CF Disease due to Residual CFTR Activity Mutations

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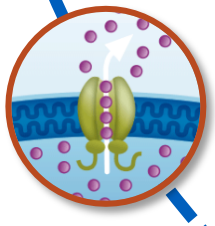
CFTR Mutations & Protein Defects: The Underlying Cause of CF

CFTR gene mutations can result in CFTR protein channel abnormalities – the underlying defect of CF disease[1]



CFTR gene mutations can reduce chloride and other ion transport (total CFTR activity) through CFTR channels by affecting:[1–3]

Quantity of CFTR channels at the cell surface,

and/or

Function of CFTR as an ion channel

Reduced quantity and/or function of CFTR channels leads to pathophysiologic changes in the epithelial cells of many organ systems[1,2,4]

1. MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10 2. Rowe SM et al. *N Engl J Med* 2005;352:1992–2001 3. Lommatzsch ST, Aris R. *Semin Respir Crit Care Med* 2009;30:531–8 4. Davis PB. *Am J Respir Crit Care Med* 2006;173:475–82

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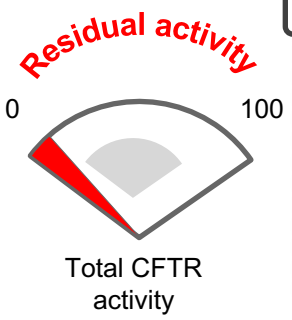
Effect of Mutations on Total CFTR Activity Depends on CFTR Quantity and Function[1-5]

Total CFTR activity = **CFTR quantity** (Synthesis; Processing/trafficking; Stability; Splicing) X **CFTR function** (Channel gating; Channel conductance)



CFTR quantity	CFTR function
Little to no CFTR quantity *at cell surface resulting in **little to no** total CFTR activity*	**Little to no CFTR function** *at cell surface resulting in **little to no** total CFTR activity*
Some CFTR quantity *at cell surface resulting in **residual** CFTR activity*	**Some CFTR function** *at cell surface resulting in **residual** CFTR activity*

1. Zielenski J. *Respiration* 2000;67:117–33; 2. MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10; 3. Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63;
4. Welsh MJ & Smith AE. *Cell* 1993;73:1251–4; 5. Castellani C. *J Cyst Fibrosis* 2008;7:179–96

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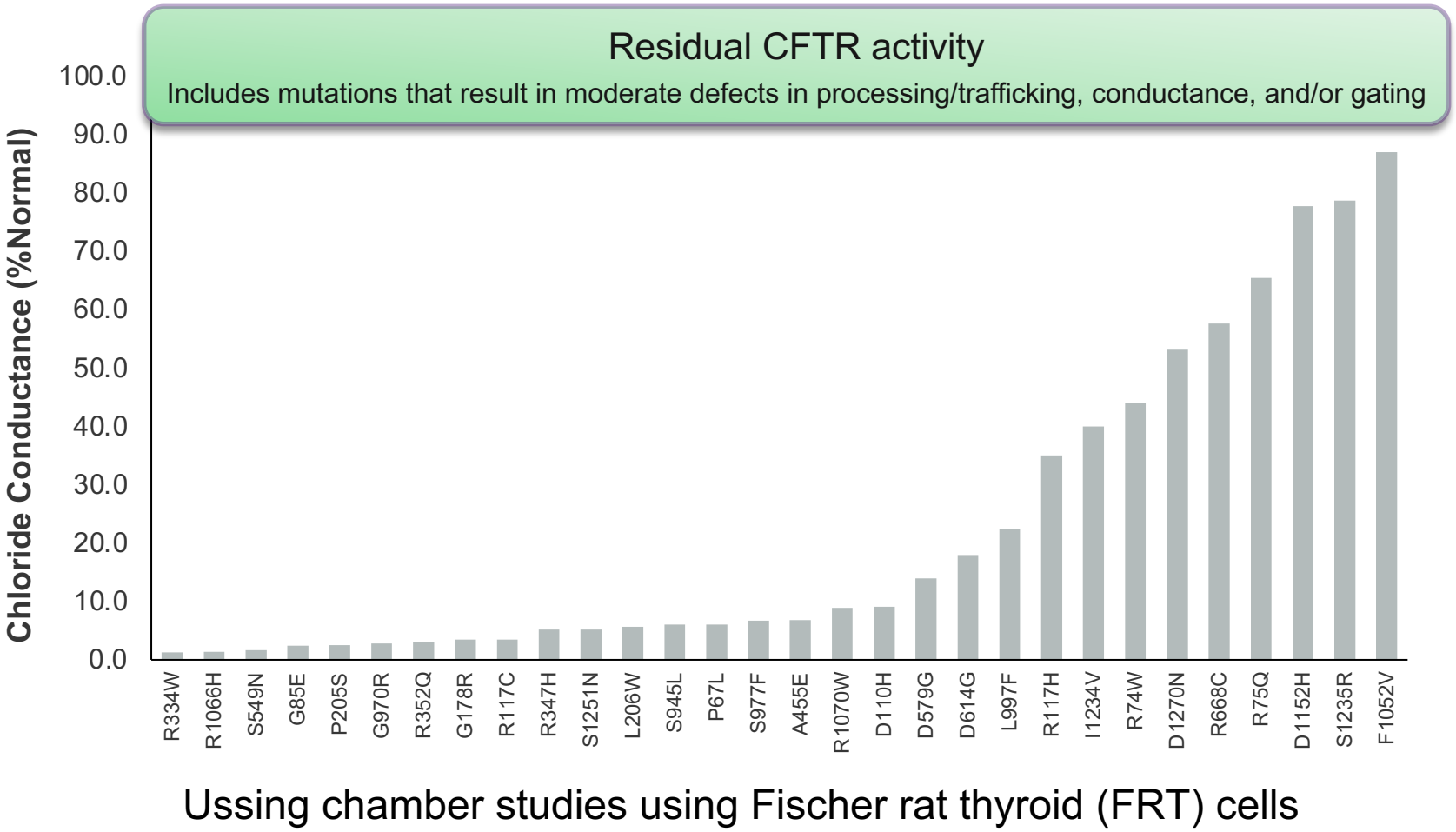
Different Mutant *CFTR* Genotypes Result in a Range of Total CFTR Protein Activity



