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[00535] All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[00536] The present invention can be implemented as a computer program product that comprises a computer program mechanism embedded in a nontransitory computer readable storage medium. For instance, the computer program product could contain the program modules shown in any combination of Figures 1 or 2 and/or described in Figures 3, 37, 38, 39, 40 or 71. These program modules can be stored on a CD-ROM, DVD, magnetic disk storage product, USB key, or any other non-transitory computer readable data or program storage product.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only. The embodiments were chosen and described in order to best explain the principles of the invention and its practical applications, to thereby enable others skilled in the art to best utilize the invention and various embodiments with various modifications as are suited to the particular use contemplated. The invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A method for determining a likelihood that a human subject afflicted with a cancer will be responsive to a treatment regimen that comprises administering a checkpoint blockade immunotherapy directed to the cancer to the subject, the method comprising:

(A) obtaining a plurality of sequencing reads from one or more samples from the human cancer subject that is representative of the cancer;

(B) determining a human leukocyte antigen (HLA) type of the human cancer subject;

(C) determining a plurality of clones, and for each respective clone α in the plurality of clones, an initial frequency X_α of the respective clone α in the one or more samples;

(D) for each respective clone α in the plurality of clones, computing a corresponding clone fitness score of the respective clone, thereby computing a plurality of clone fitness scores, each corresponding clone fitness score computed for a respective clone α by a first procedure comprising:

(a) identifying a plurality of neoantigens in the respective clone α;

(b) computing a recognition potential of each respective neoantigen in the plurality of neoantigens in the respective clone α by a second procedure comprising:

(i) computing an amplitude *A* of the respective neoantigen as a function of the relative major histocompatibility complex (MHC) affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject,

(ii) computing a probability of T-cell receptor recognition *R* of the respective neoantigen as a probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation, and

(iii) computing the recognition potential of the respective neoantigen as a function of the amplitude *A* of the respective neoantigen and the probability of T-cell receptor recognition *R* of the respective neoantigen; and

(c) determining the corresponding clone fitness score of the respective clone α as an aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α; and

(E) computing a total fitness for the one or more samples as a sum of the clone fitness scores across the plurality of clones, wherein

each clone fitness score is weighted by the initial frequency X_α of the corresponding clone α, and

the total fitness quantifies the likelihood that the human subject afflicted with the cancer will be responsive to the treatment regimen.

2. The method of claim 1, wherein the checkpoint blockade immunotherapy comprises administering an anti-CTLA-4, anti-PD1, anti-PD-L1, anti-LAG3, anti-TIM-3, anti-GITR, anti-OX40, anti-CD40, anti-TIGIT, anti4-1BB, anti-B7-H3, anti-B7-H4, or anti-BTLA compound to the cancer subject.

3. The method of claim 1, wherein the checkpoint blockade immunotherapy comprises administering ipilimumab or tremelimumab to the cancer subject.

4. The method of any one of claims 1-3, wherein the cancer is a carcinoma, a melanoma, a lymphoma/leukemia, a sarcoma, or a neuro-glial tumor.

5. The method of any one of claims 1-3, wherein the cancer is lung cancer, pancreatic cancer, colon cancer, stomach or esophagus cancer, breast cancer, ovary cancer, prostate cancer, or liver cancer.

6. The method of any one of claims 1-5, wherein

each clone α in the plurality of clones is uniquely defined by a unique set of somatic mutations, and

the plurality of clones is determined by a variant allele frequency of each respective somatic mutation in a plurality of somatic mutations determined from the plurality of sequencing reads.

7. The method of claim 6, wherein the somatic mutation is a single nucleotide variant or an indel.

8. The method of any one of claims 1-7, wherein the plurality of clones is determined by identifying a plurality of inferred copy number variations using the plurality of sequencing reads.

9. The method of any one of claims 1-8, wherein

each clone α in the plurality of clones is uniquely defined by a unique set of somatic mutations, and

the plurality of clones is determined by a combination of (i) a variant allele frequency of each respective somatic mutation in the plurality of somatic mutations determined from the plurality of sequencing reads and (ii) an identification of a plurality of inferred copy number variations using the whole-genome sequencing data.

10. The method of any one of claims 1-9, wherein the plurality of sequencing reads exhibits an average read depth of less than 40.

11. The method of any one of claims 1-9, wherein the plurality of sequencing reads exhibits an average read depth of between 25 and 60.

12. The method of any one of claims 1-11, wherein each neoantigen in the plurality of neoantigens of a clone in the plurality of clones is a nonamer peptide.

13. The method of any one of claims 1-12, wherein each neoantigen in the plurality of neoantigens of a clone in the plurality of clones is a peptide that is eight, nine, ten, or eleven residues in length.

14. The method of any one of claims 1-13, the method further comprising identifying a population of neoantigens present in the one or more samples by a third procedure comprising:

determining a plurality of somatic single nucleotide polymorphisms (SNPs) in the plurality of sequencing reads by comparison of the plurality of sequencing reads to a reference human genome; and

evaluating each respective somatic SNP in the plurality of SNPs as a neoantigen candidate by evaluation of a peptide encoded by a portion of one or more sequencing reads in the plurality of sequencing reads that includes the respective somatic SNP against a classifier that has been trained to predict peptide binding to class 1 MHC of the HLA type of the cancer subject, wherein a neoantigen candidate having a binding score below a threshold value is deemed to be a neoantigen in the population of neoantigens, and

wherein the identifying the plurality of neoantigens in the respective clone α

comprises matching the SNPs in the respective clone α to respective neoantigens in the population of neoantigens.

15. The method of claim 14, wherein the threshold value is 500 nM.

16. The method of any one of claims 1-15, wherein the determining the HLA type of the human cancer subject is determined from the plurality of sequencing reads.

17. The method of any one of claims 1-15, wherein the determining the HLA type of the human cancer subject is determined using a polymerase chain reaction using a biological sample from the cancer subject.

18. The method of any one of claims 1-17, wherein the plurality of clones consists of two clones.

19. The method of any one of claims 1-17, wherein the plurality of clones consists of between two clones and ten clones.

20. The method of any one of claims 1-19, wherein the initial frequency X_α of the respective clone α in the one or more samples is determined using the plurality of sequencing reads from the one or more samples from the human cancer subject.

21. The method of any one of claims 1-20, wherein the function of the relative class I MHC affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the human cancer subject is a ratio of the relative class I MHC affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject.

22. The method of any one of claims 1-21, wherein the function of the relative class I MHC affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject is a ratio of:

(1) a dissociation constant between the respective neoantigen and the class I MHC presented by the cancer subject given the HLA type of the cancer subject, and

(2) a dissociation constant between the wildtype counterpart of the respective

neoantigen and the class I MHC presented by the cancer subject given the HLA type of the cancer subject.

23. The method of claim 22, wherein

the dissociation constant between the respective neoantigen and the class I MHC presented by the cancer subject is obtained as output from a first classifier upon inputting into the first classifier the amino acid sequence of the neoantigen, and

the dissociation constant between the wildtype counterpart of the respective neoantigen and the class I MHC presented by the cancer subject of the HLA type of the subject is obtained as output from the first classifier upon inputting into the first classifier the amino acid sequence of the respective wildtype counterpart of the neoantigen.

24. The method of claim 23, wherein the first classifier is specific to the HLA type of the cancer subject and has been trained with the respective class I MHC binding coefficient and sequence data of each peptide epitope in a plurality of epitopes presented by class I MHC in a training population having the HLA type of the subject.

25. The method of any one of claims 1-24, wherein the probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation is computed as:

$$R = Z(k)^{-1} \sum_{\mathbf{e} \in D} \exp\left[-k(a - |\mathbf{s}, \mathbf{e}|)\right],$$

wherein

a is a number that represents a horizontal displacement of a binding curve for the respective neoantigen,

k is a number that sets the steepness of the binding curve at a,

$Z(k)$ is a partition function over the unbound state and all bound states of the respective neoantigen of the form

$$1 + \sum_{\mathbf{e} \in D} \exp\left[-k(a - |\mathbf{s}, \mathbf{e}|)\right]$$

wherein,

D is a plurality of epitopes,

each respective epitope **e** is an epitope from the plurality of epitopes that is positively recognized by T-cells after class I MHC presentation, and

$|\mathbf{s}, \mathbf{e}|$ is a measure of affinity between the respective neoantigen **s** and the respective epitope **e**.

26. The method of claim 25, wherein a is set to 26 and k is set to 4.87.

27. The method of claim 25, wherein the measure of affinity $|\mathbf{s}, \mathbf{e}|$ is computed as a sequence alignment between the sequence of the respective neoantigen **s** and the sequence of the respective epitope **e** using an amino-acid similarity matrix.

28. The method of claim 27, wherein the amino-acid similarity matrix is a Blocks Substitutions Matrix (BLOSUM) BLOSUM45 matrix, BLOSUM50 matrix, BLOSUM52 matrix, BLOSUM60 matrix, BLOSUM80 matrix, BLOSUM90 matrix, a Percent Accepted Mutation (PAM) 250 matrix, a PAM200 matrix, a PAM160 matrix, a PAM120 matrix, a PAM100 matrix, or a Gonnet substitution matrix.

29. The method of any one of claims 1-28, wherein the aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α is computed as:

$$F_\alpha = - \max_{i \in \text{Clone } \alpha} (A_i \times R_i)$$

wherein i is an index iterating over each neoantigen in the plurality of neoantigens in the respective clone α.

30. The method of claim 29, wherein the computing a total fitness for the one or more samples as a sum of the clone fitness scores across the plurality of clones is computed as:

$$n(\tau) = \sum_\alpha X_\alpha \exp(F_\alpha \tau),$$

wherein τ is a characteristic evolutionary time scale.

31. The method of claim 30, wherein τ is between 0.0 and 0.5.

32. The method of claim 30, wherein τ is 0.06.

33. The method of any one of claims 1-28, wherein the aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α is

computed as a summation of the recognition potential of each respective neoantigen in the plurality of neoantigens.

34. The method of any one of claims 1-28, wherein the aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α is computed as a summation of the recognition potential of a subset of the neoantigens in the plurality of neoantigens.

35. The method of claim 34, wherein the subset of the neoantigens in the plurality of neoantigens constitutes a predetermined number of neoantigens in the plurality of neoantigens that have the top recognition potential for the respective clone α.

36. The method of any one of claims 1-28, wherein the aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α is computed as a nonlinear combination of the recognition potential of all or a subset of the neoantigens in the plurality of neoantigens.

37. The method of any one of claims 1-36, wherein a lower total fitness score is associated with (a) a higher likelihood that the cancer subject will be responsive to the immunotherapy and (b) a longer term survival of the cancer patient.

38. A method for identifying an immunotherapy for a cancer, the method comprising:

(A) obtaining a plurality of sequencing reads from one or more samples from a human cancer subject that is representative of the cancer;

(B) determining a human leukocyte antigen (HLA) type of the human cancer subject from the plurality of sequencing reads;

(C) determining a plurality of clones, and for each respective clone α in the plurality of clones, an initial frequency X_α of the respective clone α in the one or more samples from the plurality of sequencing reads;

(D) for each respective clone α in the plurality of clones, computing a corresponding clone fitness score of the respective clone, thereby computing a plurality of clone fitness scores, each corresponding clone fitness score computed for a respective clone α by a first procedure comprising:

(a) identifying a plurality of neoantigens in the respective clone α;

(b) computing a recognition potential of each respective neoantigen in the plurality of neoantigens in the respective clone α by a second procedure comprising:

(i) computing an amplitude *A* of the respective neoantigen as a function of the relative major histocompatibility complex (MHC) affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject,

(ii) computing a probability of T-cell receptor recognition *R* of the respective neoantigen as a probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation, and

(iii) computing the recognition potential of the respective neoantigen as a function of the amplitude *A* of the respective neoantigen and the probability of T-cell receptor recognition *R* of the respective neoantigen; and

(c) determining the corresponding clone fitness score of the respective clone α as an aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α; and

(E) selecting at least a first neoantigen from a plurality of neoantigens for a respective clone α in the plurality of respective clones based upon the recognition potential of the first neoantigen as the immunotherapy for the cancer.

39. The method of claim 38, wherein the obtaining (A), the determining (B), the determining (C), and the computing (D) are repeated for a plurality of human cancer subjects across a plurality of HLA types and the first neoantigen is selected on the basis of the recognition potential of the first neoantigen across the plurality of HLA types.

40. The method of claim 38, wherein the obtaining (A), the determining (B), the determining (C), and the computing (D) are repeated for a plurality of human cancer subjects and the first neoantigen is selected on the basis of the recognition potential of the first neoantigen across the plurality of human cancer subject.

41. The method of any one of claims 38-40, wherein the cancer is a carcinoma, a melanoma, a lymphoma/leukemia, a sarcoma, or a neuro-glial tumor.

42. The method of any one of claims 38-40, wherein the cancer is lung cancer, pancreatic

cancer, colon cancer, stomach or esophagus cancer, breast cancer, ovary cancer, prostate cancer, or liver cancer.

43. The method of any one of claims 38-42, wherein

each clone α in the plurality of clones is uniquely defined by a unique set of somatic mutations, and

the plurality of clones is determined by a variant allele frequency of each respective somatic mutation in a plurality of somatic mutations determined from the whole-genome sequencing data.

44. The method of claim 43, wherein the somatic mutation is a single nucleotide variant or an indel.

45. The method of claim 38, wherein the plurality of clones is determined by identifying a plurality of inferred copy number variations using the whole-genome sequencing data.

46. The method of any one of claims 38-42, wherein

each clone α in the plurality of clones is uniquely defined by a unique set of somatic mutations, and

the plurality of clones is determined by a combination of (i) a variant allele frequency of each respective somatic mutation in the plurality of somatic mutations determined from the whole-genome sequencing data and (ii) an identification of a plurality of inferred copy number variations using the whole-genome sequencing data.

