Online Supplement
Predicting COPD Progression in Current and Former Smokers Using a Joint Model for Forced Expiratory Volume in 1 Second and Forced Expiratory Volume in 1 Second to Forced Vital Capacity Ratio

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Supplemental tables

Table S1. Summary statistics for baseline variables categorized by direction and magnitude of predicted values, 5-year data. See Figure 2 for directions on a graph ('<5%' could be any direction, but with magnitude below 5%). Units for predictors unless otherwise noted: BDR, Chronic bronchitis and current smoking are indicators (presence=1, absence=0); kg/m^2 for BMI; liters for FRC, mm for Pi10; FVC/TLC is a unitless rate.

		PRISm			GOLD 0			GOLD 1			GOLD 2 and 3		
Variable	**Direction**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
% emphysema	UR				0.33	0.35	3	2.35	2.16	5	1.59	2.21	36
BDR	UR				0.33	0.58	3	0.00	0.00	5	0.42	0.50	36
BMI	UR				35.75	7.45	3	30.45	8.27	5	30.22	5.81	36
Chronic bronchitis	UR				0.00	0.00	3	0.00	0.00	5	0.03	0.17	36
Current smoking	UR				0.33	0.58	3	0.00	0.00	5	0.31	0.47	36
FRC	UR				1.76	0.23	3	2.30	0.30	5	2.49	0.45	36
FVC/TLC	UR				0.87	0.09	3	0.82	0.07	5	0.77	0.14	36
Pi10	UR				1.82	0.08	3	2.31	0.34	5	2.50	0.60	36
% emphysema	RU										2.54		1
BDR	RU										1.00		1
BMI	RU										26.72		1
Chronic bronchitis	RU										0.00		1
Current smoking	RU										0.00		1
FRC	RU										1.76		1
FVC/TLC	RU										0.60		1
Pi10	RU										2.37		1
% emphysema	RD	0.77	0.61	4							0.36		1
BDR	RD	0.00	0.00	4							1.00		1
BMI	RD	36.65	7.29	4							38.19		1
Chronic bronchitis	RD	0.00	0.00	4							0.00		1
Current smoking	RD	0.00	0.00	4							1.00		1
FRC	RD	1.81	0.17	4							2.21		1
FVC/TLC	RD	0.47	0.03	4							0.41		1
Pi10	RD	2.12	0.70	4							2.63		1
% emphysema	DR	1.10	1.99	60	0.22	0.20	8				2.85	2.84	9
BDR	DR	0.07	0.25	60	0.00	0.00	8				0.33	0.50	9
BMI	DR	32.83	7.53	60	28.95	7.73	8				31.25	4.36	9
Chronic bronchitis	DR	0.18	0.39	60	0.13	0.35	8				0.22	0.44	9
Current smoking	DR	0.63	0.49	60	0.63	0.52	8				0.56	0.53	9
FRC	DR	2.31	0.42	60	2.26	0.34	8				3.40	0.57	9

		PRISm			GOLD 0			GOLD 1			GOLD 2 and 3		
Variable	**Direction**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
FVC/TLC	DR	0.51	0.11	60	0.60	0.07	8				0.38	0.06	9
Pi10	DR	2.42	0.49	60	1.98	0.42	8				2.70	0.26	9
% emphysema	DL	2.55	3.25	129	2.38	3.06	226				8.75	7.53	111
BDR	DL	0.28	0.45	129	0.10	0.30	226				0.32	0.47	111
BMI	DL	30.26	6.66	129	28.04	5.67	226				28.54	5.98	111
Chronic bronchitis	DL	0.31	0.46	129	0.22	0.42	226				0.25	0.44	111
Current smoking	DL	0.78	0.41	129	0.64	0.48	226				0.54	0.50	111
FRC	DL	3.32	0.74	129	3.10	0.70	226				3.90	0.73	111
FVC/TLC	DL	0.51	0.09	129	0.62	0.10	226				0.46	0.05	111
Pi10	DL	2.74	0.54	129	2.22	0.48	226				2.77	0.59	111
% emphysema	LD	5.44	8.41	18	3.28	3.58	626	7.70	6.60	213	10.63	8.49	400
BDR	LD	0.61	0.50	18	0.25	0.44	626	0.25	0.44	213	0.46	0.50	400
BMI	LD	31.48	5.60	18	27.38	4.97	626	26.01	4.23	213	26.64	5.37	400
Chronic bronchitis	LD	0.39	0.50	18	0.25	0.43	626	0.27	0.44	213	0.38	0.49	400
Current smoking	LD	0.61	0.50	18	0.79	0.41	626	0.74	0.44	213	0.70	0.46	400
FRC	LD	3.40	0.51	18	3.39	0.74	626	3.87	0.85	213	4.05	0.83	400
FVC/TLC	LD	0.58	0.07	18	0.71	0.10	626	0.66	0.09	213	0.57	0.07	400
Pi10	LD	2.52	0.51	18	2.15	0.49	626	2.24	0.48	213	2.61	0.53	400
% emphysema	LU				1.63	2.01	99	4.23	6.05	81	4.99	4.65	53
BDR	LU				0.57	0.50	99	0.72	0.45	81	0.89	0.32	53
BMI	LU				27.59	4.29	99	27.13	5.19	81	28.94	5.23	53
Chronic bronchitis	LU				0.11	0.32	99	0.14	0.34	81	0.53	0.50	53
Current smoking	LU				0.61	0.49	99	0.62	0.49	81	0.64	0.48	53
FRC	LU				2.77	0.57	99	3.38	0.86	81	3.58	0.72	53
FVC/TLC	LU				0.87	0.15	99	0.75	0.12	81	0.69	0.14	53
Pi10	LU				2.06	0.46	99	2.22	0.48	81	2.73	0.69	53
% emphysema	UL				0.46	0.53	10	2.02	3.57	35	2.90	3.19	29
BDR	UL				0.90	0.32	10	0.77	0.43	35	0.93	0.26	29
BMI	UL				29.73	4.21	10	29.61	4.66	35	31.63	7.84	29
Chronic bronchitis	UL				0.00	0.00	10	0.11	0.32	35	0.31	0.47	29
Current smoking	UL				0.50	0.53	10	0.54	0.51	35	0.34	0.48	29
FRC	UL				2.12	0.33	10	2.43	0.49	35	2.84	0.41	29
FVC/TLC	UL				0.91	0.14	10	0.85	0.13	35	0.73	0.12	29
Pi10	UL				1.91	0.34	10	2.10	0.41	35	2.70	0.47	29
% emphysema	<5%	1.23	1.82	797	1.67	2.16	2349	3.98	4.41	252	3.91	4.86	858
BDR	<5%	0.10	0.30	797	0.03	0.17	2349	0.04	0.20	252	0.24	0.43	858
BMI	<5%	31.95	7.10	797	29.62	5.88	2349	27.46	4.57	252	30.29	6.24	858
Chronic bronchitis	<5%	0.14	0.35	797	0.09	0.28	2349	0.09	0.29	252	0.19	0.39	858
Current smoking	<5%	0.58	0.49	797	0.51	0.50	2349	0.45	0.50	252	0.41	0.49	858
FRC	<5%	2.51	0.54	797	2.63	0.56	2349	3.10	0.65	252	3.08	0.62	858
FVC/TLC	<5%	0.62	0.10	797	0.69	0.10	2349	0.66	0.09	252	0.57	0.10	858
Pi10	<5%	2.38	0.53	797	1.92	0.38	2349	2.01	0.40	252	2.56	0.59	858

Table S2. Summary statistics for baseline variables categorized by direction and magnitude of predicted values, 10-year data. See Figure 2 for directions on a graph ('<5%' could be any direction, but with magnitude below 5% per 5 years). No subjects fell into RU or RD categories. Units for predictors unless otherwise noted: BDR, Chronic bronchitis and current smoking are indicators (presence=1, absence=0); kg/m^2 for BMI; liters for FRC, mm for Pi10; FVC/TLC is a unitless rate.