Ussing chamber studies using Fischer rat thyroid (FRT) cells

Sosnay PR et al. Nat Genet. 2013;45(10):1160-1167

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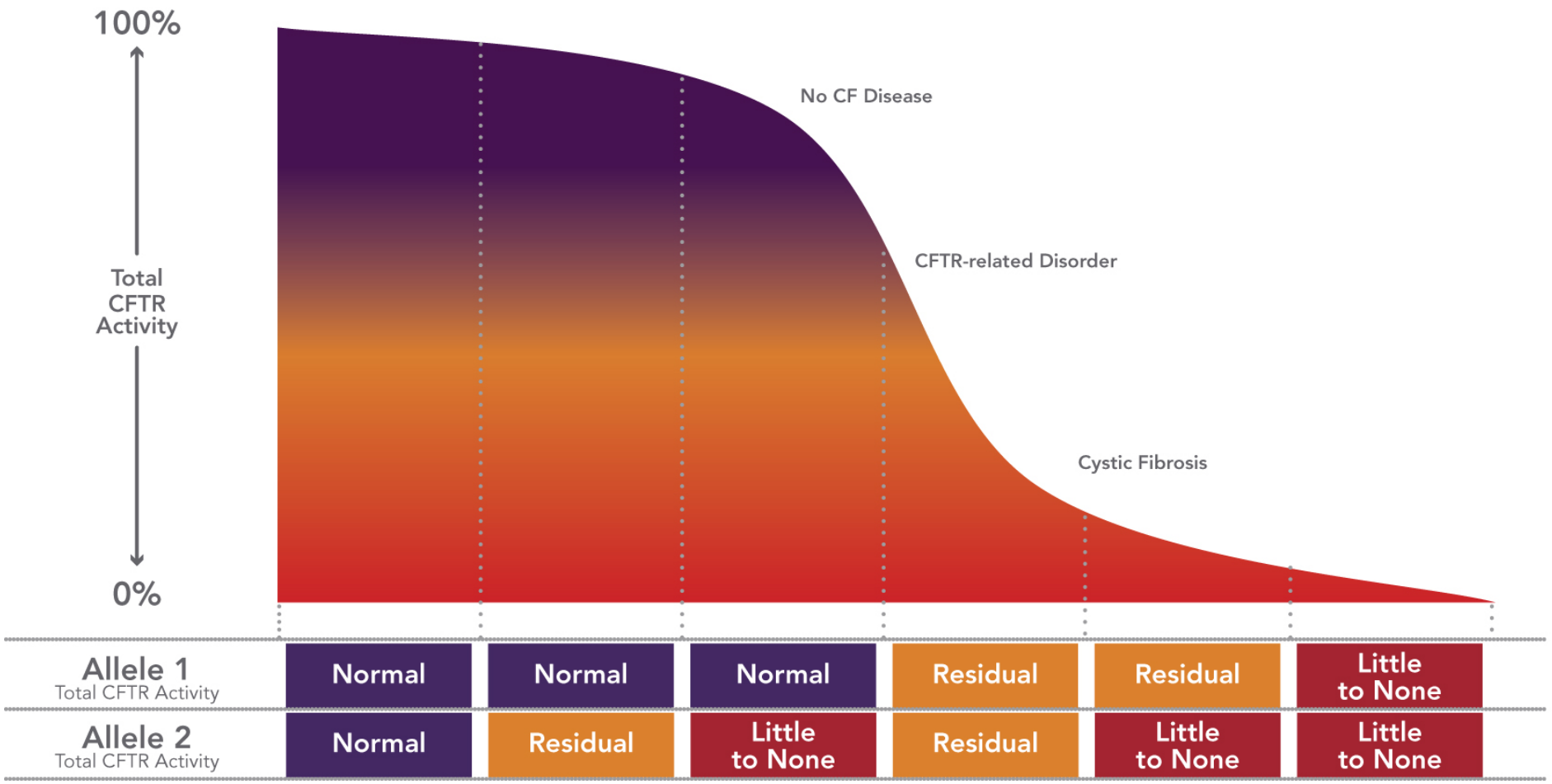
CFTR Genotype of Both Alleles is a Determinant of Total CFTR Activity and CF Phenotype



