

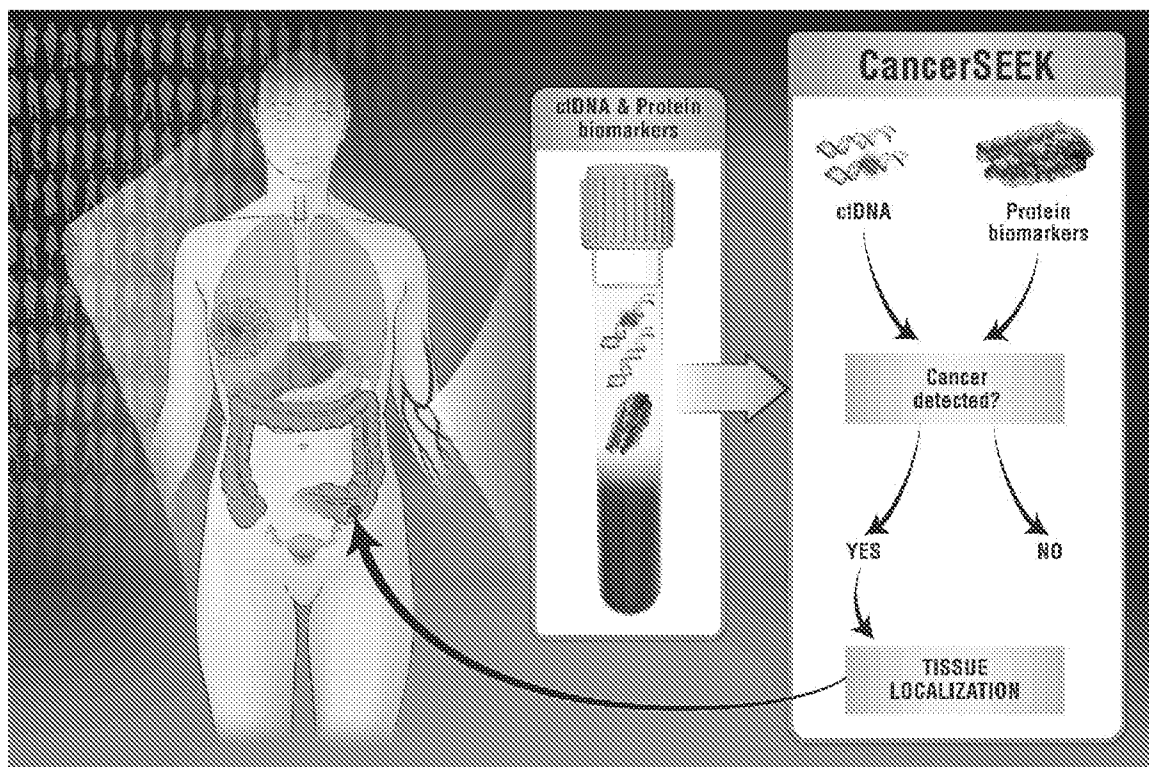


FIG. 1

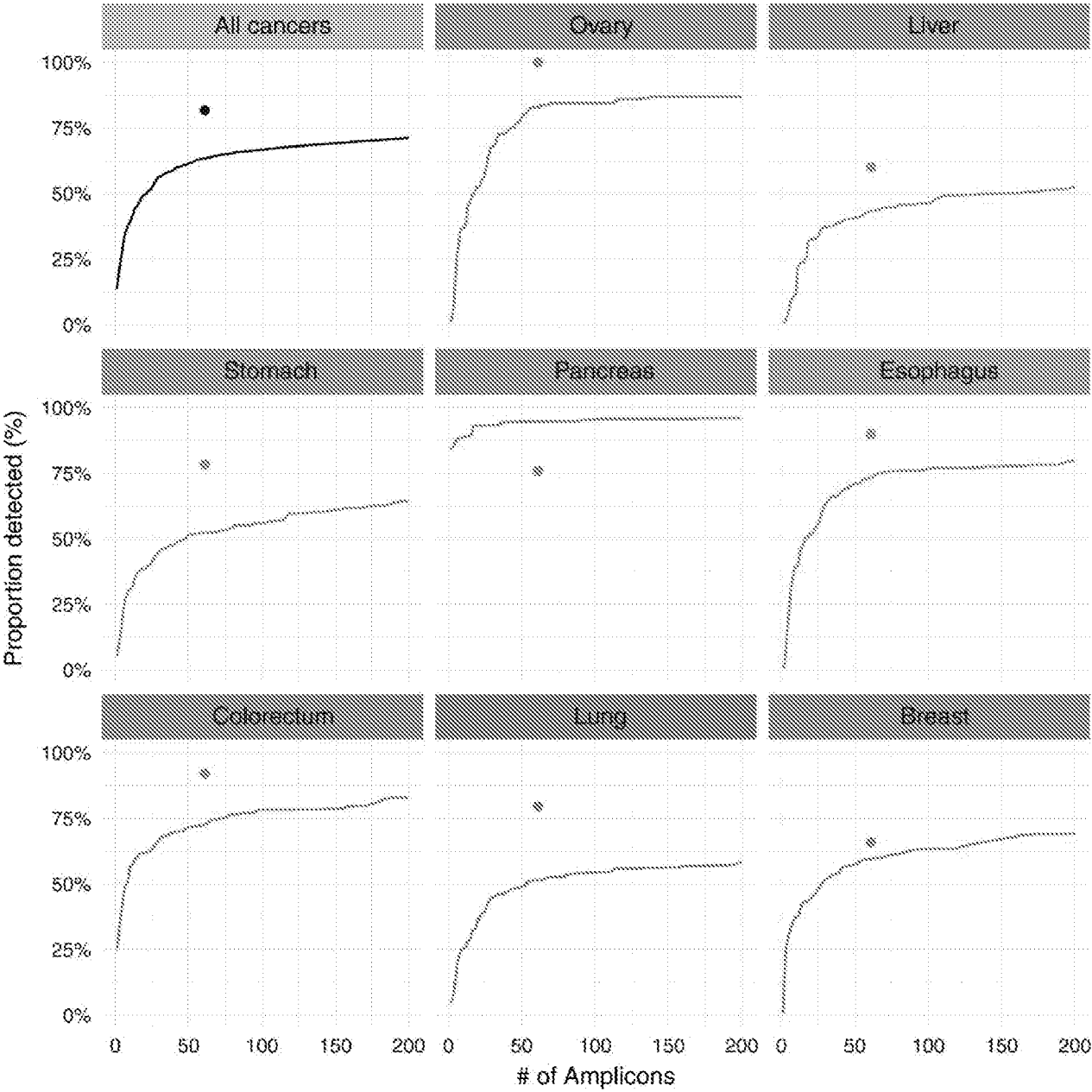


FIG. 2

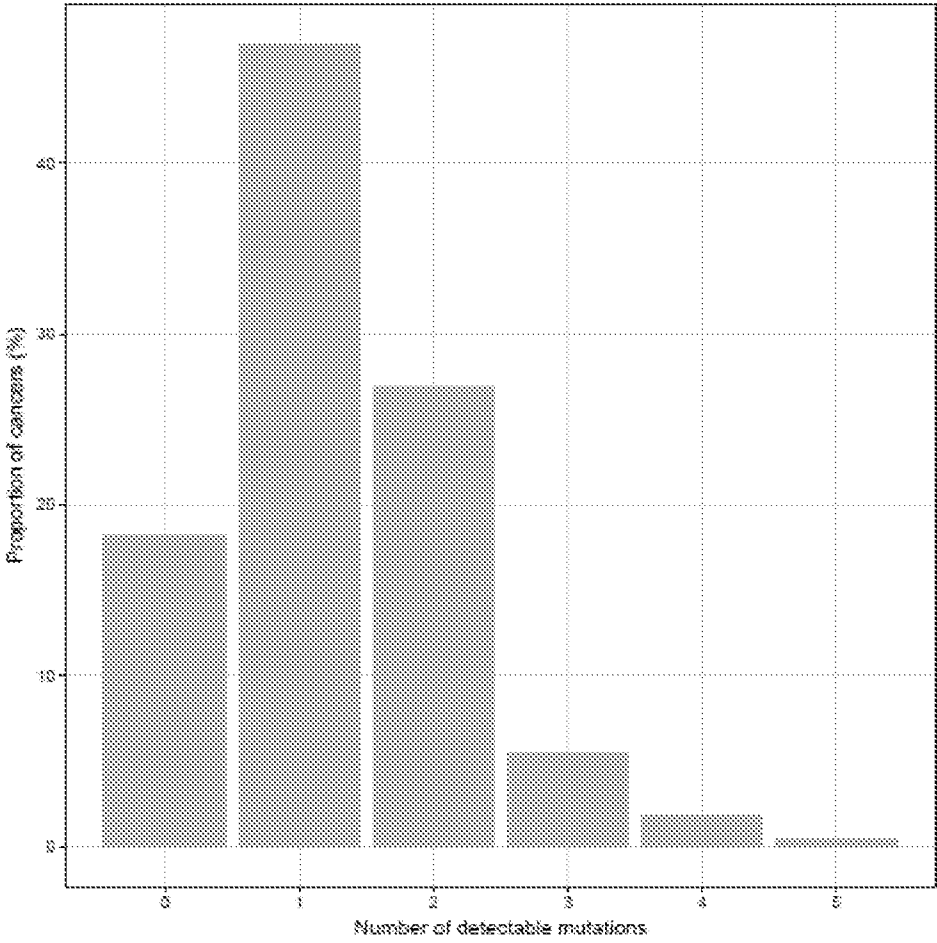


FIG. 3

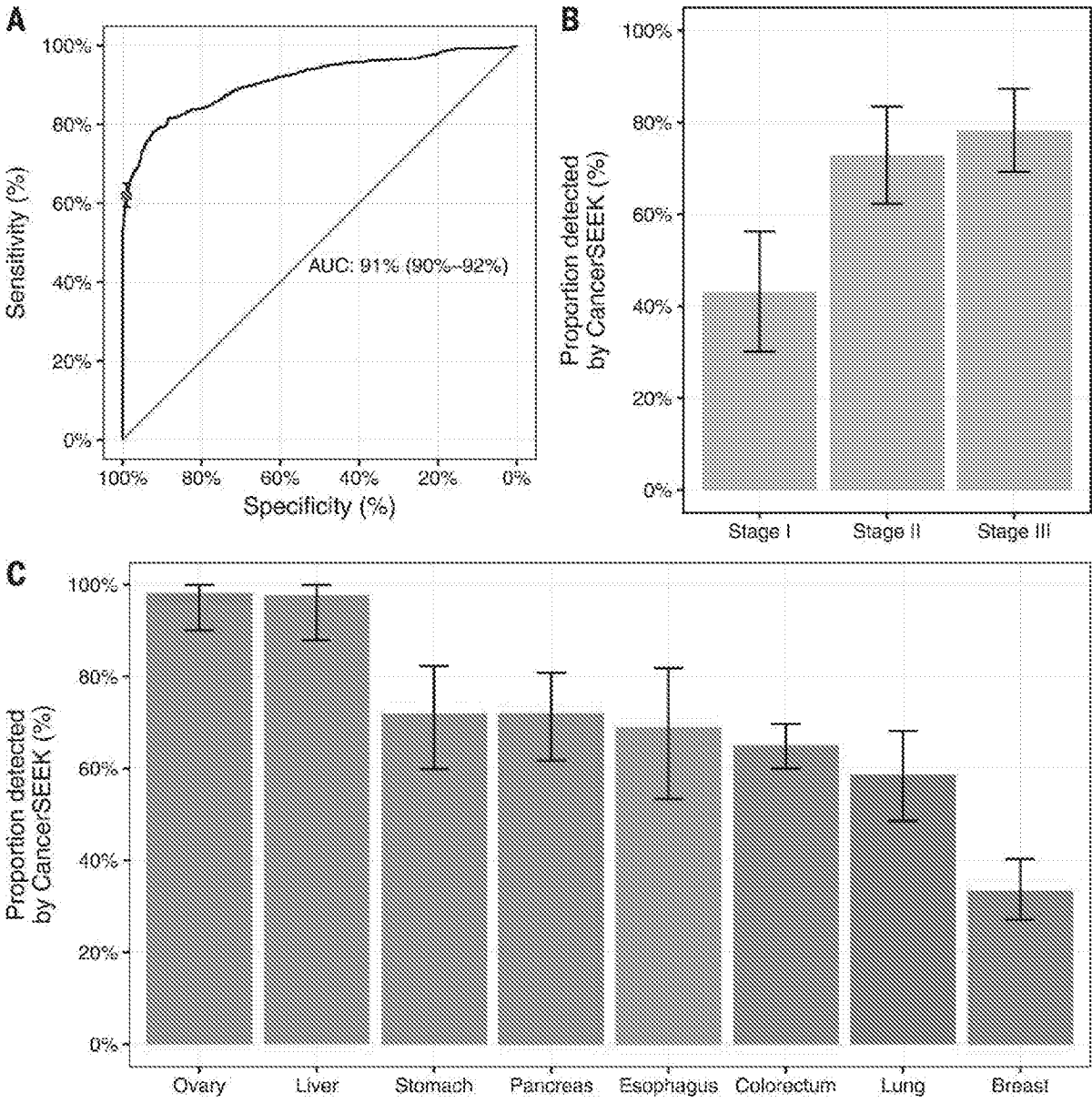


FIG. 4

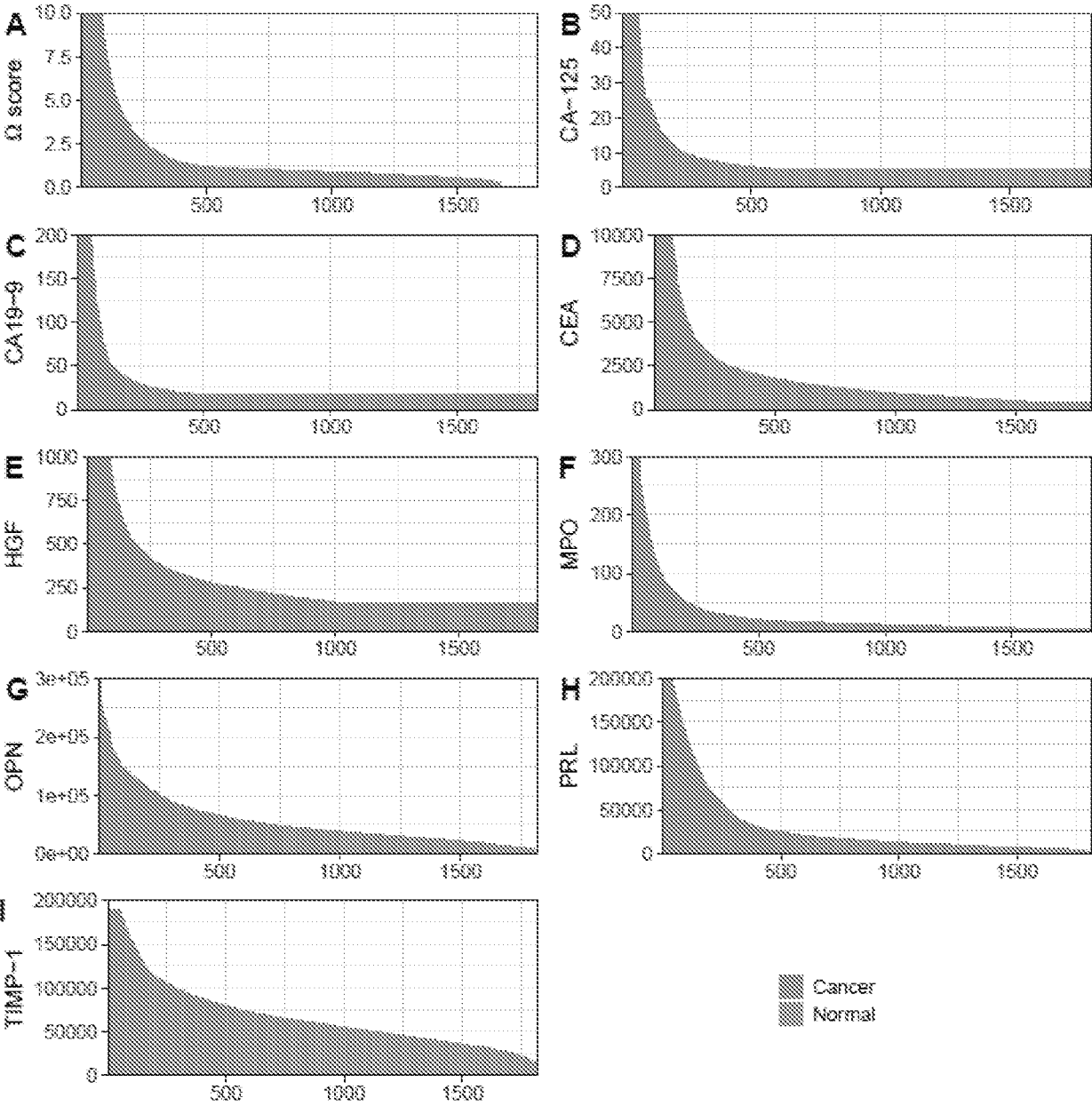


FIG. 5

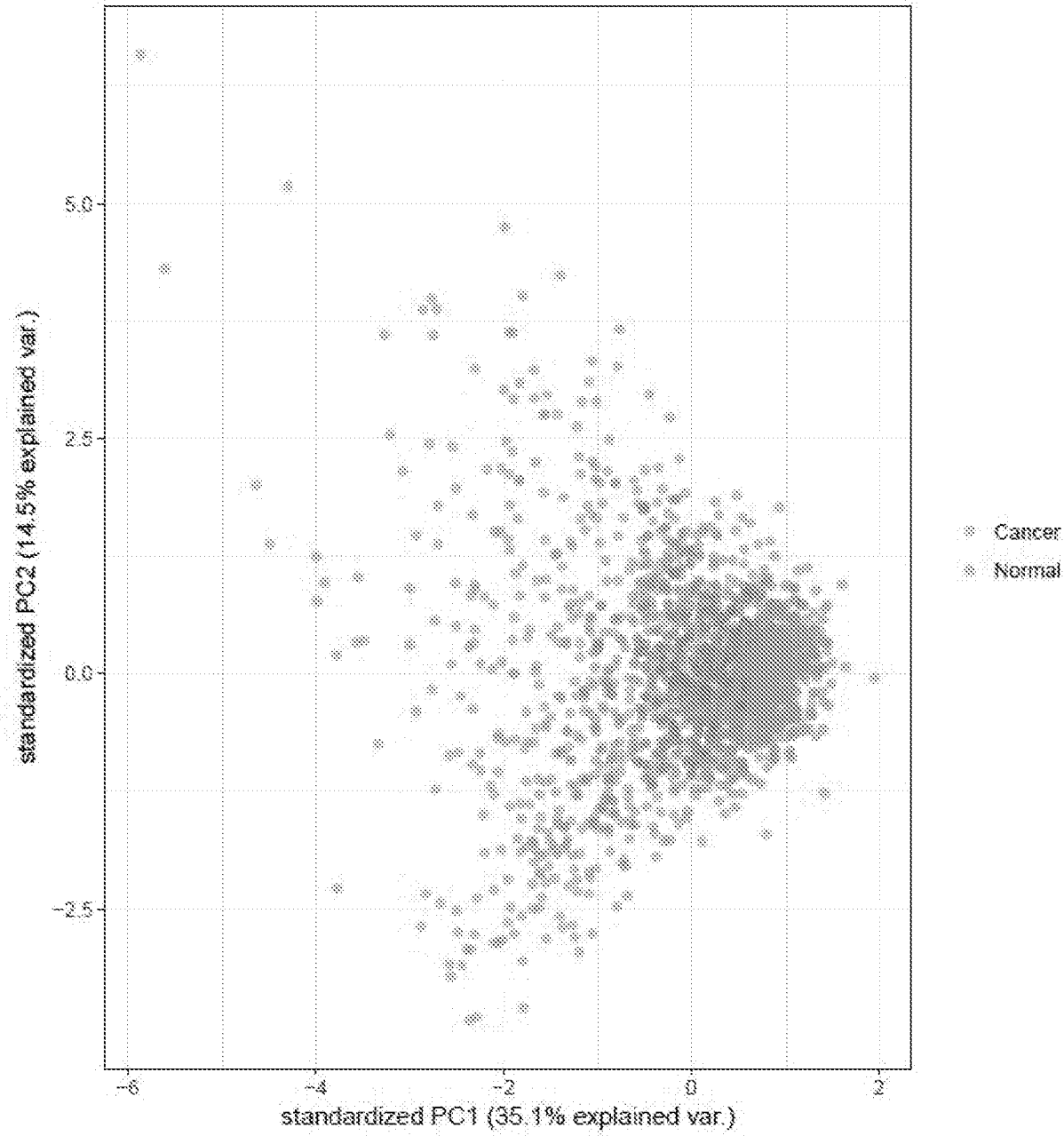


FIG. 6

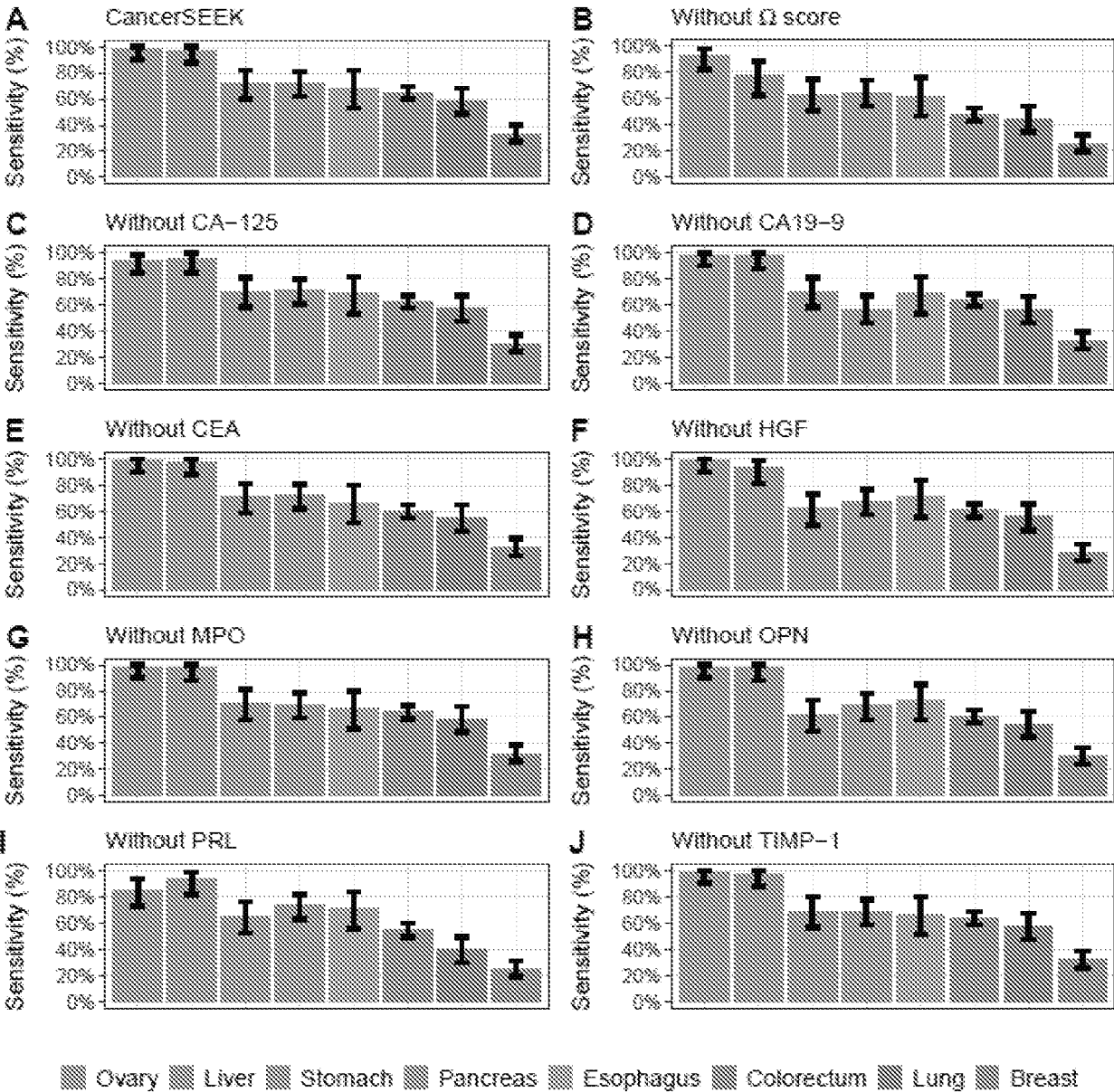


FIG. 7

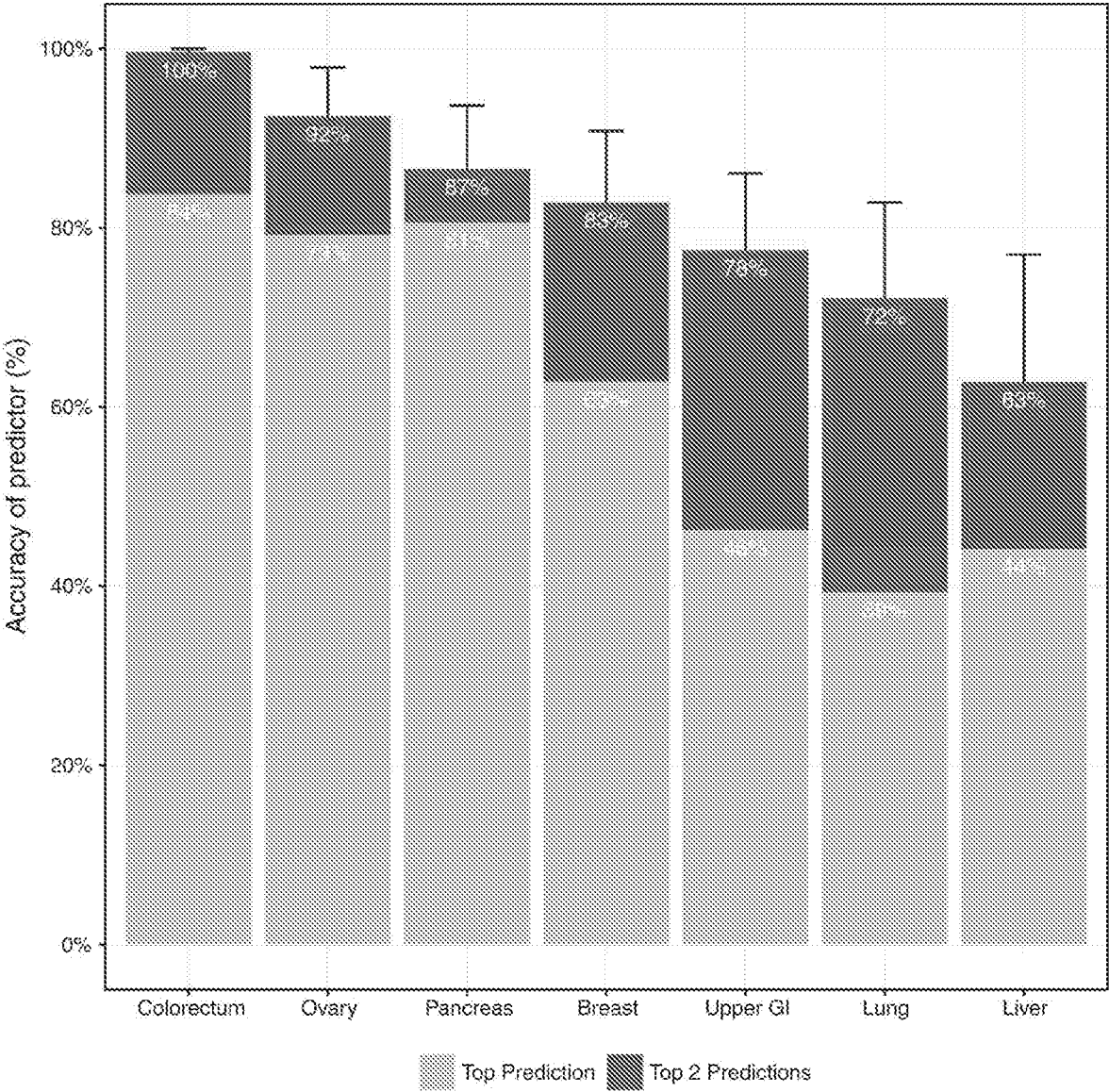


FIG. 8

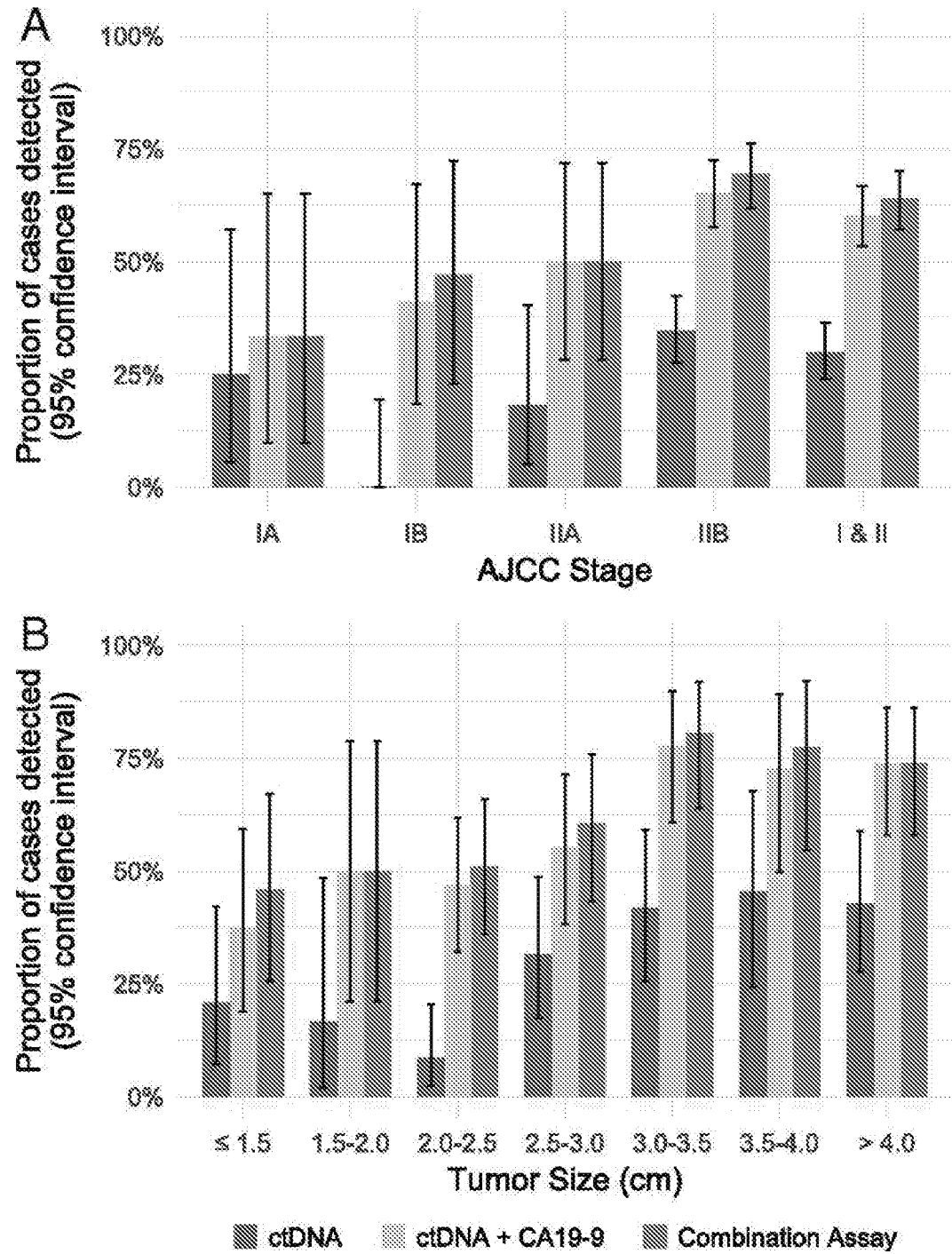


FIG. 9

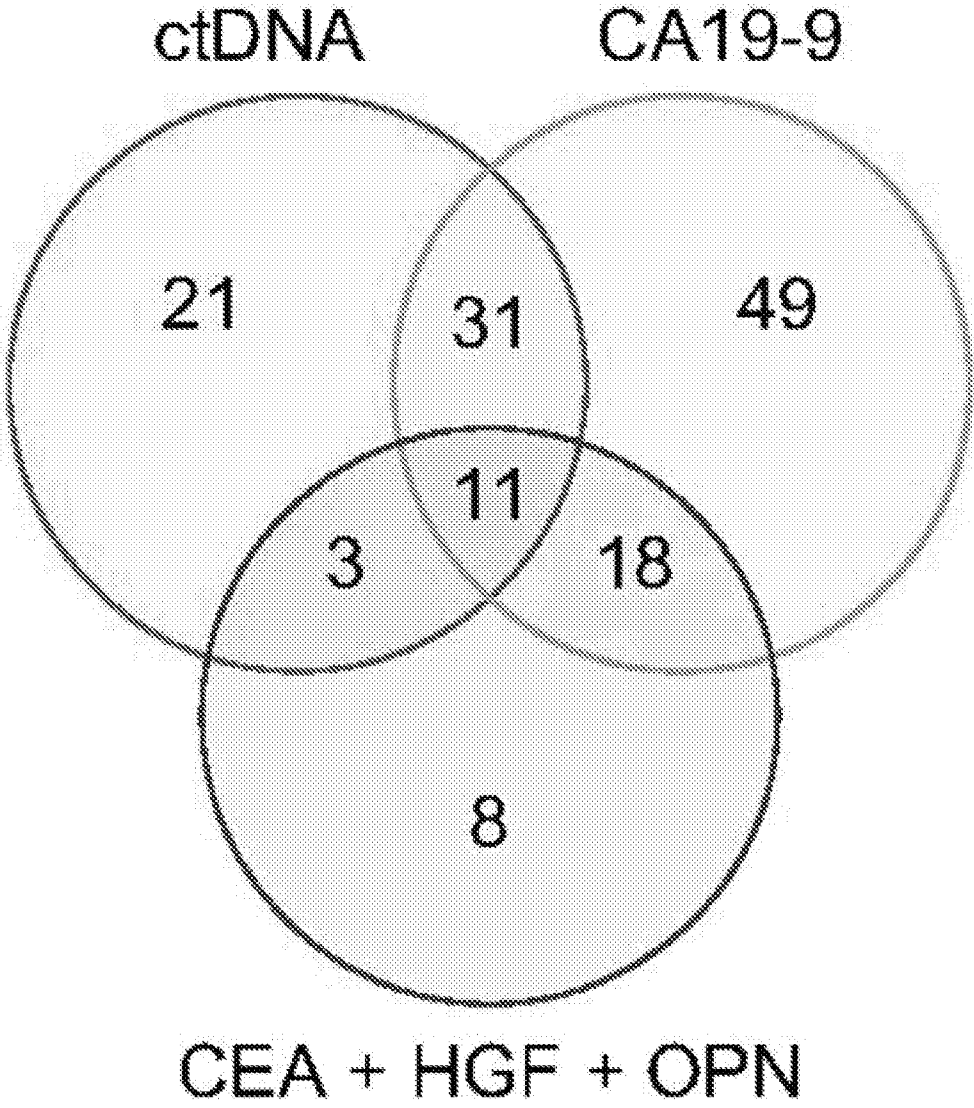


FIG. 10

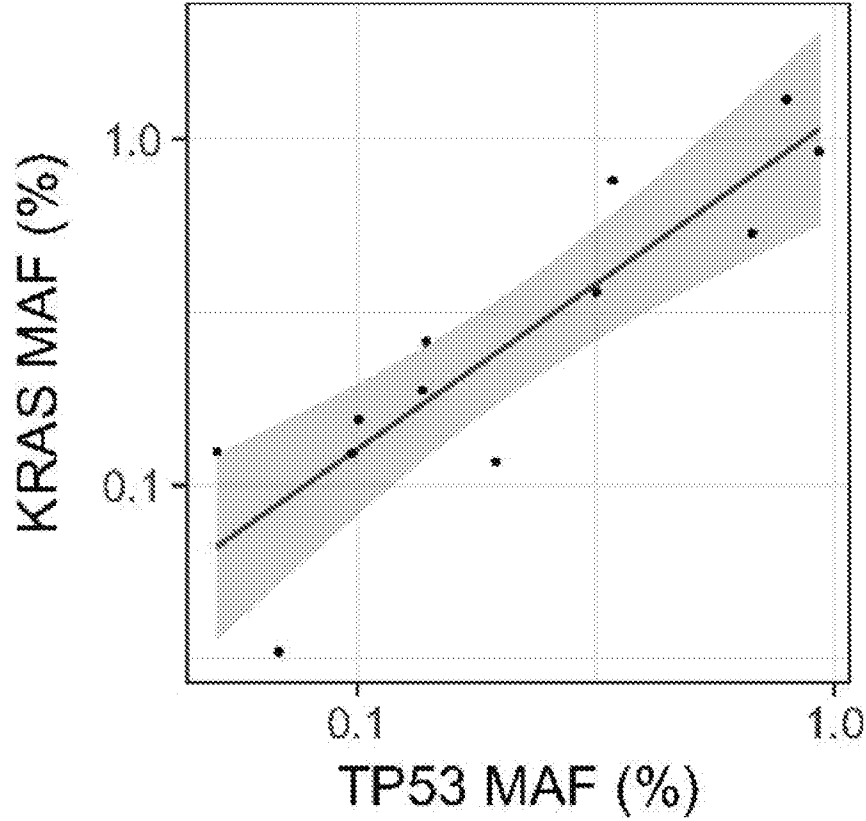


FIG. 11

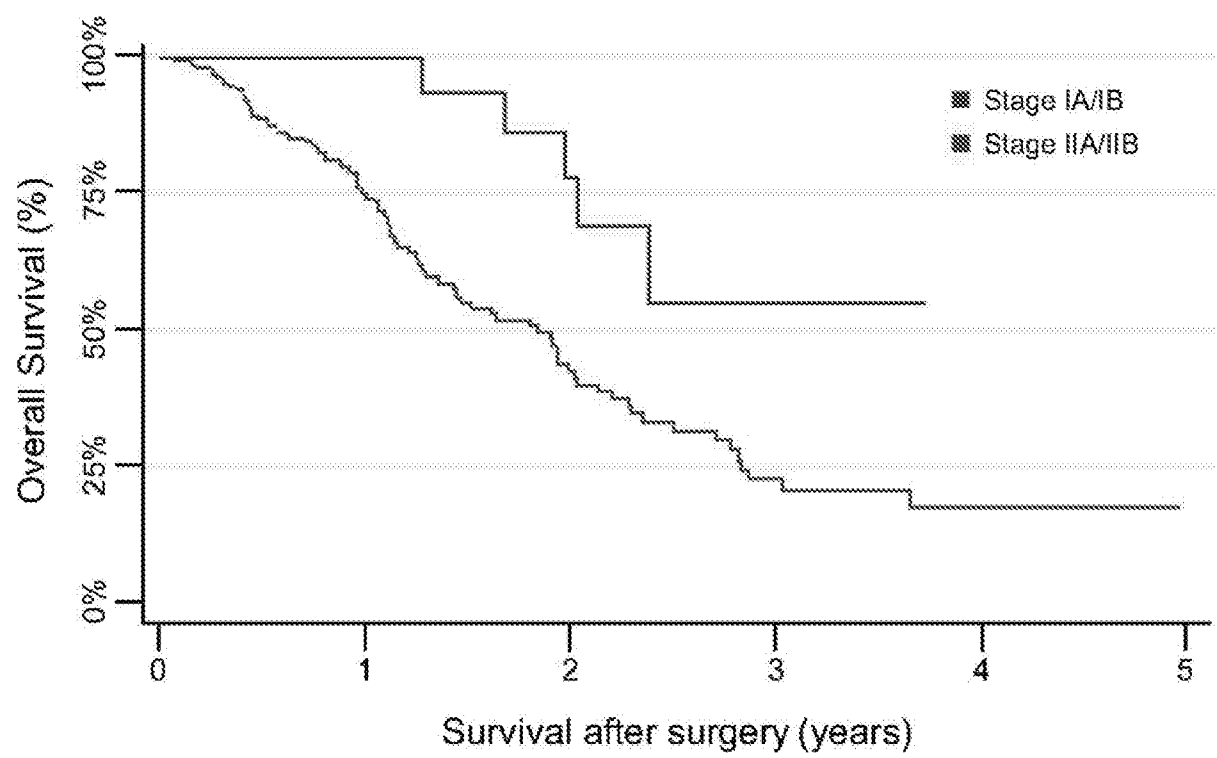
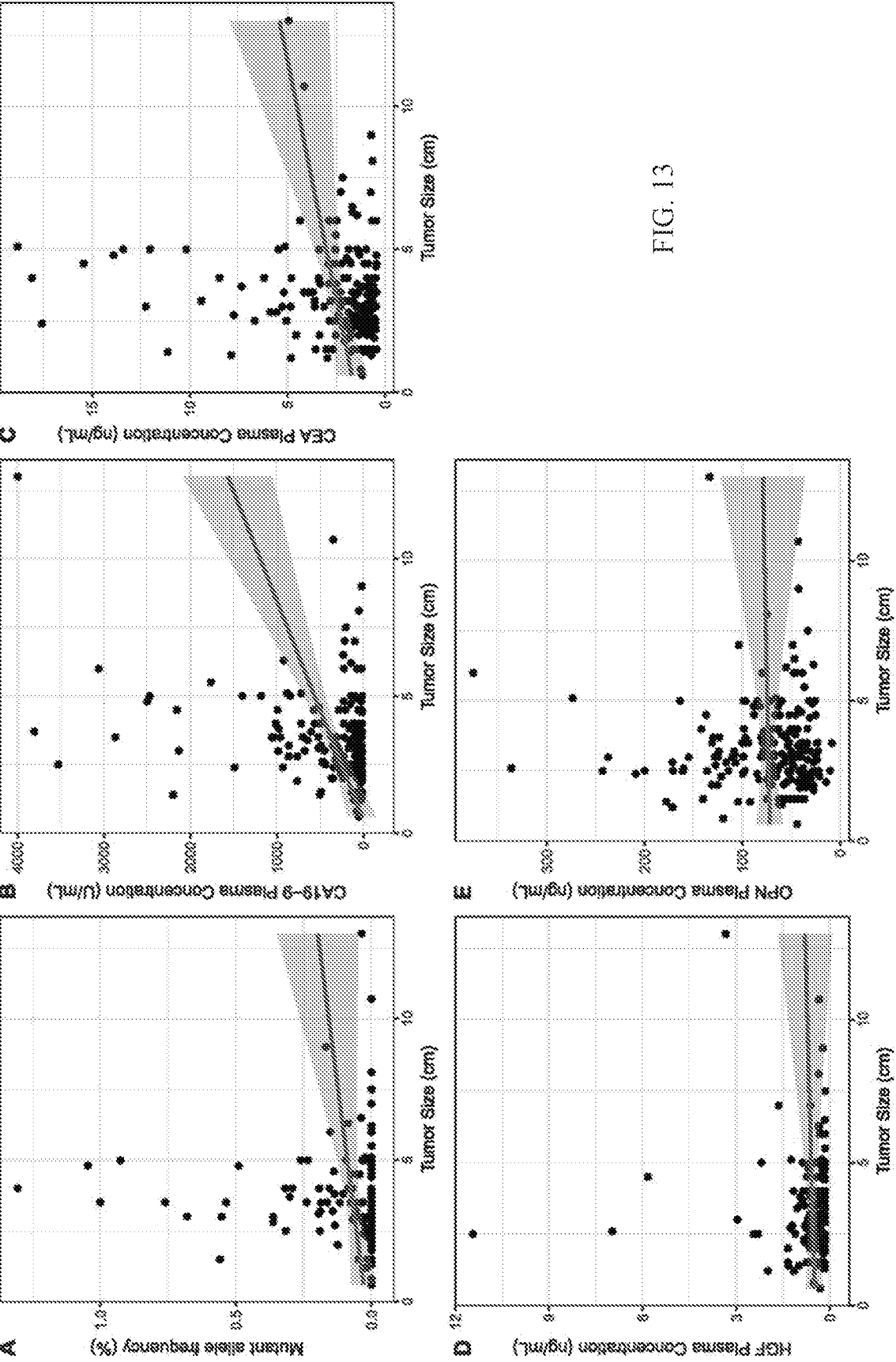


FIG. 12



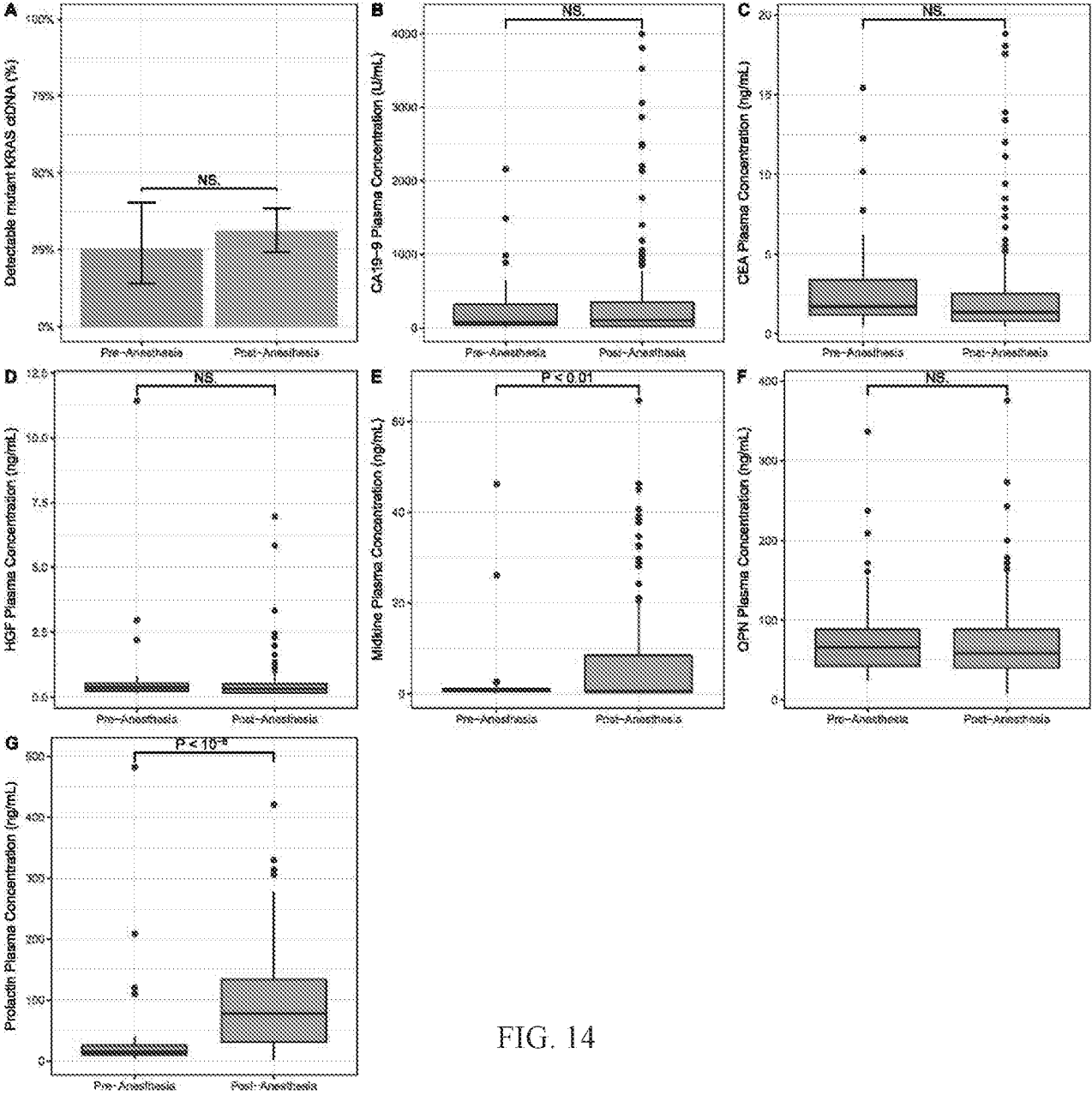


FIG. 14

