

Supplementary Table 1. Demographics and plasma levels of C4c in early stage lung cancer patients (n=39) and control individuals (n=39) from Clinica Universidad de Navarra

Characteristics	Control subjects			Lung cancer patients		
	n	C4c (AU)*	P value [†]	n	C4c (AU)*	P value [†]
Sex						
Female	5	81 (66-89)	0.801	5	146 (134-178)	0.614
Male	34	87 (69-108)		34	174 (104-211)	
Age (years)						
≤65	22	85 (62-96)	0.282	19	155 (112-198)	0.354
>65	17	87 (78-111)		20	181 (118-212)	
Smoking status						
Never				1	155	
Former	27	87 (63-109)	0.831	25	168 (100-211)	0.882
Current	12	85 (79-91)		13	173 (138-196)	
Pack-years						
≤35	18	82 (69-106)	0.888	17	173 (146-184)	0.918
>35	21	88 (63-108)		21	178 (117-211)	
Unknown				1	97	
Histology						
ADC				19	161 (100-186)	0.431
SCC				20	178 (114-225)	
Nodule size (cm)						
≤2.5				17	146 (104-175)	0.019
>2.5				22	191 (138-239)	
Stage						
I				31	160 (112-198)	0.251
II				8	189 (138-242)	
Status						
Alive				28	176 (125-205)	0.915
Death				9	173 (117-206)	
Unknown				2	117 (108-126)	

*Data are expressed as median (25th to 75th percentiles) AU: arbitrary units. [†]Two-sided Mann-Whitney U test.

Supplementary Table 2. Demographics and plasma levels of C4d in early stage lung cancer patients (n=39) and control individuals (n=39) from Clinica Universidad de Navarra*

Characteristics	Control subjects			Lung cancer patients		
	n	C4d (AU) [†]	P value [‡]	n	C4d (AU) [†]	P value [‡]
Sex						
Female	5	0.46 (0.39-0.77)	0.585	5	1.04 (0.88-1.65)	0.966
Male	34	0.58 (0.52-0.65)		34	0.95 (0.69-1.61)	
Age (years)						
≤65	22	0.57 (0.46-0.61)	0.336	19	0.89 (0.65-1.43)	0.536
>65	17	0.59 (0.53-0.66)		20	1.02 (0.72-1.84)	
Smoking status						
Never				1	0.69	
Former	27	0.58 (0.52-0.66)	0.287	25	1.16 (0.70-2.06)	0.444
Current	12	0.54 (0.44-0.63)		13	0.86 (0.78-1.08)	
Pack-years						
≤35	18	0.59 (0.48-0.73)	0.284	17	1.04 (0.8-1.43)	0.284
>35	21	0.55 (0.52-0.61)		21	0.86 (0.68-1.68)	
Unknown				1	0.58	
Histology						
ADC				19	0.88 (0.69-2.06)	0.757
SCC				20	1.05 (0.70-1.52)	
Nodule size (cm)						
≤2.5				17	0.88 (0.52-1.43)	0.213
>2.5				22	1.1 (0.73-1.66)	
Stage						
I				31	0.88 (0.68-1.68)	0.626
II				8	1.05 (0.90-1.51)	
Status						
Alive				28	0.96 (0.67-1.43)	0.896
Death				9	1.01 (0.78-1.61)	
Unknown				2	1.4 (1.07-1.73)	

*These data were previously obtained and have been already published: Ajona D, Okrój M, Pajares MJ, et al. Complement C4d-specific antibodies for the diagnosis of lung cancer. *Oncotarget*. 2017; 9: 6346-6355.

[†]Data are expressed as median (25th to 75th percentiles) AU: arbitrary units. [‡]Two-sided Mann-Whitney U test.