Adapted from Zielenski J. Respiration 2000;67:117–33

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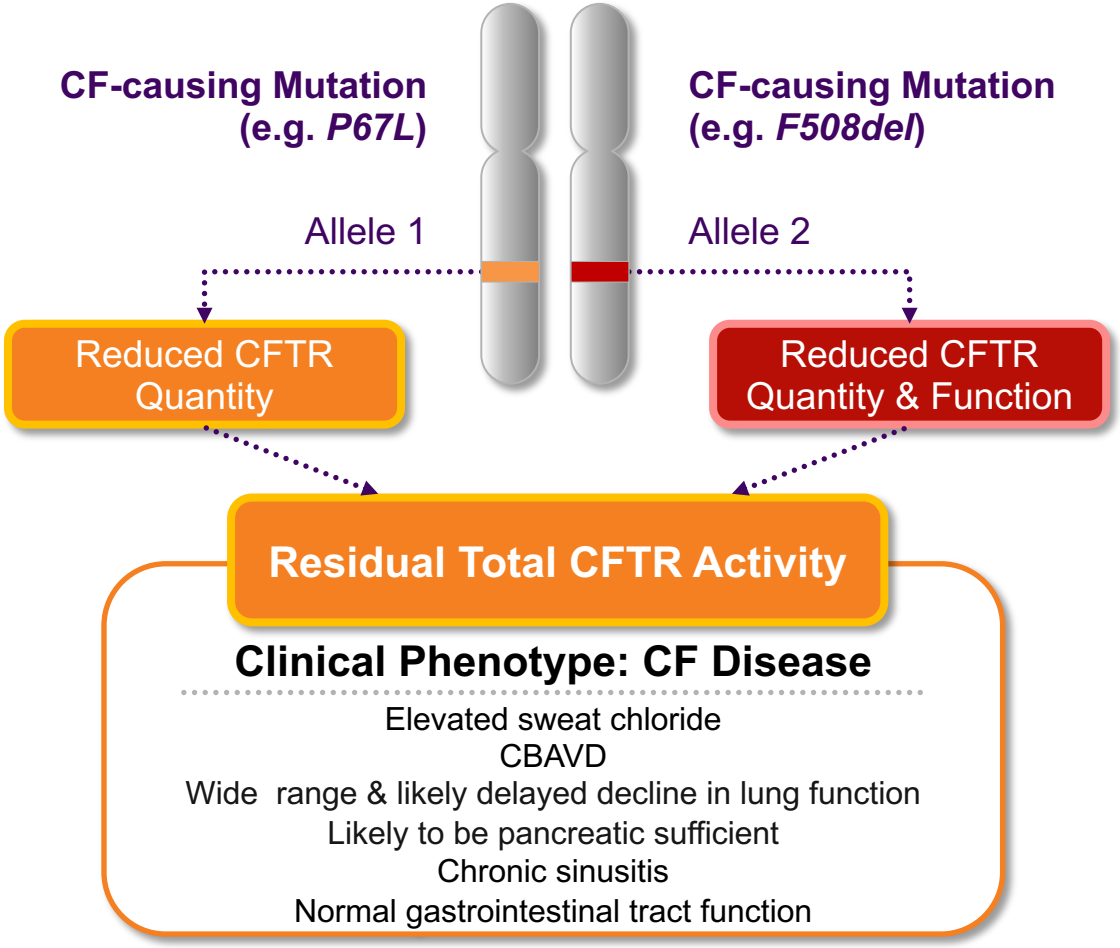
Genotype & Phenotype in Individuals with CF and Residual CFTR Activity

