

Supplemental Appendix

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Complete list of members of the SCVSA study group

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Table S1. CFTR mutations in subjects enrolled in this study.

Mutation¹	Frequency	Percent	Cumulative²%
F508del	201	87.39	87.39
G542X	3	1.30	88.70
G551D	4	1.74	90.43
N1303K	6	2.61	93.04
R553X	3	1.30	94.35
1717-1G->A	1	0.43	94.78
621+1G->T	1	0.43	95.22
G85E	1	0.43	95.65
I507del	1	0.43	96.09
3659delC	2	0.87	96.96
R560T	1	0.43	97.39
Other	6	2.61	100
Total	230	100	

Mutation²	Frequency	Percent	Cumulative³%
F508del	129	56.09	56.09
G542X	7	3.04	59.13
G551D	8	3.48	62.61
N1303K	9	3.91	66.52
W1282X	3	1.30	67.83
R117H	1	0.43	68.26
1717-1G->A	4	1.74	70.00
621+1G->T	2	0.87	70.87
2789+5G->A	1	0.43	71.30
3849+10kbC->T	2	0.87	72.17
R1162X	1	0.43	72.61
3120+1G->A	1	0.43	73.04
I507del	4	1.74	74.78
3659delC	1	0.43	75.22
R560T	1	0.43	75.65
2184delA	2	0.87	76.52
711+1G->T	1	0.43	76.96
Unknown	1	0.43	77.39
Other	52	22.61	100
Total	230	100	

Figure S1. Timeline for collection of cultures, lung function tests, pulmonary exacerbation histories, and treatment histories during the study period.

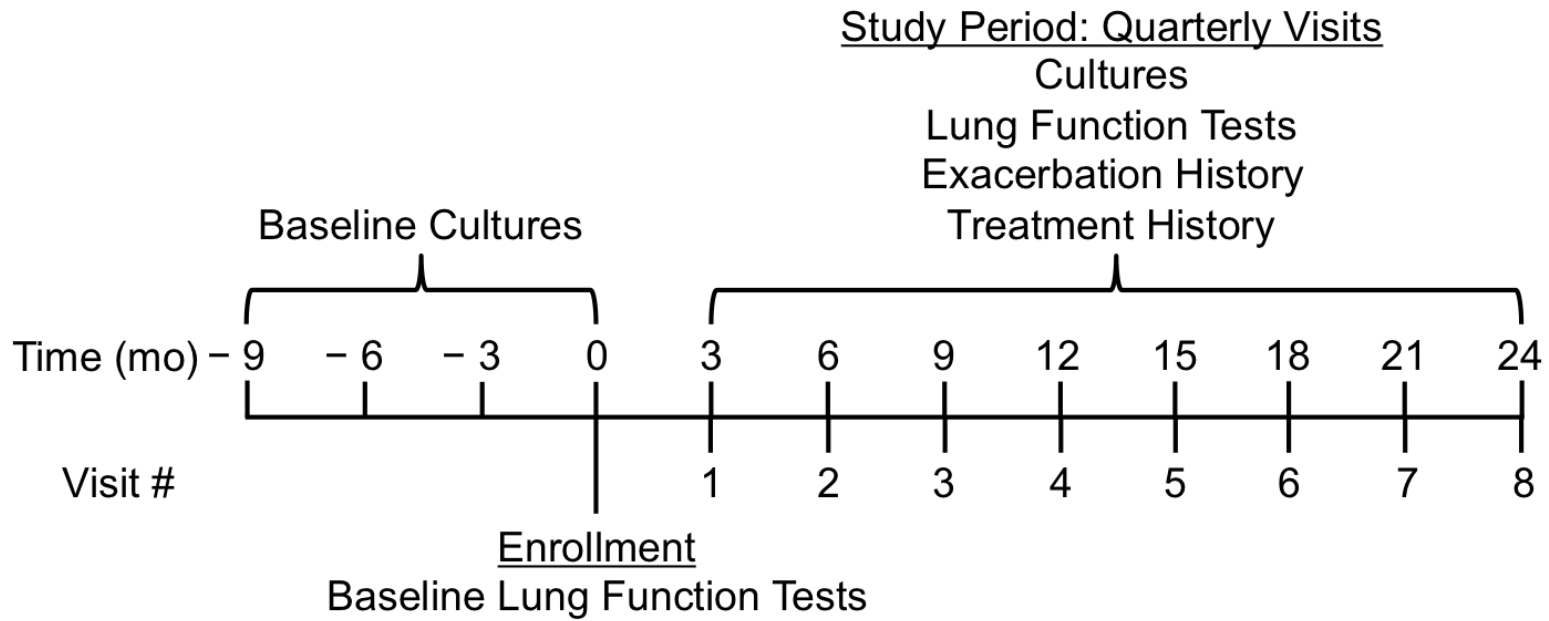


Table 52. HSV culture positivity at each site.

Site	N ^a	Ever HSV Pos ^b
Boston	51	18 (35.3%) ^b
Baylor	50	7 (14.0%)
Pittsburgh	50	17 (34.0%)
Seattle	29	6 (20.7%)
Alabama	50	16 (32.0%)
Total	230	64 (27.8%)

^a Total # of patients (N) per site

^b Number (Percent) of HSV culture-positive subjects per site

Figure S2. Frequency of isolation of *Staphylococcus aureus* normal colony (NC) and small-colony variants (SCVs) from respiratory specimens collected from study subjects, by MRSA status.

