CFTR BIOMARKERS: TIME FOR PROMOTION TO SURROGATE ENDPOINT?

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Online Data Supplement

Table S1 online supplement : NPD Discriminate Validity

NPD indices discriminate between patients with and without CF.

N and subject type		Basal potential *p*-value	Δ Amiloride *p*-value	Δ Low Chloride + Isoproterenol *p*-value	Statistic	Author
37	CF	<0.05	<0.05	<0.05	MWU	(1)
61	non-CF					
46	CF	0.00001	ND	0.00001	unpaired t-test	(2)
40	non-CF					
25	CF	<0.05	<0.05	<0.05	Not reported Assumed to be unpaired t-test	(3)
50	non-CF					
50	CF	no overlap	no overlap	no overlap	95% CI of medians	(4)
31	non-CF					
8	CF	ND	<0.001	<0.001	MWU	(5)
10	non-CF					
31	CF	0.001	0.001	0.001	ANOVA	(6)
50	non-CF					
37	CF	<0.0001	<0.0001	<0.0001	unpaired t-test	(7)
29	non-CF					
79	CF	<0.0001	<0.0001	<0.0001	MWU	(8)
26	non-CF bronchiectasis					
51	CF	<0.0001	<0.0001	<0.0001*	unpaired t-test *MWU	(9)
12	non-CF					
10	CF	<0.001	<0.01	<0.001	MWU	(10)
10	non-CF					
12	CF	<0.0001	<0.0001	<0.0001 *terbutaline	unpaired t-test	(11)
20	non-CF					

104 40 117 58	CF CF (rhinitis) non-CF (disease) non-CF (healthy)	CF vs non-CF (healthy) p<0.0001 CF vs non-CF (disease) p<0.0001 CF vs CF (rhinitis) p<0.0001	ND	ND	MWU	(12)
106 88	CF non-CF	<0.0001	<0.0001	ND	unpaired t-test	(13)
17 31	CF non-CF	0.0001	0.0001	0.0001	Unpaired t-test	(14)
67 249	CF non-CF	<0.05	<0.05	<0.05	unpaired t-test	(15)
25 12	CF non-CF	<0.0001	<0.0001	<0.0001	MWU	(16)
7 7	CF non-CF	<0.05	ND	ND	not reported	(17)
64 26	CF CBAVD	<0.001	<0.05	<0.05	ND	(18)
60 145	CF non-CF	No overlap	ND	ND	Individual data	(19)
20 20	CF non-CF	<0.002	ND	ND	MWU	(20)
13 22	CF non-CF	no overlap	ND	ND	ANOVA	(21)
3 51	CF non-CF	<0.05	<0.05	ND	unpaired t-test	(22)
19 22	CF non-CF	<0.02	ND	ND	MWU	(23)
18	CF	<0.05	p<0.05	ND	unpaired t-	(24)

34	non-CF				test	

23	CF	No overlap	ND	ND	Individual data	(25)
32	Non-CF (disease)					
54	Non-CF (healthy)					
NPD parameters differ between CF patients with severe and mild disease						
92	CF					(26)
	ΔF508-ΔF508 vs. mild genotype	P<0.001	NR	P<0.01	ANOVA	
75	CF					(27)
	FEV_1 (top vs. bottom quartile)	0.03	0.04	NS	unpaired t-test	
	BMI (<18.5 vs. >18.5)	0.03	0.05	0.01	unpaired t-test	
	Symptoms at diagnosis	NS	NS	<0.005	Tukey-Kramer	
79	CF					(8)
	PI vs. PS	NS	NS	0.01	MWU	
	FEV_1 <50% vs. FEV_1 >50%)	0.005	0.003	NS	MWUT	
	Class I to III vs. class IV	0.01	NS	NS	MWU	
24	CF					(28)
	mild vs. severe disease (WFH + FEV_1)	0.07	NS	NS	MWU	
16	CF (8 pairs)					
	mild vs. severe FEV_1	ND	NS	<0.05	paired t-test	
22	CF					(29)

