

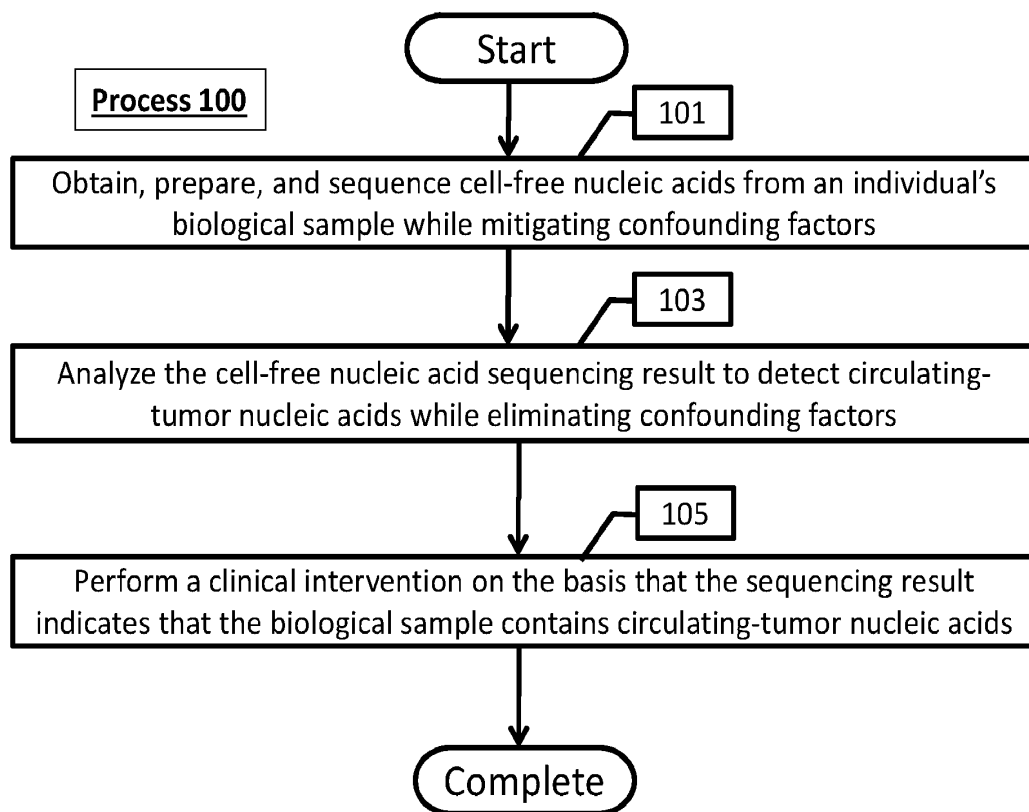
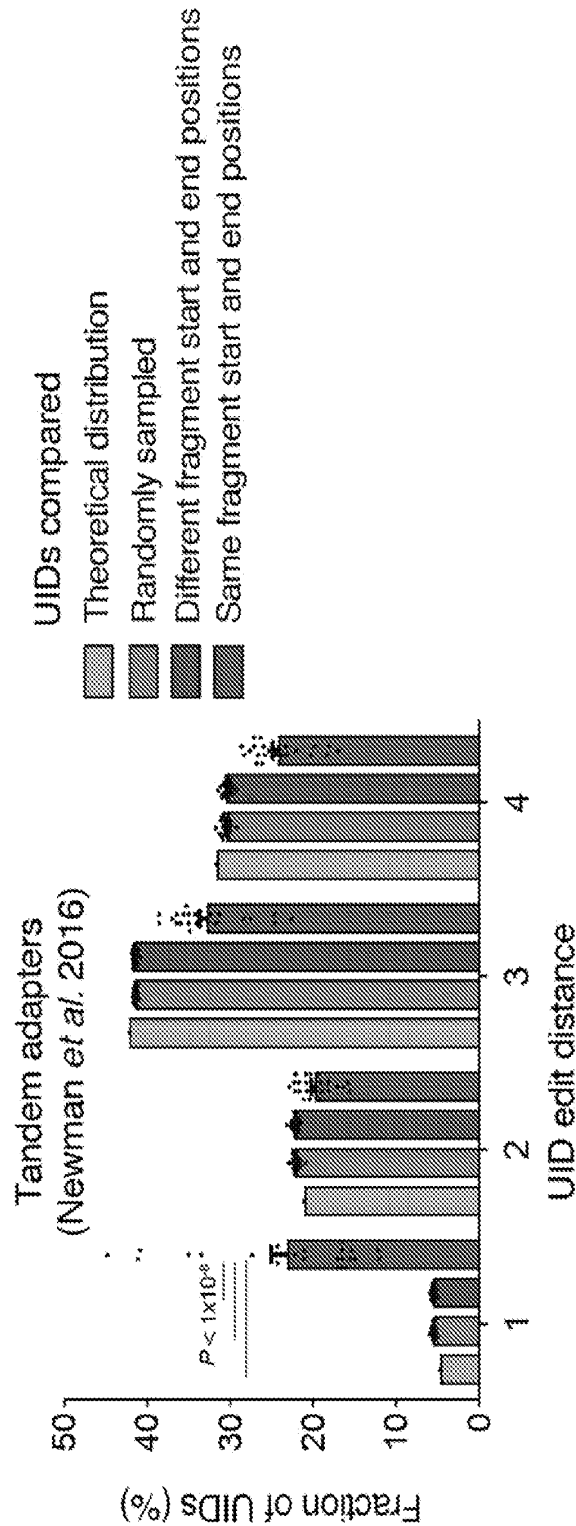
Fig. 1

Fig. 2A



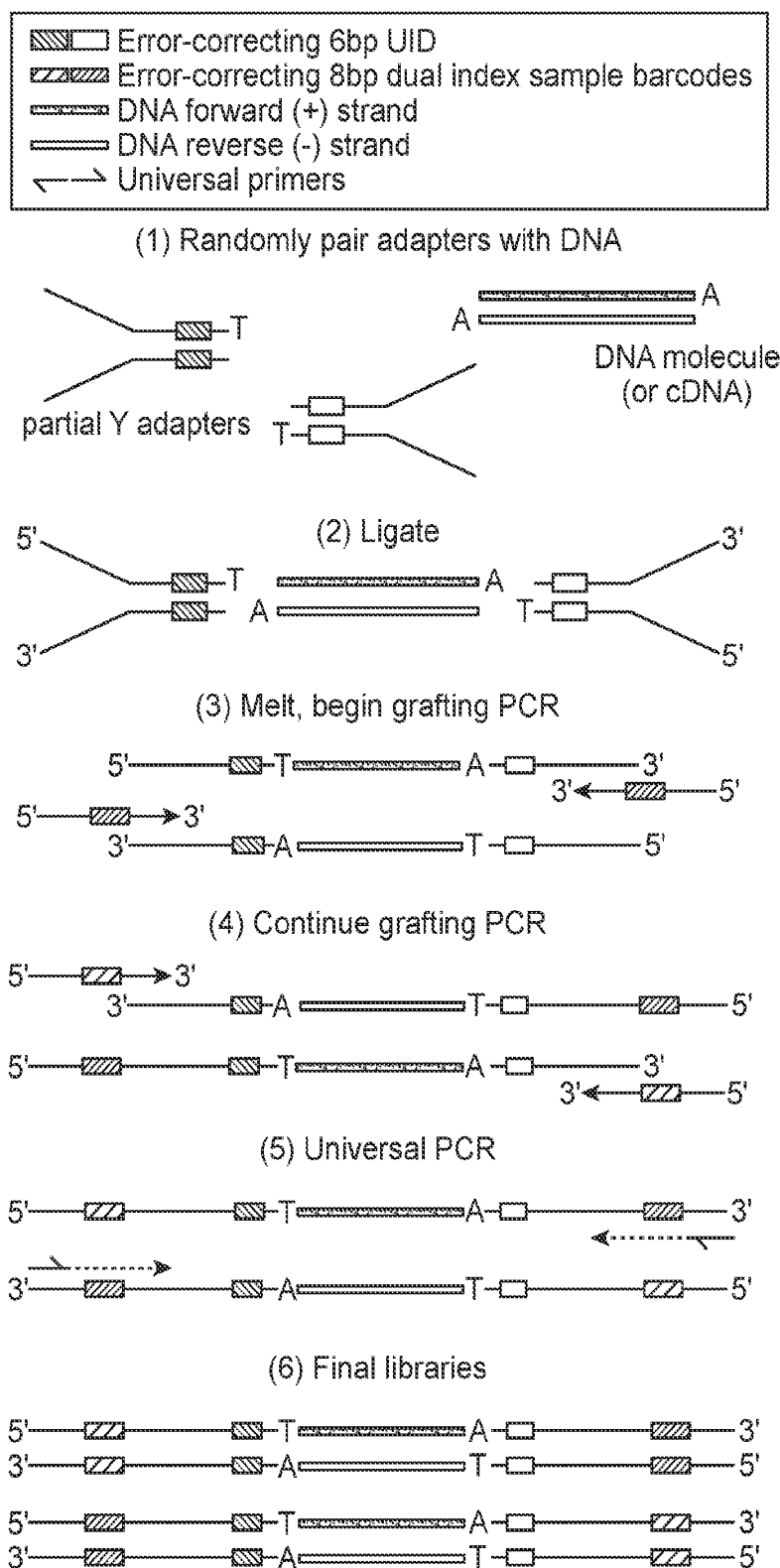


FIG. 2B

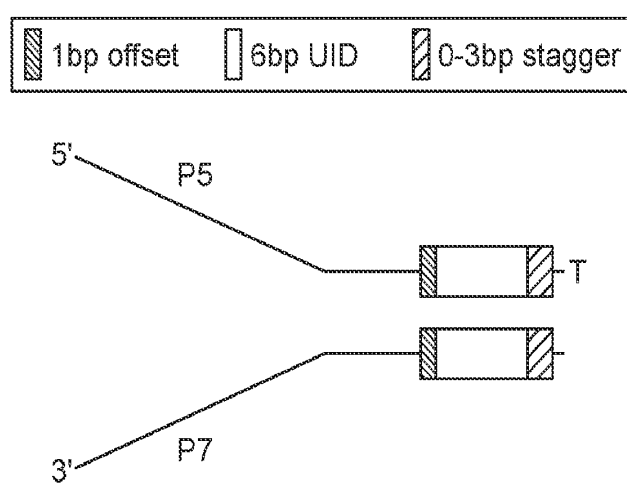
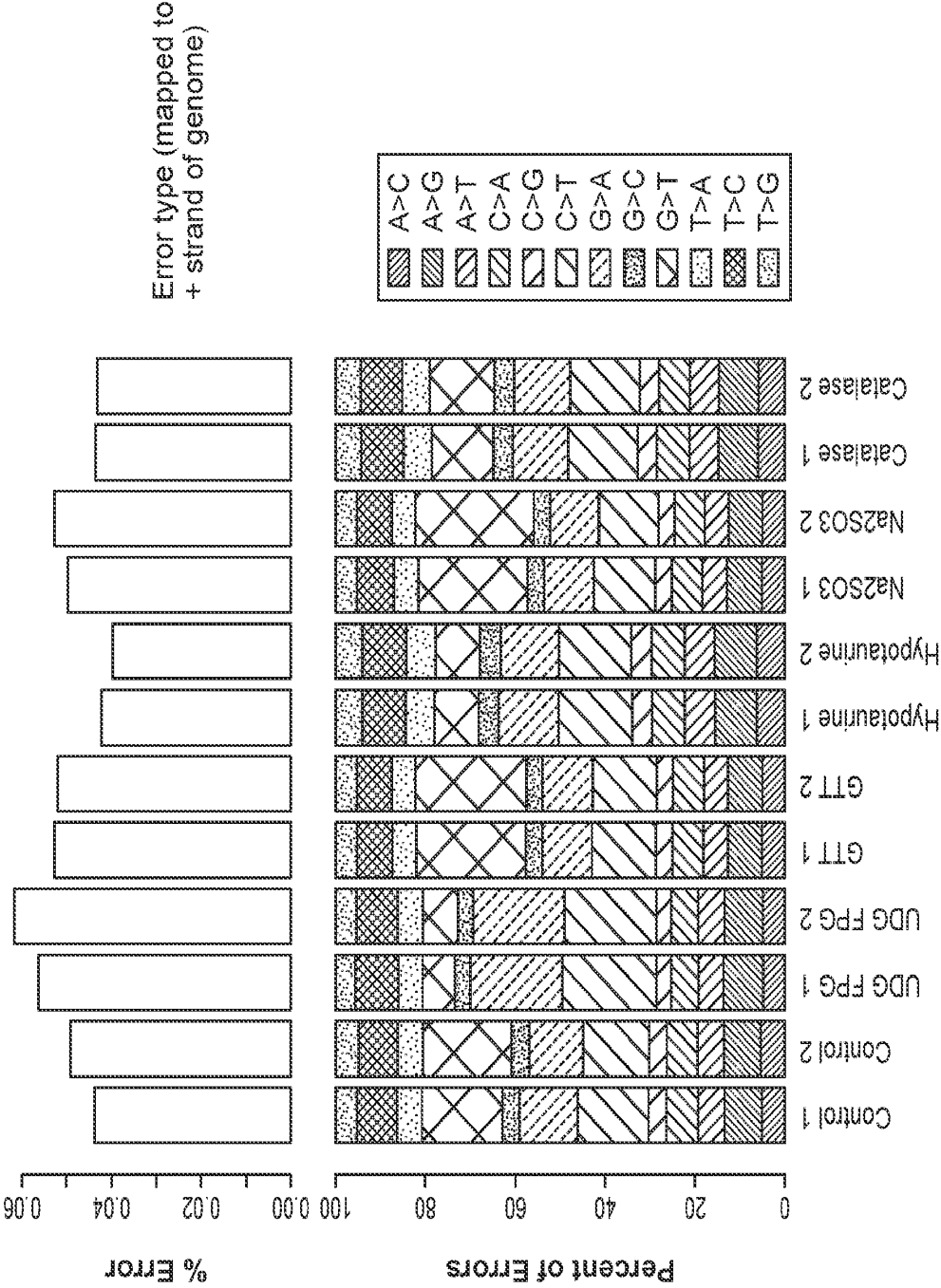


FIG. 3



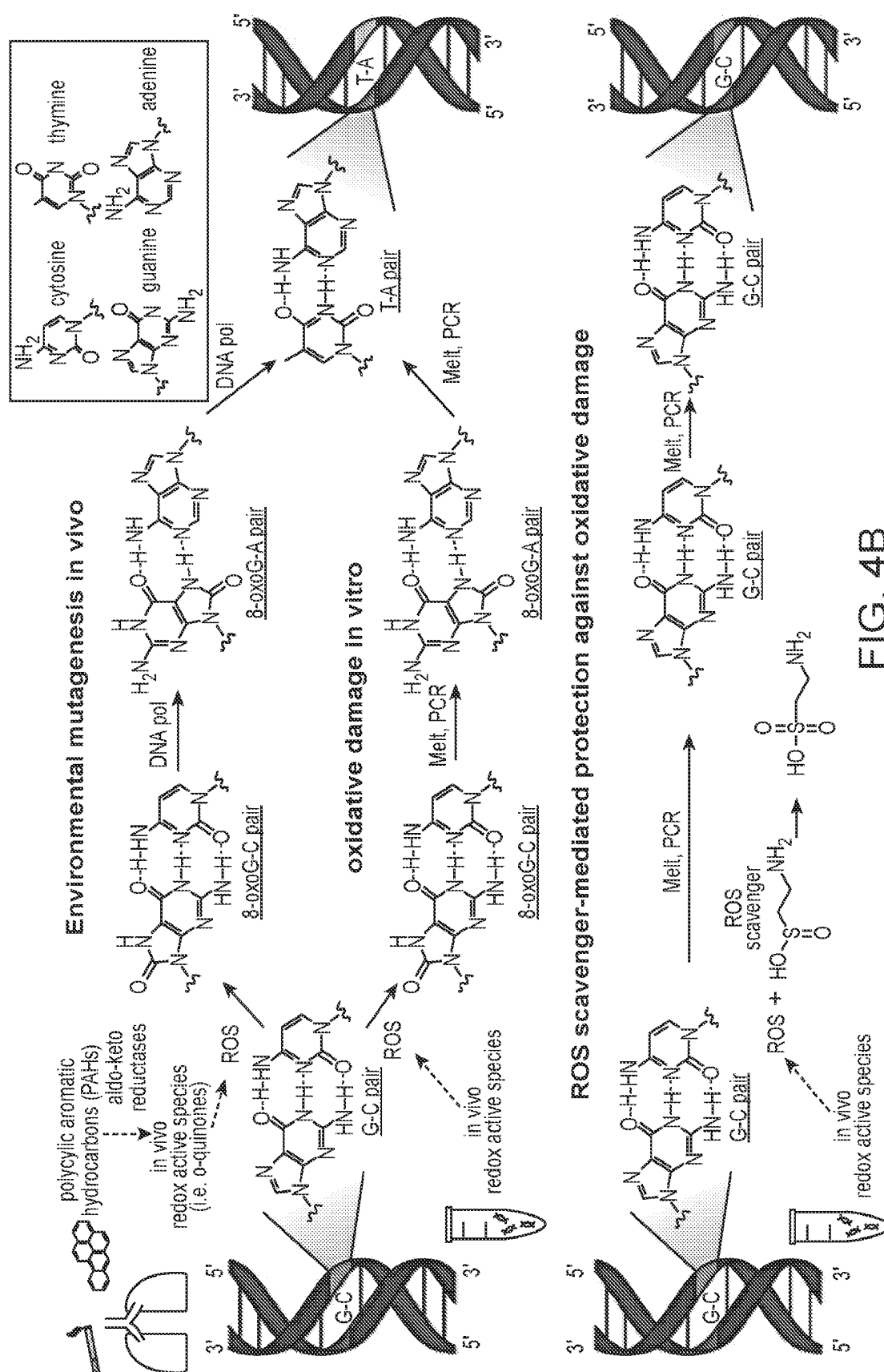


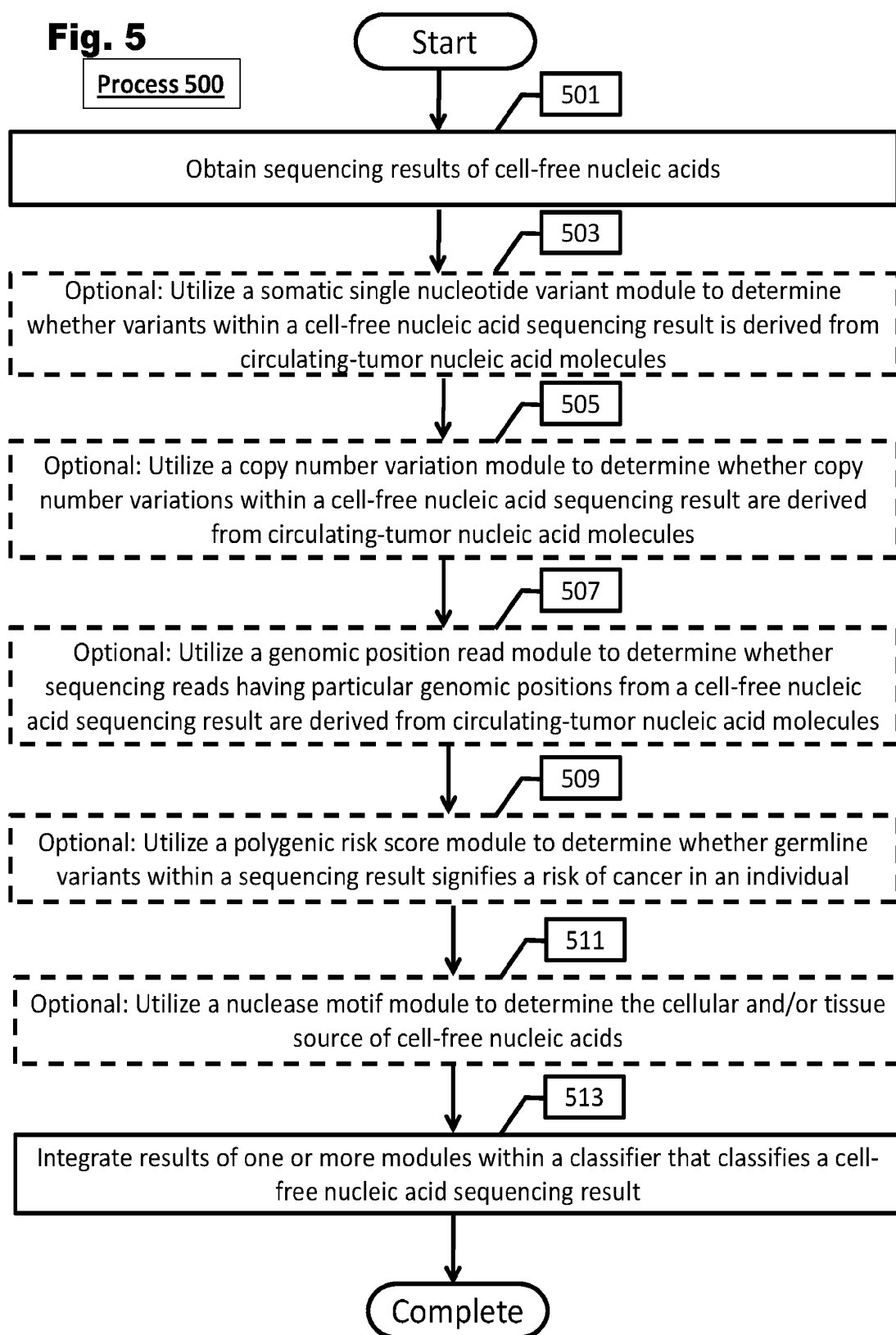
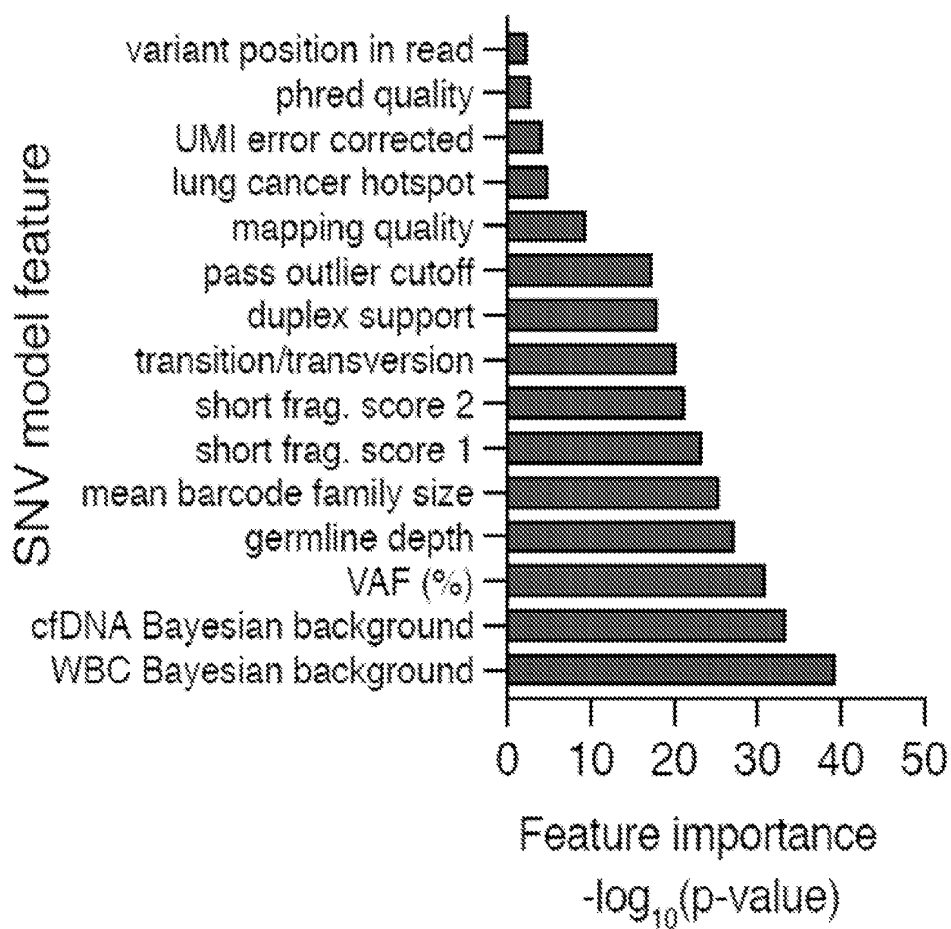
Fig. 5

Fig. 6

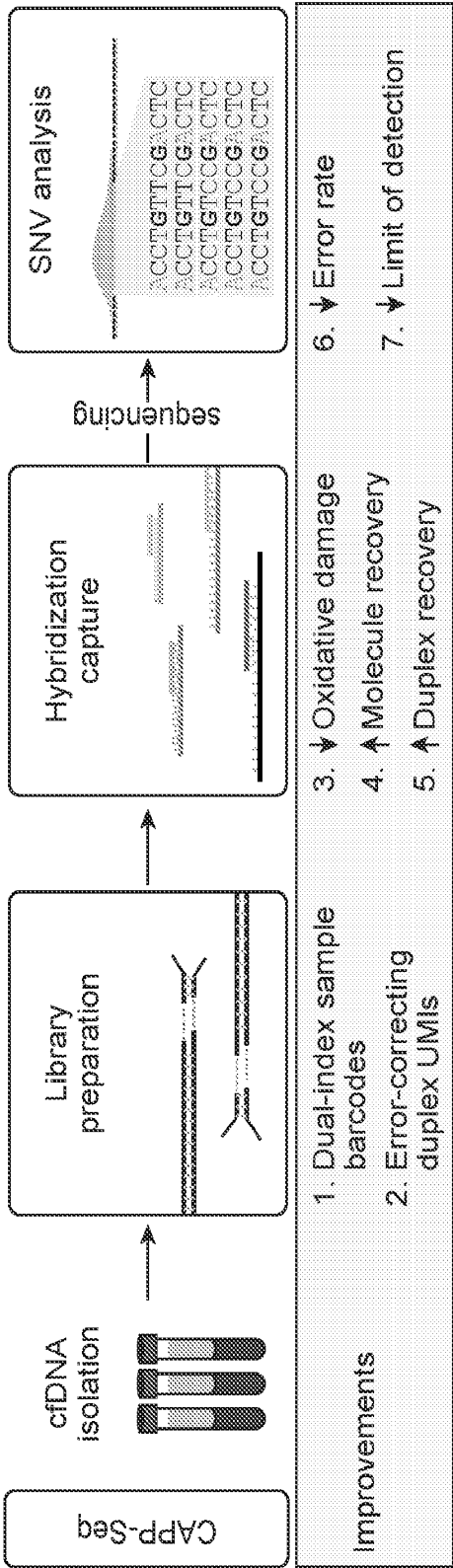


FIG. 7

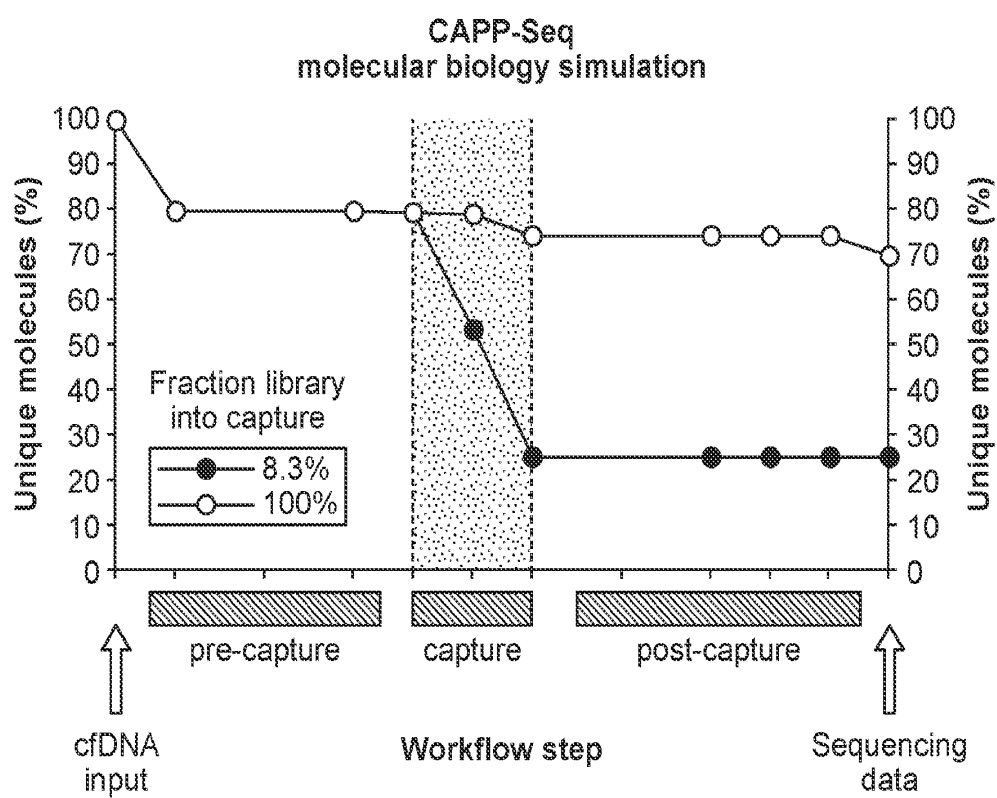


FIG. 8

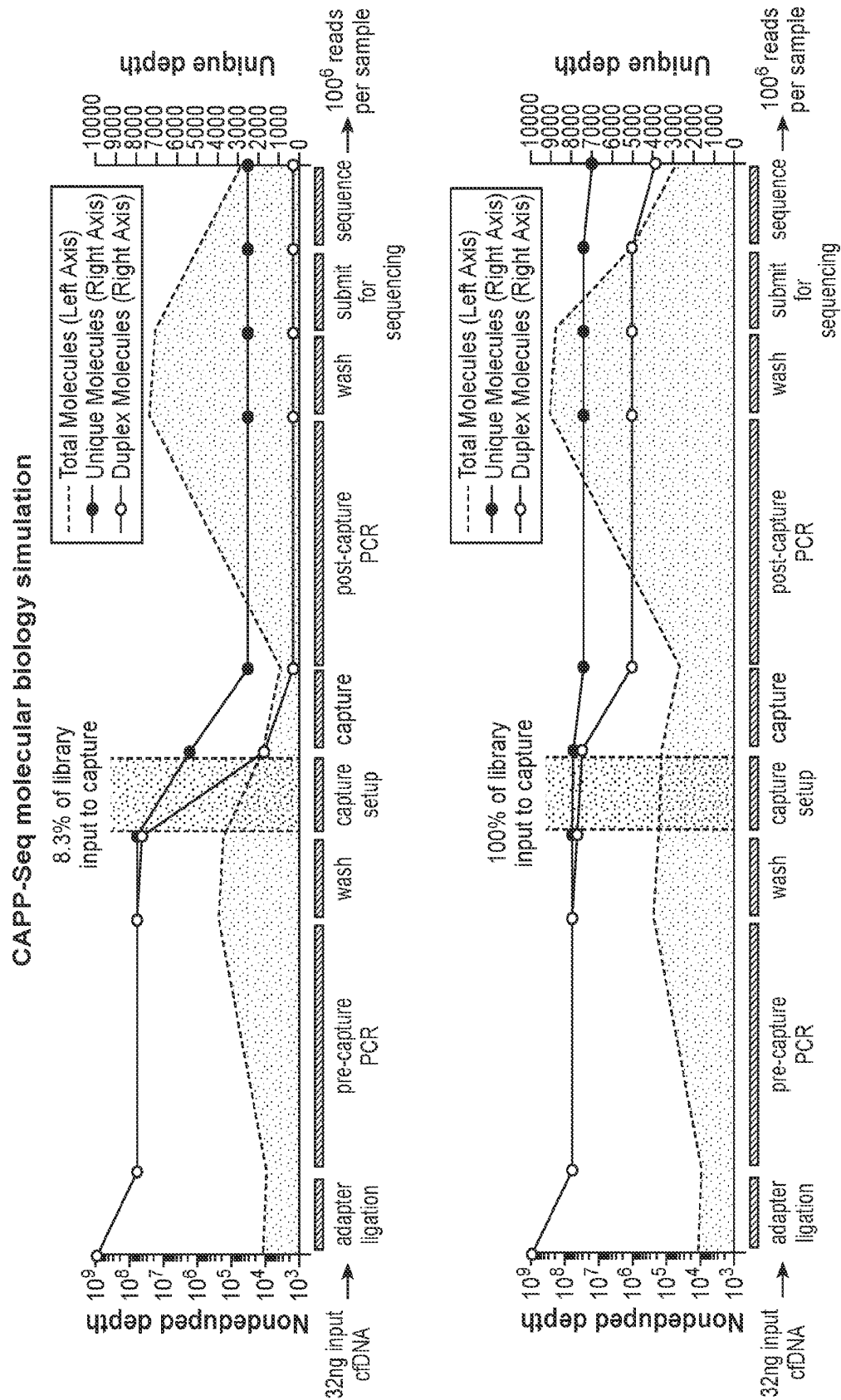
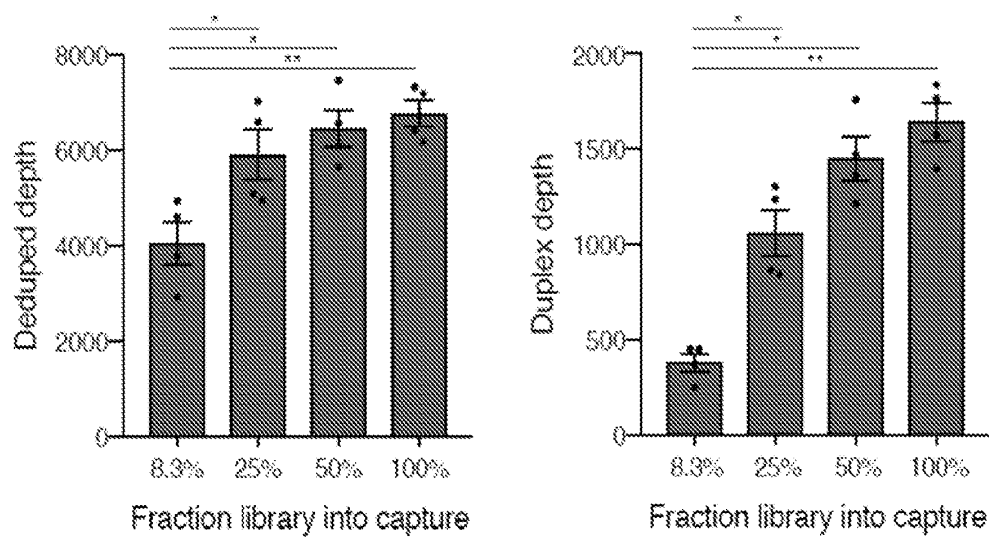