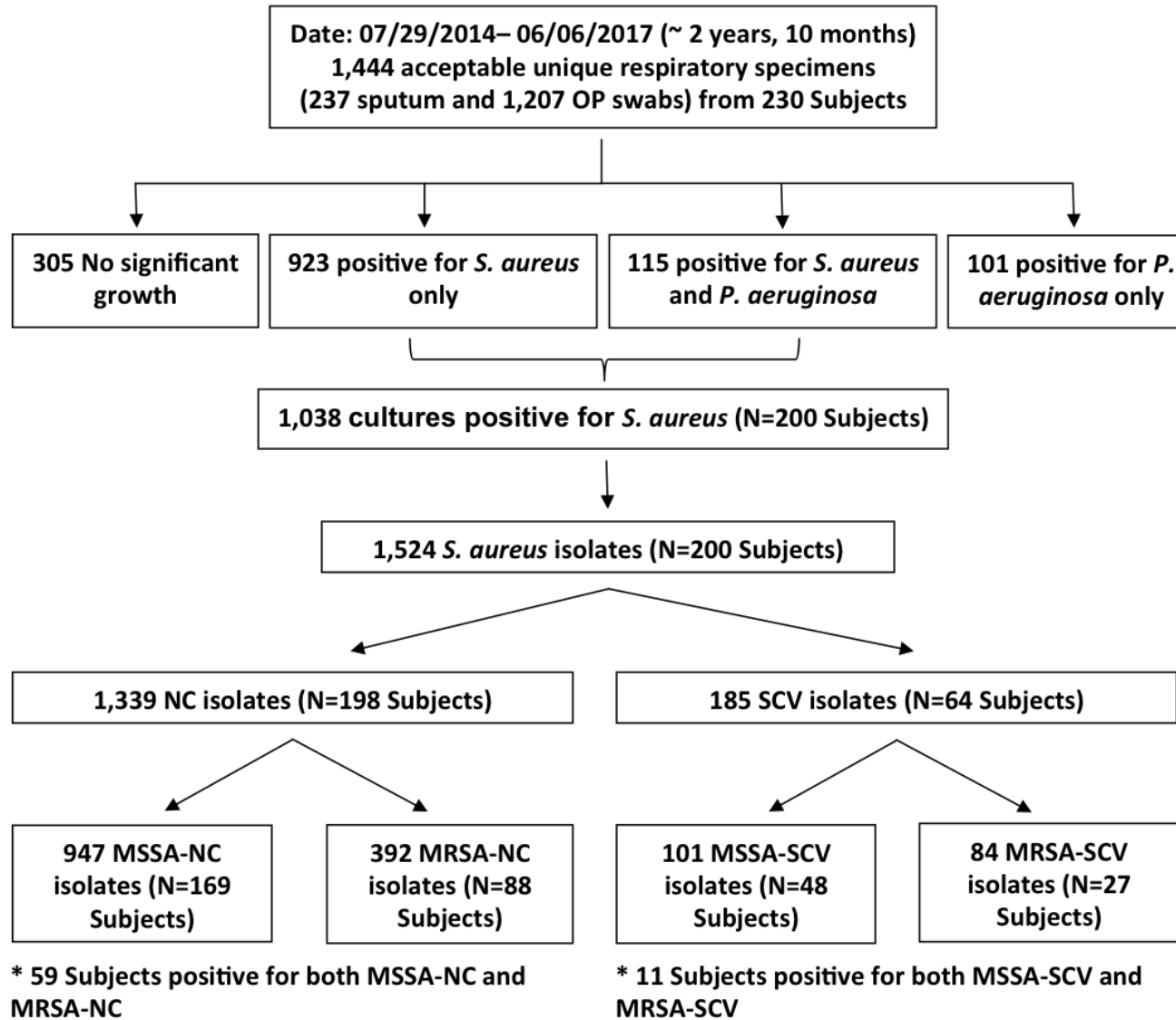


Table 53. Culture findings for subjects at baseline and SCV culture status during the study.

Organism	Baseline Culture ^a	SCV Culture Status During Study ^b		p-value
	Total Popul ^c (N=230)	Never SCV Pos ^c (N=166)	Ever SCV Pos ^c (N=64)	
<i>Pseudomonas aeruginosa</i>	66 (28.7%) ^c	49 (29.5%)	17 (26.6%)	0.66
<i>Staphylococcus aureus</i>	185 (80.4%)	124 (74.7%)	61 (95.3%)	0.0004
MRSA	57 (24.8%)	34 (20.5%)	23 (35.9%)	0.0150
MSSA-SCV	13 (5.7%)	4 (2.4%)	9 (14.1%)	0.0006
MRSA-SCV	1 (0.4%)	0 (0.0%)	1 (1.6%)	0.11
<i>Burkholderia cepacia</i> complex	7 (3.0%)	5 (3.0%)	2 (3.1%)	0.96
<i>Haemophilus</i> species	51 (22.2%)	40 (24.1%)	11 (17.2%)	0.26
<i>Stenotrophomonas maltophilia</i>	47 (20.4%)	37 (22.3%)	10 (15.6%)	0.26
<i>Achromobacter</i> sp.	6 (2.6%)	4 (2.4%)	2 (3.1%)	0.76
Nontuberculous mycobacteria (NTM)	1 (0.4%)	1 (0.6%)	0 (0.0%)	0.53
Other	212 (92.2%)	152 (91.6%)	60 (93.8%)	0.58

^a Baseline organisms represented those detected at any of 3 visits prior to enrollment by their respective study site; SCV detection protocols varied by site. Mean baseline samples per subject was 3 (SD 0.35).

^b Culture status during the study only included post-enrollment cultures and were determined by the central study laboratory.

^c Number (Percent) of subjects culture-positive at baseline for the organisms listed and the subsequent detection of SCVs during the study in these same subjects.