	Class I to II vs class III to V	NS	0.04	0.01	ANOVA	
NPD parameters differ between CF-PI, CF-PS, CBAVD and controls. NPD parameters increase incrementally across groups with no respiratory disease, carriers, diffuse idiopathic bronchiectasis and 0, 1 or 2 CFTR mutations, mild CF and severe CF.						
55	CF (severe)	Increases incrementally across groups	Increases incrementally across groups	Increases incrementally across groups	ANOVA	(26)
37	CF (mild)					
85	DB (0 CFTR)					
22	DB (1 CFTR)					
15	DB (2 CFTR)					
38	carriers (healthy)					
26	non-CF (healthy)					
26	CF-PI	no overlap: CF-PI vs. CF-PS CF vs. CBAVD, carriers or non-CF	no overlap: CF-PI vs. CF-PS CF-PI vs. CBAVD, carrier or non-CF CF-PS vs. non-CF	no overlap: CF vs. CBAVD, carrier or non-CF	95% CI medians	(4)
24	CF-PS					
60	CBAVD					
21	carriers					
31	non-CF					
39	CF-PI	P<.0001 vs CBAVD P<.0001 vs CBAVD NS vs non-CF	P<.05 vs CBAVD P<.05 vs CBAVD NS vs non -CF	P<.0005vs non-CF, P<.05 vs CBAVD P<.005 vs non –CF, p<.05 vs CF-PI and PS (Zero chloride)	unpaired t-test	(18)
25	CF-PS					
20	CBAVD					
50	non-CF (healthy)					
NPD parameters correlate with other endpoints and clinical measurements						
79	CF	FEV1% pred: p=0.04, r= 0.24 FVC% pred: p=0.03, r=0.25	p=0.009, r=-0.29 p=0.01, r=-0.28	NS NS	Spearman correlation coefficient	(8)
51	CF	NS for FEV1, CXR, Shwachman score		NS for sweat chloride BMI, symptoms at diagnosis, MI, CF-RD	Pearson or Spearman correlation coefficient	(9)

| 60 | CF | FEV1: r=-0.27, p<0.05
FVC: r=-0.26, p<0.05
Weight: r=-0.37, p<0.01 | ND | ND | Pearson correlation coefficient | (19) |

Patients grouped by NPD result differ in clinical presentation					
N and subject type		**Characteristic compared**	*p*-value	**Statistic**	**Author**
22	CF	Low Cl- secretors had lower FEV1	<0.05		(29)
	High Cl- secretors (>10mV) vs. low Cl- secretors (<10mV)	Low Cl- secretors had higher Northern Score	0.03		
Composite NPD indices are highly indicative of disease in groups of patients with "questionable" CF					
$e^{(total\ chloride\ response/amiloride\ response)}$, *value >0.7 = CF*					
70	Questionable CF 24 CF 46 non-CF	CF younger	0.013	unpaired t-test	(6)
		CF had higher sweat Cl	<0.001		
		CF had higher frequency of CFTR mutations	<0.001		
56	Questionable CF 17 CF 39 non-CF	CF had higher frequency of abdominal pain	0.018	χ^2 test	(30)
		CF had higher frequency of sinusitis	<0.01		
-0.11[Δlow chloride + isoproteronol] - 0.05[amiloride], value <0.27 = CF					
50	Questionable CF 15 CF 35 non-CF	CF younger	0.01	MWU *Fisher's exact test	(31)
		CF had higher frequency of cough and sputum	0.04*		
		CF had higher frequency of lower respiratory tract infection	0.03		
		CF had higher frequency of chronic *Staph. aureus*	0.009*		
21	Questionable CF 13 CF 8 non-CF	CF had higher sweat Cl at follow-up	0.03	MWU	(32)
		CF had higher frequency of lower respiratory tract infection	0.007		

MWU Mann-Whitney U, ND no data, NS not significant, WFH weight for height, CI confidence interval, NPD nasal potential difference, CF cystic fibrosis, PI pancreatic insufficient, PS pancreatic sufficient, CBAVD congenital bilateral absence of vas deferens, BMI body mass index, FEV_1 forced expiratory volume in one second