47. The method of any one of claims 38-46, wherein the plurality of sequencing reads exhibits an average read depth of less than 40.

48. The method of any one of claims 38-46, wherein the plurality of sequencing reads exhibits an average read depth of between 25 and 60.

49. The method of any one of claims 38-48, wherein each neoantigen in the plurality of neoantigens of a clone in the plurality of clones is a nonamer peptide.

50. The method of any one of claims 38-48, wherein each neoantigen in the plurality of

neoantigens of a clone in the plurality of clones is a peptide that is eight, nine, ten, or eleven residues in length.

51. The method of any one of claims 38-50, the method further comprising identifying a population of neoantigens present in the one or more samples by a third procedure comprising:

determining a plurality of somatic single nucleotide polymorphisms (SNPs) in the plurality of sequencing reads by comparison of the plurality of sequencing reads to a reference human genome;

evaluating each respective somatic SNP in the plurality of SNPs as a neoantigen candidate by evaluation of a peptide encoded by a portion of one or more sequencing reads in the plurality of sequencing reads that includes the respective somatic SNP against a classifier that has been trained to predict peptide binding to class 1 MHC of the HLA type of the cancer subject, wherein a neoantigen candidate having a binding score below a threshold value is deemed to be a neoantigen in the population of neoantigens, and

wherein the identifying the plurality of neoantigens in the respective clone α comprises matching the SNPs in the respective clone α to respective neoantigens in the population of neoantigens.

52. The method of claim 51, wherein the threshold value is 500 nM.

53. The method of any one of claims 38-52, wherein the determining the HLA type of the human cancer subject is determined from the plurality of sequencing reads.

54. The method of any one of claims 38-52, wherein the determining the HLA type of the human cancer subject is determined using a polymerase chain reaction using a biological sample from the cancer subject.

55. The method of any one of claims 38-54, wherein the plurality of clones consists of two clones.

56. The method of any one of claims 38-54, wherein the plurality of clones consists of between two clones and ten clones.

57. The method of any one of claims 38-56, wherein the initial frequency X_α of the respective clone α in the one or more samples is determined using the plurality of sequencing reads from the one or more samples from the human cancer subject.

58. The method of any one of claims 38-57, wherein the function of the relative class I MHC affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject is a ratio of the relative class I MHC affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject.

59. The method of any one of claims 38-58, wherein the function of the relative class I MHC affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the human cancer subject is a ratio of:

(1) a dissociation constant between the respective neoantigen and the class I MHC presented by the cancer subject given the HLA type of the cancer subject, and

(2) a dissociation constant between the wildtype counterpart of the respective neoantigen and the class I MHC presented by the cancer subject given the HLA type of the cancer subject.

60. The method of claim 59, wherein

the dissociation constant between the respective neoantigen and the class I MHC presented by the cancer subject is obtained as output from a first classifier upon inputting into the first classifier the amino acid sequence of the neoantigen, and

the dissociation constant between the wildtype counterpart of the respective neoantigen and the class I MHC presented by the cancer subject of the HLA type of the subject is obtained as output from the first classifier upon inputting into the first classifier the amino acid sequence of the respective wildtype counterpart of the neoantigen.

61. The method of claim 60, wherein the first classifier is specific to the HLA type of the cancer subject and has been trained with the respective class I MHC binding coefficient and sequence data of each peptide epitope in a plurality of epitopes presented by class I MHC in a training population having the HLA type of the subject.

62. The method of any one of claims 38-61, wherein the probability that the respective

neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation is computed as:

$$R = Z(k)^{-1} \sum_{e \in D} \exp\left[-k(a - |\mathbf{s}, \mathbf{e}|)\right],$$

wherein

a is a number that represents a horizontal displacement of a binding curve for the respective neoantigen,

k is a number that sets the steepness of the binding curve at a,

$Z(k)$ is a partition function over the unbound state and all bound states of the respective neoantigen of the form

$$1 + \sum_{e \in D} \exp\left[-k(a - |\mathbf{s}, \mathbf{e}|)\right]$$

wherein,

D is a plurality of epitopes,

each respective epitope **e** is an from the plurality of epitopes that is positively recognized by T-cells after class I MHC presentation, and

$|\mathbf{s}, \mathbf{e}|$ is a measure of affinity between the respective neoantigen **s** and the sequence of the respective epitope **e**.

63. The method of claim 62, wherein a is set to 26 and k is set to 4.87.

64. The method of claim 62, wherein the measure of affinity $|\mathbf{s}, \mathbf{e}|$ is computed as a sequence alignment between the sequence of the respective neoantigen **s** and the sequence of the respective epitope **e** using an amino-acid similarity matrix.

65. The method of claim 64, wherein the amino-acid similarity matrix is a Blocks Substitutions Matrix (BLOSUM) BLOSUM45 matrix, BLOSUM50 matrix, BLOSUM52 matrix, BLOSUM60 matrix, BLOSUM80 matrix, BLOSUM90 matrix, a Percent Accepted Mutation (PAM) 250 matrix, a PAM200 matrix, a PAM160 matrix, a PAM120 matrix, a PAM100 matrix, or a Gonnet substitution matrix.

66. The method of any one of claims 38-65, wherein the first neoantigen from a plurality of neoantigens for a respective clone α in the plurality of respective clones is selected when it has a recognition potential that is lower than the recognition potential of other neoantigens in

each plurality of neoantigens for each respective clone α in the plurality of respective clones.

67. A system for determining a likelihood that a human subject afflicted with a cancer will be responsive to a treatment regimen that comprises administering a checkpoint blockade immunotherapy directed to the cancer to the subject, comprising:

memory;

one or more processors; and

one or more modules stored in memory and configured for execution by the one or more processors, the modules comprising instructions for:

(A) obtaining a plurality of sequencing reads from one or more samples from the human cancer subject that is representative of the cancer;

(B) determining a human leukocyte antigen (HLA) type of the human cancer subject;

(C) determining a plurality of clones, and for each respective clone α in the plurality of clones, an initial frequency X_α of the respective clone α in the one or more samples;

(D) for each respective clone α in the plurality of clones, computing a corresponding clone fitness score of the respective clone, thereby computing a plurality of clone fitness scores, each corresponding clone fitness score computed for a respective clone α by a first procedure comprising:

(a) identifying a plurality of neoantigens in the respective clone α;

(b) computing a recognition potential of each respective neoantigen in the plurality of neoantigens in the respective clone α by a second procedure comprising:

(i) computing an amplitude A of the respective neoantigen as a function of the relative major histocompatibility complex (MHC) affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject,

(ii) computing a probability of T-cell receptor recognition R of the respective neoantigen as a probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation, and

(iii) computing the recognition potential of the respective neoantigen as a function of the amplitude A of the respective neoantigen and the probability of T-cell receptor recognition R of the respective neoantigen; and

(c) determining the corresponding clone fitness score of the respective clone α

as an aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α; and

(E) computing a total fitness for the one or more samples as a sum of the clone fitness scores across the plurality of clones, wherein

each clone fitness score is weighted by the initial frequency X_α of the corresponding clone α, and

the total fitness quantifies the likelihood that the human subject afflicted with the cancer will be responsive to the treatment regimen.

68. A system for determining a likelihood that a human subject afflicted with a cancer will be responsive to a treatment regimen that comprises administering a checkpoint blockade immunotherapy directed to the cancer to the subject, comprising

memory;

one or more processors; and

one or more modules stored in memory and configured for execution by the one or more processors, the modules comprising instructions for carrying out the method of any one of claims 1-37.

69. A non-transitory computer readable storage medium for determining a likelihood that a human subject afflicted with a cancer will be responsive to a treatment regimen that comprises administering a checkpoint blockade immunotherapy directed to the cancer to the subject, the non-transitory computer readable storage medium storing one or more programs for execution by one or more processors of a computer system, the one or more computer programs comprising instructions for:

(A) obtaining a plurality of sequencing reads from one or more samples from the human cancer subject that is representative of the cancer;

(B) determining a human leukocyte antigen (HLA) type of the human cancer subject;

(C) determining a plurality of clones, and for each respective clone α in the plurality of clones, an initial frequency X_α of the respective clone α in the one or more samples;

(D) for each respective clone α in the plurality of clones, computing a corresponding clone fitness score of the respective clone, thereby computing a plurality of clone fitness scores, each corresponding clone fitness score computed for a respective clone α by a first procedure comprising:

(a) identifying a plurality of neoantigens in the respective clone α;

(b) computing a recognition potential of each respective neoantigen in the plurality of neoantigens in the respective clone α by a second procedure comprising:

(i) computing an amplitude *A* of the respective neoantigen as a function of the relative major histocompatibility complex (MHC) affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject,

(ii) computing a probability of T-cell receptor recognition *R* of the respective neoantigen as a probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation, and

(iii) computing the recognition potential of the respective neoantigen as a function of the amplitude *A* of the respective neoantigen and the probability of T-cell receptor recognition *R* of the respective neoantigen; and

(c) determining the corresponding clone fitness score of the respective clone α as an aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α; and

(E) computing a total fitness for the one or more samples as a sum of the clone fitness scores across the plurality of clones, wherein

each clone fitness score is weighted by the initial frequency X_α of the corresponding clone α, and

the total fitness quantifies the likelihood that the human subject afflicted with the cancer will be responsive to the treatment regimen.

70. A non-transitory computer readable storage medium for determining a likelihood that a human subject afflicted with a cancer will be responsive to a treatment regimen that comprises administering a checkpoint blockade immunotherapy directed to the cancer to the subject, the non-transitory computer readable storage medium storing one or more programs for execution by one or more processors of a computer system, the one or more computer programs comprising instructions for carrying out the method of any one of claims 1-37.

71. A system for identifying an immunotherapy for a cancer, comprising:

memory;

one or more processors; and

one or more modules stored in memory and configured for execution by the one or more processors, the modules comprising instructions for:

(A) obtaining a plurality of sequencing reads from one or more samples from a human cancer subject that is representative of the cancer;

(B) determining a human leukocyte antigen (HLA) type of the human cancer subject from the plurality of sequencing reads;

(C) determining a plurality of clones, and for each respective clone α in the plurality of clones, an initial frequency X_α of the respective clone α in the one or more samples from the plurality of sequencing reads;

(D) for each respective clone α in the plurality of clones, computing a corresponding clone fitness score of the respective clone, thereby computing a plurality of clone fitness scores, each corresponding clone fitness score computed for a respective clone α by a first procedure comprising:

(a) identifying a plurality of neoantigens in the respective clone α;

(b) computing a recognition potential of each respective neoantigen in the plurality of neoantigens in the respective clone α by a second procedure comprising:

(i) computing an amplitude *A* of the respective neoantigen as a function of the relative major histocompatibility complex (MHC) affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject,

(ii) computing a probability of T-cell receptor recognition *R* of the respective neoantigen as a probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation, and

(iii) computing the recognition potential of the respective neoantigen as a function of the amplitude *A* of the respective neoantigen and the probability of T-cell receptor recognition *R* of the respective neoantigen; and

(c) determining the corresponding clone fitness score of the respective clone α as an aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α; and

(E) selecting at least a first neoantigen from a plurality of neoantigens for a respective clone α in the plurality of respective clones based upon the recognition potential of the first neoantigen as the immunotherapy for the cancer.

72. A system for identifying an immunotherapy for a cancer, comprising:

memory;

one or more processors; and

one or more modules stored in memory and configured for execution by the one or more processors, the modules comprising instructions for executing the method of any one of claims 38-66.

73. A non-transitory computer readable storage medium for identifying an immunotherapy for a cancer, the non-transitory computer readable storage medium storing one or more programs for execution by one or more processors of a computer system, the one or more computer programs comprising instructions for:

(A) obtaining a plurality of sequencing reads from one or more samples from a human cancer subject that is representative of the cancer;

(B) determining a human leukocyte antigen (HLA) type of the human cancer subject from the plurality of sequencing reads;

(C) determining a plurality of clones, and for each respective clone α in the plurality of clones, an initial frequency X_α of the respective clone α in the one or more samples from the plurality of sequencing reads;

(D) for each respective clone α in the plurality of clones, computing a corresponding clone fitness score of the respective clone, thereby computing a plurality of clone fitness scores, each corresponding clone fitness score computed for a respective clone α by a first procedure comprising:

(a) identifying a plurality of neoantigens in the respective clone α;

(b) computing a recognition potential of each respective neoantigen in the plurality of neoantigens in the respective clone α by a second procedure comprising:

(i) computing an amplitude A of the respective neoantigen as a function of the relative major histocompatibility complex (MHC) affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject,

(ii) computing a probability of T-cell receptor recognition R of the respective neoantigen as a probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation, and

(iii) computing the recognition potential of the respective neoantigen

as a function of the amplitude *A* of the respective neoantigen and the probability of T-cell receptor recognition *R* of the respective neoantigen; and

(c) determining the corresponding clone fitness score of the respective clone α as an aggregate of the neoantigen recognition potentials across the plurality of neoantigens in the respective clone α; and

(E) selecting at least a first neoantigen from a plurality of neoantigens for a respective clone α in the plurality of respective clones based upon the recognition potential of the first neoantigen as the immunotherapy for the cancer.

74. A non-transitory computer readable storage medium for identifying an immunotherapy for a cancer, the non-transitory computer readable storage medium storing one or more programs for execution by one or more processors of a computer system, the one or more computer programs comprising instructions for executing the method of any one of claims 38-66.

75. A method for identifying a subject having cancer as a candidate for treatment with an immunotherapy, comprising:

(a) obtaining a biological sample from the subject;

(b) measuring the number of neoantigens (neoantigen number) in the biological sample; and

(c) measuring the homology between each of the neoantigen and a microbial epitope (neoantigen-microbial homology);

wherein a neoantigen number higher than the median neoantigen number obtained from a population of subjects having the cancer and a neoantigen-microbial homology higher than the median neoantigen-microbial homology obtained from subjects having the cancer indicate that the subject is a candidate for an immunotherapy.