Figure S3. SCV detection patterns for the 64 subjects with SCVs detected at least once during the study (Visits 1-9). Each row of circles represents the culture results for one SCV culture-positive subject (y-axis, subject number). Open circles, cultures negative for SCVs; closed (red) circles, SCV-positive cultures. Baseline cultures were performed at each subject's respective site; SCV detection protocols varied by site. All study visit cultures were performed at the central study laboratory.

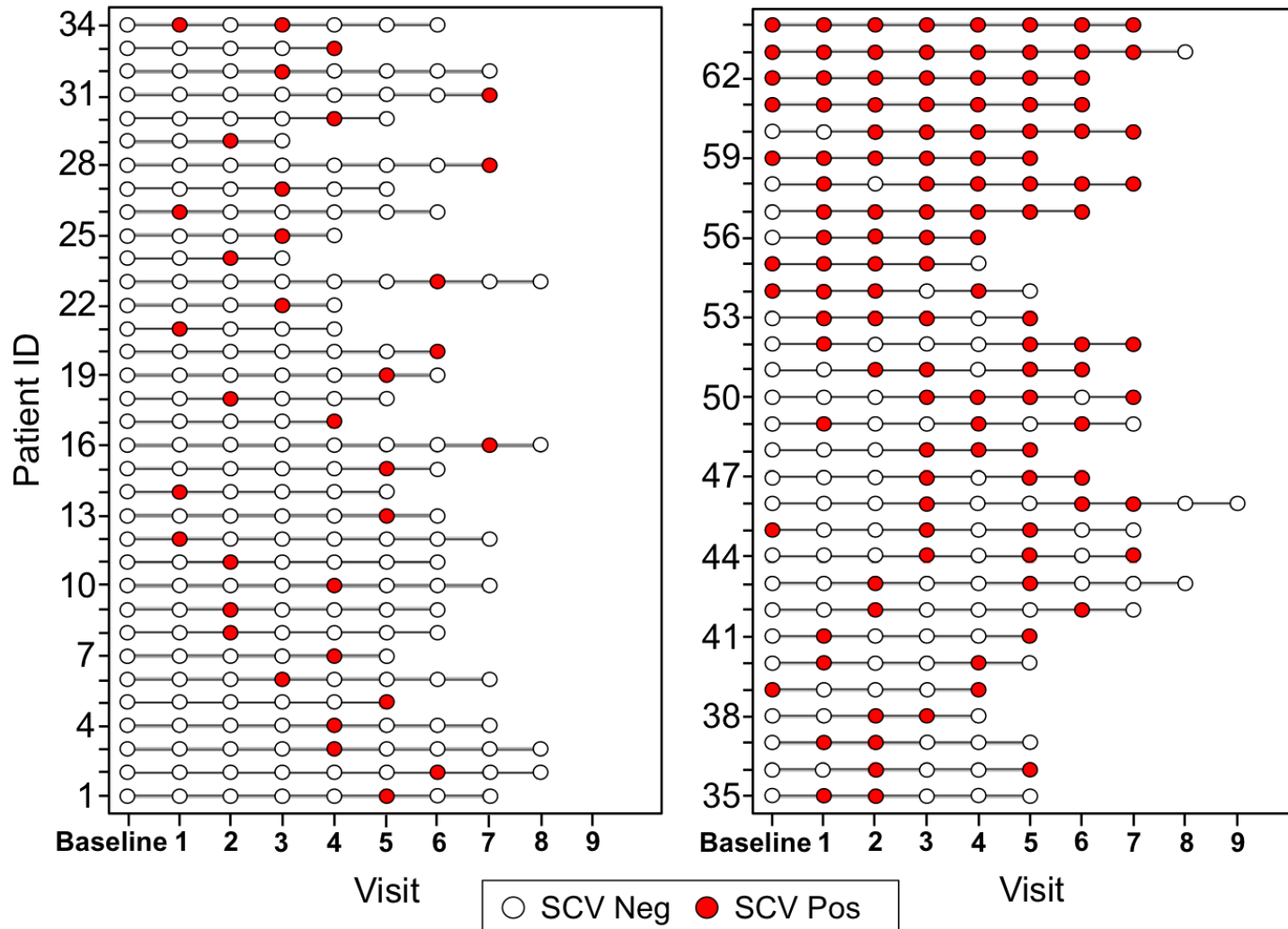


Table S4. Characteristics of Subjects positive for SCVs at 1 or more study visits.

Demographics/Characteristics ^b	Frequency of SCV Cx Positivity ^a		p-value
	SCV Cx Pos (n/N)	SCV Cx Pos (n/N)	
Age at Enrollment	12.7 (3.0)	12.2 (3.0)	0.54
Sex			0.97
Male	16 (47%)	14 (47%)	
Female	18 (53%)	16 (53%)	
Genotype			0.84
508 homozygous	20 (59%)	18 (60%)	
508 heterozygous	9 (26%)	9 (30%)	
Other	5 (15%)	3 (10%)	
GLI-EV1pp	86.31 (23.69)	89.78 (18.06)	0.52
SCV Subtype			0.0013
Ever Non-THYD SCV	25 (74%)	10 (33%)	
Ever THYD SCV	9 (26%)	20 (67%)	

^aNumber of SCV positive cultures during the study

^bAbbreviations: Cx Pos, culture positive; THYD, thymidine-dependent

Table 55. Mean GLI FEV₁ ppv over time by SCV status and auxotrophic type.