Table S2 online supplement : Reference values for NPD in subjects with CF							
N	**Adults vs. children**	**Additional info**	**Basal potential (*Max PD)**	**Δ Amiloride**	**Δ Low chloride + isoproterenol (*terbutaline)**	**Statistic**	**Author**
37	Adult		-47.3 (15.3)	29.4 (12.7)	1.6 (8.4)	Mean (SD)	(33)
7	Adult + child		-27.6(5.8)	NR	NR	Mean (SE)	(17)
20	Adult		-45(8)	NR	NR	Mean (SD)	(20)
60	Adult + child		-46.1 (-33 to -77) [-27.7 to -64.5]	NR	NR	Mean (range) [95%CI]	(19)
37	Adult	Mild disease	-43 (2)	26 (2)	-1 (1)	Mean (SEM)	(26)
55	Adult	ΔF508- ΔF508	-52 (2)	30 (2)	+2 (1)	Mean (SEM)	(26)
11	Adult + child	Premature stop mutation	-36.18 (17.16) -37.73(10.87)	NR	3.97(3.50) 3.89(3.91)	Mean (SD)	(34)
18	Adult + child	No premature stop mutation	-42.09(10.12)	NR	2.99(3.48)	Mean (SD)	(34)
8	Adult	ΔF508- ΔF508	-37.8(2.8)	NR	NR	Mean (SEM)	(5)
37	Adult + child		-39(8)[-28 to -57]	NR	NR	Mean (SD) [range]	(35)
18	Adult + child	Borderline sweat	-39(6)[-29 to -52]	NR	NR	Mean (SD) [range]	(35)
13	Adult	Medial part of inferior turbinate	-31.0(2.7)	NR	NR	Mean (SEM)	(11)
		Posterior part of inferior turbinate	-38.9(1.6)	NR	NR		
		Most negative PD	-42.9(4.7)	32.4(3.7)	-0.7(0.6)		
95	Adult		-38.0(8.2)[-20.6 to -62.5]	NR	NR	Mean (SD) [range]	(36)
79	Adult		-47 [-91 to -19]	29 [4 to 68]	2 [-8 to 17]	Median [range]	(8)

4	Adult		-41.4 (5.9)	NR	NR	Mean (SEM)	(37)
4	Adult		-49.3 (5.0)	NR	NR	Mean (SEM)	(37)
4	Adult		-51.3 (4.7)	NR	NR	Mean (SEM)	(37)
29	Adult + child	Pancreatic insufficient	*-54(9)	NR	3.6(4.7)	Mean (SD)	(38)
27	Adult + child	Pancreatic sufficient	*-45(12)	NR	1.7(5.2)	Mean (SD)	(38)
3	Neonate		-51.3 (8.0)	NR	NR	Mean (SEM)	(22)
19	Adult	Tip of inferior turbinate	-10(5.5)	NR	NR	Mean (SD)	(23)
		Distal inferior turbinate	-25(13.3)	NR	NR		
		Most negative value of inferior turbinate	-36(18.6)	NR	NR		
9	Adult	Pre-treatment (active nostril)	-53.3(4.0)	36.9 (4.7)	-4.5 (1.5)	Mean (SEM)	(14)
		Pre-treatment (placebo nostril)	-49.7 (4.4)	35.6(5.4)	-2.8(1.4)		
7	Adult + Child		-33.6 (10.0)	26.1 (11.0)	NR	Mean (SEM)	(39)
40	Adult + Child	Sub-cutaneous	-55.8(1.5)	NR	NR	Mean (SEM)	(12)
		Epi-cutaneous	-47.8(1.5)	NR	NR		
35	Adult		-49.3 (2.1)	NR	NR	Mean (SEM)	(40)
12	Adult		-47.9 (2.5)	NR	NR	Mean (SEM)	(40)
23	Adult	Premature stop mutation	-40 [-67 to -29]	NR	1.25 [-4.9 to 8.0]	Median [range]	(41)
23	Adult + Child		-53.0 (1.8)	NR	NR	Mean (SEM)	(42)
20	Adult		-70.8 (4.7)	48.0(1.9)	NR	Mean (SEM	(24)
12	Adult		-54.0 [-57.1 to -49.6]	NR	0 [0.1 to 1.8]	Median [95%CI]	(43)
			-53.3 (12.9)	NR	0.32 (2.67)	Mean (SD)	