Fig. 10

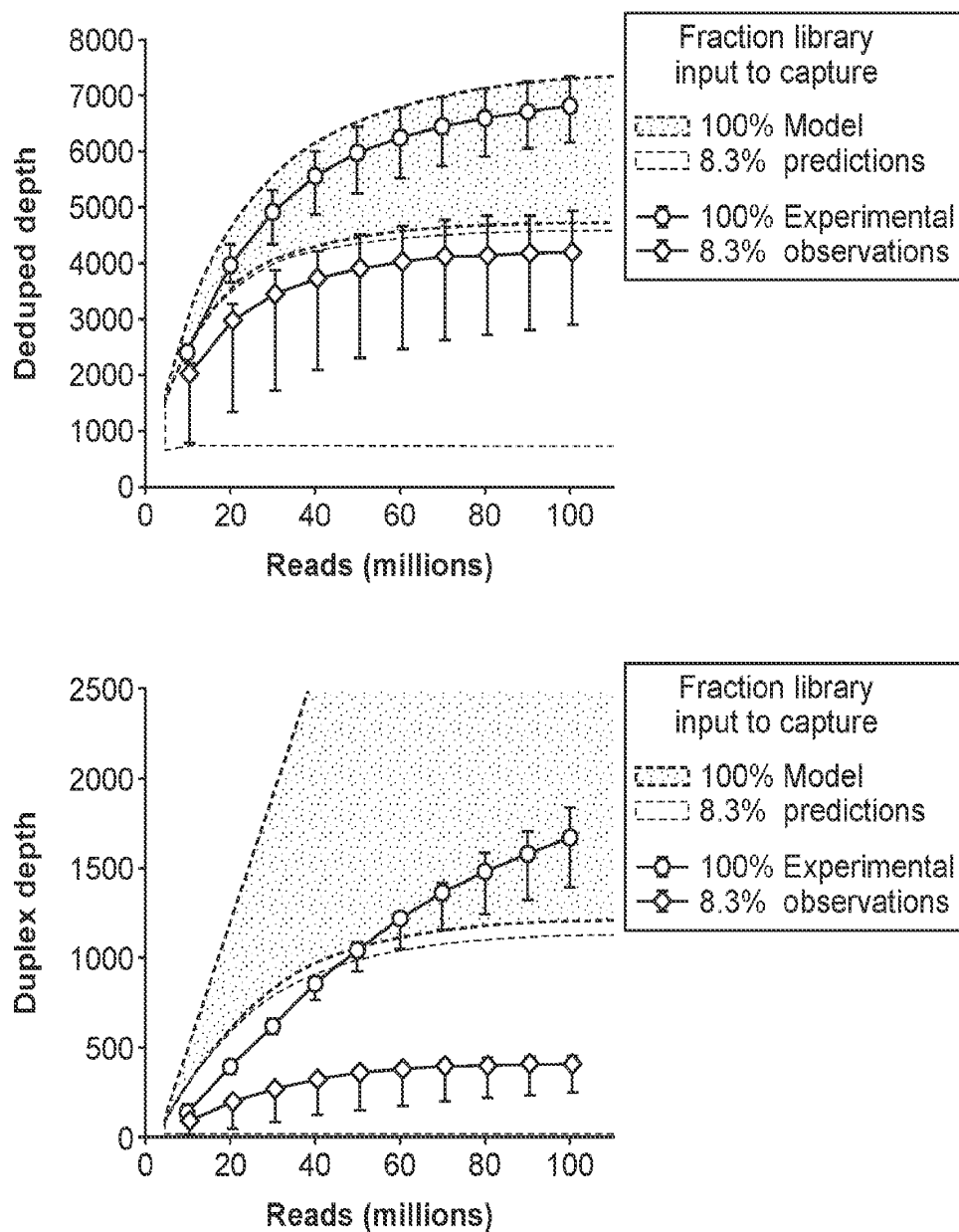
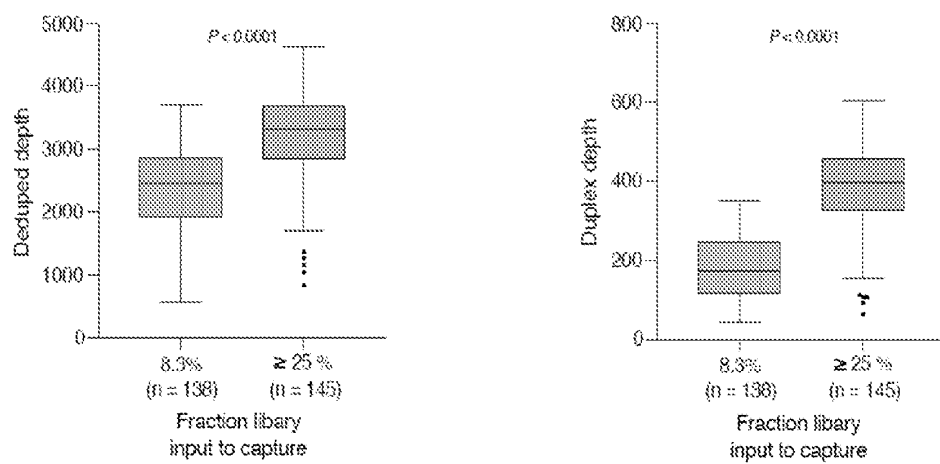


FIG. 11

Fig. 12

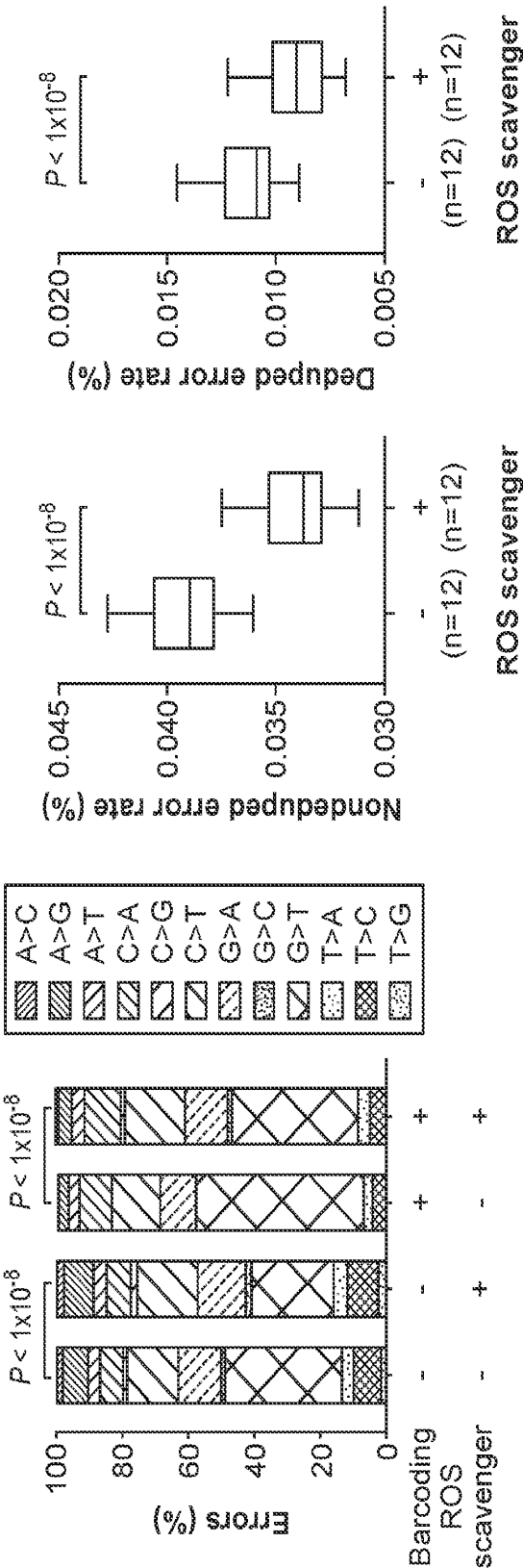


FIG. 13

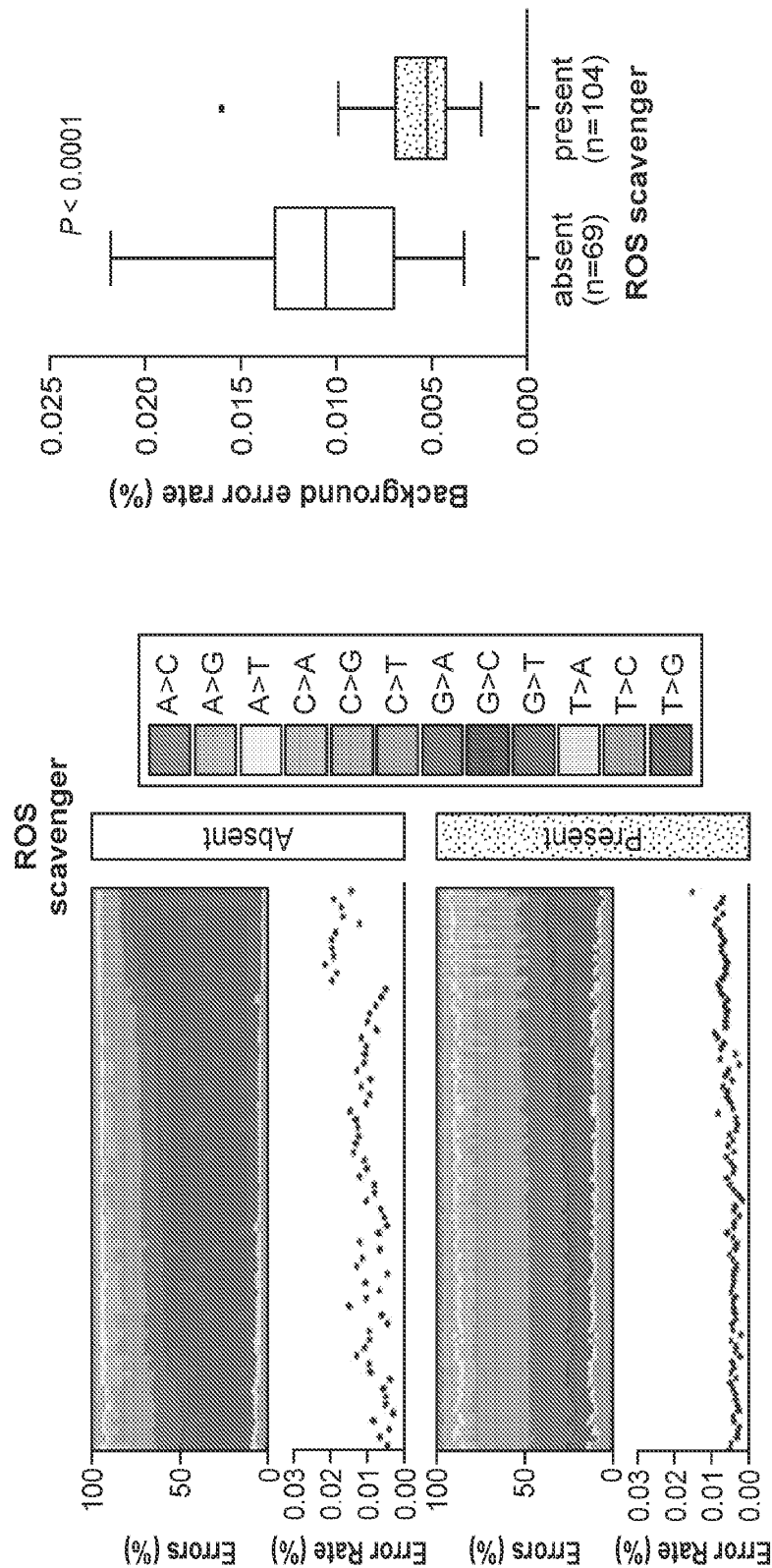


FIG. 14

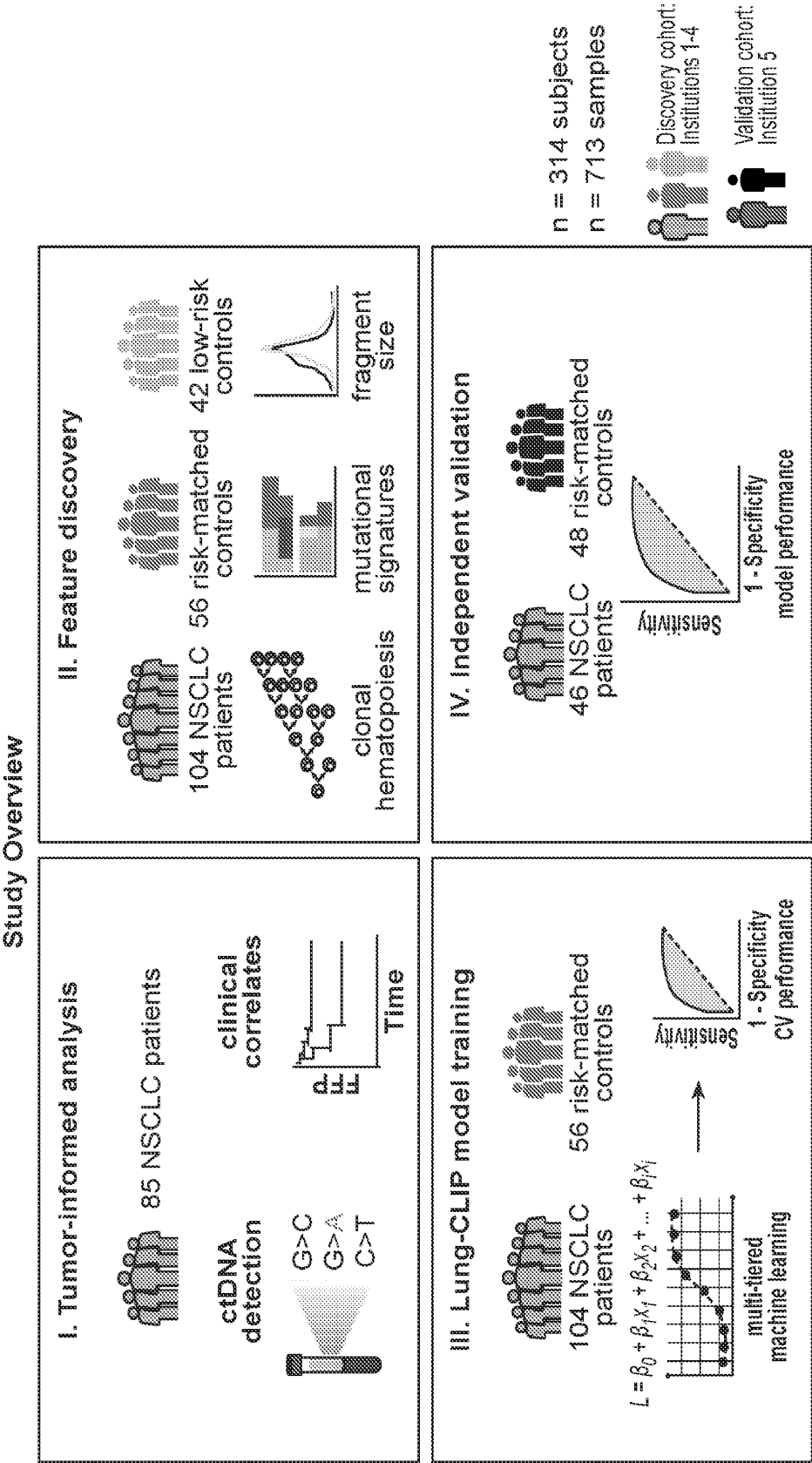


FIG. 15

Lung-CLIP discovery cohort					
Parameter	Tumor-informed NSCLC patients n = 85	CLIP training NSCLC patients n = 104	Risk-matched controls n = 56	Low-risk controls ^b n = 42	P-value ^d
Gender					0.87
Male	50 (59%)	63 (61%)	35 (62%)	22 (52%)	0.76
Female	35 (41%)	41 (39%)	21 (38%)	20 (48%)	
Age (years)					0.09
Age (years)	70 (42-87)	70 (42-87)	69 (54-83)	45 (22-70)	
Smoking					0.81
Smoking	64 (75%)	83 (80%)	56 (100%)	1 (2%)	
Yes	21 (25%)	21 (20%)	41 (98%)	41 (98%)	0.81
No	30 (0-135)	30 (0-135)	40 (20-136)	-	
Stage^a					0.81
Stage ^a	15 (18%)	21 (20%)	-	-	
IA	33 (39%)	28 (27%)	-	-	0.81
IB	9 (11%)	12 (12%)	-	-	
IIA	12 (14%)	16 (15%)	-	-	0.81
IIB	12 (14%)	17 (16%)	-	-	
IIIA	4 (5%)	10 (10%)	-	-	0.81
IIIB	63 (74%)	71 (68%)	-	-	
Histology					0.81
Histology	18 (21%)	23 (22%)	-	-	
Adenocarcinoma	2 (2%)	7 (7%)	-	-	0.81
Squamous	2 (2%)	3 (3%)	-	-	
Institution					0.81
Institution	53 (62%)	76 (73%)	56 (100%)	42 (100%)	
Stanford	18 (21%)	21 (20%)	-	-	0.81
Vanderbilt	14 (16%)	-	-	-	
Mayo Clinic	-	7 (7%)	-	-	0.81
MD Anderson	-	-	-	-	

NOS = not otherwise specified.

a = AJCC v7 staging.

b = Low-risk controls were considered for feature discovery and CH analysis only and were not used for Lung-CLIP model training.

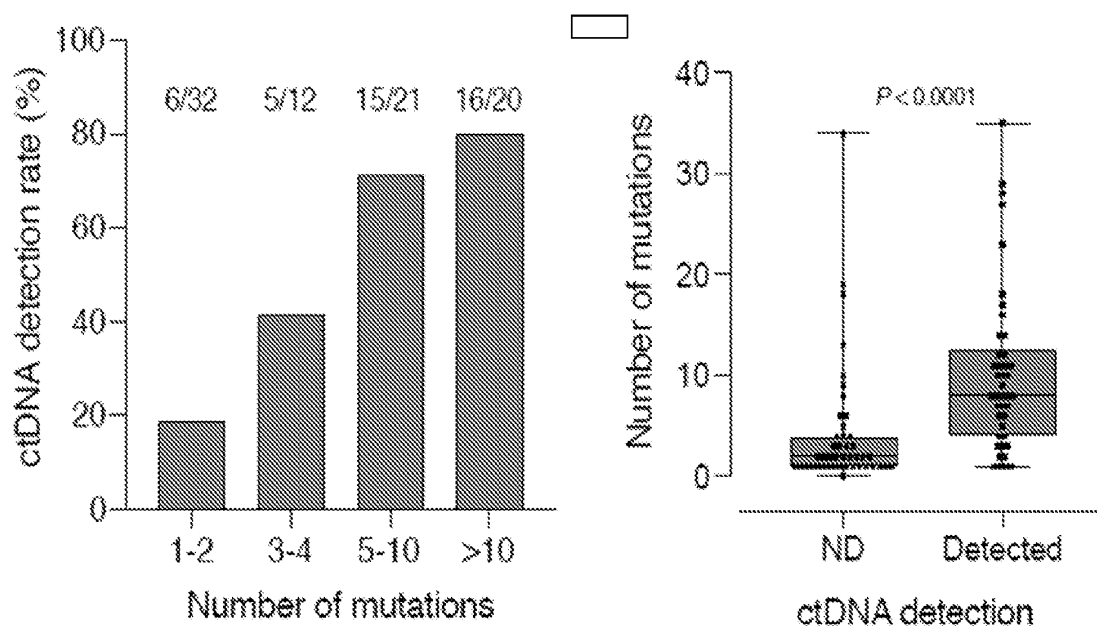
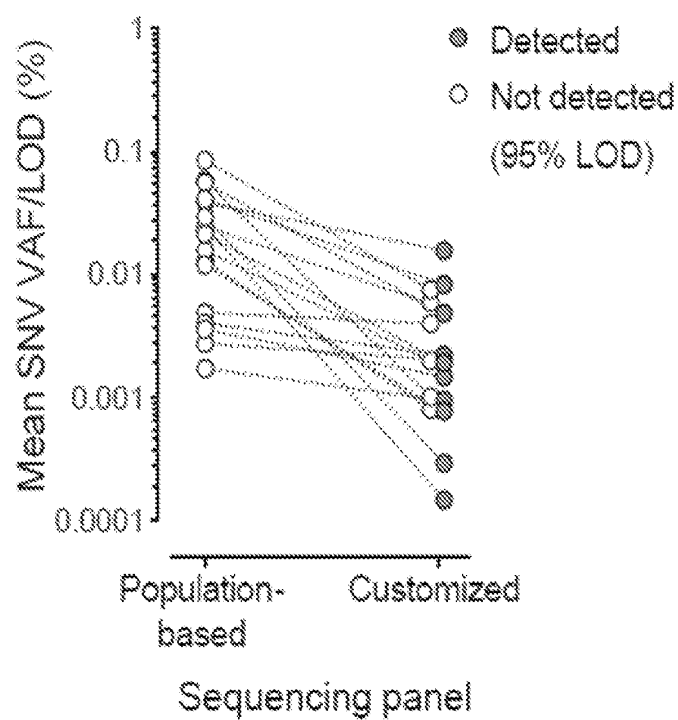
c = Sex was compared with a two-sided Fisher's Exact Test and continuous variables (age and pack-years) were compared with an un-paired two-sided t-test.

d = Lung CLIP NSCLC patients and risk-matched controls were compared.

Lung-CLIP validation cohort

Parameter	NSCLC patients n = 46	Risk-matched controls n = 48	P-value ^c
Sex			0.31
Sex	21 (46%)	28 (56%)	0.30
Male	25 (54%)	20 (44%)	
Age (years)			0.81
Age (years)	69 (52-83)	66 (55-78)	
Smoking			0.81
Smoking	46 (100%)	48 (100%)	
Yes	40 (20-165)	39 (23-132)	0.81
No	22 (48%)	-	
Stage^a			0.81
Stage ^a	10 (22%)	-	
IA	9 (20%)	-	0.81
IB	2 (4%)	-	
IIA	3 (7%)	-	0.81
IIB	36 (78%)	-	
Histology			0.81
Histology	10 (22%)	-	
Adenocarcinoma	46 (100%)	48 (100%)	0.81
Squamous	-	-	
Institution			0.81
Institution	-	-	
Harvard	-	-	0.81
Harvard	-	-	

FIG. 16

Fig. 17**Fig. 18**

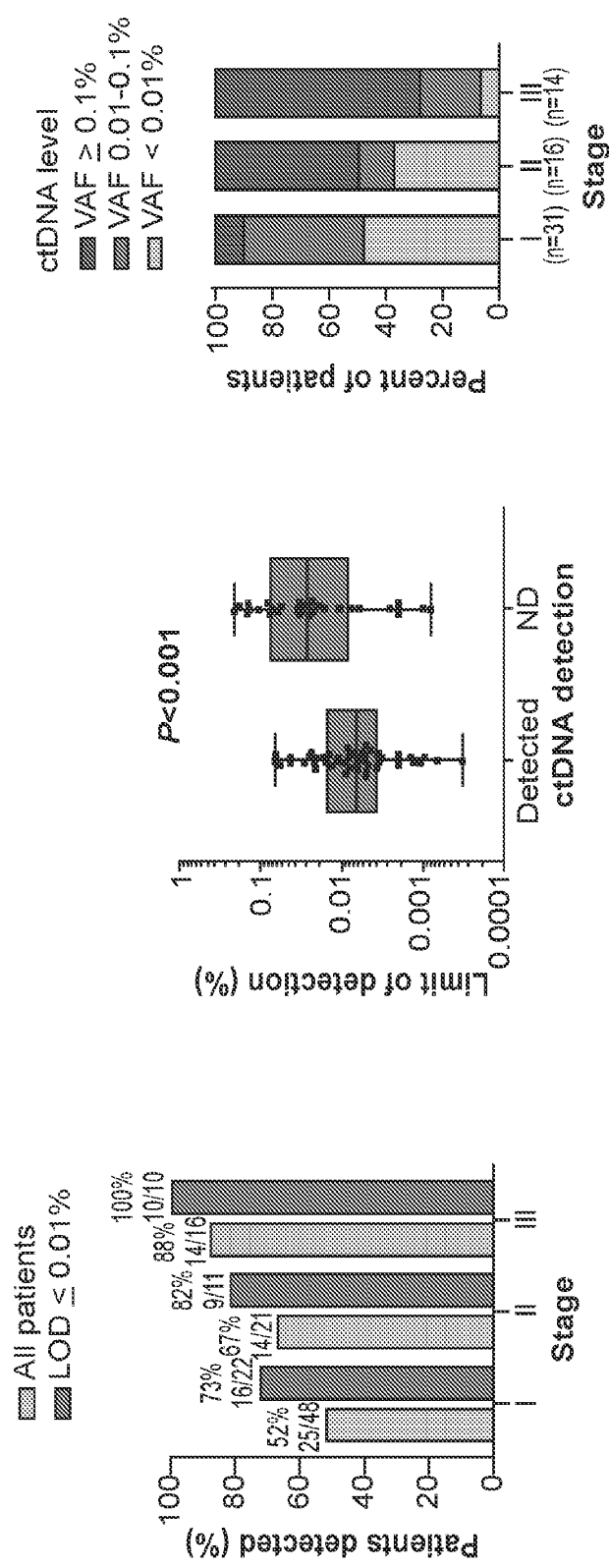
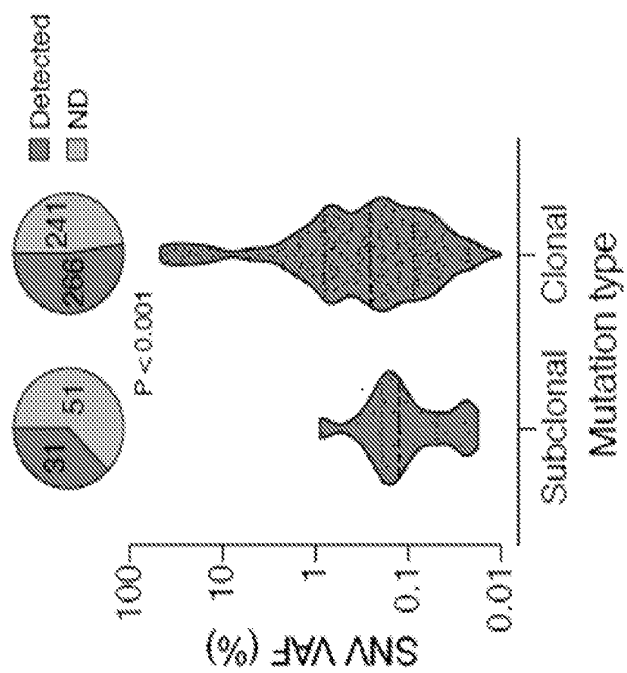


FIG. 19

Fig. 20

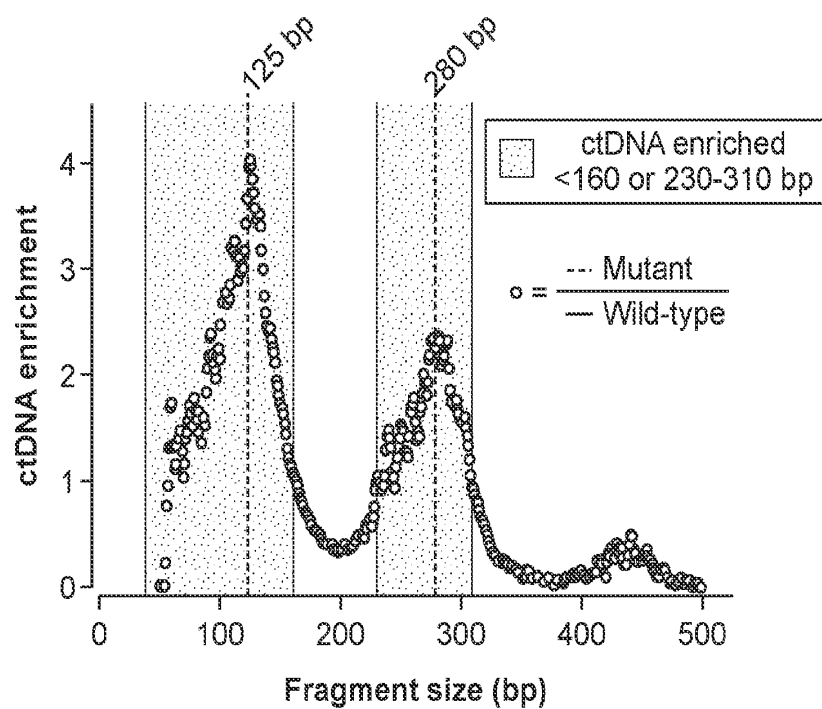
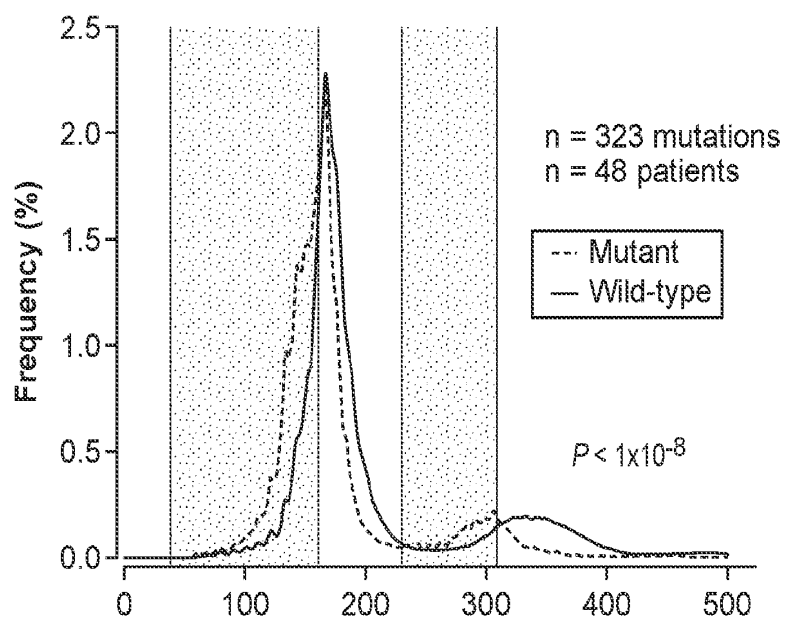
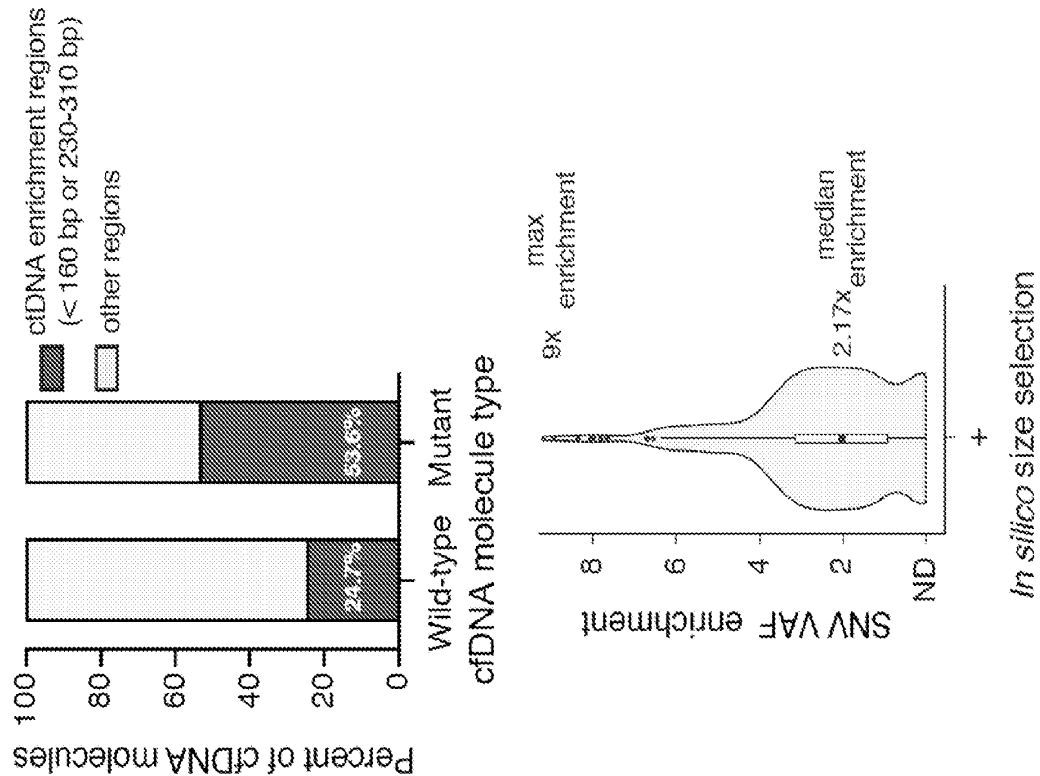


FIG. 21

Fig. 21 (cont.)