Visit	Never SCV Pos		Ever SCV Pos (All)		Ever Non-THYD ^b SCV Pos		Ever THYD SCV Pos	
	N ^a	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Baseline	164	92.4 ± 18.6	64	85.5 ± 19.0	35	90.9 ± 16.1	29	79 ± 20.5
1	157	92.4 ± 17.2	64	85.5 ± 20.2	35	90.2 ± 14.7	29	79.9 ± 24.4
2	159	91.2 ± 19.9	63	83.3 ± 19.9	34	87.9 ± 17.3	29	77.8 ± 21.7
3	154	90.6 ± 18.8	63	83.6 ± 20.9	35	87.9 ± 15.9	28	78.2 ± 25.1
4	147	91.1 ± 20.2	61	83.2 ± 21.0	34	89.3 ± 14.7	27	75.5 ± 25.1
5	129	90.6 ± 18.8	52	83.7 ± 20.6	27	88.1 ± 17.0	25	79 ± 23.3
6	86	91.6 ± 18.1	35	83.7 ± 21.5	19	90.8 ± 16.5	16	75.4 ± 24.2
7	30	92.6 ± 21.2	15	80.2 ± 31.1	9	96.9 ± 14.5	6	55.2 ± 33.4
8	2	100.0 ± 24.5	4	88.9 ± 35.3	3	106 ± 7.58	1	36.8

^aNumber of subjects

^bAbbreviation: THYD, thymidine-dependent.

Table S6. Association of SCVs with GLI FEV₁ pp in univariate and multivariate analyses.

Covariate	Univariate			Multivariate			Multivariate		
	Coeff. ^a	95%CI	p-value	Coeff.	95%CI	p-value	Coeff.	95%CI	p-value
SCV Culture Status									
Never SCV Pos*	0			0			0		
Ever SCV Pos	-7.071	(-12.195--1.948)	0.0068	-5.021	(-10.114-0.071)	0.05	-5.495	(-10.507--0.483)	0.0316
Visit number	-0.396	(-0.665--0.128)	0.0038	-0.394	(-0.662--0.125)	0.0040	-0.394	(-0.662--0.126)	0.0040
Age at enrollment				-1.103	(-1.833--0.374)	0.0030	-0.929	(-1.654--0.203)	0.0122
Sex									
Male*				0			0		
Female				-3.958	(-8.412-0.496)	0.08	-3.356	(-7.750-1.038)	0.13
Hispanic race									
Hispanic*				0			0		
Non-Hispanic				-0.705	(-11.800-10.390)	0.90	-2.233	(-13.178-8.712)	0.69
Genotype									
F508 homozyg*				0			0		
F508 heterozyg				3.783	(-1.157-8.722)	0.13	3.103	(-1.770-7.977)	0.21
Other				1.222	(-6.364-8.808)	0.75	1.178	(-6.274-8.629)	0.76
CFTR Modulator									
No*				0			0		
Yes				6.530	(-2.288-15.348)	0.15	6.043	(-2.625-14.710)	0.17
<i>P. aeruginosa</i> Cx Status									
Never PA Pos*							0		
Ever PA Pos							-7.389	(-12.353--2.425)	0.0035
Constant	92.653	(89.843-95.463)	<0.0001	105.87	(91.749-119.998)	<0.0001	107.49	(93.575-121.407)	<0.0001

*Baseline category

^aAbbreviations: Coefficient, Coeff.; Confidence Interval, CI; Culture, Cx.

Table 57. Unadjusted and adjusted analyses of association of SCVs and changes in GLIFEV₁ pp.

Covariate	Univariate			Multivariate		
	Coeff.	95% Conf. Interval	p-value	Coeff.	95% Conf. Interval	p-value
SCV Culture Status ^a						
Never SCV Pos*	0			0		
Ever SCV Pos	-6.157	(-11.649--0.666)	0.0277	-7.760	(-13.250--2.260)	0.0057
Visit number	-0.375	(-0.708--0.042)	0.0271	-0.450	(-0.870--0.040)	0.0333
Ever SCV Pos ^a Visit # ^a interaction*	-0.207	(-0.822-0.408)	0.51	-0.020	(-0.700-0.650)	0.95
Age at enrollment				-0.450	(-1.260-0.360)	0.28
Sex						
Male*				0		
Female				-4.400	(-9.180-0.380)	0.07
Hispanic race						
Hispanic*				0		
Non-Hispanic				-5.790	(-19.050-7.460)	0.39
Genotype						
F508 homozyg*				0		
F508 heterozyg				3.850	(-1.360-9.060)	0.15
Other				-3.010	(-11.250-5.240)	0.47
<i>P. aeruginosa</i> at enrollment						
Negative*				0		
Positive				-4.060	(-9.840-1.720)	0.17
MRSA at enrollment						
Negative*				0		
Positive				-3.320	(-8.850-2.210)	0.24
MRSA during study						
Negative*				0		
Positive				-1.140	(-3.150-0.860)	0.26
Constant	95.928	(93.017-98.840)	<0.0001	112.73	(96.490-128.960)	<0.0001

* Baseline category

^a Abbreviations: C, Coefficient; CI, Confidence Interval; Cx, Culture, Cx.

Table 58: Association of lung function with frequency of SCV detection.

Covariate ^a	Univariate		
	Coefficient	95% Conf. Interval	p-value
Frequency of SCV Positivity ^b			
SCV Neg*	0		
SCV Pos-1	-10.169	(-16.682--3.656)	0.0023
SCV Pos-1?	-6.440	(-13.291-0.412)	0.07
Visit number	-0.380	(-0.657--0.102)	0.0073
Constant	93.898	(90.846-96.950)	<0.0001

* Baseline category

^a Abbreviations: Cx Pos, culture positive

^b Number of SCV positive cultures during the study

Table 59. Prevalence of pulmonary exacerbations by SCV status and auxotrophic type.