75	Adult	ΔF508-ΔF508	*-49.6 [-52.4 to -46.8]	32.1 [29.2 to 34.9]	-1.5 [-0.2 to -2.7]	Mean [95%CI]	(27)
25	Adult		-46.5 (2.0)	23.9 (1.9)	1.4 (0.4)	Mean (SEM)	(16)
46	Adult		-47.5 (1.7) [-43 to -52]	27.8 (1.7) [23.3 to 32.3]	0.1 (0.4) [-1.1 to 1.3]	Mean (SEM) [95%CI]	(2)
25	Adult	ΔF508-ΔF508	-45 [-32 to -58]	NR	NR	Mean [range]	(18)
10	Adult		-26.6 (12.1)	13.6 (9.7)	1.4 (1.4)	Mean (SD)	(44)
10	Adult		-36.8 (0.7)	NR	NR	Mean (SD)	(45)
10	Adult		-36.0 (1.6)	NR	NR		
10	Adult		-39.1 (1.4)	NR	NR		
10	Adult		-36.3 (5.2)	20.2 (5.4)	5.2 (2.0)	Mean (SD)	(46)
13	Adult + child		NR	38(4)	NR	Mean (SD)	(21)
37	Child		-47 (2.6)	24 (2.2)	1 (1.3)	Mean (SEM)	(7)
9	Adolescent + child	Y122X	-56 (10)	20 (6)	-0.8 (1.3)	Mean (SD)	(47)
4	Adolescent + child	Other stop mutation	-53 (11)	22 (15)	-0.2 (0.5)		
5	Adolescent + child	No stop mutation	-52 (8)	19 (12)	0 (0.5)		
67	Adult + child		-51 (16)	28 (17)	0 (7)	Median (IQR)	(32)
89	Child		-57 (12)	32.7 (14)	1.6 (4.7)	Mean (SD)	(31)
30	Child	Premature stop mutation	NR	NR	-0.3 [-4.6 to 14.6]	Median [range]	(48)
6	NR		-52.2 (3.3)	26.1 (2.4)	NR	Mean (SEM)	(49)
4	Adult	Standard method	-46.2 (7.1)	32.1 (6.0)	2.6 (0.9)	Mean (SEM)	(50)
		Modified method	-45.6 (6.6)	34.9 (5.6)	4.6 (0.8)		
31	Adult		-45.3 (11.5) [-49.5 to -41.1]	29.8 (11.3) [25.6 to 33.9]	3.2 (3.5) [1.9 to -4.5]	Mean (SD) [95%CI]	(51)
34	Adult + child	Floor	*-41.5 [-49.5 to -30.5]	28 [17 to 39]	1 [0 to 3]	Median [IQR]	(1)
		Turbinate	*-46.5 [-54.5 to -	34.5 [20 to 41]	2 [1 to 5]		

			36.5]			
5	Adult + child	G542X or R553X (36 hospital admissions)	*-39 (9)	15 (8)	2 (4)	Mean (SD)	(10)
5	Adult + child	A544E (10 hospital admissions)	*-57 (5)	28 (10)	4 (8)		
5	NR	ΔF508-ΔF508	*-43 (9)	27 (8)	5 (4)		
51	Child		*-46.6 (1.9)	35.1 (2.2)	-1.7 (0.8)	Mean (SEM)	(9)
17	Adult + child		-45 (16)	33 (14)	3 (4)	Mean (SD)	(52)
9	Adult + child		-44 (11)	29 (7)	-0.6 (1.5)		
31	Adult + child		-49 (13)	35 (11)	3 (6)	Mean (SD)	(6)
11	Adult + child	Homozygous premature stop mutation (baseline)	-48 (10)	33 (9)	0.4 (4.6)	Mean (SD)	(53)
11	Adult + child	Homozygous premature stop mutation (placebo)	-46 (10)	34 (11)	-0.4 (2.7)		
8	Adult + child	Heterozygous premature stop mutation (baseline)	-42 (3)	32 (7)	-0.5 (2)		
8	Adult + child	Heterozygous premature stop mutation (placebo)	-41 (10)	27 (10)	-0.25 (2)		
5	Adult + child	ΔF508-ΔF508 (baseline)	-45 (11)	32 (14)	2.2 (5)		
5	Adult + child	ΔF508-ΔF508 (placebo)	-41 (14)	26 (10)	1.2 (2)		
24	Adult	Pancreatic sufficient	-44 (13)	27 (12)	2 (5)	Mean (SD)	(4)