76. A method of predicting the responsiveness of a subject having cancer to an immunotherapy, comprising:

(a) obtaining a biological sample from the subject;

(b) measuring the number of neoantigens (neoantigen number) in the biological sample; and

(c) measuring the homology between each of the neoantigen and a microbial epitope (neoantigen-microbial homology);

wherein a neoantigen number higher than the median neoantigen number obtained from a population of subjects having the cancer and a neoantigen-microbial homology higher than the median neoantigen-microbial homology obtained from subjects having the cancer indicate that the subject is likely to be responsive to an immunotherapy.

77. The method of claim 75 or 76, wherein the neoantigen-microbial homology is measured by calculating a recognition potential between each respective neoantigen and microbial epitope.

78. The method of claim 77, wherein the calculation of the recognition potential for a respective neoantigen is calculated by a first procedure comprising:

(i) computing an amplitude *A* of the respective neoantigen as a function of a relative major histocompatibility complex (MHC) affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject,

(ii) computing a probability of T-cell receptor recognition *R* of the respective neoantigen as a probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation, and

(iii) computing the recognition potential of the respective neoantigen as as a function of the amplitude *A* of the respective neoantigen and the probability of T-cell receptor recognition *R* of the respective neoantigen.

79. The method of claim 78, wherein the function of the relative class I MHC affinity of the respective neoantigen and the wildtype counterpart of the respective neoantigen given the HLA type of the subject is a ratio of:

(1) a dissociation constant between the respective neoantigen and the class I MHC presented by the cancer subject given the HLA type of the cancer subject, and

(2) a dissociation constant between the wildtype counterpart of the respective neoantigen and the class I MHC presented by the cancer subject given the HLA type of the cancer subject.

80. The method of claim 79, wherein

the dissociation constant between the respective neoantigen and the class I MHC presented by the cancer subject is obtained as output from a first classifier upon inputting into the first classifier the amino acid sequence of the neoantigen, and

the dissociation constant between the wildtype counterpart of the respective neoantigen and the class I MHC presented by the cancer subject of the HLA type of the subject is obtained as output from the first classifier upon inputting into the first classifier the amino acid sequence of the respective wildtype counterpart of the neoantigen.

81. The method of claim 80, wherein the first classifier is specific to the HLA type of the cancer subject and has been trained with the respective class I MHC binding coefficient and sequence data of each peptide epitope in a plurality of epitopes presented by class I MHC in a training population having the HLA type of the subject.

82. The method of any one of claims 78-81, wherein the probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation is determined by a second procedure that comprises:

(a) selecting a respective epitope **e** from an epitope database IEDB, wherein the respective epitope **e** is positively recognized by T-cells after class I MHC presentation;

(b) computing, for the respective epitope **e**, the probability

$$\mathrm{Pr}_{\mathrm{binding}}(\mathbf{s},\mathbf{e}) = \frac{1}{1 + e^{-k(|\mathbf{s},\mathbf{e}|-a)}}$$

wherein,

$|\mathbf{s},\mathbf{e}|$ is a sequence alignment score between the sequence of the respective neoantigen and the sequence of the respective epitope, and

k and a are constants;

(c) performing the selecting (a) and the computing (b) for each respective epitope **e** in a plurality of epitopes in the epitope database IEDB, thereby computing a plurality of probabilities $\mathrm{Pr}_{\mathrm{binding}}(\mathbf{s},\mathbf{e})$; and

(d) computing the probability of T-cell receptor recognition R of the respective neoantigen as:

$$R = 1 - \prod_{\mathbf{e}\in\mathrm{IEDB}}[1 - \mathrm{Pr}_{\mathrm{binding}}(\mathbf{s},\mathbf{e})],$$

wherein,

IEDB is the plurality of epitopes.

83. The method of claim 82, wherein a is set to 23 and k is set to 1.

84. The method of claim 82, wherein $|\mathbf{s},\mathbf{e}|$ is computed as an alignment between the

sequence of the respective neoantigen and the sequence of the respective epitope using an amino-acid similarity matrix.

85. A method for identifying a subject having a cancer as a candidate for treatment with an immunotherapy comprising:

(a) measuring the number of neoantigens (neoantigen number) in a biological sample of the subject; and

(b) measuring the number of activated T cells (activated T cell number) in a biological sample of the subject;

wherein a neoantigen number higher than the median neoantigen number obtained from a population of subjects having the cancer and an activated T cell number higher than the median activated T cell number obtained from subjects having the cancer indicate that the subject is a candidate for an immunotherapy.

86. A method of predicting the responsiveness of a subject having a cancer to an immunotherapy, comprising:

(a) measuring the number of neoantigens (neoantigen number) in a biological sample of the subject; and

(b) measuring the number of activated T cells (activated T cell number) in a biological sample of the subject;

wherein a neoantigen number higher than the median neoantigen number obtained from a population of subjects having the cancer and an activated T cell number higher than the median activated T cell number obtained from subjects having the cancer indicate that the subject is likely to be responsive to an immunotherapy.

87. The method of claim 85 or 86, wherein the activated T cells are T cells expressing one or more T cell activation marker.

88. The method of claim 87, wherein the one or more T cell activation marker is selected from the group consisting of CD3, CD8, PD-1, 4-1BB, CD69, CD107a, Granzyme B, and combinations thereof.

89. The method of any one of claims 84-88, wherein the activated T cells are selected from the group consisting of $CD3^+CD8^+$ T cells, $CD3^+CD8^+$Granzyme-B^+ T cells, and polyclonal

activated T cells.

90. The method of any one of claims 85-89, wherein the cancer is a solid tumor.

91. The method of claim 99, wherein the cancer is pancreatic cancer.

92. The method of claim 91, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC).

93. The method of any one of claims 85-92, wherein the neoantigen is selected from the neoantigenic peptides listed in Table 2.

94. A method for identifying a subject having pancreatic cancer as a candidate for treatment with an immunotherapy comprising:

(a) obtaining a biological sample from the subject; and

(b) detecting one or more neoantigen of MUC16 in the biological sample;

wherein the presence of one or more neoantigen of MUC16 in the biological sample indicates that the subject is a candidate for an immunotherapy.

95. A method for predicting the responsiveness of a subject having pancreatic cancer to an immunotherapy, comprising:

(a) obtaining a biological sample from the subject; and

(b) detecting one or more neoantigen of MUC16 in the biological sample;

wherein the presence of one or more neoantigen of MUC16 in the biological sample indicates that the subject is likely to be responsive to an immunotherapy.

96. The method claim 94 or 95, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC).

97. The method of any one of claims 75-97, wherein the neoantigen is selected from the neoantigenic peptides listed in Table 1.

98. The method of any one of claims 75-97, wherein the neoantigen is about 8 to 11 amino acids in length.

99. The method of any one of claims 75-98, wherein the neoantigen is identified by exome sequencing.

100. The method of any one of claims 75-99, wherein the immunotherapy is selected from the group consisting of therapies comprising one or more immune checkpoint-blocking antibody, adoptive T cell therapies, and combinations thereof.

101. The method of claim 100, wherein the one or more immune checkpoint-blocking antibody is selected from the group consisting of anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-TIM3 antibodies, anti-LAG3 antibodies, anti-GITR antibodies, anti-OX40 antibodies, anti-CD40 antibodies, anti-TIGIT antibodies, and anti-4-1BB antibodies, anti-B7-H3 antibodies, anti-B7-H4 antibodies, anti-BTLA antibodies.

102. A population of T cells that target one or more neoantigen in MUC16.

103. The T cell population of claim 102, wherein the one or more neoantigen is selected from the neoantigenic peptides listed in Table 1.

104. A population of T cells that target one or more neoantigen associated with a cancer, said one or more neoantigen correlating with a neoantigen-microbial homology that is higher than the median neoantigen-microbial homology occurring in subjects with the cancer.

105. A population of T cells that target one or more neoantigen associated with a cancer, said neoantigen correlating with an activated T cell number that is higher than the median activated T cell number occurring in subjects with a cancer.

106. The T cell population of claim 104 or 105, wherein the one or more neoantigen is selected from the neoantigenic peptides listed in Table 2.

107. The cell population of any one of claims 104-106, wherein the cancer is pancreatic cancer.

108. The T cell population of claim 102 or 103, wherein the T cells are selectively expanded

to target the one or more neoantigen in MUC16.

109. The T cell population of any one of claims 104, 106, and 107, wherein the T cells are selectively expanded to target the one or more neoantigen associated with a cancer, said one or more neoantigen correlating with a neoantigen-microbial homology that is higher than the median neoantigen-microbial homology occurring in subjects with the cancer.

110. The T cell population of any one of claims 105, 106, and 107, wherein the T cells are selectively expanded to target the one or more neoantigen associated with a cancer, said neoantigen correlating with an activated T cell number that is higher than the median activated T cell number occurring in subjects with the cancer.

111. The T cell population of claim 102 or 103, wherein the T cells comprise a recombinant antigen receptor that specifically binds to one or more neoantigen in MUC16.

112. The T cell population of any one of claims 104, 106, and 107, wherein the T cells comprise a recombinant antigen receptor that specifically binds to one or more neoantigen associated with a cancer, said one or more neoantigen correlating with a neoantigen-microbial homology that is higher than the median neoantigen-microbial homology occurring in subjects with the cancer.

113. The T cell population of any one of claims 105, 106, and 107, wherein the T cells comprise a recombinant antigen receptor that specifically binds to one or more neoantigen associated with a cancer, said neoantigen correlating with an activated T cell number that is higher than the median activated T cell number occurring in subjects with the cancer.

114. The T cell population of any one of claims 111-113, wherein the recombinant antigen receptor is a T cell receptor (TCR).

115. The T cell population of any one of claims 111-113, wherein the recombinant antigen receptor is a chimeric antigen receptor (CAR).

116. A composition comprising the T cell population of any one of claims 102-115.

117. A method of treating pancreatic cancer in a subject, comprising administering to the subject the T cell population of any one of claims 102-115 or the composition of claim 116.

118. The T cell population of any one of claims 102-115 for use in treating pancreatic cancer.

119. The composition of claim 116 for use in treating pancreatic cancer.

120. A vaccine comprising one or more neoantigen of MUC16, or a polynucleotide encoding said neoantigen or a protein or peptide comprising said neoantigen.

121. The vaccine of claim 120, wherein the one or more neoantigen of MUC16 is selected from the neoantigenic peptides listed in Table 1.

122. A vaccine comprising one or more neoantigen associated with a cancer, said one or more neoantigen correlating with a neoantigen-microbial homology that is higher than the median neoantigen-microbial homology occurring in subjects with the cancer, or a polynucleotide encoding said neoantigen or a protein or peptide comprising said neoantigen.

123. A vaccine comprising one or more neoantigen associated with a cancer, said neoantigen correlating with an activated T cell number that is higher than the median activated T cell number occurring in a population of subject with cancer, or a polynucleotide encoding said neoantigen or a protein or peptide comprising said neoantigen.

124. The vaccine of claim 122 or 123, wherein the one or more neoantigen is selected from the neoantigenic peptides listed in Table 2.

125. The vaccine of any one of claims 121-124, wherein the polynucleotide is an RNA or a DNA.

126. A composition comprising the vaccine of any one of claims 121-125.

127. A method of treating pancreatic cancer in a subject, comprising administering to the subject the vaccine of any one of claims 121-125 or the composition of claim 126.

128. The vaccine of any one of claims 121-125 for use in treating pancreatic cancer.

129. The composition of claim 116 or 126, which is a pharmaceutical composition that comprises a pharmaceutically acceptable carrier.

130. The method of any one of claims 1-37, wherein the recognition potential of the respective neoantigen is computed in the computing (D)(b)(iii) as the product of the amplitude A of the respective neoantigen and the probability of T-cell receptor recognition R of the respective neoantigen.

131. The method of any one of claims 38-66, wherein the recognition potential of the respective neoantigen is computed in the computing (D)(b)(iii) as the product of the amplitude A of the respective neoantigen and the probability of T-cell receptor recognition R of the respective neoantigen.

132. The method of claim 27, wherein the plurality of epitopes comprises a public database of epitopes that have been recognized by human T-cells from any human, or combination of humans, in a population of humans.

133. The method of claim 132, wherein the public database is the immune epitope database 3.0 or equivalent.

134. The method of claim 25, wherein the plurality of epitopes consists of epitopes that have been recognized by human T-cells from the human subject.

135. The method of claim 25 or any one of claims 130-134, wherein the plurality of epitopes comprises 1000 epitopes.

136. The method of claim 25 or any one of claims 130-134, wherein the plurality of epitopes comprises 10,000 epitopes.

137. The method of claim 25 or any one of claims 130-134, wherein the plurality of epitopes comprises 100,000 epitopes.

138. The method of claim 25 or any one of claims 130-134, wherein the plurality of epitopes comprises 1 x 10^6 epitopes.

139. The method of any one of claims 1-24, wherein the probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation is computed as:

$$R = Z(k)^{-1} \sum_{\mathbf{t} \in F} \exp\left[-k(a - |\mathbf{s}, \mathbf{t}|)\right],$$

wherein

a is a number that represents a horizontal displacement of a binding curve for the respective neoantigen,

k is a number that sets the steepness of the binding curve at a,

$Z(k)$ is a partition function over the unbound state and all bound states of the respective neoantigen of the form

$$1 + \sum_{\mathbf{t} \in F} \exp\left[-k(a - |\mathbf{s}, \mathbf{t}|)\right]$$

wherein,

F is a plurality of T-cell receptor sequences,

each respective T-cell receptor $\mathbf{t}$ is a T-cell receptor from the plurality of T-cell receptor sequences F, and

$|\mathbf{s}, \mathbf{t}|$ is a measure of affinity between the respective neoantigen $\mathbf{s}$ and the respective T-cell receptor $\mathbf{t}$.