Supplementary Table 3. Demographics and plasma levels of C4d-containing fragments in early stage lung cancer patients (n=39) and control individuals (n=39) from Clinica Universidad de Navarra*

Characteristics	Control subjects			Lung cancer patients		
	n	C4d-containing fragments (µg/ml) †	P value‡	n	C4d-containing fragments (µg/ml) †	P value‡
Sex						
Female	5	0.75 (0.74-0.8)	0.737	5	0.75 (0.71-0.87)	0.172
Male	34	0.69 (0.61-0.93)		34	0.87 (0.75-1.12)	
Age (years)						
≤65	22	0.75 (0.62-0.89)	0.977	19	0.79 (0.71-0.94)	0.129
>65	17	0.66 (0.62-0.94)		20	0.91 (0.81-1.14)	
Smoking status						
Never				1	0.82	
Former	27	0.68 (0.61-0.91)	0.361	25	0.93 (0.78-1.13)	0.530
Current	12	0.73 (0.65-0.95)		13	0.8 (0.71-0.93)	
Pack-years						
≤35	18	0.77 (0.63-0.91)	0.652	17	0.93 (0.79-1.04)	0.567
>35	21	0.7 (0.61-0.92)		21	0.87 (0.70-1.19)	
Unknown				1	0.74	
Histology						
ADC				19	0.82 (0.73-1.02)	0.222
SCC				20	0.9 (0.80-1.23)	
Nodule size (cm)						
≤2.5				17	0.82 (0.72-0.94)	0.229
>2.5				22	0.93 (0.78-1.12)	
Stage						
I				31	0.82 (0.73-0.95)	0.044
II				8	1.11 (0.9-1.32)	
Status						
Alive				28	0.82 (0.71-0.93)	0.012
Death				9	1.25 (1.04-1.75)	
Unknown				2	0.99 (0.93-1.05)	

*These data have been obtained from a subset of patients from a cohort in which the determination of C4d-containing fragments were already performed and published: Ajona D, Pajares MJ, Corrales L, et al. Investigation of complement activation product C4d as a diagnostic and prognostic biomarker for lung cancer. J Natl Cancer Inst. 2013; 105: 1385-1393.

†Data are expressed as median (25th to 75th percentiles). ‡Two-sided Mann-Whitney U test.

Supplementary Table 4. Plasma levels of cancer biomarkers in early stage lung cancer patients (n=39) and control individuals (n=39) from Clinica Universidad de Navarra

Marker	Control subjects*	Lung cancer patients*	P value[†]	Adjusted P value[‡]
AFP (ng/ml)	1.42 (1.09-1.98)	1.48 (1.14-2.11)	0.893	0.954
Total PSA (ng/ml)	0.40 (0.17-1.49)	0.33 (0.09-0.89)	0.475	0.954
CA15.3 (U/ml)	11.89 (6.22-15.80)	9.76 (6.70-15.72)	0.549	0.954
CA19.9 (U/ml)	19.73 (13.99-27.90)	19.55 (14.03-25.58)	0.877	0.954
MIF (ng/ml)	1.16 (0.73-2.09)	0.88 (0.55-1.69)	0.124	0.620
TRAIL (ng/ml)	0.17 (0.12-0.19)	0.17 (0.12-0.21)	0.916	0.954
Leptin (ng/ml)	15.41 (8.88-39.89)	22.24 (9.99-35.87)	0.586	0.954
IL-6 (pg/ml)	4.29 (2.92-5.95)	5.62 (4.29-8.23)	0.022	0.137
sFasL (pg/ml)	22.55 (11.70-29.82)	15.30 (11.70-26.18)	0.455	0.954
CEA (ng/ml)	1.05 (0.53-1.76)	0.90 (0.50-1.78)	0.738	0.954
CA125 (U/ml)	4.59 (3.57-6.14)	5.10 (4.07-7.19)	0.319	0.944
IL-8 (pg/ml)	4.83 (3.44-5.76)	5.14 (3.90-7.48)	0.254	0.944
HGF (ng/ml)	0.20 (0.16-0.28)	0.23 (0.19-0.26)	0.340	0.944
sFas (ng/ml)	2.00 (1.71-2.64)	1.98 (1.54-2.37)	0.463	0.954
TNF α (pg/ml)	8.53 (7.36-10.09)	8.53 (7.18-10.65)	0.996	0.996
Prolactin (ng/ml)	8.62 (4.98-11.01)	11.01 (7.18-15.95)	0.003	0.033
SCF (pg/ml)	48.76 (37.65-59.83)	50.98 (37.65-70.86)	0.569	0.954
CYFRA21.1 (ng/ml)	0.99 (0-2.20)	3.86 (1.42-5.03)	<0.001	0.002
OPN (ng/ml)	42.42 (36.43-54.65)	55.72 (33.94-72.61)	0.310	0.944
FGF2 (ng/ml)	0.12 (0.10-0.17)	0.12 (0.10-0.17)	0.798	0.954
bHCG (mU/ml)	0	0	0.864	0.954
HE4 (ng/ml)	4.94 (3.08-5.50)	4.94 (3.74-5.50)	0.860	0.954
TGF α (ng/ml)	0	0	0.890	0.954
VEGF (pg/ml)	0	0	0.847	0.954
CRP (μ g/ml)	1.80 (0.90-3.30)	4.10 (1.90-15.30)	0.004	0.033

