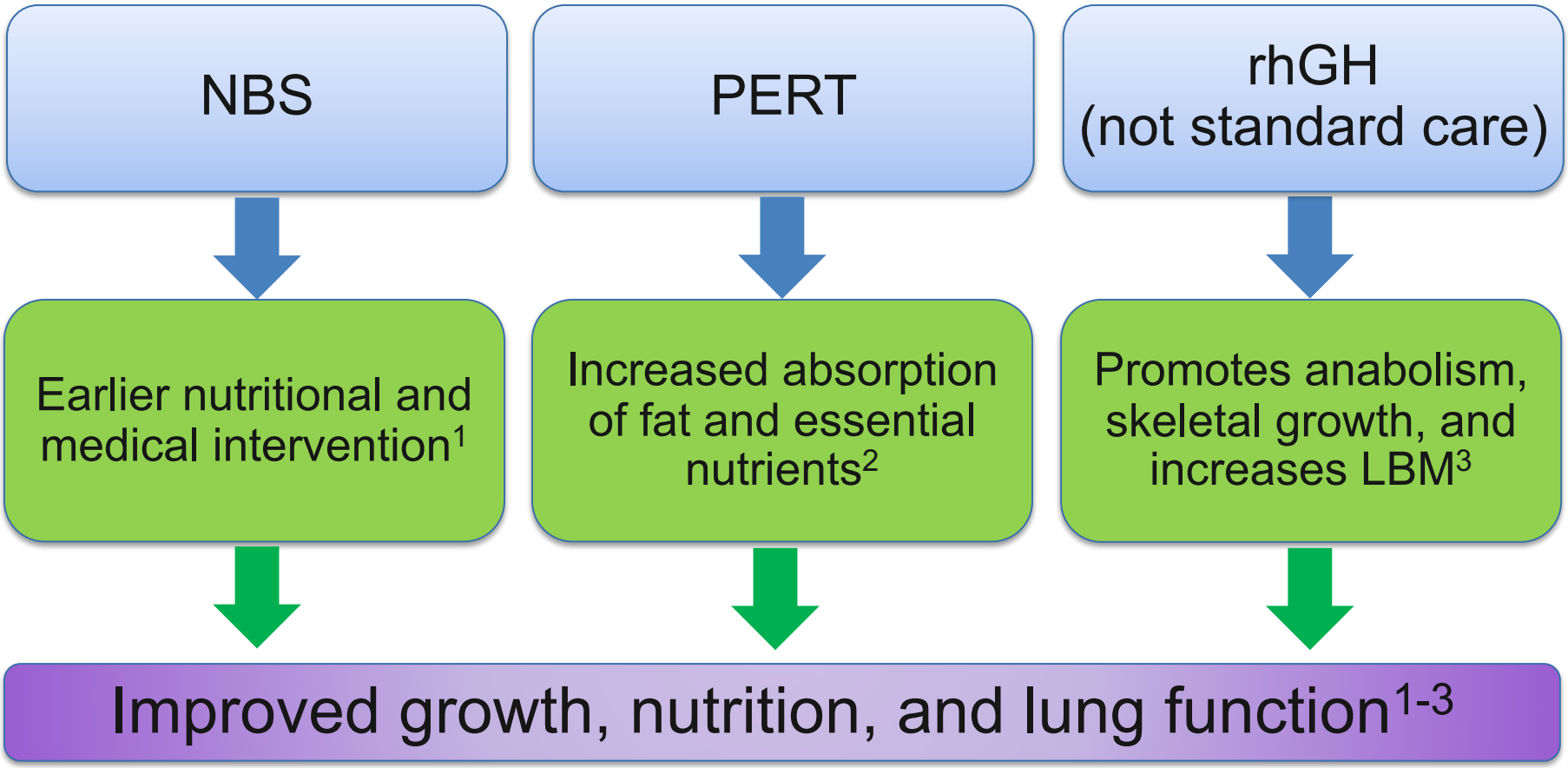




- Successive birth cohorts show improved weight and height percentiles, most notably in the youngest cohorts
- Similar improvements have occurred in BMI percentiles and WFH percentiles (not shown)

Cystic Fibrosis Foundation (CFF) Patient Registry. 2018 Annual Data Report. Bethesda, MD: CFF; 2019.