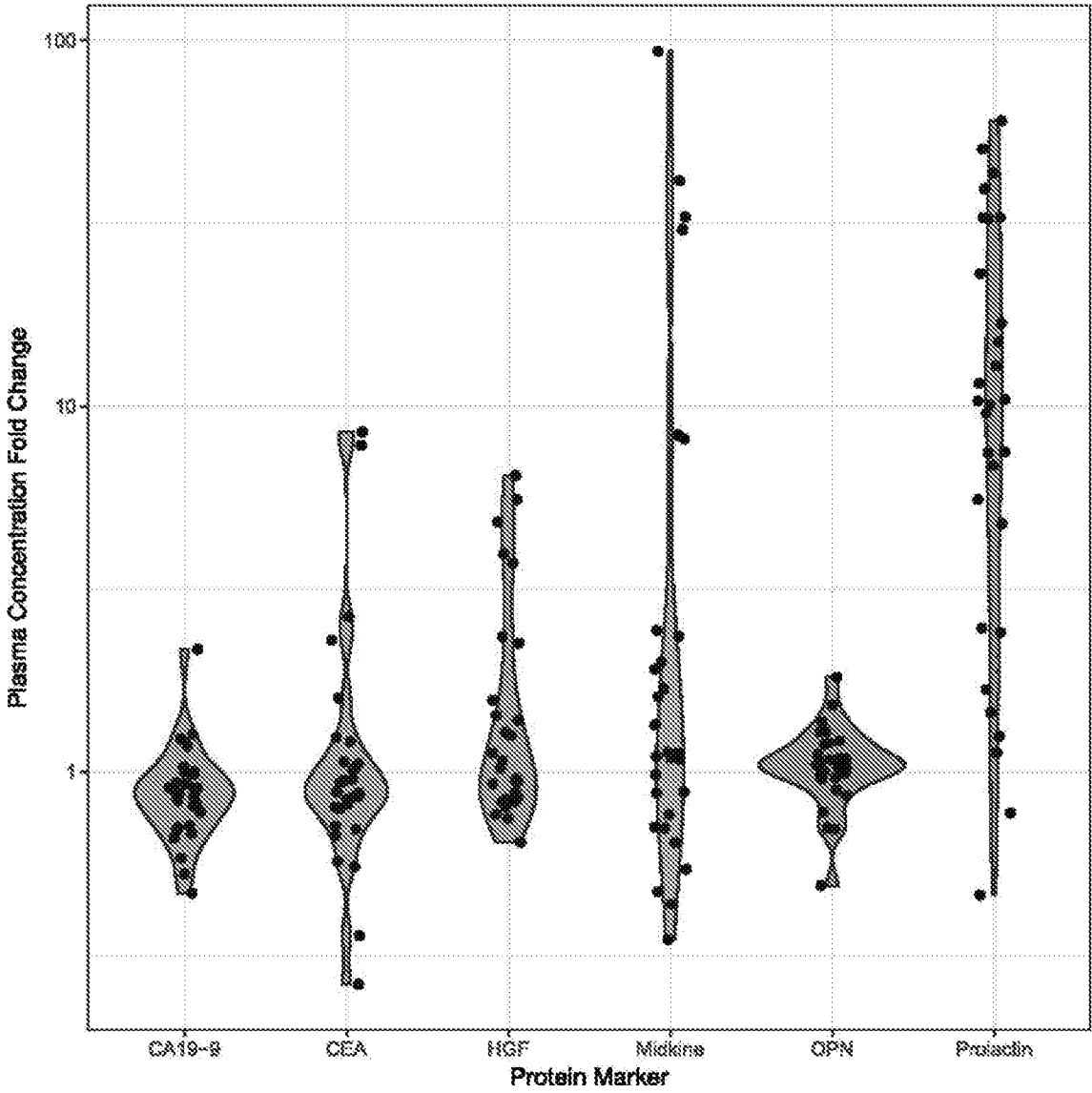


FIG. 15

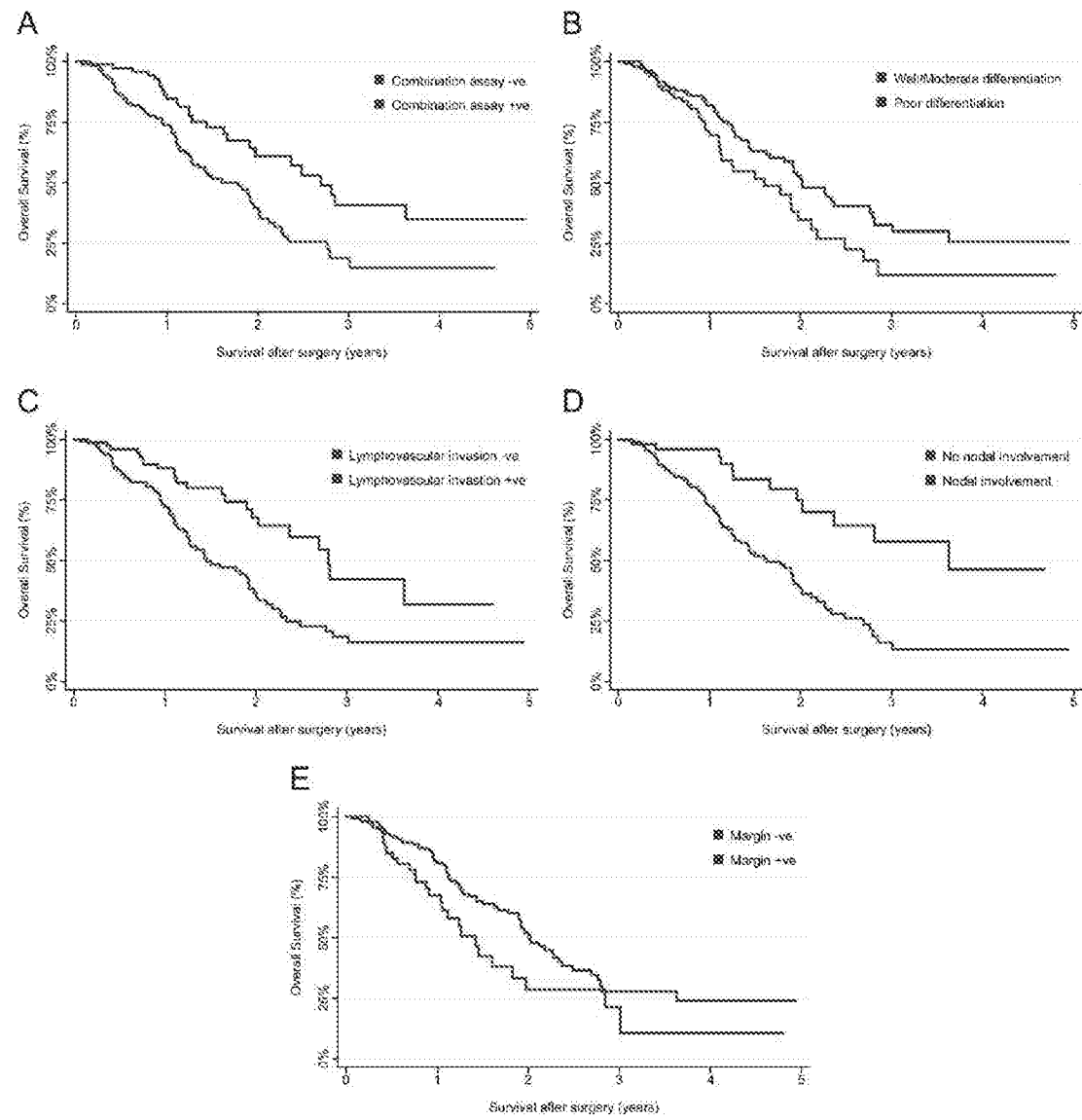


FIG. 16

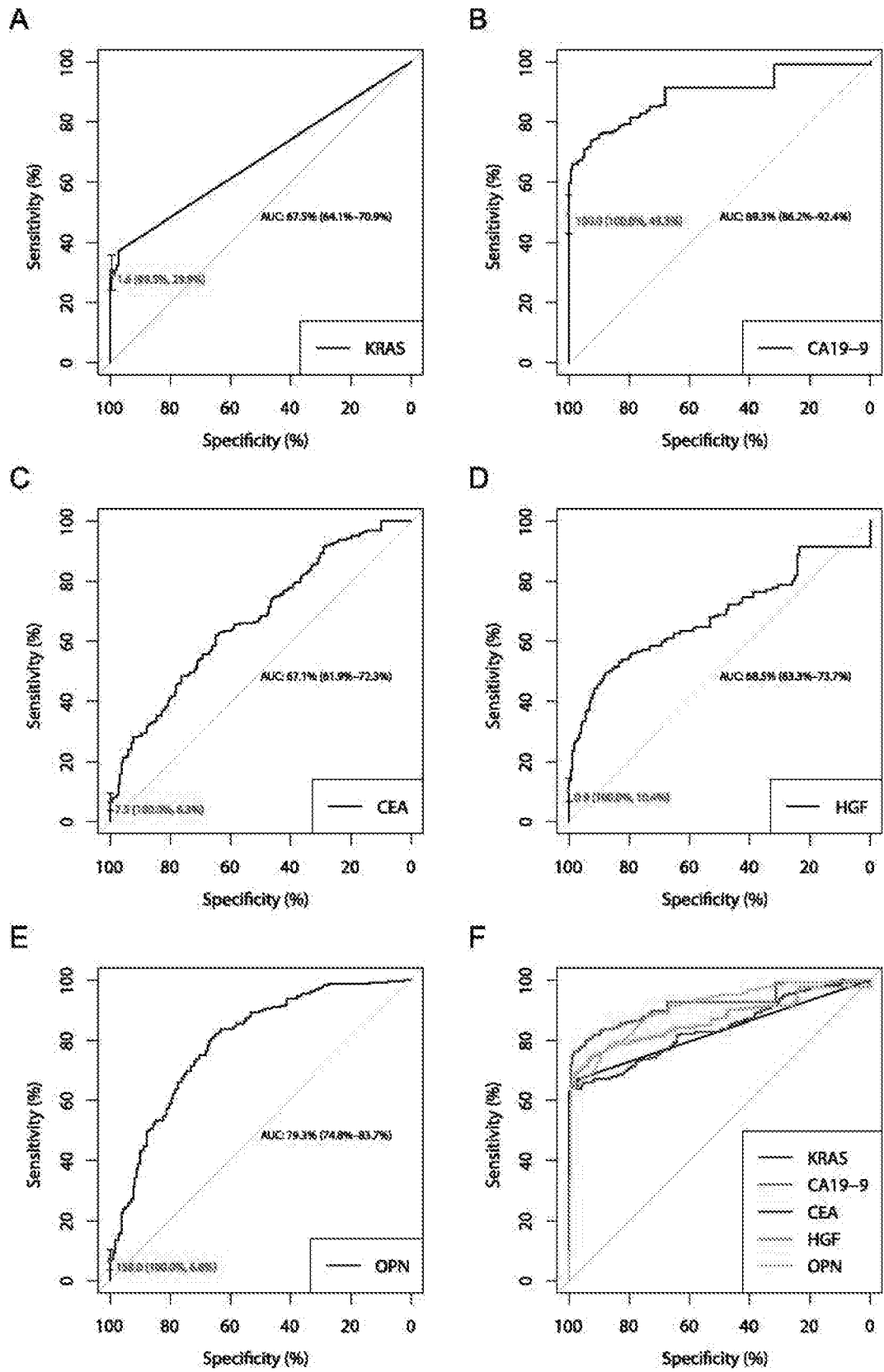


FIG. 17

A

Tumor Type	SEER Incidence	Total #	# ctDNA Positive	# Protein Positive	# ctDNA + Protein Positive	% ctDNA Positive	% Protein Positive	% ctDNA + Protein Positive
Breast	43.8	150	24	30	47	16%	20%	31%
CRC	10	322	130	168	231	40%	52%	72%
Esophagus	0.63	43	21	28	34	49%	65%	79%
Gastric	1.34	65	20	38	39	31%	58%	60%
Liver	1.5	53	39	43	50	74%	81%	94%
Lung	3.31	109	43	30	61	39%	28%	56%
Ovarian	3.83	86	43	45	59	50%	52%	69%
Pancreas	3.8	412	91	248	271	22%	60%	66%
All Cancers	68.21	1240	411	630	792	33%	51%	64%
All Cancers (Incidence Weighted)	68.21	12239	3102.55	4341.11	5974.96	25%	35%	49%