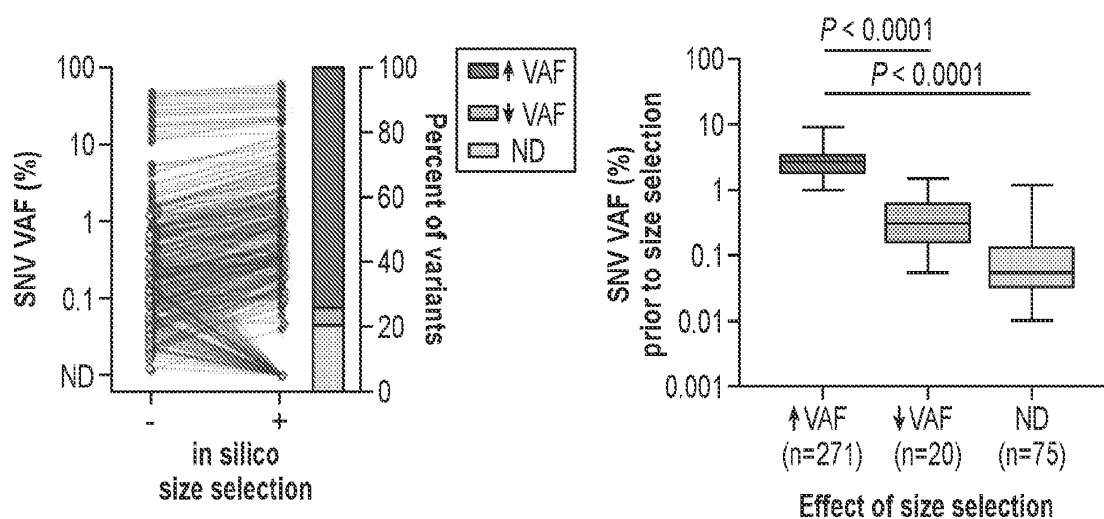


FIG. 22

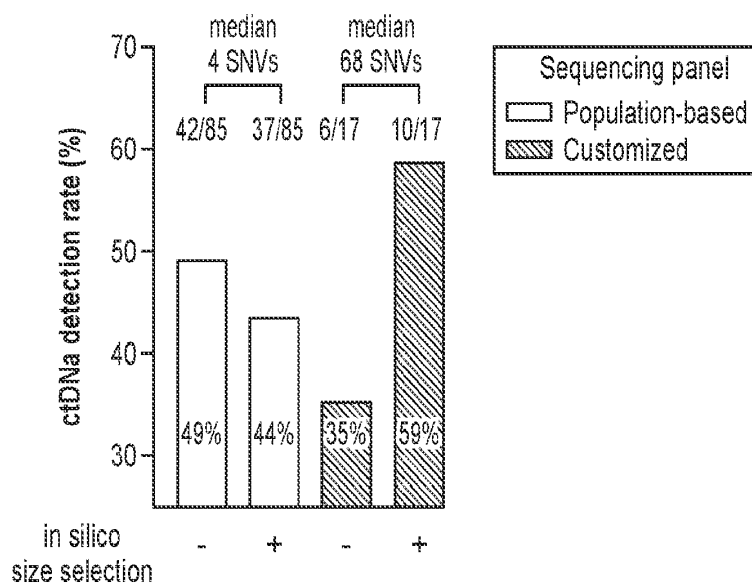
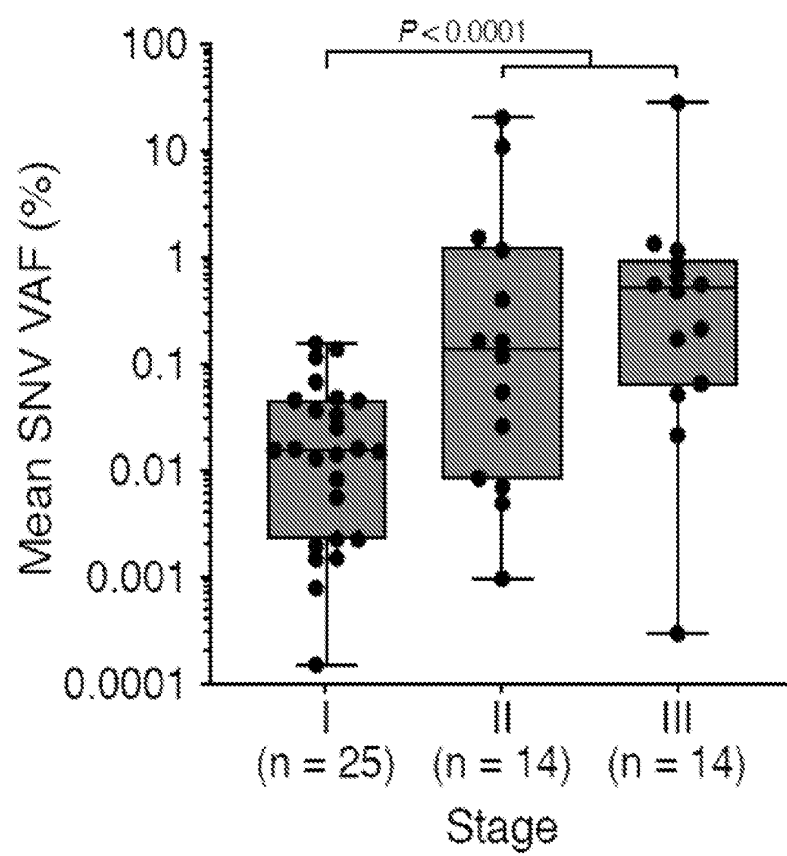


FIG. 23

Fig. 24

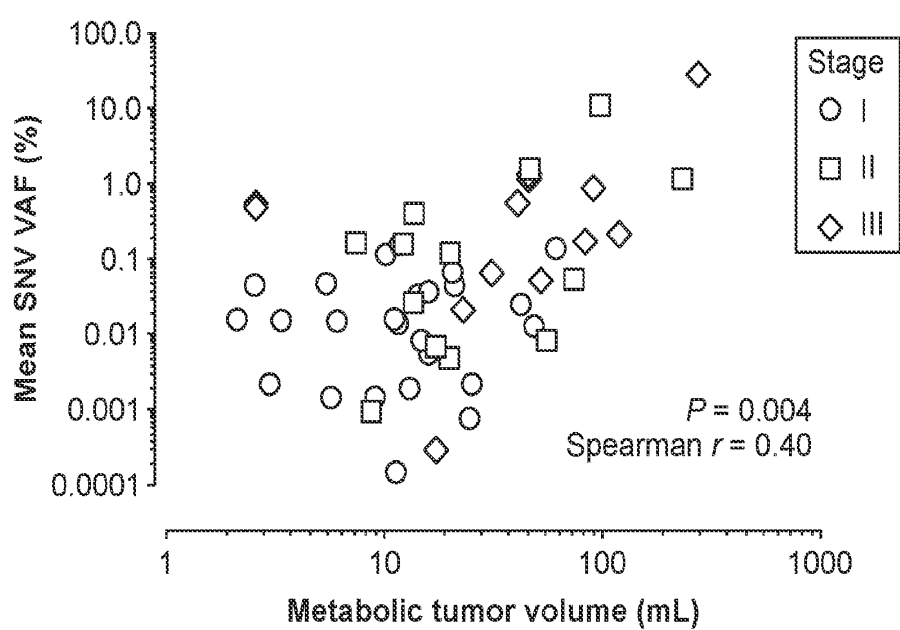


FIG. 25

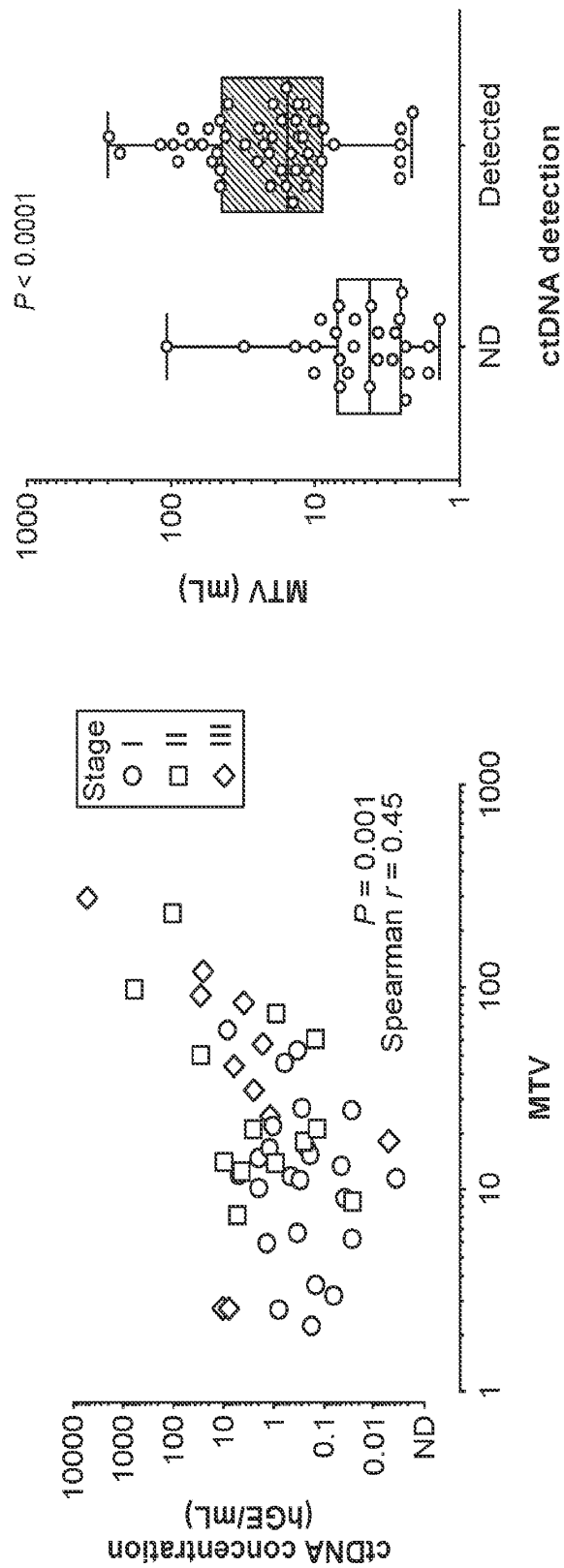
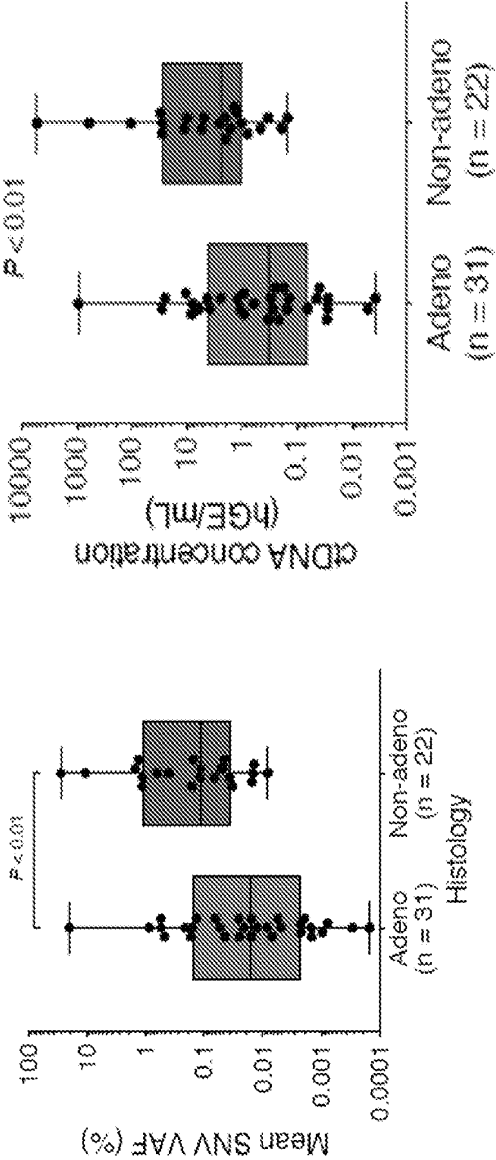


FIG. 26

Fig. 27



Predictors of ctDNA levels	
Factor	Multivariable P-value
Tumor Volume	< 1x10 ⁻⁴
Median MTV (mL)	
Histology	< 1x10 ⁻⁶
Adeno	
Non-Adeno	
Stage	0.004
I	
II	
III	

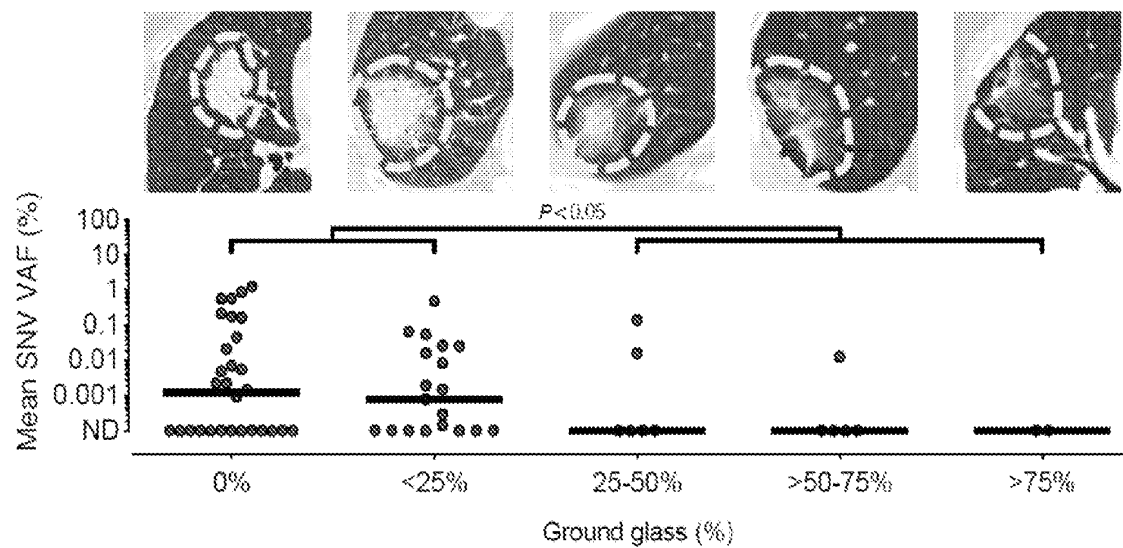
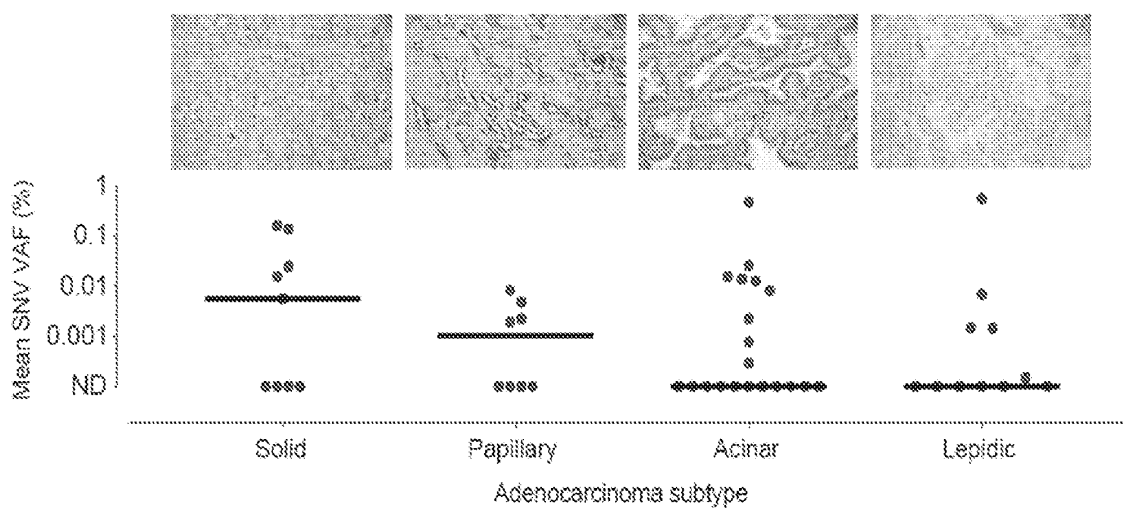
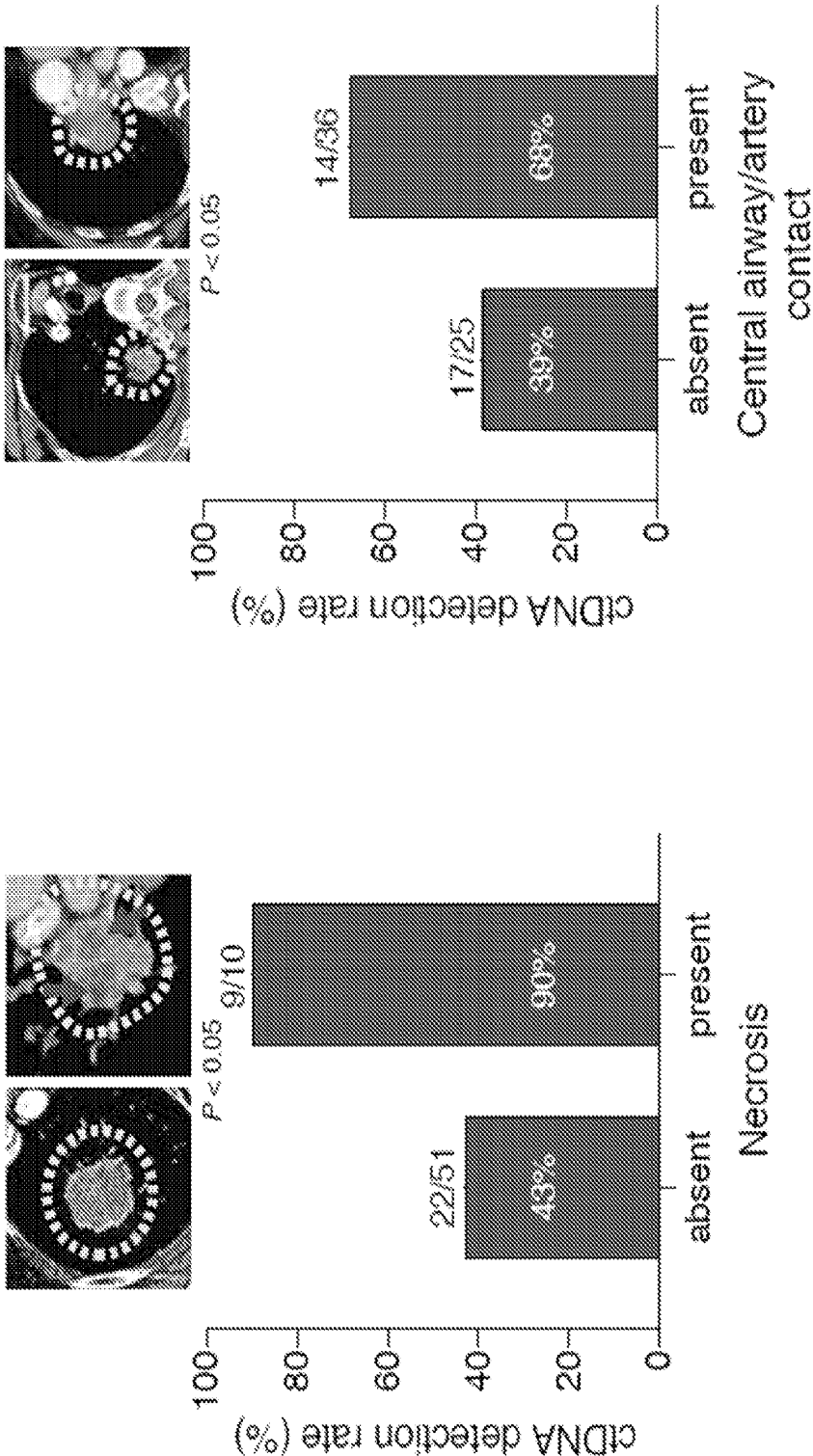
Fig. 28**Fig. 29**

Fig. 30



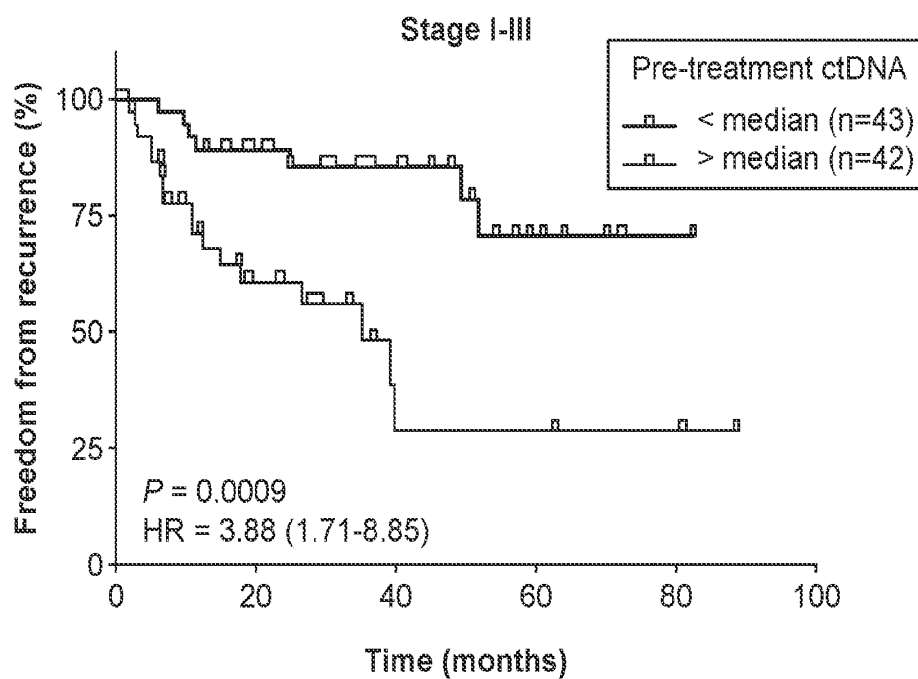


FIG. 31

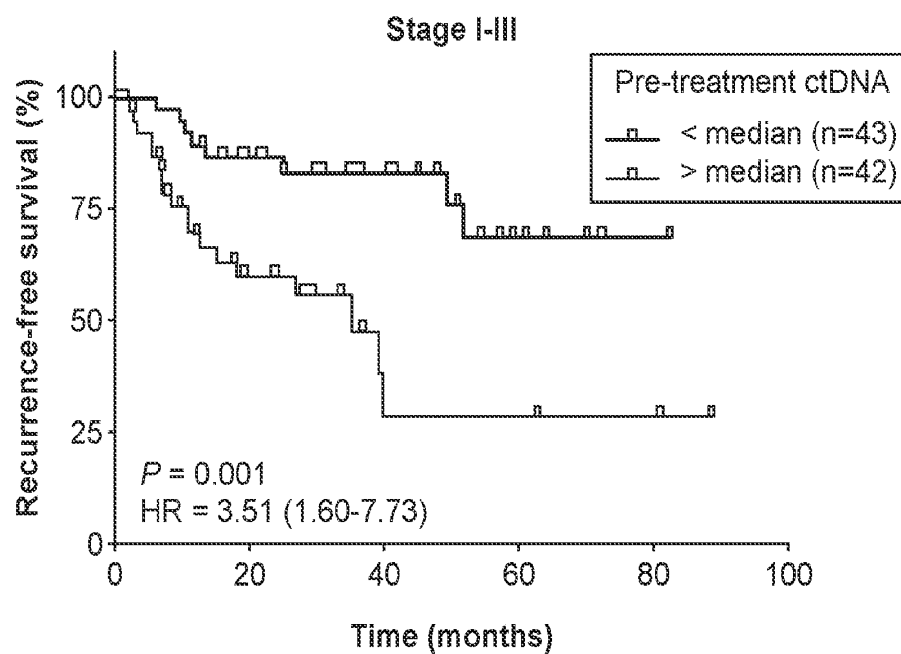


FIG. 32

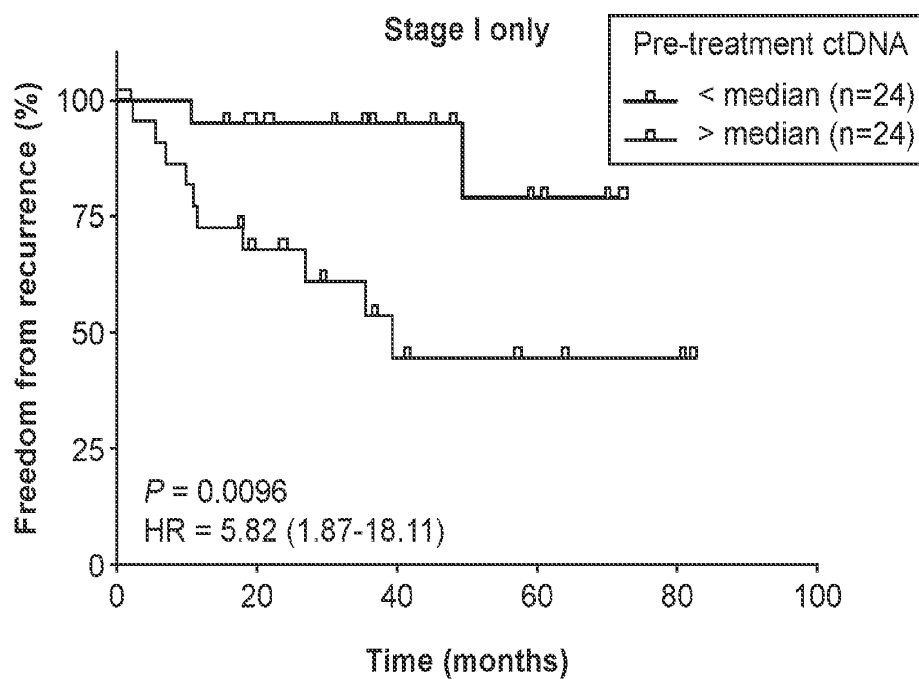


FIG. 33

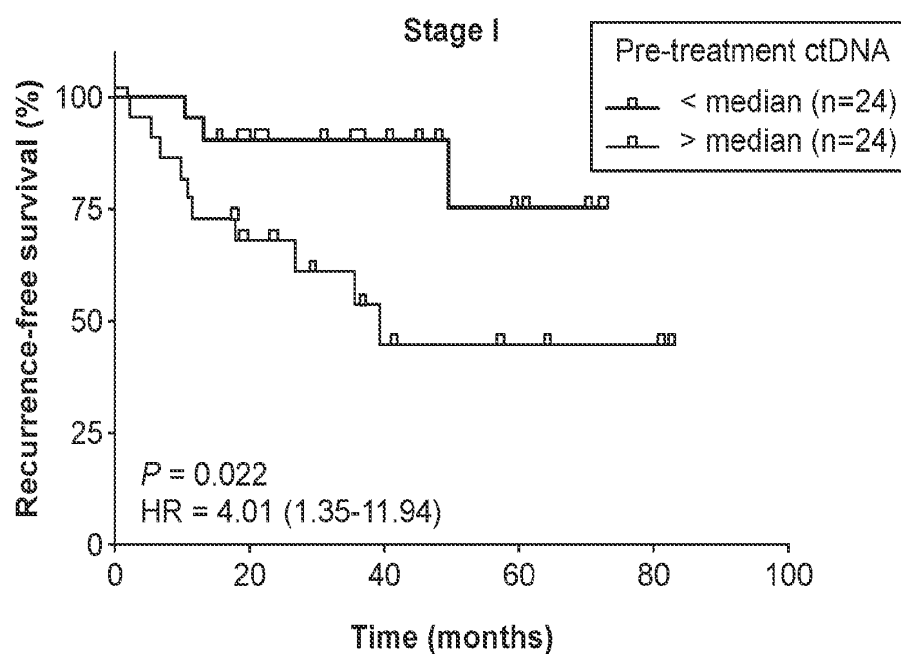
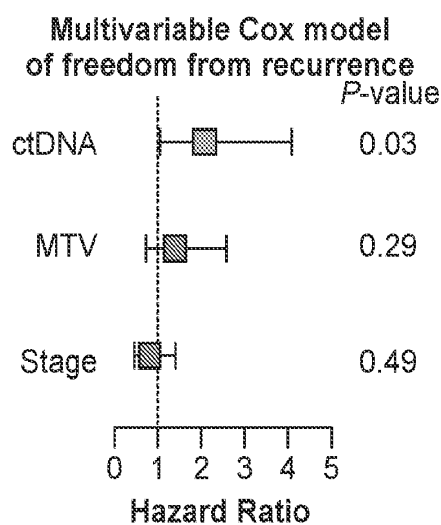


FIG. 34



Parameter	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Freedom from recurrence				
ctDNA - log10(VAF)	2.14 (1.38 to 3.30)	0.0006	2.08 (1.06 to 4.08)	0.032
Metabolic tumor volume - log10(mL)	1.88 (1.16 to 3.06)	0.011	1.40 (0.75 to 2.59)	0.286
Stage (I-III)	1.42 (0.96 to 2.12)	0.082	0.82 (0.47 to 1.43)	0.488
Freedom from metastasis				
ctDNA - log10(VAF)	2.29 (1.37 to 3.83)	0.0015	2.24 (1.05 to 4.79)	0.036
Metabolic tumor volume - log10(mL)	1.91 (1.11 to 3.28)	0.019	1.33 (0.68 to 2.61)	0.402
Stage (I-III)	1.48 (0.94 to 2.33)	0.093	0.85 (0.46 to 1.55)	0.591
Recurrence free survival				
ctDNA - log10(VAF)	2.00 (1.32 to 3.02)	0.0011	1.80 (0.97 to 3.35)	0.063
Metabolic tumor volume - log10(mL)	1.89 (1.19 to 3.01)	0.0073	1.51 (0.84 to 2.72)	0.173
Stage (I-III)	1.40 (0.95 to 2.06)	0.085	0.84 (0.50 to 1.43)	0.529
Metastasis free survival				
ctDNA - log10(VAF)	2.06 (1.27 to 3.32)	0.0033	1.84 (0.93 to 3.64)	0.081
Metabolic tumor volume - log10(mL)	1.91 (1.14 to 3.18)	0.0134	1.47 (0.78 to 2.79)	0.237
Stage (I-III)	1.43 (0.93 to 2.21)	0.106	0.88 (0.50 to 1.55)	0.647
Overall survival				
ctDNA - log10(VAF)	1.50 (0.93 to 2.42)	0.095	1.70 (0.75 to 3.83)	0.201
Metabolic tumor volume - log10(mL)	1.86 (1.06 to 3.24)	0.029	1.75 (0.75 to 4.08)	0.191
Stage (I-III)	0.95 (0.53 to 1.72)	0.875	0.58 (0.27 to 1.25)	0.164