Improved Growth Rates in CF Result From Improvements in Care



NBS, newborn screening; rhGH, recombinant growth hormone.

1. Zhang Z et al. *Pediatrics.* 2016;137(5):e20152907. 2. Woestenenk JW et al. *J Pediatr Gastroenterol Nutr.* 2015;61(3):355-360. 3. Stalvey MS et al. *Pediatr Pulmonol.* 2012;47(3):252-263.

Recommendations Have Been Issued for Nutrition-Related Management

Guidelines for Nutrition-Related Management of Children With CF Developed by The Cystic Fibrosis Foundation (CFF)[1], European Cystic Fibrosis Society (ECFS)[2,3], and Dietitians Association of Australia[4]

Recommendation	Children Aged <2 Years	Children Aged 2 to 20 Years
Energy intake	Adapt to achieve normal growth; may require up to 150% of dietary reference values for age[3]	110% to 200% of healthy population[1,4]
Behavioral and nutritional counseling	Recommended for age 1 to 2 years[1]	Recommended for age 2 to 12 years; insufficient evidence for >12 years[1]
Oral and enteral supplementation	Recommended for fat-soluble vitamins in pancreatic insufficient[3]	Recommended[1,2,4]
PERT	Recommended[1,3-4a]	Recommended[1,4a]
Maintain growth status to support pulmonary function	WFH ≥50th percentile[1,2]	BMI ≥50th percentile[1,2]

PERT, pancreatic enzyme replacement therapy.
[a]PERT is normally used only for patients with pancreatic insufficiency. The CFF recommends 500 to 2500 units lipase per kg per meal; or <10,000 units per kg per day; or <4000 units per gram dietary fat per day. For infants with pancreatic insufficiency, the starting dose should be about 2000 IU lipase per 100 ml standard formula according to the ECFS Neonatal Screening Working Group.
Reprinted from *Journal of the American Dietetic Association*, 108(5), Stallings VA et al, Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review, 832-839, © 2008, with permission from Elsevier.
1. Stallings VA et al. *J Am Diet Assoc*. 2008;108(5):832-839. 2. Smyth AR et al. *J Cyst Fibros* 2014;13:S23-S42. 3. Sermet-Gaudelus I et al. *J Cyst Fibros* 2010;9:323 329. 4. Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis. September 2006

Flowchart of Nutritional Monitoring in Infants <2 Years of Age With CF

STEP 1

Calculate average daily weight gain and compare with expected below. If expected gain not achieved proceed to STEP 2

Age Range	Females-Males (g/d)	Age Range	Females-Males (g/d)
Birth-1 mo	26-30	4-5 mo	16-17
1-2 mo	29-35	5-6 mo	14-15
2-3 mo	23-26	6-9 mo	10-13
3-4 mo	19-29	9-24 mo	7-10

STEP 2

Compare intake values based on normal well-nourished infants below. Proceed to STEP 3

Age Range	Intake (kcal/kg/d)
Birth-3 mo	≥115-130
3-6 mo	≥100-110
6-24 mo	≥100

STEP 3

A. Increase caloric density
B. Increase PERT dose
C. Consider the following before proceeding to STEP 4

Issue
Increased expenditure or metabolic issues
Poor absorption
Socioeconomic/education issues
Poor appetite

STEP 4

A. Intervene and follow at 2- to 6-week intervals
B. Discuss gastrostomy tube placement with family

Borowitz D et al. *J Pediatrics.* 2009;155(6):S73-S93.