Example genotype: *P67L/F508del*



CF phenotype is also influenced by non-*CFTR* modifier genes and environmental factors

CBAVD- Congenital Bilateral Absence of Vas Deferens

Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63; Griesenbach U et al. *Thorax* 1999;54(Suppl 2):S19–23; Zielenski J. *Respiration* 2000;67:117–33; Davis PB. *Am J Respir Crit Care Med* 2006;173:475–82; Wilschanski M & Durie PR. *Gut* 2007;56:1153–63; Castellani C et al. *J Cyst Fibrosis* 2008;7:179–96; https://cftr2.org/mutations_history Accessed April 2020

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Clinical Phenotypes Are Heterogeneous in Patients with Residual CFTR Activity

	Masvidal	Genotype-Phenotype Consortium	Castaldo	Gilfillan	De Braekeleer	Antinolo
	2789+5G>A (n=11)	*R117H* (n=23)	*D614G* (n=3)	*P67L* (n=13)	*A455E* (n=14)	*R334W* (n=12)
Age at diagnosis, years (SD)	21 (8)	10 (11)	40, 40, 31	23 (11)	6 (5)	15 (15)
Sweat Chloride, mmol/L(SD)	103 (23)	82 (19)	79, 55, 97	57 (9)	79 (19)	96 (9)
$ppFEV_1$ (SD)	82 (31)	73 (22)	51, 84, 88		85 (17)	59 (27)
PI, %	27	13	PS, PS, PI	23	50	33
Pseudomonas colonization, %	64	30	Y, N, N		50	33

$ppFEV_1$, percent predicted forced expiratory volume in 1 second; PS, pancreatic sufficient; PI, pancreatic insufficient; N, no; Y, yes.

- Lower rates of pancreatic insufficiency
- Highly variable sweat chloride concentration
- Highly variable lung function

Masvidal L et al. *Eur J Hum Genet*. 2014;22(6):784-791. The Cystic Fibrosis Genotype–Phenotype Consortium. *N Engl J Med*. 1993;329(18):1308-1313. Castaldo G et al. *J Cystic Fibros*. 2006;5(3):193-195. Gilfillan A et al. *J Med Genet*. 1998;35(2):122-125. De Braekeleer M et al. *Hum Genet*. 1997;101(2):208-211. Antinolo G et al. *J Med Genet*. 1997;34(2):89-91.