Visit ^a	Never SCV Pos			Ever SCV Pos (All)			Ever Non-THYD SCV Pos			Ever THYD SCV Pos		
	Total (N) ^b	# with PEx ^c	%	Total (N)	# with PEx	%	Total (N)	# with PEx	%	Total (N)	# with PEx	%
1	166	82	49.4%	64	34	53.1%	35	17	48.6%	29	17	58.6%
2	166	62	37.3%	64	28	43.8%	35	11	31.4%	29	17	58.6%
3	162	63	38.9%	64	36	56.3%	35	18	51.4%	29	18	62.1%
4	158	63	39.9%	63	38	60.3%	35	17	48.6%	28	21	75.0%
5	149	50	33.6%	61	27	44.3%	34	9	26.5%	27	18	66.7%
6	131	44	33.6%	52	21	40.4%	27	10	37.0%	25	11	44.0%
7	91	25	27.5%	35	16	45.7%	19	7	36.8%	16	9	56.3%
8	30	8	26.7%	15	4	26.7%	9	1	11.1%	6	3	50.0%

^a Visit 1 represented the first quarterly visit after enrollment. Retrospective analysis of pulmonary exacerbations was not performed preventing the addition of baseline values in this table.

^b Total number of subjects.

^c Number of subjects with pulmonary exacerbation (PEx) in the study quarter between the indicated study visit and the prior study visit.

Table 10. Association of SCVs and occurrence of pulmonary exacerbations in univariate and multivariate analyses.

Covariate	Univariate			Multivariate			Multivariate			Multivariate		
	OR ^a	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
SCV Culture Status												
Never SCV Pos*	1.000			1			1			1		????????
Ever SCV Pos	1.727	(1.185-2.516)	0.0045	1.546	(1.065-2.244)	0.0219	1.492	(1.037-2.147)	0.0312	1.414	(0.984-2.032)	0.06
Visit number	0.900	(0.846-0.958)	0.0009	0.898	(0.844-0.956)	0.0007	0.898	(0.844-0.956)	0.0007	0.896	(0.842-0.954)	0.0006
Age at enrollment				1.082	(1.024-1.142)	0.0046	1.097	(1.040-1.158)	0.0007	1.082	(1.025-1.142)	0.0034
Sex												?
Male*				1			1			1		????????
Female				1.472	(1.056-2.051)	0.0225	1.546	(1.116-2.142)	0.0088	1.482	(1.073-2.045)	0.0149
Hispanic race												?
Hispanic*				1			1			1		????????
Non-Hispanic				0.763	(0.335-1.737)	0.52	0.664	(0.296-1.486)	0.32	0.687	(0.312-1.510)	0.35
Genotype												?
508 Homoz*				1			1			1		????????
508 Heteroz				1.063	(0.739-1.529)	0.74	1.005	(0.704-1.437)	0.98	0.997	(0.700-1.419)	0.99
Other				0.720	(0.408-1.273)	0.26	0.716	(0.411-1.249)	0.24	0.68	(0.392-1.181)	0.17
CFTR Modulator												?
No*				1			1			1		????????
Yes				0.550	(0.279-1.085)	0.09	0.535	(0.275-1.039)	0.07	0.571	(0.297-1.098)	0.09
<i>P. aeruginosa</i> Cx Status												?
Never PA Pos*							1			1		????????
Ever PA Pos							0.547	(0.377-0.792)	0.0014	0.508	(0.350-0.737)	0.0004
GLI FEV1pp at enrollment										0.991	(0.982-0.999)	0.0389

* Baseline category

^a Abbreviations: OR, Odds Ratio; CI, Confidence Interval; Cx, Culture.

Table S11: Association of pulmonary exacerbations with frequency of SCV detection.

Covariate ^a	Univariate		
	Odds Ratio	95% Conf. Interval	p-value
Frequency of SCV Cx Positivity ^b			
SCV Neg*	1		
SCV Cx Pos=1	1.221	(0.749-1.992)	0.42
SCV Cx Pos>1	2.166	(1.293-3.627)	0.0034
Visit number	0.933	(0.873-0.997)	0.0422

* Baseline category

^a Abbreviations: Cx Pos, Culture positive

^b Number of SCV positive cultures during the study

Table S12: Association between treatment and subsequent SCV detection in a multivariate analysis.

Covariate ^b	Multivariate ^a		
	Odds Ratio	95% Conf. Interval	p-value
Aminoglycoside			
█████ No*	1		
█████ Yes	1.417	(0.765-2.626)	0.27
Beta-lactam			
█████ No*	1		
█████ Yes	0.759	(0.393-1.467)	0.41
Fluoroquinolone			
█████ No*	1		
█████ Yes	0.844	(0.451-1.577)	0.60
Glycopeptide			
█████ No*	1		
█████ Yes	0.986	(0.342-2.841)	0.98
Lincosamide			
█████ No*	1		
█████ Yes	0.956	(0.236-3.869)	0.95
Macrolide			
█████ No*	1		
█████ Yes	1.318	(0.724-2.401)	0.37
Polymyxin			
█████ No*	1		
█████ Yes	4.258	(0.954-18.997)	0.06
Rifamycin			
█████ No*	1		
█████ Yes	0.285	(0.034-2.410)	0.25
Sulfonamide			
█████ No*	1		
█████ Yes	1.892	(1.026-3.488)	0.0407
Tetracycline			
█████ No*	1		
█████ Yes	1.216	(0.565-2.615)	0.62
Anti-fungal			
█████ No*	1		
█████ Yes	2.949	(0.245-35.487)	0.39
Hypertonic Saline			
█████ No*	1		
█████ Yes	0.430	(0.222-0.831)	0.0121
Inhaled Steroid			
█████ No*	1		
█████ Yes	1.486	(0.809-2.733)	0.20
Dornase Alfa			
█████ No*	1		
█████ Yes	3.267	(1.059-10.073)	0.0394

* Baseline category

^a Covariates in the multivariate analysis for each antibiotic included the following: Age at enrollment; Sex (Male*, Female); Hispanic race (Hispanic*, Non-hispanic); Genotype (F508 homozyg*, F508 heterozyg, Other)

^b Treatment exposures were evaluated for the study quarter prior to the culture under consideration.