		PRISm			GOLD 0			GOLD 1			GOLD 2 and 3		
Variable	**Direction**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
% emphysema	UR							42.84		1	0.65	0.40	3
BDR	UR							1.00		1	1.00	0.00	3
BMI	UR							21.34		1	30.89	6.91	3
Chronic bronchitis	UR							0.00		1	0.00	0.00	3
Current smoking	UR							0.00		1	0.00	0.00	3
FRC	UR							2.16		1	2.04	0.32	3
FVC/TLC	UR							0.52		1	0.79	0.22	3
Pi10	UR							1.35		1	2.51	0.26	3
% emphysema	DR	1.83	2.63	13	0.11		1				3.51	1.47	3
BDR	DR	0.23	0.44	13	0.00		1				0.00	0.00	3
BMI	DR	32.94	6.46	13	35.28		1				33.64	3.50	3
Chronic bronchitis	DR	0.31	0.48	13	0.00		1				0.33	0.58	3
Current smoking	DR	0.38	0.51	13	0.00		1				0.33	0.58	3
FRC	DR	2.68	0.43	13	2.65		1				3.59	0.34	3
FVC/TLC	DR	0.35	0.05	13	0.47		1				0.32	0.03	3
Pi10	DR	2.60	0.58	13	1.54		1				2.79	0.21	3
% emphysema	DL	2.99	3.68	75	2.96	3.85	47				6.81	5.99	63
BDR	DL	0.24	0.43	75	0.21	0.41	47				0.25	0.44	63
BMI	DL	29.51	6.81	75	27.37	5.74	47				28.14	6.00	63
Chronic bronchitis	DL	0.35	0.48	75	0.34	0.48	47				0.44	0.50	63
Current smoking	DL	0.76	0.43	75	0.68	0.47	47				0.70	0.46	63
FRC	DL	3.30	0.77	75	3.31	0.72	47				3.66	0.74	63
FVC/TLC	DL	0.47	0.07	75	0.56	0.10	47				0.44	0.05	63
Pi10	DL	2.73	0.55	75	2.34	0.41	47				2.78	0.57	63
% emphysema	LD	3.27	3.15	28	3.67	3.84	274	6.63	5.87	215	8.74	7.56	524
BDR	LD	0.50	0.51	28	0.45	0.50	274	0.37	0.48	215	0.46	0.50	524
BMI	LD	28.89	5.32	28	26.56	4.57	274	25.96	4.38	215	26.73	5.23	524
Chronic bronchitis	LD	0.29	0.46	28	0.27	0.44	274	0.26	0.44	215	0.33	0.47	524
Current smoking	LD	0.86	0.36	28	0.84	0.36	274	0.79	0.41	215	0.73	0.44	524
FRC	LD	3.61	0.65	28	3.61	0.68	274	3.89	0.81	215	4.00	0.79	524
FVC/TLC	LD	0.61	0.08	28	0.71	0.12	274	0.67	0.10	215	0.57	0.08	524
Pi10	LD	2.81	0.48	28	2.32	0.50	274	2.27	0.48	215	2.66	0.54	524
% emphysema	LU				1.39	3.43	12	3.41	4.75	19	4.45	4.56	26
BDR	LU				0.42	0.51	12	0.89	0.32	19	0.96	0.20	26
BMI	LU				29.77	4.18	12	27.67	4.71	19	29.45	4.89	26
Chronic bronchitis	LU				0.00	0.00	12	0.05	0.23	19	0.15	0.37	26
Current smoking	LU				0.50	0.52	12	0.68	0.48	19	0.69	0.47	26
FRC	LU				2.77	0.66	12	3.11	0.47	19	3.30	0.64	26
FVC/TLC	LU				1.13	0.10	12	0.86	0.12	19	0.75	0.18	26
Pi10	LU				2.51	0.37	12	2.33	0.38	19	2.83	0.66	26
% emphysema	UL							1.47	1.90	11	0.54	0.42	6

		PRISm			GOLD 0			GOLD 1			GOLD 2 and 3		
Variable	**Direction**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
BDR	UL							1.00	0.00	11	1.00	0.00	6
BMI	UL							29.16	5.31	11	30.52	2.73	6
Chronic bronchitis	UL							0.18	0.40	11	0.33	0.52	6
Current smoking	UL							0.45	0.52	11	0.67	0.52	6
FRC	UL							2.28	0.44	11	2.58	0.60	6
FVC/TLC	UL							0.96	0.17	11	0.86	0.07	6
Pi10	UL							2.06	0.36	11	2.76	0.43	6
% emphysema	<5%	1.28	2.19	892	1.85	2.39	2987	4.46	5.32	340	4.44	6.07	873
BDR	<5%	0.11	0.31	892	0.06	0.24	2987	0.12	0.33	340	0.26	0.44	873
BMI	<5%	32.06	7.10	892	29.28	5.78	2987	27.63	4.70	340	30.67	6.32	873
Chronic bronchitis	<5%	0.15	0.36	892	0.11	0.32	2987	0.11	0.31	340	0.20	0.40	873
Current smoking	<5%	0.59	0.49	892	0.55	0.50	2987	0.45	0.50	340	0.35	0.48	873
FRC	<5%	2.53	0.56	892	2.73	0.62	2987	3.10	0.74	340	3.03	0.63	873
FVC/TLC	<5%	0.61	0.10	892	0.69	0.10	2987	0.67	0.10	340	0.58	0.11	873
Pi10	<5%	2.39	0.53	892	1.95	0.40	2987	2.03	0.42	340	2.54	0.59	873

Table S3. Characteristics of a sample of 4 subjects, including calculations of predicted changes in FEV_1, FEV_1/FVC, and magnitude and angle calculations for predicted movement. Predicted values include 95% confidence intervals.

	Subject	1	2	3	4
BL status	**BL GOLD**	1	0	2	PRISm
	BL Age, years	67.5	50.5	60.9	73.8
	BL FEV_1, pp	80.0	81.2	57.8	73.1
	BL FEV1/FVC (%)	57	72	59	70
	BMI	25.88	25.67	33.86	37.02
	Current smoker?	N	N	N	N
	Bronchodilator response?	N	N	N	N
	Chronic Bronchitis	N	Y	N	N
	FRC, liters	4.10	2.77	2.97	3.72
	% emphysema	36.3	16.3	7.7	3.0
	Pi10, mm	2.17	1.37	2.64	2.06
	FVC/TLC, rate	0.6	0.7	0.5	0.6
5-year predicted and observed changes	**Obs FEV_1, pp**	-16.1	Not available	4.6	3.7
	Pred FEV_1, pp	-8.4 (-12.7, -4.2)	-1.2 (-3.3, 0.9)	-0.6 (-2.0, 0.8)	-0.9 (-1.9, 0.1)
	Obs FEV_1/FVC (%)	-7	Not available	2	-1
	Pred FEV_1/FVC (%)	-2.0 (-4.5, 0.4)	-1.2 (-2.4, 0.1)	-1.9 (-2.8, -1.0)	-0.6 (-1.2, 0.1)
	Obs Magnitude (%)	17.6	Not available	5.0	3.8
	Pred Magnitude (%)	8.7 (4.3, 13.1)	1.7 (-0.4, 3.8)	2.0 (0.8, 3.2)	1.0 (-0.1, 2.1)
	Pred Angle (°)	13.5 (-0.6, 27.6)	43.4 (-0.3, 87.1)	72.4 (36.5, 108.3)	33.2 (4.3, 62.1)
10-year predicted and observed changes	**Obs FEV_1, pp**	-27.0	Not available	0.5	-3.7
	Pred FEV_1, pp	-6.5 (-14.2, 1.3)	-2.4 (-6.4, 1.7)	-3.7 (-6.8, -0.7)	-3.2 (-5.3, -1,0)
	Obs FEV_1/FVC (%)	-7	Not available	6	-1
	Pred FEV_1/FVC (%)	-0.9 (-5.3, 3.5)	-4.3 (-6.8, -1.9)	-4.5 (-6.4, -2.6)	-1.0 (-2.4, 0.5)
	Obs Magnitude (%)	27.9	Not available	6.0	3.8
	Pred Magnitude (%)	6.5 (-1.4, 14.5)	4.9 (1.3, 8.6)	5.8 (2.9, 8.8)	3.3 (1.0, 5.6)
	Pred Angle (°)	7.8 (-26.6, 42.2)	61.4 (25.4, 97.3)	50.3 (31.5, 69.1)	17.2 (-1.9, 36.4)