26	Adult	Pancreatic insufficient	-54 (9)	36 (8)	4 (5)		
36	Adult		-44(9)[-31 to -65]	NR	2(4)[-6 to 12]	Mean (SD) [?]	(54)
25	Adult	1st measurement	-40(12)	27(9)	2.1(3.8)	Mean (SD)	(3)
		2nd measurement	-39(11)	26(10)	0.4(2.9)		
4	Adult	Pre-drug	-35.8(9.5)	21.9(6.8)	0.78(3.3)	Mean (SEM)	(55)
		Pre-vehicle	-29.7(8.0)	11.4(8.3)	2.1(4.5)		

N	Age group	Additional info	Basal potential (*Max PD)	Δ Amiloride	Δ Low chloride + isoproterenol (*terbutaline)	Statistic	Author
			Table S3 online supplement : Reference values for NPD in healthy controls				
20	Adult		-18 (5)	NR	NR	Mean (SD)	(20)
64	Adult + child		-19.0 (-8 to -30)			Mean (range)	(19)
7	Adult + child		-27.6 (5.8)	NR	NR	Mean (SE)	(17)
26	Adult		-16 (2)	7 (1)	-5 (1)	Mean (SEM)	(26)
32	Adult	Room temperature	-19.3 (6.9)	10.4 (5.6)	-6.9(6.4)	Mean (SD)	(56)
		Warmed	-18.8 (7.7)	11.0 (6.1)	-13.3(8.8)		
10	Adult		-17.2 (0.76)	NR	NR	Mean (SEM)	(5)
24	Adult + child		-15 (4) [-6 to -23]	NR	NR	Mean (SD) [range]	(35)
32	Adult	Medial part of inferior turbinate	10.3 (1.2)	NR	NR	Mean (SEM) [95%CI]	(11)
		Posterior part of inferior turbinate	3.2 (0.9)	NR	NR		
		Most negative PD	-15.1 (1.8) [+1 to -32]	10.1 (1.2)	-13.2(1.8)		
50	Adult		-25 (8)*	NR	-24.6(10.4)	Mean (SD)	(38)
24	Neonate		-16.4 (0.8)	NR	NR	Mean (SEM)	(22)
22	Adult	Tip of inferior turbinate	-10 (3.7)	NR	NR	Men (SD)	(23)
		Distal inferior turbinate	-13 (4.6)				
		Most negative value of inferior turbinate	-17 (5.1)				
9	Adult		-7.1 (5.1)	10 (3.1)	NR	Mean (SEM)	(39)

58	Adult + Child	Subcutaneous	-15.1 (1.4)	NR	NR	Mean (SEM)	(12)
		Epicutaneous	-17.9 (0.8)				

10	Adult (young ♀)	Anterior surface of inferior turbinate	-2.9 (0.3)	NR	NR	Mean (SEM)	(25)
		Medial surface of inferior turbinate	-13.7 (1.5)				
		Inferior surface of inferior turbinate	-26.9 (2.7)				
		Floor	-20.6 (3.2)				
		Septum	-13.1 (1.5)				
10	Adult (young ♂)	Anterior surface of inferior turbinate	-4.0 (0.5)	NR	NR		
		Medial surface of inferior turbinate	-13.6 (1.4)				
		Inferior surface of inferior turbinate	-23.3 (1.7)				
		Floor	-14.7 (3.2)				
		Septum	-10.5 (0.9)				
8	Adult (older ♂)	Anterior surface of inferior turbinate	-5.2 (0.6)	NR	NR		
		Medial surface of inferior turbinate	-11.4 (1.1)				
		Inferior surface of inferior turbinate	-16.5 (1.5)				
		Floor	-9.4 (2.2)				
		Septum	-8.7 (0.8)				
54	Adult		-24.7 (0.9)	NR	NR	Mean (SEM)	(42)
43	Adult		-27.9 (1.3)	22.8 (2.5)	NR	Mean (SEM)	(24)
176	Adult + child		-22.3 (0.6)	NR	NR	Mean (SEM)	(15)
27	NR		-17 (1.3) *	NR	-14.7 (1.3)	Mean (SD)	(57)
12	Adult		-15.9 (1.2)	8.7 (0.7)	-10.0(1.1)	Mean (SEM)	(16)
6	Adult		-14.0 (0.8)	8.1 (0.6)	-26.2(1.1)	Mean (SEM)	(2)