*Data are expressed as median (25th to 75th percentiles). [†]Two-sided Mann-Whitney U test. [‡]FDR-adjusted P values (Benjamini-Hochberg method)

Supplementary Table 5. Simple logistic regression for the evaluation of C4c, prolactin, CYFRA 21.1 and CRP as potential diagnostic markers for lung cancer using the case-control set of samples from Clinica Universidad de Navarra

Marker	LR chi²	P value*
C4c	39.18	<0.001
IL-6	1.80	0.180
Prolactin	7.40	0.006
CYFRA 21.1	24.38	<0.001
CRP	14.52	<0.001

*The likelihood ratio chi-square (LR chi²) test was used to evaluate the goodness of fit of the markers

Supplementary Table 6. C4c-containing lung cancer diagnostic models generated by logistic regression using combinations of C4c plasma levels and plasma levels of prolactin, CYFRA 21.1 and/or CRP in lung cancer patients (n=39) and control subjects (n=39) from Clinica Universidad de Navarra

Biomarker/s	Diagnostic parameters*						
	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	LR+	LR-
C4c	72 (55-85)	95 (83-99)	83 (73-91)	93 (78-98)	77 (67-85)	14.00 (3.58-54.78)	0.30 (0.18-0.49)
C4c+prolactin	77 (61-89)	95 (83-99)	86 (76-93)	94 (79-98)	80 (70-88)	15.00 (3.85-58.49)	0.24 (0.14-0.43)
C4c+CYFRA	82 (66-92)	95 (82-99)	88 (79-95)	94 (80-98)	84 (72-91)	15.59 (4.01-60.55)	0.19 (0.10-0.37)
C4c+CRP	77 (61-89)	95 (83-99)	86 (76-93)	94 (79-98)	80 (70-88)	15.00 (3.85-58.49)	0.24 (0.14-0.43)
C4c+prolactin+CYFRA	82 (66-92)	92 (79-98)	87 (77-94)	91 (78-97)	84 (72-91)	10.39 (3.47-31.09)	0.19 (0.10-0.38)
C4c+prolactin+CRP	77 (61-89)	95 (83-99)	86 (76-93)	94 (79-98)	80 (70-88)	15.00 (3.85-58.49)	0.24 (0.14-0.43)
C4c+CYFRA+CRP	82 (66-92)	95 (82-99)	88 (79-95)	94 (80-98)	84 (72-91)	15.59 (4.01-60.55)	0.19 (0.10-0.37)
C4c+prolactin+CYFRA+CRP	79 (64-91)	95 (82-99)	87 (77-94)	94 (80-98)	82 (71-89)	15.10 (3.88-58.75)	0.22 (0.12-0.40)

*Diagnostic statistics were calculated at the maximum Youden index in each model. PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

Supplementary Table 7. Comparison of the performance of the diagnostic model based on C4c, CYFRA 21-1 and CRP with the performance of a model without C4c

Model	LR chi2	P value*
C4c/CYFRA/CRP	52.05	<0.001
CYFRA/CRP	27.94	

*Values from the likelihood ratio chi-square test obtained in the two diagnostic models were compared using the likelihood-ratio test