Cox Proportional-Hazards models

FIG. 35

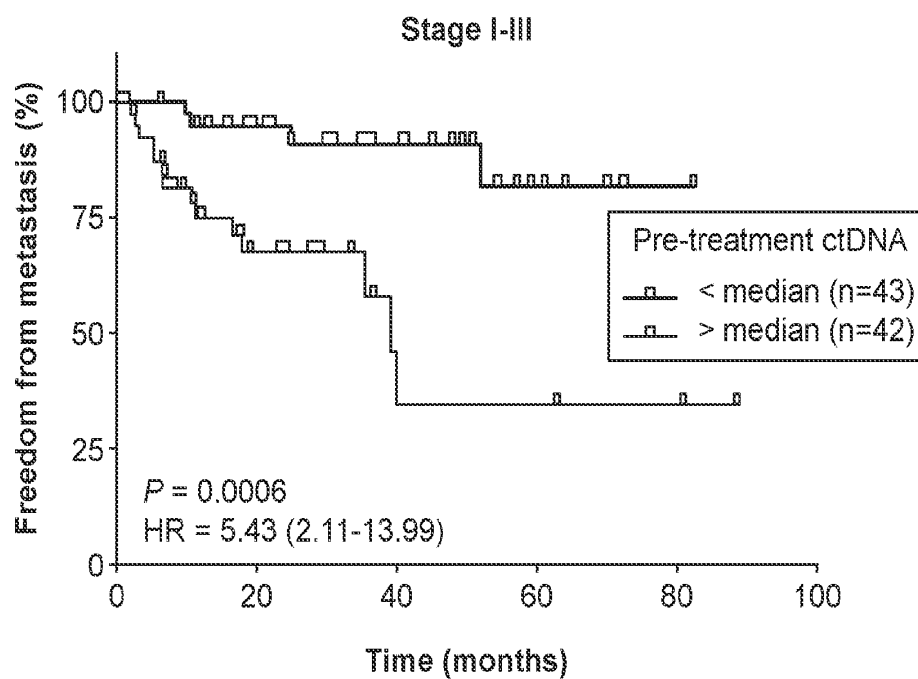


FIG. 36

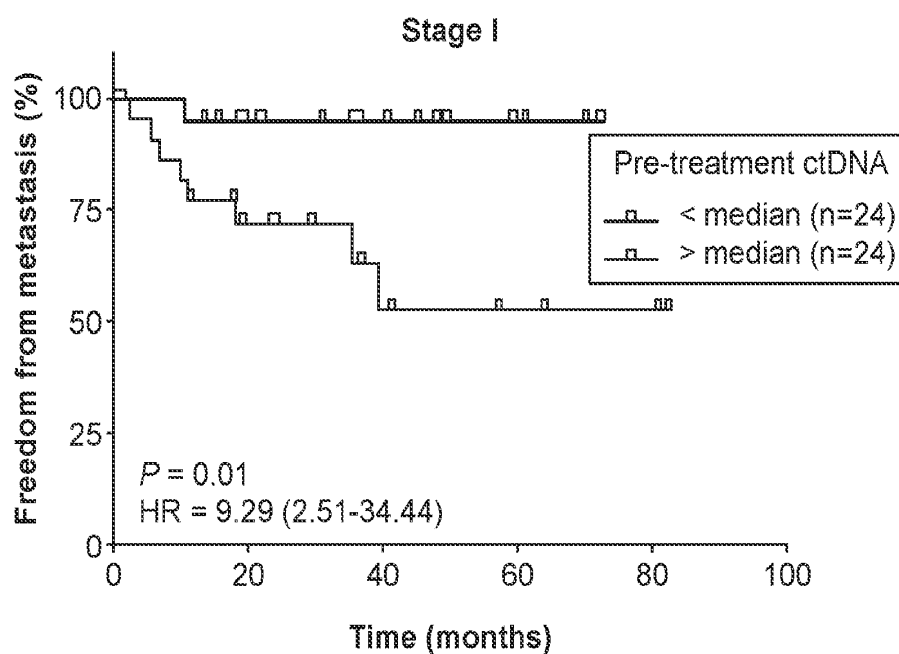


FIG. 37

Fig. 38

		High ctDNA		Low ctDNA	
Stage	IB	IB	IB	IB	IA
Histology	Adenocarcinoma	Squamous	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Tumor diameter	3.4 cm	3.5 cm	5.0 cm	2.9 cm	
Pre-tx ctDNA	0.04%	0.014%	ctDNA not detected	ctDNA not detected	ctDNA not detected
Follow up	Skeletal metastasis at 207 days	Peritoneal carcinomatosis at 547 days	Alive without disease at 1,461 days	Alive without disease at 1,160 days	

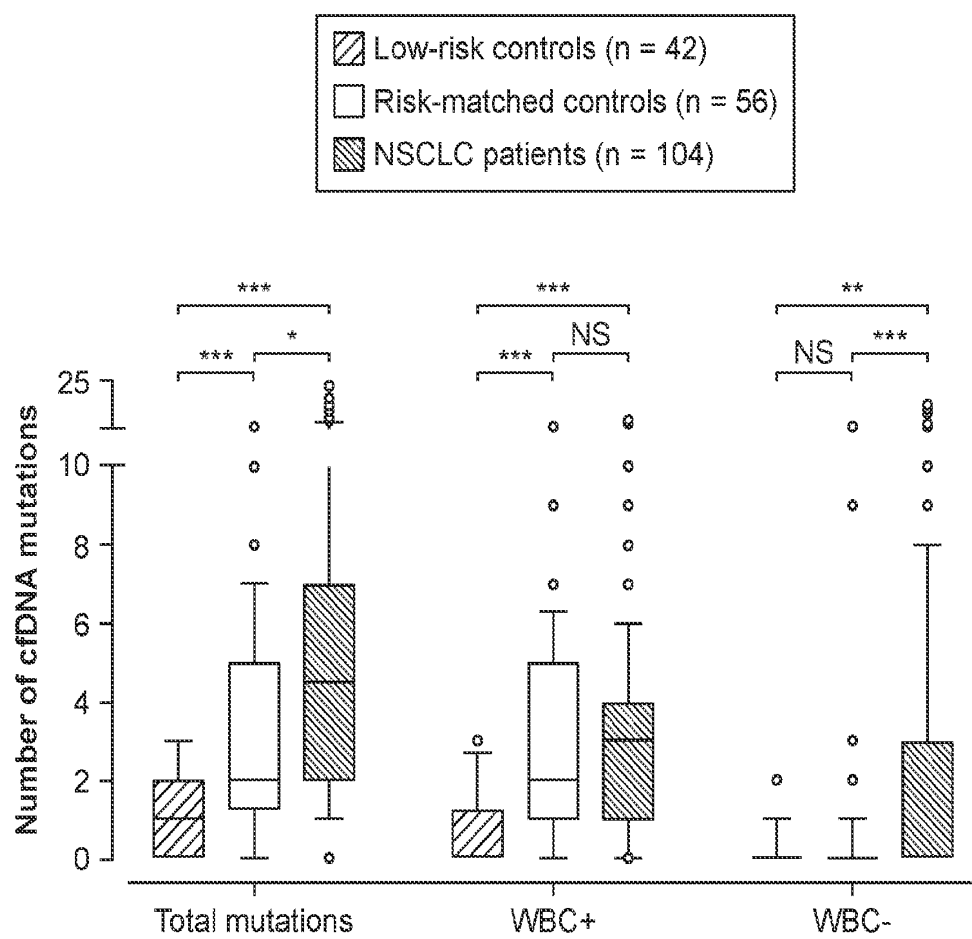


FIG. 39

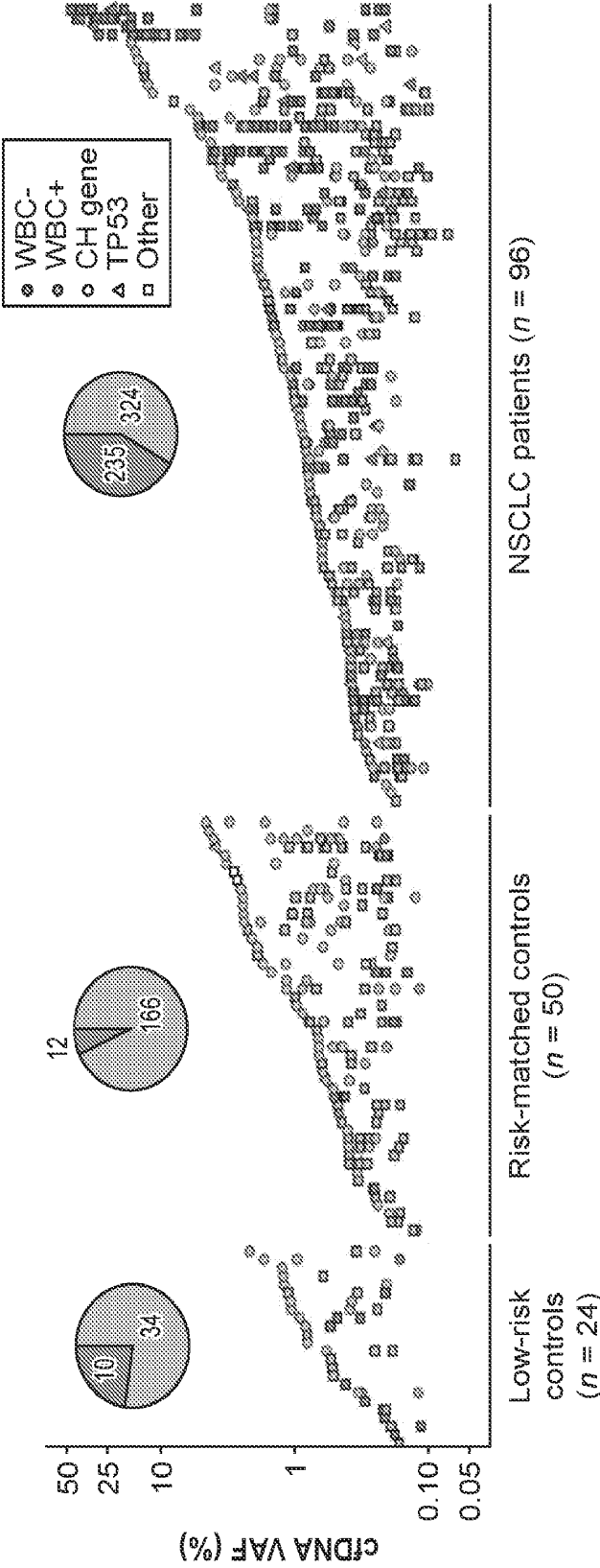


FIG. 40

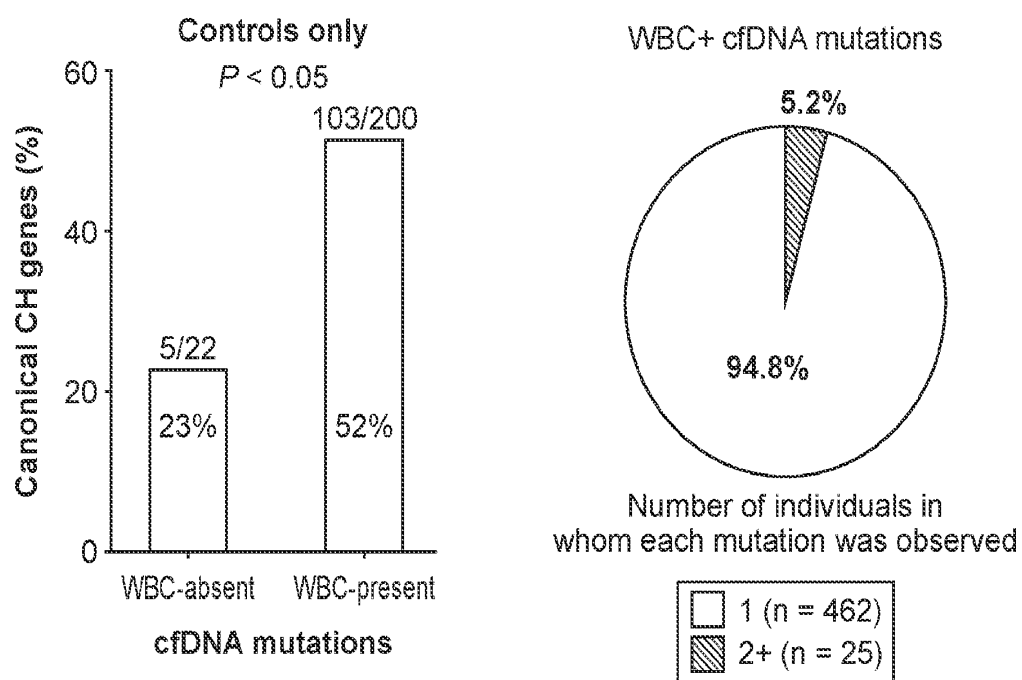


FIG. 41

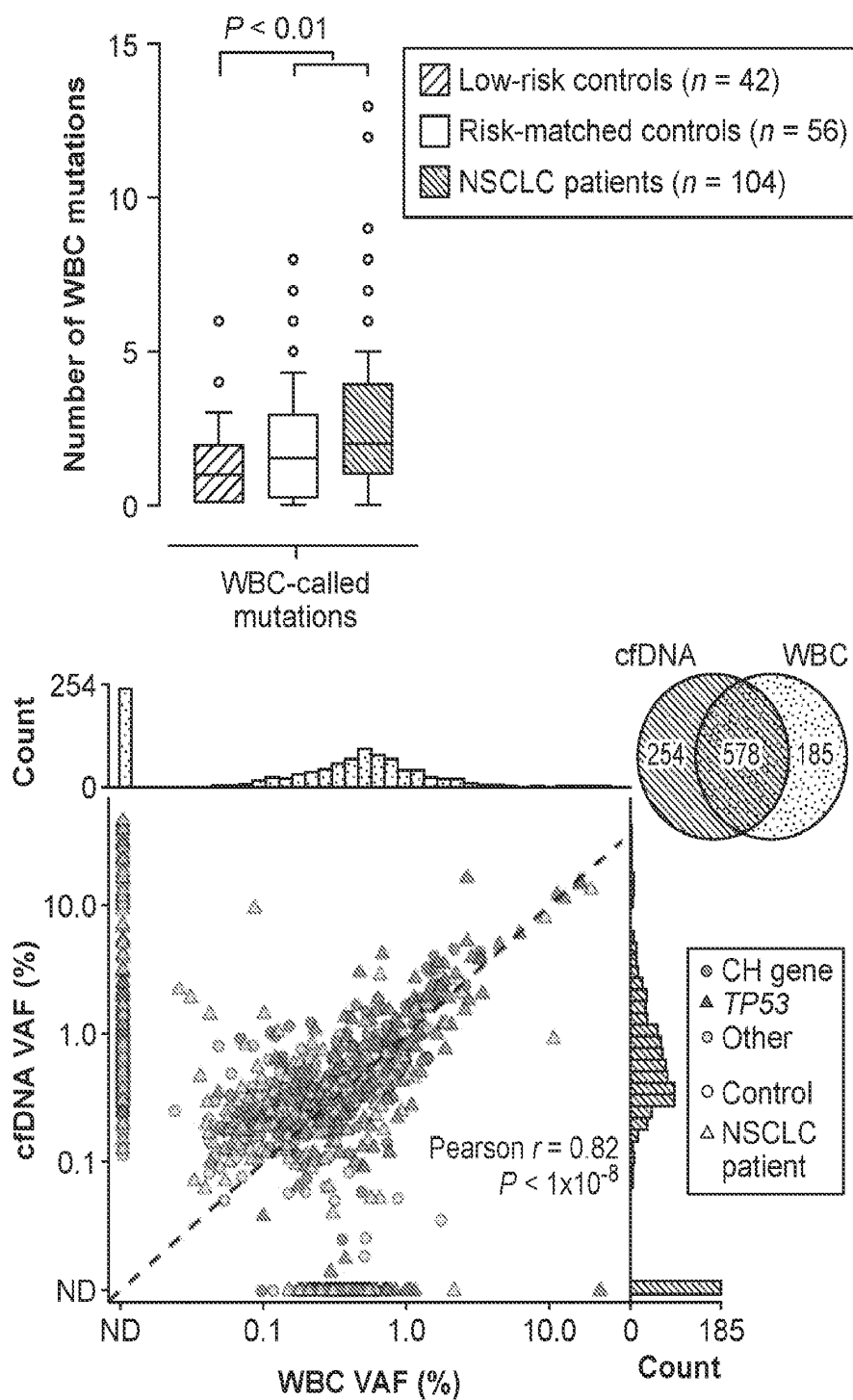
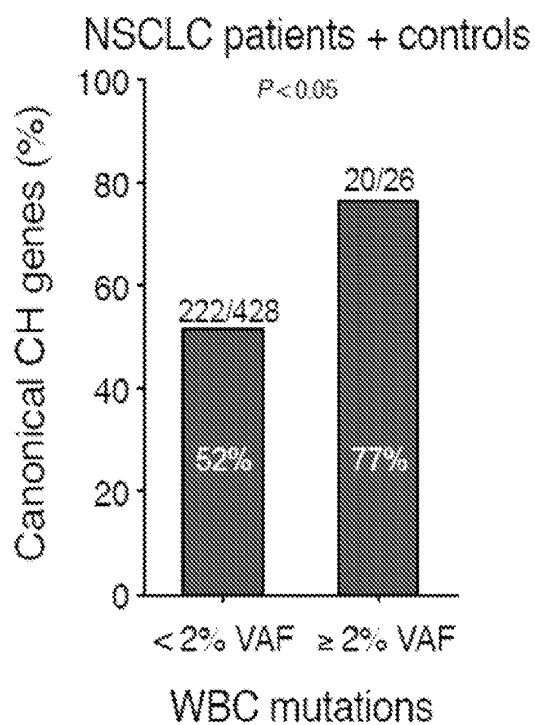
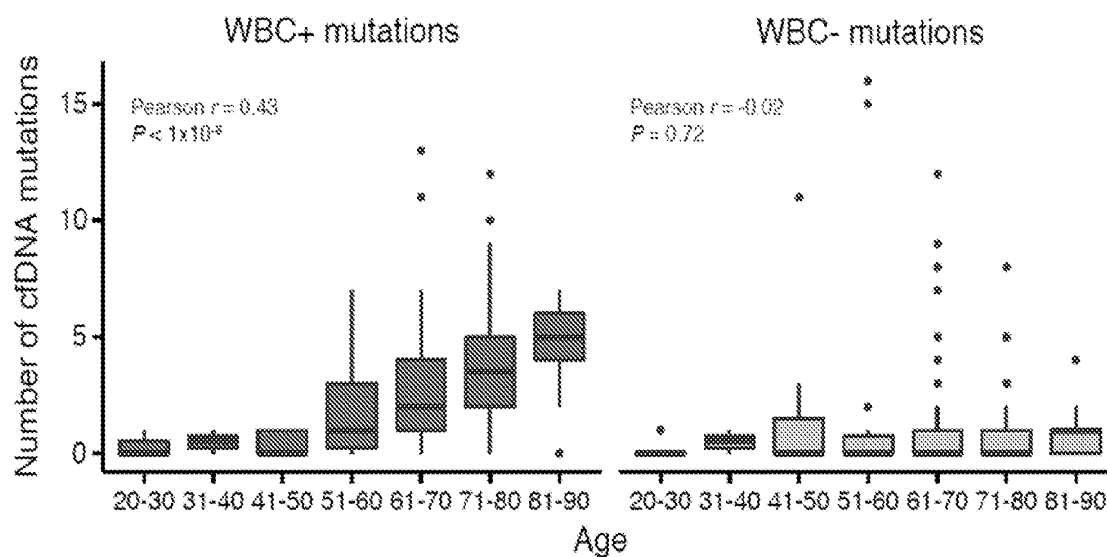


FIG. 42

SUBSTITUTE SHEET (RULE 26)

Fig. 43**Fig. 44**

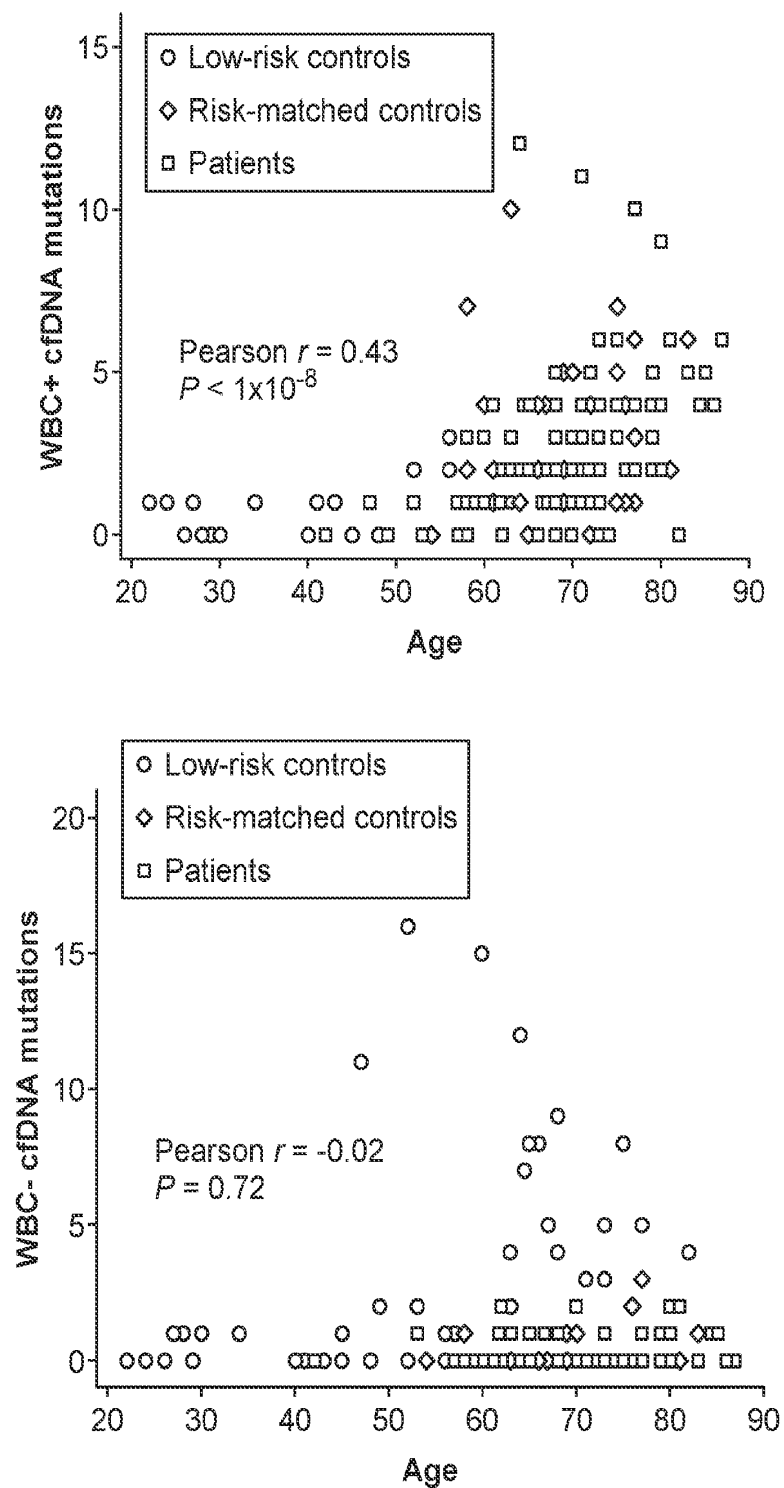


FIG. 45

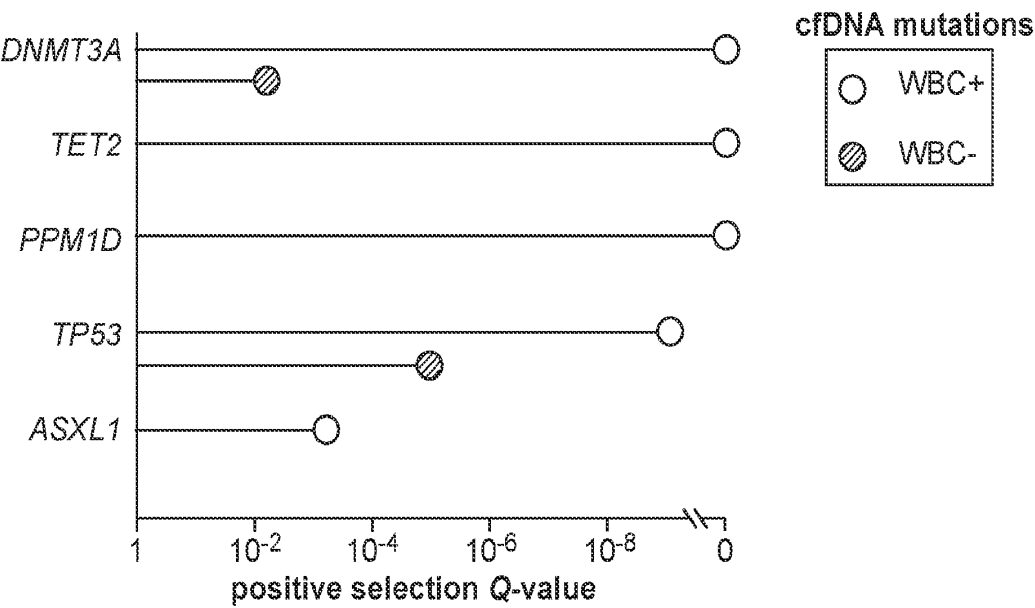
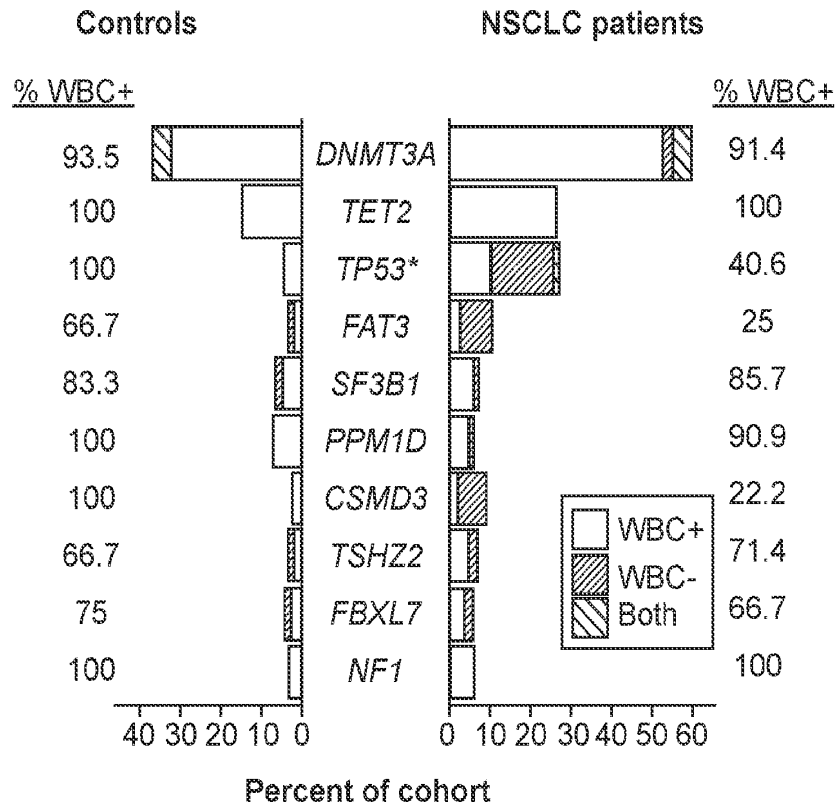
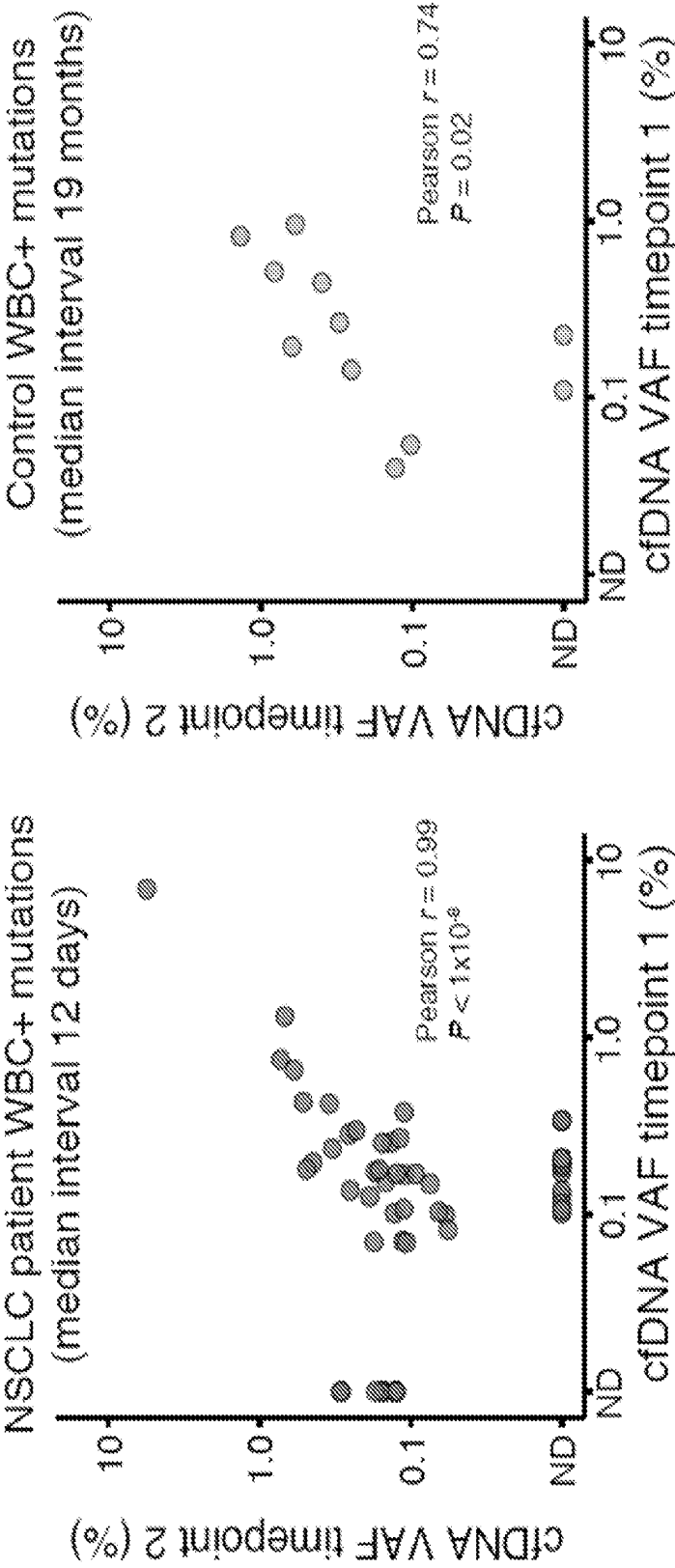