Table 13. SCV auxotrophic types cultured from CF subjects.

Auxotrophy^a	MSSA-SCV (N=101)	MRSA-SCV (N=84)	Total (N=185)
Thymidine	35 (34.7) ^b	68 (81.0)	103 (55.7)
Hemin	3 (3.0)	0 (0.0)	3 (1.6)
Menadione	6 (5.9)	0 (0.0)	6 (3.2)
Fatty Acid	25 (24.8)	2 (2.4)	27 (14.6)
Menadione + Fatty Acid	1 (1.0)	0 (0.0)	1 (0.5)
Carbon Dioxide	4 (4.0)	0 (0.0)	4 (2.2)
No Complementation	19 (18.8)	13 (15.5)	32 (17.3)
Not Determined	8 (7.9)	1 (1.2)	9 (4.9)

^a Auxotrophic types of SCVs. 7.3% of all SCVs did not complement with the conditions tested but showed poor growth on lab media. 79 SCVs reverted during culture, and auxotrophy could not be determined.

^b Number (Percent of MSSA-SCV, MRSA-SCV, or of the Total) of each auxotrophic SCV subtype.

Table S14. Association of SCV subtypes and GLIFEV₁pp in univariate and multivariate analyses.

Covariate	Univariate			Multivariate			Multivariate		
	Coeff. ^a	95%CI	p-value	Coeff.	95%CI	p-value	Coeff.	95%CI	p-value
SCV Culture Status									
Never SCV Pos*	0			0			0		
Ever Non-THYD SCV Pos	-2.687	(-9.152-3.778)	0.42	-1.127	(-7.458-5.203)	0.73	-1.384	(-7.617-4.849)	0.66
Ever THYD SCV Pos	-13.095	(-20.090--6.100)	0.0003	-10.003	(-16.862--3.144)	0.0043	-10.489	(-17.249--3.730)	0.0024
Visit Number	-0.367	(-0.693--0.040)	0.0274	-0.365	(-0.691--0.039)	0.0280	-0.364	(-0.690--0.038)	0.0284
Age at Enrollment				-1.189	(-1.917--0.460)	0.0014	-1.024	(-1.751--0.297)	0.0058
Sex									
Male*				0			0		
Female				-4.330	(-8.794-0.134)	0.06	-3.643	(-8.065-0.779)	0.11
Hispanic Race									
Hispanic*				0			0		
Non-Hispanic				-1.942	(-12.973-9.089)	0.73	-3.483	(-14.397-7.431)	0.53
Genotype									
F508 Homoz*				0			0		
F508 Heteroz				4.691	(-0.231-9.614)	0.06	4.001	(-0.870-8.871)	0.11
Other				1.402	(-6.250-9.053)	0.72	1.187	(-6.345-8.720)	0.76
CFTR Modulator									
No*				0			0		
Yes				6.876	(-1.865-15.617)	0.12	6.524	(-2.083-15.131)	0.14
<i>P. aeruginosa</i> CX Status									
Never PA Pos*							0		
Ever PA Pos							-6.913	(-11.921--1.904)	0.0068
Constant	92.72	(89.737-95.704)	<0.0001	107.933	(93.839-122.027)	<0.0001	109.421	(95.506-123.335)	<0.0001

*Baseline category

^aAbbreviations: C Coefficient, CI Coeff.; CI Confidence Interval, CI; Culture, CX; THYD, Thymidine-dependent.

Table S15. Association of SCVs with lung function based on MRSA status in univariate and multivariate analyses.

Covariate	Univariate			Multivariate			Multivariate		
	Coeff. ^a	95% CI	p-value	Coeff.	95% CI	p-value	Coeff.	95% CI	p-value
MRSA/Cx status									
MSSA/NC*	0			0			0		
MSSA/SCV	-9.409	(-17.455--1.363)	0.0217	-7.773	(-15.664--0.117)	0.05	-7.924	(-15.841--0.007)	0.0498
MRSA/NC	-4.944	(-10.499--0.610)	0.08	-3.869	(-9.387--1.649)	0.17	-5.115	(-10.738--0.508)	0.08
MRSA/SCV	-10.524	(-18.205--2.842)	0.0073	-7.780	(-15.439--0.122)	0.0461	-8.435	(-16.149--0.721)	0.0318
Visit number	-0.379	(-0.657--0.102)	0.0074	-0.378	(-0.655--0.101)	0.0075	-0.289	(-0.620--0.042)	0.09
Age at enrollment				-0.916	(-1.694--0.138)	0.0209	-0.850	(-1.637--0.063)	0.0340
Sex									
Male*	0			0			0		
Female				-4.863	(-9.595--0.131)	0.0436	-4.496	(-9.303--0.311)	0.07
Hispanic race									
Hispanic*	0			0			0		
Non-Hispanic				-3.690	(-15.337--7.956)	0.54	-4.897	(-16.646--6.851)	0.41
Genotype									
508homoz*	0			0			0		
508heteroz				2.846	(-2.389--8.080)	0.29	3.115	(-2.155--8.384)	0.25
Other				0.364	(-7.653--8.380)	0.93	0.522	(-7.699--8.743)	0.90
CFTR Modulator									
No*	0			0			0		
Yes				6.663	(-2.846--16.173)	0.17	7.339	(-2.235--16.913)	0.13
<i>P. aeruginosa</i> Cx status									
Never PA Pos*	0			0			0		
Ever PA Pos							-4.769	(-10.362--0.825)	0.10
Constant	95.407	(91.487--99.327)	<0.0001	109.861	(95.006--124.716)	<0.0001	111.052	(95.970--126.134)	<0.0001

*Baseline category

^aAbbreviations: C Coefficient, CI Confidence Interval, Cx Culture, NC Normal Colony, NC

Table 16. Association of SCVs and occurrence of pulmonary exacerbations based on MRSA status in univariate and multivariate analyses.