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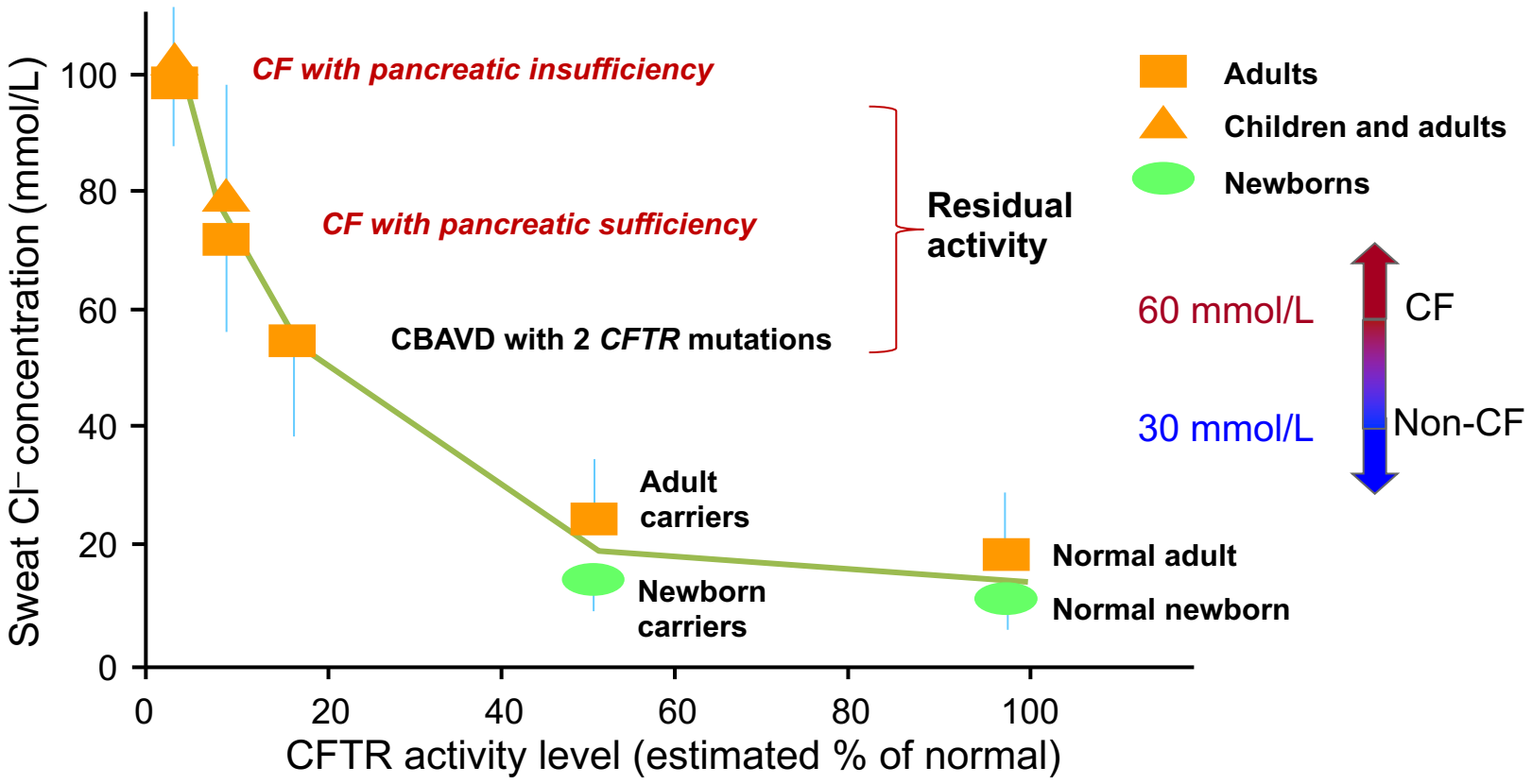
Sweat Chloride and Pancreatic Status are Indicators of CFTR Activity



*Note: Three important assumptions are made: (1) Sweat chloride levels are vs **predicted** CFTR activity; (2) normal individuals are assumed to have 100% CFTR activity; (3) carriers are assumed to have 50% CFTR activity.*

Adapted from Rowe et al. *Proc Am Thorac Soc*. 2007;4(4):387-398.
Farrell PM et al. *J Pediatr*. 2008;153(2):S4-S14.