Diagnostic parameters*	C4c/CYFRA/CRP	CYFRA/CRP
Sensitivity (%)	82 (66-92)	74 (58-87)
Specificity (%)	95 (82-99)	79 (63-90)
Accuracy (%)	88 (79-95)	77 (66-86)
Positive predictive value (%)	94 (80-98)	78 (66-87)
Negative predictive value (%)	84 (72-91)	75 (63-84)
Positive likelihood ratio	15.59 (4.01-60.55)	3.53 (1.86-6.72)
Negative likelihood ratio	0.19 (0.10-0.37)	0.32 (0.19-0.57)

*Diagnostic parameters were calculated at the maximum Youden index

Supplementary Table 8. Association between the probabilities of malignancy obtained from the multivariate model based on C4c/CYFRA 21-1/CRP plasma levels, and the demographic and clinical characteristics of lung cancer patients (n=39) and matched controls (n=38) from Clinica Universidad de Navarra

Characteristics	Controls			Cases		
	n	Probability*	P value [†]	n	Probability*	P value [†]
Sex						
Female	5	0.14 (0.11-0.33)	0.983	5	0.83 (0.60-0.89)	0.166
Male	33	0.15 (0.11-0.31)		34	0.95 (0.74-0.99)	
Age (years)						
≤65	22	0.12 (0.06-0.25)	0.029	19	0.90 (0.63-0.99)	0.399
>65	16	0.27 (0.14-0.35)		20	0.96 (0.78-0.99)	
Smoking status						
Never smoker			0.826	1	0.83	0.860
Ex-smoker	26	0.17 (0.08-0.32)		25	0.95 (0.66-0.99)	
Current smoker	12	0.13 (0.11-0.31)		13	0.92 (0.72-0.99)	
Pack-years						
≤35	17	0.16 (0.11-0.35)	0.258	17	0.92 (0.83-0.99)	0.362
>35	21	0.13 (0.11-0.27)		21	0.94 (0.72-0.99)	
Unknown				1	0.20	
Histology						
ADC				19	0.83 (0.50-0.95)	0.012
SCC				20	0.99 (0.87-1.00)	
Nodule size (cm)						
≤2.5				17	0.80 (0.57-0.90)	0.003
>2.5				22	0.98 (0.92-1.00)	
Stage						
I				31	0.90 (0.63-0.99)	0.186
II				8	0.97 (0.89-1.00)	
Status						
Alive				28	0.91 (0.71-0.99)	0.020
Death				9	1.00 (0.97-1.00)	
Unknown				2	0.40 (0.31-0.48)	

*Data are expressed as median (25th to 75th percentiles). [†]Two-sided Mann-Whitney U test.

Supplementary Table 9. Demographics and their association with the probabilities of malignancy obtained from the multivariate model based on C4c/CYFRA 21.1/CRP plasma levels in control individuals (n=49) and advanced NSCLC patients (n=50) from Clinica Universidad de Navarra

Characteristics	Control subjects			Lung cancer patients		
	n	Probability*	P value[†]	n	Probability*	P value[†]
Sex						
Female	11	0.24 (0.20-0.68)	0.443	11	0.52 (0.37-0.93)	0.114
Male	38	0.24 (0.17-0.39)		39	0.75 (0.45-0.99)	
Age (years)						
≤65	31	0.22 (0.19-0.30)	0.097	32	0.71 (0.38-0.96)	0.558
>65	18	0.35 (0.20-0.42)		18	0.75 (0.45-0.99)	
Smoking status						
Former	24	0.29 (0.19-0.44)	0.379	31	0.77 (0.55-0.99)	0.095
Current	25	0.24 (0.19-0.32)		19	0.62 (0.36-0.91)	
Pack-years						
≤35	19	0.22 (0.19-0.44)	0.697	15	0.46 (0.38-0.75)	0.043
>35	30	0.29 (0.19-0.39)		35	0.77 (0.62-0.99)	
Histology						
ADC				39	0.71 (0.38-0.93)	0.237
SCC				11	0.97 (0.55-0.99)	
Stage						
III				21	0.66 (0.37-0.99)	0.731
IV				29	0.75 (0.45-0.95)	

*Data are expressed as median (25th to 75th percentiles). [†]Two-sided Mann-Whitney U test.