Covariate	Univariate			Multivariate			Multivariate			Multivariate		
	OR ^a	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
MRSA/Cx status				1								
MSSA/NC*	1			1			1			1		
MSSA/SCV	1.131 (0.623-2.054)	0.69		1.054 (0.588-1.890)	0.86		1.060 (0.598-1.877)	0.84		0.958 (0.543-1.691)	0.88	
MRSA/NC	1.623 (1.075-2.450)	0.0212		1.538 (1.022-2.314)	0.0389		1.443 (0.965-2.159)	0.07		1.360 (0.914-2.026)	0.13	
MRSA/SCV	2.900 (1.641-5.125)	0.0002		2.533 (1.445-4.442)	0.0012		2.385 (1.375-4.136)	0.0020		2.149 (1.244-3.713)	0.0061	
Visit number	0.928 (0.866-0.994)	0.0323		0.930 (0.870-0.993)	0.0312		0.929 (0.870-0.993)	0.0305		0.928 (0.868-0.991)	0.0269	
Age at enrollment				1.074 (1.014-1.138)	0.0152		1.083 (1.023-1.147)	0.0059		1.069 (1.010-1.132)	0.0212	
Sex												
Male*				1			1			1		
Female				1.574 (1.107-2.240)	0.0117		1.658 (1.171-2.347)	0.0044		1.580 (1.121-2.227)	0.0091	
Hispanic race												
Hispanic*				1			1			1		
Non-Hispanic				0.986 (0.415-2.343)	0.97		0.870 (0.371-2.037)	0.75		0.833 (0.361-1.922)	0.67	
Genotype												
F508 homozyg*				1			1			1		
F508 heterozyg				1.118 (0.761-1.643)	0.57		1.084 (0.743-1.581)	0.68		1.069 (0.737-1.551)	0.72	
Other				0.815 (0.446-1.488)	0.51		0.818 (0.454-1.476)	0.51		0.763 (0.426-1.370)	0.37	
CFTR Modulator												
No*				1			1			1		
Yes				0.565 (0.272-1.174)	0.13		0.560 (0.273-1.149)	0.11		0.583 (0.289-1.179)	0.13	
<i>P. aeruginosa</i> Cx status												
Never PA Pos*							1			1		
Ever PA Pos							0.568 (0.378-0.851)	0.0062		0.542 (0.363-0.810)	0.0028	
GLI FEV1 pp at enrollment										0.990 (0.980-0.999)	0.0307	

* Baseline category

^a Abbreviations: OR, Odds Ratio; CI, Confidence Interval; Cx, Culture; NC, Normal Colony; SCV, S. pneumoniae Culture Variant

Table S17. Analysis of the Association of Lung Function and History of Antibiotic Use during the Study.

Covariate	Univariate ^a		
	Difference	95% Conf. Interval	p-value
Ever treated with Aminoglycoside			
No*	0		????????
Yes	-4.89	(-9.63--0.15)	0.0395
Ever treated with Beta-lactam			?
No*	0		????????
Yes	-6.85	(-12.00--1.69)	0.0069
Ever treated with Fluoroquinolone			?
No*	0		????????
Yes	-8.23	(-12.92--3.55)	0.0006
Ever treated with Macrolide			?
No*	0		????????
Yes	-3.49	(-8.25-1.27)	0.15
Ever treated with Sulfonamide			?
No*	0		????????
Yes	-2.96	(-7.81-1.88)	0.23
Ever treated with Tetracycline			?
No*	0		????????
Yes	-8.01	(-13.98--2.05)	0.0050

*Baseline category

Table S18. Analysis of the association of pulmonary exacerbation and history of antibiotic use during the study.

Covariate	Univariate		
	Odds Ratio	95% Conf. Interval	p-value
Ever treated with Aminoglycoside			
No*	1		
Yes	0.533	(0.397-0.716)	<0.0001
Ever treated with Beta-lactam			
No*	1		
Yes	2.586	(1.883-3.553)	<0.0001
Ever treated with Fluoroquinolone			
No*	1		
Yes	2.240	(1.665-3.014)	0.00034
Ever treated with Macrolide			
No*	1		
Yes	0.927	(0.702-1.225)	0.59
Ever treated with Sulfonamide			
No*	1		
Yes	3.117	(2.344-4.145)	<0.0001
Ever treated with Tetracycline			
No*	1		
Yes	2.180	(1.548-3.071)	<0.0001