FIG. 46

Fig. 47



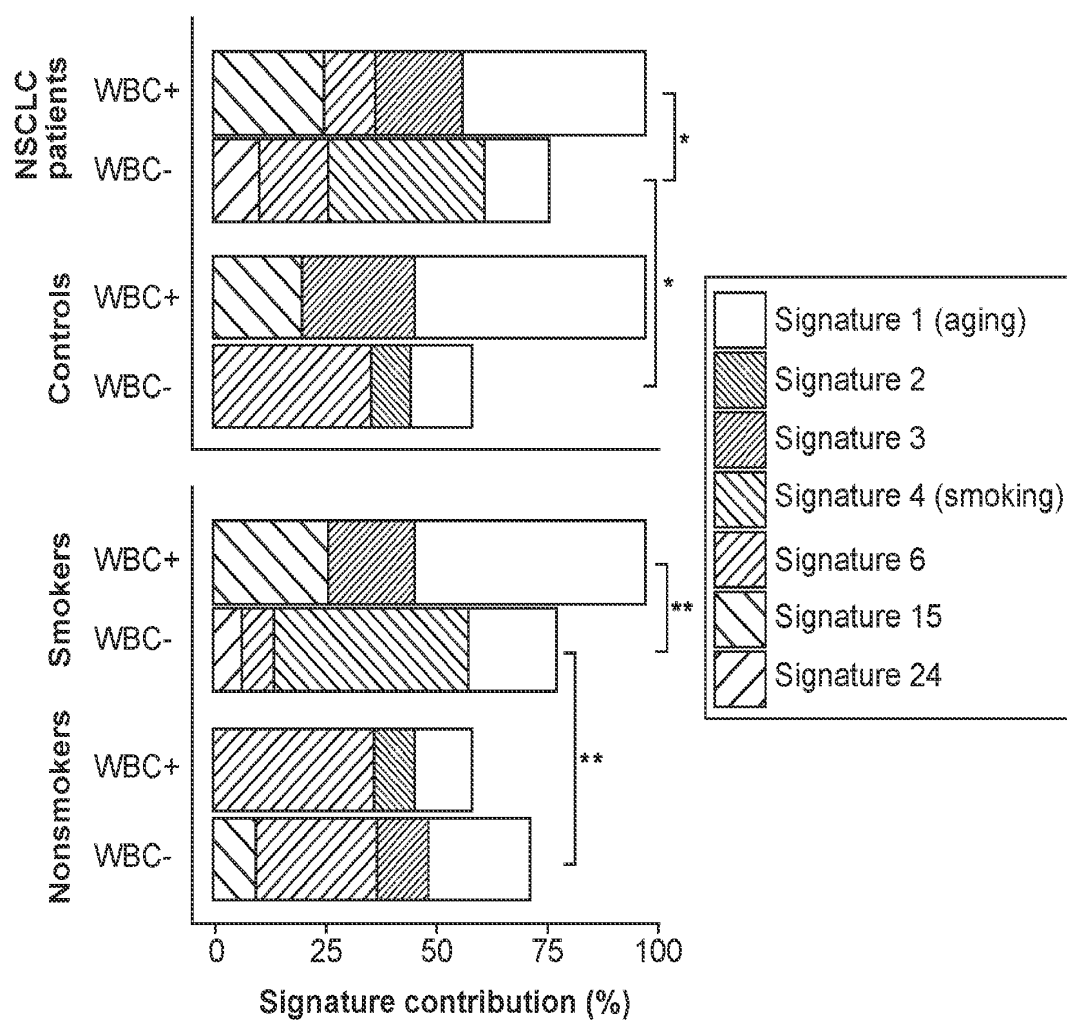


FIG. 48

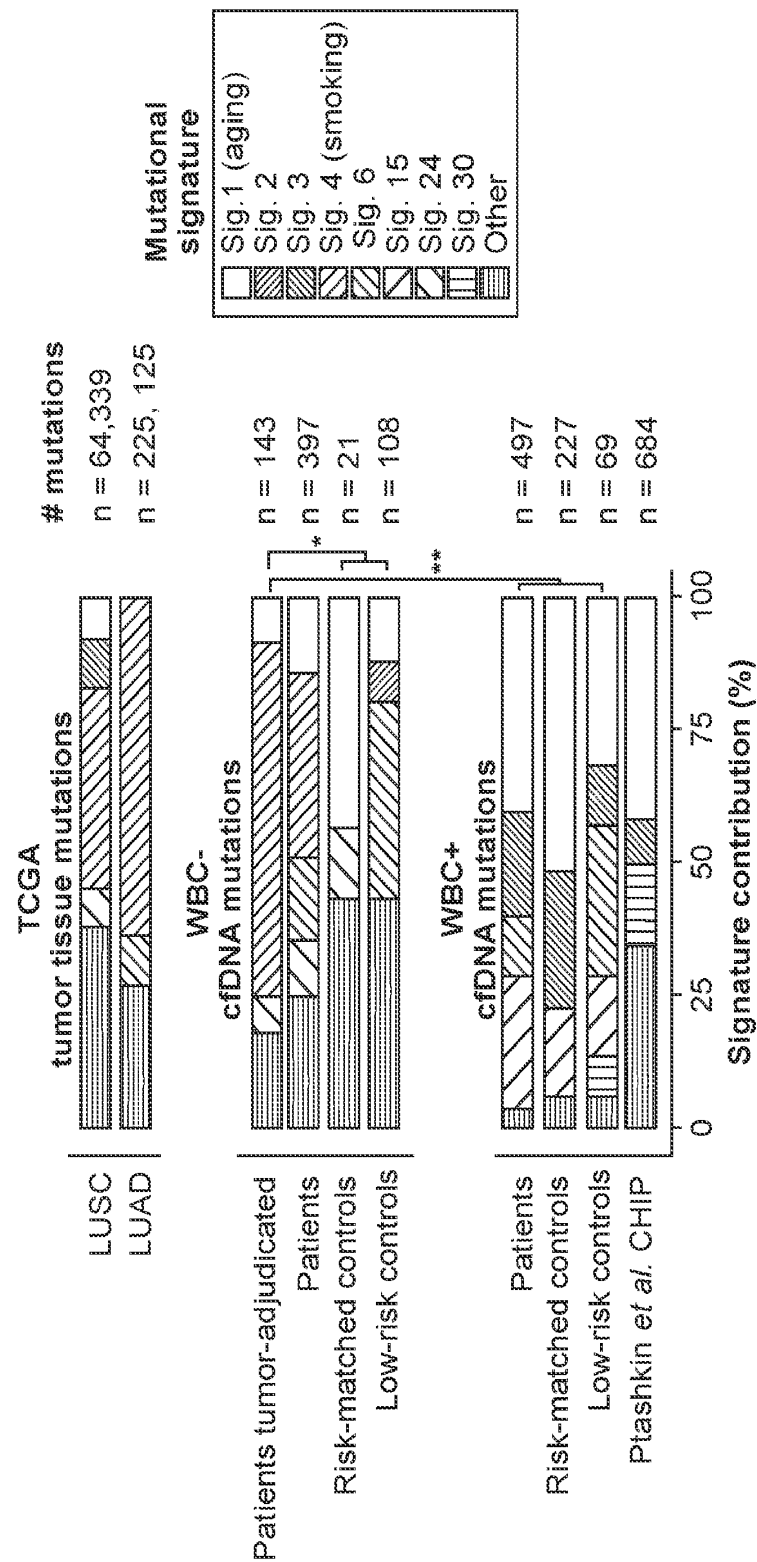


FIG. 49

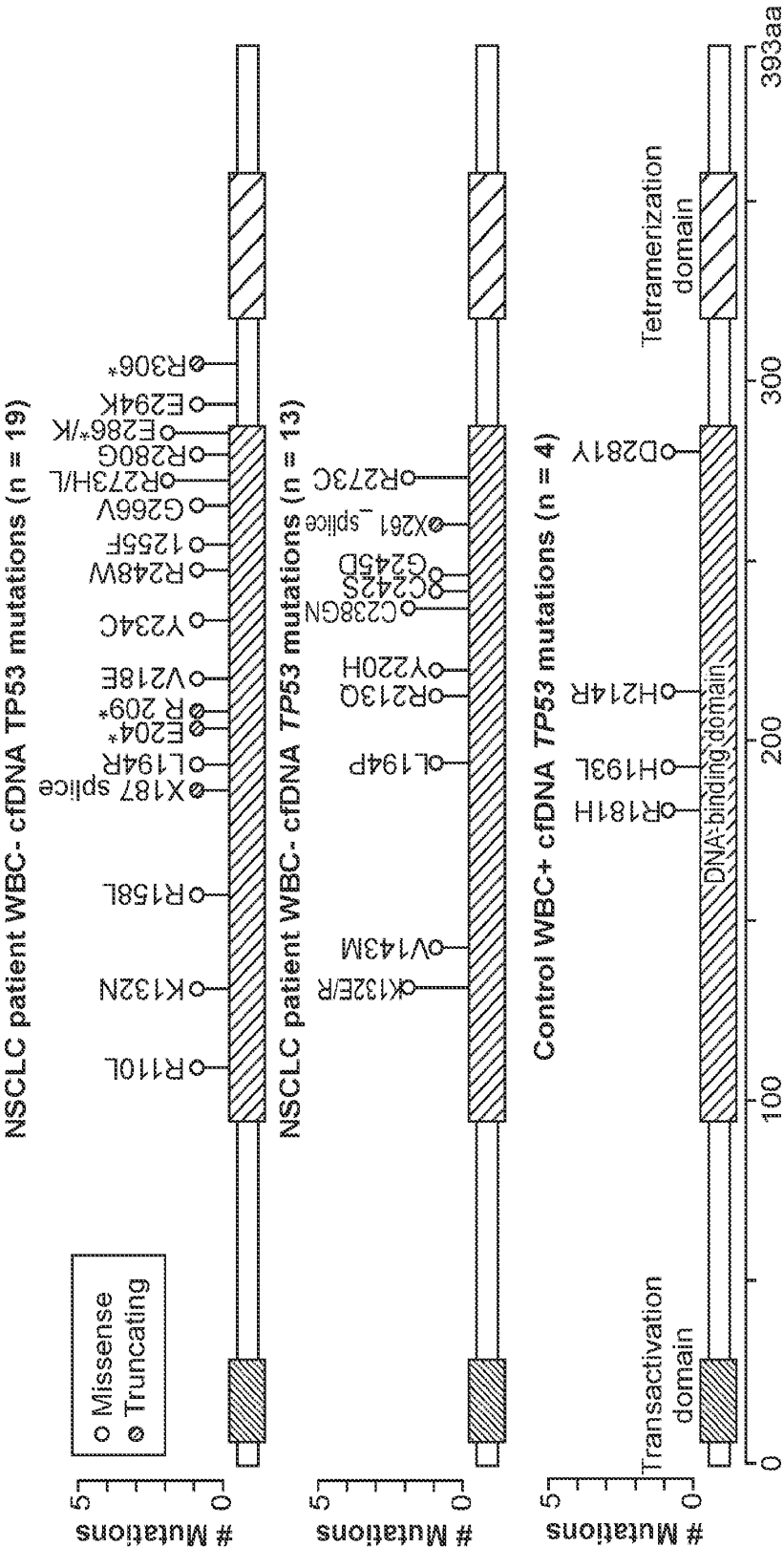


FIG. 50

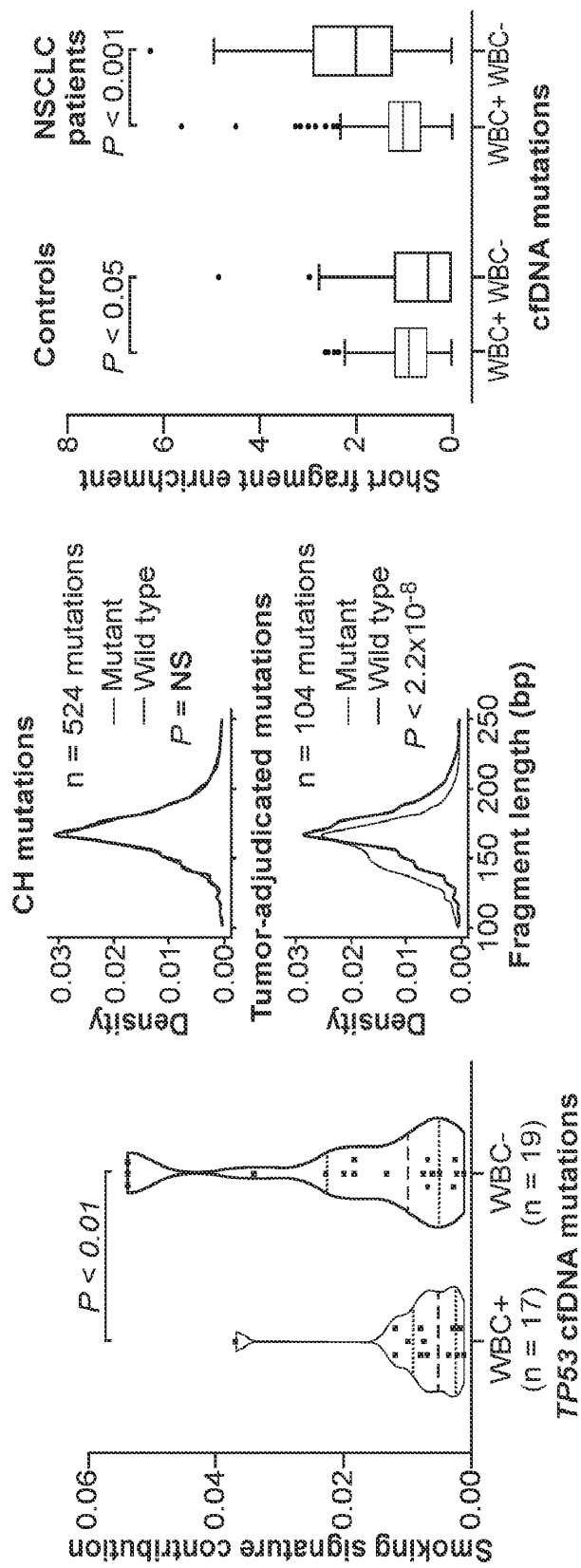


FIG. 51

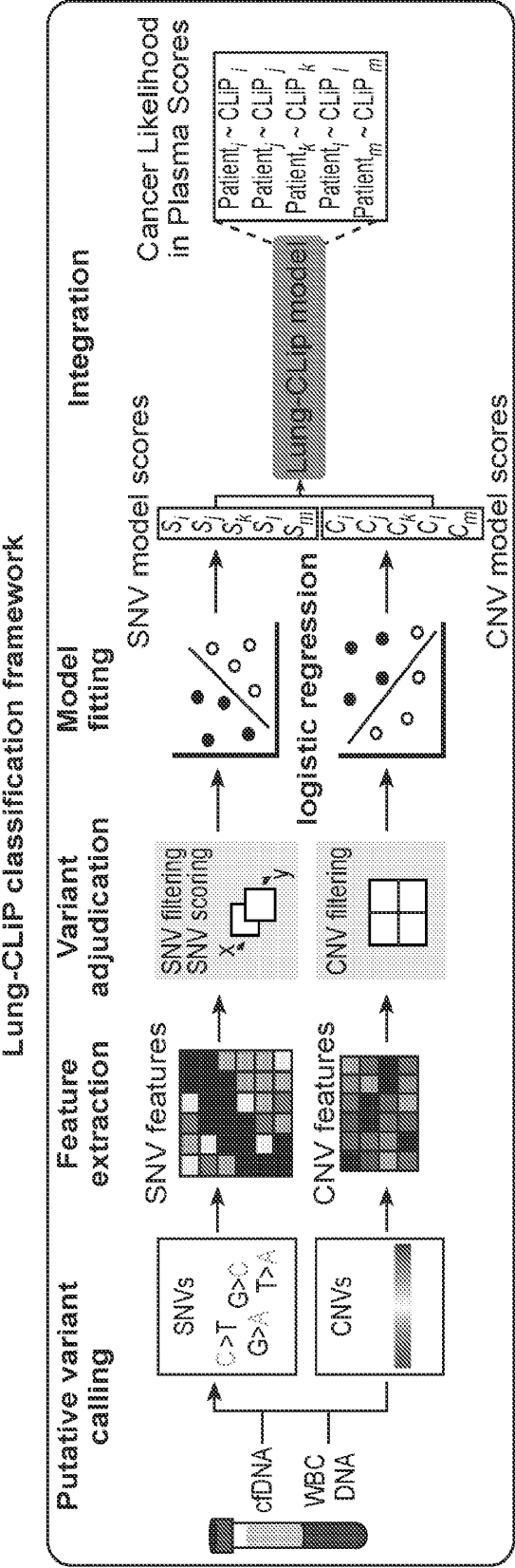


FIG. 52

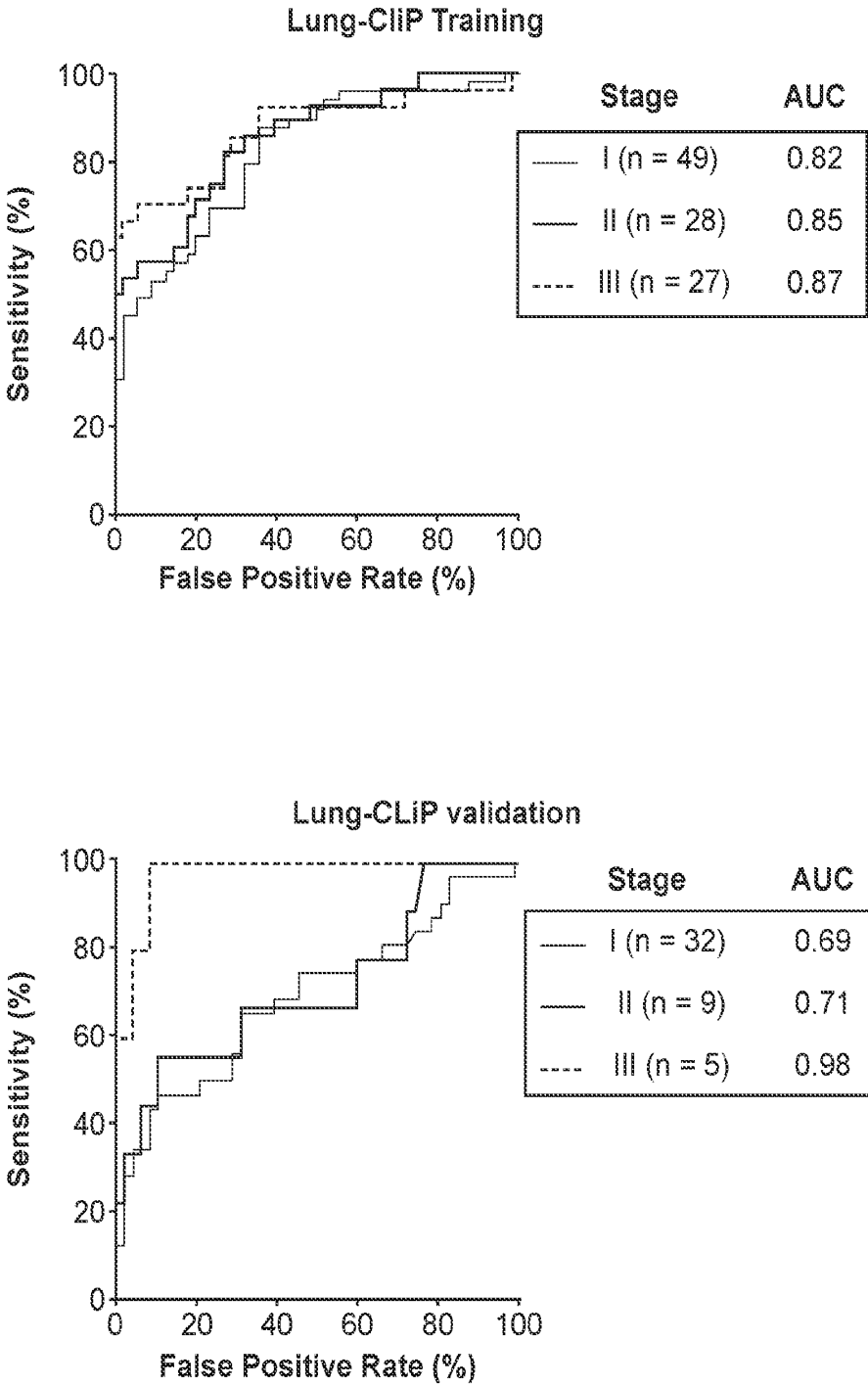
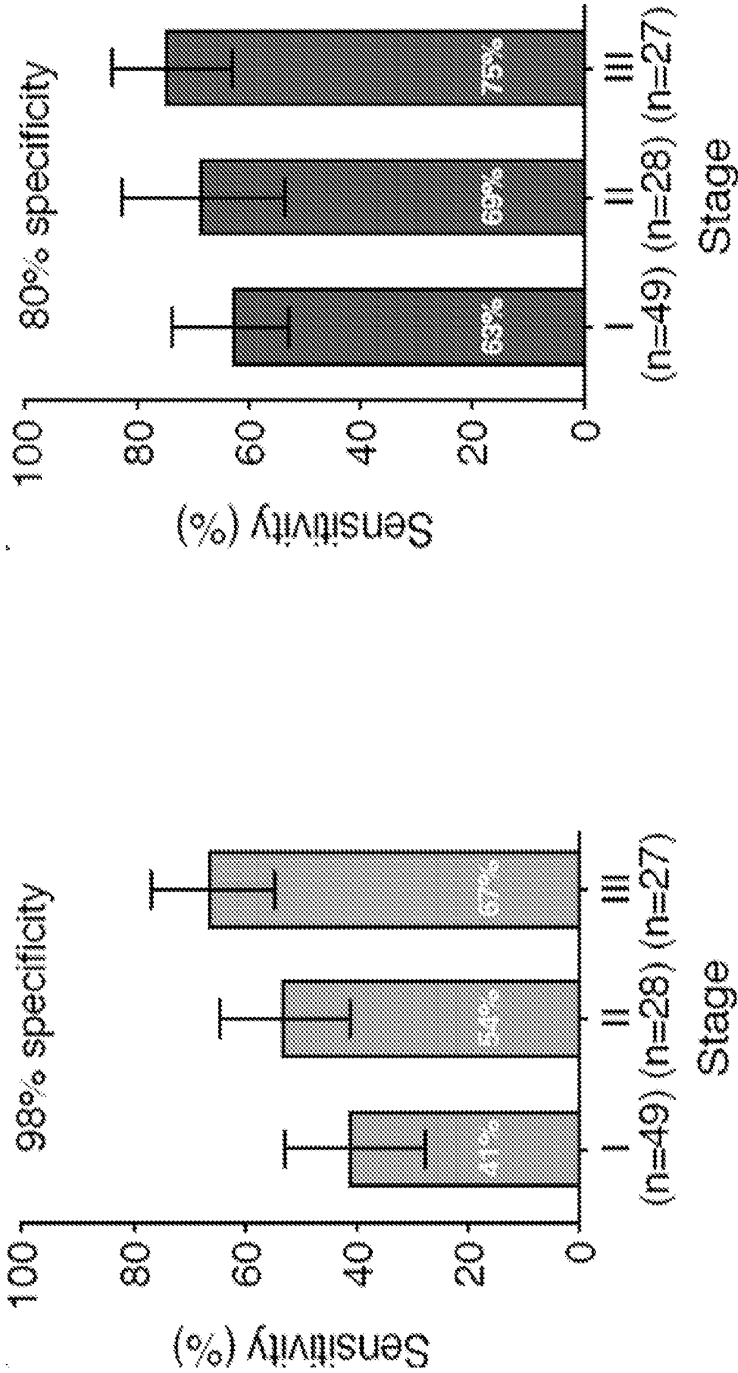


FIG. 53

Fig. 54



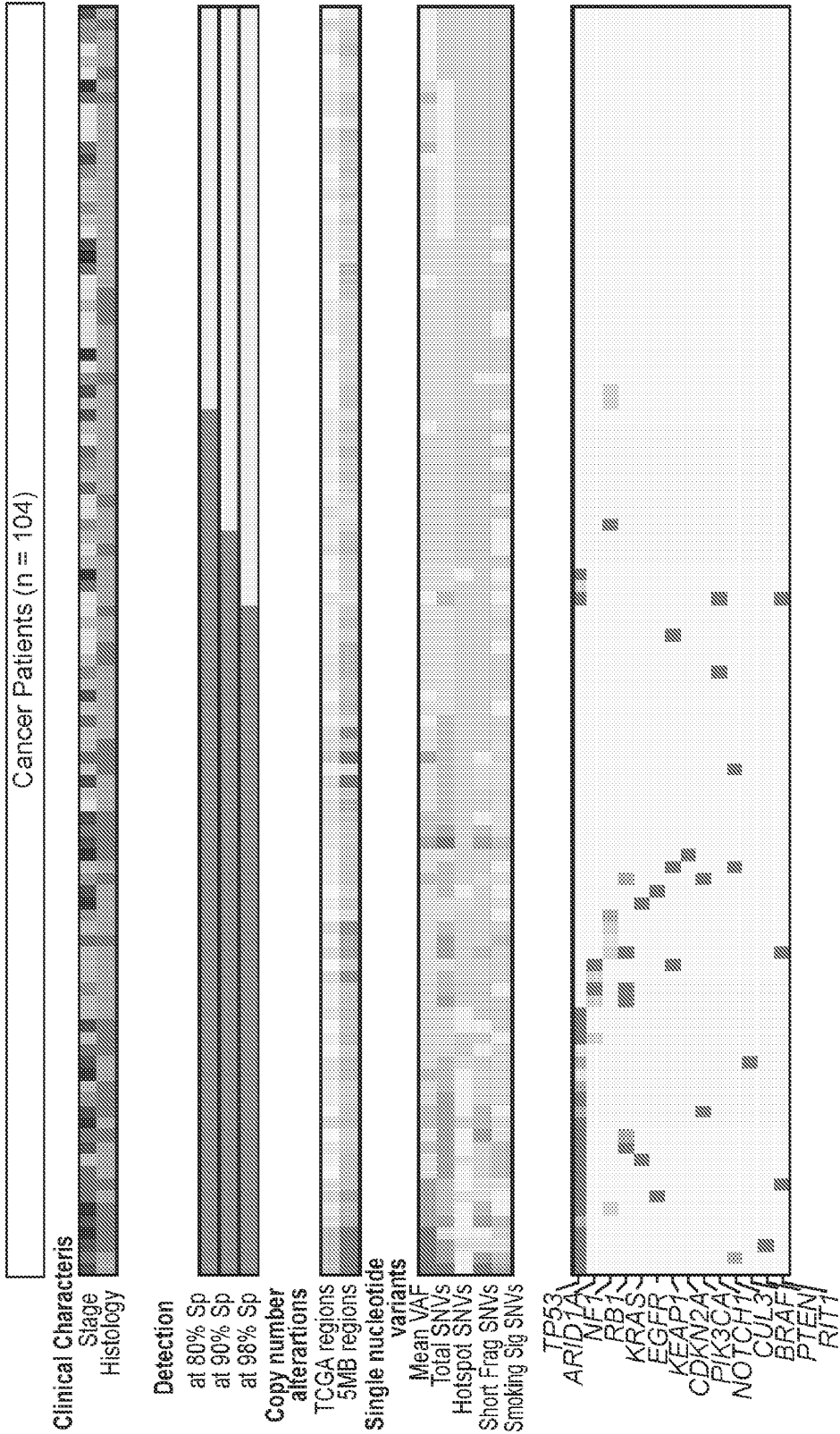


FIG. 55

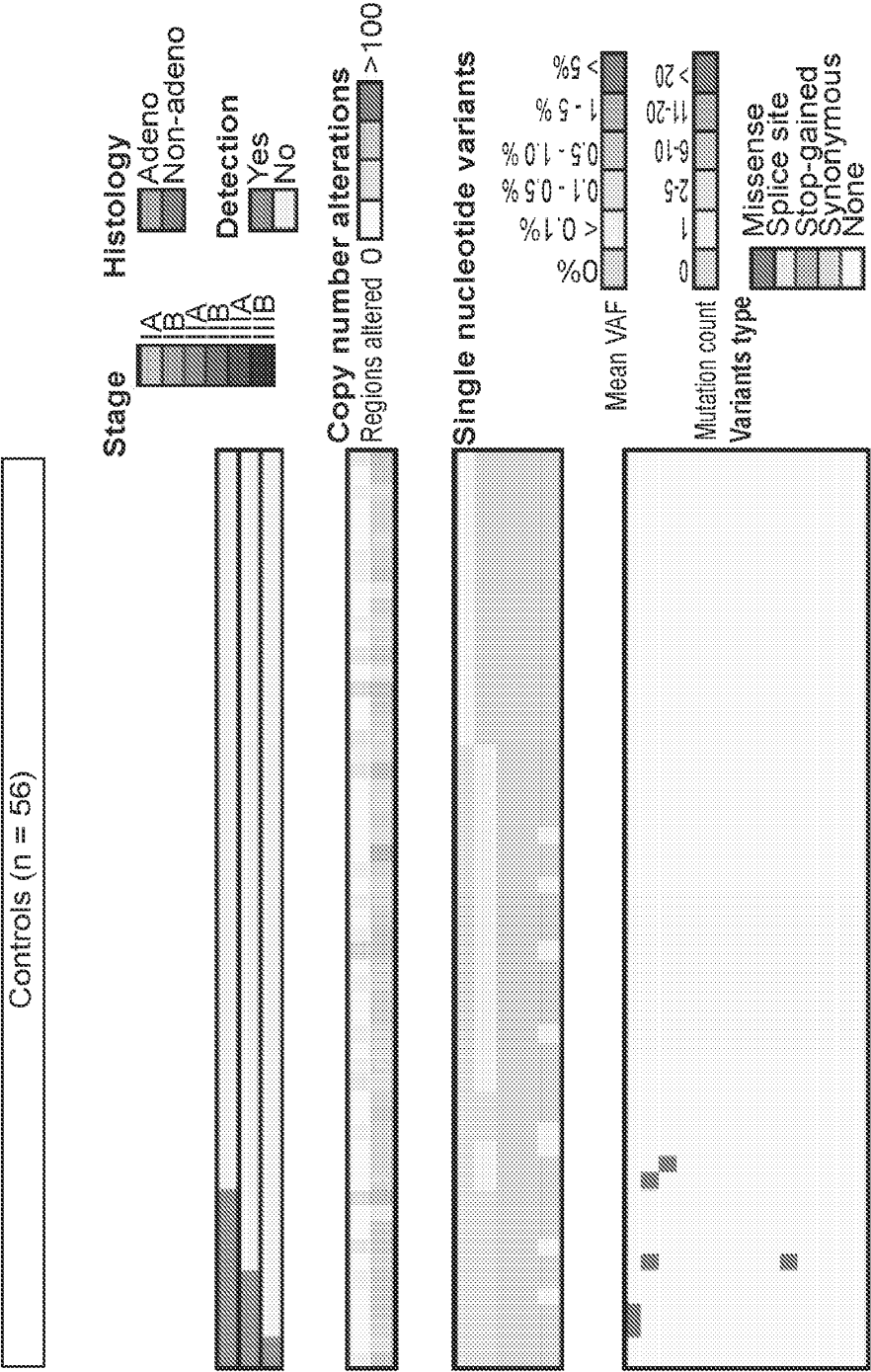


FIG. 55 (Cont.)

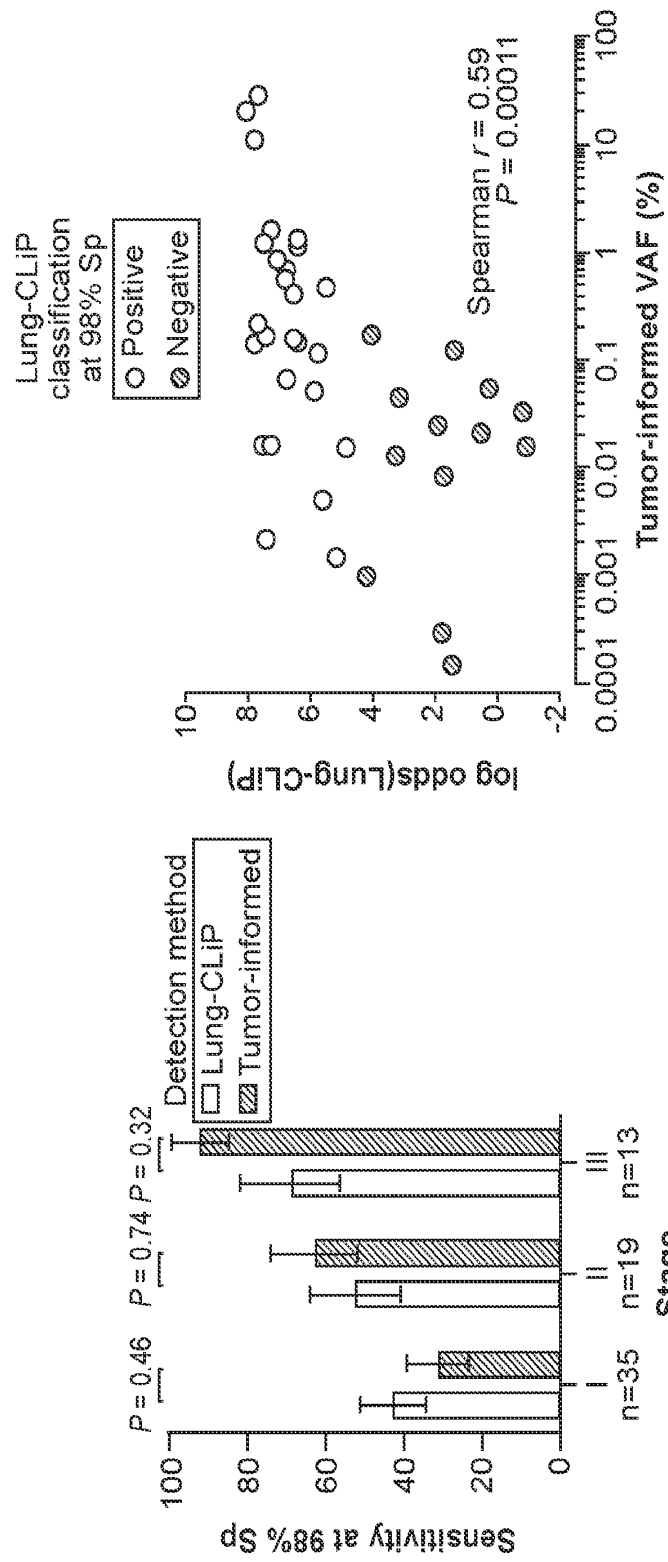
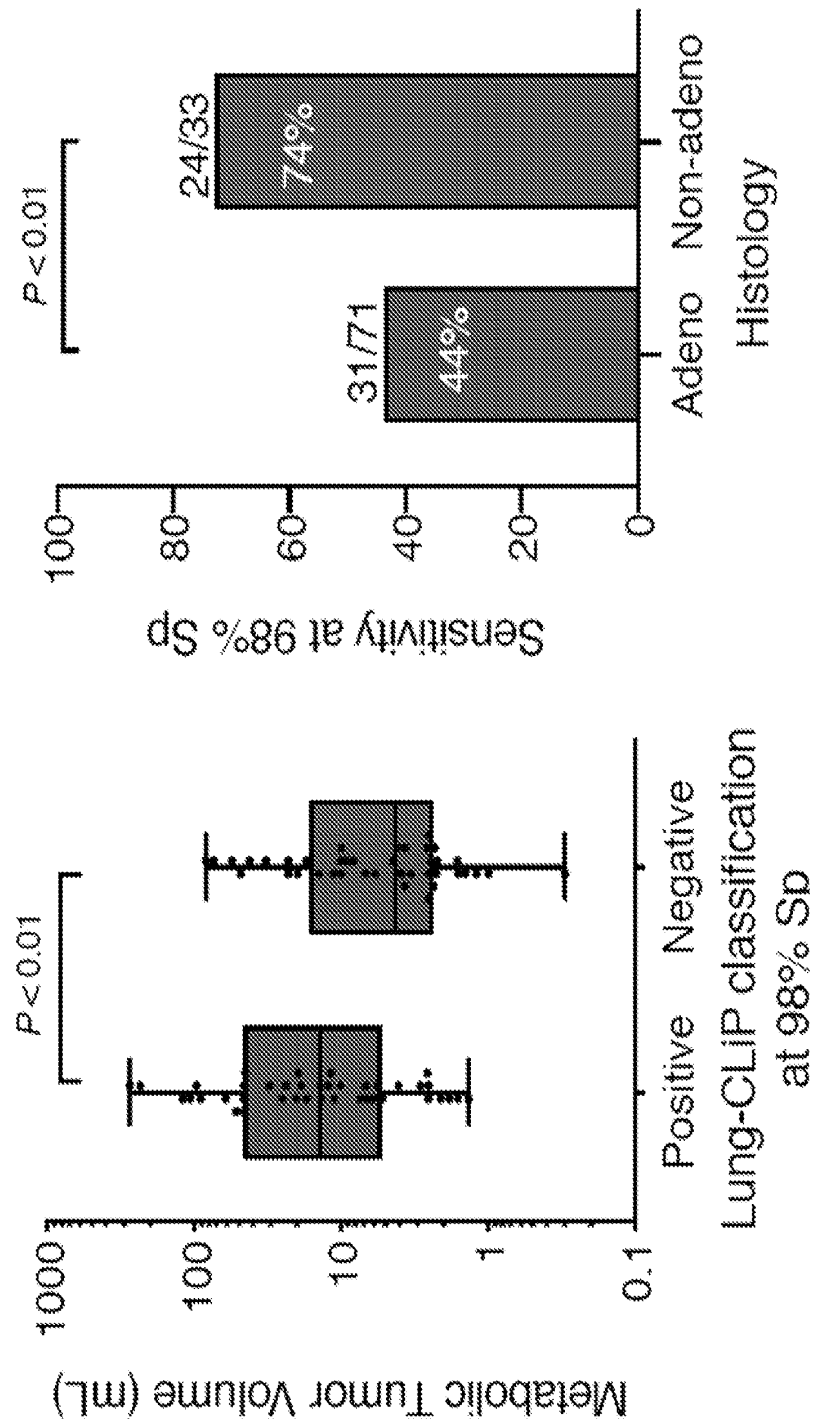