Table S4. Mean (SD) for predicted magnitude and angle, overall and by GOLD group

Baseline group	n	5-year changes		10-year changes	
		Magnitude	Angle*	Magnitude	Angle*
Overall	6413	4.55 (3.21)	30 (63)	7.08 (4.66)	38 (44)
PRISm	1008	3.77 (2.37)	75 (72)	6.12 (3.58)	61 (45)
GOLD 0	3321	4.10 (2.58)	34 (50)	5.71 (3.34)	44 (41)
GOLD 1	586	6.35 (4.13)	-8 (38)	9.55 (5.02)	8 (32)
GOLD 2 & 3	1498	5.36 (4.00)	7 (69)	9.80 (5.94)	21 (41)

*See methods for how angle was defined; 0° is associated with a drop in FEV_1 but no drop in FEV_1/FVC; 45° is associated with equal drops in FEV_1 and FEV_1/FVC; 90° is associated with no drop in FEV_1 but a drop in FEV_1/FVC. Units are % for magnitude, degrees for angle.

Table S5. Observed and predicted GOLD status at P1 (baseline) versus P2 (5 years later). While observed data were available for n=3864 subjects, predicted values could be calculated for n=6413 subjects (see text for details). Yellow highlighted are diagonal entries; green highlighted are off-diagonal entries of at least 2%. Predicted joint changes in FEV_1 and FEV_1/FVC for all subjects were based on fitted linear mixed models. G0=GOLD 0 (normal spirometry), P=PRISm, G*x*=GOLD *x*, for *x*=1, 2, 3, 4.

		P2 class (observed)						P2 class (predicted)					
		G0	**P**	**G1**	**G2**	**G3**	**G4**	**G0**	**P**	**G1**	**G2**	**G3**	**G4**
P1 class (Count)	**G0**	1646	194	150	74	1	0	2991	83	196	51	0	0
	P	119	298	13	105	15	3	37	750	0	212	9	0
	G1	97	13	168	101	1	0	72	6	346	162	0	0
	G2	27	72	55	531	124	9	1	22	4	1294	93	0
	G3	1	6	0	16	24	1	0	0	0	18	64	2
P1 class (Percentage)	**G0**	43%	5%	4%	2%	0%	0%	47%	1%	3%	1%	0%	0%
	P	3%	8%	0%	3%	0%	0%	1%	12%	0%	3%	0%	0%
	G1	3%	0%	4%	3%	0%	0%	1%	0%	5%	3%	0%	0%
	G2	1%	2%	1%	14%	3%	0%	0%	0%	0%	20%	1%	0%
	G3	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	1%	0%

Table S6. Observed and predicted GOLD status at P1 (baseline) versus P3 (10 years later). While observed data were available for n=1415 subjects, predicted values could be calculated for n=6413 subjects (see text for details). Yellow highlighted are diagonal entries; green highlighted are off-diagonal entries of at least 2%. Predicted joint changes in FEV_1 and FEV_1/FVC for all subjects were based on fitted linear mixed models. G0=GOLD 0 (normal spirometry), P=PRISm, G*x*=GOLD *x*, for *x*=1, 2, 3, 4.

		P3 class (observed)						P3 class (predicted)					
		G0	**P**	**G1**	**G2**	**G3**	**G4**	**G0**	**P**	**G1**	**G2**	**G3**	**G4**
P1 class (Count)	**G0**	571	89	91	39	1	0	2623	182	367	149	0	0
	P	33	80	5	48	10	1	14	621	0	352	21	0
	G1	32	14	61	52	3	1	27	8	279	272	0	0
	G2	8	22	16	145	70	9	0	18	1	1114	278	3
	G3	0	3	0	3	8	0	0	0	0	5	77	2
P1 class (Percentage)	**G0**	40%	6%	6%	3%	0%	0%	41%	3%	6%	2%	0%	0%
	P	2%	6%	0%	3%	1%	0%	0%	10%	0%	5%	0%	0%
	G1	2%	1%	4%	4%	0%	0%	0%	0%	4%	4%	0%	0%
	G2	1%	2%	1%	10%	5%	1%	0%	0%	0%	17%	4%	0%
	G3	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	1%	0%

Supplemental figures

Figure S1: Percentages of subjects with predicted changes in different directions given in bars, for 10-year data, by GOLD stage. Those presented here had predicted changes of at least 5% in vector magnitude per 5 years. Total number of subjects by direction given in red. Directions are UR=upper right, RU=right upper, RD=right down, DR=down right, DL=down left, LD=left down, LU=left up, UL=up left. Those represented comprise 21% of predicted values available; the remaining predicted values had magnitudes less than 5% per 5 years.