VERTEX

Flowchart of Nutritional Monitoring in Children Aged 2-5 years With CF

STEP 1
Preschooler weighed and measured

Target Measurements	
BMI percentile	≥50th
WFA percentile	>10th
Rate of weight gain	≥5-8 g/d

- If all the above target measurements are met, continue with routine nutritional care
- If not, proceed to STEP 2

STEP 2
Initial Evaluation

Look for Cause of Low Growth
Diet history
Stool history
PERT history
Vitamin/mineral history

- Address cause if possible and reassess target measurements in ≤8 weeks
- If target measurements are not met, proceed to STEP 3

STEP 3
Consultation and In-Depth Evaluation

Consider the Following
GI consult
Behavior/psych consult
Other consult (eg, diabetes, metabolic disease)

- Address cause if possible and reassess target measurements in ≤8 weeks
- If target measurements are not met, proceed to STEP 4

STEP 4
Consider Gastrostomy Tube Feeding (G-Tube)

G-Tube Feeding Advantages
Has been shown to improve weight and pulmonary function
Decreases stress around eating
Use for medication administration

Lahiri T et al. *Pediatrics.* 2016;137(4).

VERTEX

Recommendations for Making Healthy Choices When Adding Calories[1-3]

People with CF may need about 1.5 times as many calories as people without CF

Dietary Factor	Recommendation
Fat	35% to 40% of calories
Fiber	Patient's age + 5 grams per day (eg, 10-year-old patient needs 15 g)
Protein	~20% of calories
Salt	Increased amount, consult with doctor
Vitamins and minerals	Specialized multivitamins

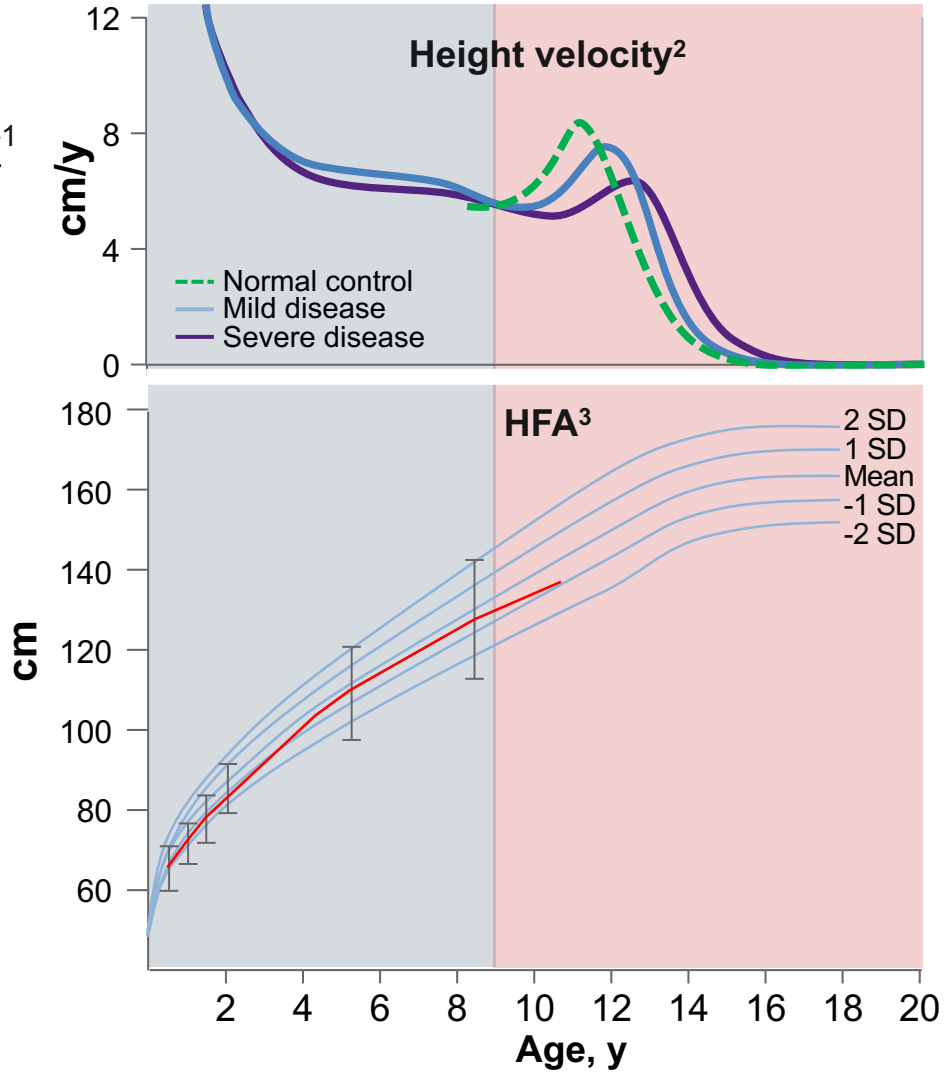
Ideas for Adding Calories and Protein to Meals	
Any food	Add "nut dust" (ground-up nuts)
Bread (whole grain)	Add butter
Fruits	Add high-calorie dips or whipped cream
Hamburger	Add eggs
Milk	Mix equal parts milk and half-and-half
Shakes	Add powdered milk
Vegetables	Add butter or oils