FIG. 56

Fig. 57



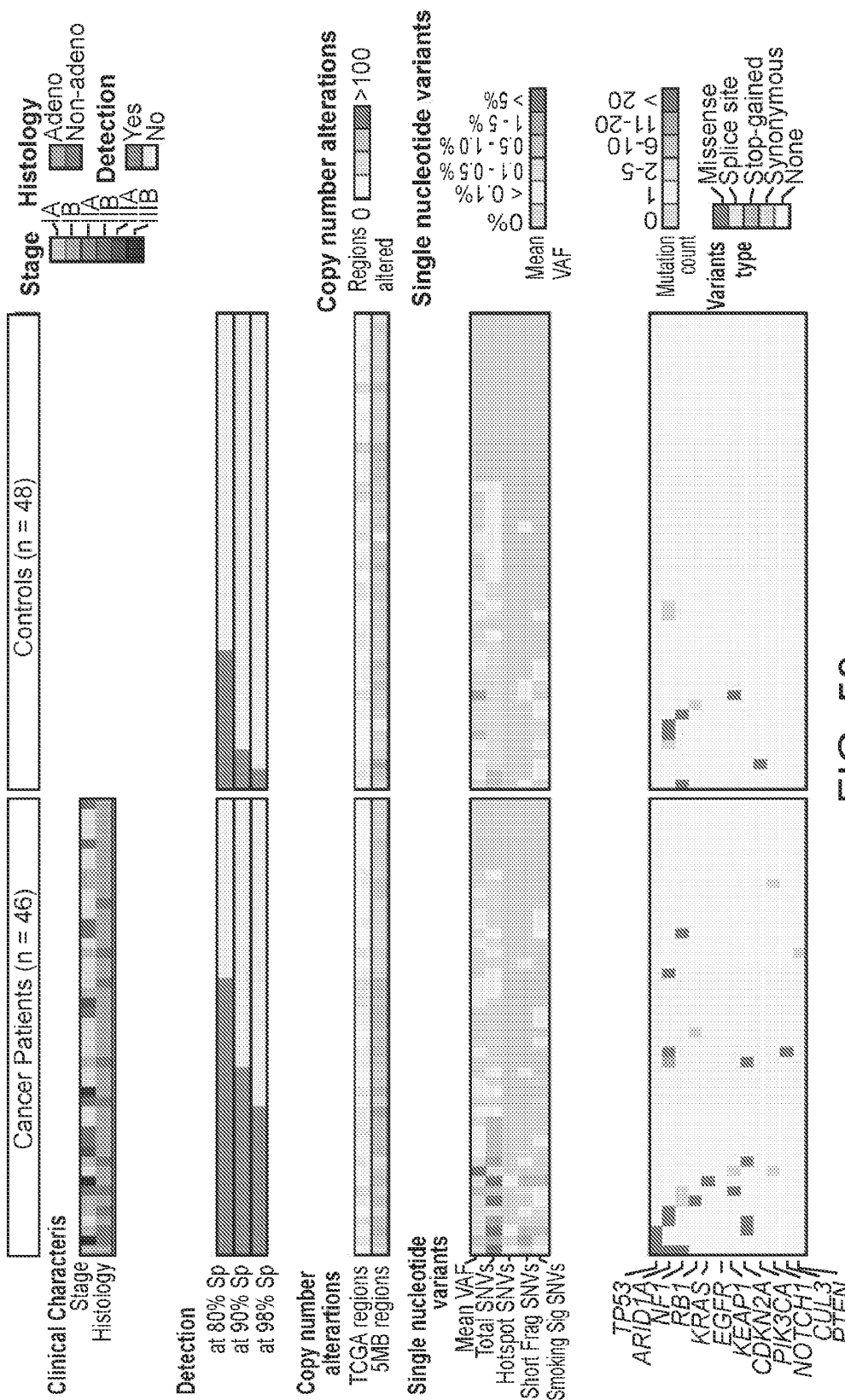


FIG. 58

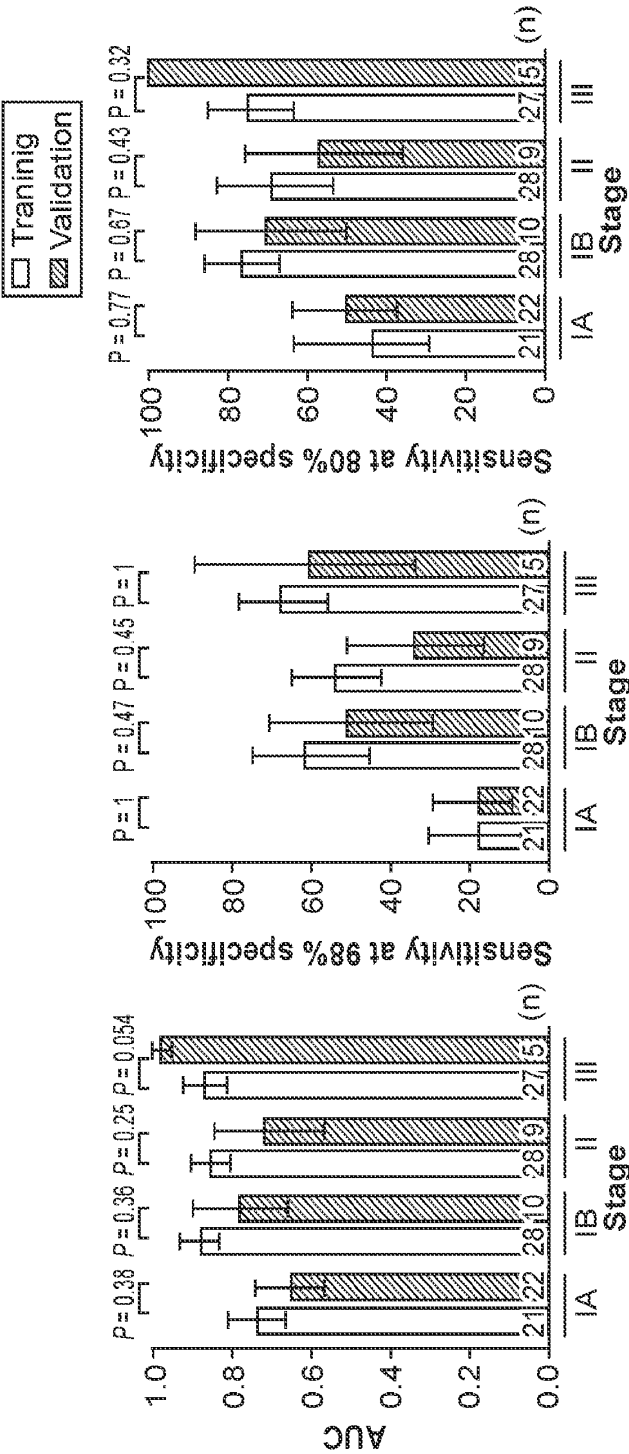


FIG. 59

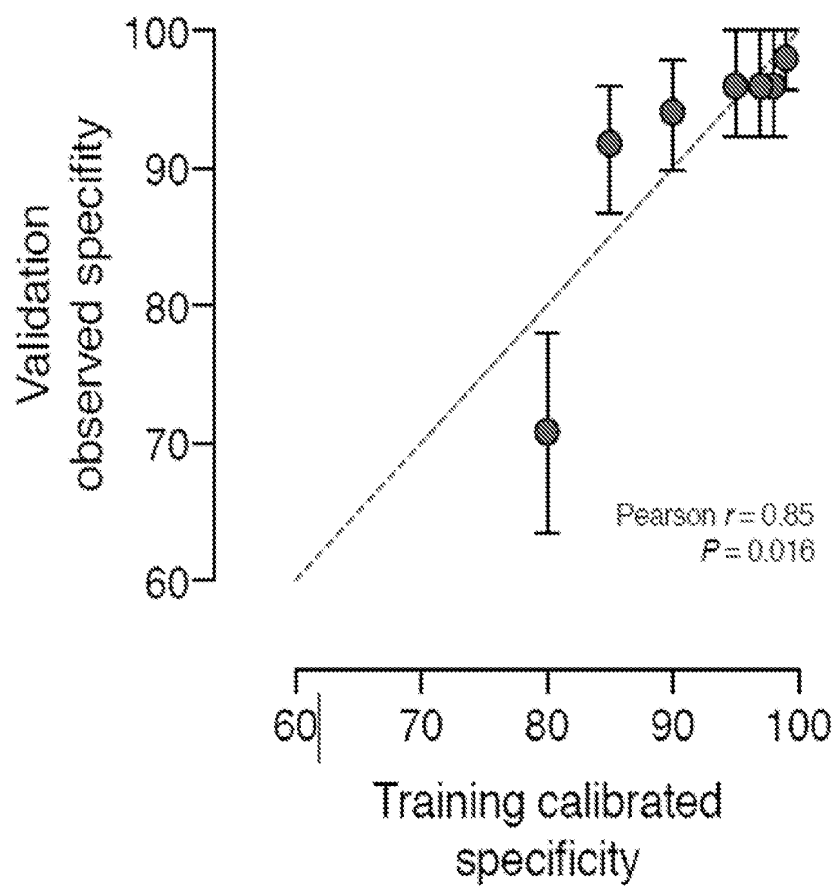
Fig. 60

Fig. 61

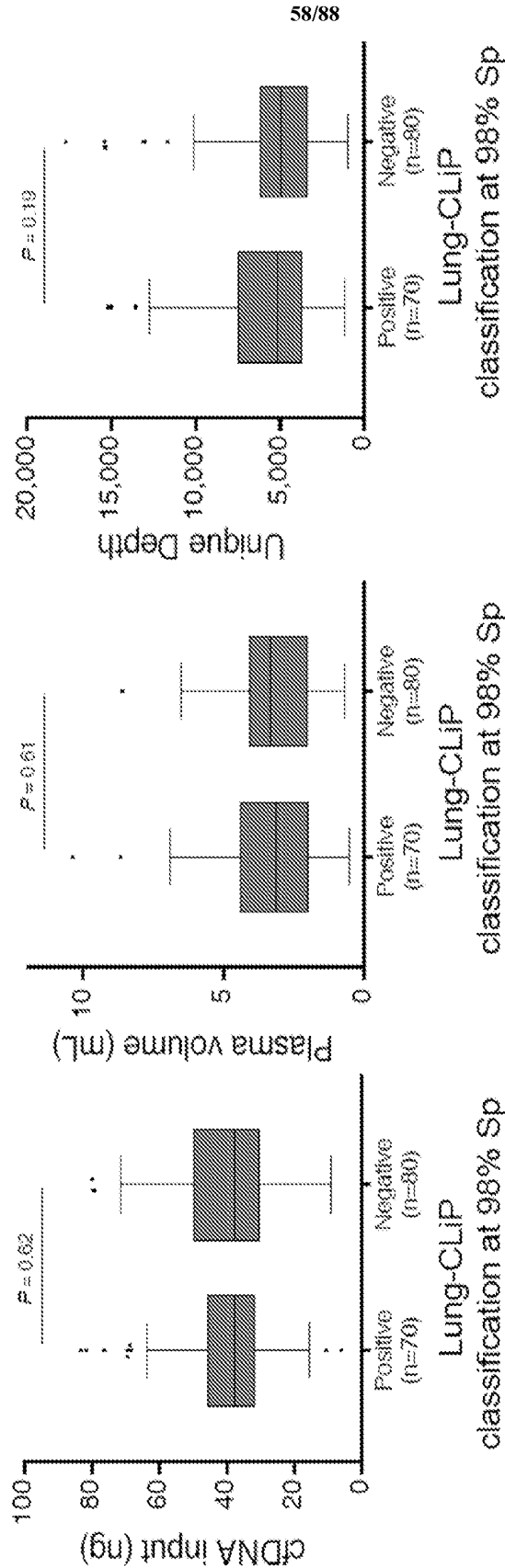


Fig. 62

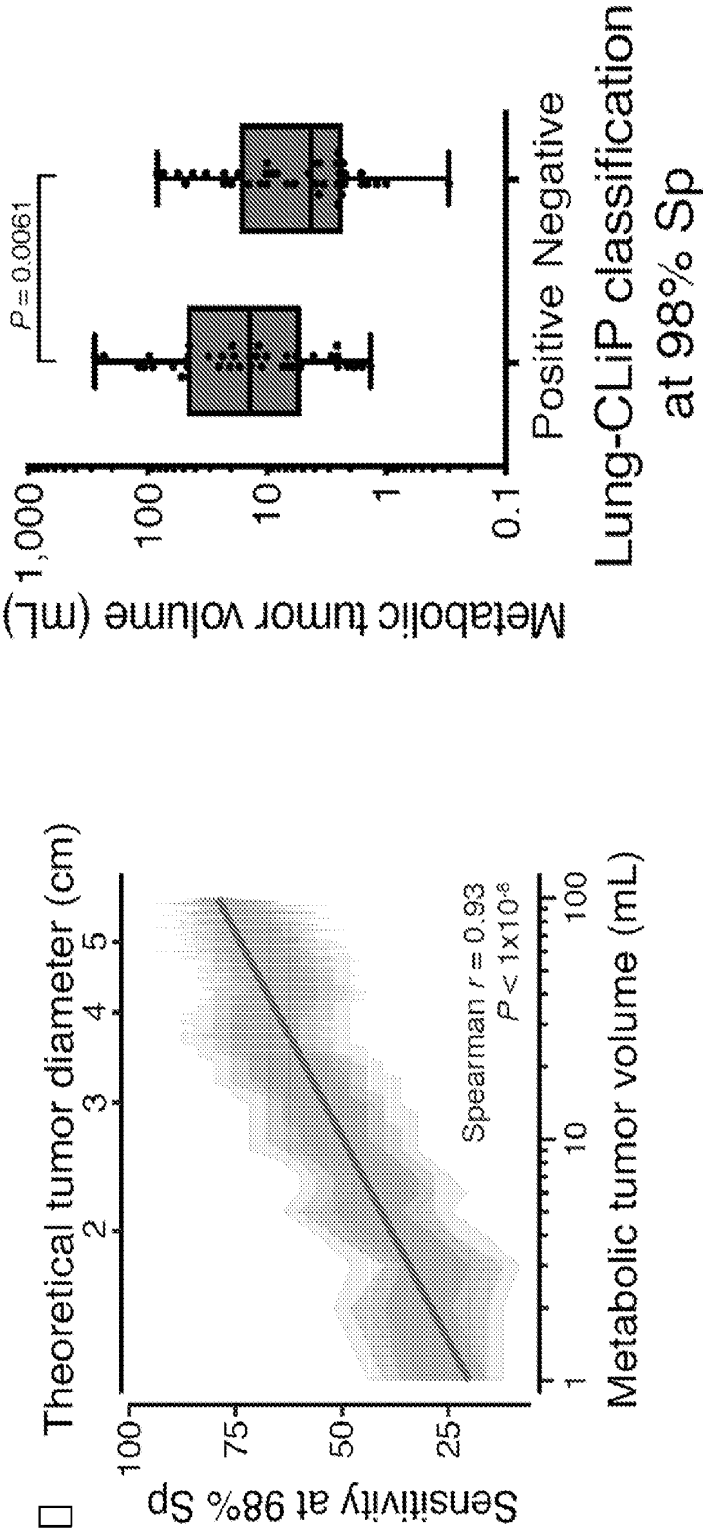


Fig. 63

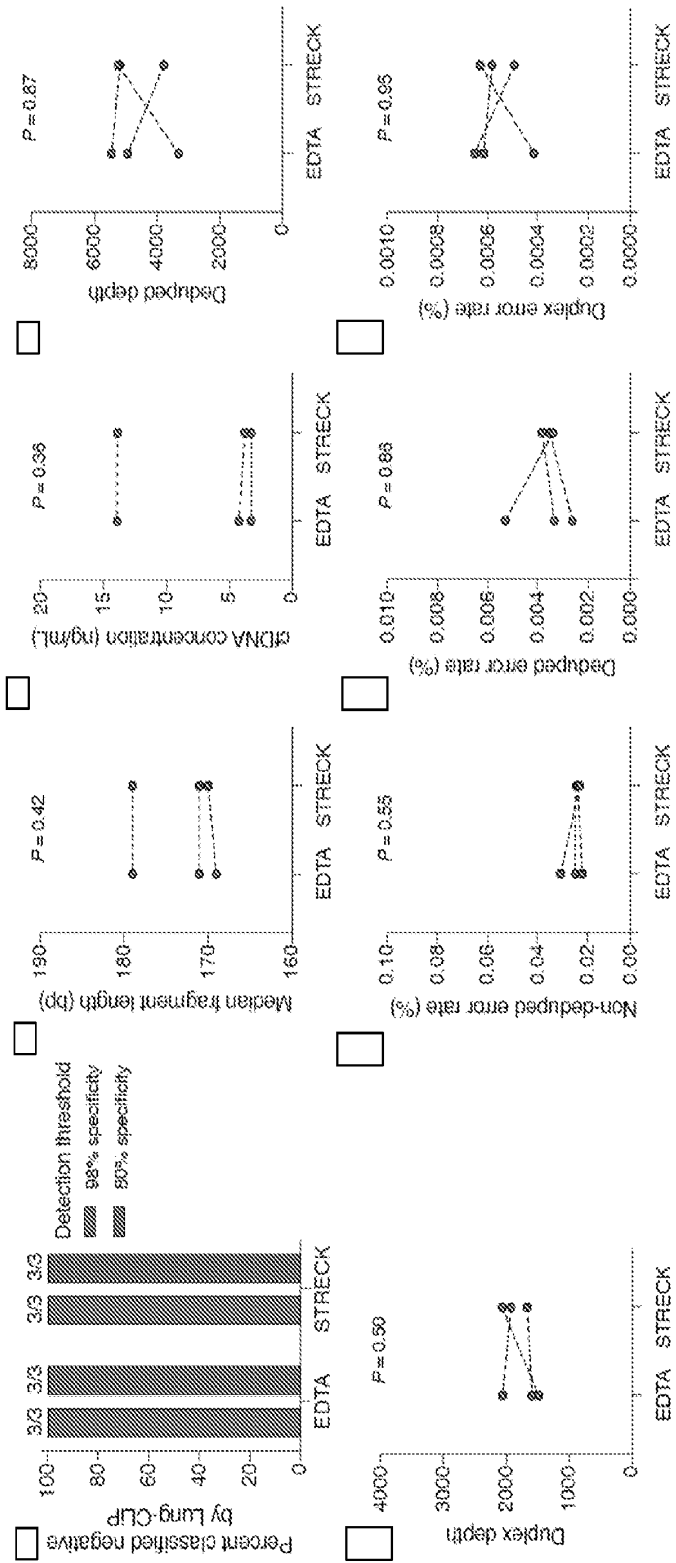


Fig. 64

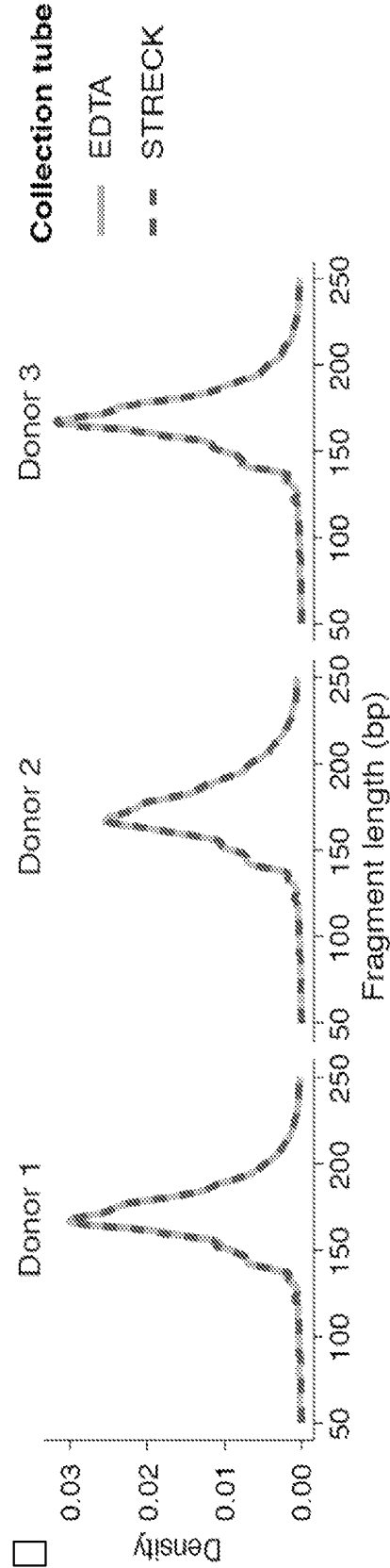
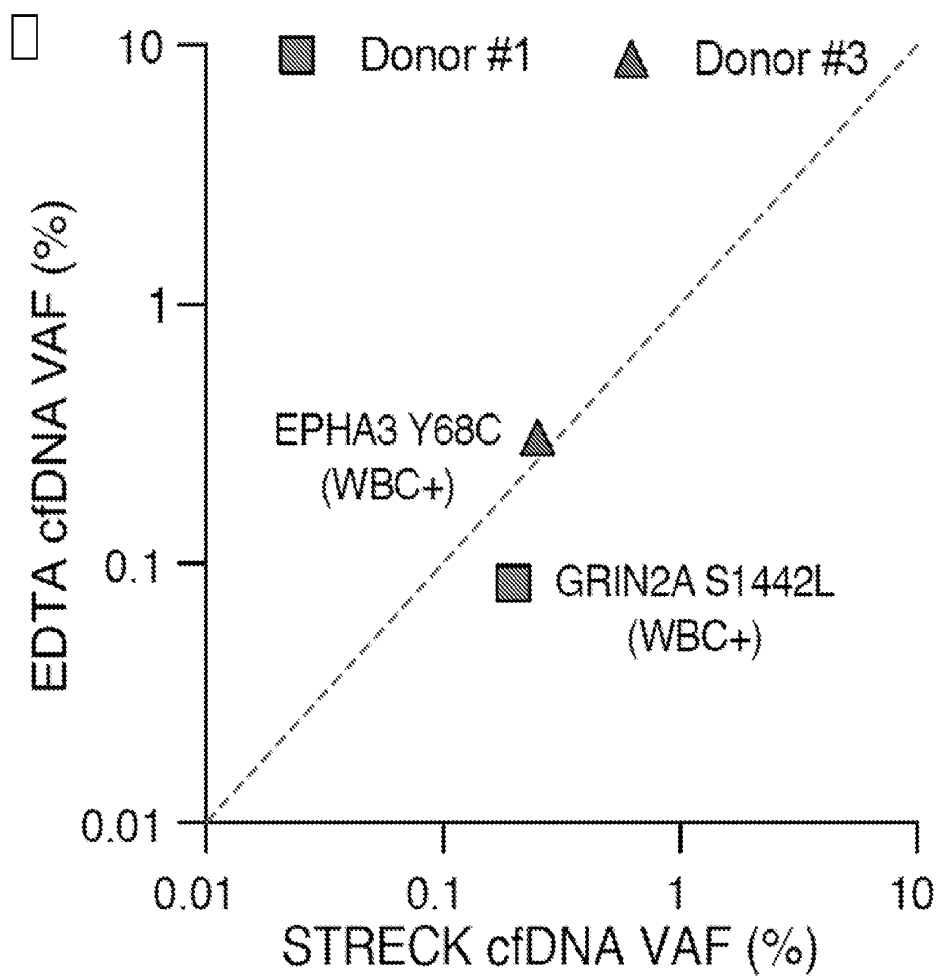