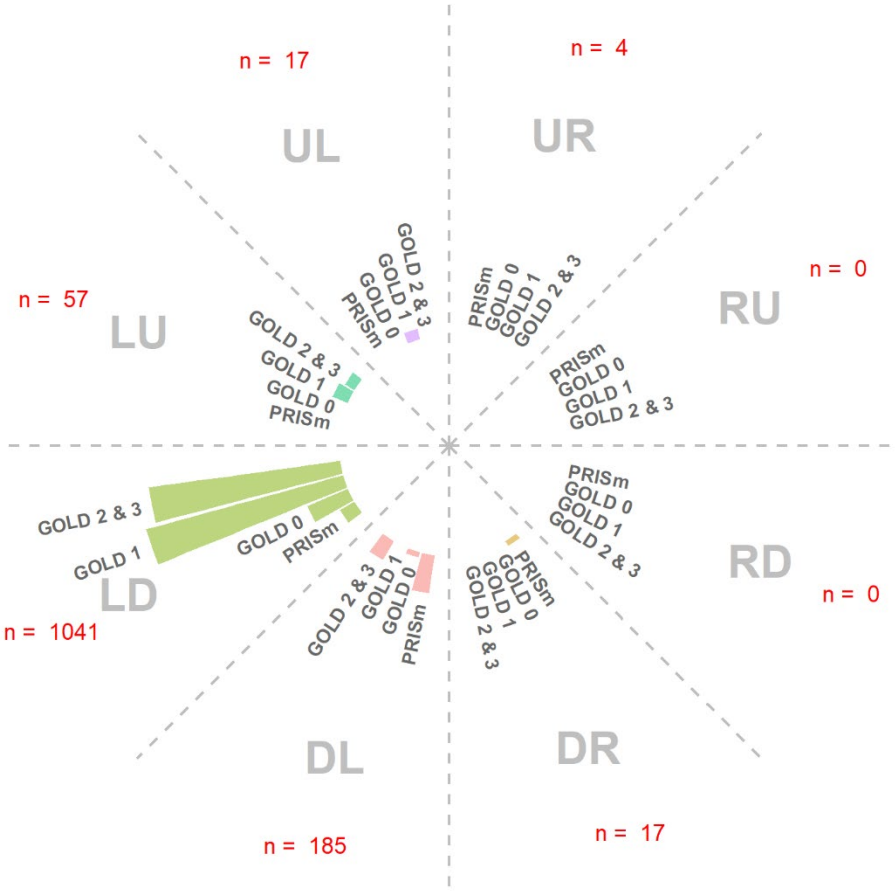
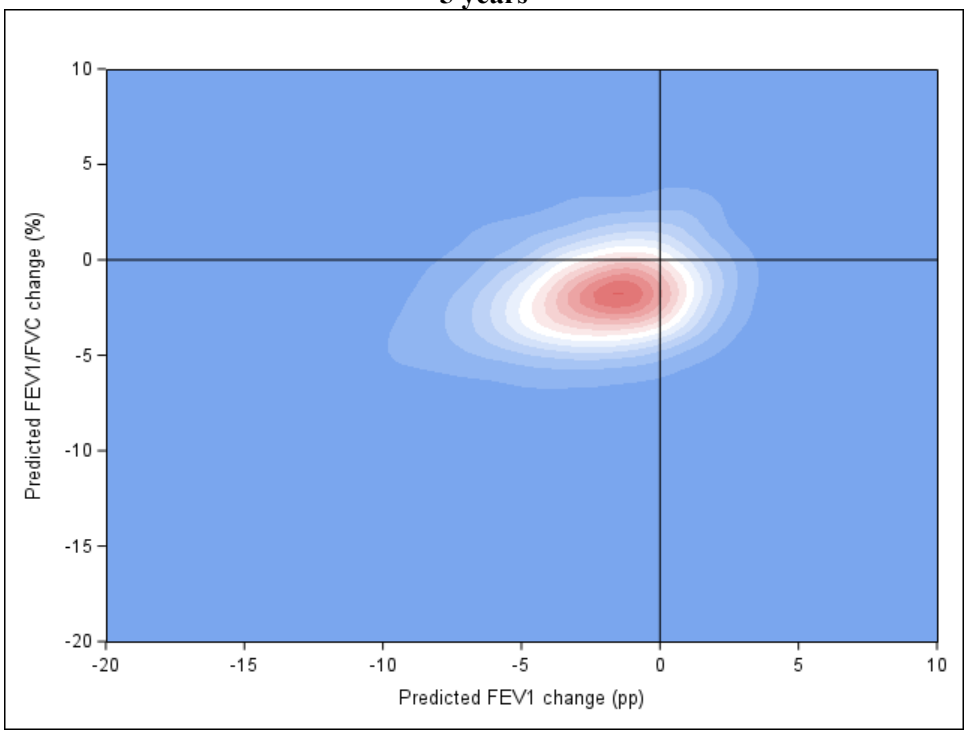


Figure S2: Density histograms of joint predicted change in FEV_1 and FEV_1/FVC, for 5-year (top) and 10-year (bottom) data. Darker red indicates highest area of predicted progression. Values in the lower left quadrant are associated with predicted loss in FEV_1 and FEV_1/FVC.

5 years



10 years

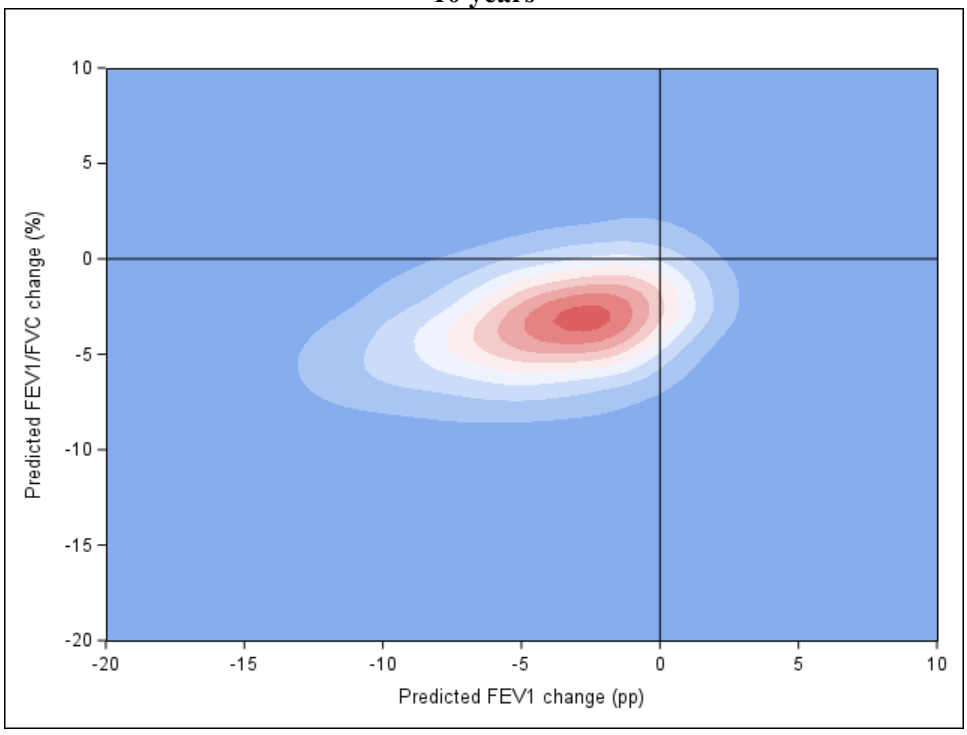
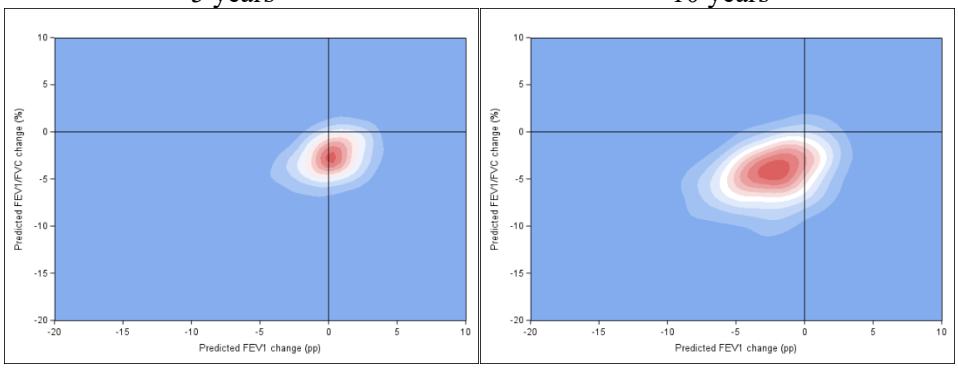


Figure S3: Density histograms of joint predicted change in FEV_1 and FEV_1/FVC, by GOLD group, for 5-year (left) and 10-year (right) data. Darker red indicates highest area of predicted progression. Values in the lower left quadrant are associated with predicted loss in FEV_1 and FEV_1/FVC. For PRISm subjects, 5-year predicted changes mainly involve FEV_1/FVC, while those for GOLD 1 mainly involve FEV_1. However, for both groups, 10-year predicted changes tend to involve both outcomes. Both GOLD 0 and 2&3 are more centered on the unit diagonal for both time frames, but greater 10-year progression is predicted for FEV_1 than FEV_1/FVC for GOLD 0, while for GOLD 2&3 it is more balanced.