B

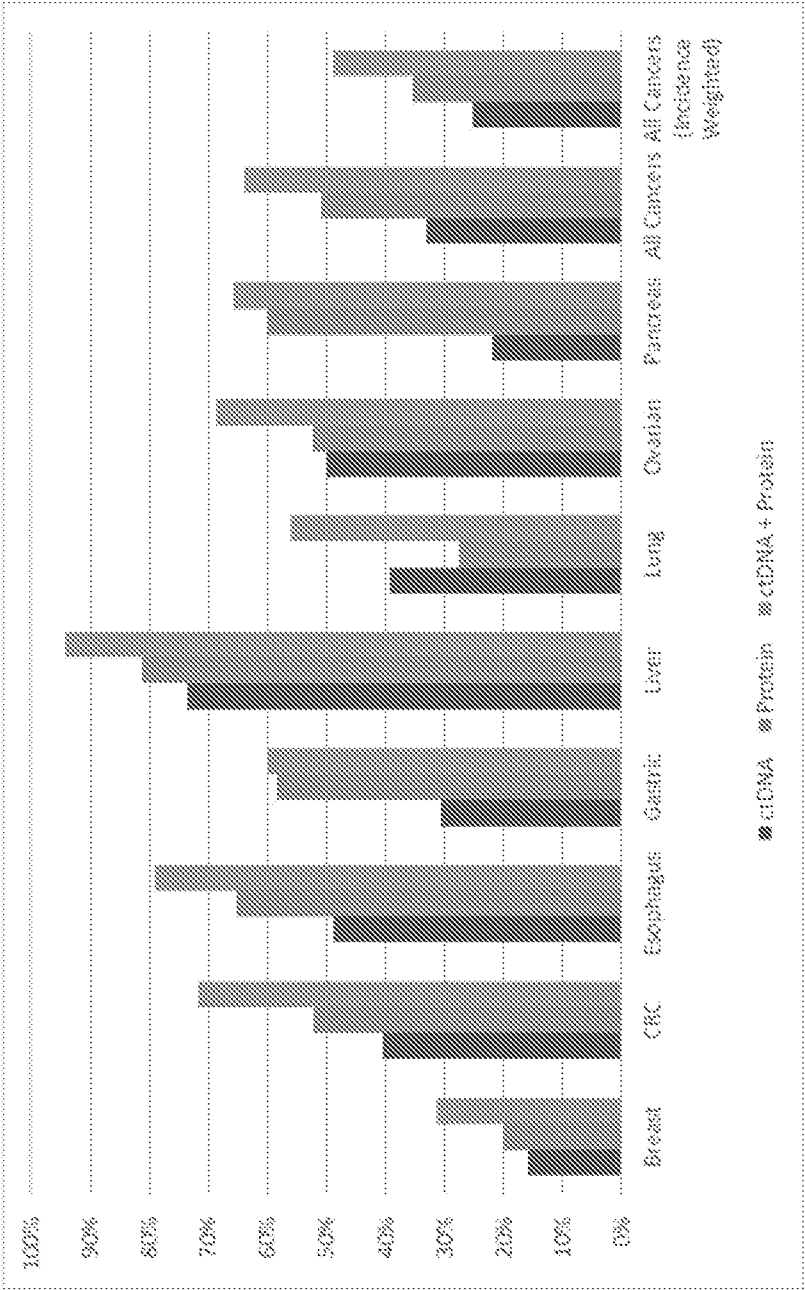


FIG. 18

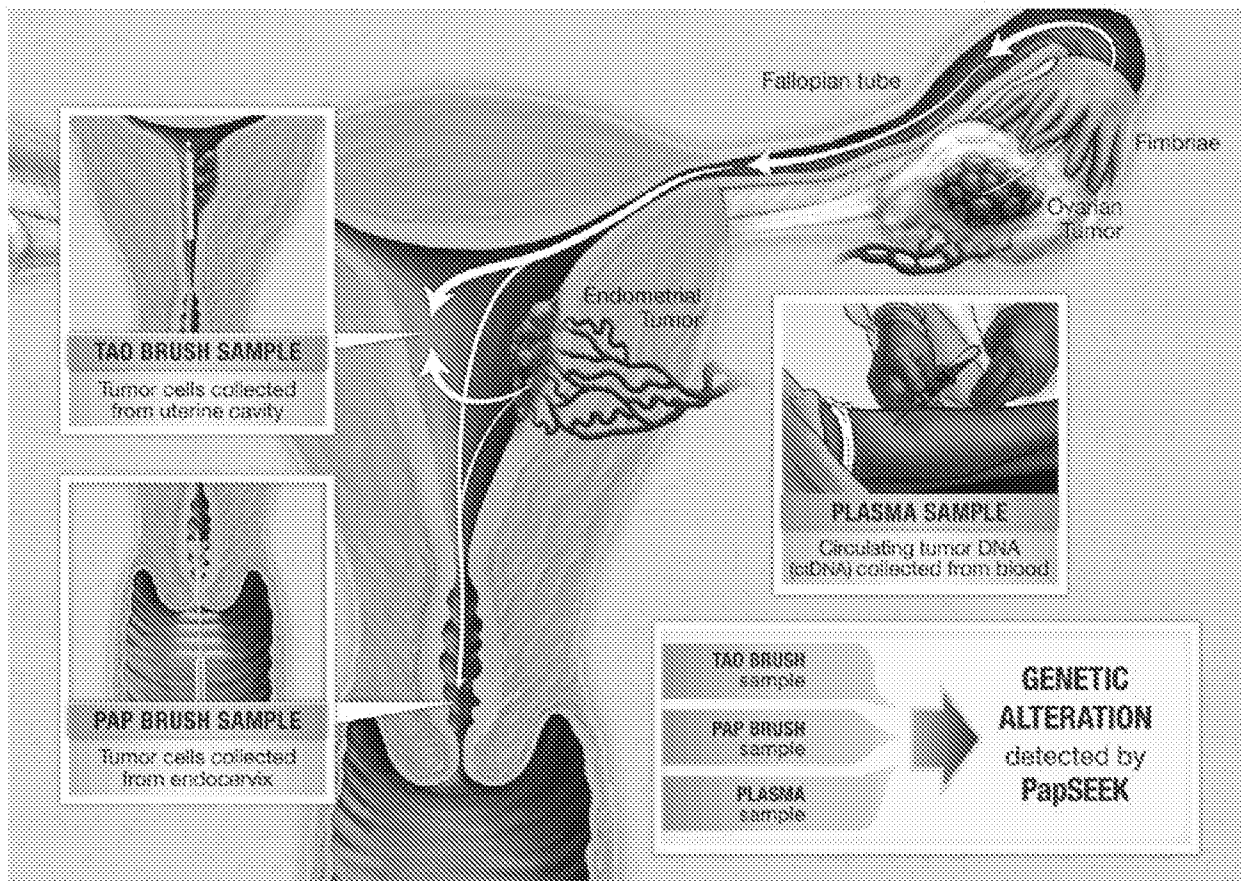


FIG. 19

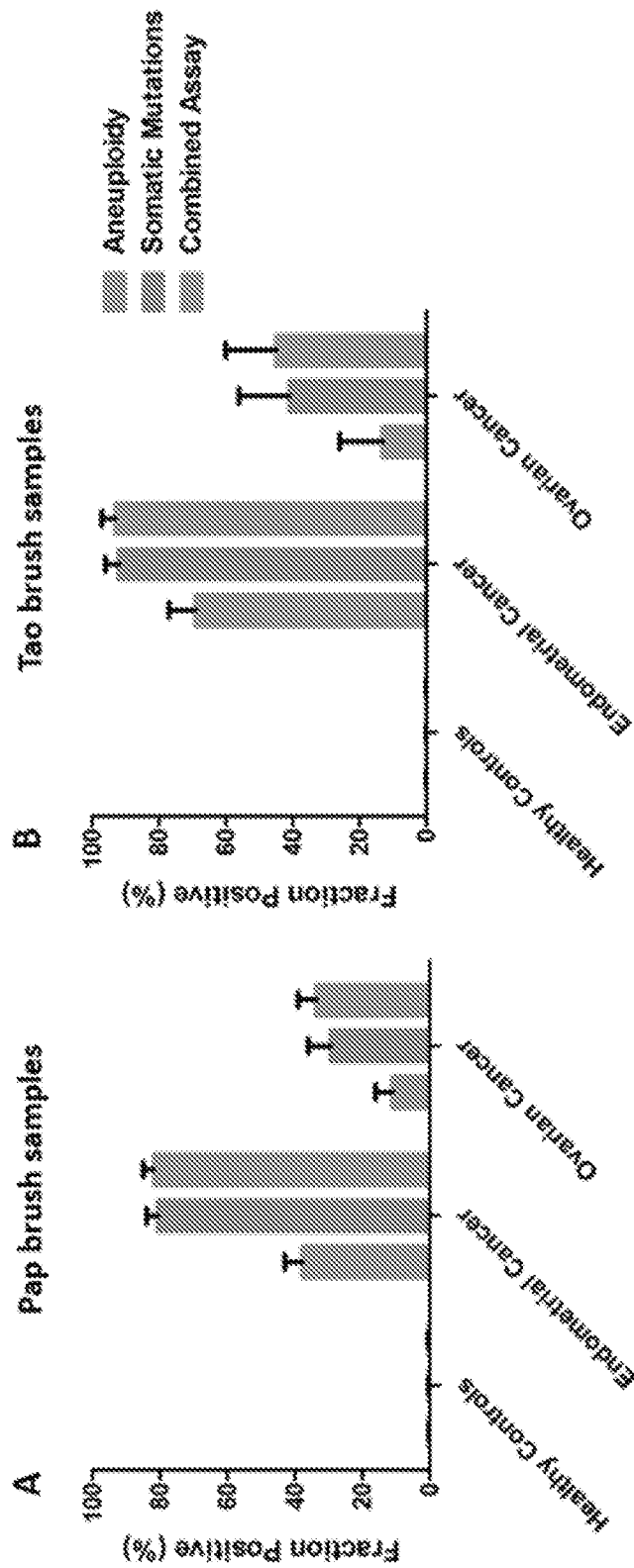


FIG. 20

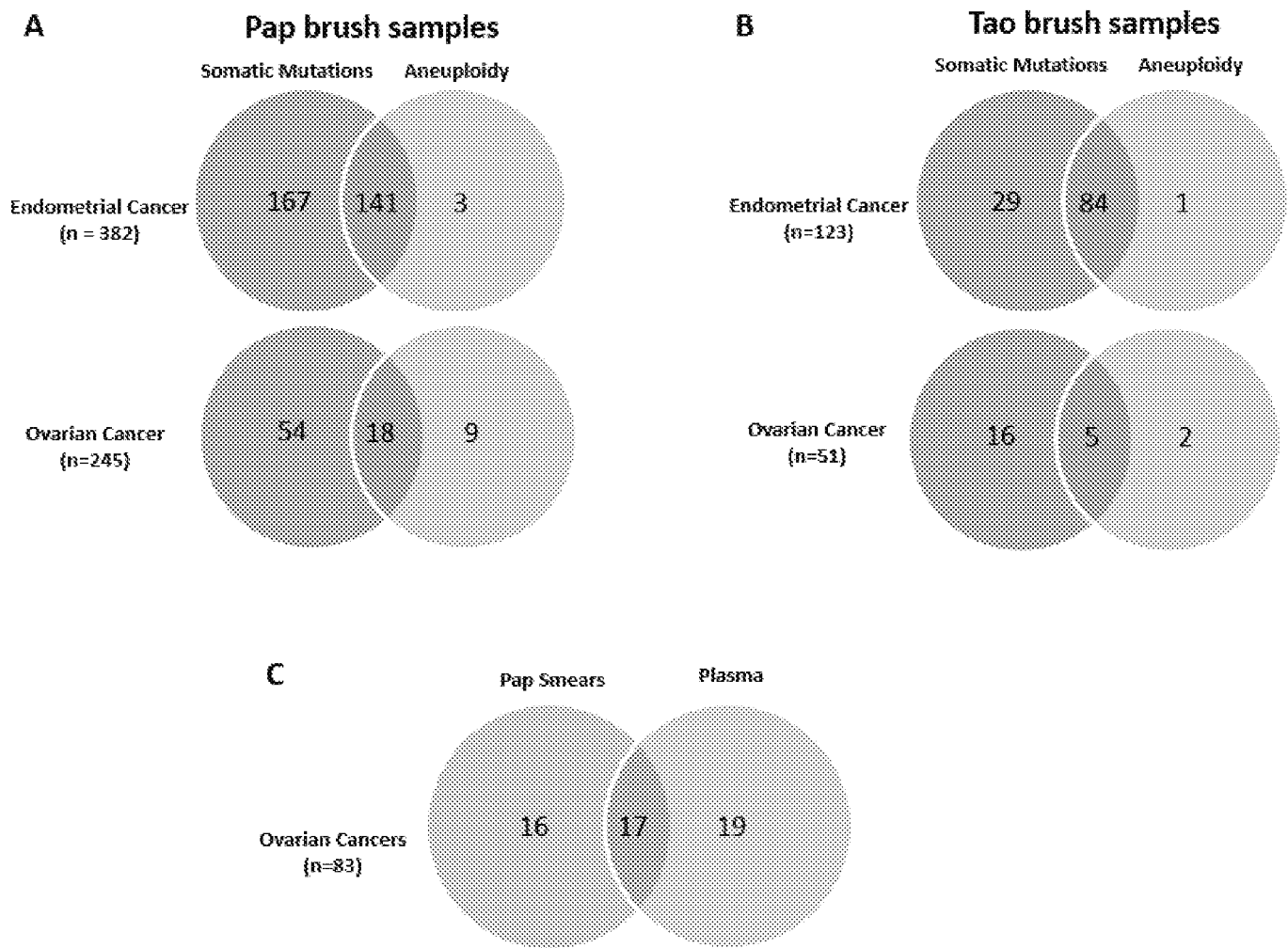


FIG. 21

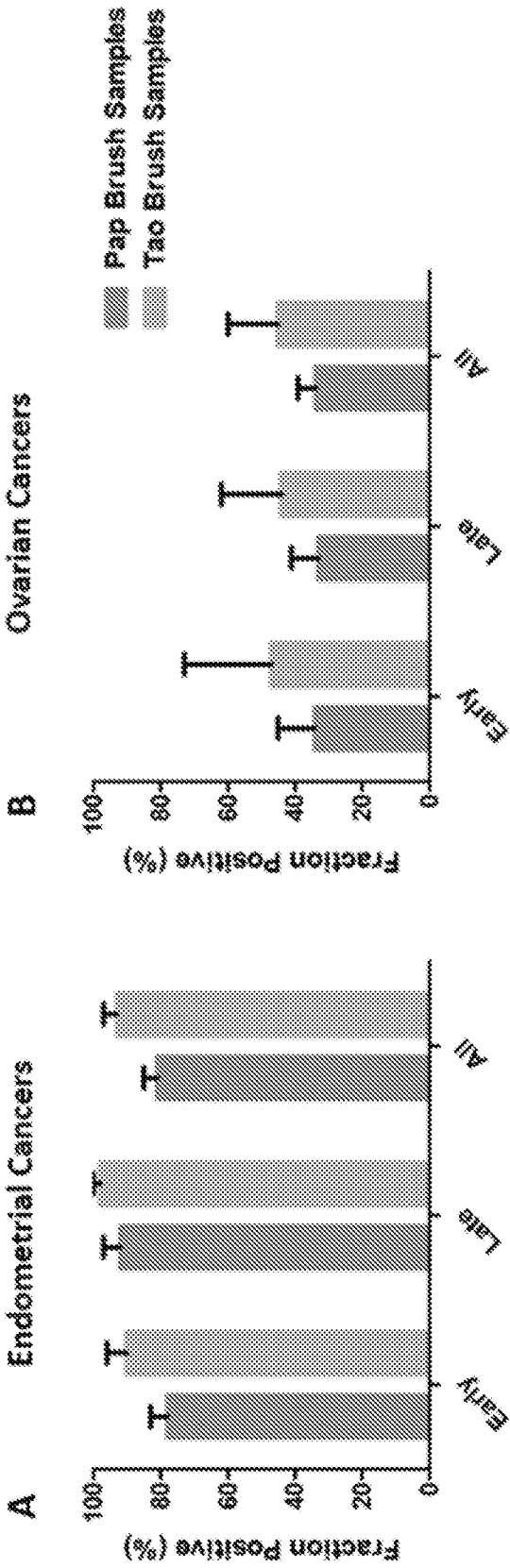


FIG. 22

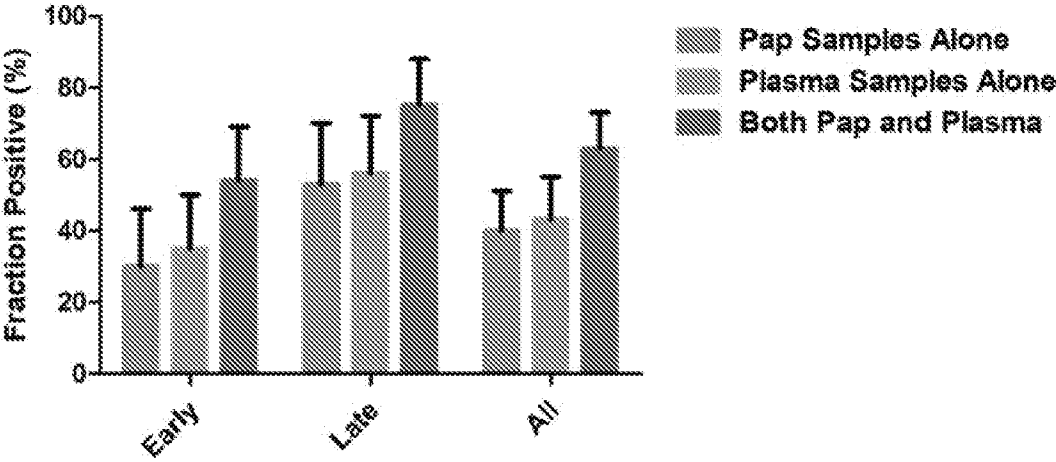


FIG. 23

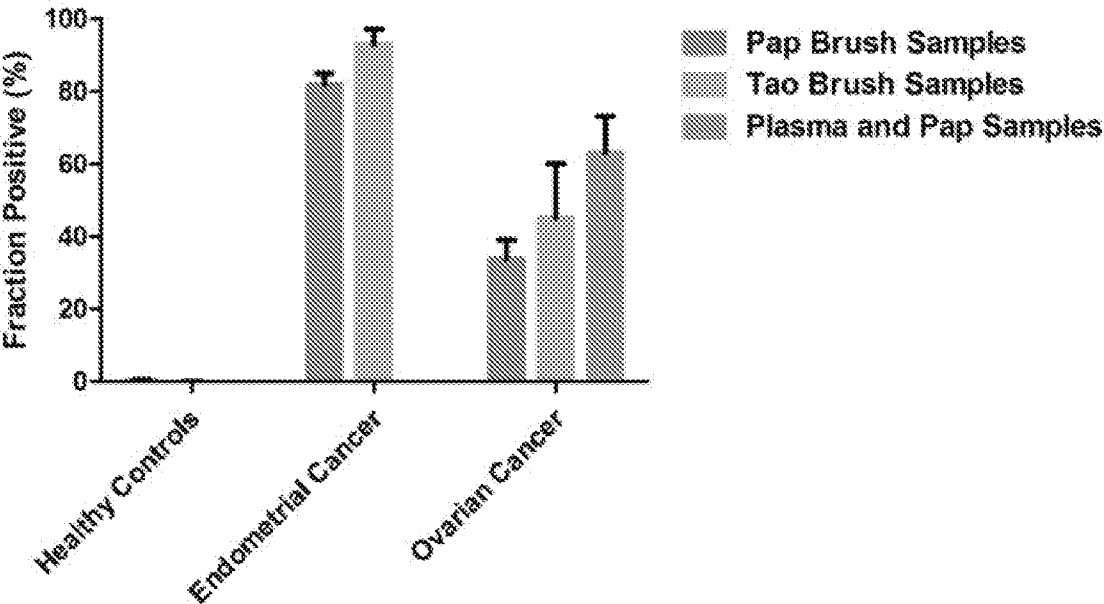


FIG. 24

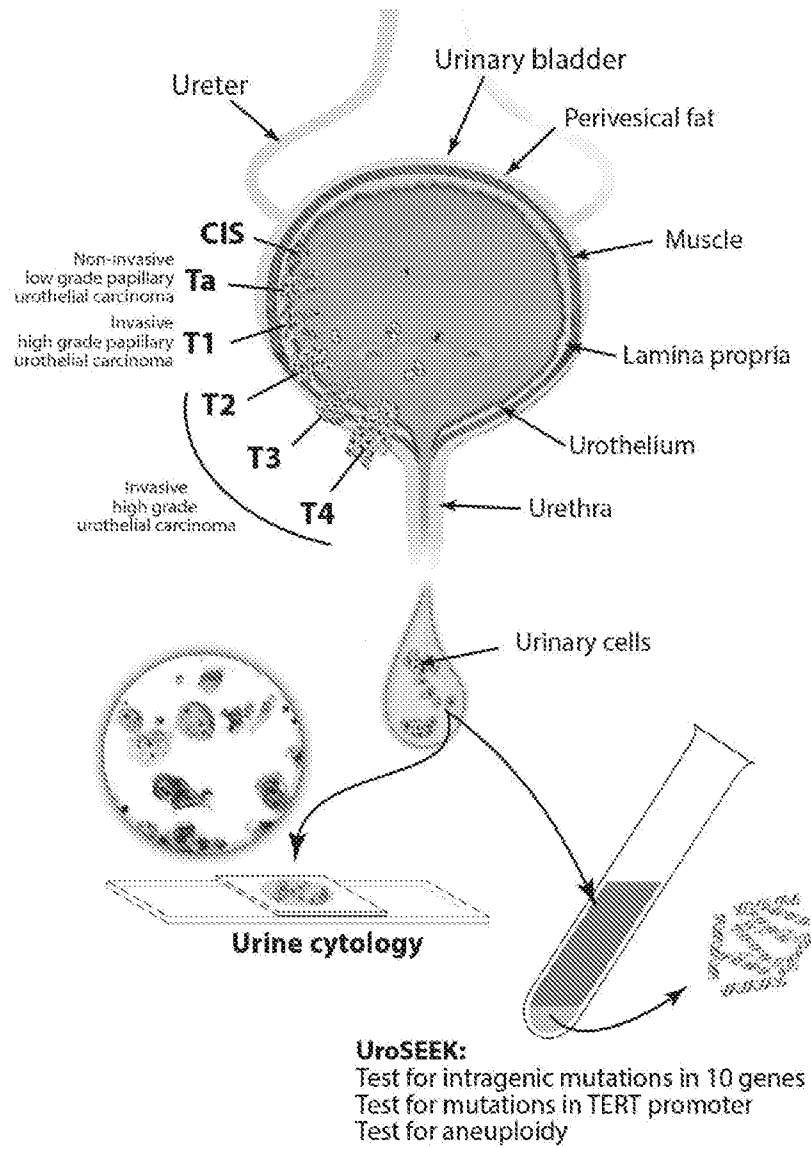


FIG. 25

Early Detection Cohort		Surveillance Cohort	
Urine collected at patient presentation (n= 570)		Urine collected following surgery (n= 322)	
Developed Bladder Cancer 31%	Did Not Develop Bladder Cancer 69%	Developed Bladder Cancer 58%	Did not Develop Bladder Cancer 42%
UroSEEK positive 83%	UroSEEK positive 7%	UroSEEK positive 68%	UroSEEK positive 20%
Cytology positive 43%	Cytology positive 0%	Cytology positive 25%	Cytology positive 0%
Sensitivity (UroSEEK/Cytology Combined) 95%	Specificity (UroSEEK/Cytology Combined) 93%	Sensitivity (UroSEEK/Cytology Combined) 71%	Specificity (UroSEEK/Cytology Combined) 82%