140. The method of claim 139, wherein the plurality of T-cell receptors is a database of T-cell receptors drawn from a population of humans.

141. The method of claim 139, wherein the plurality of T-cell receptors is drawn exclusively from the subject.

142. The method of any one of claims 139-141, wherein the plurality of T-cell receptors comprises 1000 T-cell receptors.

143. The method of any one of claims 139-141, wherein the plurality of T-cell receptors comprises 10,000 T-cell receptors.

144. The method of any one of claims 139-141, wherein the plurality of T-cell receptors comprises 100,000 T-cell receptors.

145. The method of any one of claims 139-141, wherein the plurality of T-cell receptors comprises 1 x 10^6 T-cell receptors.

146. The method of claim 64, wherein the plurality of epitopes comprises a public database of epitopes that have been recognized by one or more humans in a population of humans.

147. The method of claim 146, wherein the public database is the immune epitope database 3.0 or equivalent.

148. The method of claim 62, wherein the plurality of epitopes consists of epitopes that have been recognized by human T-cells from the human subject.

149. The method of claim 62, wherein the plurality of epitopes comprises 1000 epitopes.

150. The method of claim 62, wherein the plurality of epitopes comprises 10,000 epitopes.

151. The method of claim 62, wherein the plurality of epitopes comprises 100,000 epitopes.

152. The method of claim 62, wherein the plurality of epitopes comprises 1 x 10^6 epitopes.

153. The method of any one of claims 38-61, wherein the probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation is computed as:

$$R = Z(k)^{-1} \sum_{t \in F} \exp\left[-k(a - |\mathbf{s}, \mathbf{t}|)\right],$$

wherein

a is a number that represents a horizontal displacement of a binding curve for the respective neoantigen,

k is a number that sets the steepness of the binding curve at a,

$Z(k)$ is a partition function over the unbound state and all bound states of the respective neoantigen of the form

$$1 + \sum_{\mathbf{t} \in F} \exp\left[-k(a - |\mathbf{s}, \mathbf{t}|)\right]$$

wherein,

F is a plurality of T-cell receptor sequences,

each respective T-cell receptor $\mathbf{t}$ is a T-cell receptor from the plurality of T-cell receptor sequences F, and

$|\mathbf{s}, \mathbf{t}|$ is a measure of affinity between the respective neoantigen $\mathbf{s}$ and the respective T-cell receptor $\mathbf{t}$.

154. The method of claim 153, wherein the plurality of T-cell receptors is a database of T-cell receptors drawn from a population of humans.

155. The method of claim 153, wherein the plurality of T-cell receptors is drawn exclusively from the subject.

156. The method of claim 153, wherein the plurality of T-cell receptors comprises 1000 T-cell receptors.

157. The method of claim 153, wherein the plurality of T-cell receptors comprises 10,000 T-cell receptors.

158. The method of claim 153, wherein the plurality of T-cell receptors comprises 100,000 T-cell receptors.

159. The method of claim 153, wherein the plurality of T-cell receptors comprises 1×10^6 T-cell receptors.

160. The system of 67, wherein the recognition potential of the respective neoantigen is computed in the computing (D)(b)(iii) as the product of the amplitude A of the respective neoantigen and the probability of T-cell receptor recognition R of the respective neoantigen.

161. The non-transitory computer readable storage medium of claim 69, wherein the

recognition potential of the respective neoantigen is computed in the computing (D)(b)(iii) as the product of the amplitude A of the respective neoantigen and the probability of T-cell receptor recognition R of the respective neoantigen.

162. The system of 71, wherein the recognition potential of the respective neoantigen is computed in the computing (D)(b)(iii) as the product of the amplitude A of the respective neoantigen and the probability of T-cell receptor recognition R of the respective neoantigen.

163. The non-transitory computer readable storage medium of claim 73, wherein the recognition potential of the respective neoantigen is computed in the computing (D)(b)(iii) as the product of the amplitude A of the respective neoantigen and the probability of T-cell receptor recognition R of the respective neoantigen.

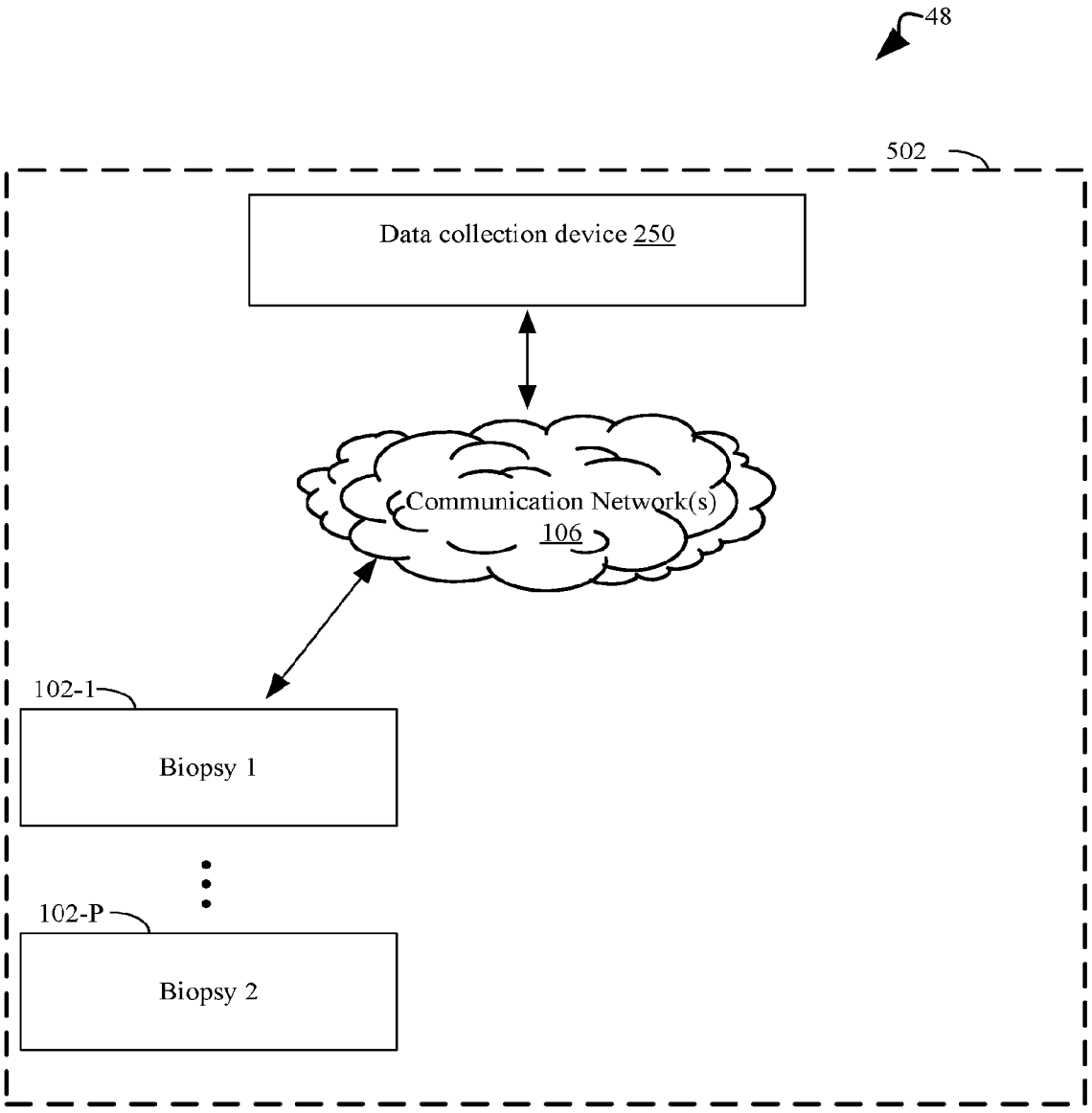

48
502
Data collection device 250
Communication Network(s)
106
102-1
Biopsy 1
102-P
Biopsy 2

Fig. 1

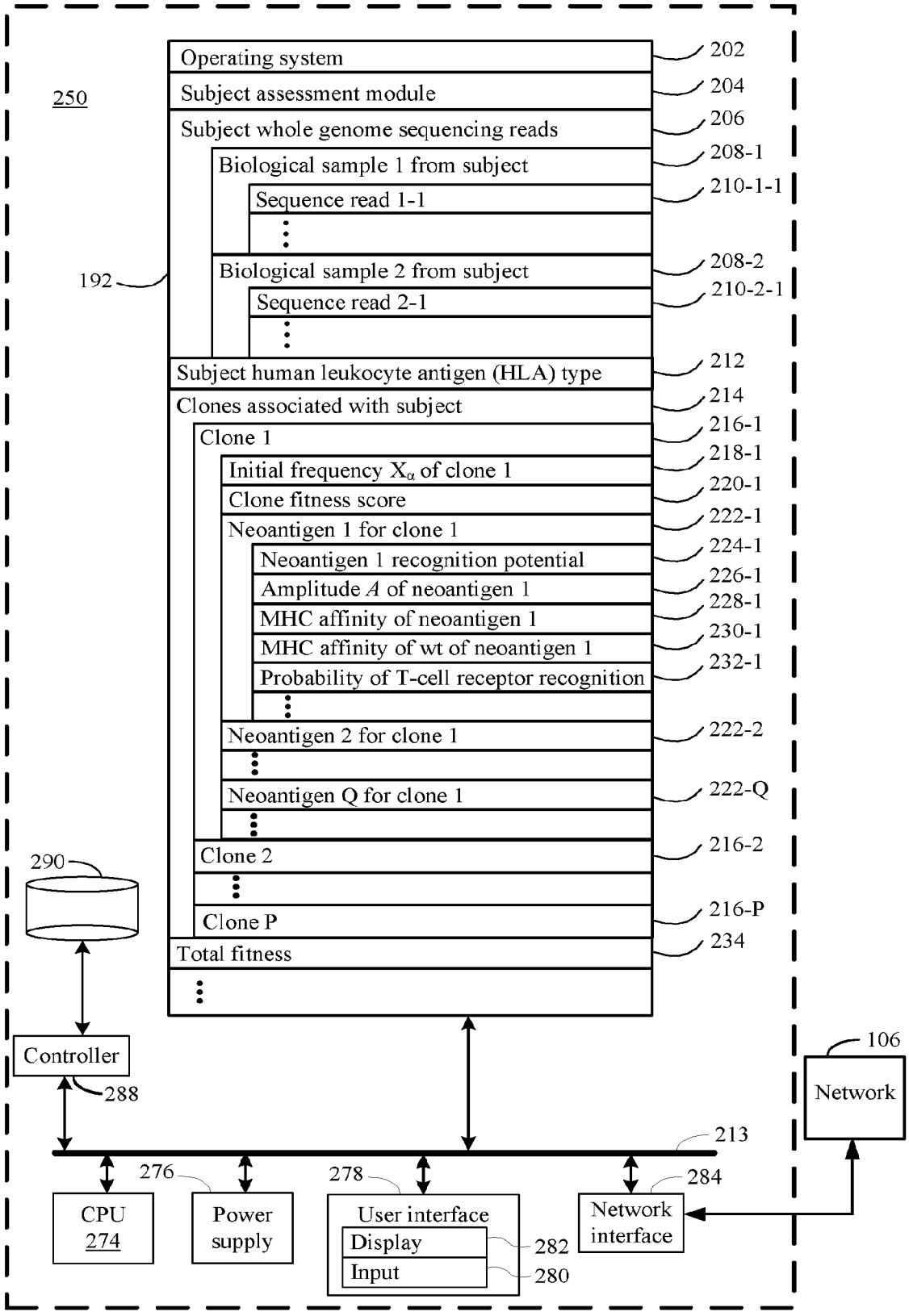

250
Operating system
Subject assessment module
Subject whole genome sequencing reads
Biological sample 1 from subject
Sequence read 1-1
Biological sample 2 from subject
Sequence read 2-1
Subject human leukocyte antigen (HLA) type
Clones associated with subject
Clone 1
Initial frequency X_α of clone 1
Clone fitness score
Neoantigen 1 for clone 1
Neoantigen 1 recognition potential
Amplitude A of neoantigen 1
MHC affinity of neoantigen 1
MHC affinity of wt of neoantigen 1
Probability of T-cell receptor recognition
Neoantigen 2 for clone 1
Neoantigen Q for clone 1
Clone 2
Clone P
Total fitness
192
202
204
206
208-1
210-1-1
208-2
210-2-1
212
214
216-1
218-1
220-1
222-1
224-1
226-1
228-1
230-1
232-1
222-2
222-Q
216-2
216-P
234
290
Controller
288
213
106
Network
276
278
284
CPU 274
Power supply
User interface
Display
Input
282
280
Network interface