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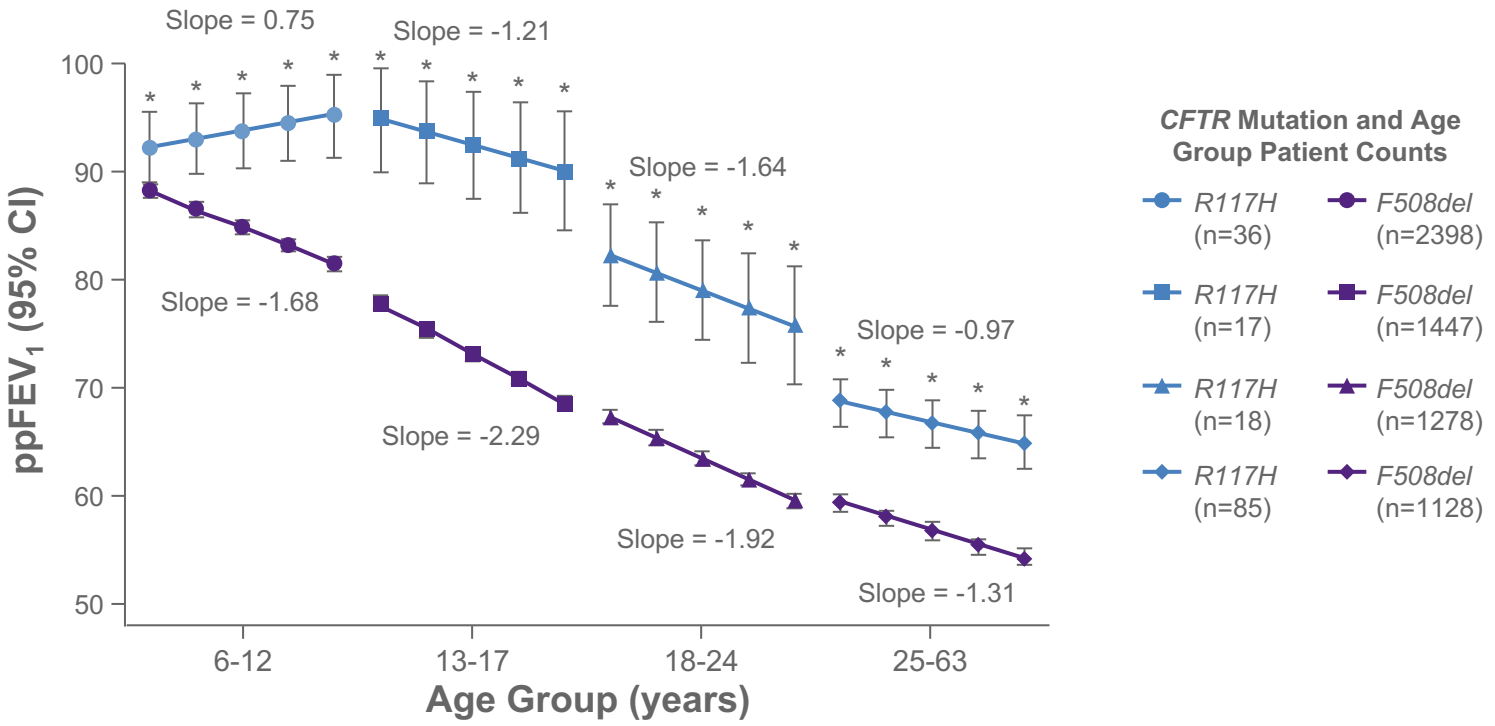
Lung Disease in Patients With CF and Residual CFTR Activity May Be Delayed, But Not Lessened, Compared With Patients Homozygous for the F508del *CFTR* Mutation

Estimated Intercept and 4-Year Slopes of ppFEV$_1$ by Mutation and Age Group



*P<0.001.
Each data point represents a study year. Bars represent standard errors. Intercept and slopes not adjusted for age

- Patients with CF 6 to 12 years of age with the residual function genotype *R117H* did not experience a decline in lung function over 4 years compared with age-matched *F508del* homozygous patients
- However, patients with residual function genotypes in older age groups experienced similar lung function decline compared with age-matched *F508del* homozygous patients

Wagener JS et al. NACFC. 2015. Poster 415.