| 11 | Adult | | -13.2 (4.6) | 4.5 (2.5) | -13(8.4) | Mean (SD) | (44) |

17	Adult		-26 (2) * -15 (2) *	10 (2)	NR	Mean (SEM)	(21)
32	Adult		-15 (1.5)	7.1 (1.2)	-15(1.7)	Mean (SEM)	(7)
29	NR		-15 (11)*	6 (6.7)	-15(11)	Median(IQR)	(32)
33	NR		-16.8 (6.5)	7.7 (5)	-18.3 (10.6)	Mean (SD)	(31)
6	Adult		-14.7 (4)	8.1 (1.3)	NR	Mean (SEM)	(58)
6	Adult	Standard method	-20.7 (1.7)	12.4 (1.7)	-12.4 (1.3)	Mean (SEM)	(50)
		Modified method	-18.5 (1.2)	13.0 (0.8)	-13.9(1.7)		
52	Adult		-18.2 (8.3) [-20.5 to -15.9]	10.5 (6.1) [8.8 to -12.2]	-23.7(10.2) [-26.5 to -20.9]	Mean (SD) [95%CI]	(51)
56	Adult	Floor	-16 (-20.5 to -12)*	7 (5 to 9.5)	-14(-18.5 to -9)	Median (IQR)	(1)
		Turbinate	-15.5 (-23 to -12.5)*	7 (5 to 10)	-14.5 (-21 to -10)		
10	Adult		-26 (5) *	8 (4)	-12(7)	Mean (SD)	(10)
12	NR		-19.8 (2.7)*	13.7 (1.6)	-15.7(2.3	Mean (SEM)	(9)
35	Adult		-19 (8)	10.5 (5)	-13(8)	Mean (SD)	(52)
50	Adult		-16 (5)	10 (4)	-12(7)	Mean (SD)	(6)
25	Adult		-24 (8)	13 (4)	-16(12)	Mean (SD)	(4)
39	Adult		-20 (8) [-9 to -44]	NR	-21(9) [-5 to -44]	Mean (SD)[range]	(54)
50	NR		-16 (5)	10 (4)	-12(7)	Mean (SD)	(3)
4	Adult	Pre-drug	-14.8 (3.7)	3.6 (5.3)	-5.0 (7.0)	Mean (SEM)	(55)
		Pre-vehicle	-9.6 (2.4)	4.8 (1.9)	-7.2 (1.4)		

Table S4 online supplement: Sweat chloride reliability				
Despite the general consensus that the sweat test remains the best diagnostic test for CF, very few recent studies report on sweat test reliability				
N and subject type	**N measurements**	**Results**	**Statistic**	**Author**
295 subjects tested for clinical purposes	2	21 ± 4.3 mmol/L, 20.2%	mean ± SD, CV	(59)
47 subjects with Cl^- 30-70		ND± 7.2 mmol/L, 17.2%		
4 non-CF	8-12	subject 1: 12.8, (3.3), 26%, [7 to 19] subject 2: 15.5, (5.1), 33%, [6 to 24] subject 3: 36.4, (10.6), 29%, [16 to 57] subject 4: 38.4, (5.5), 14%, [28 to 49]	Mean, (SD), CV, [95%CI]	(60)
1 non-CF	6	12%	Intra-individual variation	(61)
37 CF	2	<0.0001	sig. within subject variance	(33)
		<0.0001	sig. total variance	
21 CF + non-CF	2	r=0.988		(62)
165 CF + non-CF	2	Cl^- <40: 99% Cl^- >60: 100% Cl^- 40-60: ND	% agreement between 2 tests	(63)