1. Johns Hopkins Cystic Fibrosis Center. Clinical-care: Nutrition. https://hopkinscf.org/clinical-care/nutrition/. Accessed April 2020. 2. The Canadian Guide to Nutrition and Cystic Fibrosis. 3. Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis. September 2006

Realistic Goals for Growth in Patients With CF

Typical Growth Patterns

Infants → age 9 y[1]
- Normal pattern
- Lower centiles



Adolescents[1]
- Delayed maturation
- Delayed puberty
- Attenuated height

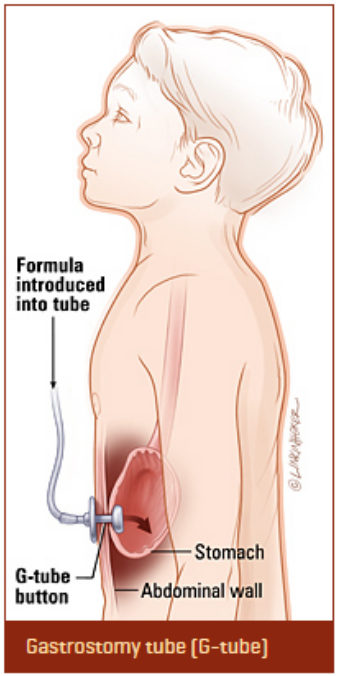
Top figure: Reprinted with permission from Assael BM et al. Growth and long-term lung function in cystic fibrosis: a longitudinal study of patients diagnosed by neonatal screening. *Pediatr Pulmonol*. 2009;44(3):209-215. © 2009 Wiley-Liss, Inc. Bottom figure: Reprinted from *Journal of Cystic Fibrosis*, 2(2), Keller BM et al, Growth in prepubertal children with cystic fibrosis, homozygous for the Delta F508 mutation, 76-83, © 2003, with permission from Elsevier.

1. Thaker V et al. *Cochrane Database Syst Rev.* 2013;6:CD008901. 2. Assael B et al. *Pediatr Pulmonol.* 2009;44(3):209-215. 3. Keller BM et al. *J Cyst Fibros. 2.* 2003;2(2):76-83.