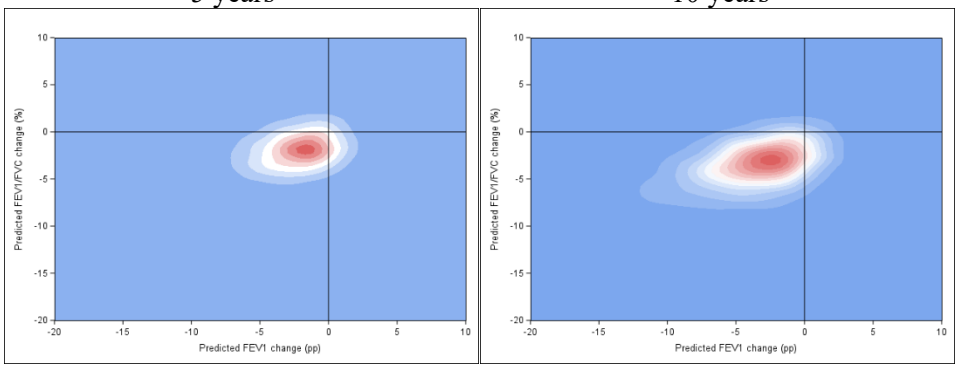
PRISm

5 years | 10 years



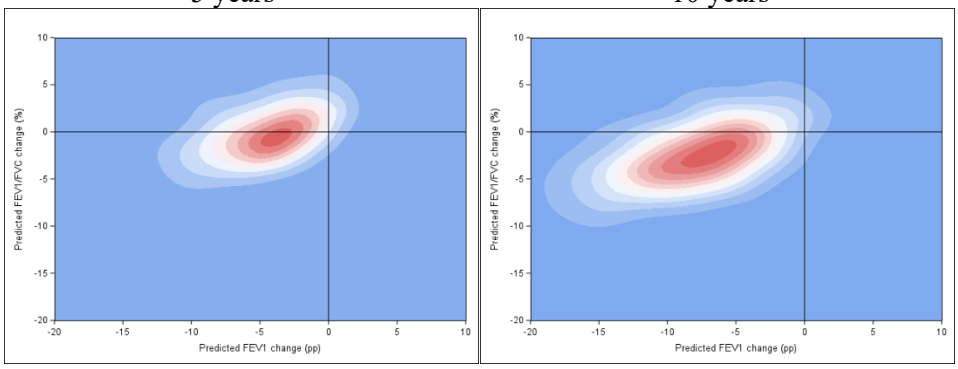
GOLD 0

5 years | 10 years



GOLD 1

5 years | 10 years



GOLD 2&3

5 years | 10 years

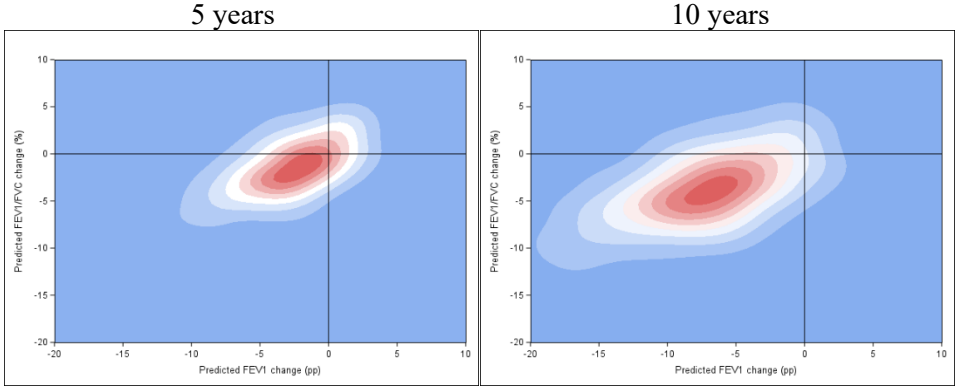
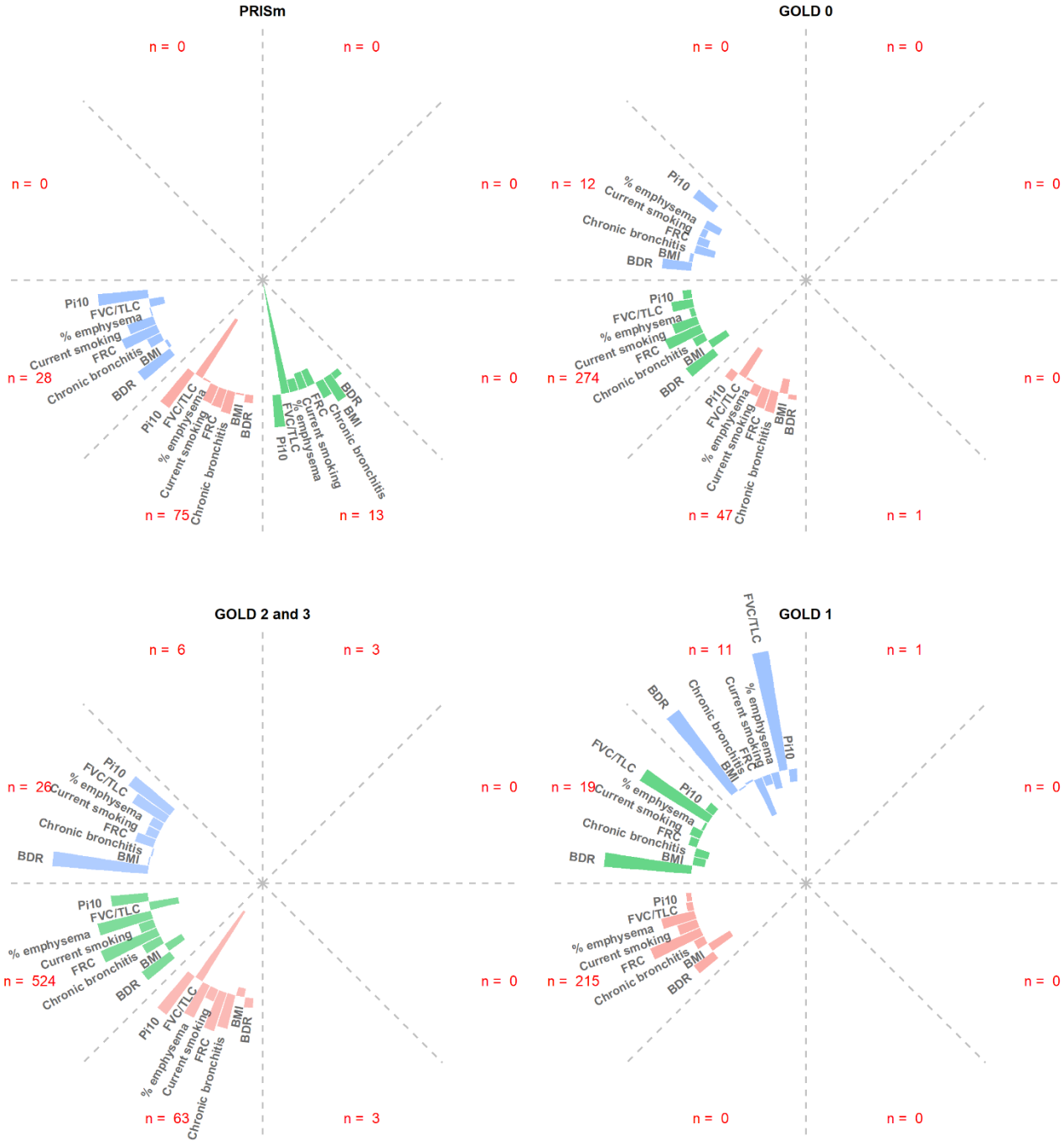


Figure S4: Average baseline characteristics of PRISm, GOLD 0, GOLD 2&3 and GOLD 1 subjects by predicted direction of (FEV_1, FEV_1/FVC) change for the 10-year model. Each bar was computed as $\bar{Z}_d^p = (\bar{X}_d^p - \bar{X}^p)/s^p$, where $\bar{X}_d^p$ is the baseline average for variable p for all subjects with predicted values going in direction d (based on linear mixed model fits) and $\bar{X}^p$ and s^p are the mean and standard deviation for variable p among all study subjects at baseline. Those with predicted (FEV_1, FEV_1/FVC) vectors with magnitude<5% per 5 years were excluded, and data were suppressed for directions and GOLD groups with fewer than 8 subjects.