Table S5 online supplement: Sweat chloride discriminate validity				
N and subject type	**Comparison**	**Result**	**Statistic**	**Author**
The sweat chloride value allows discrimination between subjects with and without CF and also between subjects with CF				
55 CF (severe) 37 CF (mild) 85 DB (0 CFTR) 22 DB (1 CFTR) 15 DB (2 CFTR) 38 carriers (healthy) 26 non-CF (healthy)	CF (severe) vs. CF (mild) DB (0 CFTR) vs. Non-CF (healthy) DB (2 CFTR) vs. CF (mild) DB (2 CFTR) vs. DB (0 CFTR) DB (2 CFTR) vs. DB (1 CFTR)	$p<0.001$ $p<0.001$ $p<0.05$ $p<0.001$ $p<0.01$	ANOVA	(26)
17 CF with P. aeruginosa 17 CF without P. aeruginosa	CF with P. aeruginosa vs CF without P. aeruginosa	First test $p=0.004$ Second test $p=0.02$	MWU	(64)
26 CF-PI 24 CF-PS 31 non-CF	CF-PI vs. non-CF CF-PS vs. non-CF CF-PI vs. CF-PS	$p<0.001$ NR $p<0.001$	MWU	(4)
20 CF 52 carriers 32 non-CF	CF vs. non CF CF vs. carrier non-CF vs. carrier	$p<0.0001$ $p<0.0001$ $p<0.01$	MWU	(7)
230 CF ΔF508 34 CF-PS	CF ΔF508 vs. CF-PS	$p<0.0001$	Wilcoxon	(65)
103 CF 184 non-CF	CF vs. Non-CF	Cut-off of 49mmol/L Sensitivity =0.973 Specificity=0.973	sensitivity and specificity	(62)
115 CF 128 carriers 464 non-CF	CF vs. non CF CF vs. carrier non-CF vs. carrier	no overlap in 95%CI $p<0.05$* no overlap in 95%CI $p<0.05$* no overlap in 95%CI $p<0.05$**	*unpaired t-test **Wilcoxon rank sum	(66)
20 CF	CF vs. non-CF	sensitivity = 100%	sensitivity and	(67)

40	Non-CF		specificity = 100%	specificity	
8 7	CF non-CF	CF vs non-CF	P<0.001	unpaired t-test	(68)

CF subjects with higher sweat chloride values have greater disease severity					
62 103 59	CF-PI (Cl⁻ >60) CF-PS (Cl⁻ >60) CFTR dysfunction (Cl⁻ 30 to 60)	CF-PI younger at diagnosis	p=0.03	MWU (CFTR dysfunction vs. CF-PS)	(69)
		CF-PI had higher frequency of isolation of *S. aureus* or *P. aeruginosa*	p=0.05		
		CF-PI had higher frequency of MI or DIOS	p=0.05		
		CF-PI had higher frequency of liver disease	p=0.04		
54 40 19	ΔF508 621+1G→T A455E	621+1G→T vs. A455E ΔF508 vs. A455E	p<0.05 p<0.05	ANOVA	(70)
294	ΔF508/ ΔF508 (class II)			unpaired t-test	(71)
20	ΔF508/splice (class I)	ΔF508/ ΔF508 vs ΔF508/splice	p<0.05		
17	ΔF508/missense (class IV)	ΔF508/ ΔF508 vs ΔF508/missense	p<0.05		

Sweat test Convergent Validity

There is excellent correlation between sweat chloride values determined by the original Gibson-Cooke method with gauze collection and the adapted Macroduct sweat collection system. When comparing both methods by Bland-Altman plot, the limits of agreement are however wide.					
20 41 7 14	CF Questionable CF Carrier Non CF	gauze vs. Macroduct	r =0.93, p<0.0001	linear regression	(72)
			0	mean difference	
			-20 to +20	95% limits of agreement	
1014	CF and non-CF	gauze vs. Macroduct	r=0.99, p=NR	linear regression	(73)

150	Infants 4-6 weeks dd	gauze vs. Macroduct	11.2 (8-13) mmol/L	median (IQR)	(74)
			-1 mmol/L	mean difference	
			-10.8 to 9.8 mmol/L	limits of agreement	

103	CF	gauze vs. Macroduct	R=0.988	not reported	(62)
184	Non-CF		21mmol/L	mean difference	
			38.6 to 3.3	limits of agreement	
94	CF	gauze vs. Macroduct	r=0.987	not reported	(62)
86	non-CF		-11.7 to 14.0	limits of agreement	