Supplementary Table 10. Demographics and their association with the probabilities of malignancy obtained from the multivariate model based on C4c/CYFRA 21.1/CRP plasma levels in control individuals (n=48) and SCLC patients (n=47) from the biobank of the University of Navarra

Characteristics	Control subjects			Lung cancer patients		
	n	Probability*	P value[†]	n	Probability*	P value[†]
Sex						
Female	12	0.44 (0.35-0.53)	0.505	11	0.47 (0.37-0.64)	0.327
Male	36	0.42 (0.34-0.48)		36	0.53 (0.41-0.66)	
Age (years)						
≤65	30	0.42 (0.34-0.50)	0.983	35	0.53 (0.39-0.66)	0.558
>65	18	0.41 (0.34-0.51)		12	0.50 (0.45-0.70)	
Smoking status						
Former	20	0.41 (0.31-0.48)	0.478	21	0.49 (0.39-0.66)	0.982
Current	26	0.42 (0.38-0.51)		24	0.54 (0.40-0.66)	
Unknown	2	0.48 (0.47-0.49)		2	0.44 (0.42-0.47)	
Pack-years						
≤35	30	0.41 (0.34-0.50)	0.475	14	0.52 (0.43-0.66)	0.579
>35	16	0.44 (0.35-0.51)		30	0.53 (0.39-0.67)	
Unknown	2	0.48 (0.47-0.49)		3	0.43 (0.42-0.47)	
Stage						
Limited				10	0.57 (0.37-0.66)	0.790
Extensive				32	0.52 (0.40-0.73)	
Unknown				5	0.48 (0.47-0.49)	

*Data are expressed as median (25th to 75th percentiles). [†]Two-sided Mann-Whitney U test.

Supplementary Table 11. Demographics and their association with the probabilities of malignancy obtained from the multivariate model based on C4c/CYFRA 21.1/CRP plasma levels in a screened population of asymptomatic individuals from Clinica Universidad de Navarra (n=93 for controls, and n=30 for lung cancer cases)

Characteristics	Control subjects			Lung cancer patients		
	n	Probability*	P value [†]	n	Probability*	P value [†]
Sex						
Female	10	0.16 (0.15-0.21)	0.191	4	0.33 (0.21-0.43)	0.714
Male	83	0.20 (0.16-0.28)		26	0.30 (0.24-0.38)	
Age (years)						
≤65	63	0.20 (0.14-0.28)	0.987	22	0.29 (0.24-0.39)	0.707
>65	30	0.19 (0.17-0.25)		8	0.35 (0.23-0.38)	
Smoking status						
Former	54	0.20 (0.15-0.28)	0.691	13	0.31 (0.27-0.39)	0.414
Current	39	0.19 (0.16-0.27)		17	0.29 (0.22-0.38)	
Pack-years						
≤35	29	0.17 (0.14-0.25)	0.046	8	0.26 (0.19-0.28)	0.083
>35	64	0.21 (0.17-0.28)		22	0.34 (0.27-0.39)	
Histology						
ADC				20	0.29 (0.23-0.38)	0.320
SCC				4	0.38 (0.29-0.45)	
LCC				4	0.30 (0.22-0.37)	
Carcinoid				1	0.10	
Anaplastic				1	0.39	
Nodule size (cm)						
≤1.5				17	0.30 (0.27-0.38)	0.438
>1.5				11	0.28 (0.10-0.43)	
Unknown				2	0.33 (0.27-0.39)	
Stage						
I				24	0.29 (0.20-0.41)	0.678
II/III/IV				6	0.31 (0.29-0.37)	

*Data are expressed as median (25th to 75th percentiles). [†]Two-sided Mann-Whitney U test, or two-sided Kruskal-Wallis test.