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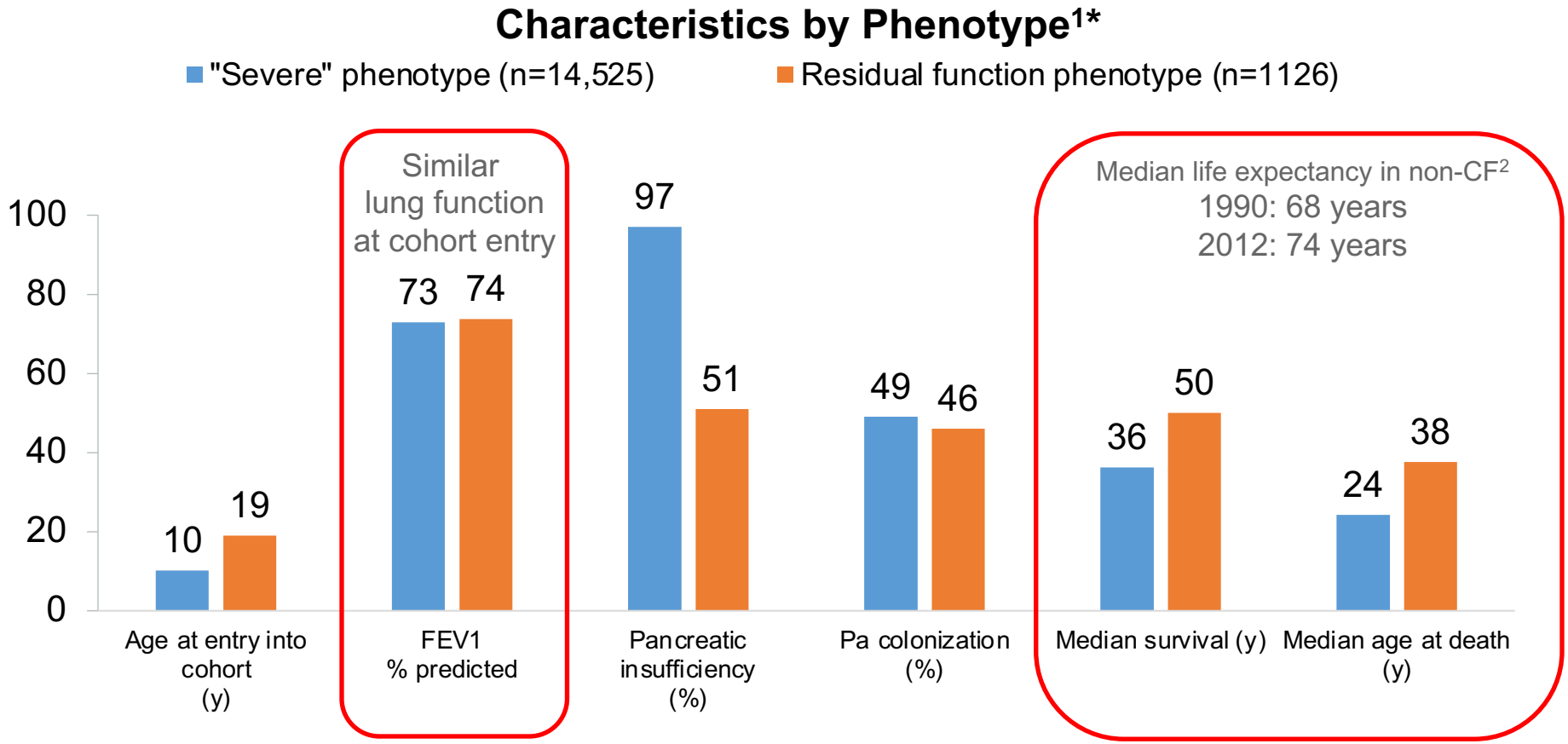
Once Symptoms Appear, Life Expectancy and Lung Function in Patients With CF With Residual Activity Phenotypes Are Similar to Those With Minimal Activity



*Clinical characteristics assessed during the year of cohort entry, and followed between 1993 and 2002.[1]
Severe mutations: Both alleles: *G542X, R553X, W1282X, R1162X, 621–1G>T, 1717–1G>A, 1078T, 3659delC, F508del, I507del, N1303K, S549N, G85E, G551D,* and *R560T.*
Residual function mutations: At least 1 allele: *R117H, R334W, R347P, 3849+10KbC>T, 2789+5G>A,* and *A455E.*
Pa, pseudomonas aeruginosa

1. McKone EF et al. *Chest*. 2006;130(5):1441-1447. 2. World Health Organization. World Health Statistics, 2014.

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Summary

- As of 10 January 2020, a total of 432 variants are annotated on the CFTR website, which 352 are CF-causing[1]
- Some *CFTR* mutations are associated with almost complete loss of CFTR activity while others are associated with residual activity
- A patient's phenotype is primarily related to the effect of mutations on CFTR activity
- Phenotypes are variable in patients with mutations associated with residual CFTR activity
- Patients with residual CFTR activity phenotypes may be diagnosed later in life than *F508del* homozygotes, but median survival is still below the median survival in the overall non CF population worldwide

1. https://cftr2.org/mutations_history Accessed April 2020

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