Fig. 2

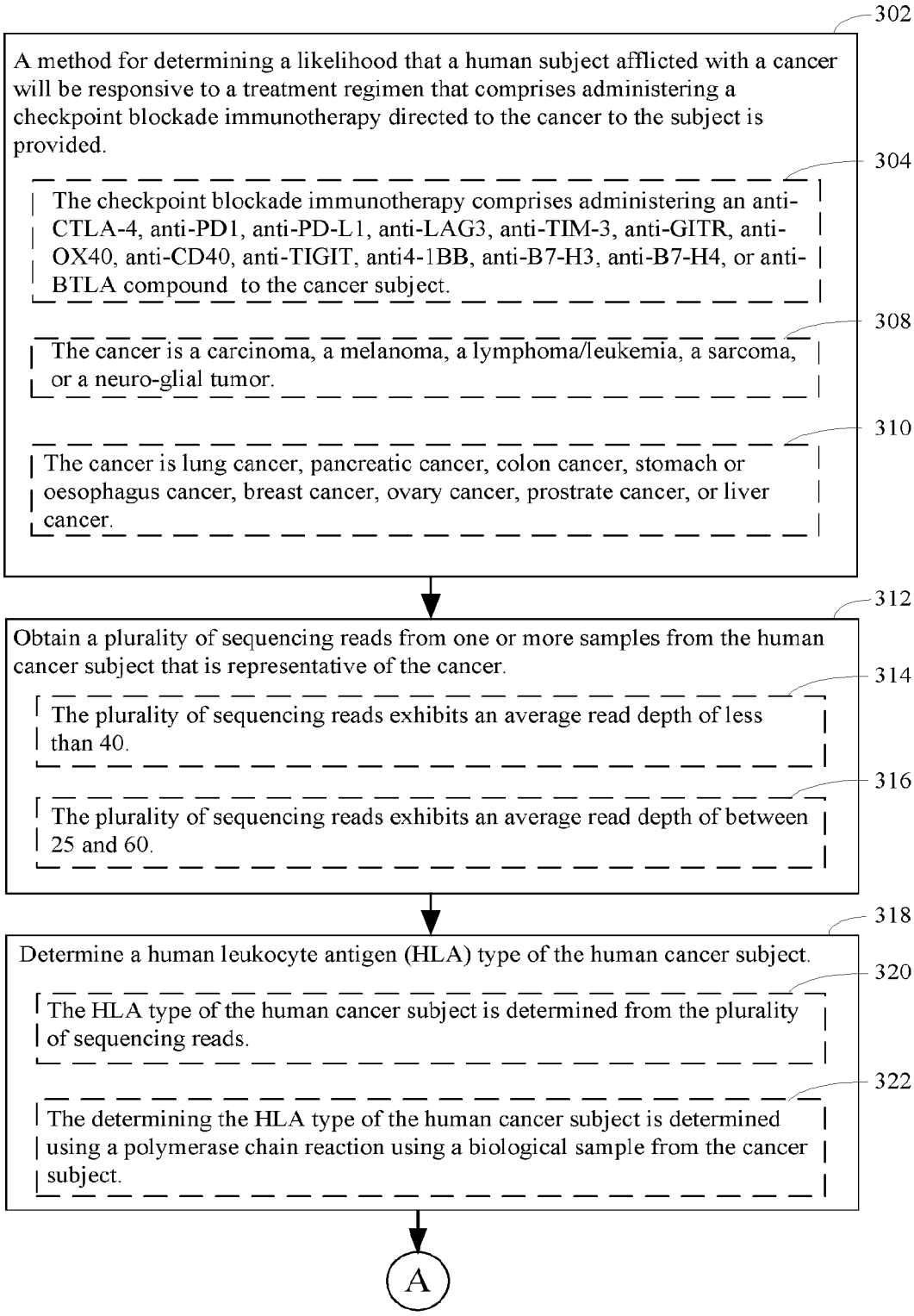

302
A method for determining a likelihood that a human subject afflicted with a cancer will be responsive to a treatment regimen that comprises administering a checkpoint blockade immunotherapy directed to the cancer to the subject is provided.
304
The checkpoint blockade immunotherapy comprises administering an anti-CTLA-4, anti-PD1, anti-PD-L1, anti-LAG3, anti-TIM-3, anti-GITR, anti-OX40, anti-CD40, anti-TIGIT, anti4-1BB, anti-B7-H3, anti-B7-H4, or anti-BTLA compound to the cancer subject.
308
The cancer is a carcinoma, a melanoma, a lymphoma/leukemia, a sarcoma, or a neuro-glial tumor.
310
The cancer is lung cancer, pancreatic cancer, colon cancer, stomach or oesophagus cancer, breast cancer, ovary cancer, prostrate cancer, or liver cancer.
312
Obtain a plurality of sequencing reads from one or more samples from the human cancer subject that is representative of the cancer.
314
The plurality of sequencing reads exhibits an average read depth of less than 40.
316
The plurality of sequencing reads exhibits an average read depth of between 25 and 60.
318
Determine a human leukocyte antigen (HLA) type of the human cancer subject.
320
The HLA type of the human cancer subject is determined from the plurality of sequencing reads.
322
The determining the HLA type of the human cancer subject is determined using a polymerase chain reaction using a biological sample from the cancer subject.
A

Fig. 3A

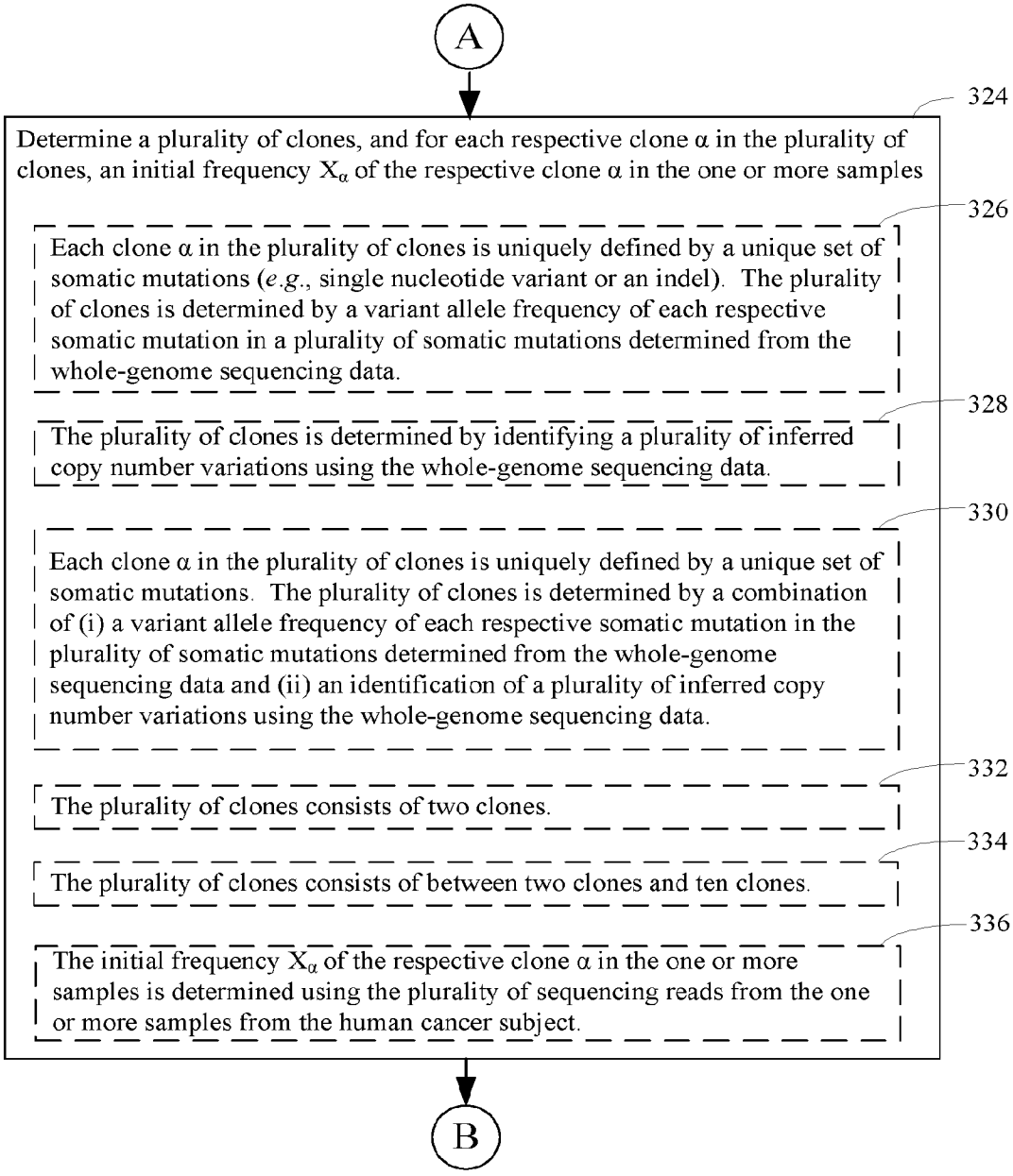

A
324
Determine a plurality of clones, and for each respective clone α in the plurality of clones, an initial frequency X_α of the respective clone α in the one or more samples
326
Each clone α in the plurality of clones is uniquely defined by a unique set of somatic mutations (*e.g.*, single nucleotide variant or an indel). The plurality of clones is determined by a variant allele frequency of each respective somatic mutation in a plurality of somatic mutations determined from the whole-genome sequencing data.
328
The plurality of clones is determined by identifying a plurality of inferred copy number variations using the whole-genome sequencing data.
330
Each clone α in the plurality of clones is uniquely defined by a unique set of somatic mutations. The plurality of clones is determined by a combination of (i) a variant allele frequency of each respective somatic mutation in the plurality of somatic mutations determined from the whole-genome sequencing data and (ii) an identification of a plurality of inferred copy number variations using the whole-genome sequencing data.
332
The plurality of clones consists of two clones.
334
The plurality of clones consists of between two clones and ten clones.
336
The initial frequency X_α of the respective clone α in the one or more samples is determined using the plurality of sequencing reads from the one or more samples from the human cancer subject.
B

Fig. 3B

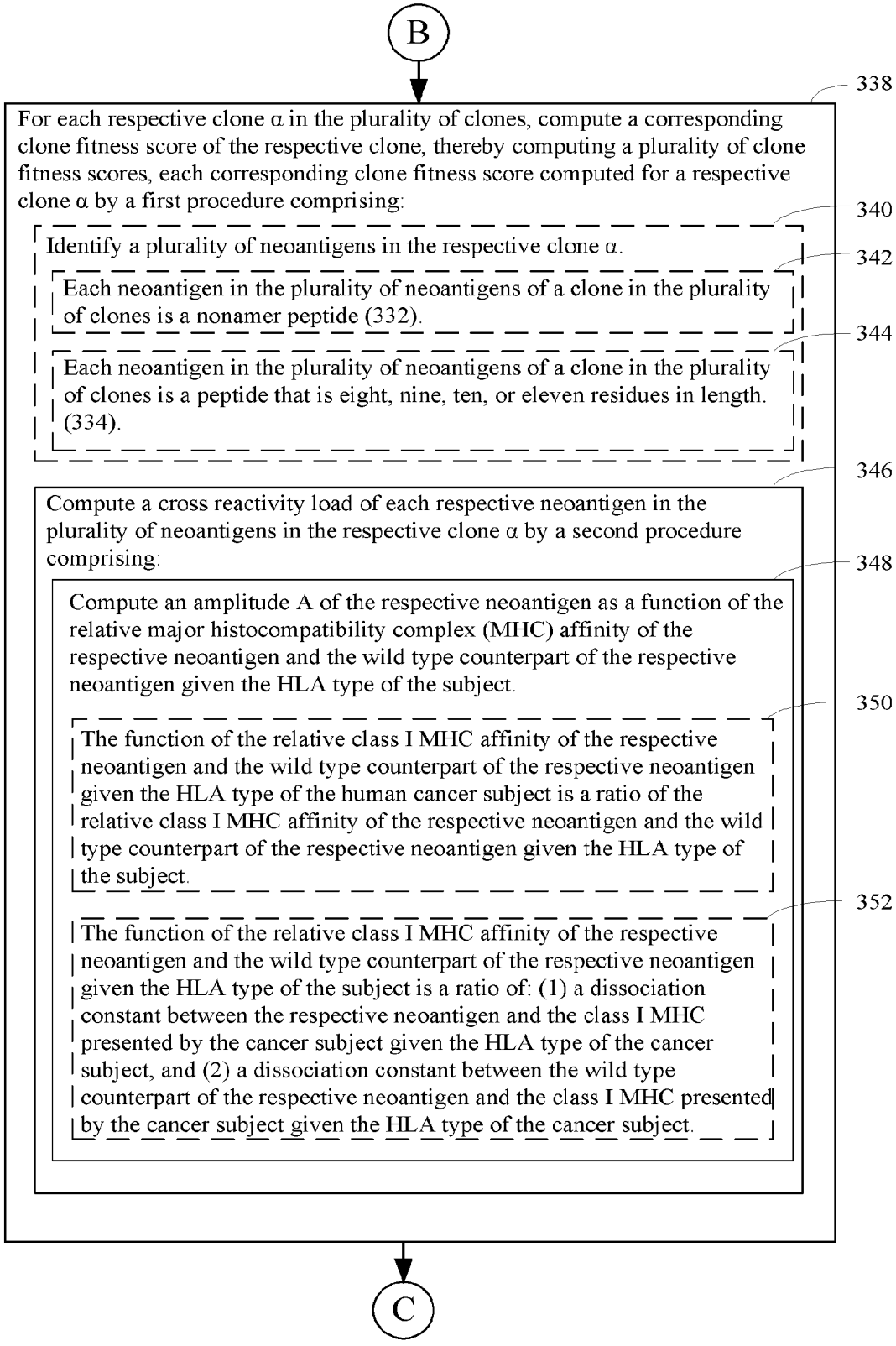

B
338
For each respective clone α in the plurality of clones, compute a corresponding clone fitness score of the respective clone, thereby computing a plurality of clone fitness scores, each corresponding clone fitness score computed for a respective clone α by a first procedure comprising:
340
Identify a plurality of neoantigens in the respective clone α.
342
Each neoantigen in the plurality of neoantigens of a clone in the plurality of clones is a nonamer peptide (332).
344
Each neoantigen in the plurality of neoantigens of a clone in the plurality of clones is a peptide that is eight, nine, ten, or eleven residues in length. (334).
346
Compute a cross reactivity load of each respective neoantigen in the plurality of neoantigens in the respective clone α by a second procedure comprising:
348
Compute an amplitude A of the respective neoantigen as a function of the relative major histocompatibility complex (MHC) affinity of the respective neoantigen and the wild type counterpart of the respective neoantigen given the HLA type of the subject.
350
The function of the relative class I MHC affinity of the respective neoantigen and the wild type counterpart of the respective neoantigen given the HLA type of the human cancer subject is a ratio of the relative class I MHC affinity of the respective neoantigen and the wild type counterpart of the respective neoantigen given the HLA type of the subject.
352
The function of the relative class I MHC affinity of the respective neoantigen and the wild type counterpart of the respective neoantigen given the HLA type of the subject is a ratio of: (1) a dissociation constant between the respective neoantigen and the class I MHC presented by the cancer subject given the HLA type of the cancer subject, and (2) a dissociation constant between the wild type counterpart of the respective neoantigen and the class I MHC presented by the cancer subject given the HLA type of the cancer subject.
C