Supplementary Table 12. Demographics and their association with the probabilities of malignancy obtained from the multivariate model based on C4c/CYFRA 21.1/CRP plasma levels in a screened population of asymptomatic individuals from Clinica Universidad de Navarra who do not meet the 55 to 74 years old, and at least 30 pack-years NLST selection criteria (n=36 for controls, and n=13 for lung cancer cases)

Characteristics	Control subjects			Lung cancer patients		
	n	Probability*	P value[†]	n	Probability*	P value[†]
Sex						
Female	8	0.16 (0.15-0.20)	0.790	3	0.27 (0.21-0.37)	0.866
Male	28	0.19 (0.163-0.24)		10	0.30 (0.27-0.42)	
Age (years)						
≤65	23	0.16 (0.13-0.25)	0.270	9	0.29 (0.27-0.43)	0.877
>65	13	0.19 (0.19-0.22)		4	0.33 (0.23-0.41)	
Smoking status						
Former	20	0.17 (0.15-0.22)	0.949	8	0.35 (0.28-0.44)	0.242
Current	16	0.19 (0.13-0.24)		5	0.27 (0.09-0.29)	
Pack-years						
≤35	20	0.17 (0.14-0.23)	0.464	6	0.27 (0.19-0.28)	0.199
>35	16	0.19 (0.15-0.23)		7	0.39 (0.30-0.44)	
Histology						
ADC				7	0.29 (0.27-0.42)	0.345
SCC				1	0.46	
LCC				4	0.30 (0.25-0.34)	
Carcinoid				1	0.09	
Nodule size (cm)						
≤1.5				6	0.34 (0.28-0.44)	0.580
>1.5				6	0.30 (0.14-0.40)	
Unknown				1	0.27	
Stage						
I				10	0.33 (0.19-0.44)	0.735
II/III/IV				3	0.29 (0.28-0.30)	

*Data are expressed as median (25th to 75th percentiles). [†]Two-sided Mann-Whitney U test, or two-sided Kruskal-Wallis test.

Supplementary Table 13. Demographics and their association with the probabilities of malignancy obtained from the multivariate model based on C4c/CYFRA 21.1/CRP plasma levels in patients with benign or malignant indeterminate pulmonary nodules (n=62 and n=76, respectively) from Vanderbilt University Medical Center

Characteristics	Benign lung nodules			Malignant lung nodules		
	n	Probability score*	P value [†]	n	Probability score*	P value [†]
Sex						
Female	26	0.30 (0.13-0.51)	0.887	26	0.82 (0.42-0.95)	0.467
Male	36	0.30 (0.22-0.39)		50	0.83 (0.57-0.99)	
Age (years)						
≤65	46	0.31 (0.21-0.41)	0.987	33	0.88 (0.46-0.99)	0.509
>65	16	0.26 (0.18-0.48)		43	0.79 (0.57-0.97)	
Smoking status						
Never	16	0.41 (0.22-0.56)	0.226	2	0.65 (0.62-0.68)	0.375
Former	24	0.30 (0.21-0.39)		42	0.80 (0.50-0.96)	
Current	22	0.25 (0.20-0.34)		32	0.91 (0.53-1.00)	
Pack-years						
≤35	32	0.31 (0.21-0.49)	0.414	17	0.72 (0.62-0.85)	0.601
>35	30	0.27 (0.20-0.39)		59	0.83 (0.50-0.99)	
COPD						
No	38	0.31 (0.20-0.46)	0.866	18	0.86 (0.36-0.98)	0.775
Yes	22	0.27 (0.20-0.39)		54	0.82 (0.58-0.99)	
Unknown	2	0.41 (0.32-0.51)		4	0.60 (0.40-0.80)	
Nodule size (cm)						
≤2.5	42	0.29 (0.22-0.46)	0.972	26	0.49 (0.30-0.79)	<0.001
>2.5	16	0.35 (0.20-0.43)		50	0.90 (0.70-1.00)	
Unknown	4	0.23 (0.13-0.40)				
Upper lobe nodule						
No	27	0.36 (0.22-0.49)	0.415	32	0.82 (0.44-0.99)	0.883
Yes	30	0.29 (0.20-0.39)		44	0.82 (0.57-0.98)	
Unknown	5	0.31 (0.27-0.32)				
Nodule spiculation						
No	50	0.29 (0.20-0.44)	0.817	49	0.83 (0.59-1.00)	0.346
Yes	12	0.31 (0.16-0.41)		25	0.79 (0.50-0.96)	
Unknown				2	0.17 (0.11-0.23)	
Histology						
ADC				26	0.82 (0.50-0.95)	0.669
SCC				16	0.87 (0.50-1.00)	
LCC				6	0.62 (0.35-1.00)	
NSCLC NOS				13	0.88 (0.72-0.98)	
SCLC				15	0.63 (0.41-1.00)	
Stage NSCLC						
I/II				17	0.83 (0.35-0.95)	0.272
III/IV				40	0.83 (0.62-0.99)	
Unknown				4	0.81 (0.55-0.91)	
Stage SCLC						
Limited				8	0.52 (0.27-0.80)	0.064
Extensive				7	0.94 (0.50-1.00)	