Sweat chloride normal values		
chloride > 60 mmol/L	consistent with CF	(75-78)
chloride < 40 mmol/L (<30mmol/L for infants)	negative	
chloride 40-60 mmol/L	borderline/indeterminate	

DB = diffuse idiopathic bronchiectasis

Table S6 online supplement: Clinimetric properties for intestinal current measurement			
N and subject type	**Result**	**Statistic**	**Author**
Reliability *No data available*			
Discriminate Validity			
Chloride secretion measured with ICM discriminates CF from normal and also discriminates between patients with CF (CF-PI vs. CF-PS, F508del homozygotes vs. F508del heterozygotes)			
47 CF (34 CF-PI; 13 CF-PS) 28 Non-CF	Cumulative chloride response (Δ Isc carbachol + cAMP + histamine) > 34 μA/cm^2 is non-CF < 34 μA/cm^2 is CF 100% sensitivity and 100% specificity in cohort of known patients	MWU	(79)
45 CF 13 carriers 19 non-CF	Δ Isc cAMP p<0.05 CF vs carrier p<0.05 CF vs non-CF	unpaired t-test	(80)
8 CF 26 non-CF	Δ Isc amiloride p<0.05 CF vs non-CF Δ Isc carbachol P<0.05 CF vs non-CF	unpaired t-test	(81)
14 CF 34 non-CF	Δ Isc amiloride p<0.0001 CF vs non-CF Δ Isc amiloride + IBXM/forskolin p<0.0001 CF vs non-CF	unpaired t-test	(82)
42 CF-PI 9 CF-PS	Δ Isc carbachol p <0.01 CF-PI vs CF-PS	MWU	(83)
12 F508del homozygous 8 F508del heterozygous 28 non-CF	Δ Isc acetylcholine p<0.05 homozygous vs. heterozygous	MWU	(84)
5 CF	Δ Isc acetylcholine	unpaired t-	(85)

12	non-CF	P<0.01 CF vs non-CF	test	
6	CF	Δ Isc acetylcholine	Fisher's	(86)
6	non-CF	p<0.05 CF vs non-CF	exact t-test	
		Δ Isc prostaglandin E2		
		p<0.05 CF vs non-CF		
3	CF	Δ Isc to secretagogues	Descriptive	(87)
5	non-CF	Zero response in CF		

Residual chloride secretion on ICM is highly indicative of milder disease compared to absent secretion				
45	CF	$CF_{residual}$ were older at diagnosis p<0.0001[b]	[a]unpaired t-test	(80)
	27 CF_{absent}	$CF_{residual}$ had lower sweat chloride p=0.01[a]	[b]MWU	
	18 $CF_{residual}$	$CF_{residual}$ had higher weight for height p=0.03[a]	[c]X^2	
		$CF_{residual}$ had higher frequency of pancreatic sufficiency p<0.0001[c]		
		$CF_{residual}$ had higher FVC & FEV_1%pred at age 20 yrs p<0.05		
51	CF	$CF_{residual}$ and $CF_{high\ residual}$ older at diagnosis p<.01, <0.05	MWU	(83)
	30 CF_{absent}	$CF_{residual}$ and $CF_{high\ residual}$ higher frequency of pancreatic		
	11 $CF_{residual}$	sufficiency p<.001		
	10 $CF_{high\ residual}$			

Convergent Validity				
The ICM result is convergent with the CFTR mutation analysis result				
Δ Isc carbachol + cAMP + histamine (< 34 $\mu A/cm^2$ = CF)				
61	Questionable CF	100% classified as CF had two mutations	Descriptive	(79)
	6 CF	1.8% classified as "CF unlikely" had two mutations		
	55 CF unlikely			
45	CF	ΔF508 homozygous - no residual chloride secretion	Descriptive	(80)
		At least one mild mutation - absent or residual chloride secretion		
51	CF	CF subjects with 1 A455E mutation have greater carbachol induced chloride secretion (p=0.01)	MWU	(83)
The ICM result is convergent with the sweat chloride				
47	CF	Cumulative chloride response (Δ Isc carbachol + cAMP +	Pearson	(79)

	histamine) r = 0.61	correlation	
Responsiveness *No data available*			
Reference values *See Table 1 – Derichs et al Thorax 2010; 65: 594-599 (79)*			

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