Fig. 3C

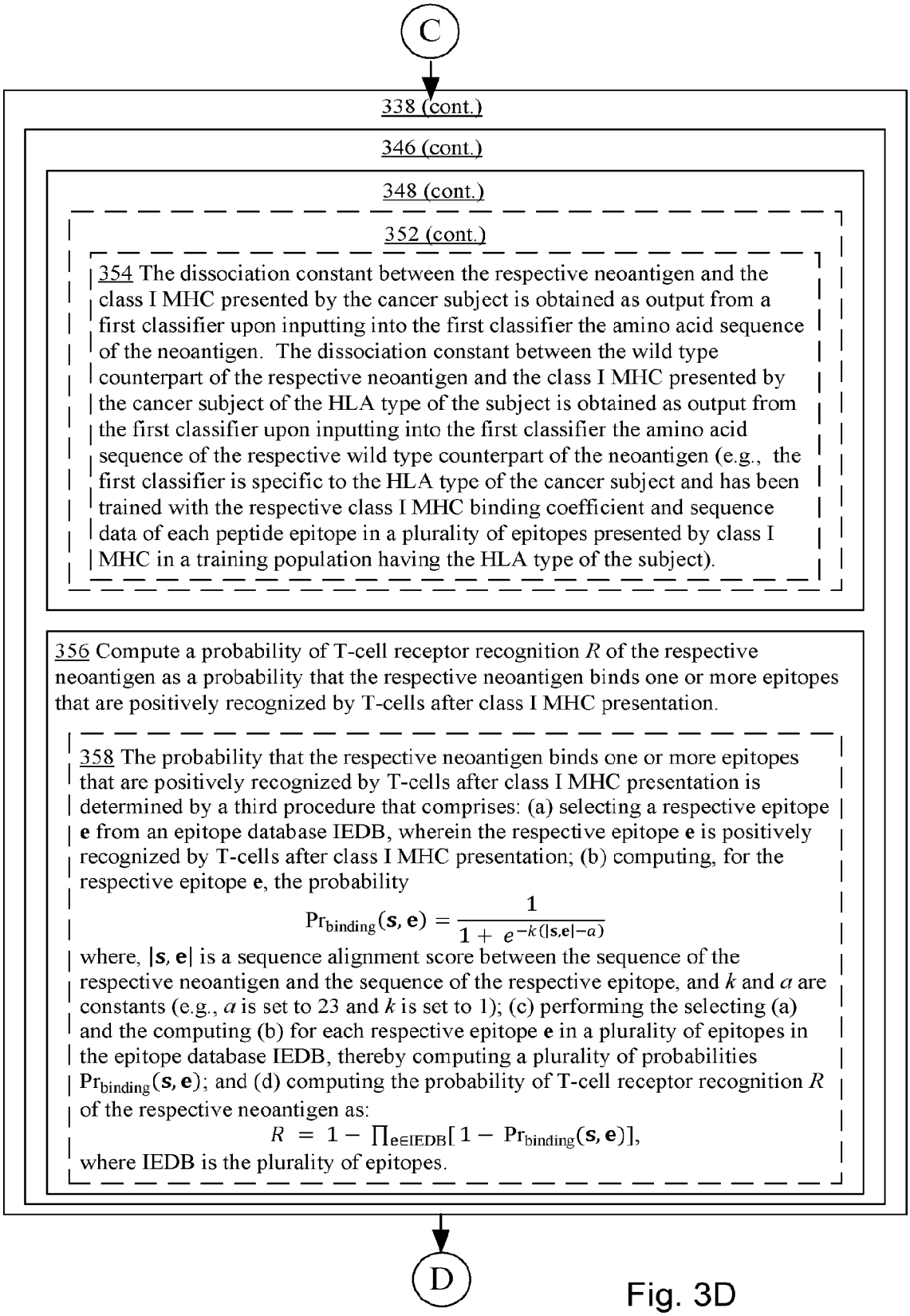

C
338 (cont.)
346 (cont.)
348 (cont.)
352 (cont.)
354 The dissociation constant between the respective neoantigen and the class I MHC presented by the cancer subject is obtained as output from a first classifier upon inputting into the first classifier the amino acid sequence of the neoantigen. The dissociation constant between the wild type counterpart of the respective neoantigen and the class I MHC presented by the cancer subject of the HLA type of the subject is obtained as output from the first classifier upon inputting into the first classifier the amino acid sequence of the respective wild type counterpart of the neoantigen (e.g., the first classifier is specific to the HLA type of the cancer subject and has been trained with the respective class I MHC binding coefficient and sequence data of each peptide epitope in a plurality of epitopes presented by class I MHC in a training population having the HLA type of the subject).
356 Compute a probability of T-cell receptor recognition R of the respective neoantigen as a probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation.
358 The probability that the respective neoantigen binds one or more epitopes that are positively recognized by T-cells after class I MHC presentation is determined by a third procedure that comprises: (a) selecting a respective epitope e from an epitope database IEDB, wherein the respective epitope e is positively recognized by T-cells after class I MHC presentation; (b) computing, for the respective epitope e, the probability
$$\Pr_{\text{binding}}(\mathbf{s}, \mathbf{e}) = \frac{1}{1 + e^{-k(|\mathbf{s},\mathbf{e}|-a)}}$$
where, $|\mathbf{s}, \mathbf{e}|$ is a sequence alignment score between the sequence of the respective neoantigen and the sequence of the respective epitope, and k and a are constants (e.g., a is set to 23 and k is set to 1); (c) performing the selecting (a) and the computing (b) for each respective epitope e in a plurality of epitopes in the epitope database IEDB, thereby computing a plurality of probabilities $\Pr_{\text{binding}}(\mathbf{s}, \mathbf{e})$; and (d) computing the probability of T-cell receptor recognition R of the respective neoantigen as:
$$R = 1 - \prod_{\mathbf{e} \in \text{IEDB}} [1 - \Pr_{\text{binding}}(\mathbf{s}, \mathbf{e})],$$
where IEDB is the plurality of epitopes.
D

Fig. 3D

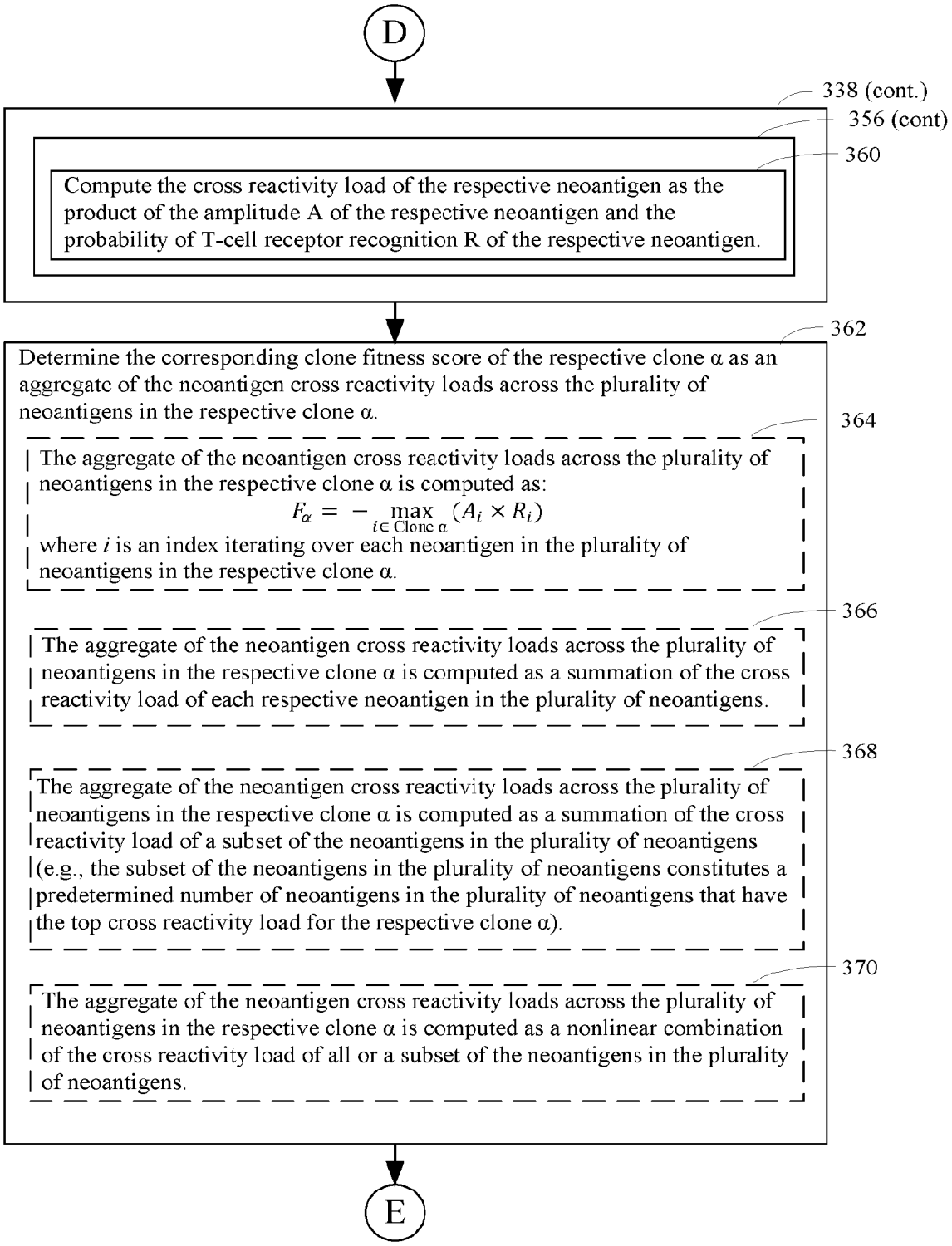

D
338 (cont.)
356 (cont)
360
Compute the cross reactivity load of the respective neoantigen as the product of the amplitude A of the respective neoantigen and the probability of T-cell receptor recognition R of the respective neoantigen.
362
Determine the corresponding clone fitness score of the respective clone α as an aggregate of the neoantigen cross reactivity loads across the plurality of neoantigens in the respective clone α.
364
The aggregate of the neoantigen cross reactivity loads across the plurality of neoantigens in the respective clone α is computed as:
$F_\alpha = -\max_{i \in \text{Clone } \alpha} (A_i \times R_i)$
where i is an index iterating over each neoantigen in the plurality of neoantigens in the respective clone α.
366
The aggregate of the neoantigen cross reactivity loads across the plurality of neoantigens in the respective clone α is computed as a summation of the cross reactivity load of each respective neoantigen in the plurality of neoantigens.
368
The aggregate of the neoantigen cross reactivity loads across the plurality of neoantigens in the respective clone α is computed as a summation of the cross reactivity load of a subset of the neoantigens in the plurality of neoantigens (e.g., the subset of the neoantigens in the plurality of neoantigens constitutes a predetermined number of neoantigens in the plurality of neoantigens that have the top cross reactivity load for the respective clone α).
370
The aggregate of the neoantigen cross reactivity loads across the plurality of neoantigens in the respective clone α is computed as a nonlinear combination of the cross reactivity load of all or a subset of the neoantigens in the plurality of neoantigens.
E

Fig. 3E

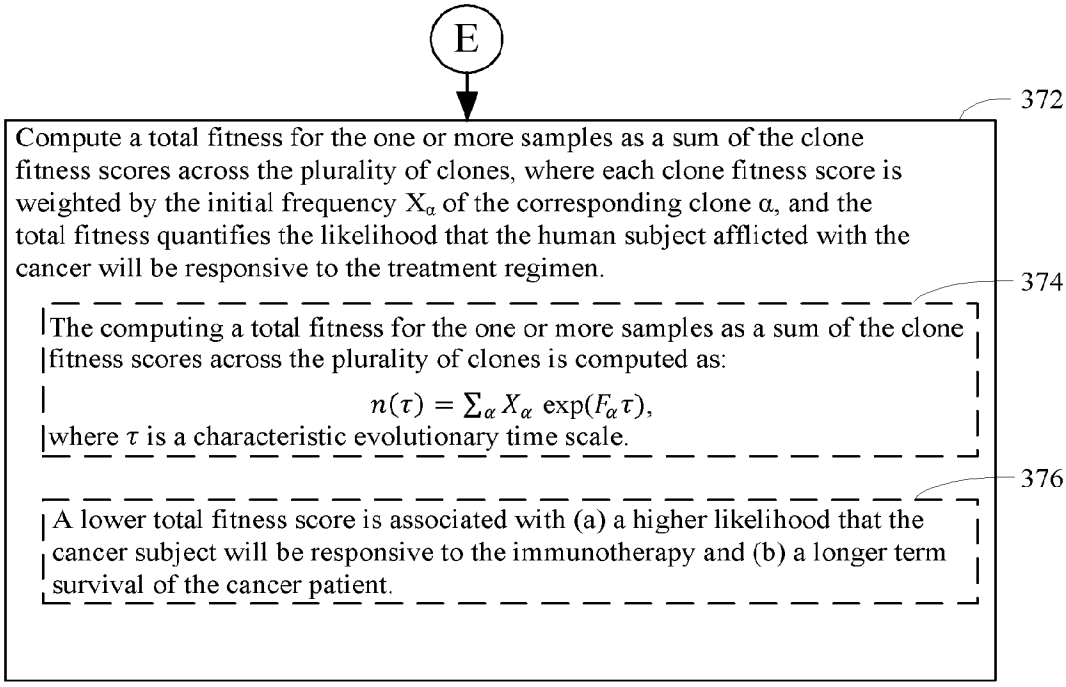

E
372
Compute a total fitness for the one or more samples as a sum of the clone fitness scores across the plurality of clones, where each clone fitness score is weighted by the initial frequency X_α of the corresponding clone α, and the total fitness quantifies the likelihood that the human subject afflicted with the cancer will be responsive to the treatment regimen.
374
The computing a total fitness for the one or more samples as a sum of the clone fitness scores across the plurality of clones is computed as:
$n(\tau) = \sum_\alpha X_\alpha \exp(F_\alpha \tau)$,
where τ is a characteristic evolutionary time scale.
376
A lower total fitness score is associated with (a) a higher likelihood that the cancer subject will be responsive to the immunotherapy and (b) a longer term survival of the cancer patient.