Appendix A. Initial set of variables tried in model selection procedures.

I. *Demographic variables (11)* Age, Height, Weight, Asthma indicator, bronchodilator response indicator, BMI, current med use indicator, gender, race, current smoking status indicator, pack years smoking history
II. *Spirometry and exercise (4)* FEV_1, FVC, FEV_1/FVC, 6-minute walk distance (6MWD)
III. *Genetic (1)* Polygenic risk score composite variable
IV. *Symptoms (8)* Chronic bronchitis indicator, MMRC dyspnea score, SGRQ (total, active, impact, symptoms), all exacerbations, severe exacerbations
V. *Comorbidity indicators (10)* Diabetes, High Cholesterol, Macular Degeneration, Gastro Esophageal Reflux, Stomach Ulcers, Pneumothorax, Cardiovascular disease, Cancer (composite of types available), bones_joints, stroke_tia
VI. *CT variables (12)* Adjusted lung density, Perc15 inspiratory, Perc15 expiratory, Pctemph (Thirona), Pctgastrap (Thirona), Pi10 (Thirona), Wallareapct_seg (Thirona), AWT segmental (Thirona), functional residual capacity (FRC, Thirona), TLC (Total lung capacity, Thirona), FRC/TLC, FVC/TLC

(Alternatively considered *visual emphysema severity* and *visual wall thickening* in place of CT variables mentioned above)

Also considered years since quit smoking, but removed from final models since it only applies to former smokers.

Appendix B: Details of model selection

Initial model selection was carried out using stepwise selection from the 46 variables in univariate models for change in FEV_1 and change in FEV_1/FVC, with significance to enter and significance to stay initially at 0.05, then at 0.01 for confirmation. (Lower values were used due to the relatively large sample sizes involved.) Models were fit separately for 5 and 10-year change scores. Predictors were then selected to use in the joint models if significant in at least 2 of 4 univariate models (by time frame and outcome type). Additionally, FEV_1 was included as a predictor since it (along with FEV_1/FVC) helps define GOLD status and the starting point for change; FEV_1 and FEV_1/FVC were treated as modifiers in the model, as described below, while the other selected predictors were considered core predictors. Squared and cubic terms were also considered for the continuous core predictors. Diagnostics were also performed to ensure that selected predictors were not highly collinear.

The joint model was built using linear mixed models.[10] Measures on the 2 outcomes (FEV_1 change and FEV_1/FVC change) were accounted for by including a binary indicator (*type*); i.e., this predictor accounts for repeated measures on type of outcome measure. Interactions were included for each of FEV_1 and FEV_1/FVC by the core predictors, and also between *type* and all other predictors in the model. Thus the interaction terms in the model had the form *x***type*, *x**FEV_1, *x**FEV_1/FVC, *x***type**FEV_1, *x***type**FEV_1/FVC, for each predictor *x*. Terms were then removed using a backward selection process (paired by *type*), using the Akaike Information Criterion (AIC) as a gauge for removal, using the set of terms with the largest p-value, but not removing lower-order terms if they were included in higher-order terms still in the model. After the backward selection process, several terms were then retested for inclusion back into the model based on AIC; chronic bronchitis was the only predictor added at this stage. Interaction terms between core predictors were then also tested for inclusion in the model. For all of these additions, only associated interaction terms that improved the AIC were included.

The final model included FEV_1, FEV_1/FVC, Pi10, % emphysema, FRC, FVC/TLC, BMI, current smoking status, BDR and chronic bronchitis, plus squared terms for Pi10, % emphysema and FVC/TLC, and a cubic term for FVC/TLC; interactions were also included between FEV_1 and each of the following: BDR, FVC/TLC, $(FVC/TLC)^2$, $(FVC/TLC)^3$, and between FEV_1/FVC and each of the following: % emphysema, smoking status, BDR, FVC/TLC, $(FVC/TLC)^2$, $(FVC/TLC)^3$. Finally, the following interactions between core predictors were included: BDR*chronic bronchitis, % emphysema*smoking status, and FRC*BDR. Including the intercept, this yielded 28 terms, and thus 2×28=56 coefficients in the final model that accounted for the 2 outcome types and was also flexible and well-conditioned on starting FEV_1 and FEV_1/FVC.

Appendix C: Determining magnitude and angle of the ($FEV1_\Delta$, FEV_1/FVC_Δ) prediction vector, and associated variances for confidence interval construction

Determining magnitude and change

The joint model naturally provides predicted changes of FEV_1 and FEV_1/FVC, which can be transformed into magnitude and angle. To simplify notation, we let FC=FEV_1/FVC below, and indicate 5 or 10-year change in these variables with subscript Δ.

Magnitude of change was summarized using Euclidean distance. Specifically, it is

$$magnitude = \sqrt{FEV1_\Delta^2 + FC_\Delta^2}$$

Direction of change was summarized using the angle of the vector using the arc-tangent function. Specifically, for nonzero values of x and y, the angle is defined as

$$direction = (180°/\pi) * [\arctan\left(\frac{FC_\Delta}{FEV1_\Delta}\right)] \quad \text{if } FEV1_\Delta<0$$

$$= (180°/\pi) * [\arctan\left(\frac{FC_\Delta}{FEV1_\Delta}\right) + \pi] \quad \text{if } FEV1_\Delta \geq 0 \text{ and } FC_\Delta <0$$

$$= (180°/\pi) * [\arctan\left(\frac{FC_\Delta}{FEV1_\Delta}\right) - \pi] \quad \text{if } FEV1_\Delta \geq 0 \text{ and } FC_\Delta \geq 0$$

Further, if FEV_1=0, then the angle is set to 90° for FC<0 and -90° for FC>0; if FEV_1=0° and FC=0°, the angle is undefined. However, in practice zero values are unlikely when using predicted values to a number of decimal places, since the outcomes are modeled as continuous variables. The angles were chosen so that the reference is the vector moving left from the origin. The angle then increases from 0° as this vector is rotated counterclockwise from the reference, and decreases from 0° as it is rotated clockwise from the reference. This orientation was chosen because the most common direction of vectors is leftwards and down. Since magnitude and direction use a combination of FEV_1 and FC, joint inference is critical, and takes advantage of the moderately high correlation between the variables for inference.