Fig. 65

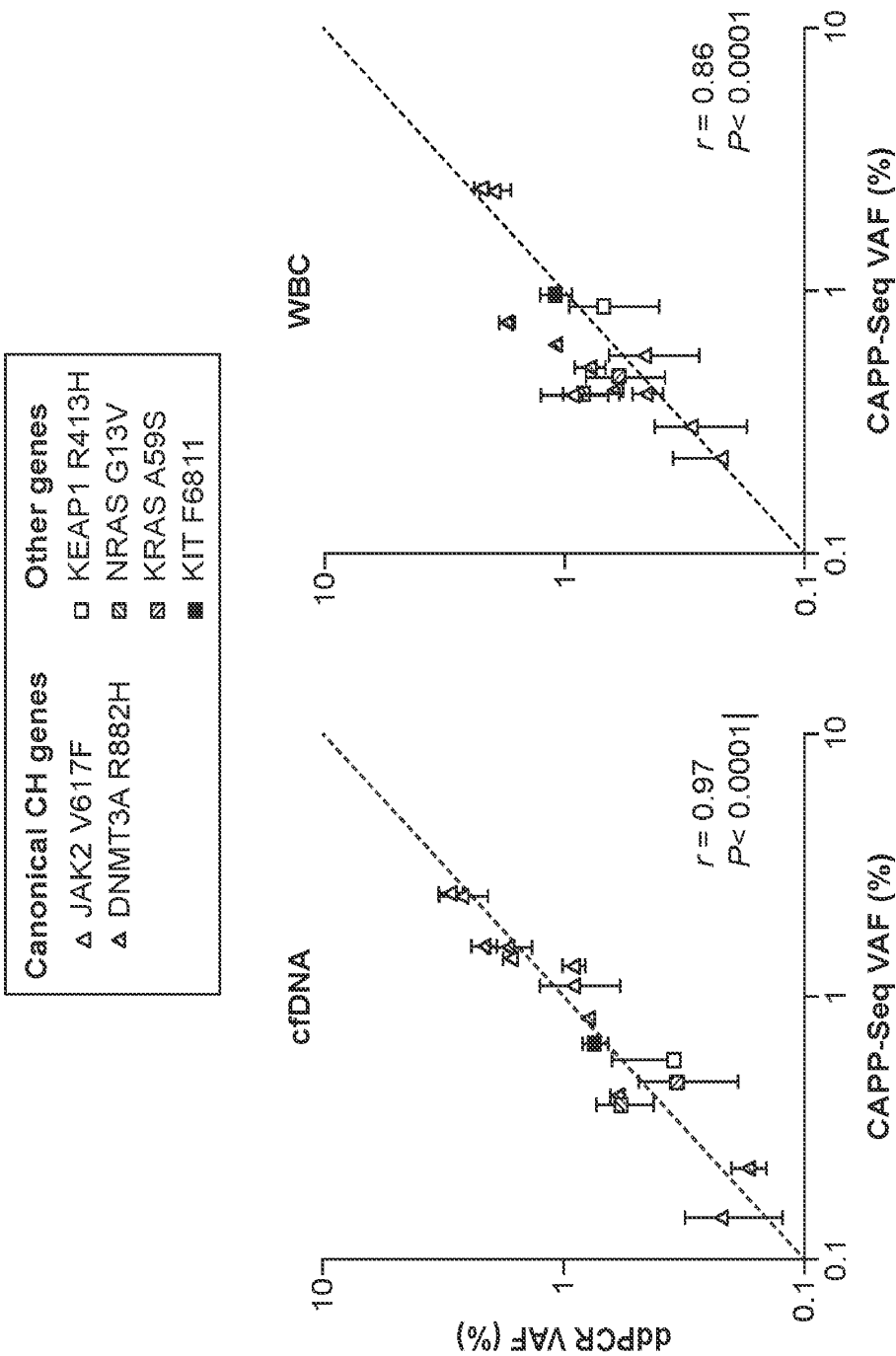


FIG. 66A

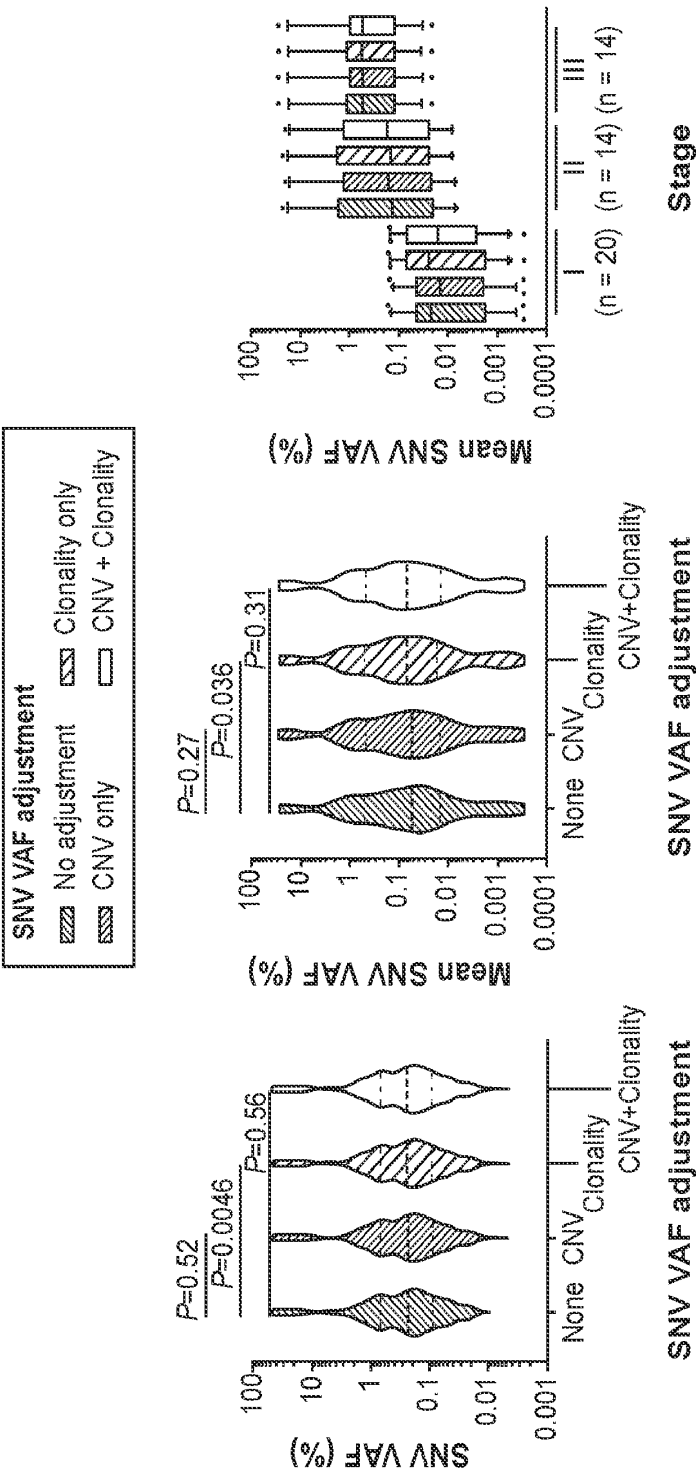


FIG. 66B

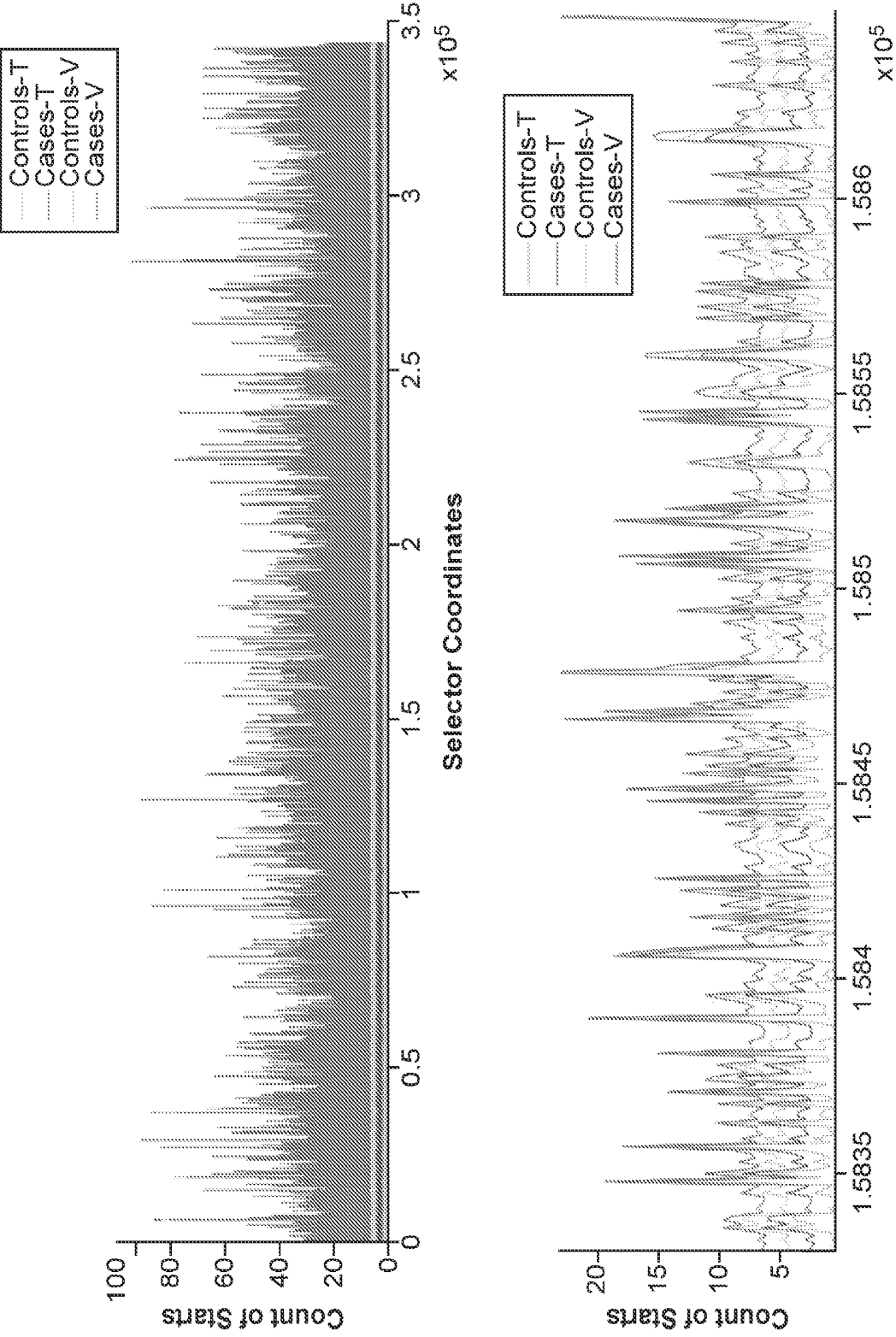


FIG. 67

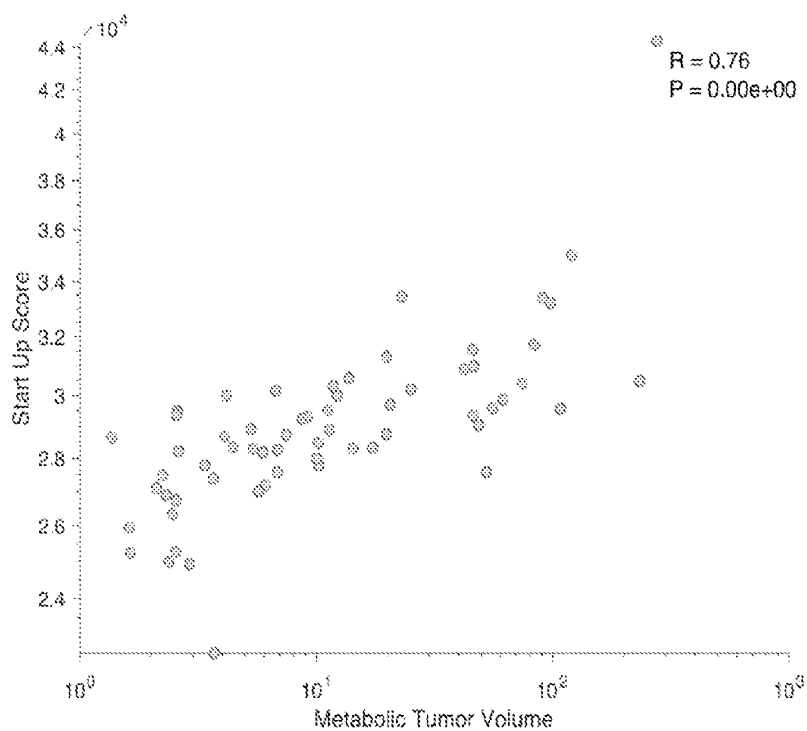
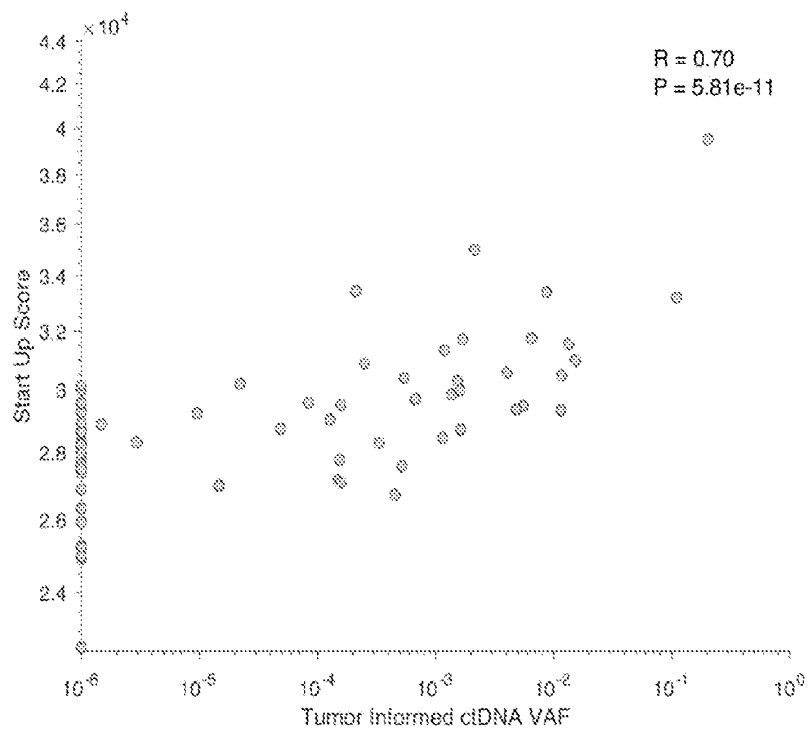
Fig. 68

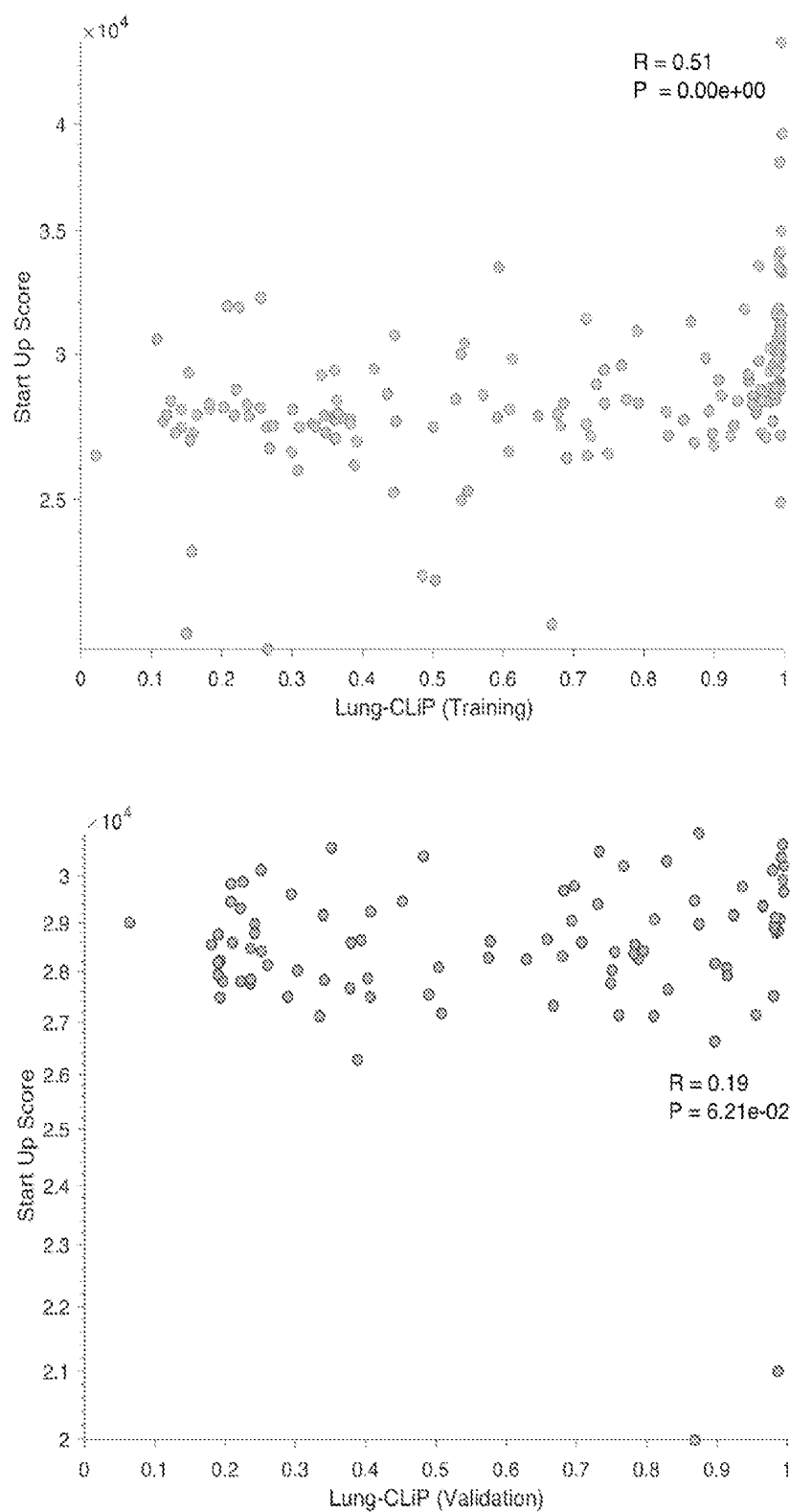
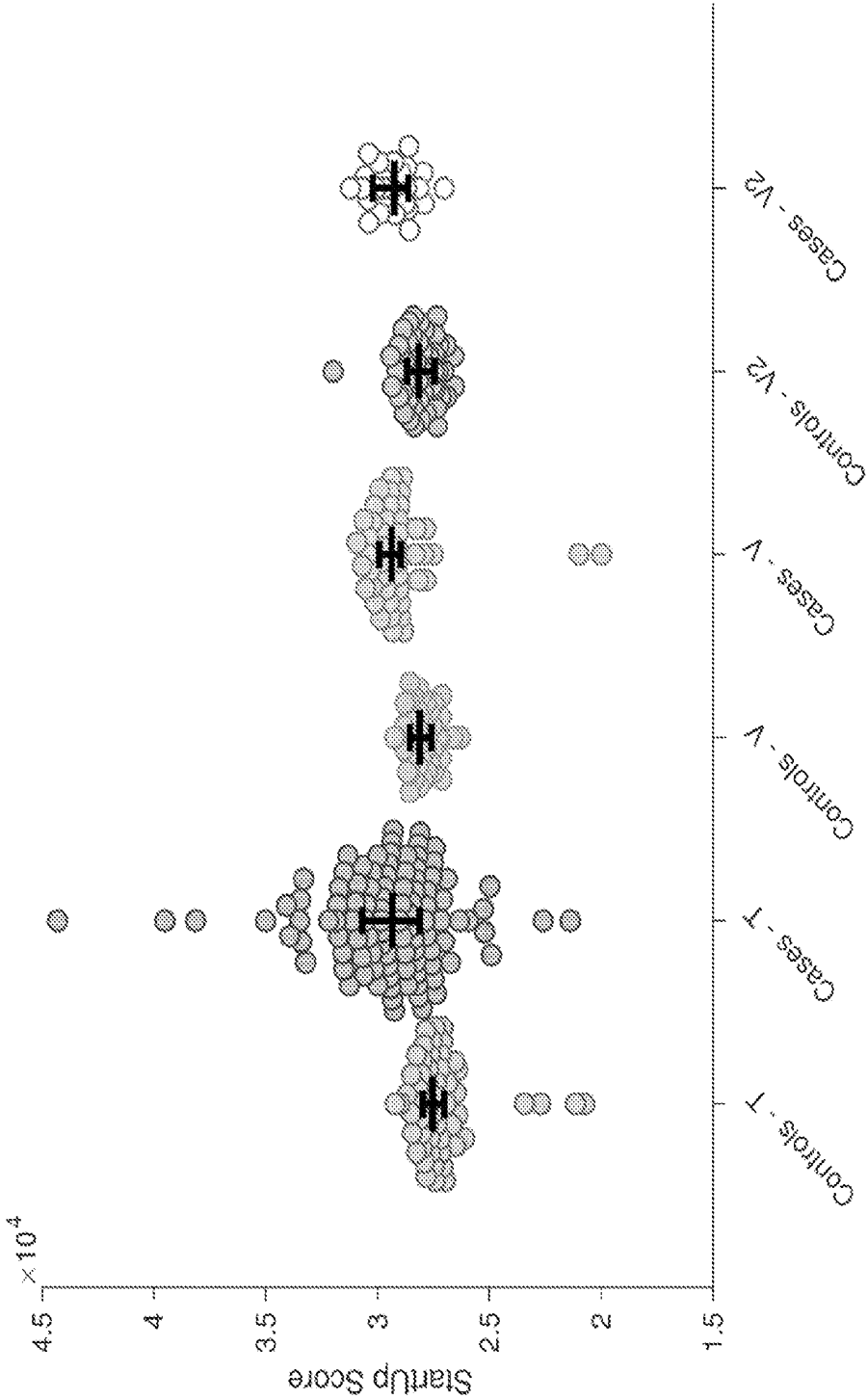
Fig. 69

Fig. 70



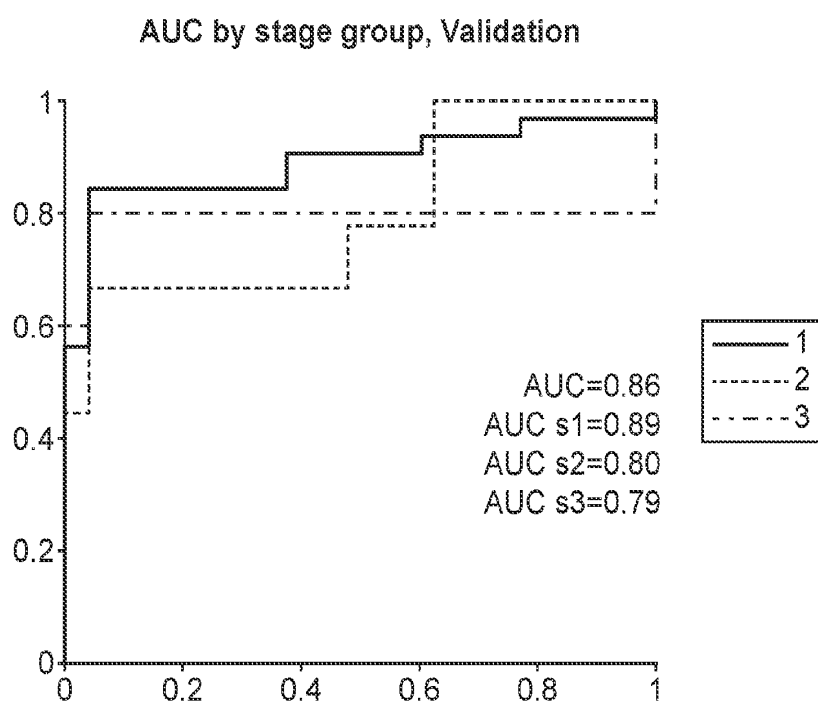


FIG. 71

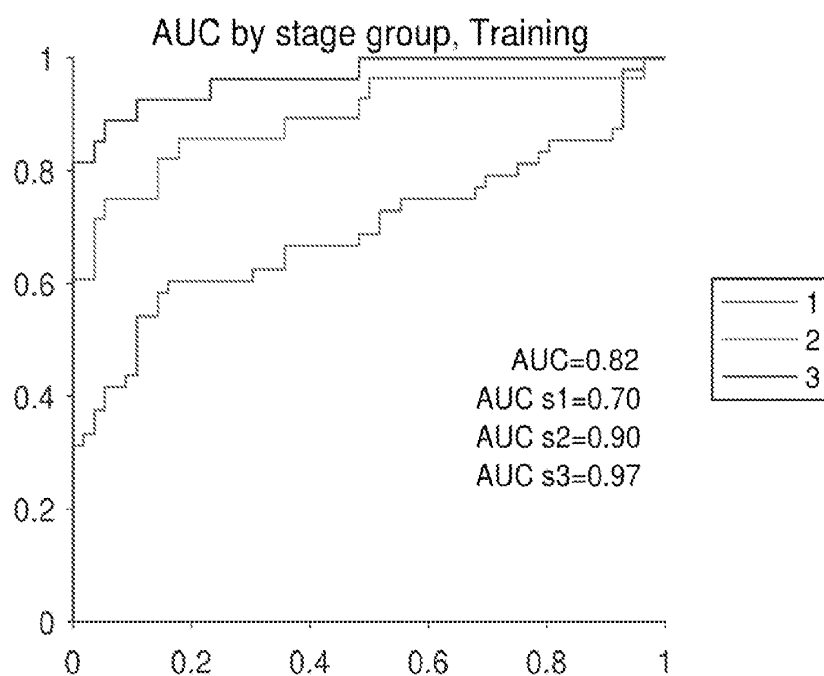
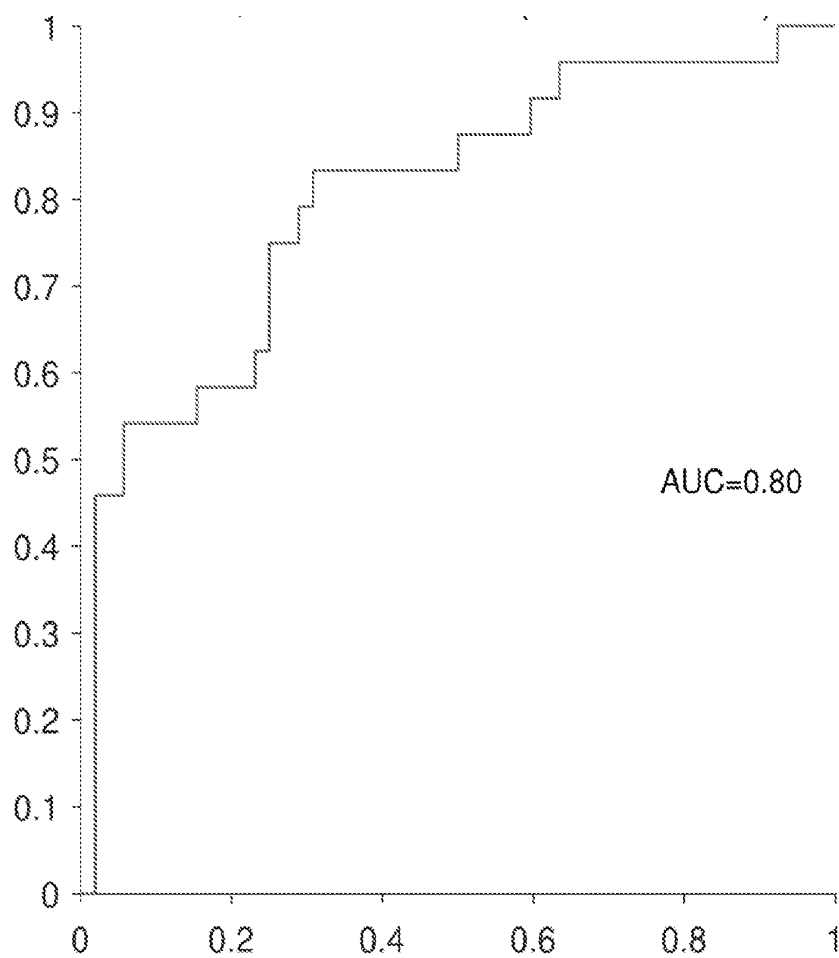
Fig. 71 (cont.)

Fig. 72

N = 24 NSCLC patients and 52 controls

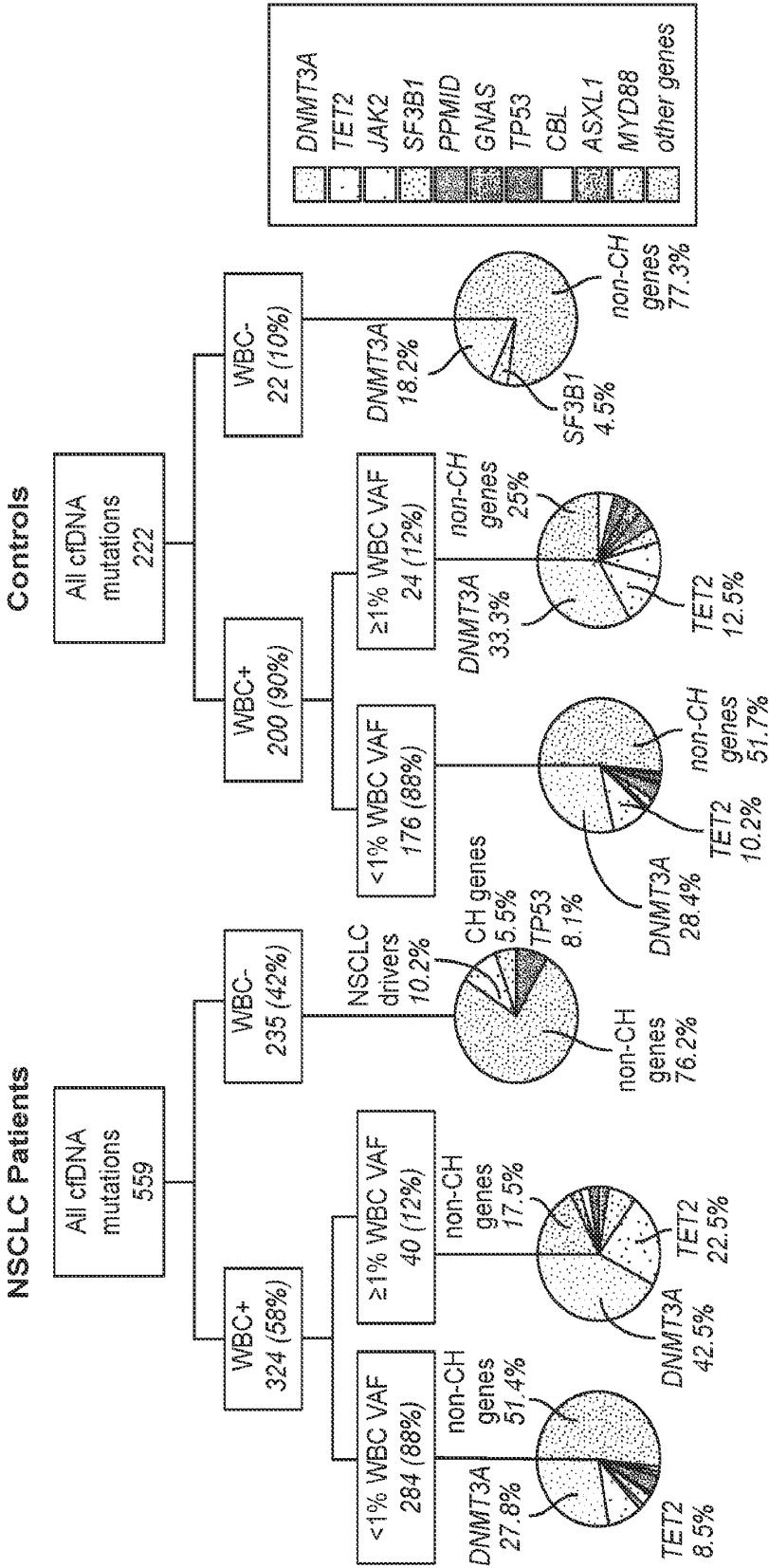
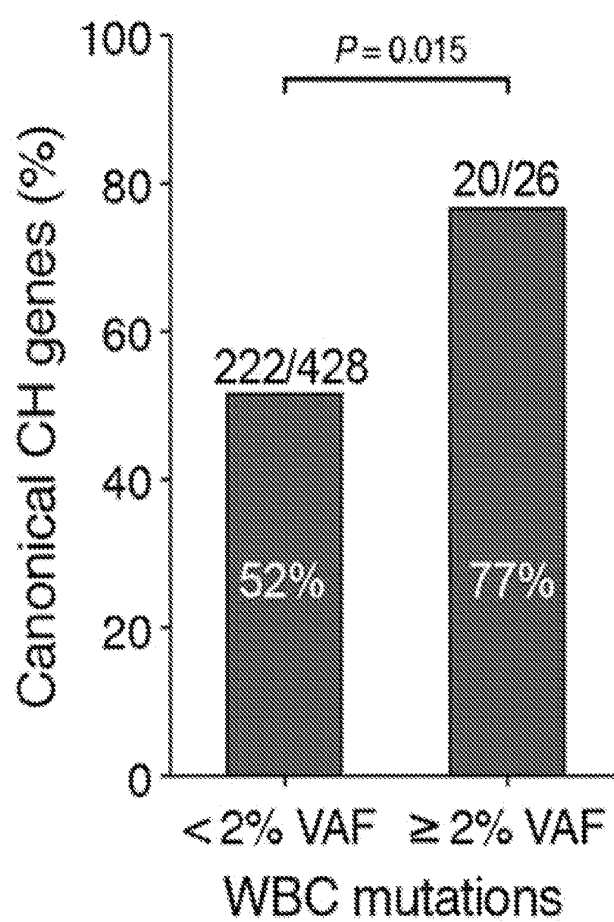


FIG. 73

Fig. 74

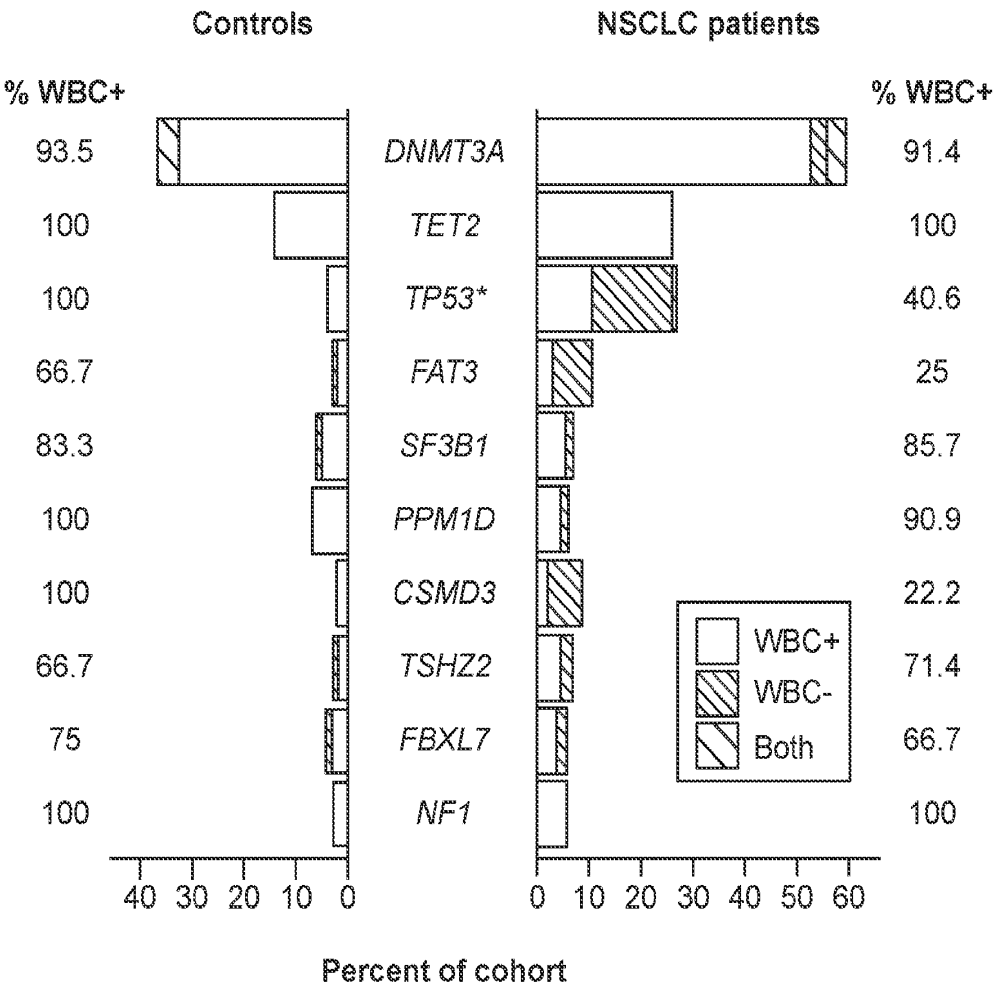


FIG. 75

Fig. 76

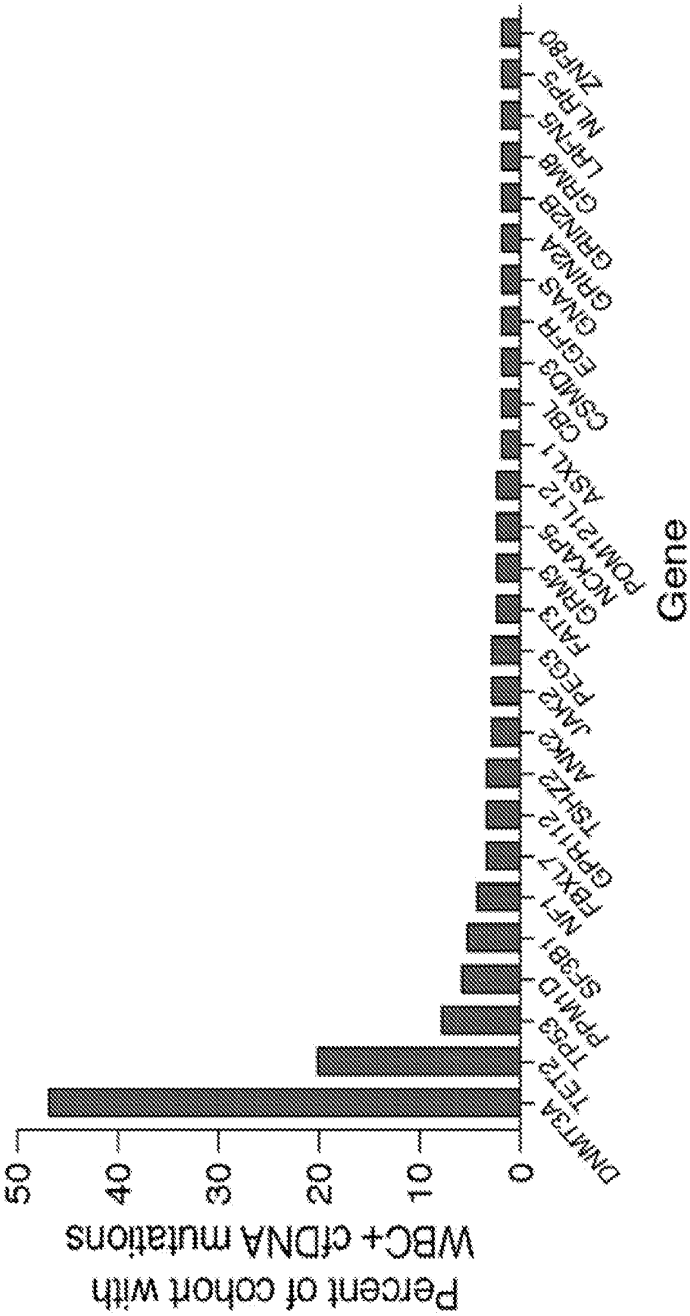
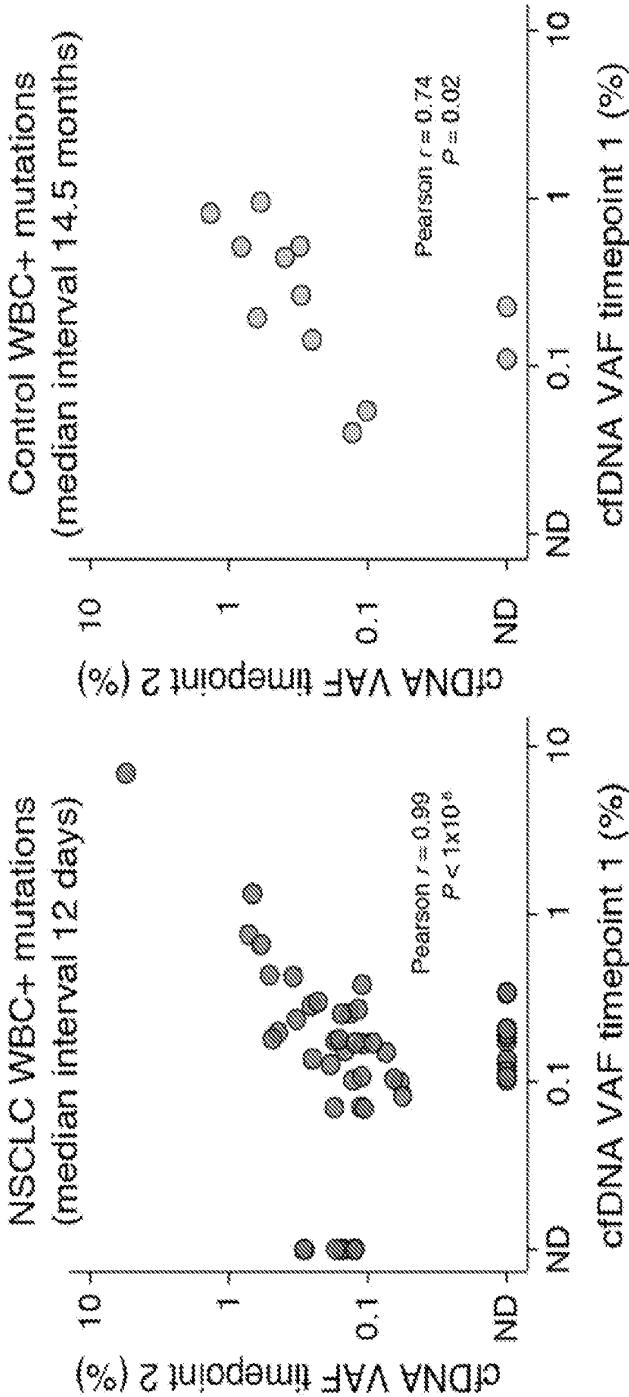