FIG. 26

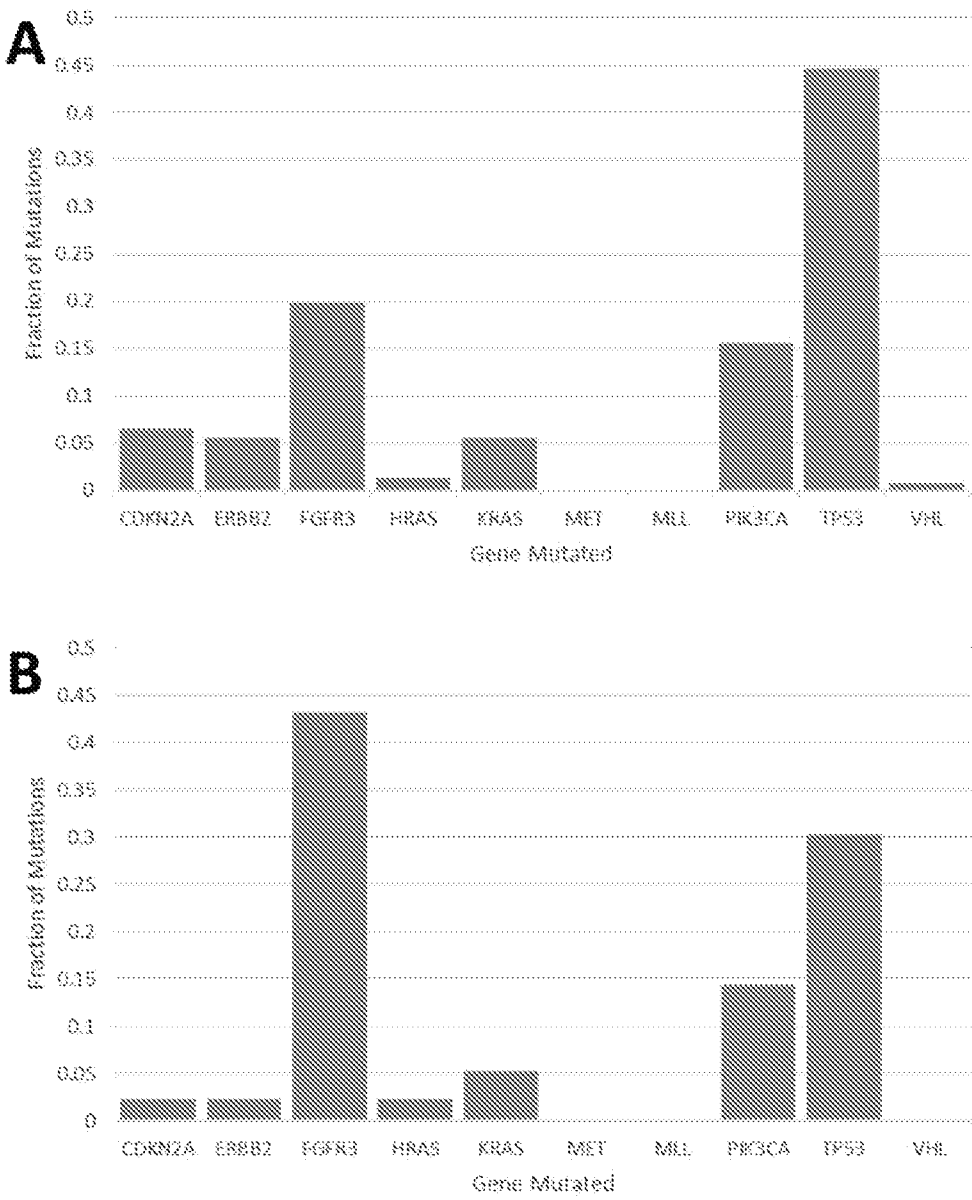


FIG. 27

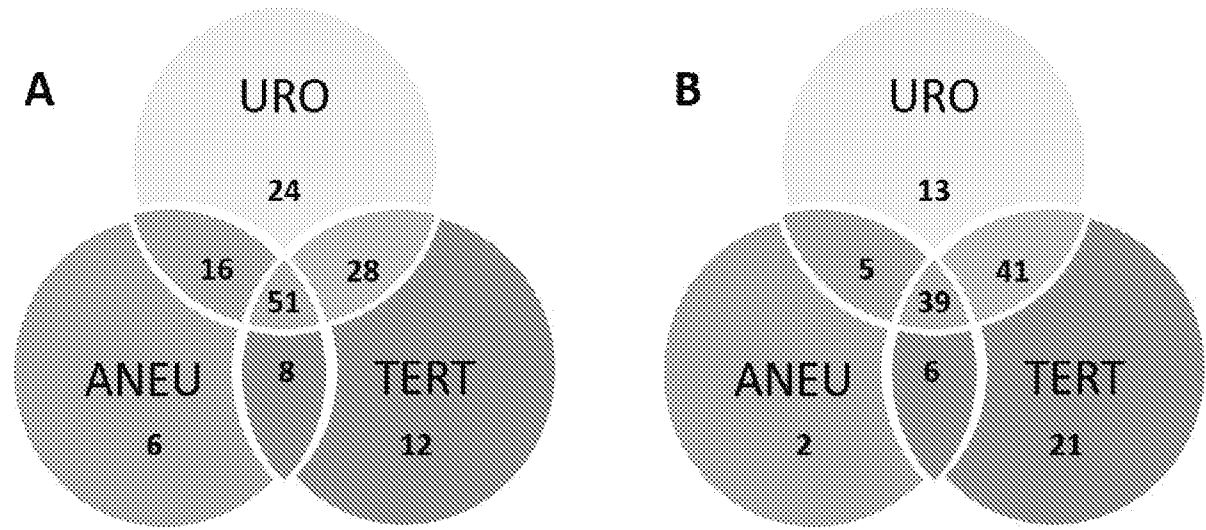


FIG. 28



FIG. 29

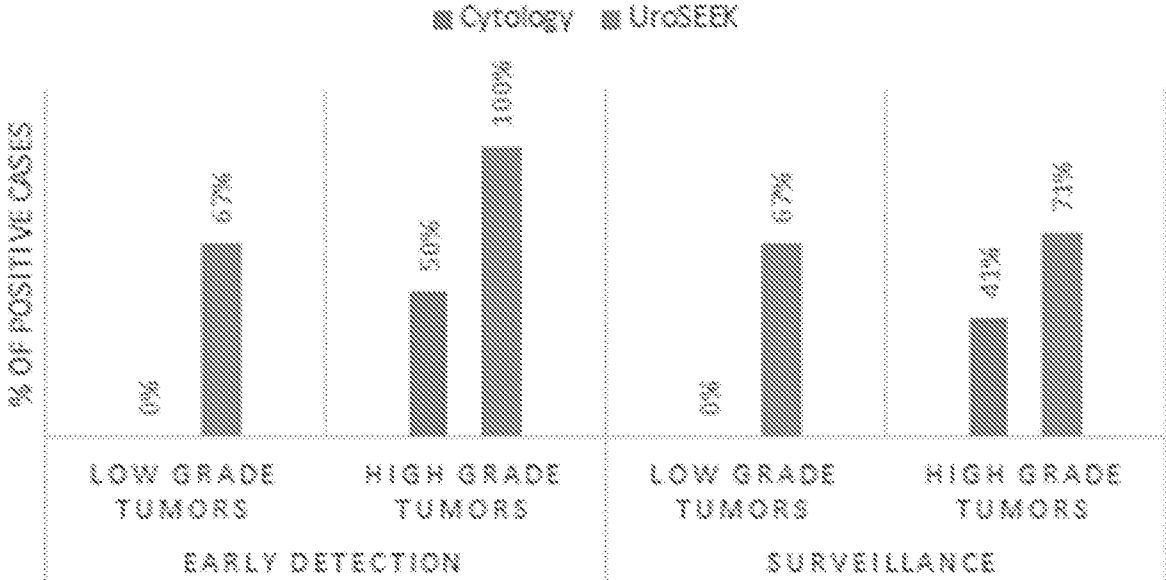


FIG. 30

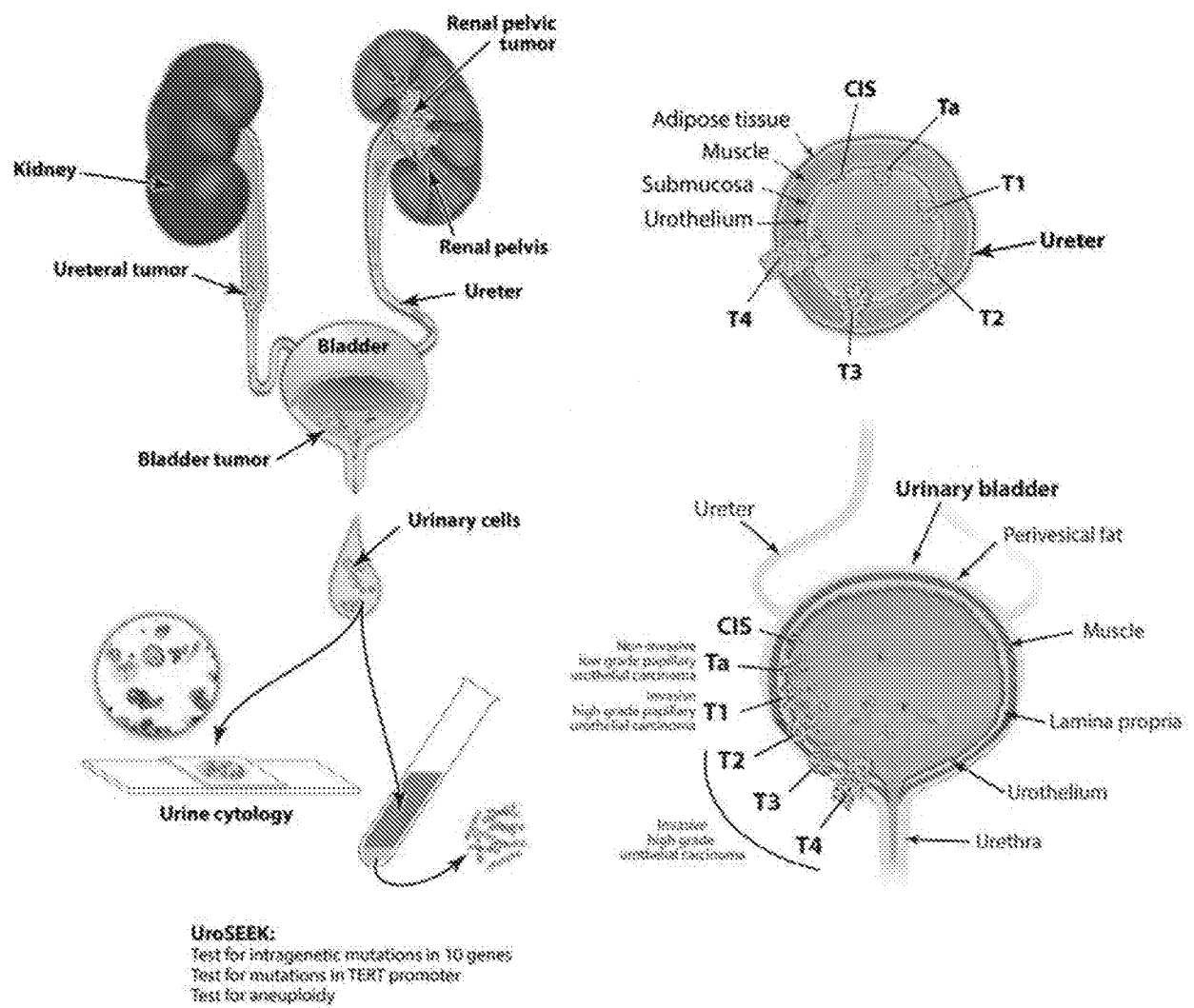


FIG. 31

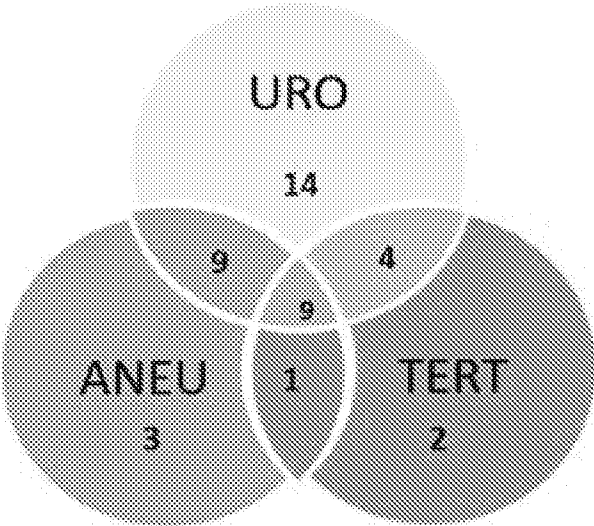


FIG. 32

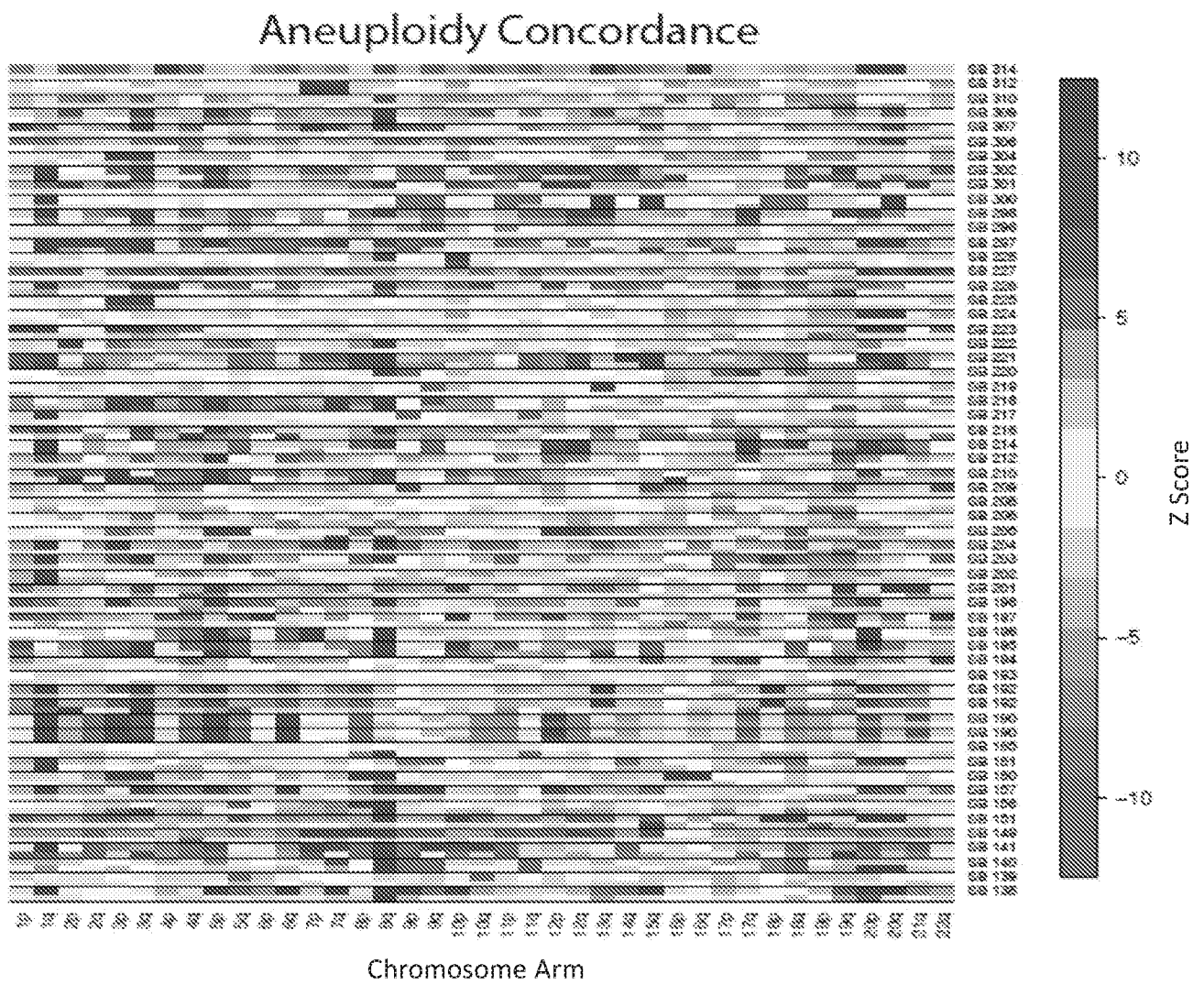


FIG. 33

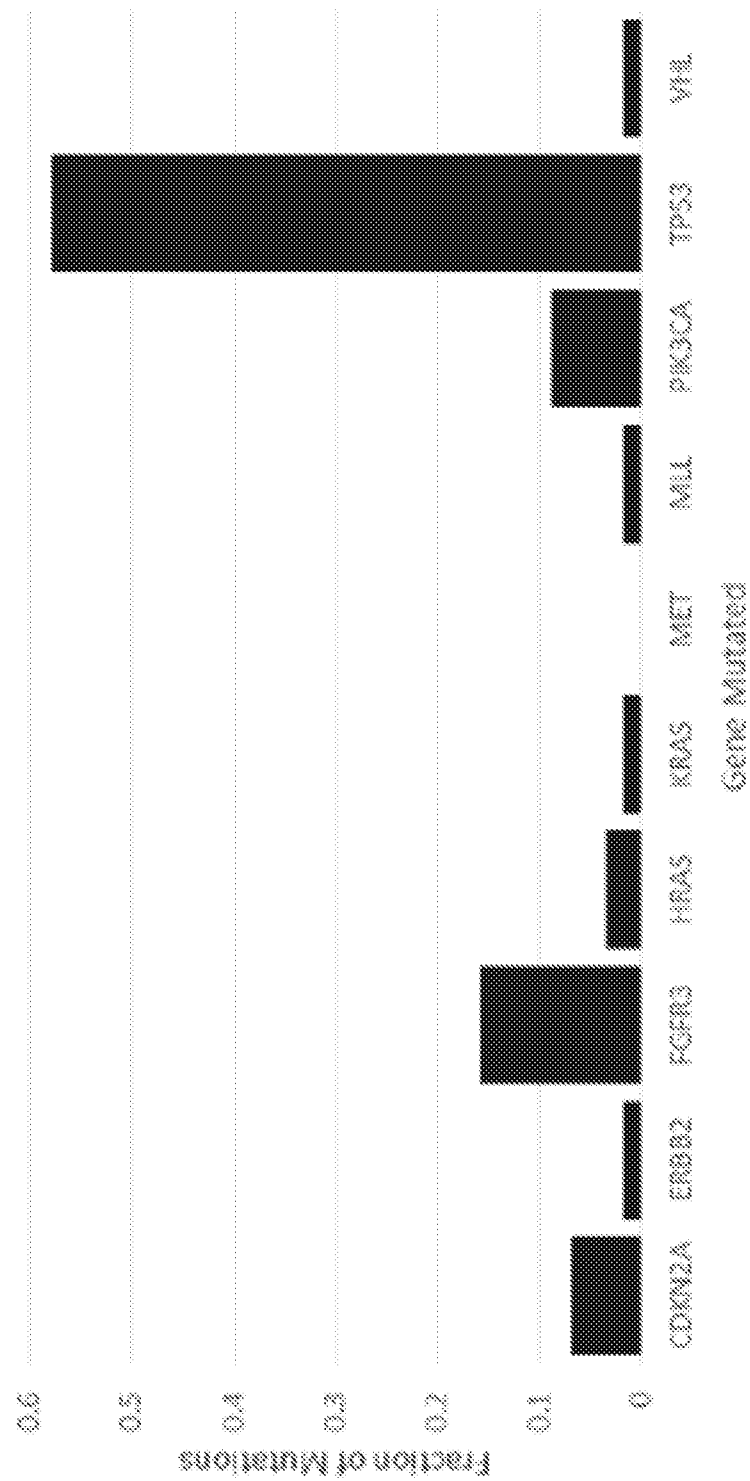


FIG. 34

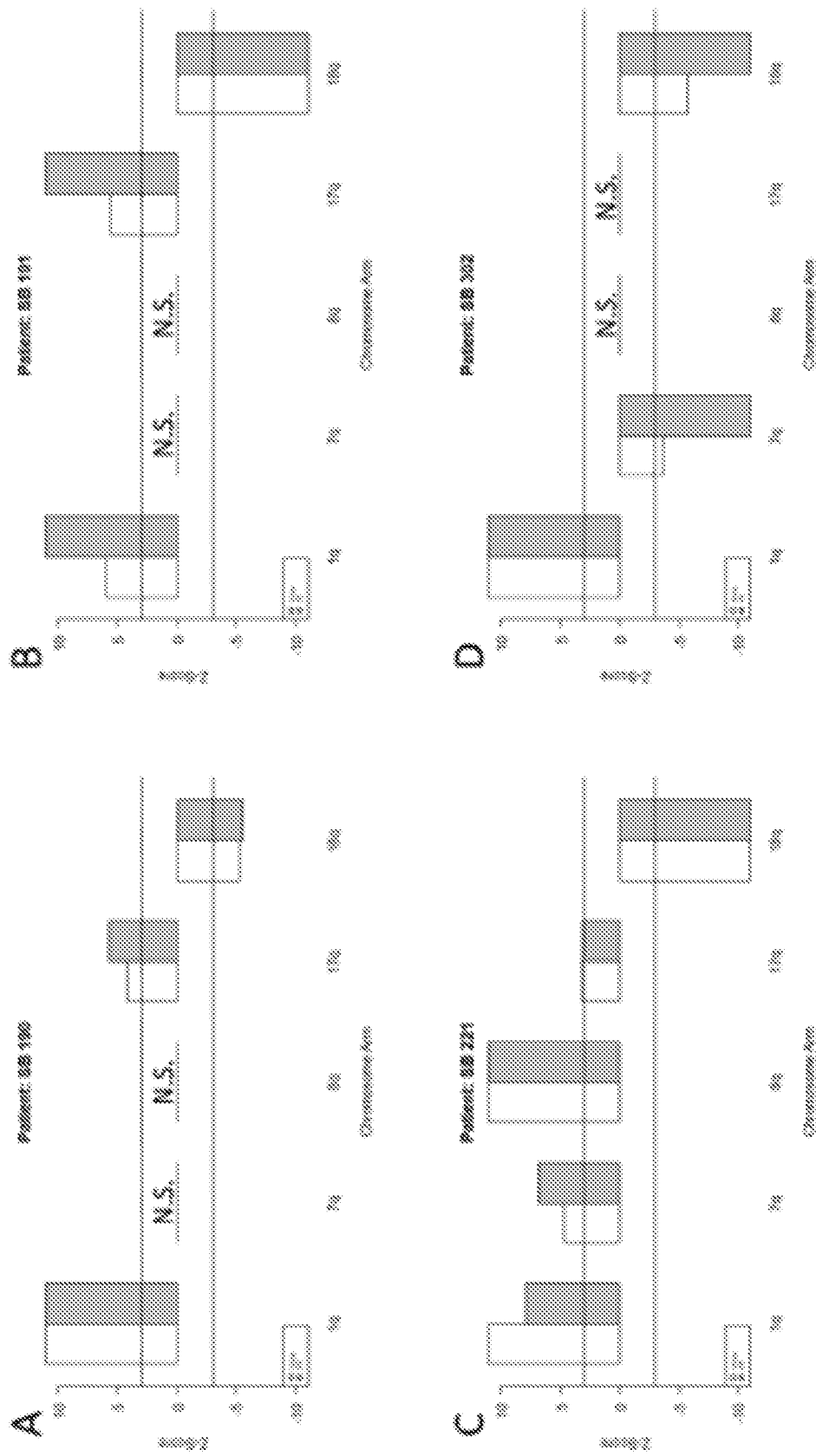


FIG. 35

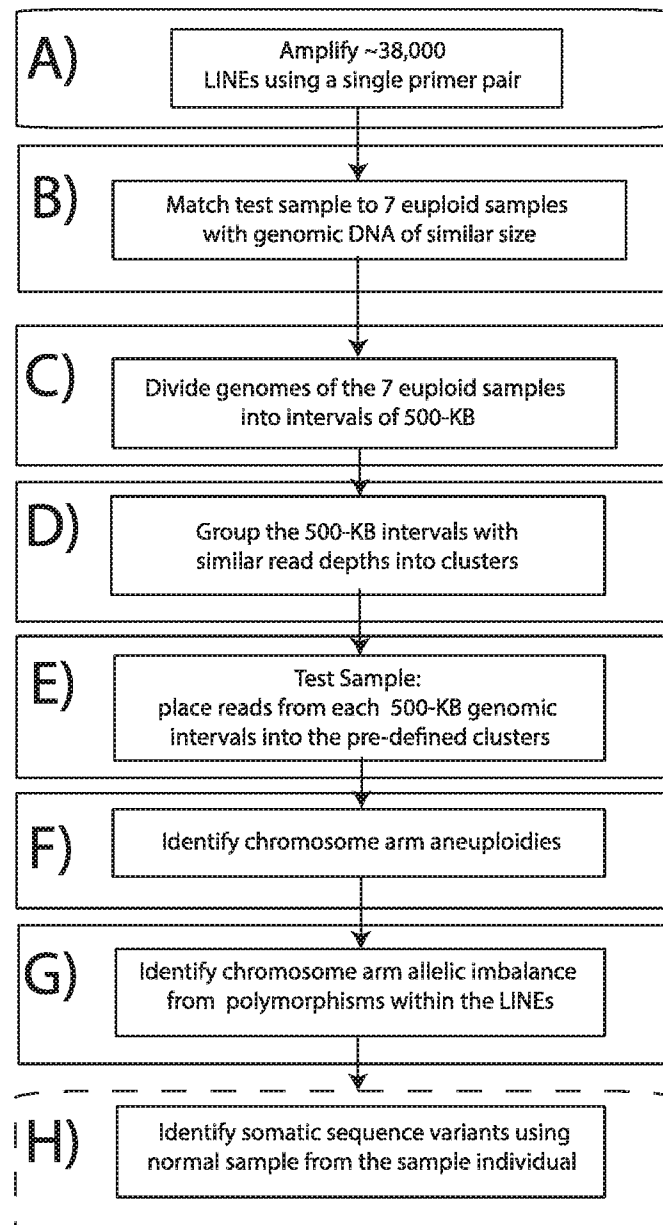


FIG. 36

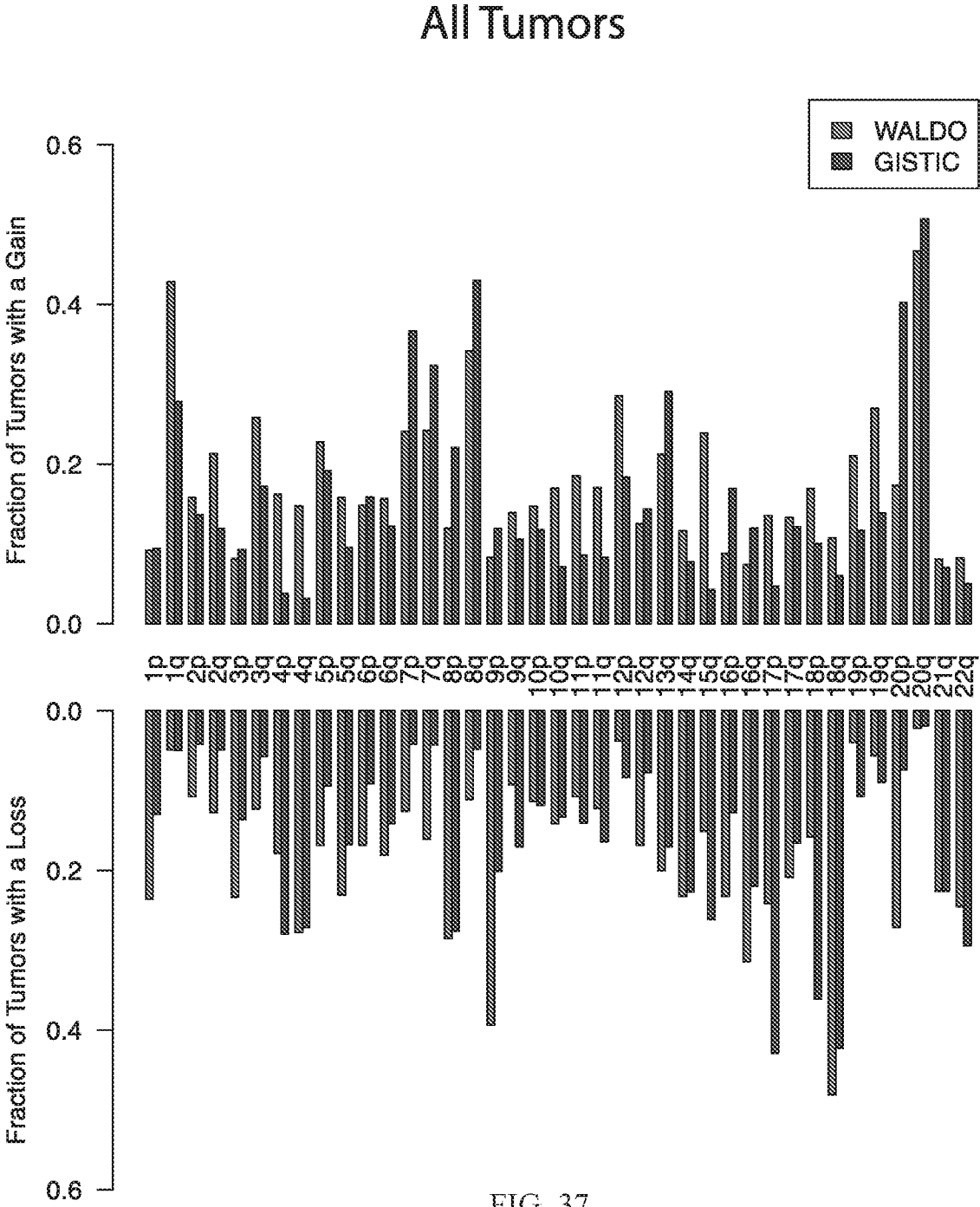


FIG. 37

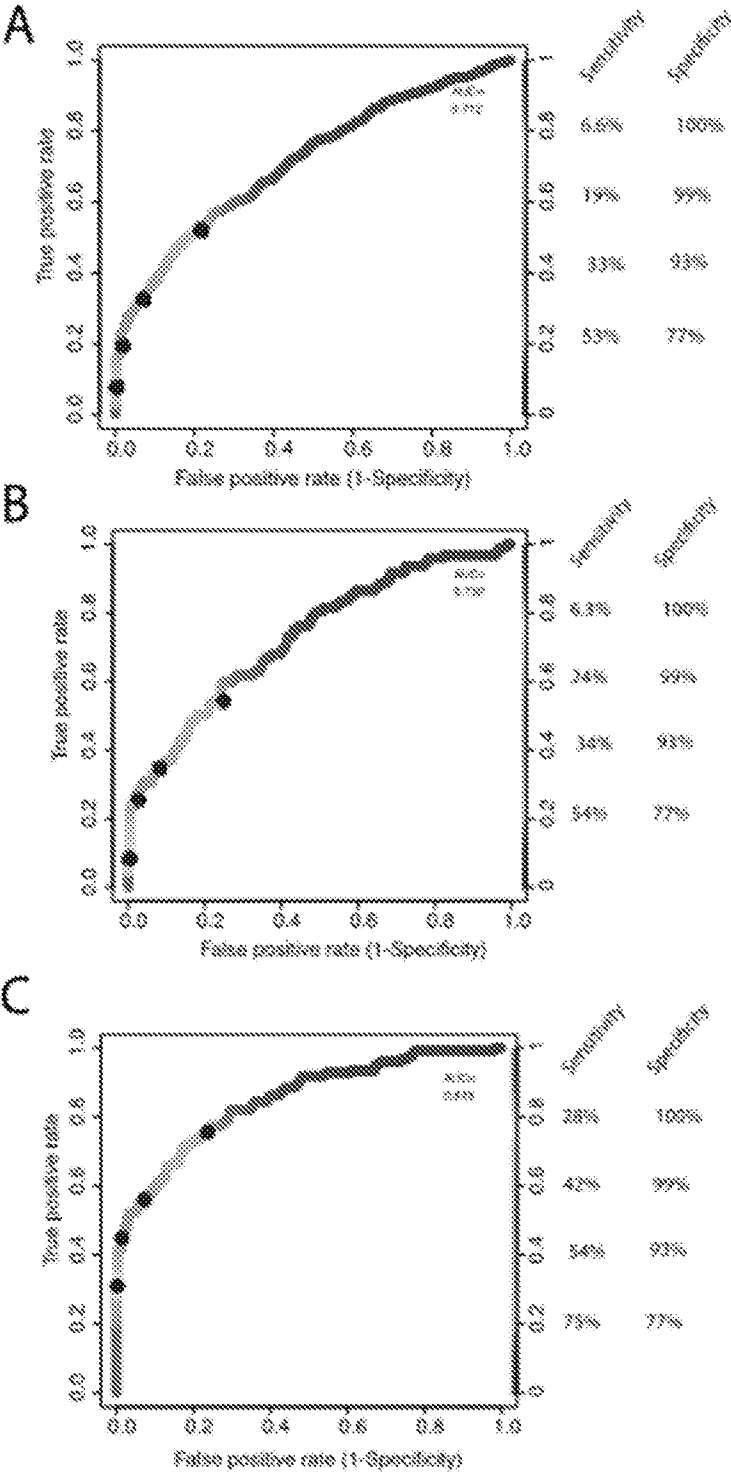


FIG. 38

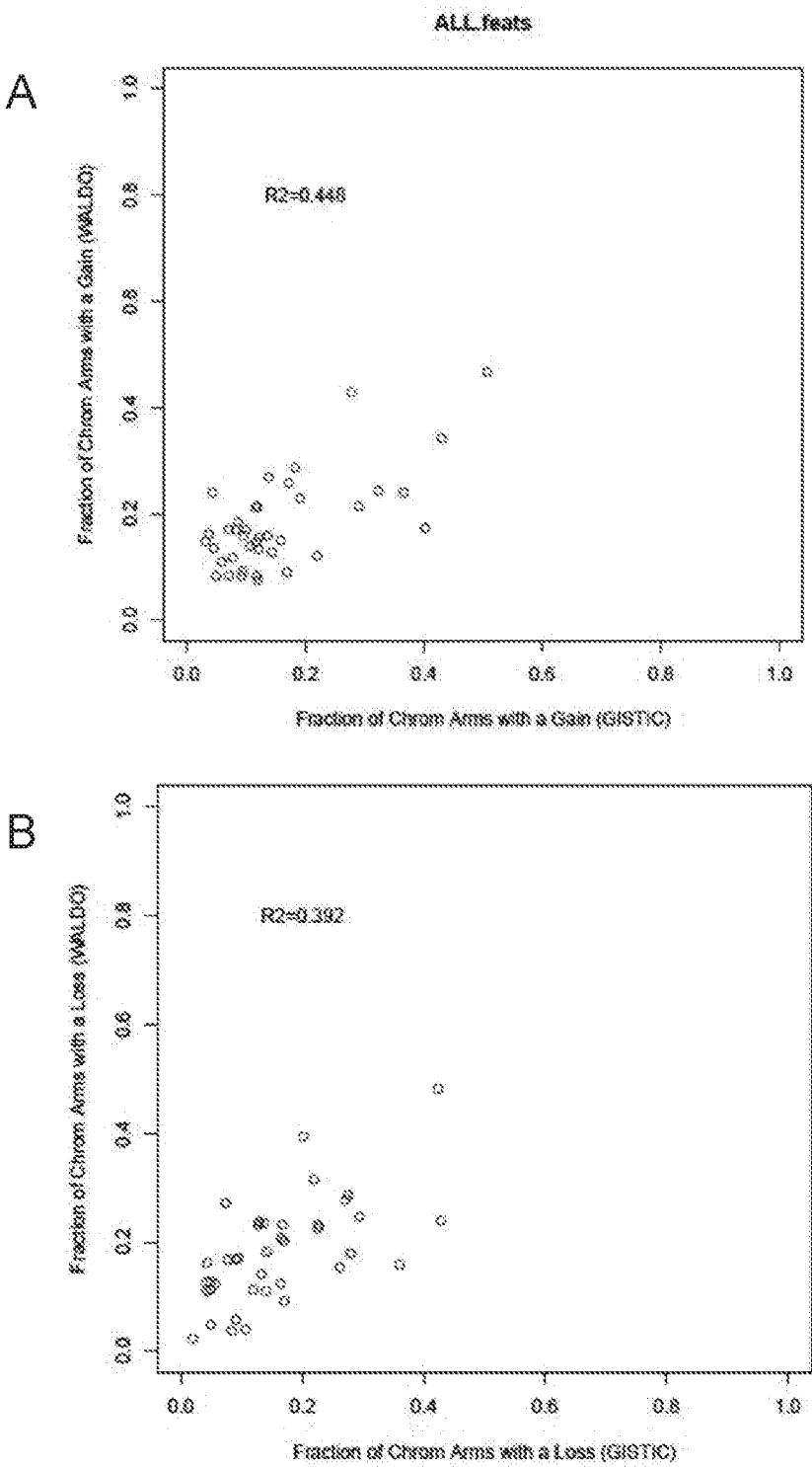


FIG. 39

A

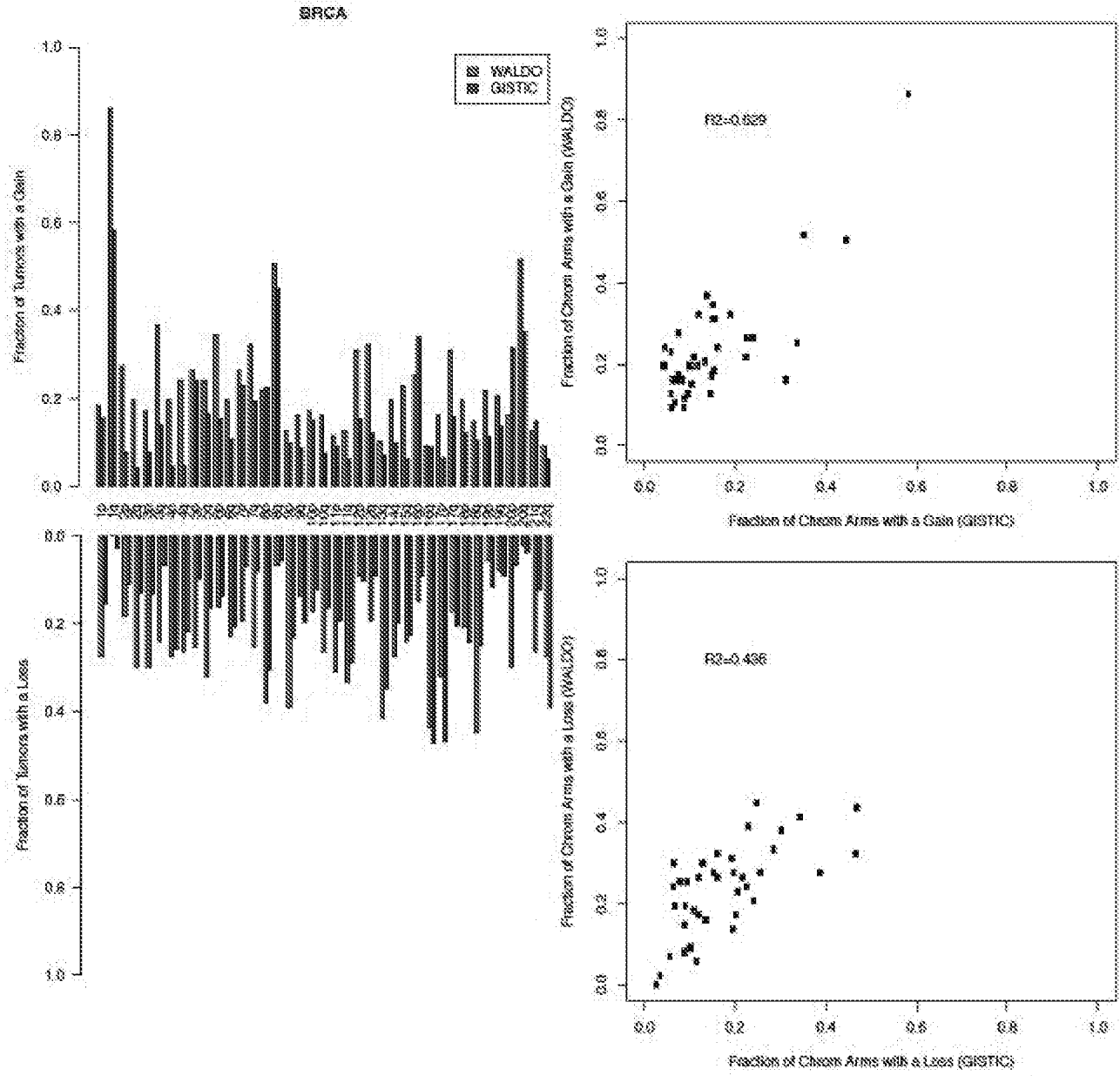


FIG. 40

B

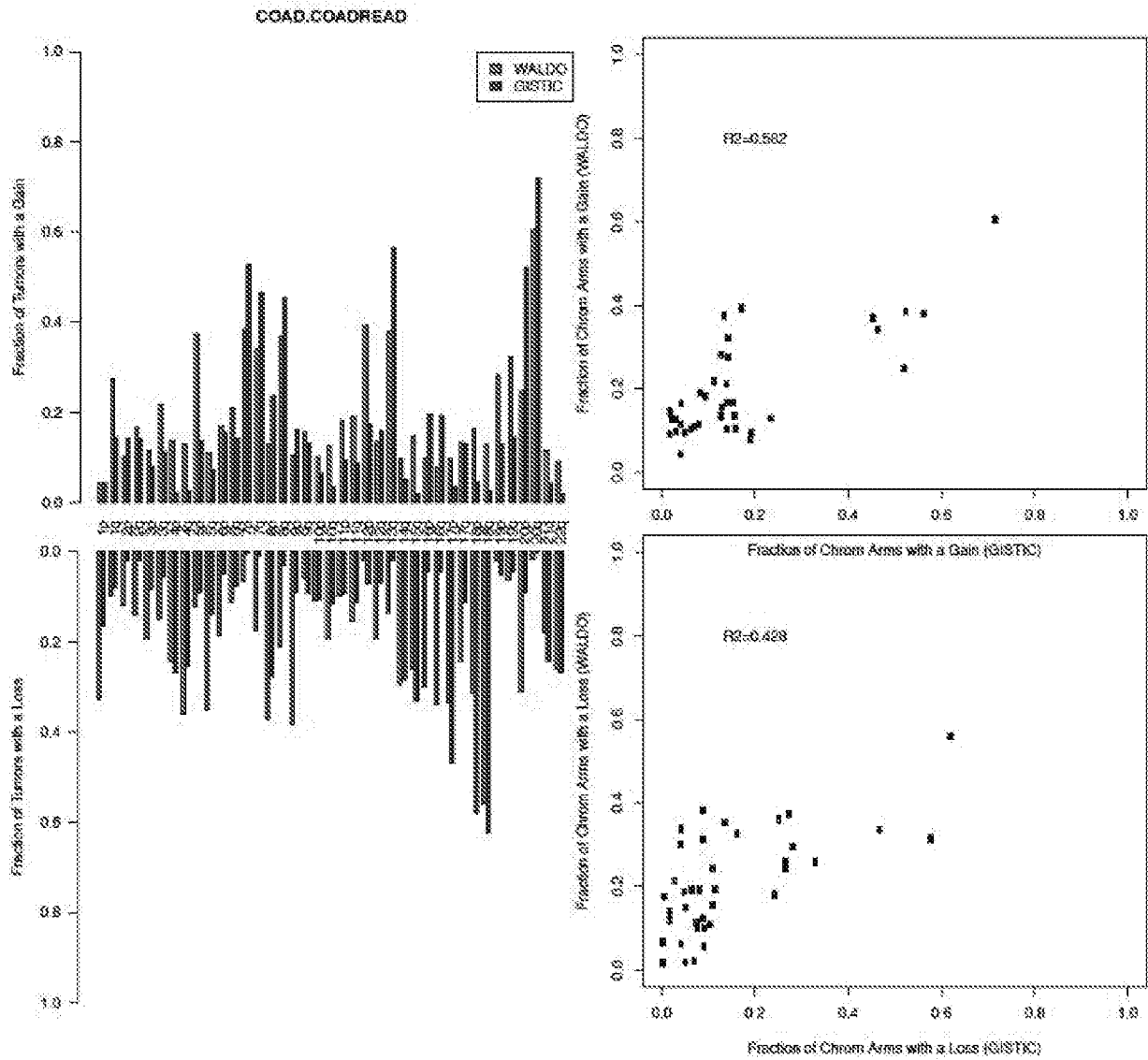


FIG. 40 (continued)

C

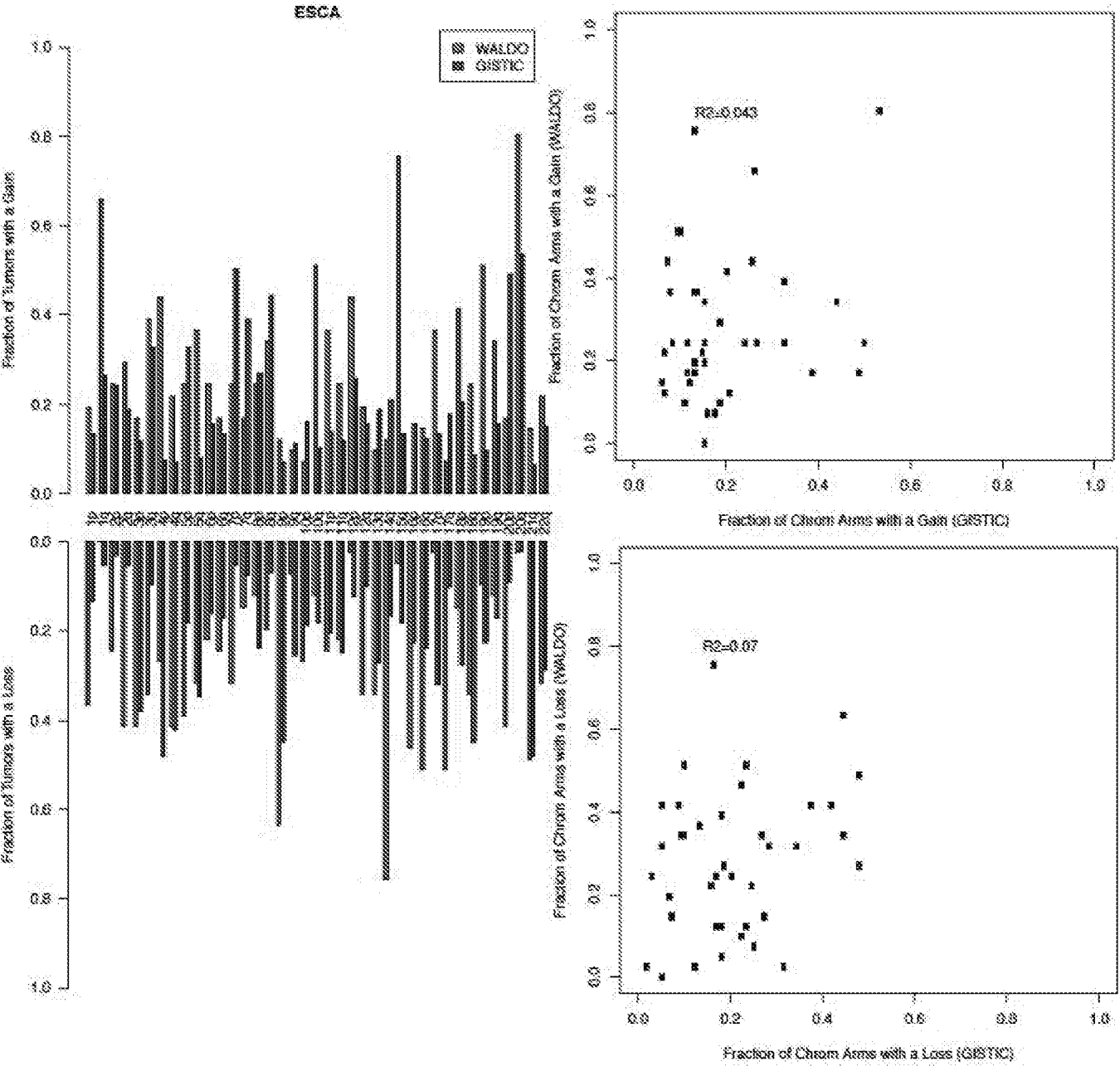


FIG. 40 (continued)

D

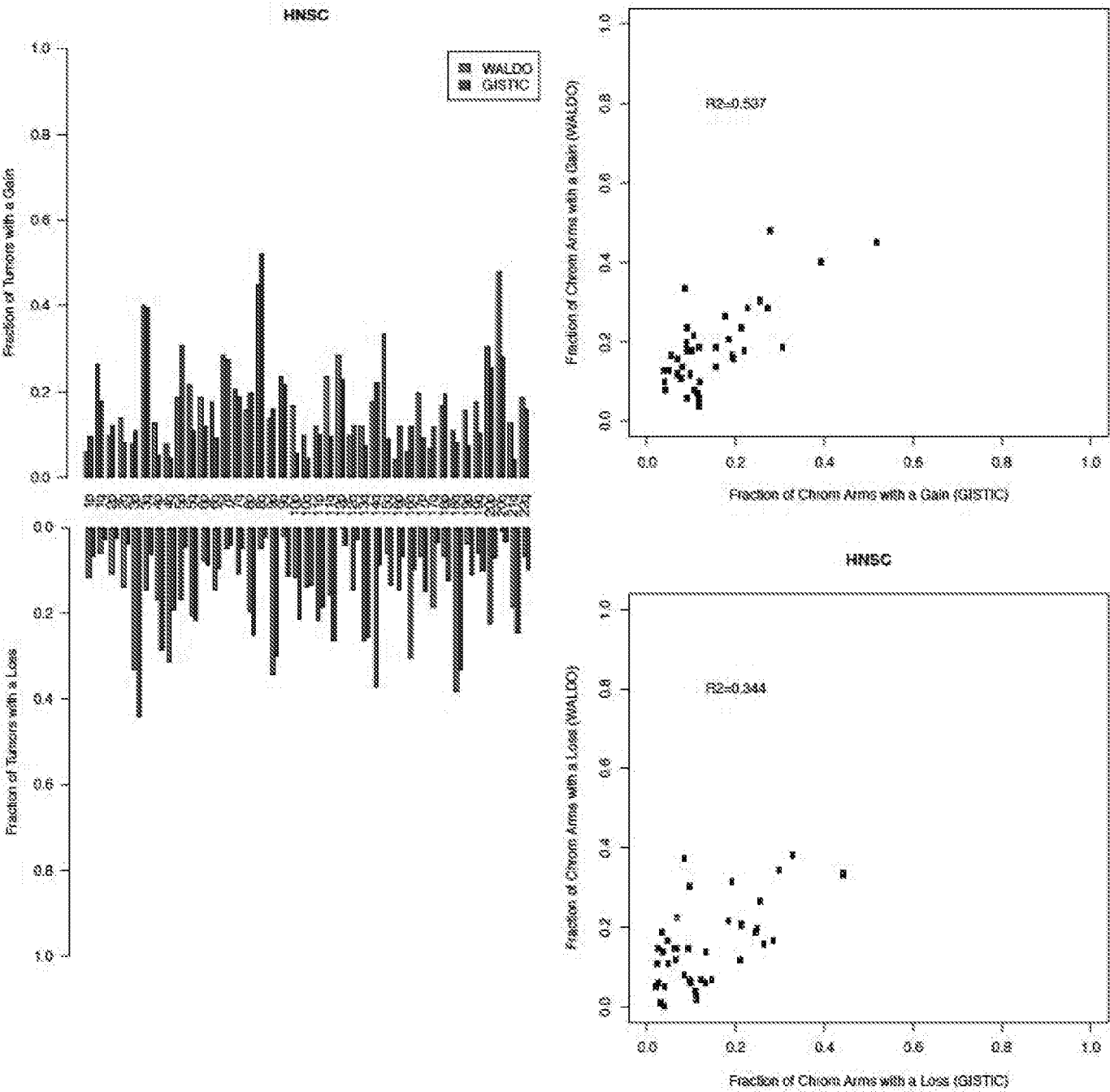


FIG. 40 (continued)

E

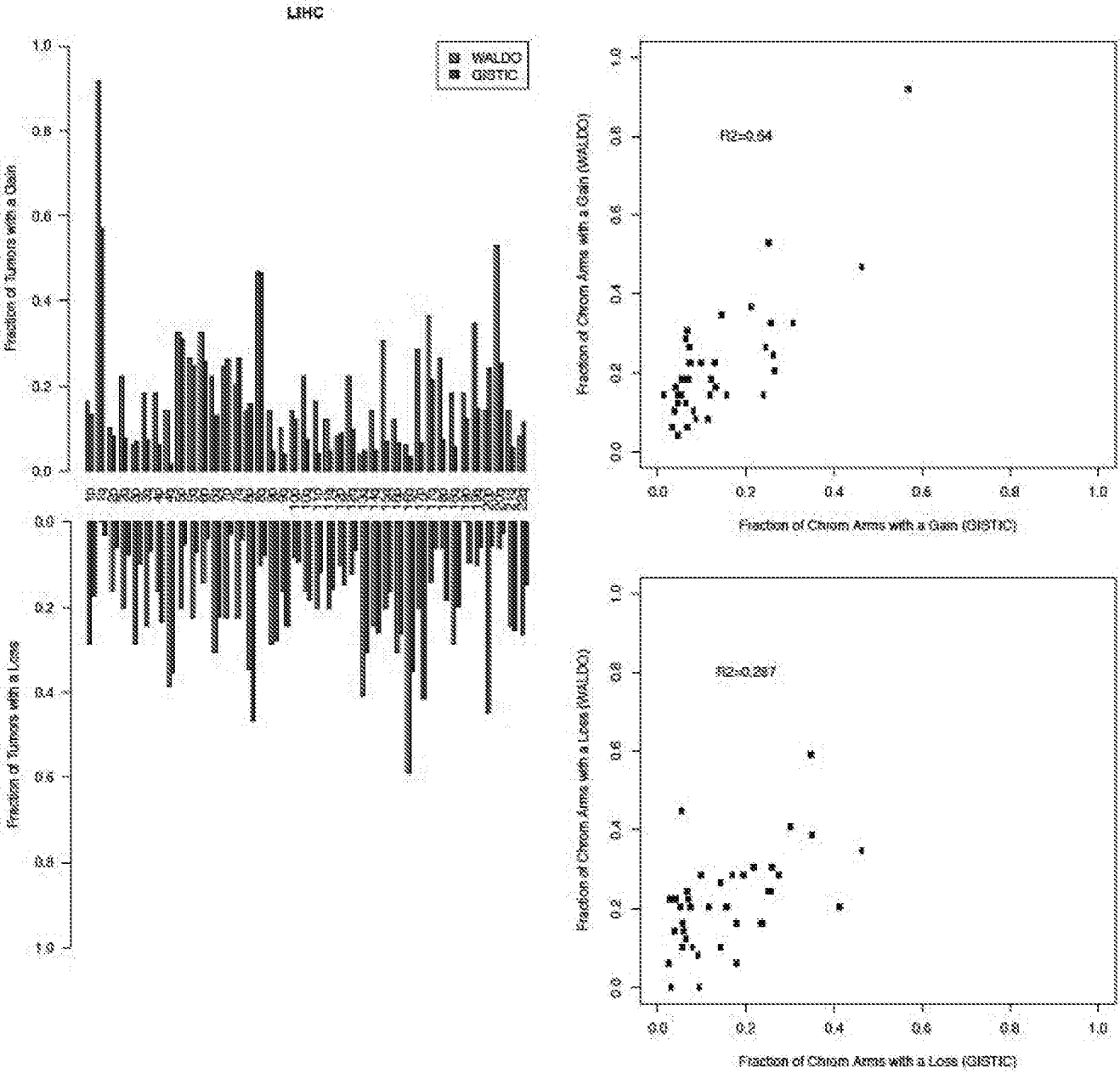


FIG. 40 (continued)

F

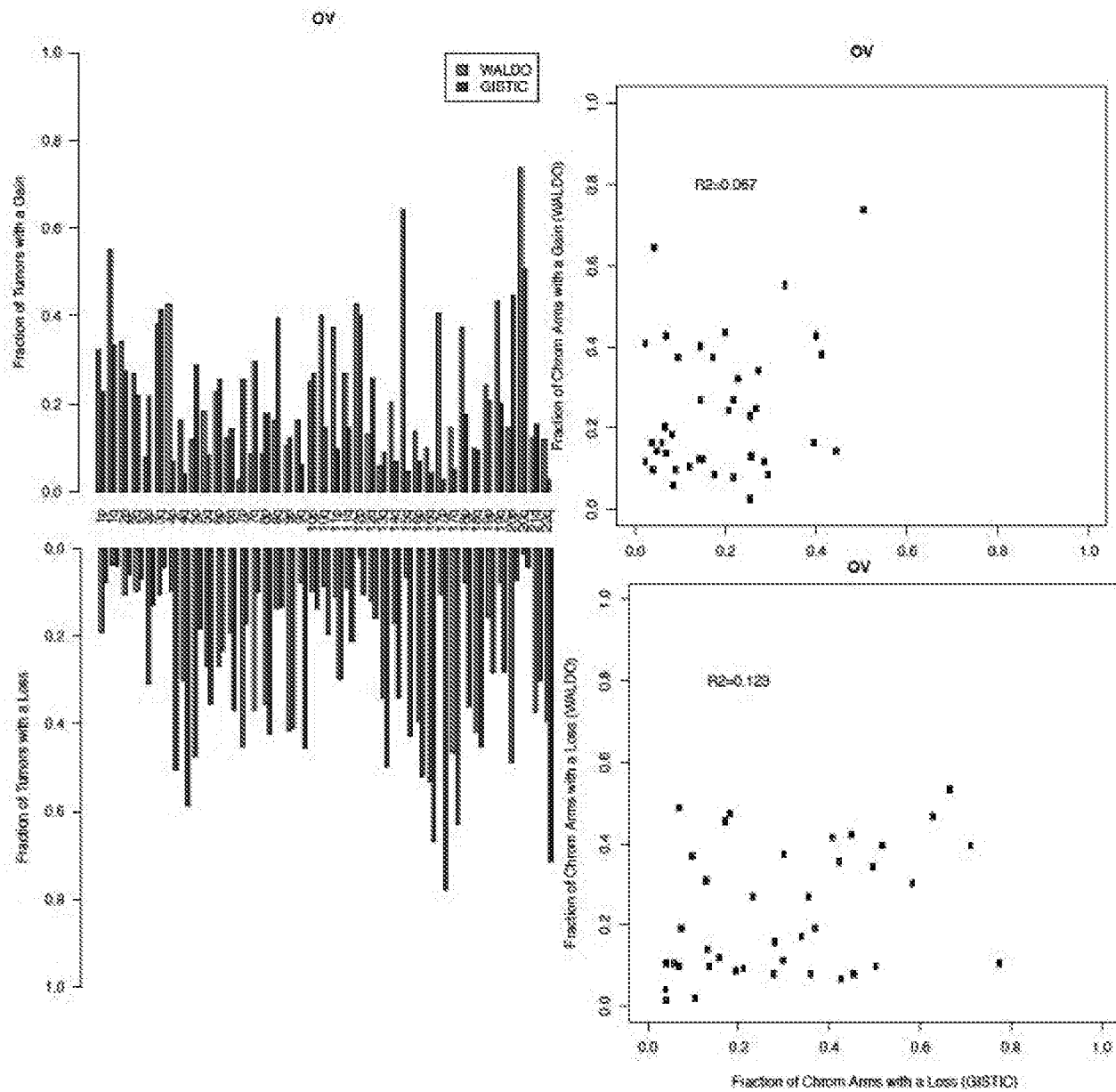


FIG. 40 (continued)