Determining variance for magnitude and direction associated with predicted values

Along with predicted change for direction and magnitude, confidence and prediction intervals can be constructed for each subject by employing the delta method to obtain the variance of predicted change in magnitude and direction. To implement the delta method, we can compute the Jacobian for the functions describing the direction and magnitude, and the variance of the predicted change in FEV_1 and FC as shown below.

$$Var_{magnitude} = J_{magnitude} * Var_{predicted\ \Delta\ in\ FEV1\ and\ FC} * J_{magnitude}^T,$$

and

$$Var_{direction} = J_{direction} * Var_{predicted\ \Delta\ in\ FEV1\ and\ FC} * J_{direction}^T,$$

where

$$J_{magnitude} = \left[\frac{\partial\sqrt{FEV1_\Delta^2 + FC_\Delta^2}}{\partial FEV1_\Delta}, \quad \frac{\partial\sqrt{FEV1_\Delta^2 + FC_\Delta^2}}{\partial FC_\Delta}\right]$$

$$= \left[\frac{FEV1_\Delta}{\sqrt{FEV1_\Delta^2 + FC_\Delta^2}}, \quad \frac{FC_\Delta}{\sqrt{FEV1_\Delta^2 + FC_\Delta^2}}\right],$$

$$J_{direction} = \left[\frac{\partial\left(\frac{180°}{\pi}\right) * \left[\arctan\left(\frac{FC_\Delta}{FEV1_\Delta}\right)\right]}{\partial FEV1_\Delta}, \quad \frac{\partial\left(\frac{180°}{\pi}\right) * \left[\arctan\left(\frac{FC_\Delta}{FEV1_\Delta}\right)\right]}{\partial FC_\Delta}\right]$$

$$= \left(\frac{180°}{\pi}\right)\left[\frac{-FC_\Delta}{FEV1_\Delta^2+FC_\Delta^2}, \quad \frac{FEV1_\Delta}{FEV1_\Delta^2+FC_\Delta^2}\right],$$

and

$$Var_{predicted\ \Delta\ in\ FEV1\ and\ FC} = X_{new} * COV(\hat{\beta}) * X_{new}^t,$$

where X_{new} are rows corresponding to predicted values of interest, one applicable to FEV_1 (*type*=0) and the other to FEV_1/FVC (*type*=1), and $\hat{\beta}$ is the vector of estimators of beta coefficients in the linear mixed model.

Appendix D: parameter estimates for terms in model. For binary terms BDR, Chronic_bronchitis and smokcignow, coefficients indicate presence, e.g., coefficient for BDR is associated with presence of BDR. Type was set to 0 for $(FEV_1)_\Delta$ and 1 for $(FEV1/FVC)_\Delta$; terms including 'type' indicate additional effect for $(FEV1/FVC)_\Delta$ in relation to the similar term without 'type'.

5-year model

The Mixed Procedure

Model Information	
Dependent Variable	y21
Covariance Structures	Variance Components, Unstructured
Subject Effect	sid
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment
Number of Observations Used	7728 (3864 subjects, 2 measures per subject)

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
ccenter		0.8621
UN(1,1)	**sid**	92.6995
UN(2,1)	**sid**	21.4883
UN(2,2)	**sid**	29.1765

Fit Statistics

-2 Res Log Likelihood	51835.8
AIC (Smaller is Better)	51843.8

Effect	Estimate	SE	DF	tValue	Probt	Lower	Upper
Intercept	93.8959469	74.0321	20	1.27	0.2193	-60.5322	248.32
fc_v1	-0.97170509	1.1563	7652	-0.84	0.4008	-3.2384	1.295
fev1_v1	0.02611338	0.5487	7652	0.05	0.962	-1.0495	1.1017
BDR	0.1995994	4.583	7652	0.04	0.9653	-8.7843	9.1835
BDR*fc_v1	0.06155619	0.05803	7652	1.06	0.2889	-0.0522	0.1753
BDR*fev1_v1	-0.08451182	0.03023	7652	-2.8	0.0052	-0.1438	-0.0253
BDR*Chronic_Bronchitis	-1.66652109	1.0926	7652	-1.53	0.1272	-3.8083	0.4753
BMI	0.03580445	0.02864	7652	1.25	0.2112	-0.02033	0.09194
Chronic_Bronchitis	-0.8846941	0.5092	7652	-1.74	0.0823	-1.8828	0.1134
emph	-0.68499669	0.2956	7652	-2.32	0.0205	-1.2645	-0.1055
emph2	0.00542861	0.00373	7652	1.45	0.1458	-0.00189	0.01274
emph*fc_v1	0.00526923	0.00382	7652	1.38	0.1677	-0.00222	0.01276
emph*SmokCigNow	-0.38915125	0.0852	7652	-4.57	<.0001	-0.5562	-0.2221
FRC_Thirona	-1.54945722	0.2684	7652	-5.77	<.0001	-2.0755	-1.0234
FRC_Thirona*BDR	-0.04234439	0.5944	7652	-0.07	0.9432	-1.2075	1.1229
fvc_tlc	-297.090838	317.18	7652	-0.94	0.349	-918.86	324.68
fvc_tlc*fc_v1	4.08288741	4.9369	7652	0.83	0.4083	-5.5947	13.7605

fvc_tlc*fev1_v1	-0.54310078	2.3834	7652	-0.23	0.8198	-5.2151	4.1289
fvc_tlc2	408.420318	441.82	7652	0.92	0.3553	-457.66	1274.51
fvc_tlc2*fc_v1	-5.64695993	6.8528	7652	-0.82	0.4099	-19.0803	7.7864
fvc_tlc2*fev1_v1	0.78114455	3.4377	7652	0.23	0.8203	-5.9577	7.52
fvc_tlc3	-166.031292	199.36	7652	-0.83	0.405	-556.83	224.77
fvc_tlc3*fc_v1	2.42542423	3.0825	7652	0.79	0.4314	-3.6171	8.468
fvc_tlc3*fev1_v1	-0.45017247	1.6307	7652	-0.28	0.7825	-3.6469	2.7465
pi10	-8.16031517	1.8341	7652	-4.45	<.0001	-11.7557	-4.5649
pi102	1.20986049	0.3512	7652	3.44	0.0006	0.5214	1.8983
SmokCigNow	-4.05746367	3.06	7652	-1.33	0.1849	-10.0558	1.9409
SmokCigNow*fc_v1	0.05076538	0.03993	7652	1.27	0.2036	-0.0275	0.129
type	24.5394548	68.2638	7652	0.36	0.7192	-109.28	158.36
type*fc_v1	-1.29452743	1.0664	7652	-1.21	0.2248	-3.385	0.796
type*fev1_v1	0.51875588	0.5058	7652	1.03	0.3051	-0.4727	1.5102
type*BDR	11.3063708	4.2243	7652	2.68	0.0075	3.0256	19.5872
type*BDR*fc_v1	-0.20040579	0.0535	7652	-3.75	0.0002	-0.3053	-0.0955
type*BDR*fev1_v1	0.12622725	0.02786	7652	4.53	<.0001	0.07161	0.1808
type*BDR*Chronic_Bronch	1.77690265	1.0078	7652	1.76	0.0779	-0.1986	3.7524
type*BMI	0.05707092	0.02638	7652	2.16	0.0305	0.00537	0.1088
type*Chronic_Bronchitis	0.15851442	0.4692	7652	0.34	0.7355	-0.7613	1.0783
type*emph	-0.60473646	0.2725	7652	-2.22	0.0265	-1.139	-0.0705
type*emph2	0.00822166	0.00343	7652	2.4	0.0166	0.0015	0.01495
type*emph*fc_v1	0.00575555	0.00352	7652	1.64	0.1019	-0.00114	0.01265
type*emph*SmokCigNow	0.30135891	0.07839	7652	3.84	0.0001	0.1477	0.455
type*FRC_Thirona	0.65008398	0.2464	7652	2.64	0.0084	0.167	1.1332
type*FRC_Thirona*BDR	-1.69853194	0.548	7652	-3.1	0.0019	-2.7727	-0.6244
type*fvc_tlc	-84.5074792	292.5	7652	-0.29	0.7727	-657.88	488.86
type*fvc_tlc*fc_v1	4.13542717	4.5532	7652	0.91	0.3638	-4.7902	13.061
type*fvc_tlc*fev1_v1	-1.7574046	2.1971	7652	-0.8	0.4238	-6.0643	2.5494
type*fvc_tlc2	141.812597	407.45	7652	0.35	0.7278	-656.9	940.53
type*fvc_tlc2*fc_v1	-5.60096155	6.3206	7652	-0.89	0.3756	-17.991	6.7891
type*fvc_tlc2*fev1_v1	2.31221026	3.1691	7652	0.73	0.4656	-3.9001	8.5245
type*fvc_tlc3	-73.2128118	183.86	7652	-0.4	0.6905	-433.63	287.21
type*fvc_tlc3*fc_v1	2.35762161	2.8431	7652	0.83	0.407	-3.2157	7.931
type*fvc_tlc3*fev1_v1	-0.84502576	1.5032	7652	-0.56	0.574	-3.7918	2.1017
type*pi10	0.94937154	1.6892	7652	0.56	0.5741	-2.362	4.2607
type*pi102	-0.14066406	0.3236	7652	-0.43	0.6638	-0.7749	0.4936
type*SmokCigNow	-2.52725949	2.8152	7652	-0.9	0.3694	-8.0459	2.9914
type*SmokCigNow*fc_v1	0.02690247	0.03671	7652	0.73	0.4637	-0.04506	0.09887