Fig. 77



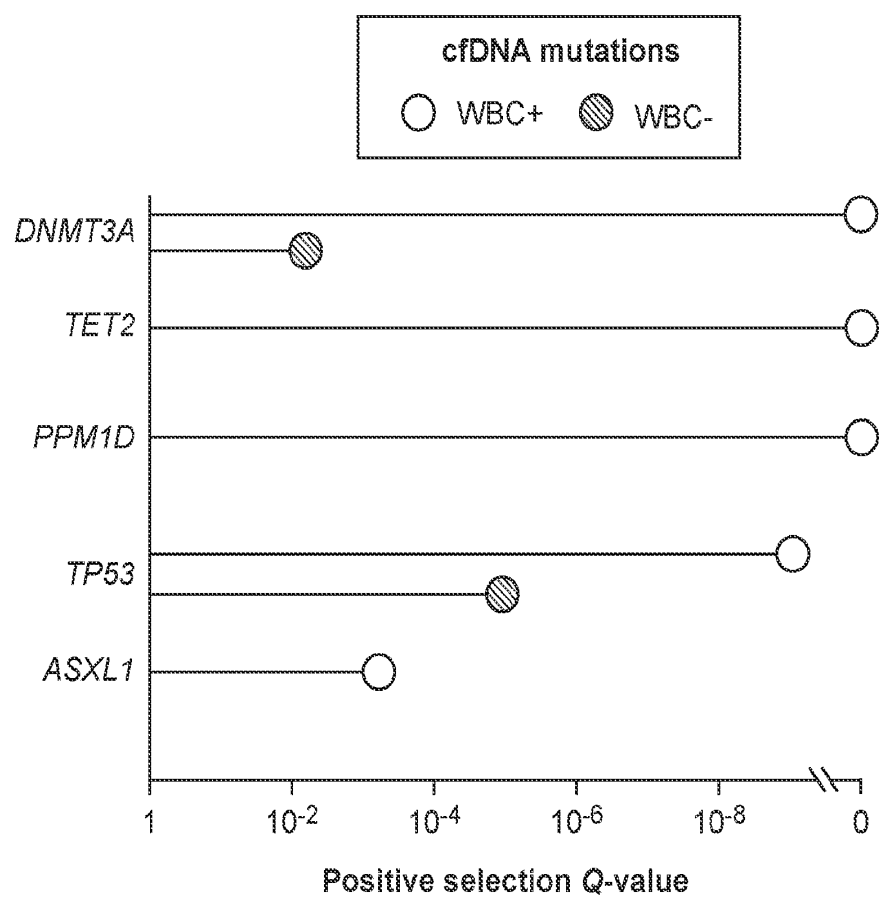


FIG. 78

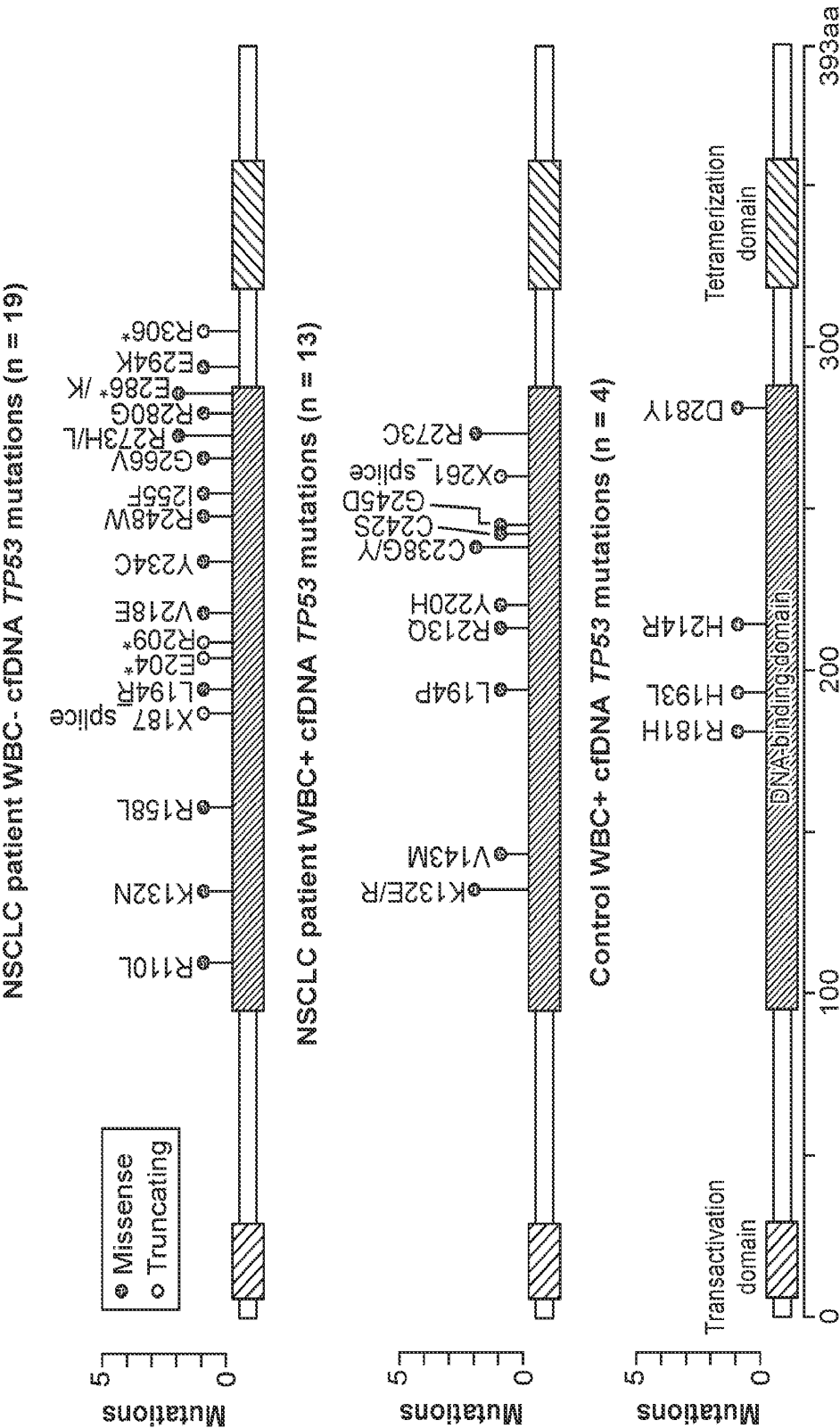


FIG. 79

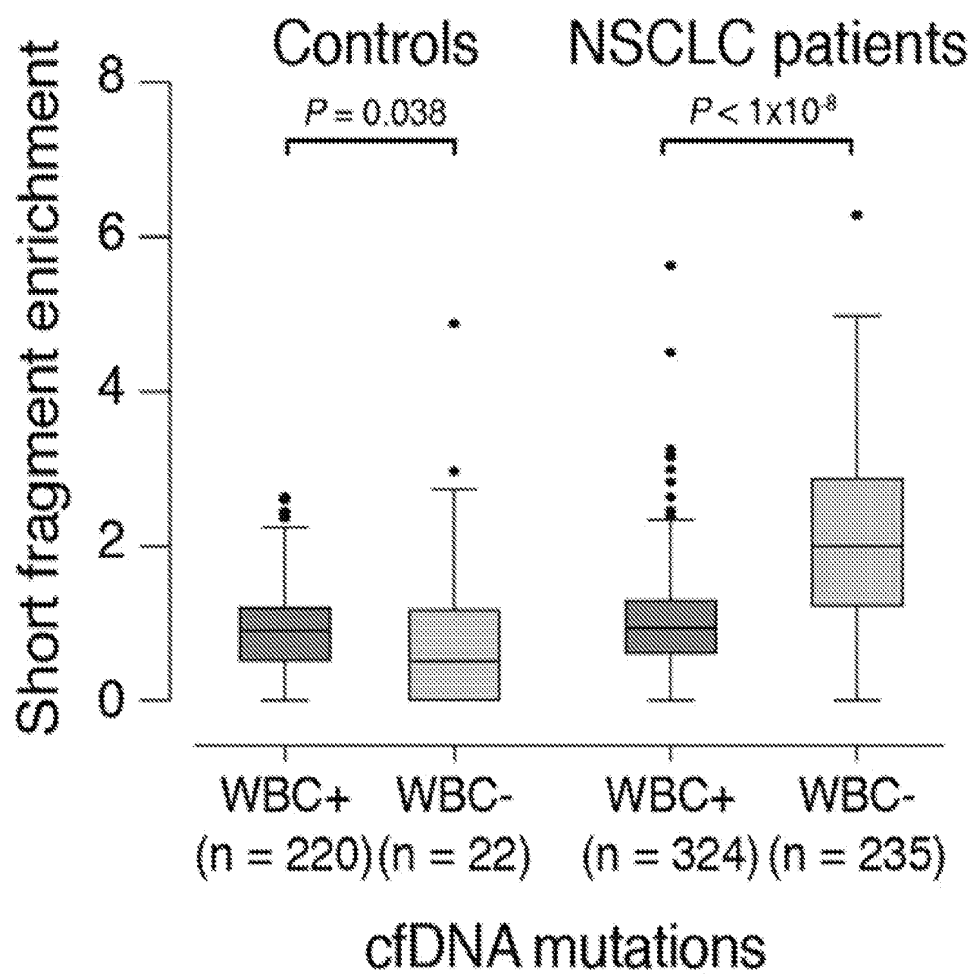
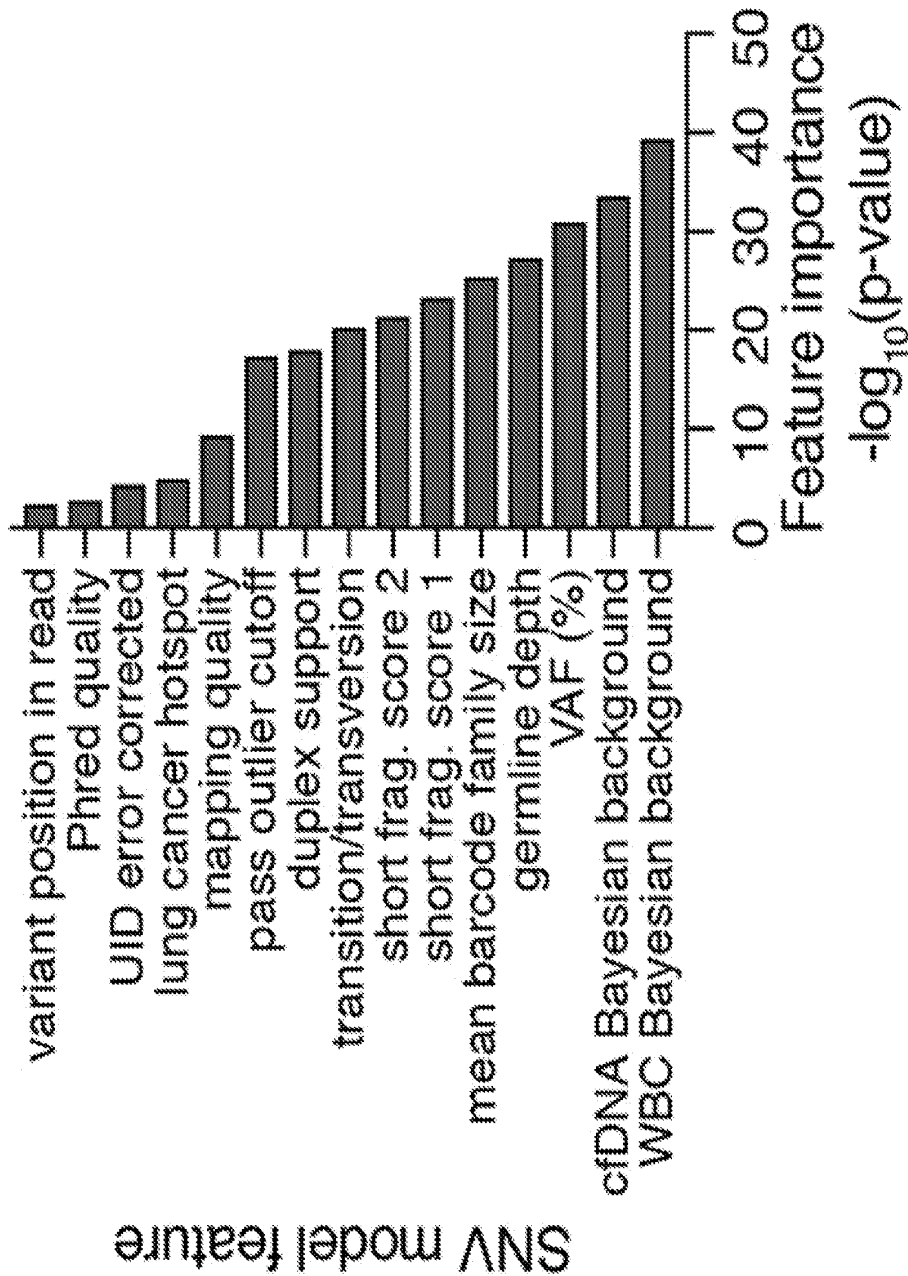
Fig. 80

Fig. 81



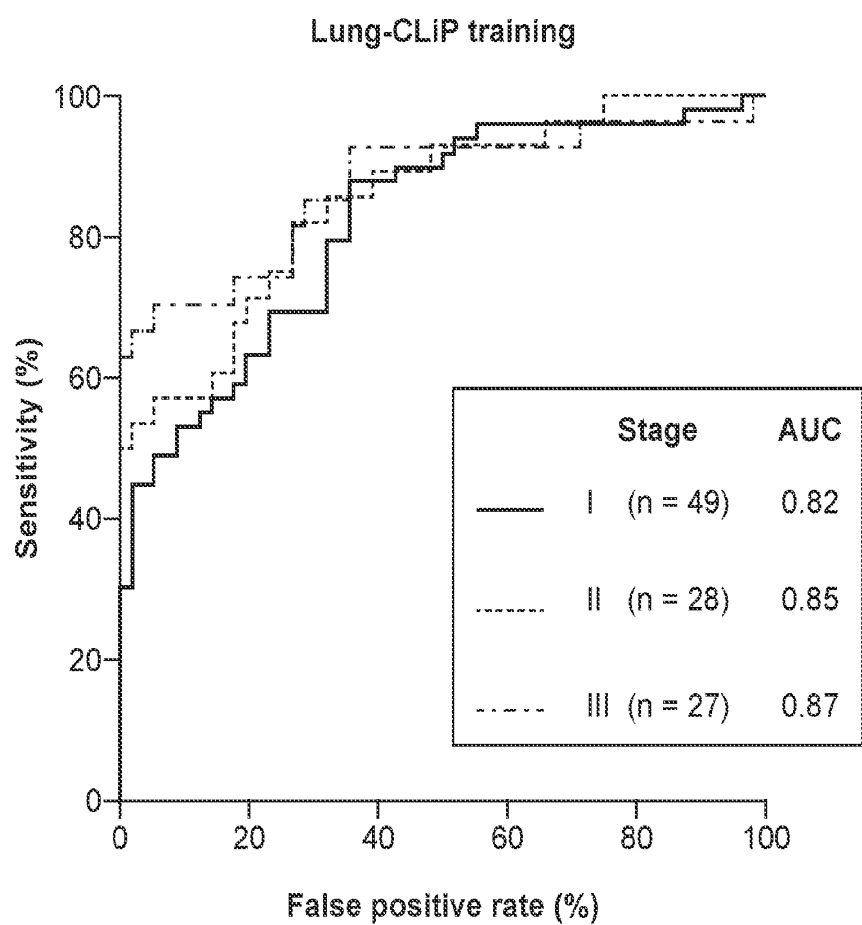


FIG. 82

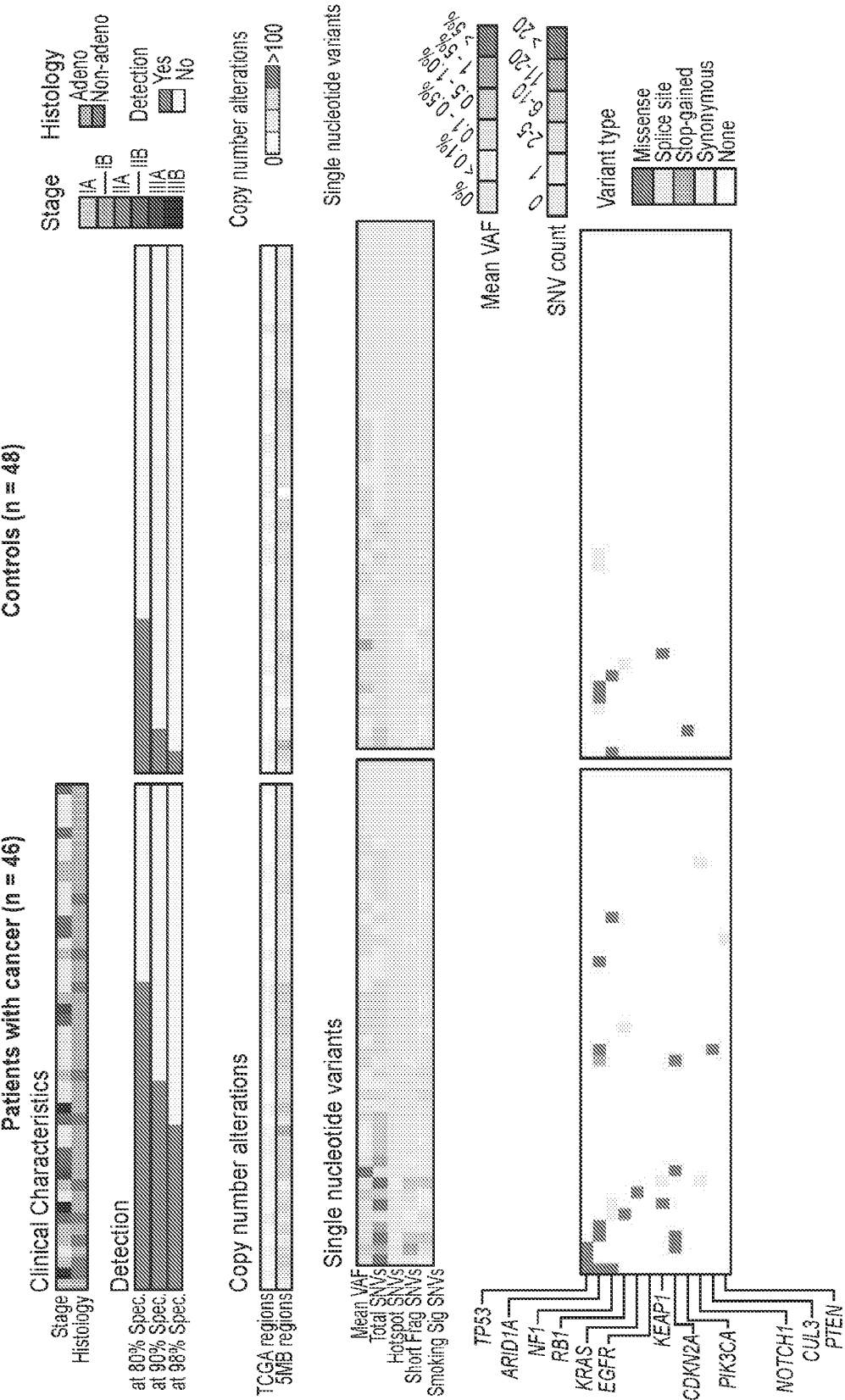


FIG. 83

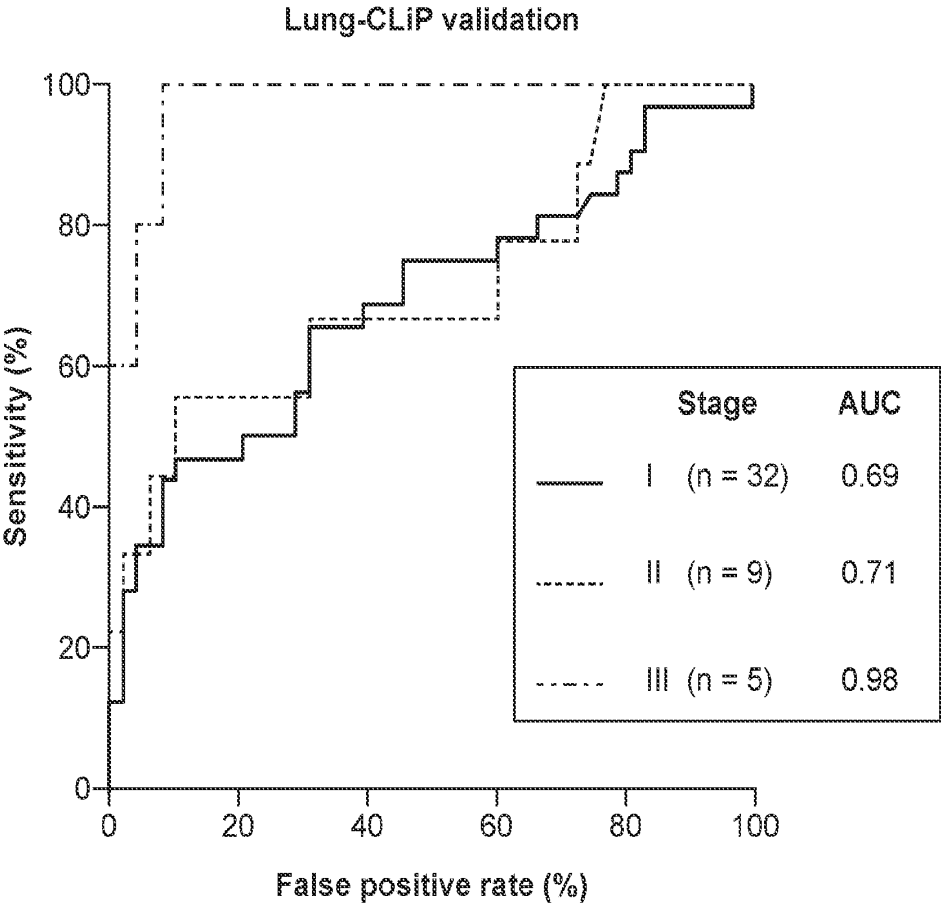


FIG. 84

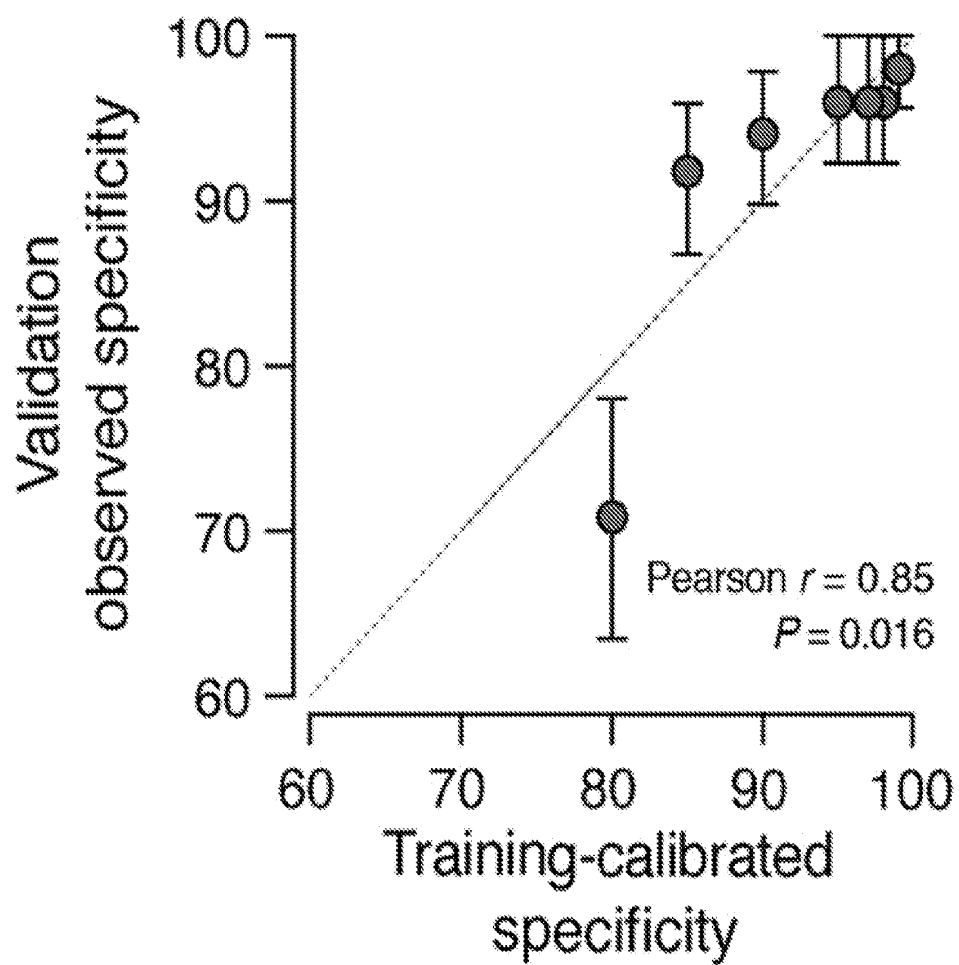
Fig. 85

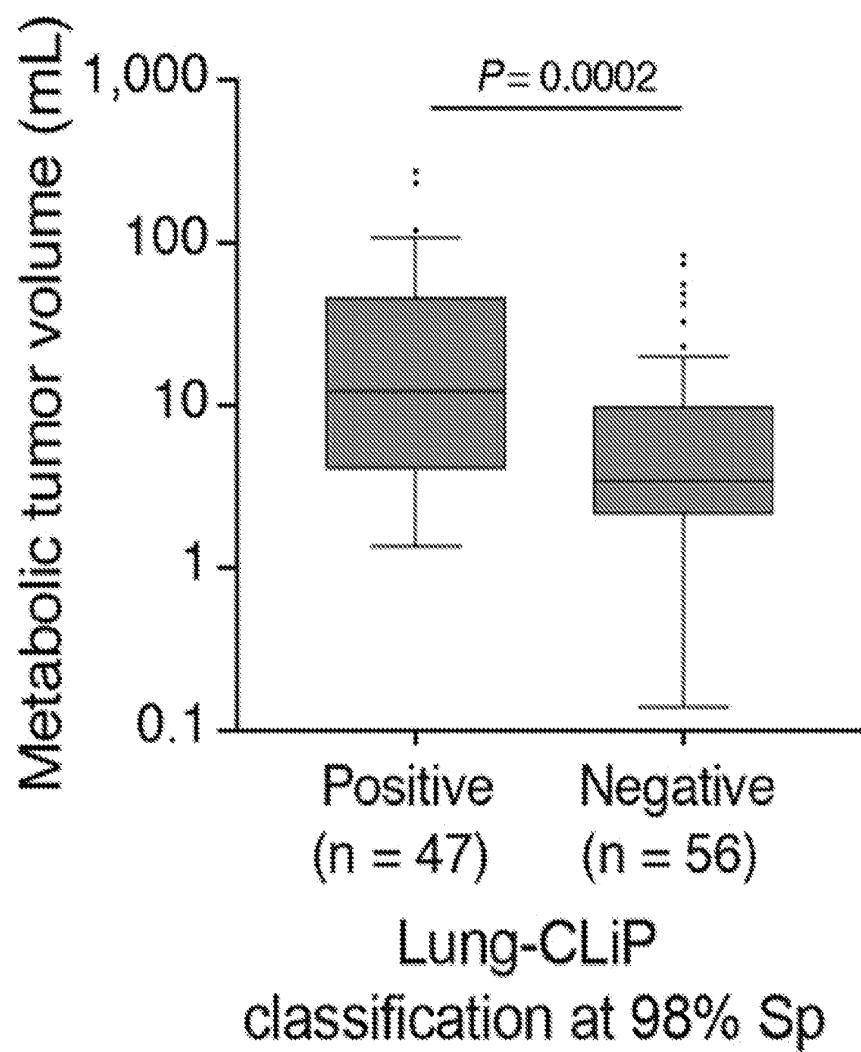
Fig. 86A

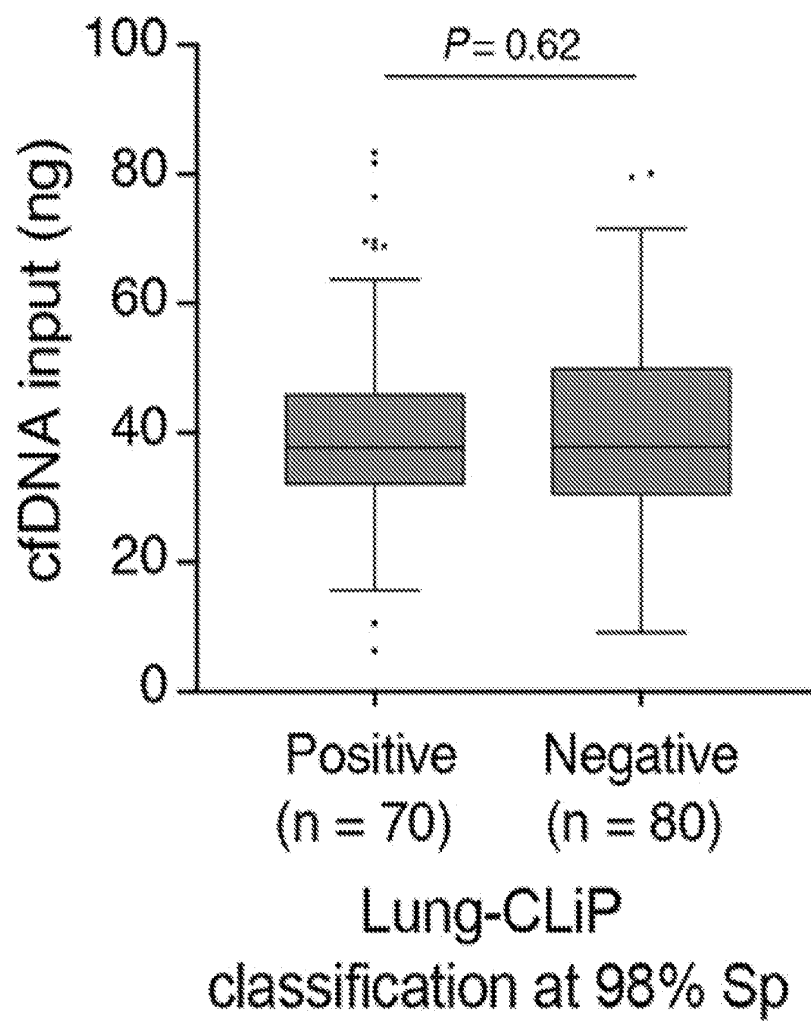
Fig. 86B

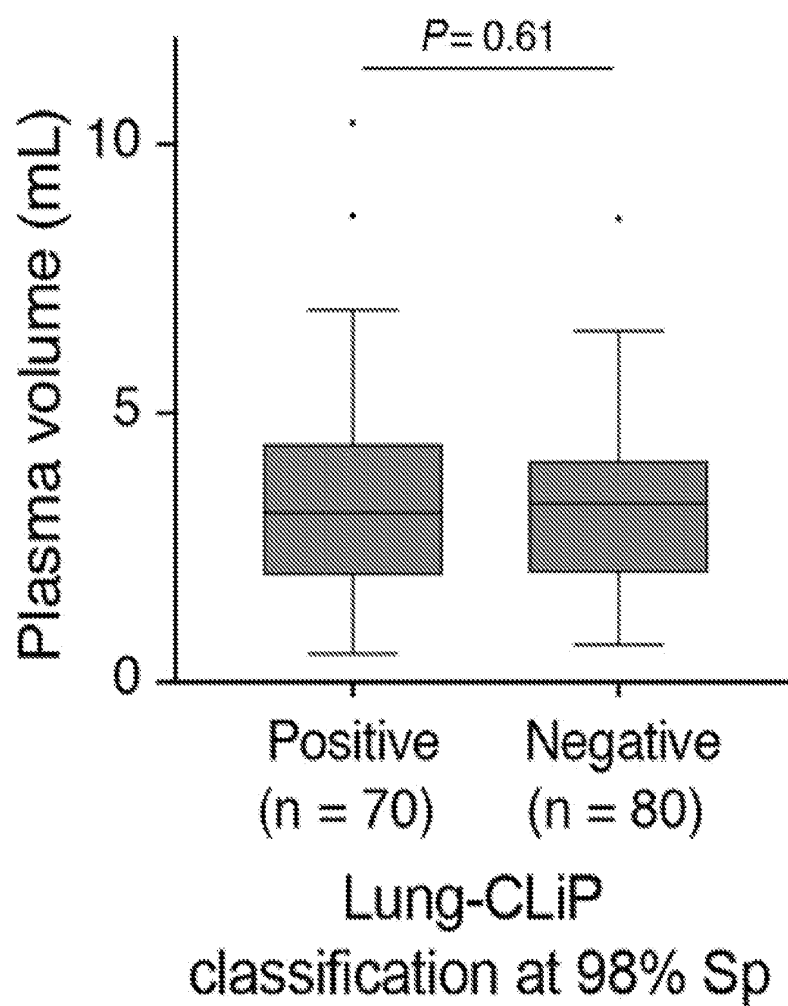
Fig. 86C

Fig. 86D