Fig. 3F

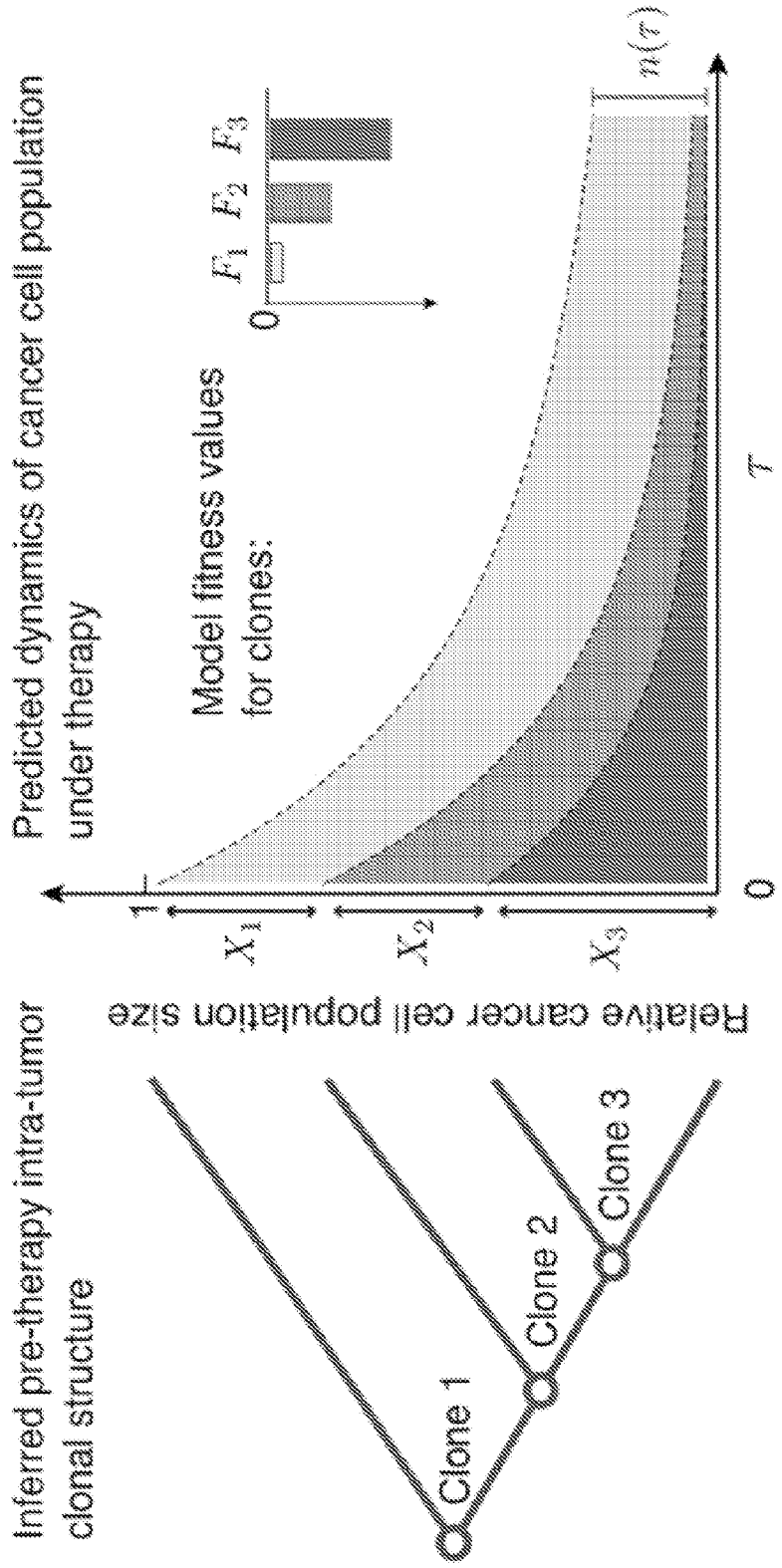

Predicted dynamics of cancer cell population under therapy
Model fitness values for clones:
F_1 F_2 F_3
0
$m(\tau)$
1
X_1
X_2
X_3
0
T
Relative cancer cell population size
Inferred pre-therapy intra-tumor clonal structure
Clone 1
Clone 2
Clone 3

Fig. 4

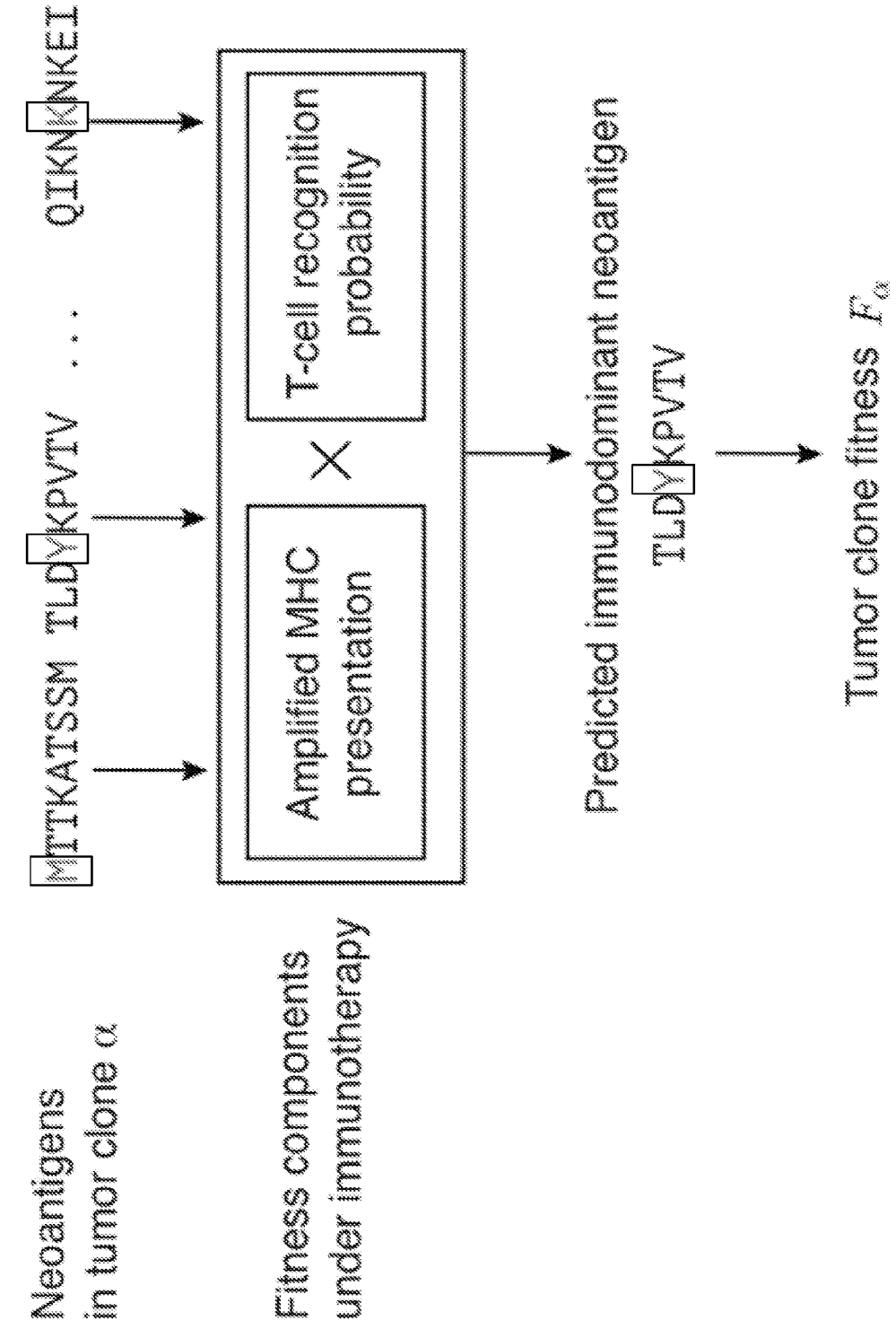

Neoantigens in tumor clone α
MTTKATSSM
TLDYKPVTV
. . .
QTKNKNKEI
Fitness components under immunotherapy
Amplified MHC presentation
X
T-cell recognition probability
Predicted immunodominant neoantigen
TLDYKPVTV
Tumor clone fitness F_α

Fig. 5

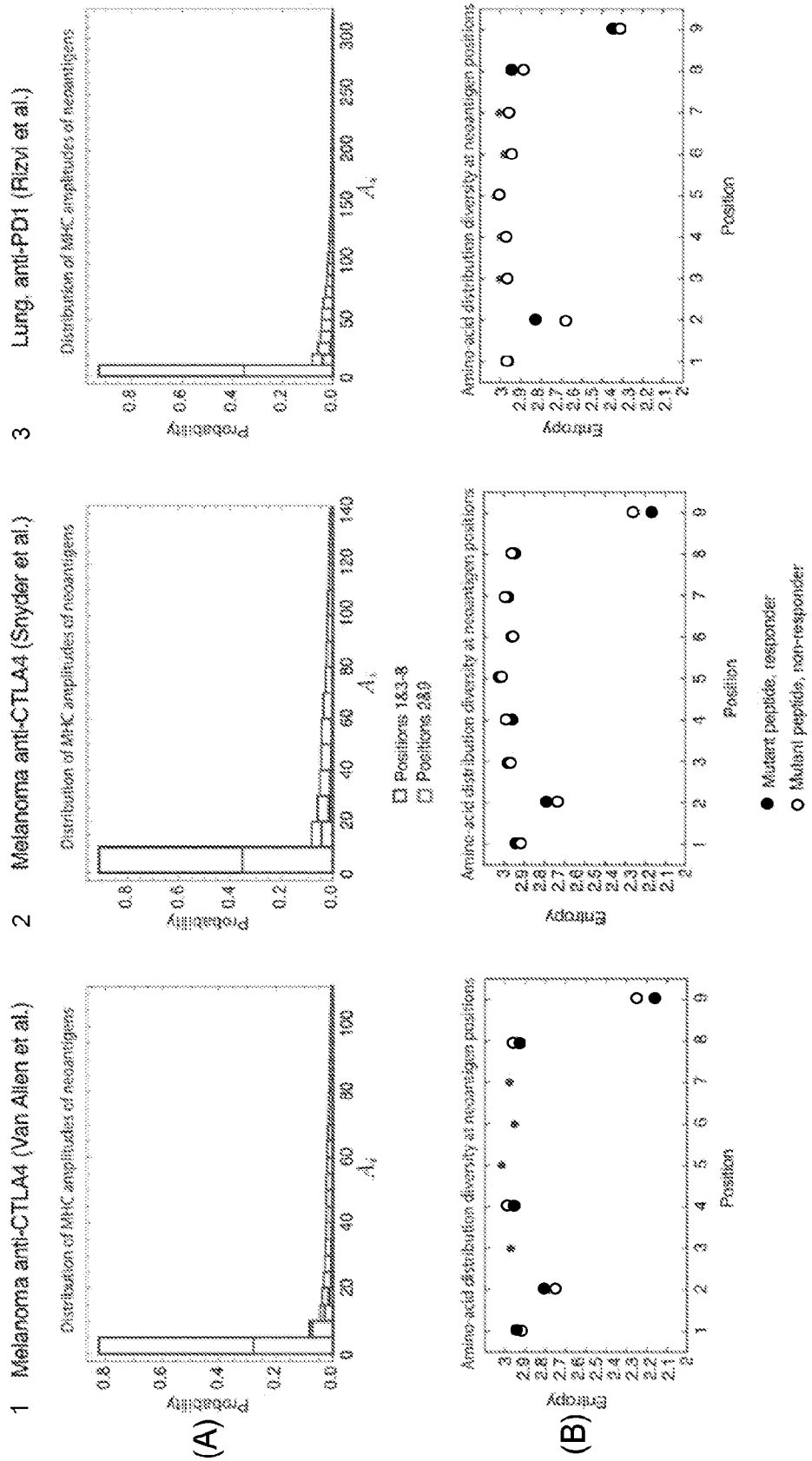

1 Melanoma anti-CTLA4 (Van Allen et al.)
2 Melanoma anti-CTLA4 (Snyder et al.)
3 Lung, anti-PD1 (Rizvi et al.)
Distribution of MHC amplitudes of neoantigens
Probability
A_t
Positions 1&3-8
Positions 2&9
(A)
Amino acid distribution diversity at neoantigen positions
Entropy
Position
Mutant peptide, responder
Mutant peptide, non-responder
(B)