Referral Consultations for Patients With Low Growth

In-Depth Diagnostic Evaluation and Consultations

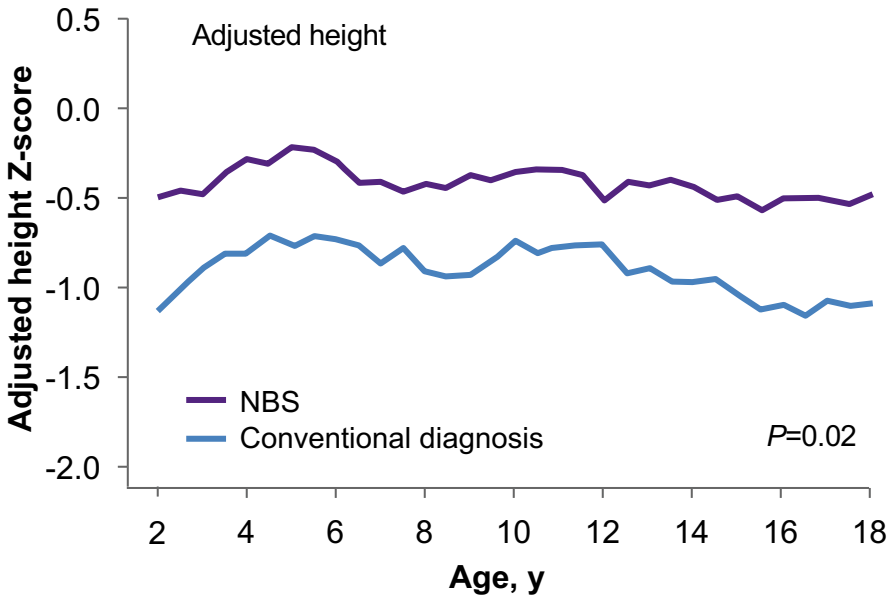
- Children who continue to be at nutritional risk despite having addressed pulmonary, social, and dietary factors should be referred to one or more of the following specialists for further evaluation
  - Pediatric gastroenterologists
  - Endocrinologists
  - Behavioral specialists
- When oral supplementation does not meet the necessary calorie requirements for adequate weight gain, use of enteral feedings via a G-tube should be considered



Lahiri T et al. *Pediatrics.* 2016;137(4).

Growth Benefits of NBS Are Sustained Long-term Through Adolescence

Children with CF diagnosed by NBS are taller compared with conventional diagnosis (CD)



Height status is better before and after puberty in children with CF diagnosed by NBS compared to CD

Growth Status	NBS n=33	CD n=29	*P*
Prepubertal status at age 7 years			
Unadjusted height percentile	47 ± 30	27 ± 27	0.05
Adjusted height percentile	35 ± 27	20 ± 25	0.05
Nutritional status at age 18 years			
Unadjusted height percentile	50 ± 29	29 ± 26	0.03
Adjusted height percentile	32 ± 22	15 ± 14	0.003

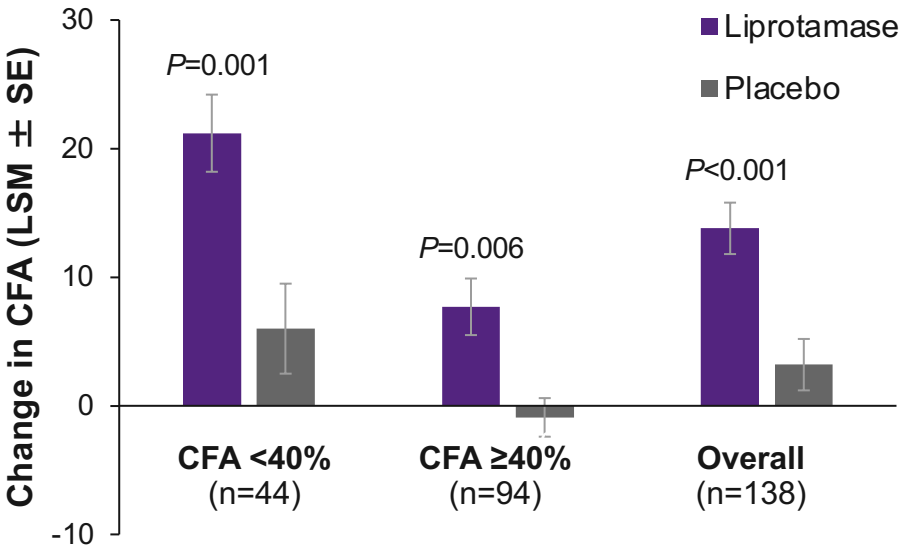
- From age 2 to 18 years, patients diagnosed by NBS were significantly taller compared with conventionally diagnosed patients by ~10 percentile after adjusting for genetic potential (28th vs 19th)
- The benefit in growth from NBS remains relatively constant both pre and post puberty

CD, conventional diagnosis.