*Baseline category

Table 19. History and frequency of treatment during the study

Medication	Ever Treated ^a (N=230)	Baseline ^b (N=230)	Visit1 ^b (N=230)	Visit2 ^b (N=226)	Visit3 ^b (N=221)	Visit4 ^b (N=210)	Visit5 ^b (N=183)	Visit6 ^b (N=126)	Visit7 ^b (N=45)
Beta-lactam	161(70.0%) ^a	96(41.7%) ^b	51(22.2%)	55(24.3%)	51(23.1%)	40(19.0%)	37(20.2%)	22(17.5%)	13(28.9%)
Aminoglycoside	120(52.2%)	88(38.3%)	29(12.6%)	17(7.5%)	30(13.6%)	29(13.8%)	26(14.2%)	19(15.1%)	10(22.2%)
Macrolide	109(47.4%)	93(40.4%)	7(3.0%)	6(2.7%)	5(2.3%)	4(1.9%)	9(4.9%)	12(9.5%)	5(11.1%)
Fluoroquinolone	101(43.9%)	50(21.7%)	22(9.6%)	21(9.3%)	23(10.4%)	11(5.2%)	17(9.3%)	8(6.3%)	0(0.0%)
Sulfonamide	93(40.4%)	47(20.4%)	26(11.3%)	22(9.7%)	26(11.8%)	23(11.0%)	13(7.1%)	12(9.5%)	5(11.1%)
Tetracycline	44(19.1%)	25(10.9%)	6(2.6%)	7(3.1%)	8(3.6%)	11(5.2%)	5(2.7%)	3(2.4%)	2(4.4%)
Glycopeptide	20(8.7%)	10(4.3%)	3(1.3%)	2(0.9%)	1(0.5%)	1(0.5%)	3(1.6%)	2(1.6%)	0(0.0%)
Polymyxin	9(3.9%)	7(3.0%)	2(0.9%)	3(1.3%)	1(0.5%)	0(0.0%)	3(1.6%)	1(0.8%)	1(2.2%)
Rifamycin	8(3.5%)	3(1.3%)	0(0.0%)	1(0.4%)	1(0.5%)	1(0.5%)	1(0.5%)	1(0.8%)	0(0.0%)
Oxazolidinone	14(6.1%)	5(2.2%)	2(0.9%)	1(0.4%)	2(0.9%)	1(0.5%)	3(1.6%)	1(0.8%)	1(2.2%)
Lincosamide	12(5.2%)	5(2.2%)	1(0.4%)	1(0.4%)	5(2.3%)	0(0.0%)	1(0.5%)	1(0.8%)	0(0.0%)
Nitroimidazole	4(1.7%)	2(0.9%)	1(0.4%)	1(0.4%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Antifungal	3(1.3%)	2(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2(1.1%)	0(0.0%)	0(0.0%)
Ethambutol	2(0.9%)	1(0.4%)	0(0.0%)	0(0.0%)	1(0.5%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

^a Number (Percent of total subjects) treated with an antibiotic from the specified drug class at any point during the study.

^b Number (Percent of subjects at each study visit) treated with an antibiotic from the specified drug class.

Table 20. Frequency of sulfonamide treatment of MSSA and MRSA culture-positive subjects during the study.

MRSA Cx Status	Sulfonamide Treatment		Total N(%)
	No N(%) ^a	Yes N(%)	
MSSA Pos	69(59.5)	34(40.5)	103(51.5)
MRSA Pos	47(40.5)	50(59.5)*	97(48.5)
Total	116(100)	84(100)	200(100)

^aNumber (Percent) of subjects treated (Yes) or not treated (No) with sulfonamides.

Pearson Chi-square(1) = 7.0464

*Sulfonamide treatment significantly higher in MRSA vs. MSSA Cx positive subjects (p-value = 0.0079).

Table S21. STROBE Statement.

	Item No	Recommendation	Comment
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Indicated in the Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Provided in the Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Explained in the Introduction, paragraphs 5 and 6.
Objectives	3	State specific objectives, including any prespecified hypotheses	Stated in the Introduction, paragraph 6.
Methods			
Study design	4	Present key elements of study design early in the paper	Presented in the Abstract, subsection "Methods", and Methods, subsection "Study Design"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Described in the Methods, subsection "Study Design"
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Described in the Methods, subsection "Study Design"
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Described in the Methods, subsections "Study Design", "Prevalence and correlates of infection with SCVs", and "Analysis of the association of SCVs, lung function, and pulmonary exacerbation risk"
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Described in the Methods, subsections "Statistical methods", "Prevalence and correlates of infection with SCVs", and "Analysis of the association of SCVs, lung

			function, and pulmonary exacerbation risk"
Bias	9	Describe any efforts to address potential sources of bias	Described in Methods, subsection "Statistical methods"
Study size	10	Explain how the study size was arrived at	Described in Methods, subsection "Statistical methods"
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Described in Methods, subsection "Statistical methods"
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Described in Methods, subsection "Statistical methods"
		(b) Describe any methods used to examine subgroups and interactions	Described in the Methods, subsections "Statistical methods", "Prevalence and correlates of infection with SCVs", and "Analysis of the association of SCVs, lung function, and pulmonary exacerbation risk"
		(c) Explain how missing data were addressed	N/A
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results		Comment	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Described in the Methods, subsections "Study Design" and Results, paragraph 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Supplementary Figure S2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Described in the Methods, subsections "Study Design", and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Described in the Methods, subsections "Statistical methods",
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Described in the Methods, subsections "Study Design", and Results, paragraph 1

Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Described in Results
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Described in Results and presented in Table 2 and 3 and Supplementary Tables S6, S7, S8, S10, S11, S12, S14, S15, S16, S17 and S18.
		(b) Report category boundaries when continuous variables were categorized	Described in Results and presented in Figures 1-2 and Table 3, Supplemental Tables S2, S3, S4, S5, S6, S7, S8, S9, S10, S11, S12, S13, S14, S15, S16, S17, S18, S20, and Supplemental Figure 2.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Described in Results
Discussion			
Key results	18	Summarise key results with reference to study objectives	Described in Discussion, paragraphs 1-3
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Described in Discussion, paragraphs 5-6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Described in Conclusion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Described in Conclusion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Described in Acknowledgements