G

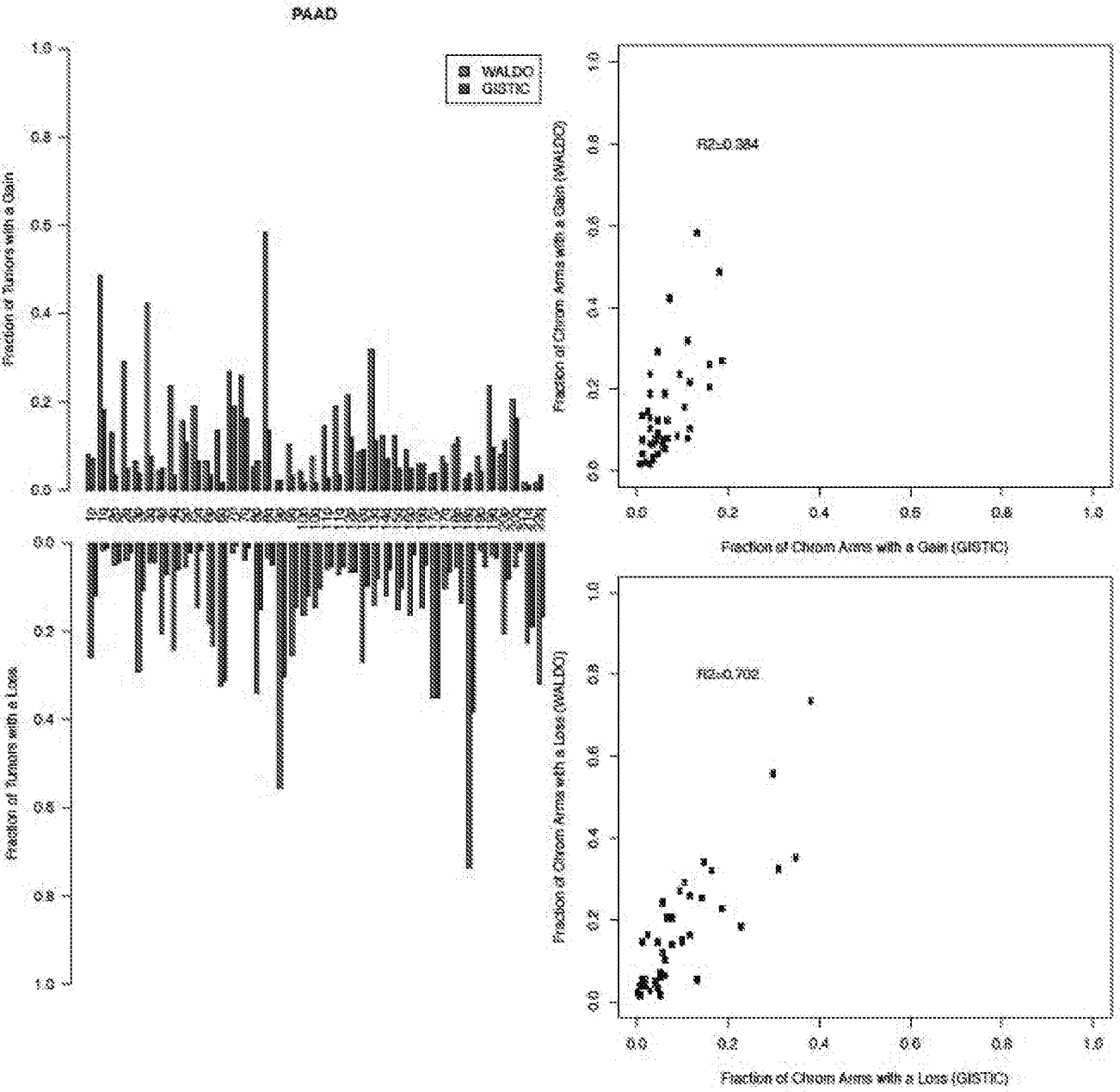


FIG. 40 (continued)

H

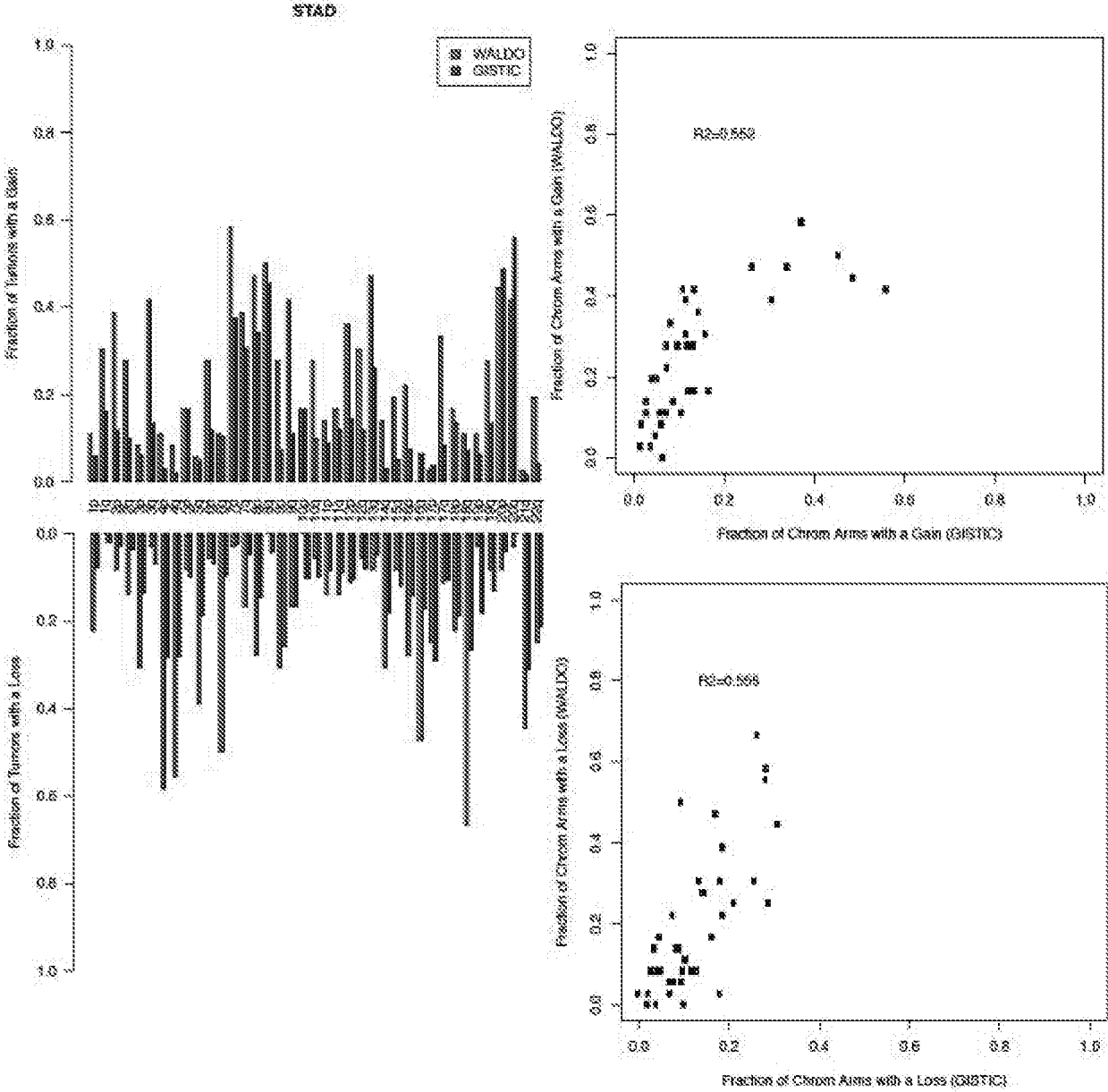


FIG. 40 (continued)

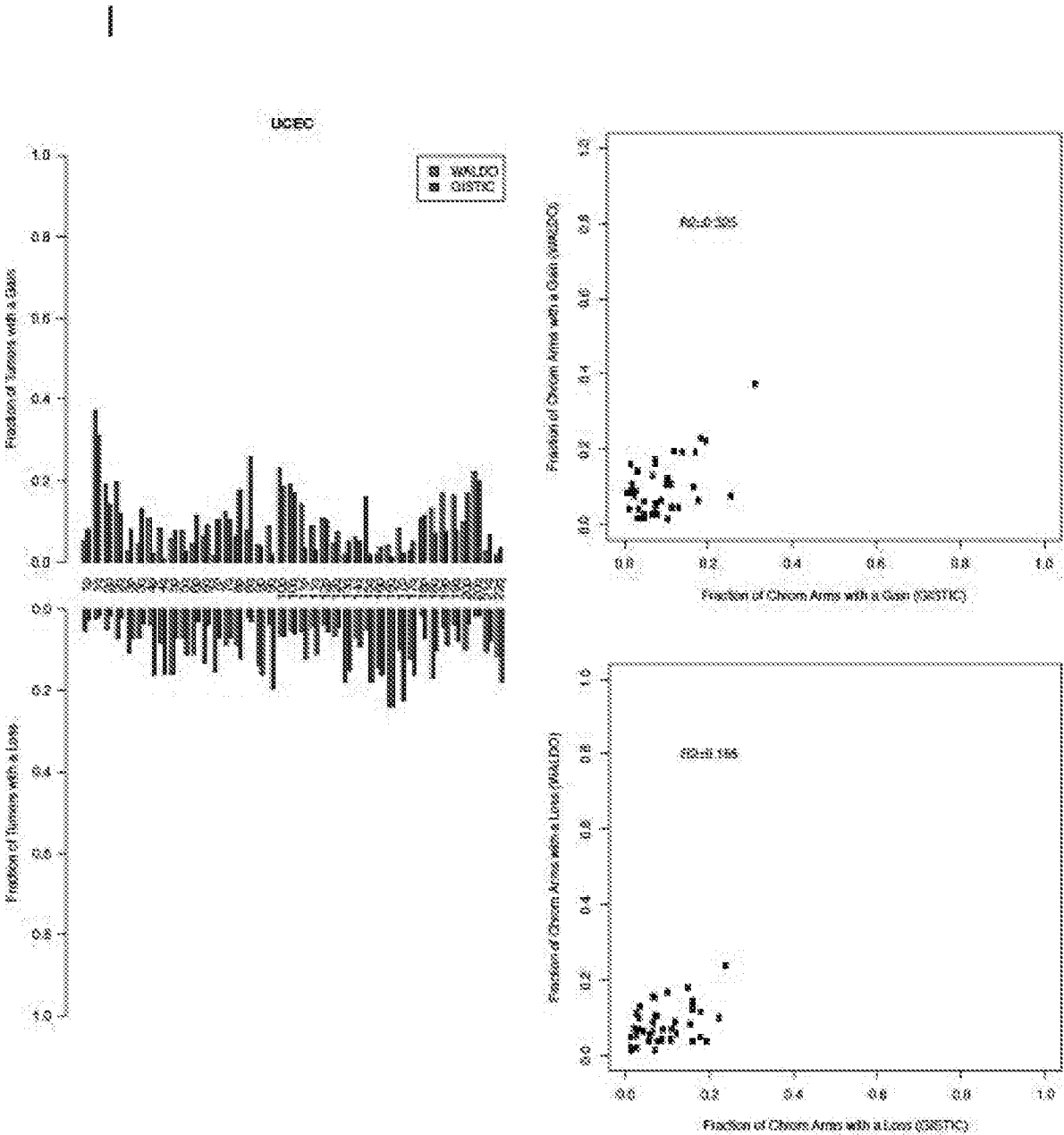


FIG. 40 (continued)

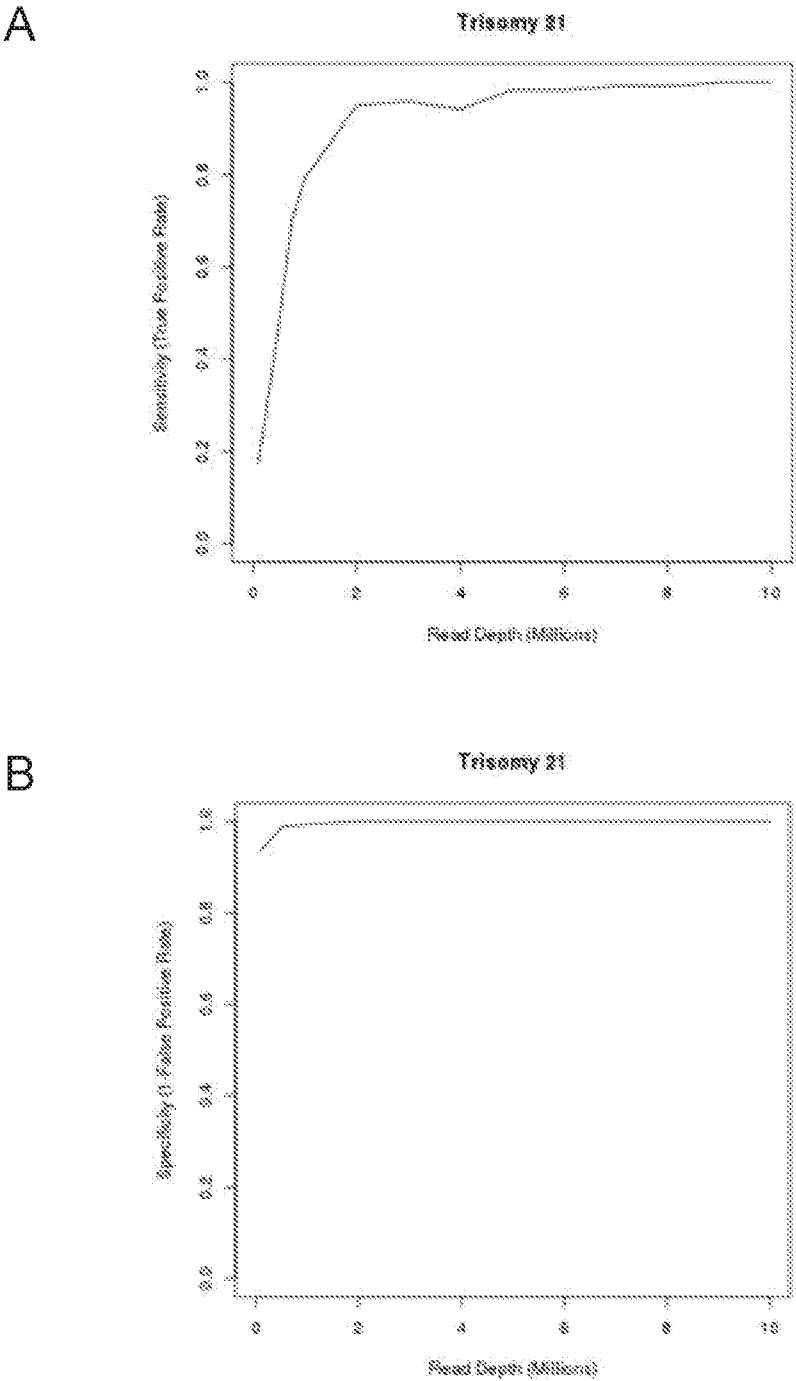


FIG. 41

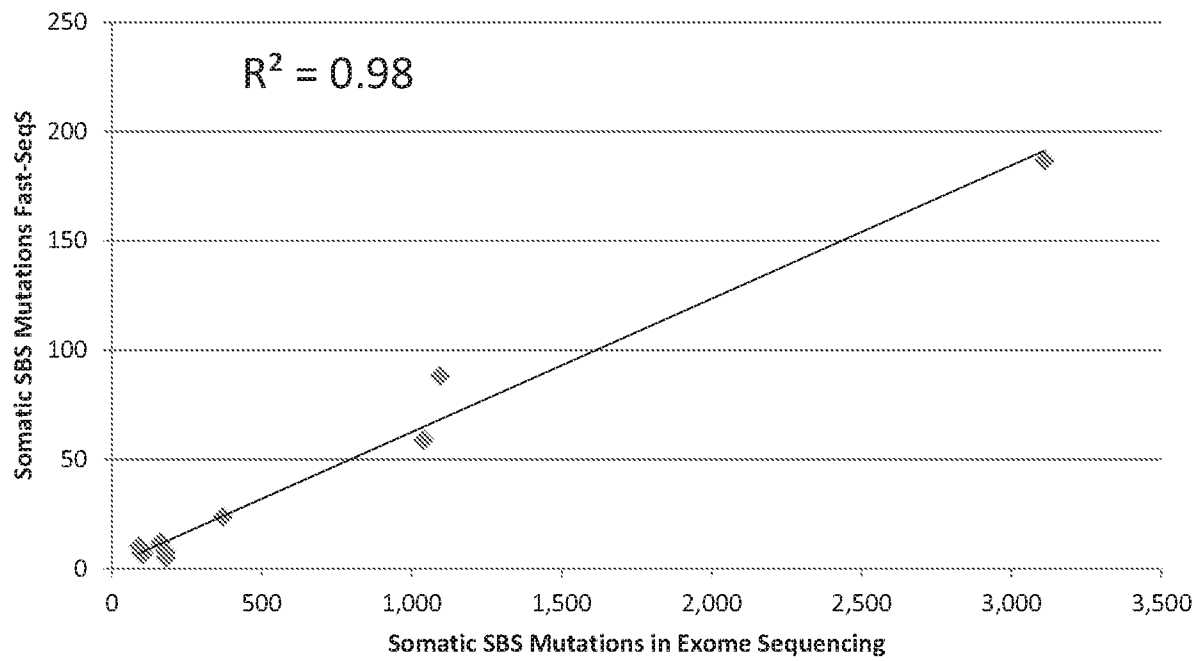


FIG. 42

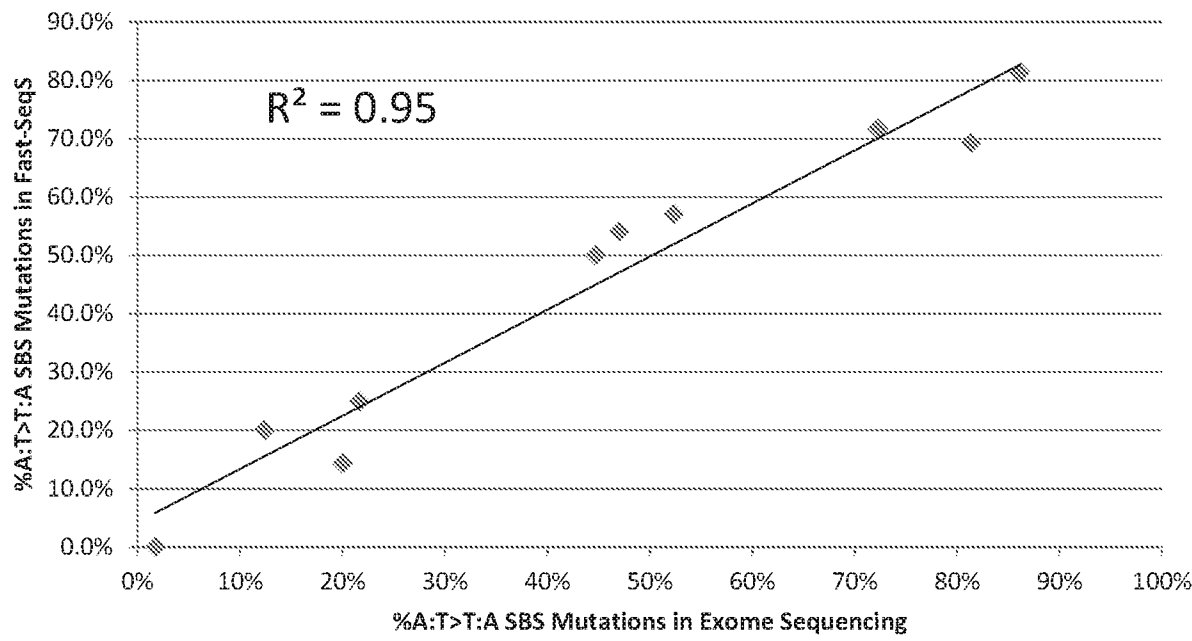


FIG. 43

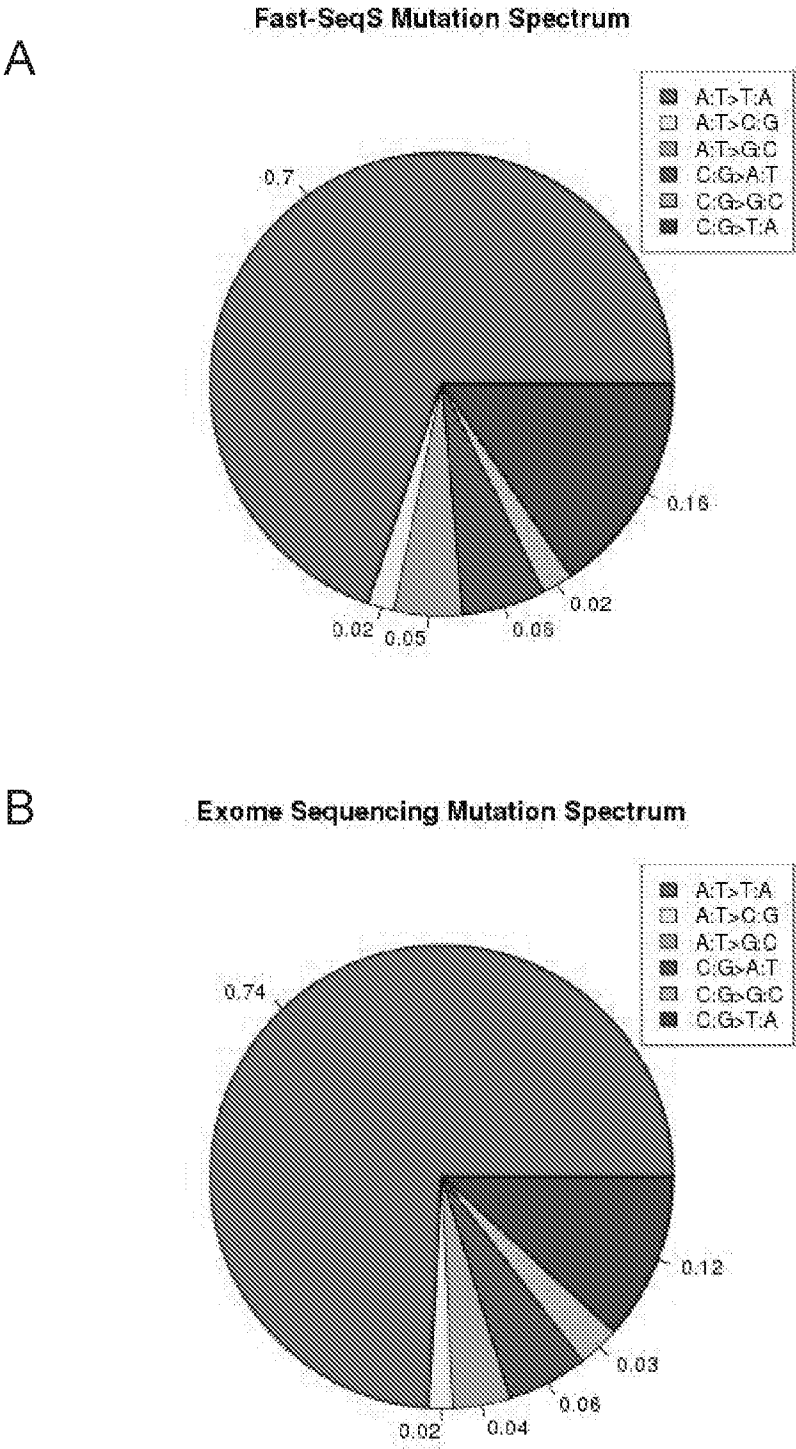


FIG. 44

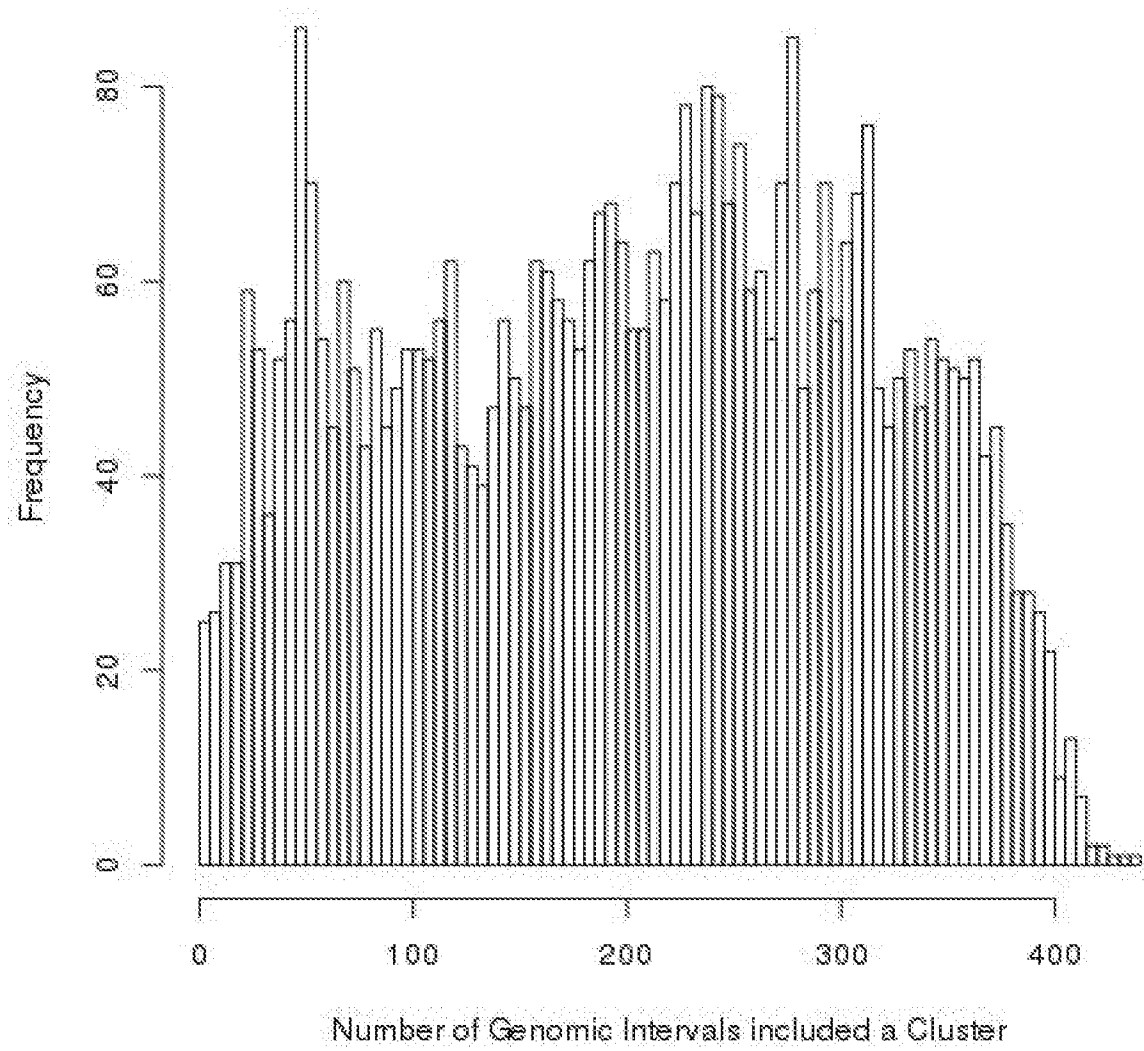


FIG. 45

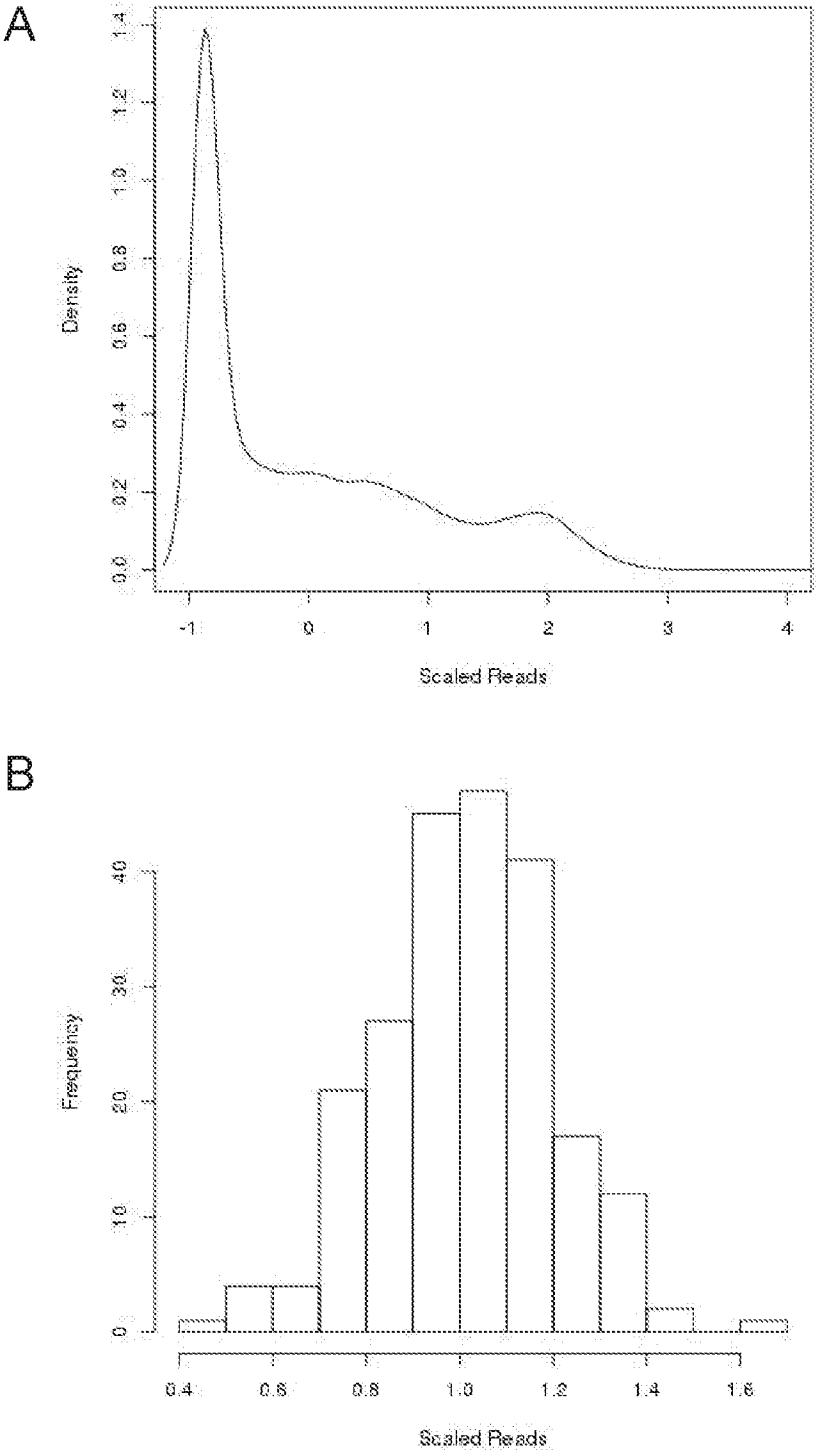


FIG. 46

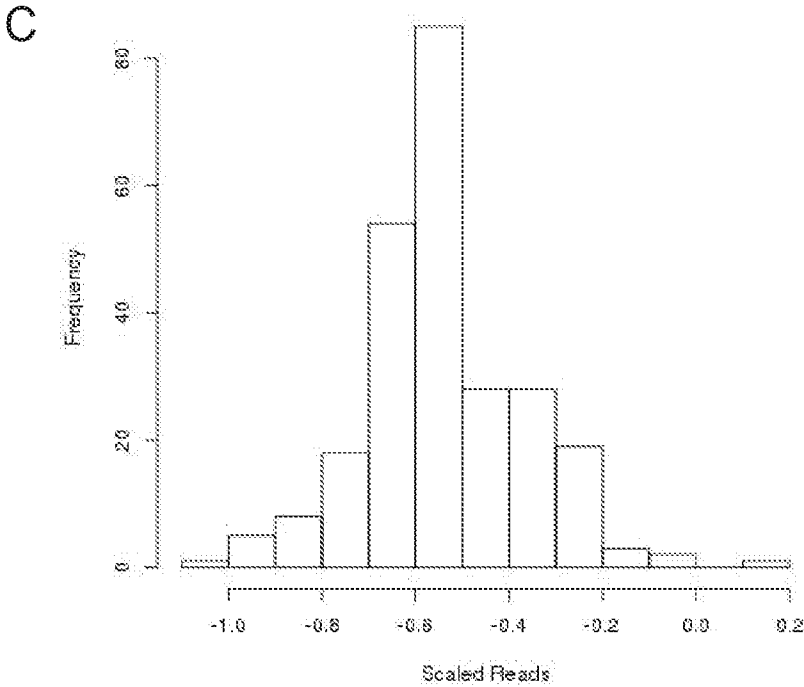
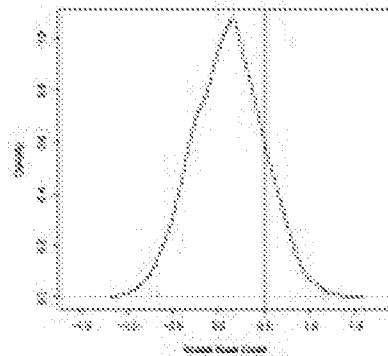


FIG. 46

Call Aneuploidy on a Chromosome Arm



500kb Genomic Interval 1

Estimate parameters

$$R_1 = 40(p_1, \sigma_1^2)$$

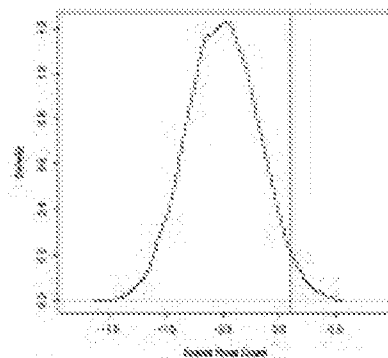
$$R_2 = 60(p_2, \sigma_2^2)$$

$$p_1 = 0.0$$

$$p_2 = 0.1$$

$$\sigma_1^2 = 0.15$$

$$2 \cdot (1 - 0.05) p_1 = 0.15, \sigma_1^2 = 0.15 \mid R_1 = 40 \mid 0.05 p_2 = 0.20 \mid 0.05 p_2 = 0.20$$