*Data are expressed as median (25th to 75th percentiles). [†]Two-sided Mann-Whitney U test, or Two-sided Kruskal-Wallis test.

Supplementary Table 14. Summary of the diagnostic performance of the protein model based on C4c/CYFRA 21.1/CRP plasma levels in combination with three different clinical models for the prediction of lung nodule malignancy in patients with benign and malignant indeterminate pulmonary nodules from Vanderbilt University Medical Center

Gould model

(58 patients with benign and 76 patients with malignant indeterminate pulmonary nodules)

Diagnostic parameters*	Protein model	Gould model	Combined model
Sensitivity (%)	70 (58-80)	87 (77-94)	76 (65-85)
Specificity (%)	93 (83-98)	72 (59-83)	91 (81-97)
Accuracy (%)	80 (72-86)	81 (73-87)	83 (75-89)
Positive predictive value (%)	93 (84-97)	80 (73-86)	92 (83-96)
Negative predictive value (%)	70 (62-77)	81 (70-88)	75 (66-82)
Positive likelihood ratio	10.11 (3.88-26.33)	3.15 (2.06-4.82)	8.85 (3.79-20.65)
Negative likelihood ratio	0.33 (0.23-0.46)	0.18 (0.10-0.33)	0.26 (0.17-0.39)

*Diagnostic parameters were calculated at the maximum Youden index. 95% CIs are also shown.

Mayo model

(48 patients with benign and 65 patients with malignant indeterminate pulmonary nodules)

Diagnostic parameters*	Protein model	Mayo model	Combined model
Sensitivity (%)	78 (67-88)	91 (81-96)	78 (67-88)
Specificity (%)	90 (77-97)	65 (49-78)	94 (83-99)
Accuracy (%)	83 (75-90)	80 (71-87)	85 (77-91)
Positive predictive value (%)	91 (82-96)	78 (70-84)	94 (85-98)
Negative predictive value (%)	75 (66-83)	84 (70-92)	76 (67-84)
Positive likelihood ratio	7.53 (3.25-17.44)	2.56 (1.74-3.78)	12.55 (4.17-37.83)
Negative likelihood ratio	0.24 (0.15-0.39)	0.14 (0.06-0.32)	0.23 (0.14-0.37)

*Diagnostic parameters were calculated at the maximum Youden index. 95% CIs are also shown.

Brock model

(55 patients with benign and 74 patients with malignant indeterminate pulmonary nodules)

Diagnostic parameters*	Protein model	Brock model	Combined model
Sensitivity (%)	72 (60-82)	77 (66-86)	77 (66-86)
Specificity (%)	95 (85-99)	67 (53-79)	89 (78-96)
Accuracy (%)	81 (74-88)	73 (64-80)	82 (74-88)
Positive predictive value (%)	95 (85-98)	76 (68-83)	90 (82-95)
Negative predictive value (%)	71 (63-78)	69 (58-77)	74 (65-82)
Positive likelihood ratio	13.13 (4.33-39.83)	2.35 (1.58-3.51)	7.06 (3.28-15.18)
Negative likelihood ratio	0.30 (0.21-0.43)	0.34 (0.22-0.54)	0.26 (0.17-0.40)

*Diagnostic parameters were calculated at the maximum Youden index. 95% CIs are also shown.