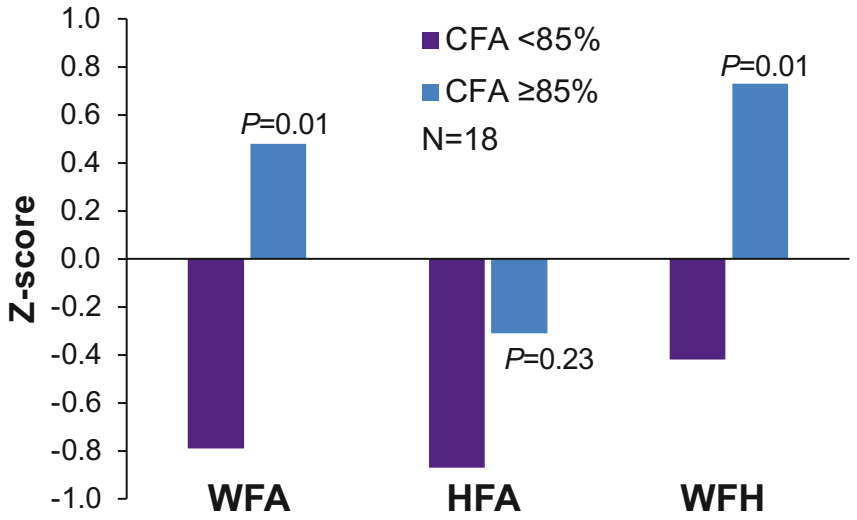
Zhang Z et al. *Pediatrics.* 2016;137(5):e20152907.

PERT Has Been Proven to Improve Growth Rate

PERT increases fat absorption in patients with CF[1]



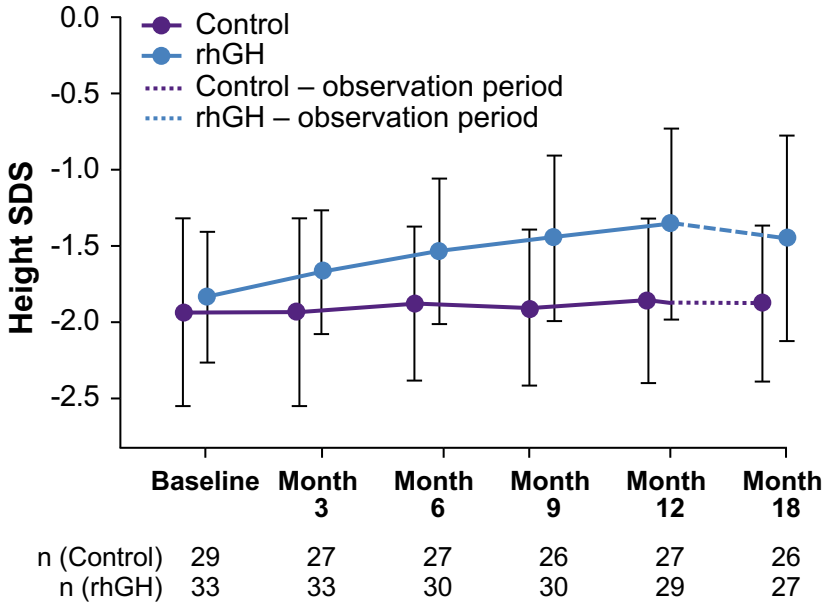
Elevated CFA after PERT is associated with improved growth in patients with CF[2]