500kb Genomic Interval 2

Estimate parameters

$$R_1 = 5(p_1, \sigma_1^2)$$

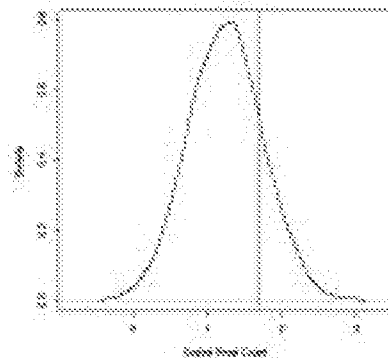
$$R_2 = 40(p_2, \sigma_2^2)$$

$$p_1 = 0.1$$

$$p_2 = 0.0$$

$$\sigma_1^2 = 0.1$$

$$2 \cdot (1 - 0.05) p_1 = 0.1, \sigma_1^2 = 0.1 \mid R_1 = 5 \mid 0.05 p_2 = 0.20 \mid 0.05 p_2 = 0.20$$



500kb Genomic Interval 3

Estimate parameters

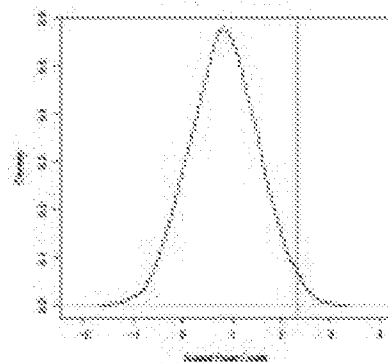
$$R_1 = 50(p_1, \sigma_1^2)$$

$$p_1 = 1.0$$

$$\sigma_1^2 = 1.25$$

$$\sigma_1^2 = 0.25$$

$$2 \cdot (1 - 0.05) p_1 = 1.25, \sigma_1^2 = 0.25 \mid R_1 = 50 \mid 0.05 p_2 = 0.20 \mid 0.05 p_2 = 0.20$$



Chromosome Arm

$$\sum_{i=1}^3 R_i = \sum_{i=1}^3 \sum_{j=1}^2 p_{ij} \sigma_{ij}^2$$

$$\sum_{i=1}^3 R_i = (0.5 + 0.1 + 1.7) = 2.3$$

$$\sum_{i=1}^3 p_{ij} = 0.1 + (-0.5) + 1.25 = 0.85$$

$$\sum_{i=1}^3 \sigma_{ij}^2 = 0.15 + 0.1 + 0.25 = 0.5$$

$$5 \cdot 0.85 (\sum_{i=1}^3 p_{ij} = 0.85, \sum_{i=1}^3 \sigma_{ij}^2 = 0.5) \mid \sum_{i=1}^3 R_i = 2.3 = 0.85 \cdot 2.7 < 0.5$$

$$\sigma_1^2 = 0.25$$

Chromosome arm is gained

FIG. 47

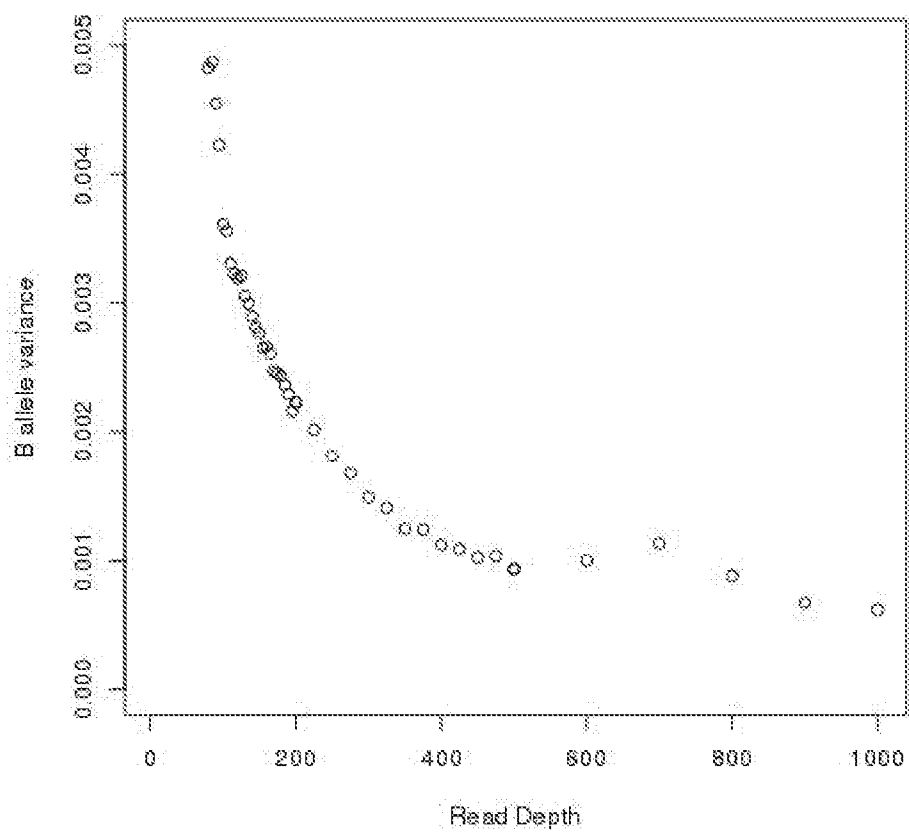


FIG. 48

Synthetics with one arm alterations

```

N <- number of normal WBC samples used
f <- desired neoplastic cell fraction
r <- chromosome arm (1p..22q)
r_type <- alteration type (gain or loss)
p(r) <- probability of arm gain (0.5 default)
rho <- desired unique read depth of synthetic sample (9M default)
j<-desired number of repeats

For j=1:5
  For i=1:N
    s <- sample[i]
    U <- get UIDs from s
    For f in 1:F
      For r in 1p:22q #select alteration types and spike-in to t
        For r_type in gain loss
          h <- new synthetic sample
          t <- copy of s
          u_ref <- get all reference allele UIDs that that map
                    to chr arm r
          if r_type== gain
            t <- add duplicate u_ref reads
          else (r_type == loss)
            t <- subtract u_ref reads
          Endif
          h_normal<-random select (1-f)*rho UIDs from s
          h_aneuploid<-random select f*rho UIDs from t
          h<-h_normal+h_aneuploid
        End
      End
    End
  End
End

```

FIG. 49

```

N <- number of normal WBC samples used
d <- desired degree of aneuploidy (number arms altered)
f <- desired neoplastic cell fraction
r <- chromosome arm (1p..22q)
r_type <- arm alteration type (gain or loss)
p(r) <- probability of arm gain (0.5 default)
rho <- desired unique read depth of synthetic sample (9M default)
j <- desired number of repeats

For j=1:5
  For i=1:N
    s <- sample[i]
    U <- get UIDs from s
    For f in 1:F
      h <- new synthetic sample
      For d in (5,10,15,20,25) #desired numbers of altered arms
        t <- copy of s
        For a in 1:d #select alteration types and spike-in to t
          r <- random select arm
          r_type <- alteration type with p(r)
          u_ref <- get all reference allele UIDs that that map
                     to chr arm r
          if r_type== gain
            t <- add duplicate u_ref reads
          else (r_type == loss)
            t <- subtract u_ref reads
          Endif
        h_normal <- random select (1-f)*rho UIDs from s
        h_aneuploid <- random select f*rho UIDs from t
        h <- h_normal + h_aneuploid
      End
    End
  End
End

```

FIG. 50

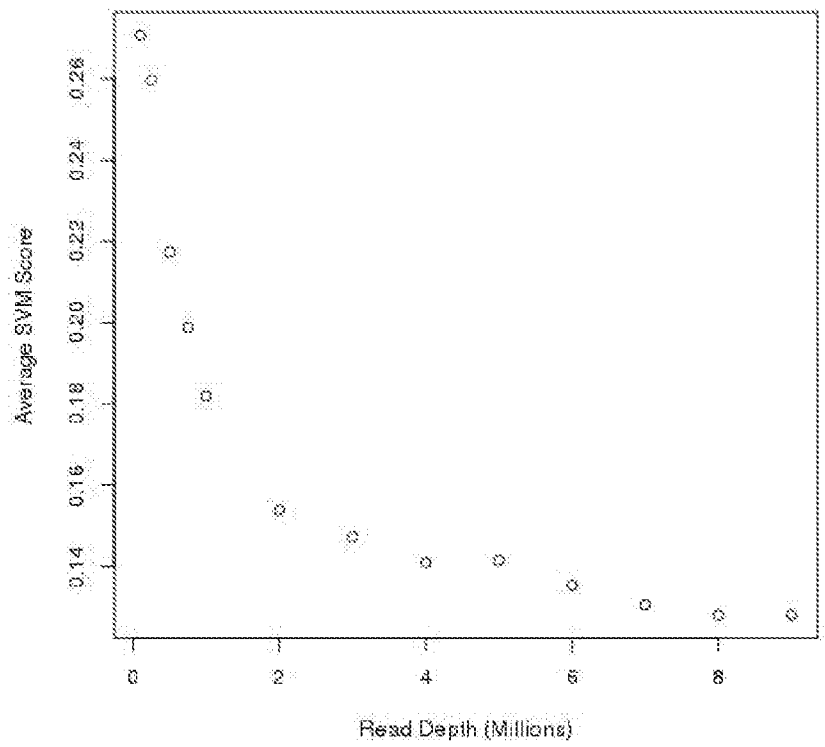


FIG. 51

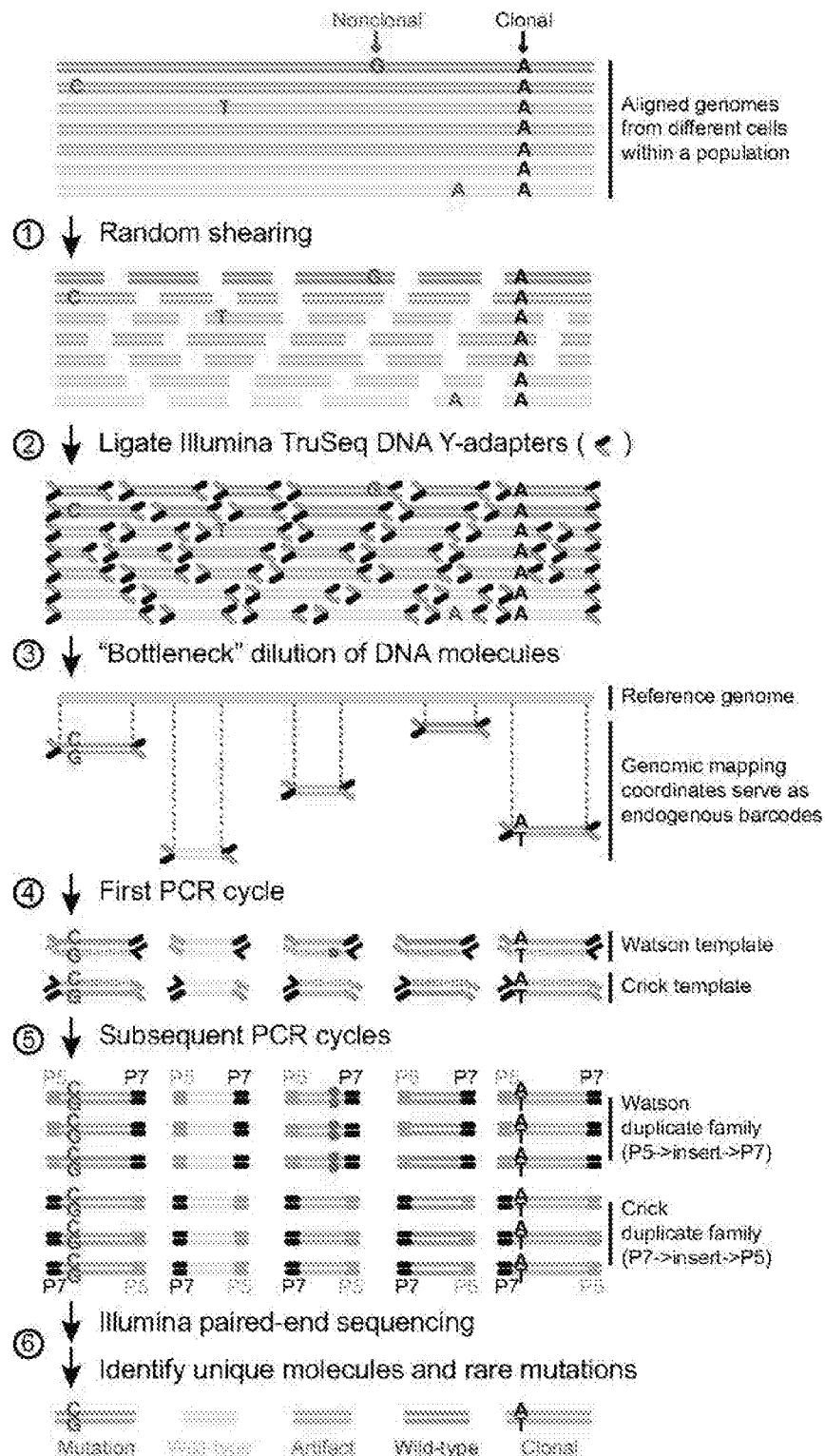


FIG. 52

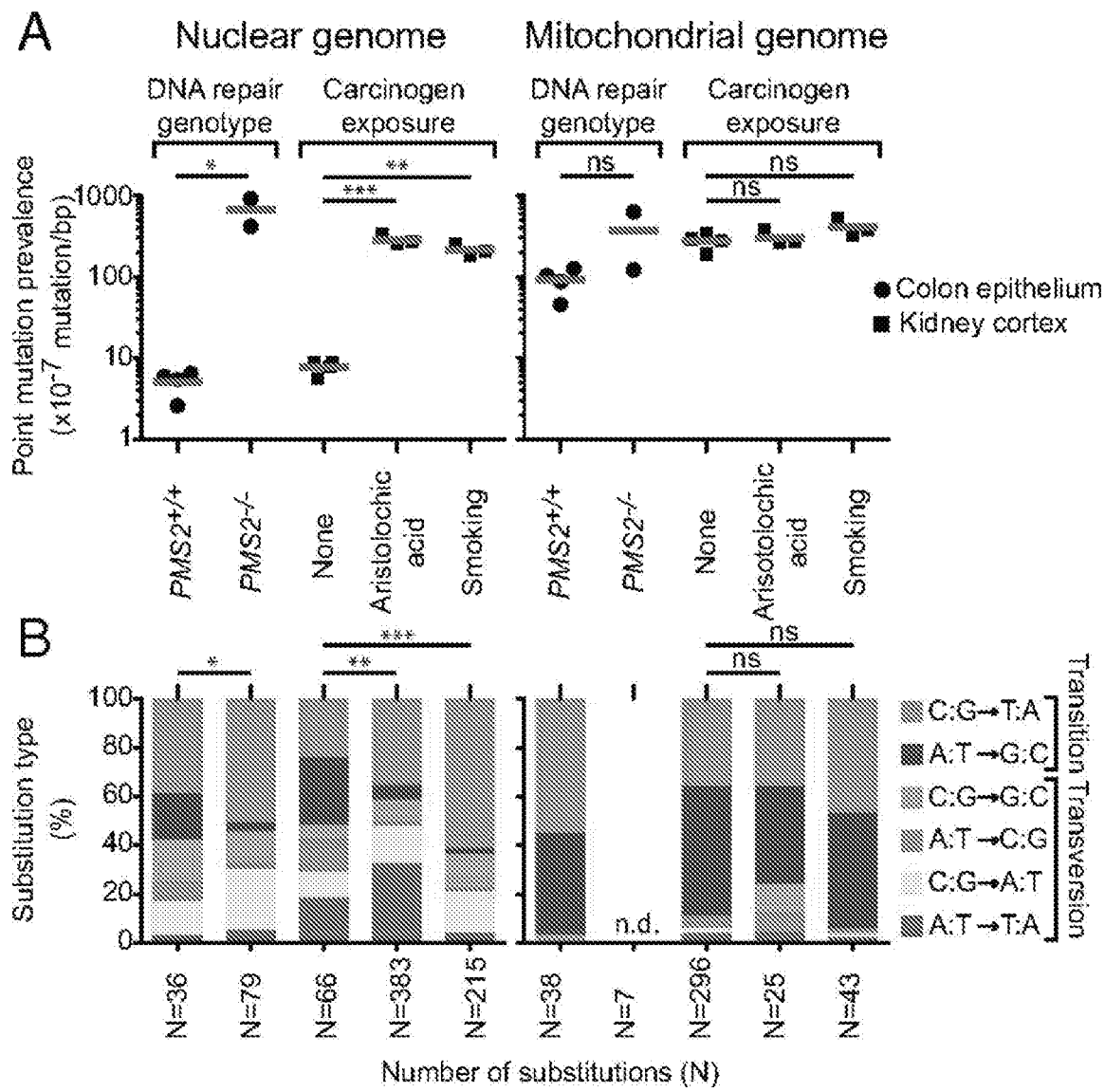


FIG. 53

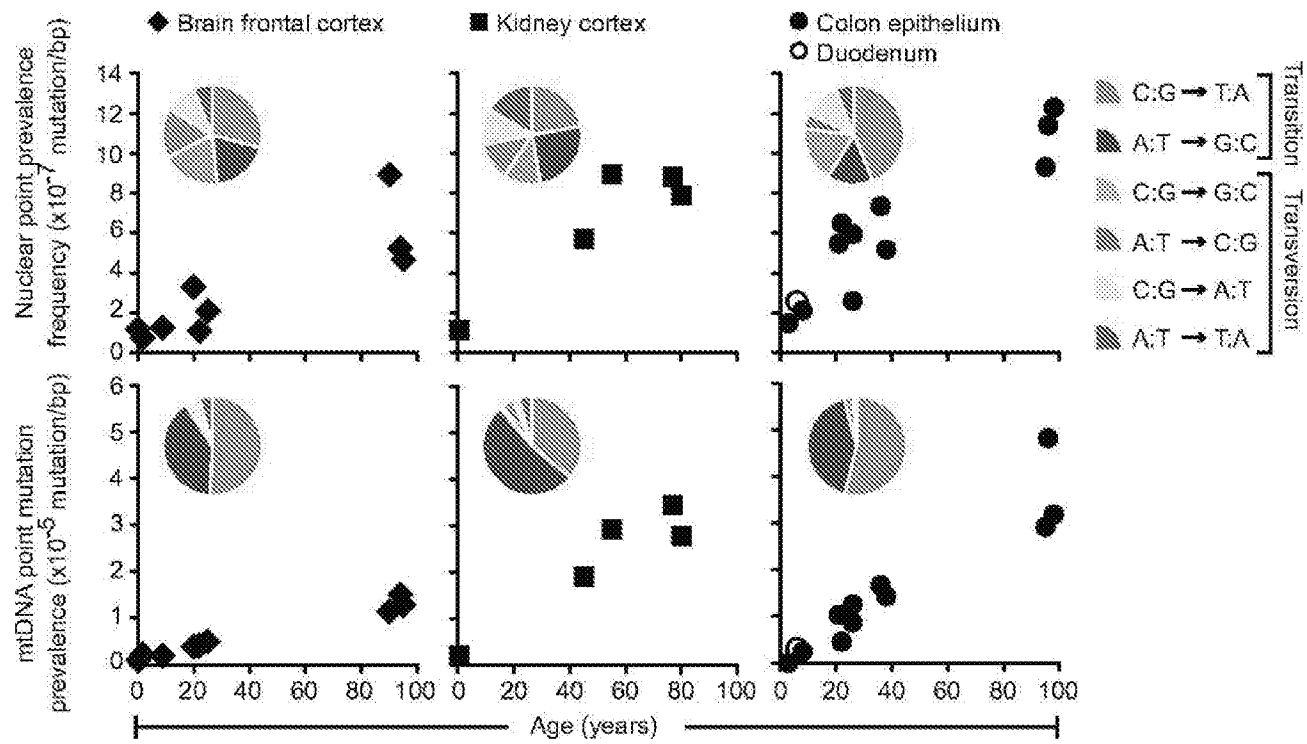


FIG. 54

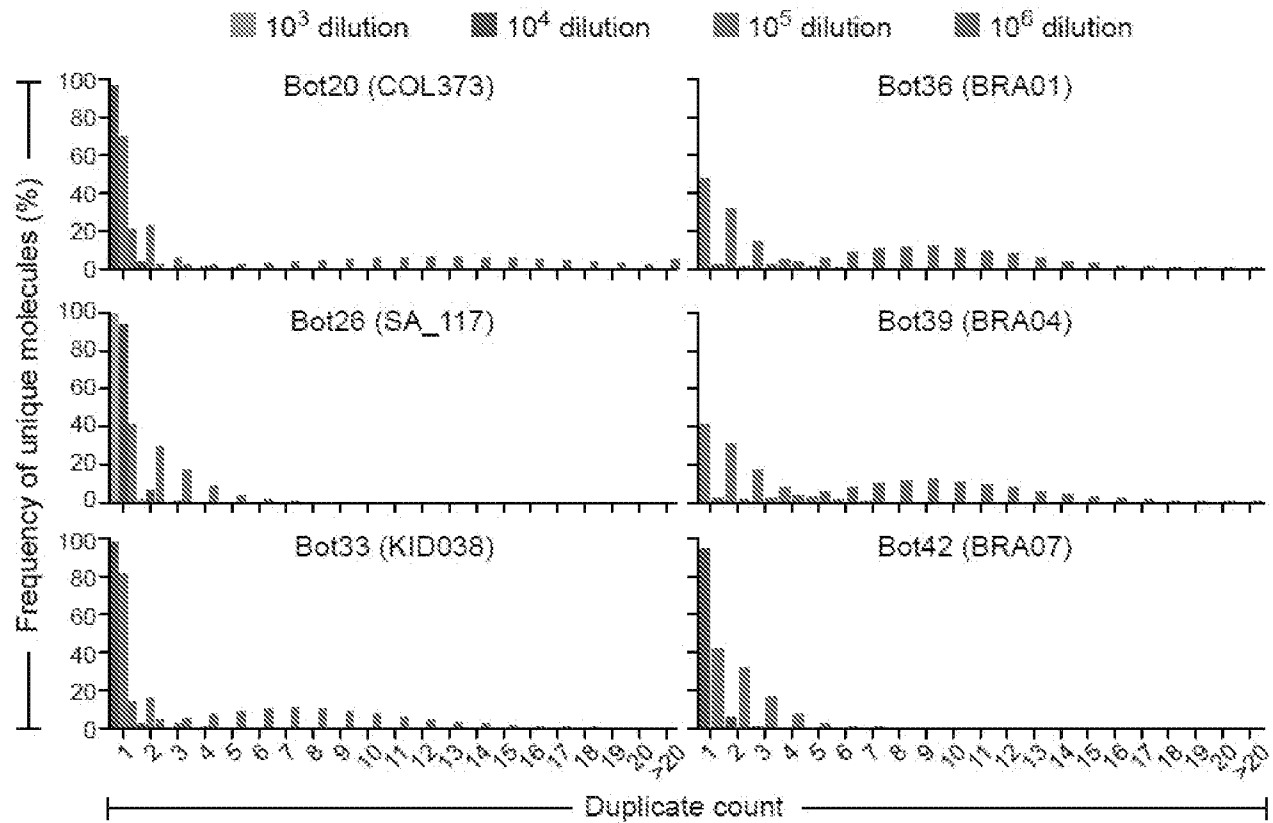
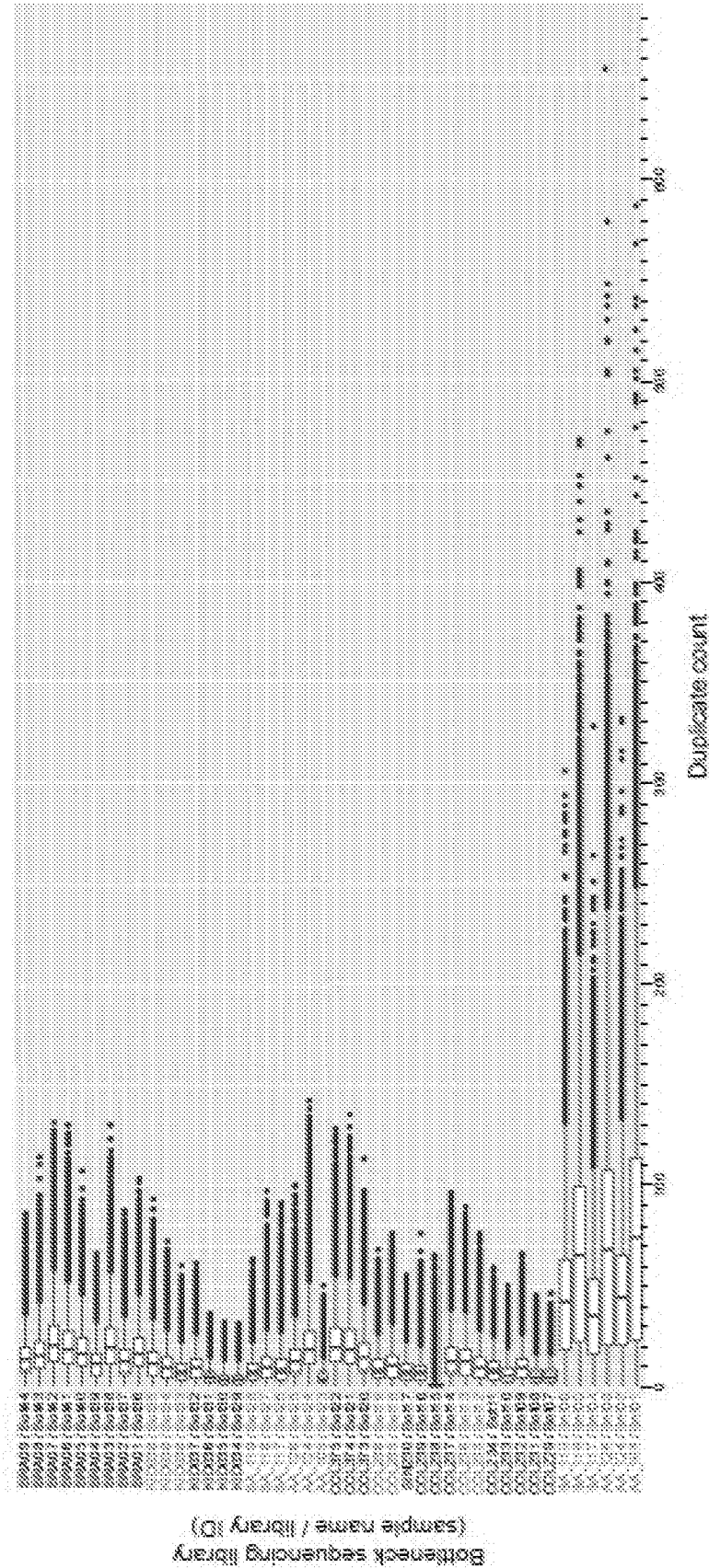


FIG. 55



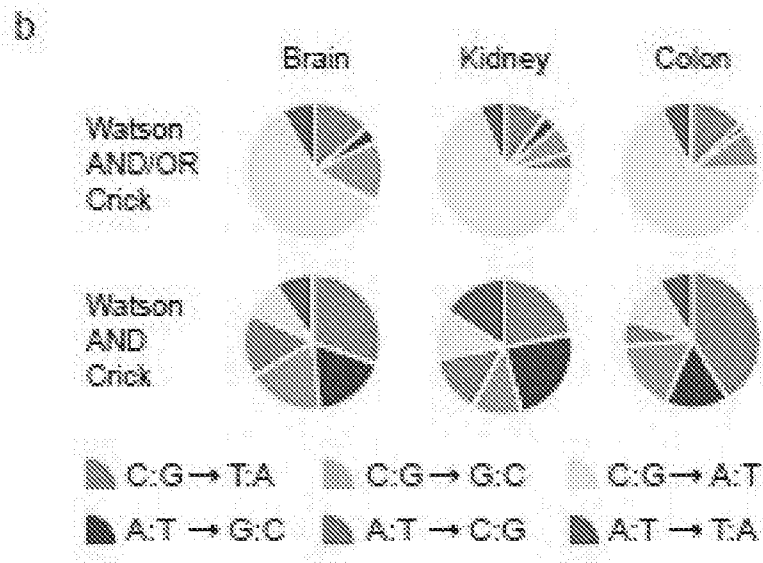
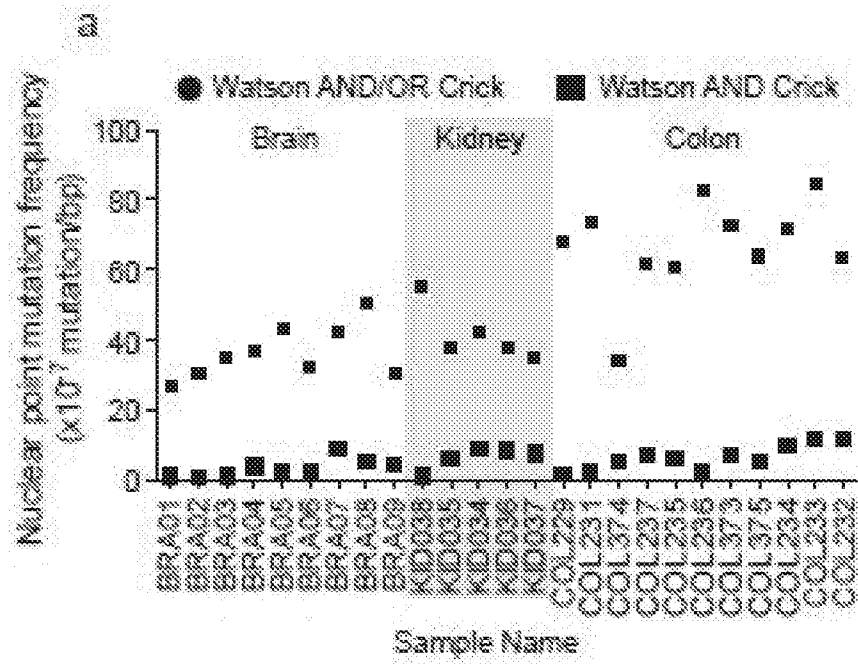