10-year model

The Mixed Procedure

Model Information	
Dependent Variable	y31
Covariance Structures	Variance Components, Unstructured
Subject Effect	sid
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment
Number of Observations Used	2830 (1415 subjects, 2 measures per subject)

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
ccenter		4.6756
UN(1,1)	**sid**	129.65
UN(2,1)	**sid**	32.8318
UN(2,2)	**sid**	39.1260

Fit Statistics

-2 Res Log Likelihood	19790.0
AIC (Smaller is Better)	19798.0

Effect	Estimate	SE	DF	tValue	Probt	Lower	Upper
Intercept	104.356168	131.07	20	0.8	0.4353	-169.04	377.75
fc_v1	-0.34207126	2.1592	2754	-0.16	0.8741	-4.5759	3.8918
fev1_v1	-0.16041405	1.0647	2754	-0.15	0.8803	-2.2481	1.9273
BDR	6.50005628	9.4918	2754	0.68	0.4935	-12.1116	25.1118
BDR*fc_v1	0.01804909	0.1148	2754	0.16	0.875	-0.207	0.2431
BDR*fev1_v1	-0.06768703	0.0595	2754	-1.14	0.2554	-0.1844	0.04898
BDR*Chronic_Bronchitis	3.24318149	2.3459	2754	1.38	0.1669	-1.3567	7.8431
BMI	0.07096398	0.0582	2754	1.22	0.2228	-0.04316	0.1851
Chronic_Bronchitis	-1.14787712	1.0017	2754	-1.15	0.2519	-3.112	0.8162
emph	-1.56455397	0.5297	2754	-2.95	0.0032	-2.6032	-0.526
emph2	0.02048518	0.00674	2754	3.04	0.0024	0.00727	0.0337
emph*fc_v1	0.01272689	0.00683	2754	1.86	0.0626	-0.00067	0.02612
emph*SmokCigNow	-0.15728088	0.1608	2754	-0.98	0.3282	-0.4727	0.1581
FRC_Thirona	-2.02867731	0.5304	2754	-3.83	0.0001	-3.0686	-0.9887
FRC_Thirona*BDR	-2.08536054	1.2918	2754	-1.61	0.1066	-4.6184	0.4477
fvc_tlc	-277.994023	539.43	2754	-0.52	0.6064	-1335.72	779.74
fvc_tlc*fc_v1	0.4474361	8.9767	2754	0.05	0.9603	-17.1543	18.0492
fvc_tlc*fev1_v1	0.69200329	4.5474	2754	0.15	0.8791	-8.2247	9.6087
fvc_tlc2	341.669851	715.4	2754	0.48	0.633	-1061.1	1744.44
fvc_tlc2*fc_v1	0.44515782	12.1656	2754	0.04	0.9708	-23.4094	24.2997

fvc_tlc2*fev1_v1	-1.35871498	6.4848	2754	-0.21	0.8341	-14.0743	11.3569
fvc_tlc3	-126.604497	303.27	2754	-0.42	0.6764	-721.27	468.06
fvc_tlc3*fc_v1	-0.73314693	5.3503	2754	-0.14	0.891	-11.2242	9.7579
fvc_tlc3*fev1_v1	0.74973082	3.0484	2754	0.25	0.8057	-5.2276	6.727
pi10	-13.7413885	3.6766	2754	-3.74	0.0002	-20.9505	-6.5323
pi102	2.12873319	0.7275	2754	2.93	0.0035	0.7023	3.5551
SmokCigNow	-15.4764508	6.0278	2754	-2.57	0.0103	-27.2958	-3.6571
SmokCigNow*fc_v1	0.18068678	0.07826	2754	2.31	0.021	0.02723	0.3341
type	83.31756	116.69	2754	0.71	0.4753	-145.49	312.12
type*fc_v1	-2.88519754	1.9228	2754	-1.5	0.1336	-6.6554	0.885
type*fev1_v1	0.31505102	0.9482	2754	0.33	0.7397	-1.5441	2.1742
type*BDR	15.4984415	8.4434	2754	1.84	0.0665	-1.0576	32.0545
type*BDR*fc_v1	-0.1930867	0.1022	2754	-1.89	0.059	-0.3935	0.00734
type*BDR*fev1_v1	0.07102939	0.05297	2754	1.34	0.18	-0.03283	0.1749
type*BDR*Chronic_Bronch	-1.43892088	2.0887	2754	-0.69	0.4909	-5.5346	2.6567
type*BMI	0.09848875	0.05178	2754	1.9	0.0573	-0.00305	0.2
type*Chronic_Bronchitis	-0.76009119	0.8908	2754	-0.85	0.3936	-2.5068	0.9867
type*emph	0.08563291	0.4715	2754	0.18	0.8559	-0.8389	1.0102
type*emph2	0.0001895	0.00598	2754	0.03	0.9747	-0.01153	0.01191
type*emph*fc_v1	-0.00198614	0.00608	2754	-0.33	0.744	-0.01391	0.00994
type*emph*SmokCigNow	0.12973761	0.1428	2754	0.91	0.3636	-0.1502	0.4097
type*FRC_Thirona	1.71102712	0.4704	2754	3.64	0.0003	0.7887	2.6333
type*FRC_Thirona*BDR	-1.33667413	1.1489	2754	-1.16	0.2448	-3.5895	0.9161
type*fvc_tlc	-377.220314	480.39	2754	-0.79	0.4324	-1319.18	564.74
type*fvc_tlc*fc_v1	11.2474767	7.9937	2754	1.41	0.1595	-4.4268	26.9218
type*fvc_tlc*fev1_v1	-1.39440987	4.0493	2754	-0.34	0.7306	-9.3344	6.5455
type*fvc_tlc2	528.75402	637.15	2754	0.83	0.4067	-720.58	1778.09
type*fvc_tlc2*fc_v1	-15.5380308	10.8331	2754	-1.43	0.1516	-36.7799	5.7039
type*fvc_tlc2*fev1_v1	2.3377842	5.7739	2754	0.4	0.6856	-8.9838	13.6593
type*fvc_tlc3	-224.796506	270.12	2754	-0.83	0.4054	-754.46	304.87
type*fvc_tlc3*fc_v1	6.78231153	4.7643	2754	1.42	0.1547	-2.5597	16.1243
type*fvc_tlc3*fev1_v1	-1.16269997	2.7141	2754	-0.43	0.6684	-6.4846	4.1592
type*pi10	5.2211404	3.2708	2754	1.6	0.1105	-1.1923	11.6346
type*pi102	-0.84431345	0.6474	2754	-1.3	0.1923	-2.1137	0.4251
type*SmokCigNow	4.45846096	5.3544	2754	0.83	0.4051	-6.0406	14.9575
type*SmokCigNow*fc_v1	-0.05243408	0.06951	2754	-0.75	0.4507	-0.1887	0.08387