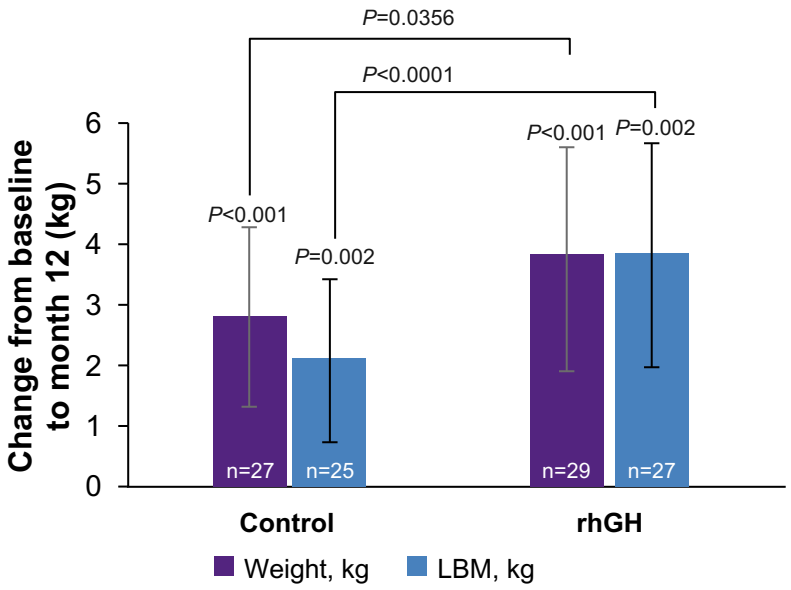


- Patients with CF who are pancreatic insufficient and receiving PERT have higher CFA,[1] which is associated with better growth[2]

CFA, coefficient of fat absorption; PERT, pancreatic enzyme replacement therapy.
Figure on left: Reprinted from *Journal of Cystic Fibrosis*, 10(6), Borowitz D et al, International phase III trial of liprotamase efficacy and safety in pancreatic-insufficient cystic fibrosis patients, 443-452, © 2011, with permission from Elsevier.
1. Borowitz D et al. *J Cyst Fibros.* 2011;10(6):443-452. 2. Woestenenk JW et al. *J Pediatr Gastroenterol Nutr.* 2015;61(3):355-360.

rhGH Has Been Shown to Improve Growth Rates in CF Patients





- In healthy children, LBM increases with age. Children with CF have lower levels of LBM and the difference between children with CF and healthy children increases with age
- LBM decline is associated with worsening lung function
- rhGH increased height, weight, and LBM in patients with CF up to 12 months and the effects are sustained up to 6 months after discontinuing treatment
- Lung function (FEV_1) improved[a] in patients receiving rhGH compared with control (not shown)

SDS, standard deviation score; rhGH, recombinant human growth hormone; LBM, lean body mass.
[a]After adjusting for baseline disease severity, age, and height SDS.

Stalvey MS et al. *Pediatr Pulmonol.* 2012;47(3):252-263.

Summary

- Mutations in the *CFTR* gene lead to CF, affecting many systems in the body that impact growth, including, lungs, pancreas, gastrointestinal tract, and bone
- Low growth rates in patients with CF are associated with
  - Higher rates of mortality
  - Reduced lung function
  - Higher rates of CFRD
  - Delayed puberty
  - Bone disease
- Growth rates in children with CF have improved over time due to improvements in care, including NBS, PERT, close monitoring of nutrition, rhGH

VERTEX

Interactive Question 1

- Abnormal growth velocity curves in CF are often due to delayed puberty

  A. True

  B. False

Interactive Question 1

- Abnormal growth velocity curves in CF are often due to delayed puberty

  A. True

  B. False

Interactive Question 2

- It is recommended that children with CF aged 2 to 20 years maintain a BMI of…

  A. ≥30th percentile

  B. ≥40th percentile

  C. ≥50th percentile

  D. ≥60th percentile

Interactive Question 2

- It is recommended that children with CF aged 2 to 20 years maintain a BMI of…

  A. ≥30th percentile

  B. ≥40th percentile

  C. ≥50th percentile

  D. ≥60th percentile

Interactive Question 3

- Growth rates in children with CF correlate with…

  A. CFTR genotype

  B. Lung function

  C. Mortality

  D. All of the above

  E. Both B and C

Interactive Question 3

- Growth rates in children with CF correlate with…

  A. CFTR genotype

  B. Lung function

  C. Mortality

  D. All of the above

  E. Both B and C