FIG. 57

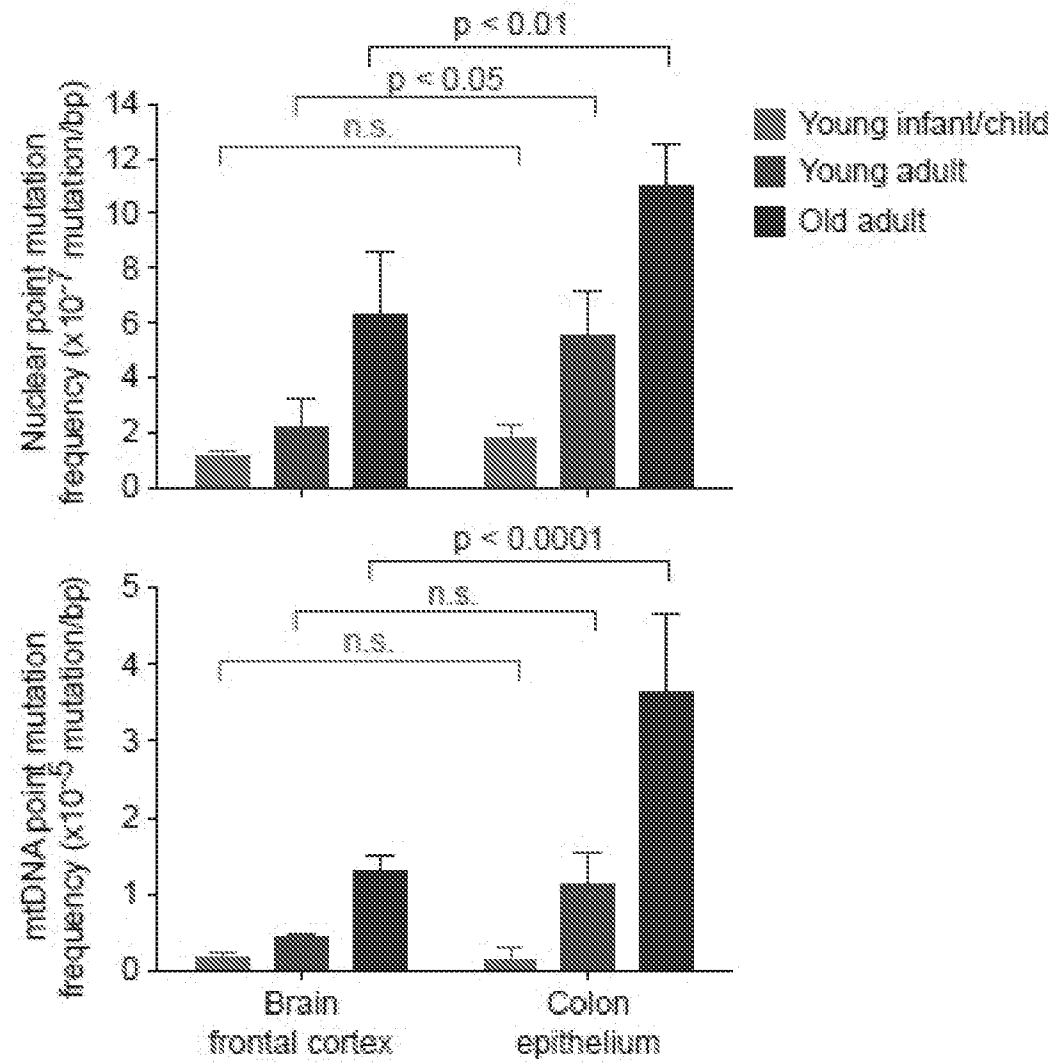


FIG. 58

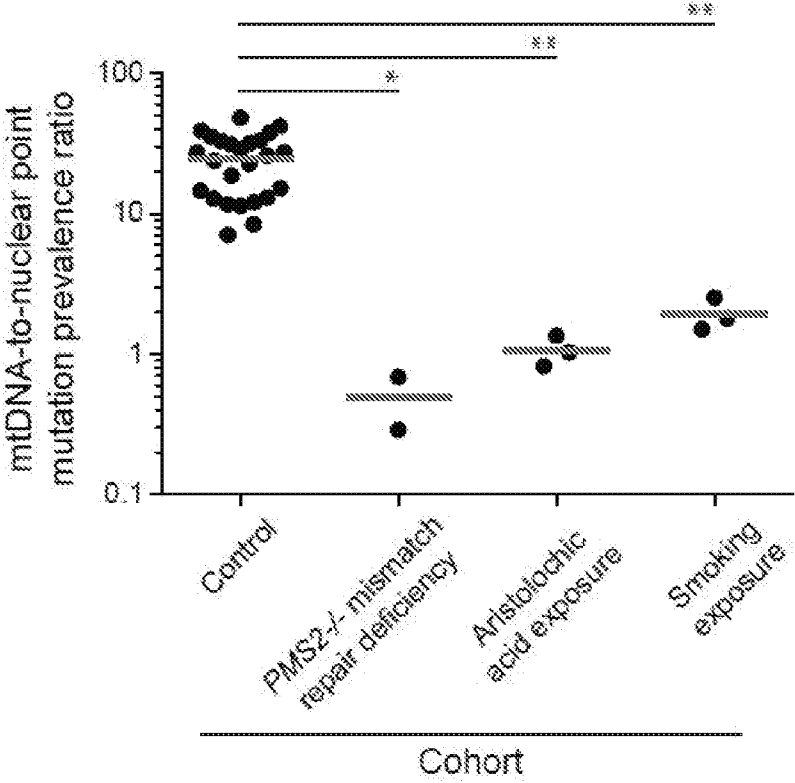


FIG. 59

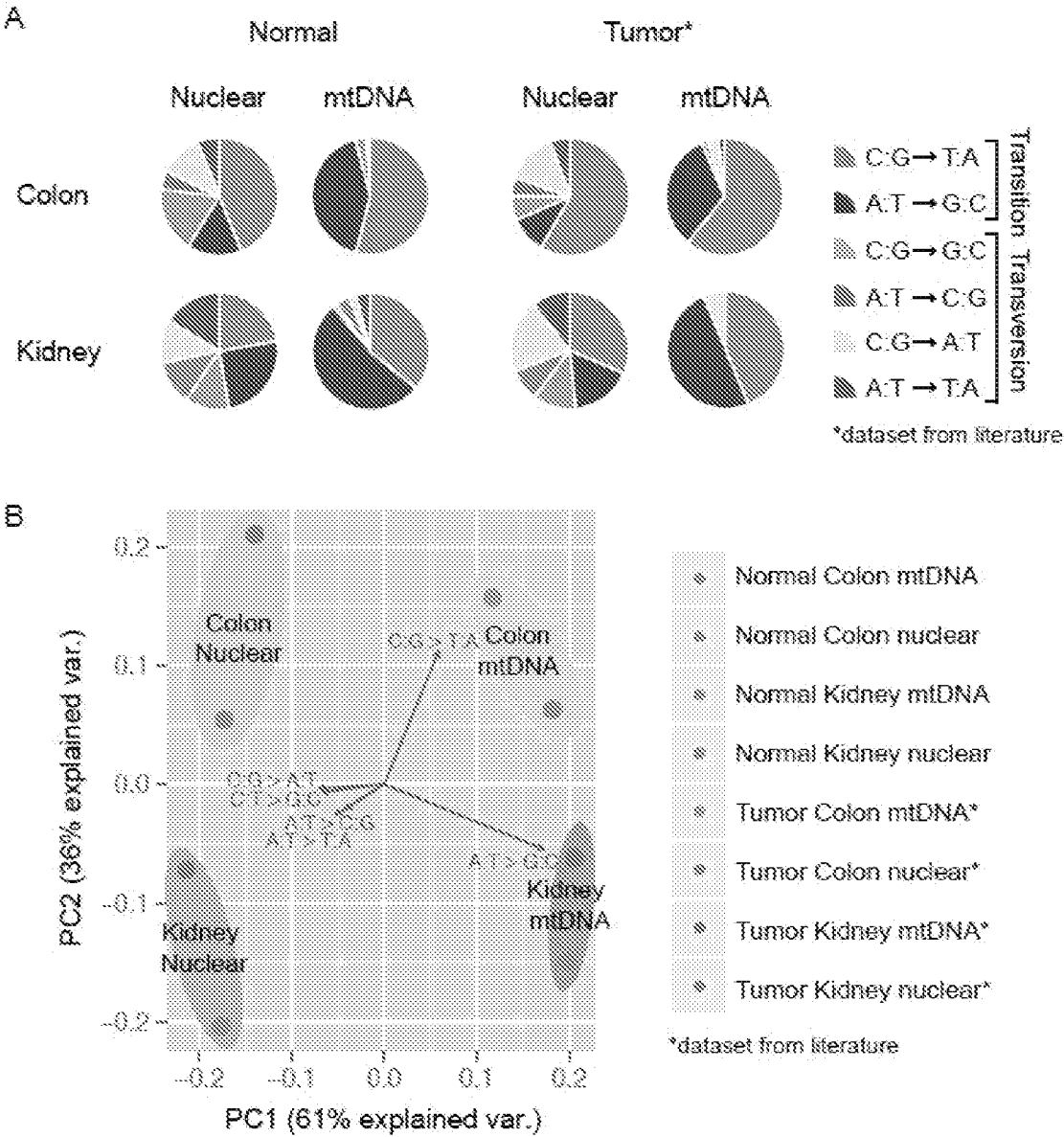


FIG. 60

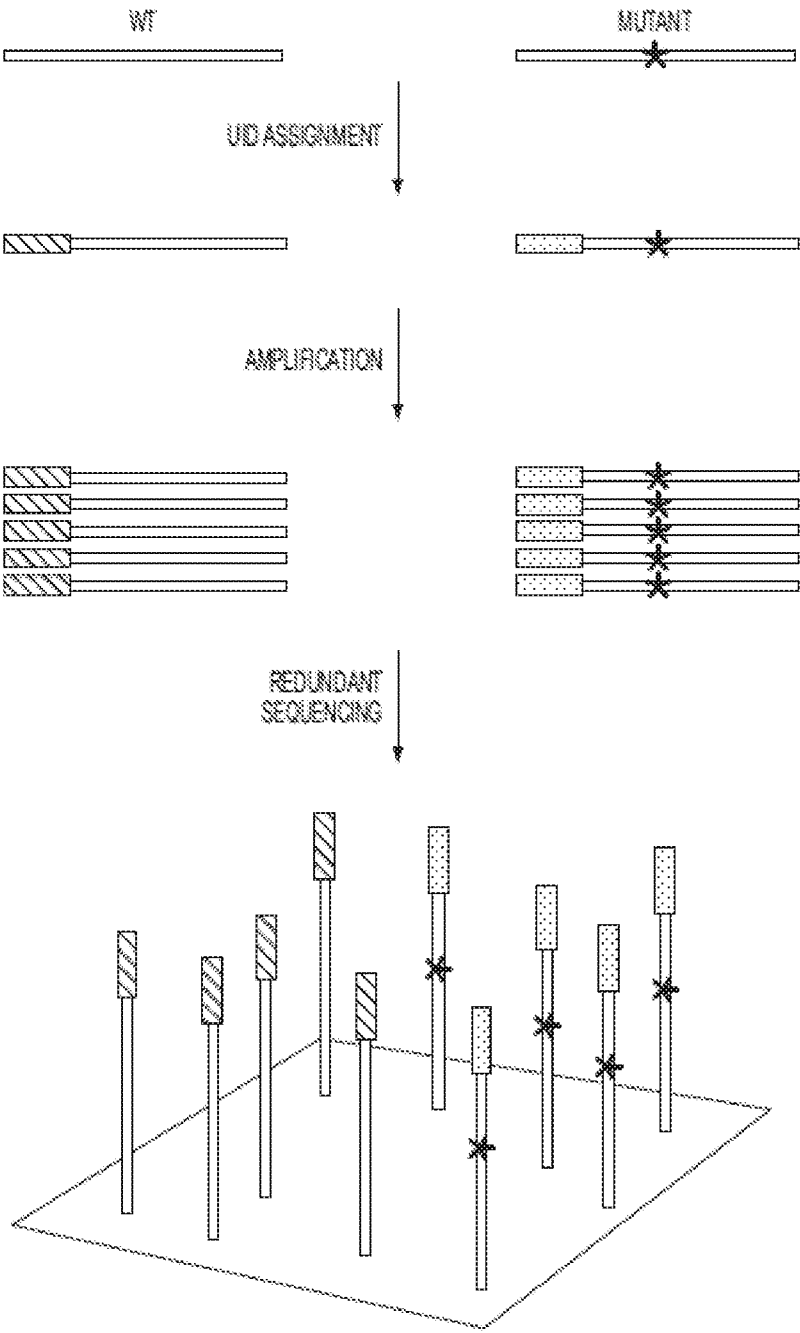


FIG. 61

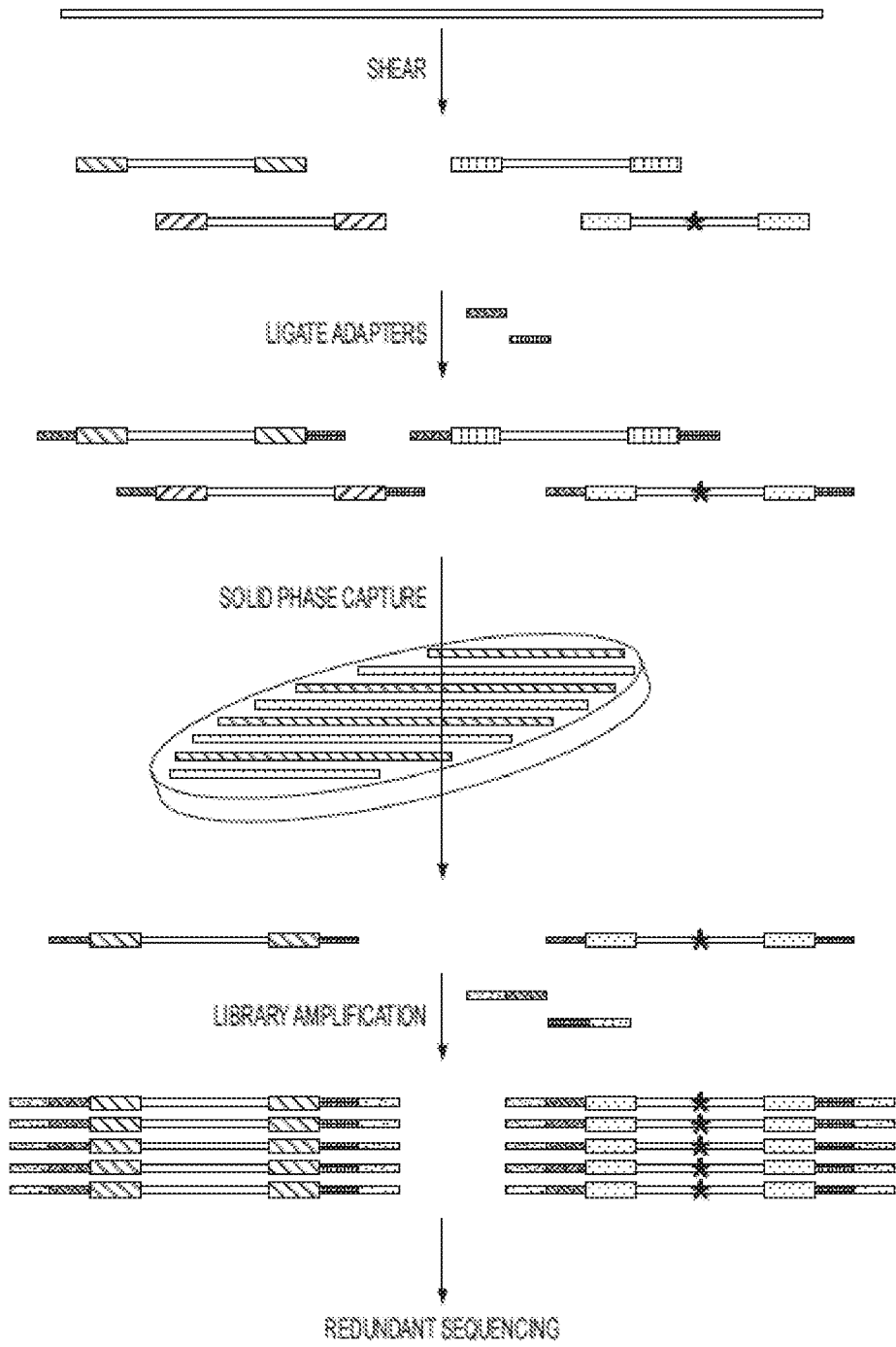


FIG. 62

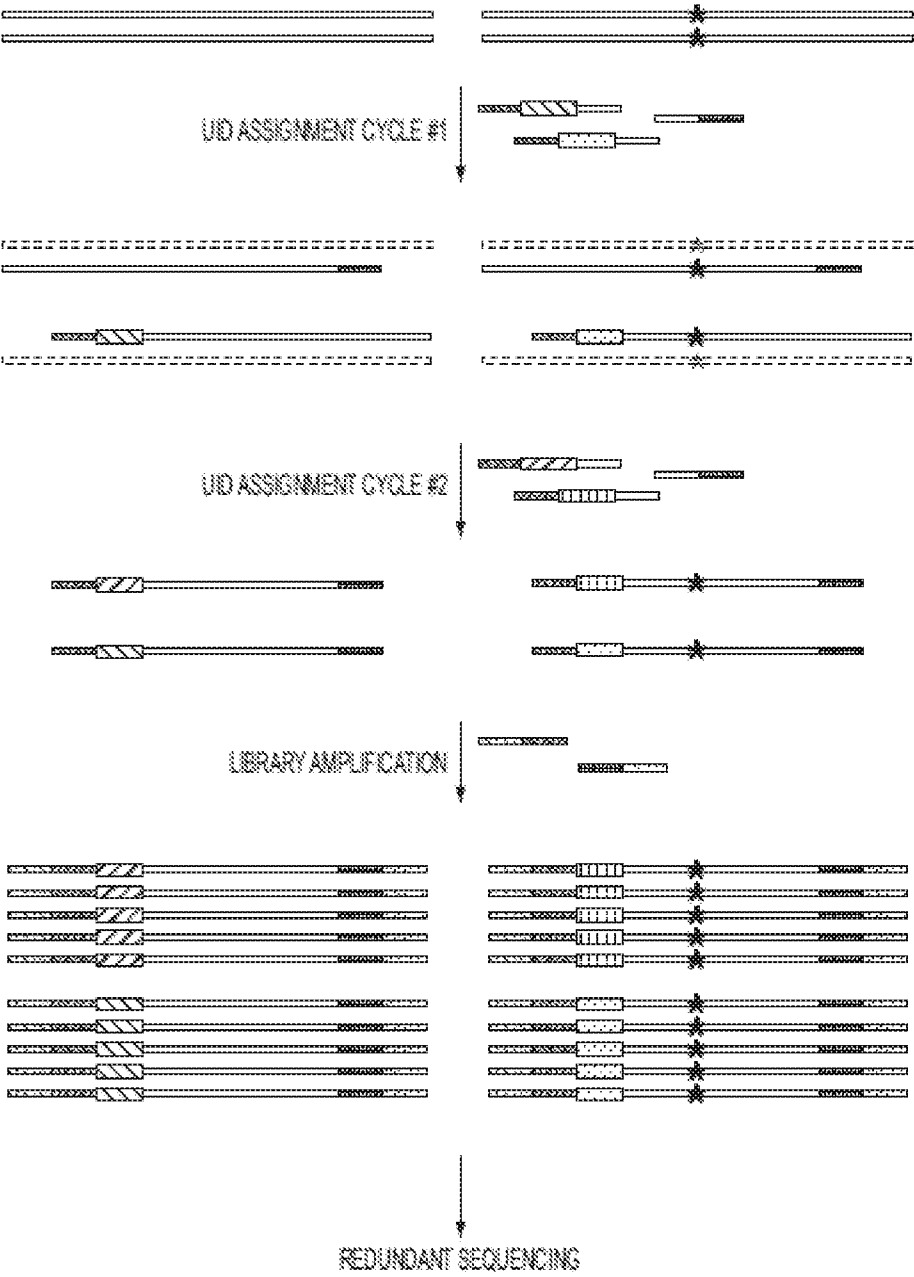
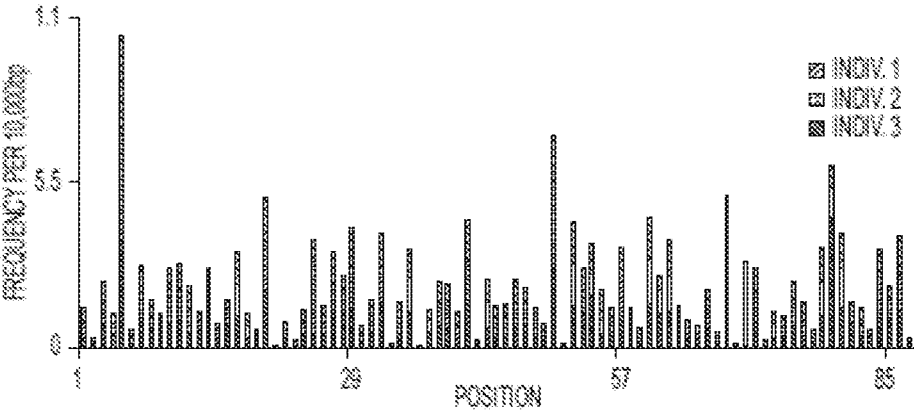


FIG. 63

A



B

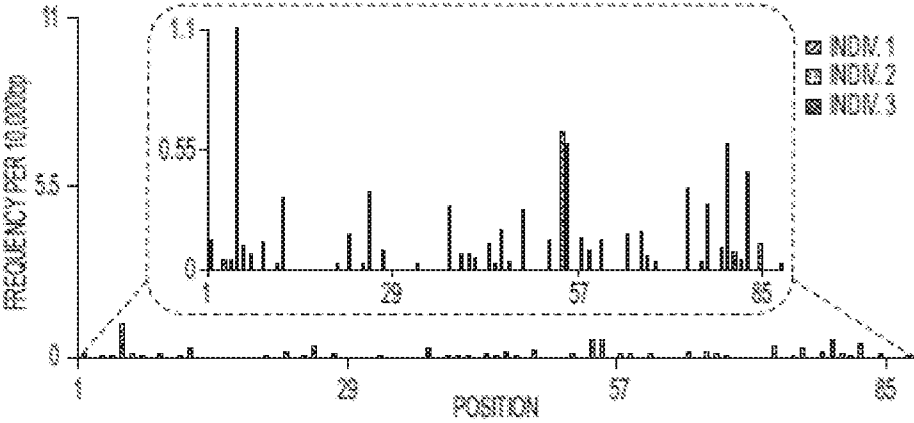


FIG. 64

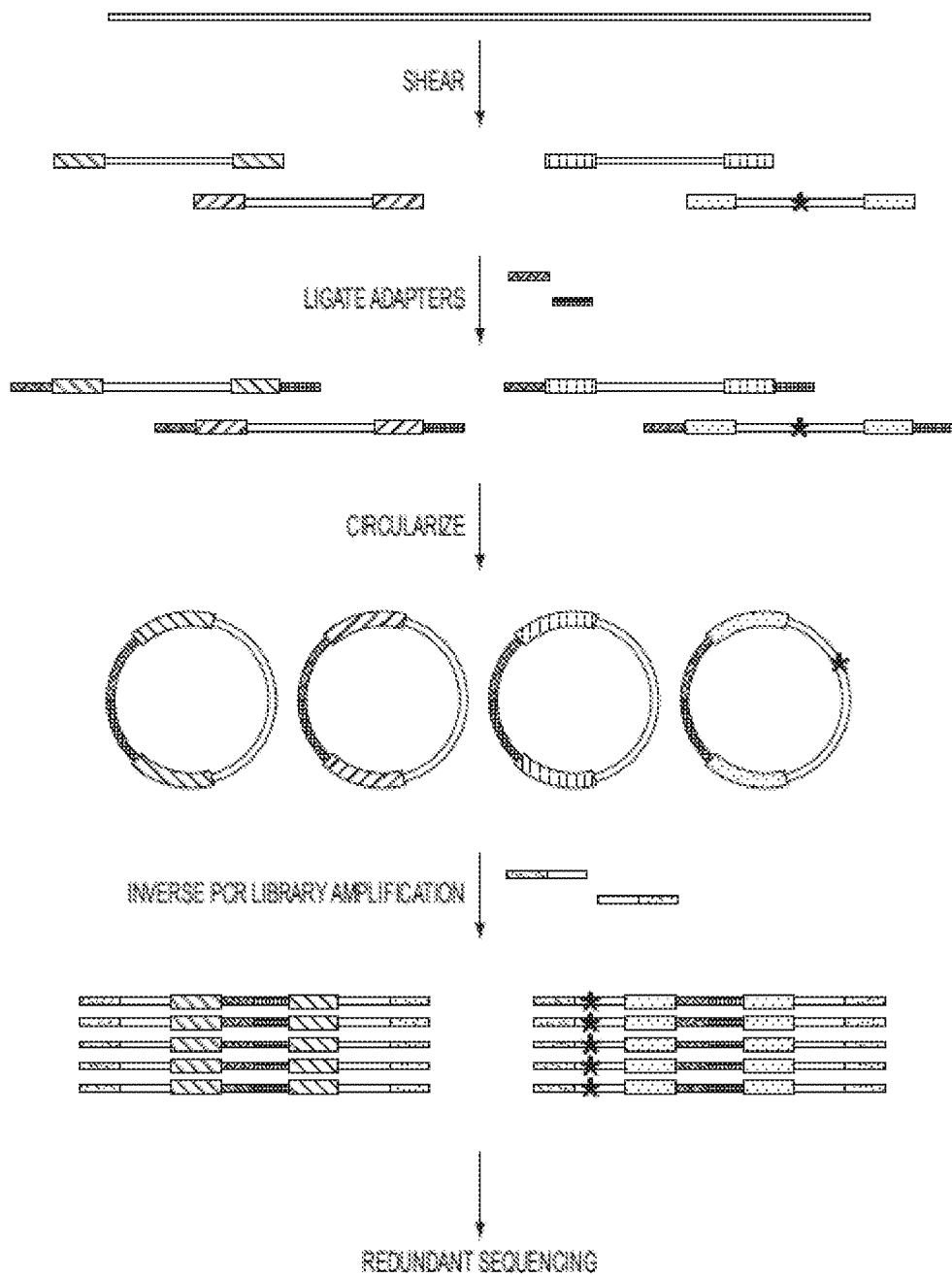


FIG. 65

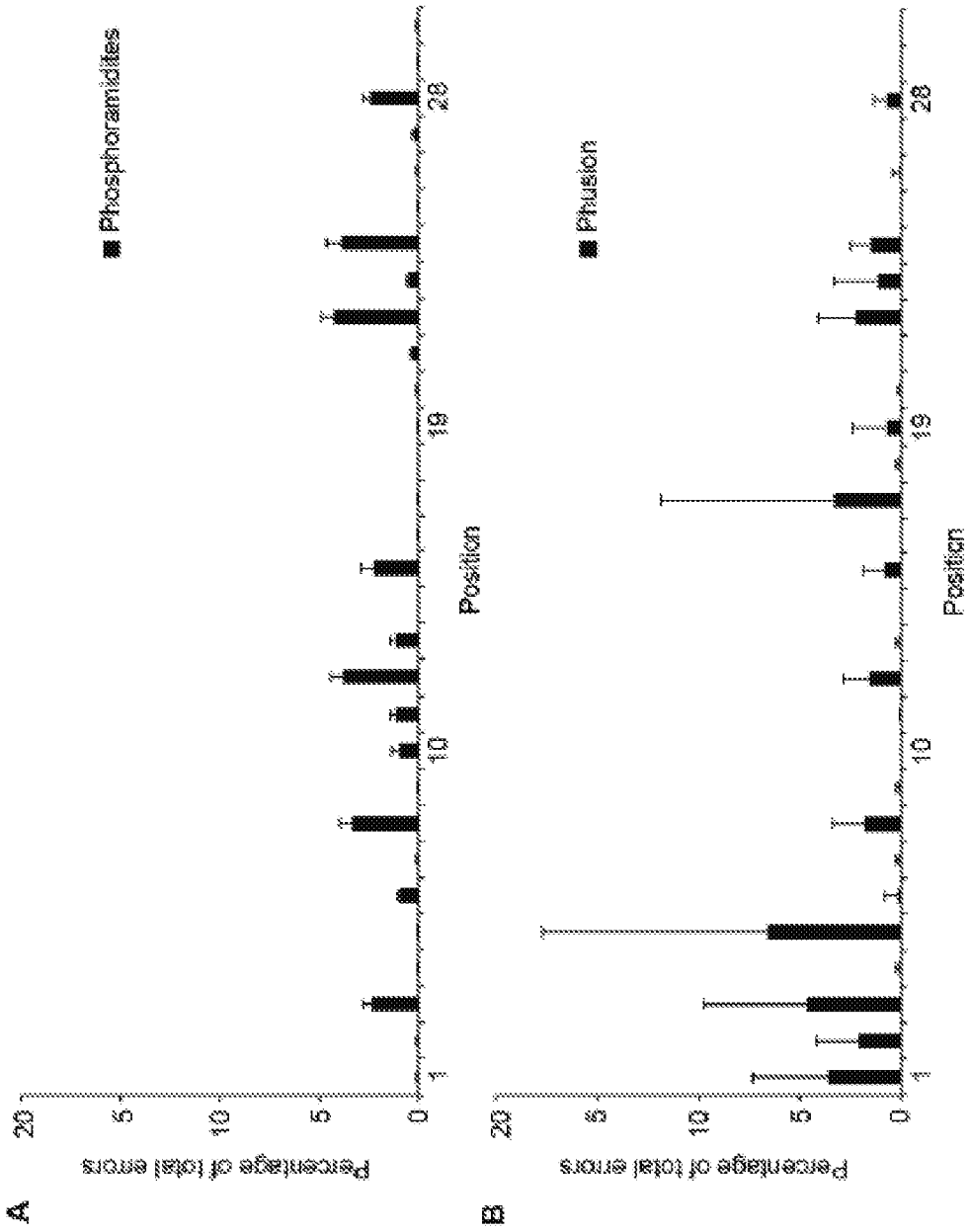


FIG. 66

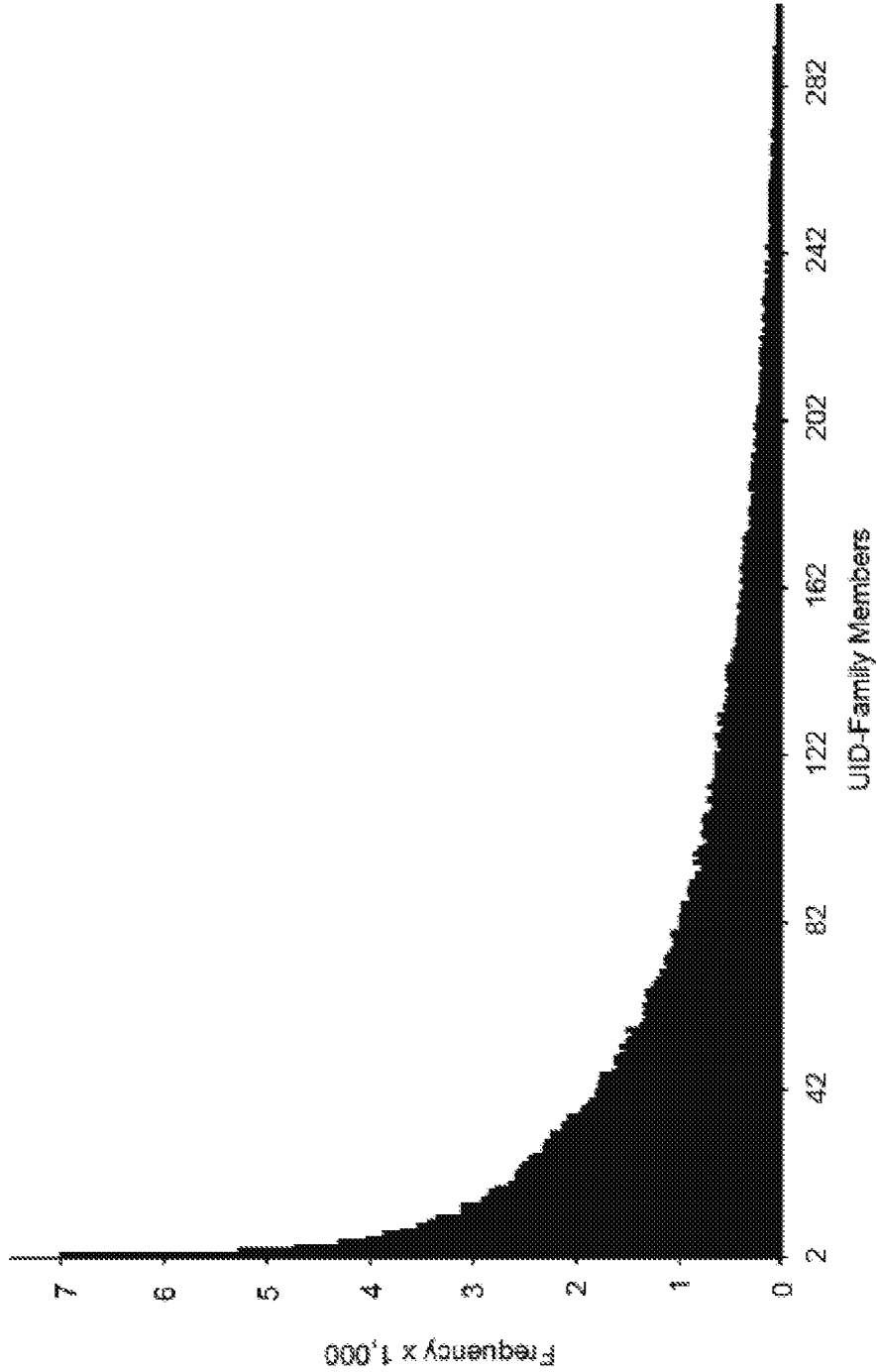


FIG. 67

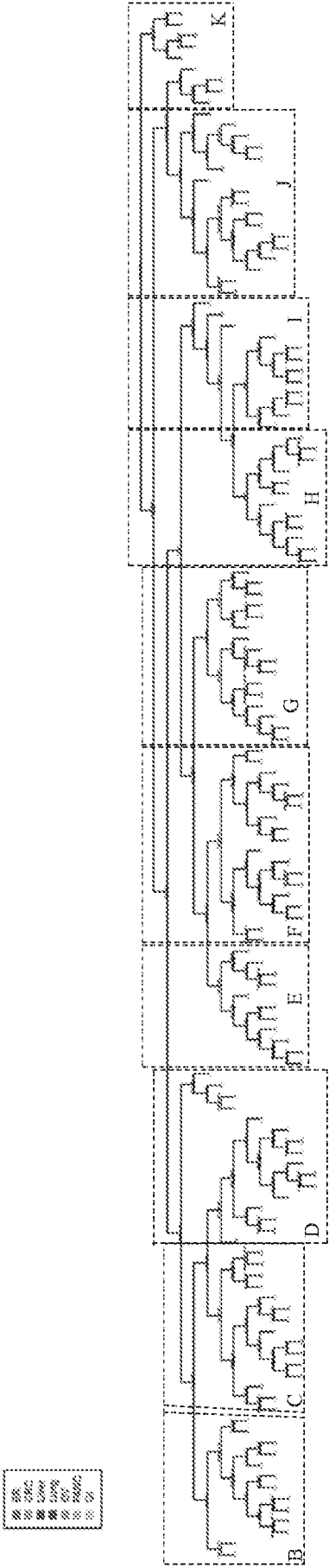


FIG. 68A

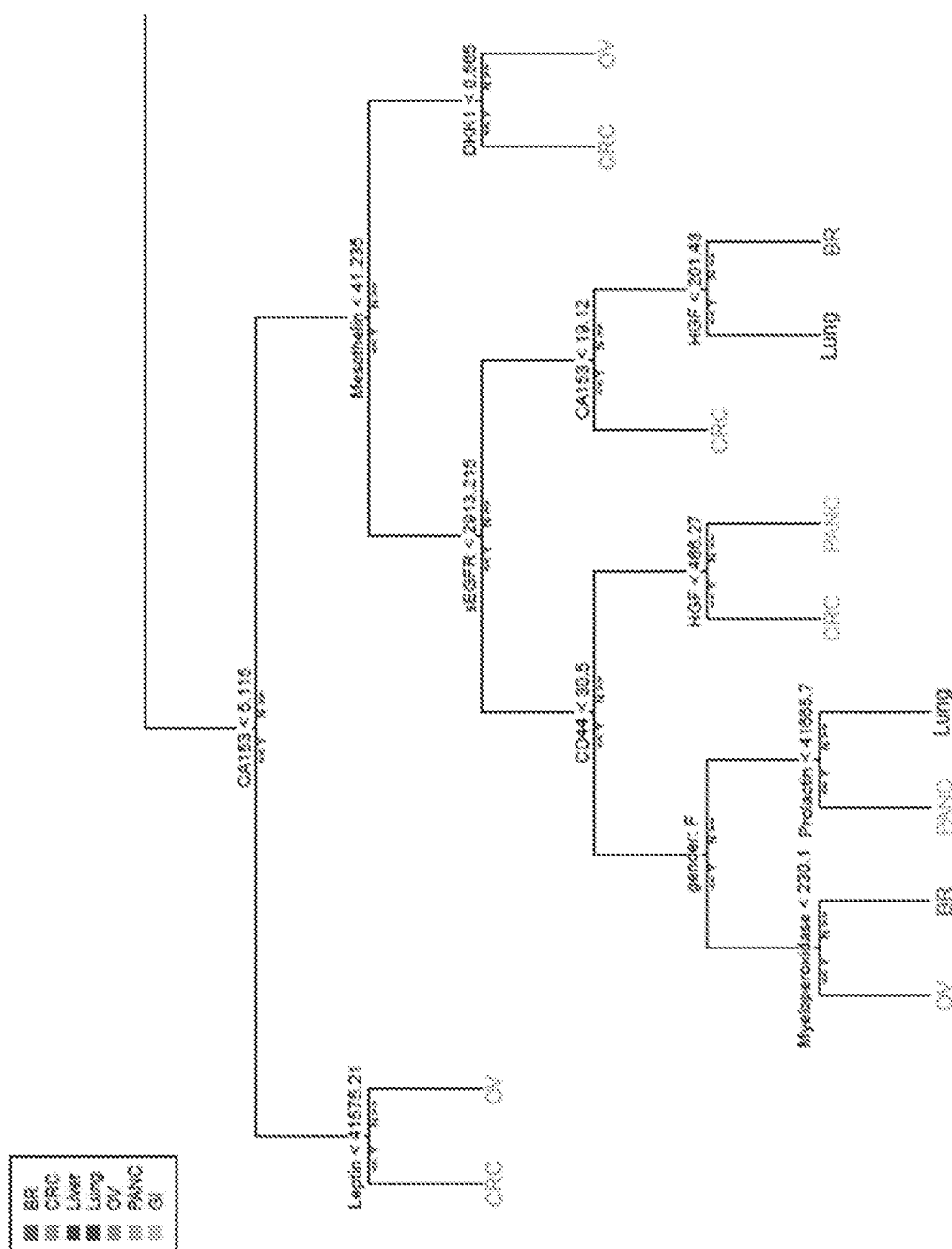
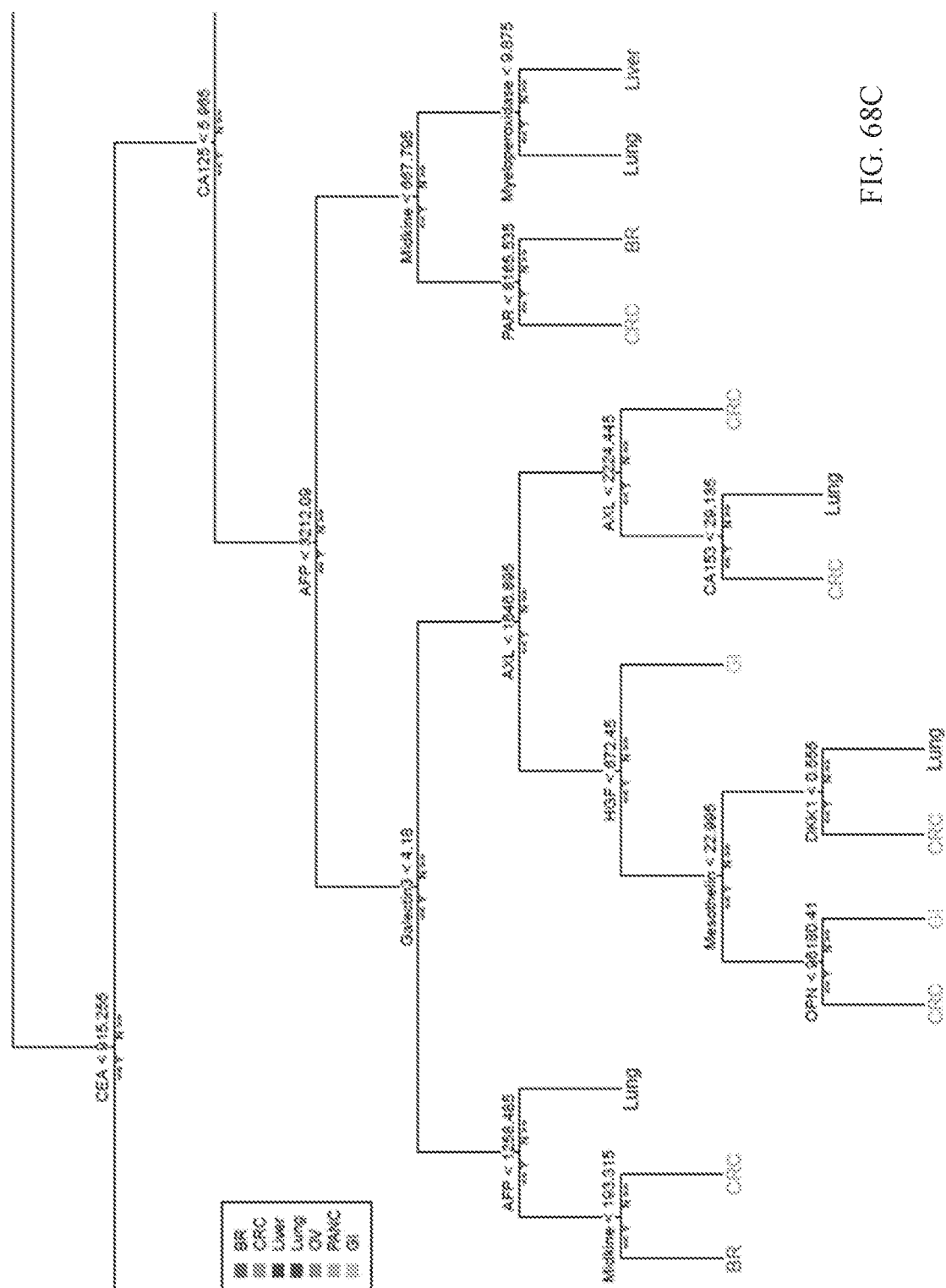
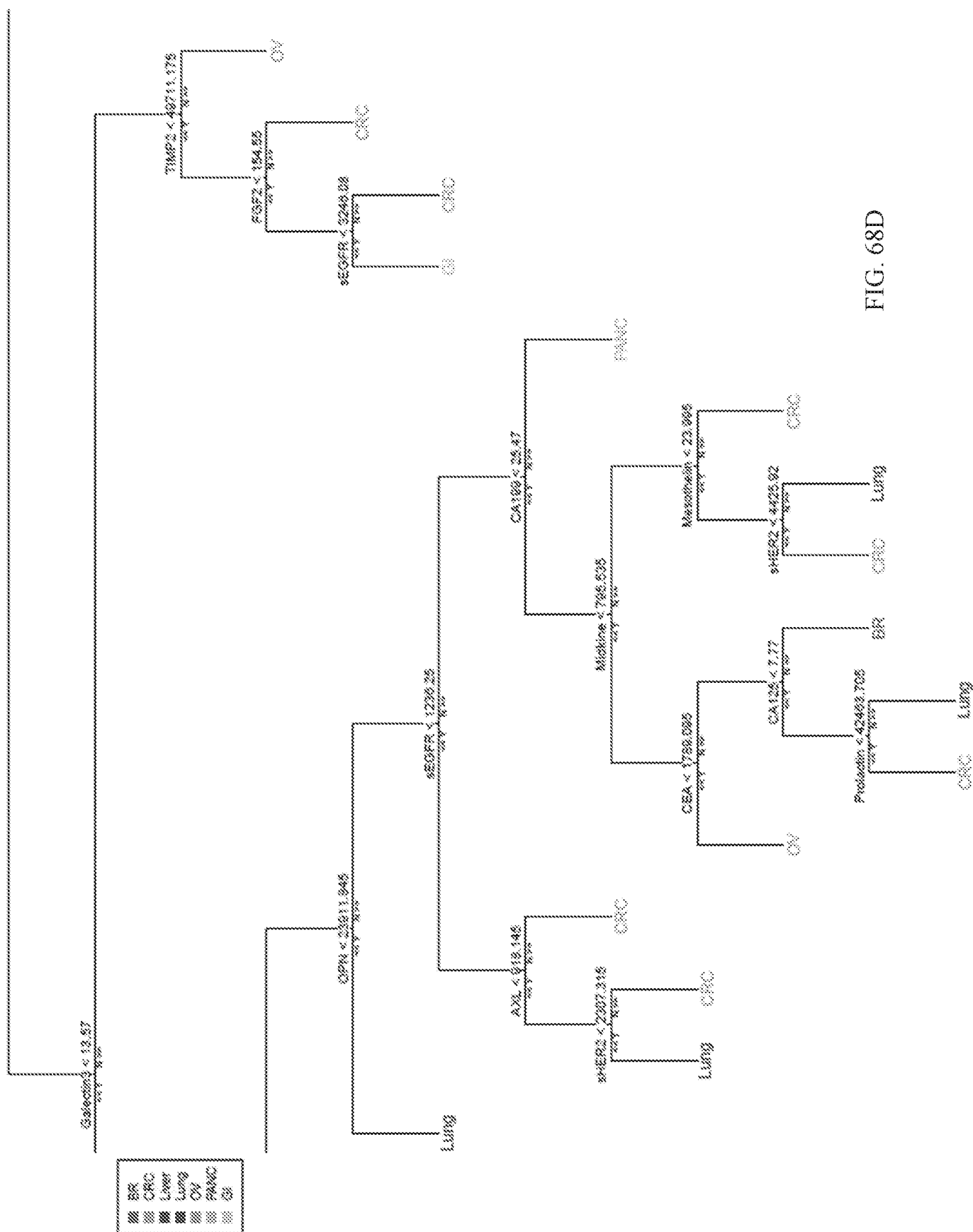


FIG. 68B





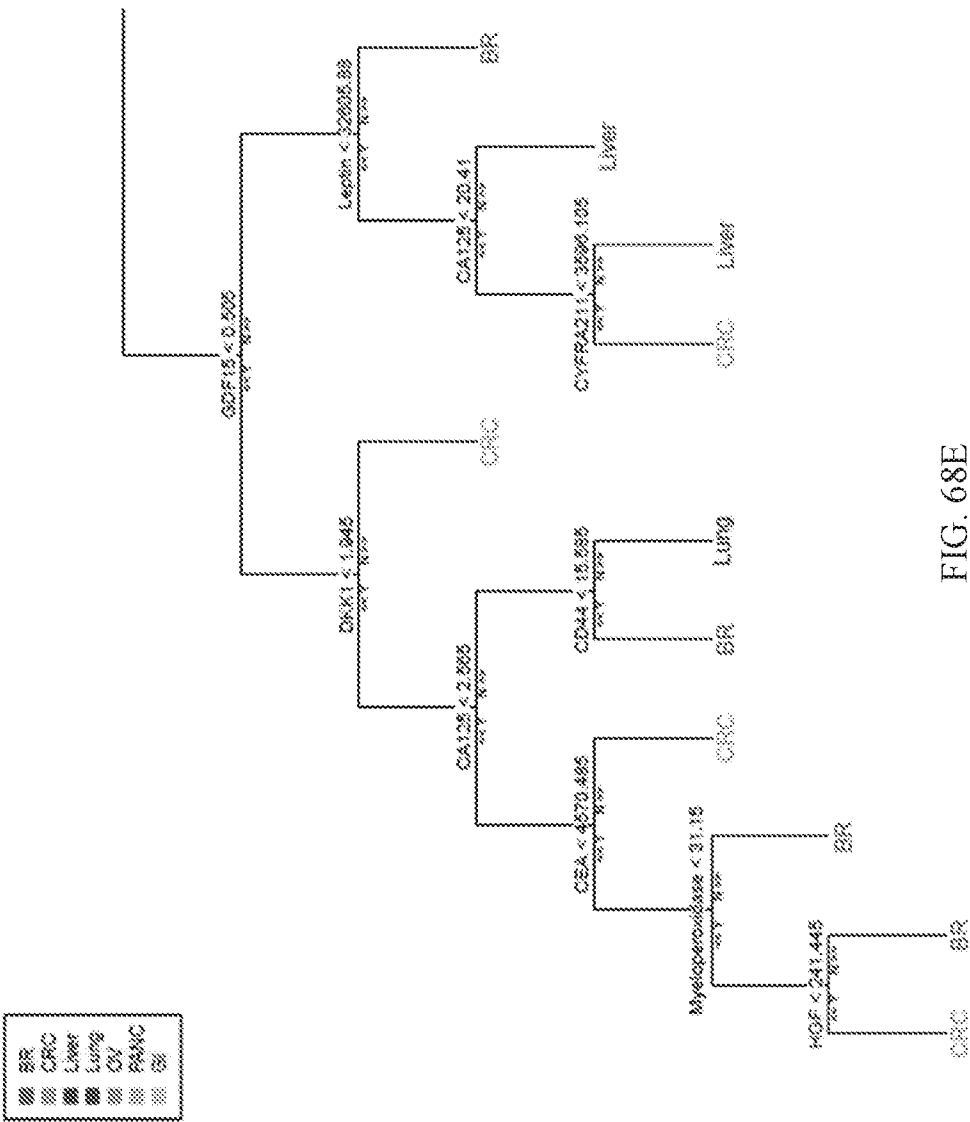


FIG. 68E

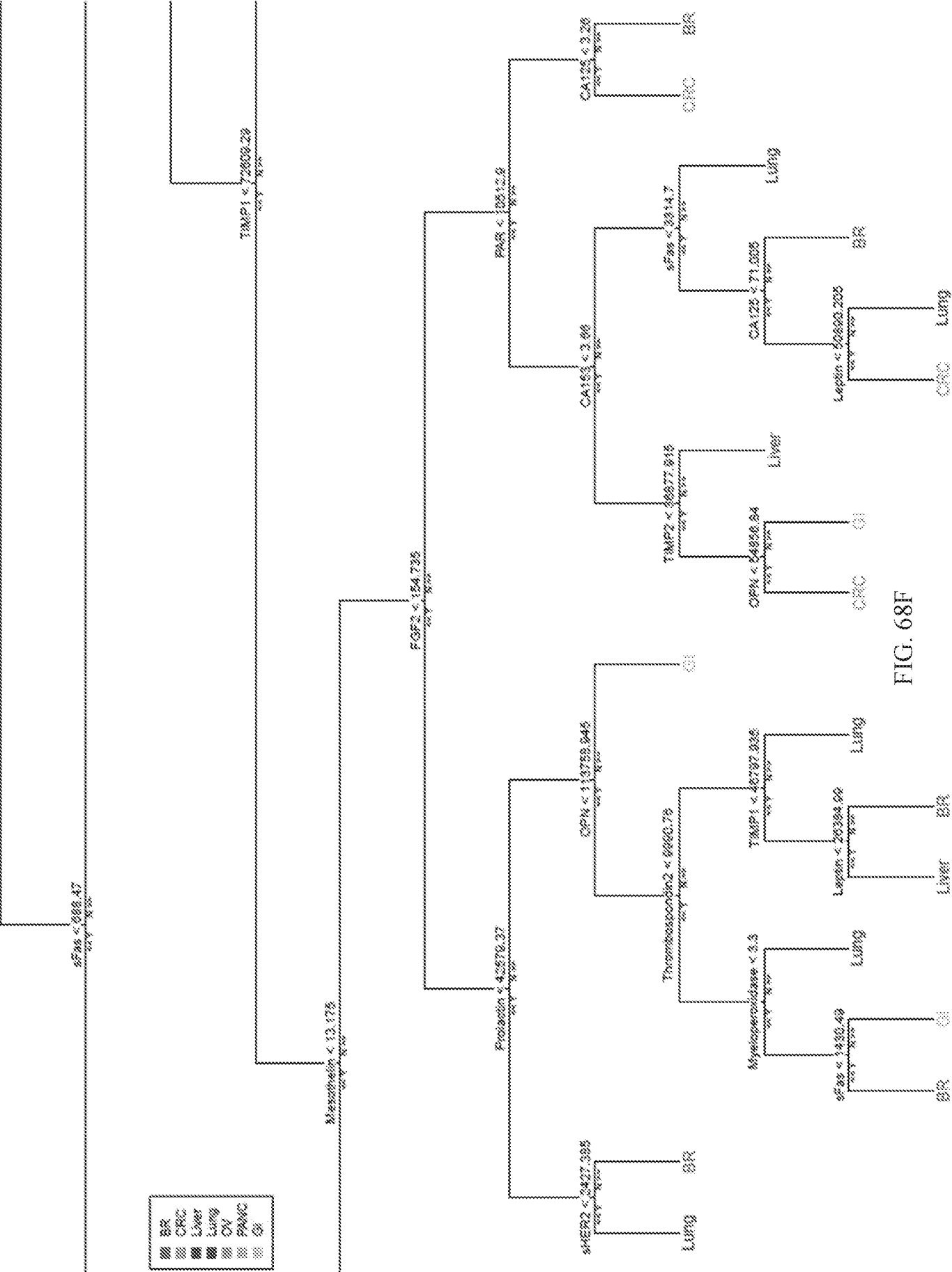
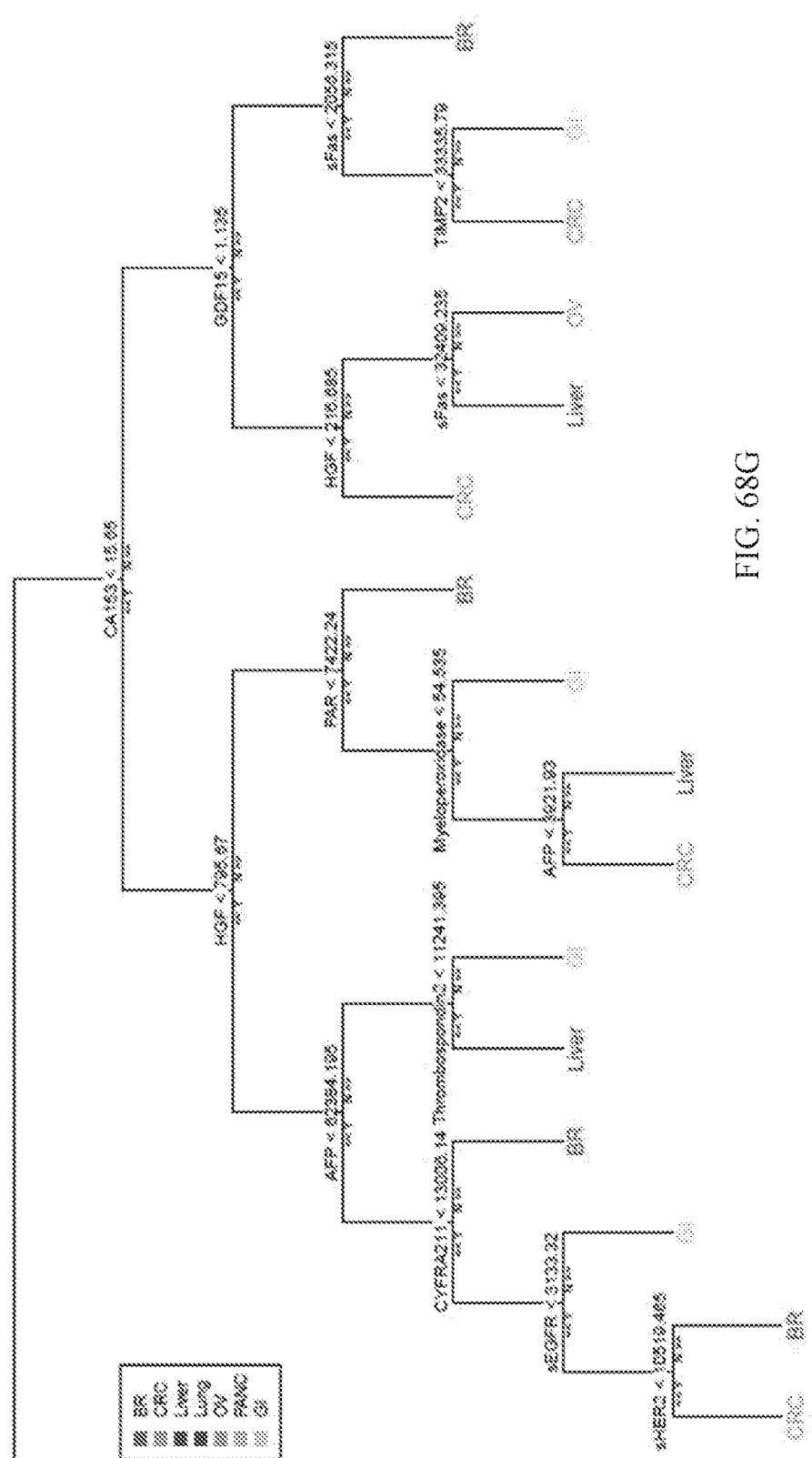
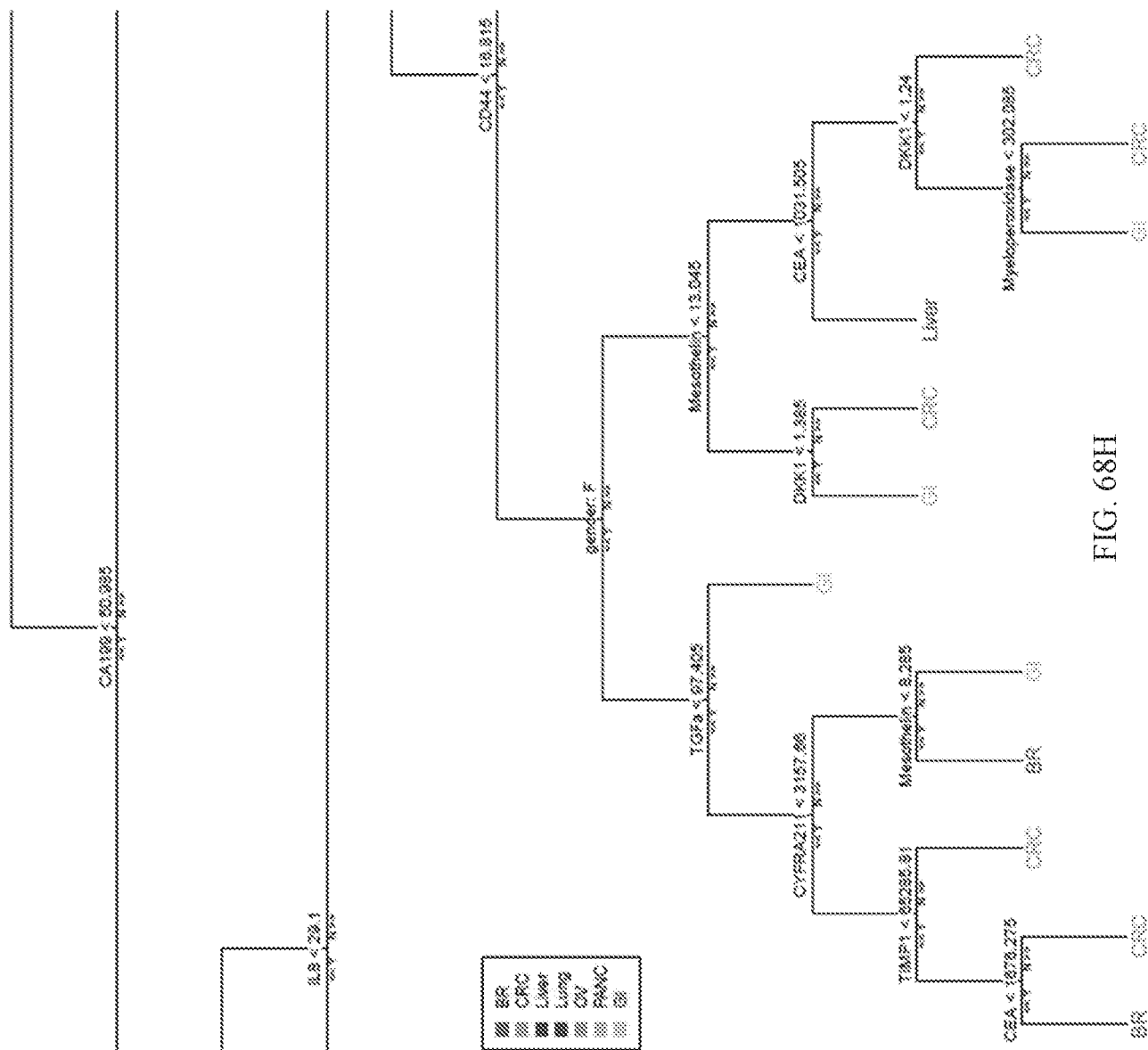
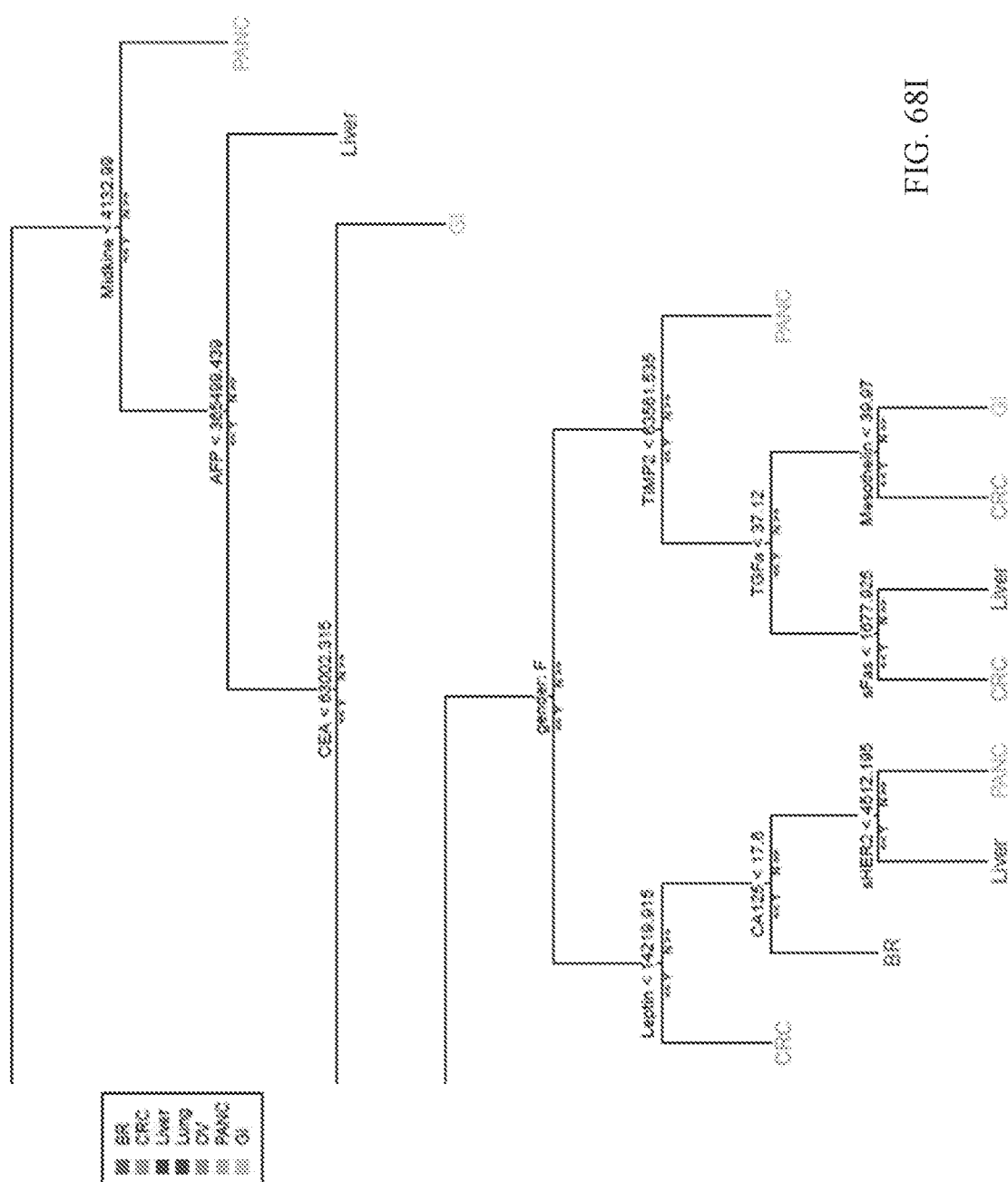


FIG. 68F







CA125 < 172.815

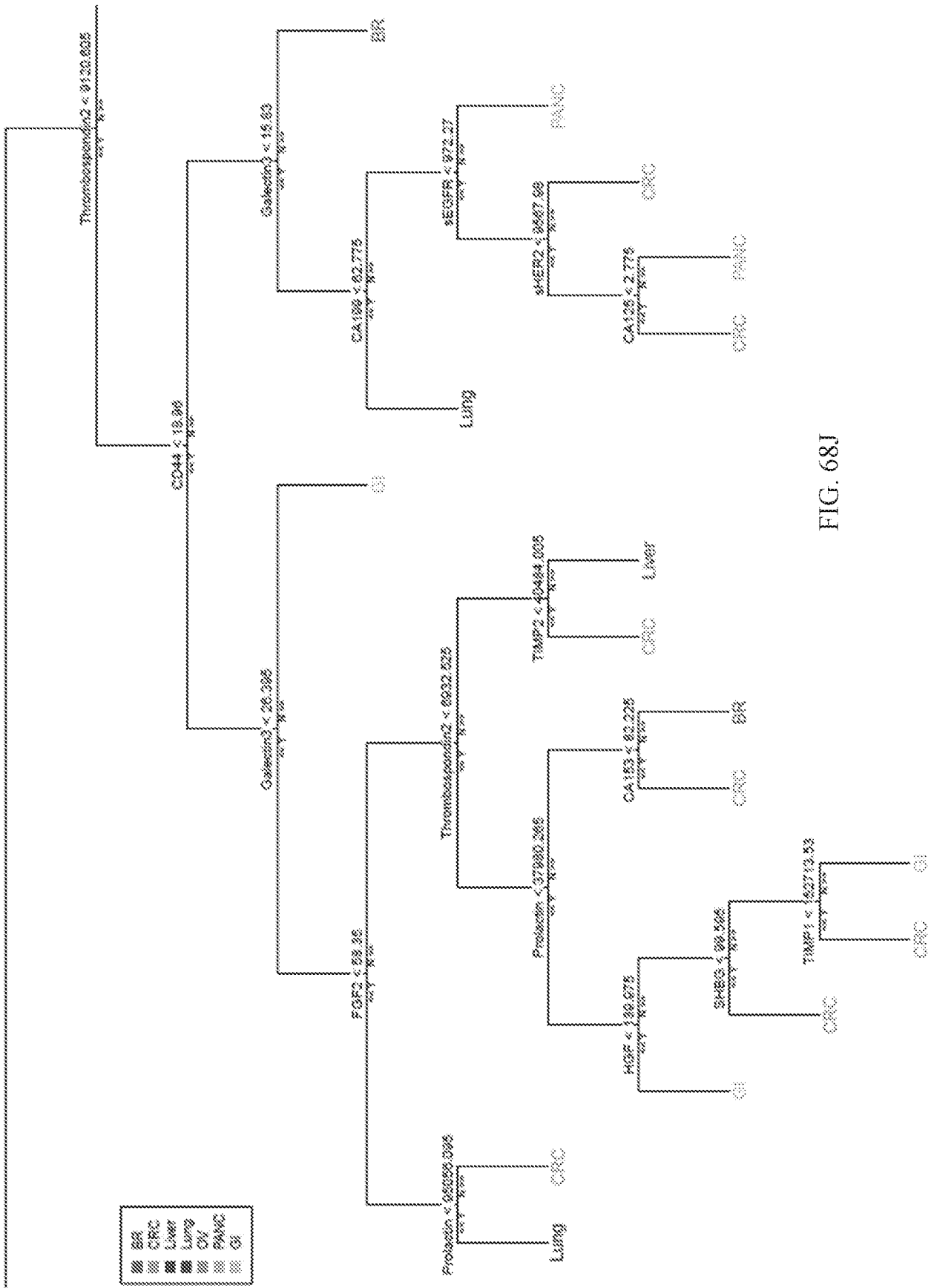


FIG. 68J

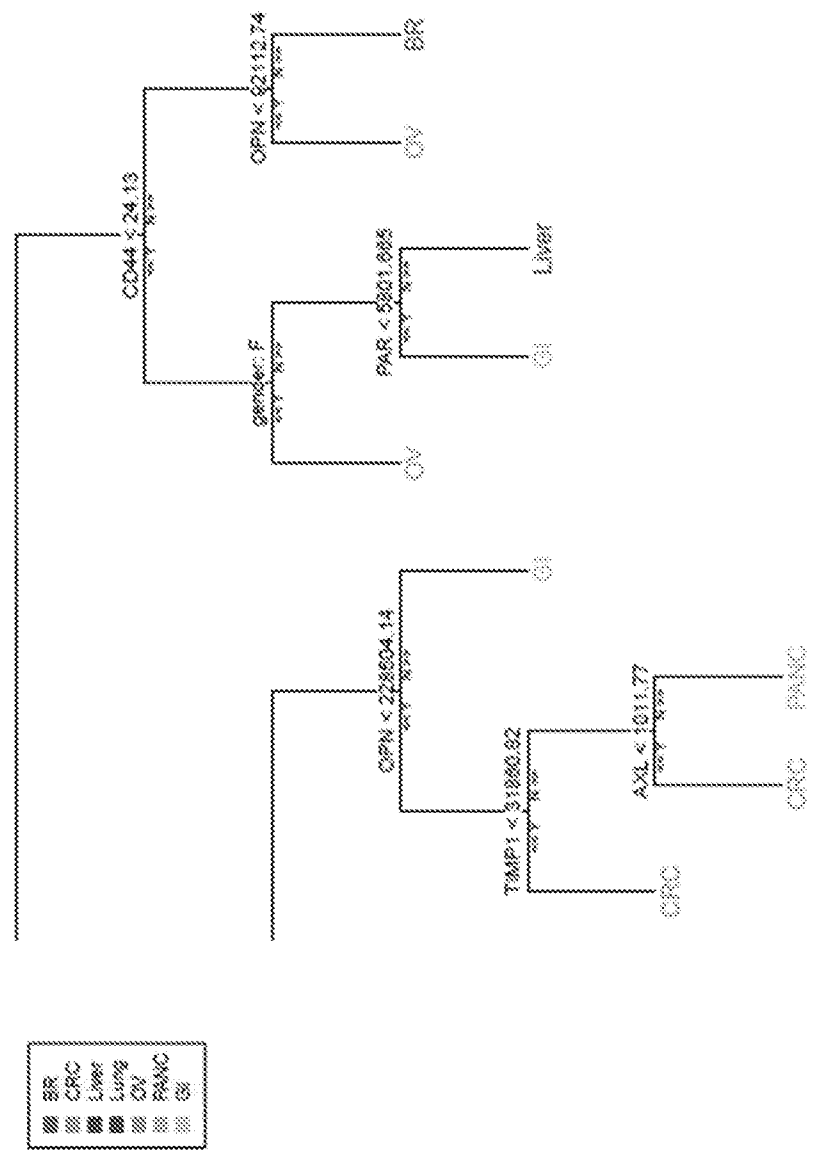


FIG. 68K

```

## R version 3.5.0 (2018-04-23)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 17134)
##
## Matrix product: default
##
## locale:
## [1] LC_COLLATE=English_United States.1252
## [2] LC_CTYPE=English_United States.1252
## [3] LC_MONETARY=English_United States.1252
## [4] LC_NUMERIC=C
## [5] LC_TIME=English_United States.1252
##
## attached base packages:
## [1] stats      graphics  grDevices  utils      datasets  methods   base
##
## other attached packages:
## [1] caret_2.0-39      ggplot2_2.0.0      lattice_0.20-35
## [4] rpart_4.1-1       DT_0.4             randomForest_4.5-14
##
## loaded via a namespace (and not attached):
## [1] magrittr_1.5-2      dplyr_0.7.0         tidyr_0.8.1
## [4] rstatix_0.4.1-1     splines_3.5.0       forecast_1.4.4
## [7] prodlim_2018.04.18  assertr_0.2.0       rstatix_0.4.1-1
## [10] rpart_4.1-1         DRR_0.0.2           yaml_2.1.19
## [13] rpart_4.1-1         ipred_0.9-6         pillar_1.2.3
## [16] backports_1.1.2     glue_1.2.0          digest_0.6.15
## [19] RDT_1.2             colorspace_1.2-2    recipes_0.1.2
## [22] gbm_2.1.3           httr_1.1.4          Matrix_1.2-14
## [25] plyr_1.8.4          psych_1.8.4         timeDate_2043.102
## [28] pkgconfig_2.0.1     CVST_0.2-2          broom_0.4.5
## [31] purrr_0.2.5         xtable_1.8-2        scales_0.5.0
## [34] power_0.1.2         lava_1.6.2          rstatix_0.4.1-1
## [37] rstatix_0.4.1-1     withr_2.1.2         rstatix_0.4.1-1
## [40] lme4_0.2.1          nlme_3.1-137        survival_2.42-4
## [43] magrittr_1.5        evaluate_0.11       nlme_3.1-137
## [46] MASS_7.3-30         dplyr_0.7.0         foreign_0.8-70
## [49] class_7.3-14        tools_3.5.0         data.table_1.12.4
## [52] rstatix_0.4.1-1     kernlab_0.9-26      MASS_7.3-30
## [55] bindr_0.2.2         pls_2.8-0            compiler_3.5.0
## [58] Rcpp_0.12.10        shiny_0.14.0        rstatix_0.4.1-1
## [61] iterators_1.0.8     htmlwidgets_1.2     rstatix_0.4.1-1
## [64] geometry_0.3-6      rstatix_0.4.1-1     ModelMatrix_1.1.0
## [67] codetools_0.2-15    akima_1.4-5          reshape2_1.4.3
## [70] R6_2.2.2            lubridate_1.7.4     knitr_1.20
## [73] dplyr_0.7.6         bindr_0.2.1         rstatix_0.4.1-1
## [76] stringi_1.2.5       parallel_3.5.0      Rcpp_0.12.10
## [79] xtable_1.8-2        DEoptimR_1.0-9      rstatix_0.4.1-1

```

FIG. 69

```
## [1] "Tumor samples: n = 626"
```

```
## [1] "Proteins: AFP, CA125, CA153, CA199, CEA, CYPBAG11, FGF2, HD4, HGF, IL6, IL8, Leptin, OSM, Prolactin, sFas,
s, TGFA, TIMP1, TIMP2, Galectin3, Myeloperoxidase, SHBG, SMR1, GDF15, NSE, OPG, CD44, Macuhelin, Midkine, ANK, P
AP, sEGFR, sHER2, Thrombospondin3"
```

```
## [1] "Predictions from randomForest:"
```

```
##
##   Breast      CRC      Liver      Lung      Ovarian Pancreas      st_ovo
##      48      382      17      25      41      82      41
```

```
## 18635 rules (length<=6) were extracted from the first 500 trees.
```

```
## [1] "Predictions from inTrees classifier:"
```

```
## predictions
##   Breast      CRC      Liver      Lung      Ovarian Pancreas      st_ovo
##      57      352      19      26      45      50      57
```

```
## [1] "Accuracies from the paper:"
```

```
##   Breast      CRC      Liver      Lung      Ovarian Pancreas      st_ovo
##   0.62      0.64      0.44      0.39      0.79      0.61      0.46
```

```
## [1] "Accuracies from inTrees classifier:"
```

```
##   Breast      CRC      Liver      Lung      Ovarian Pancreas      st_ovo
## 0.6376812 0.8893281 0.3863836 0.4098261 0.8112288 0.7558824 0.6025641
```

FIG. 69 (continued)