Fig. 6

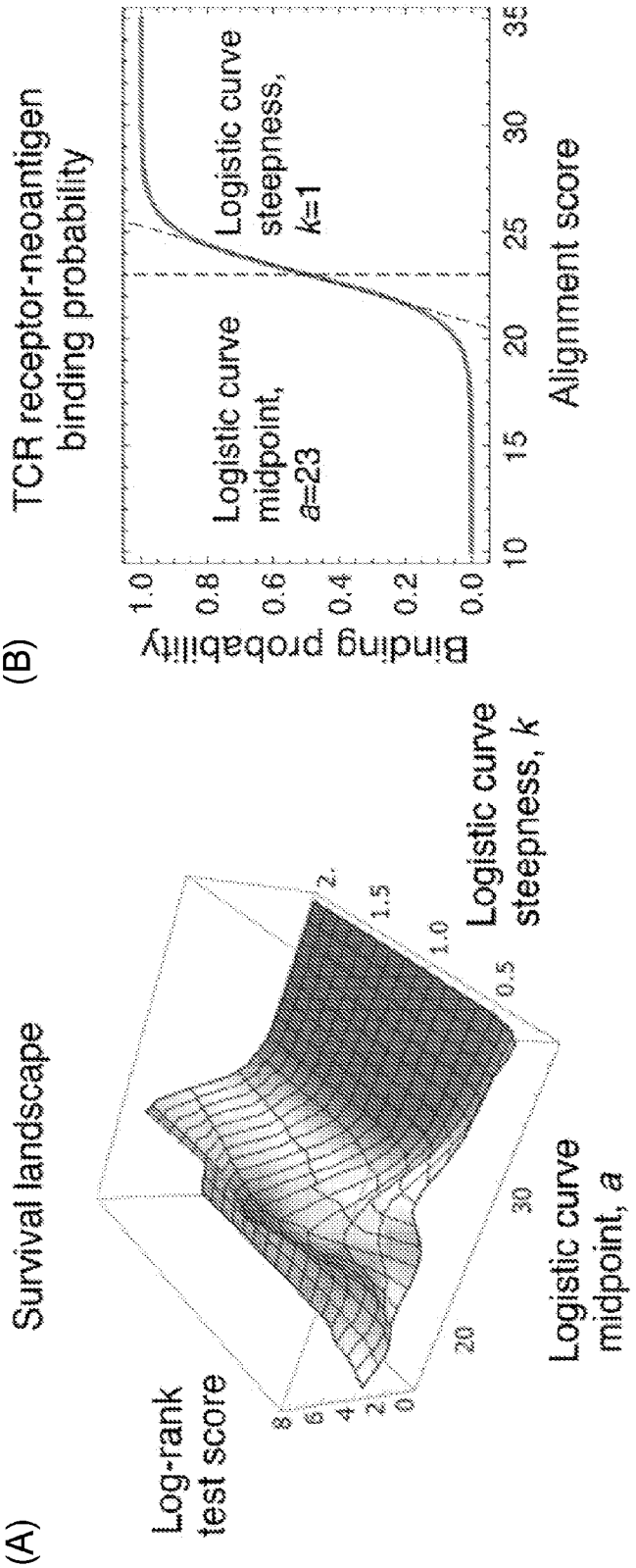

(A)
Survival landscape
Log-rank test score
Logistic curve midpoint, a
Logistic curve steepness, k
(B)
TCR receptor-neoantigen binding probability
Binding probability
Alignment score
Logistic curve midpoint, a=23
Logistic curve steepness, k=1

Fig. 7

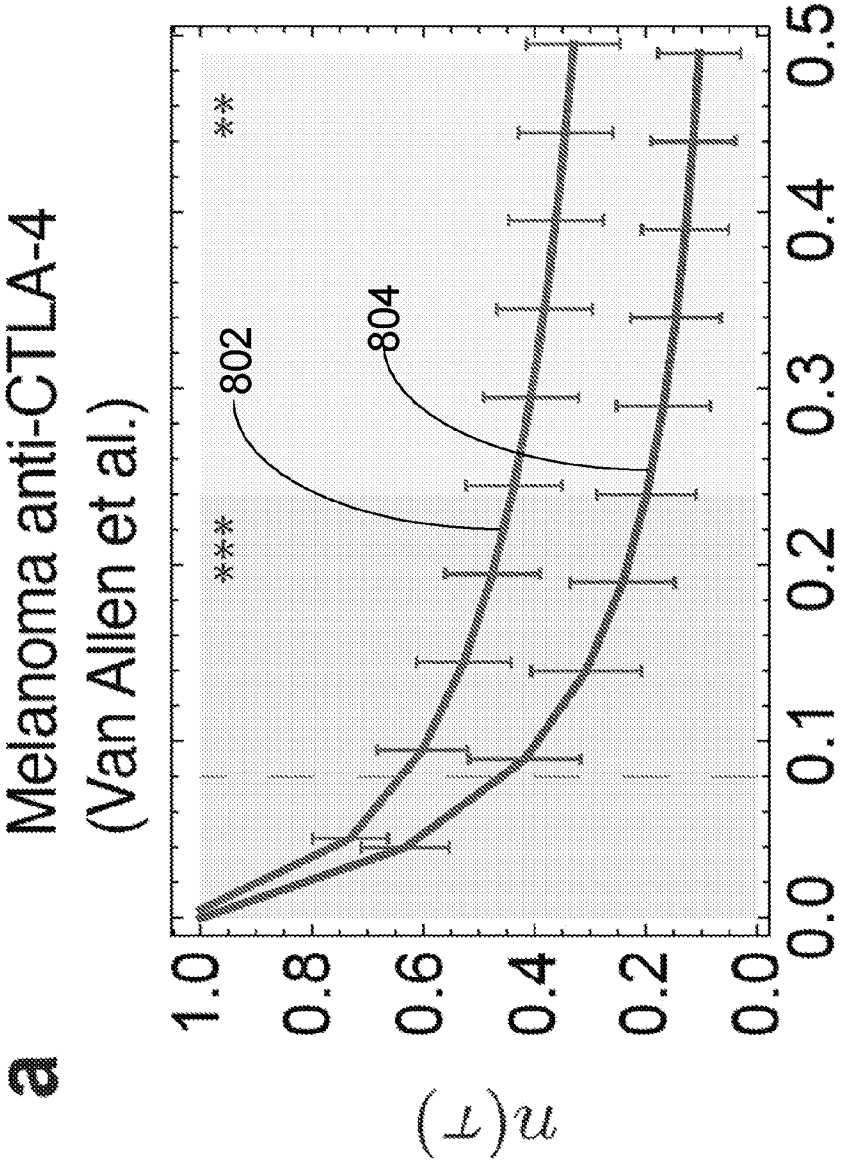

a
Melanoma anti-CTLA-4
(Van Allen et al.)
802
804
***
**
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.1
0.2
0.3
0.4
0.5
$m(\tau)$
τ
804 Responders (n=22)
802 Non-responders (n=71)

Fig. 8

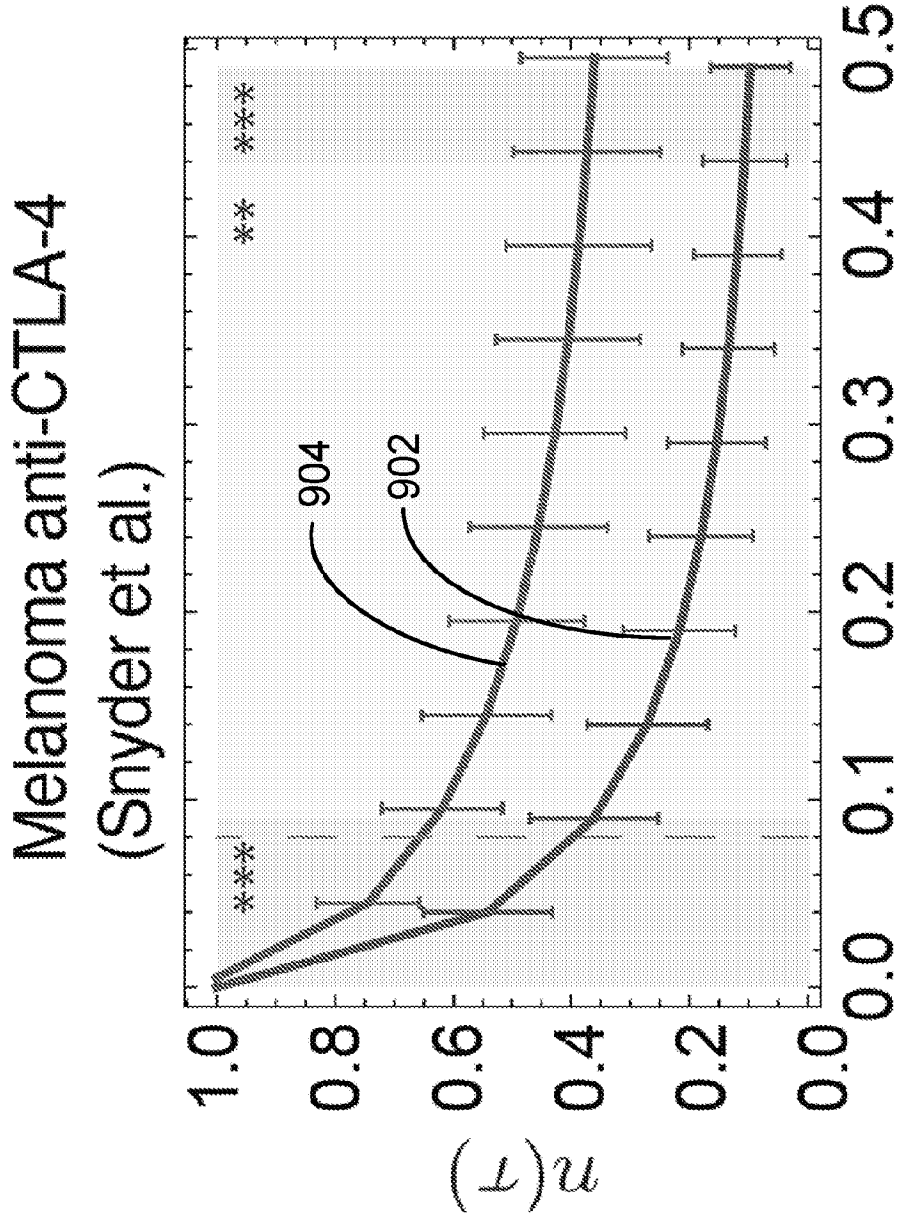

Melanoma anti-CTLA-4
(Snyder et al.)
$n(\tau)$
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.1
0.2
0.3
0.4
0.5
τ
***
**
***
904
902
902 Responders (n=27)
904 Non-responders (n=37)

Fig. 9

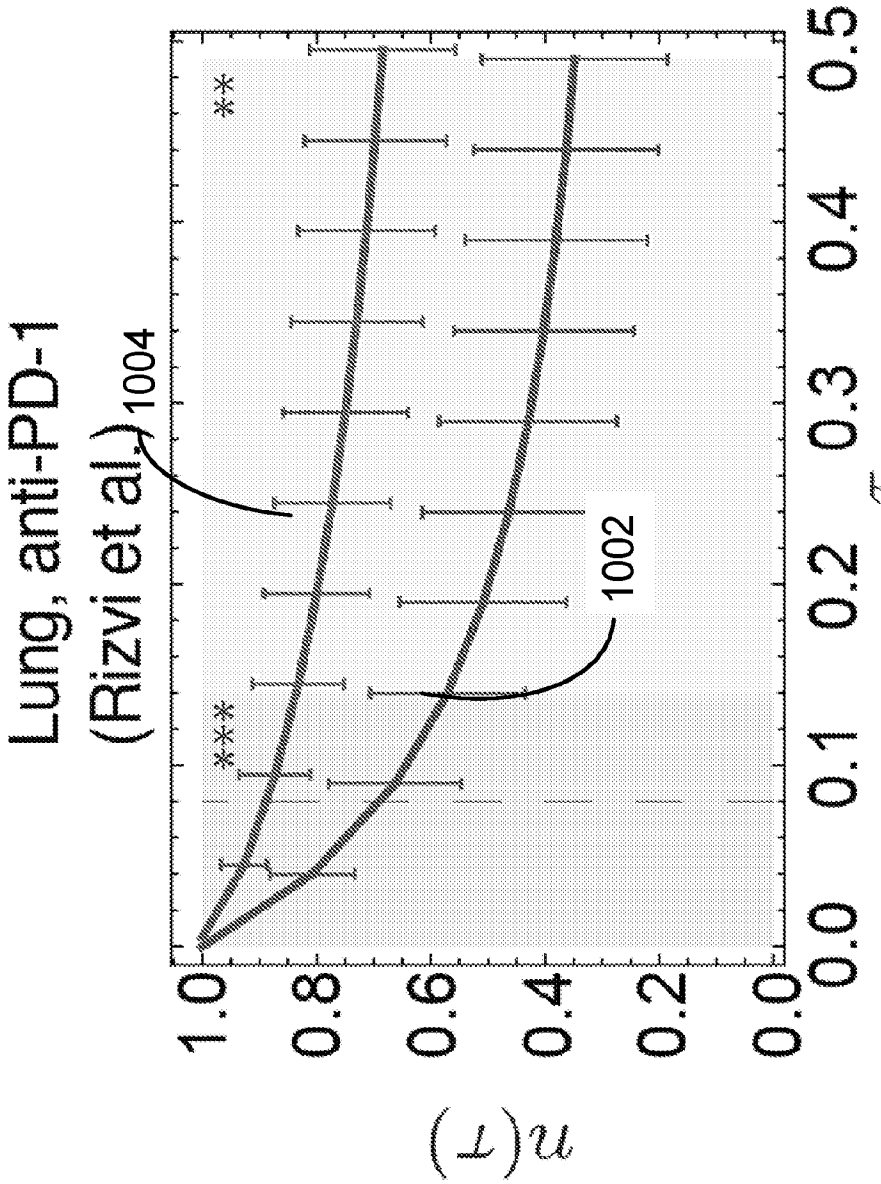

Lung, anti-PD-1
(Rizvi et al.)
1004
1002
***
**
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.1
0.2
0.3
0.4
0.5
τ
$n(\tau)$
1002 = Responders (n=14)
1004 = Non-responders (n=20)

Fig. 10

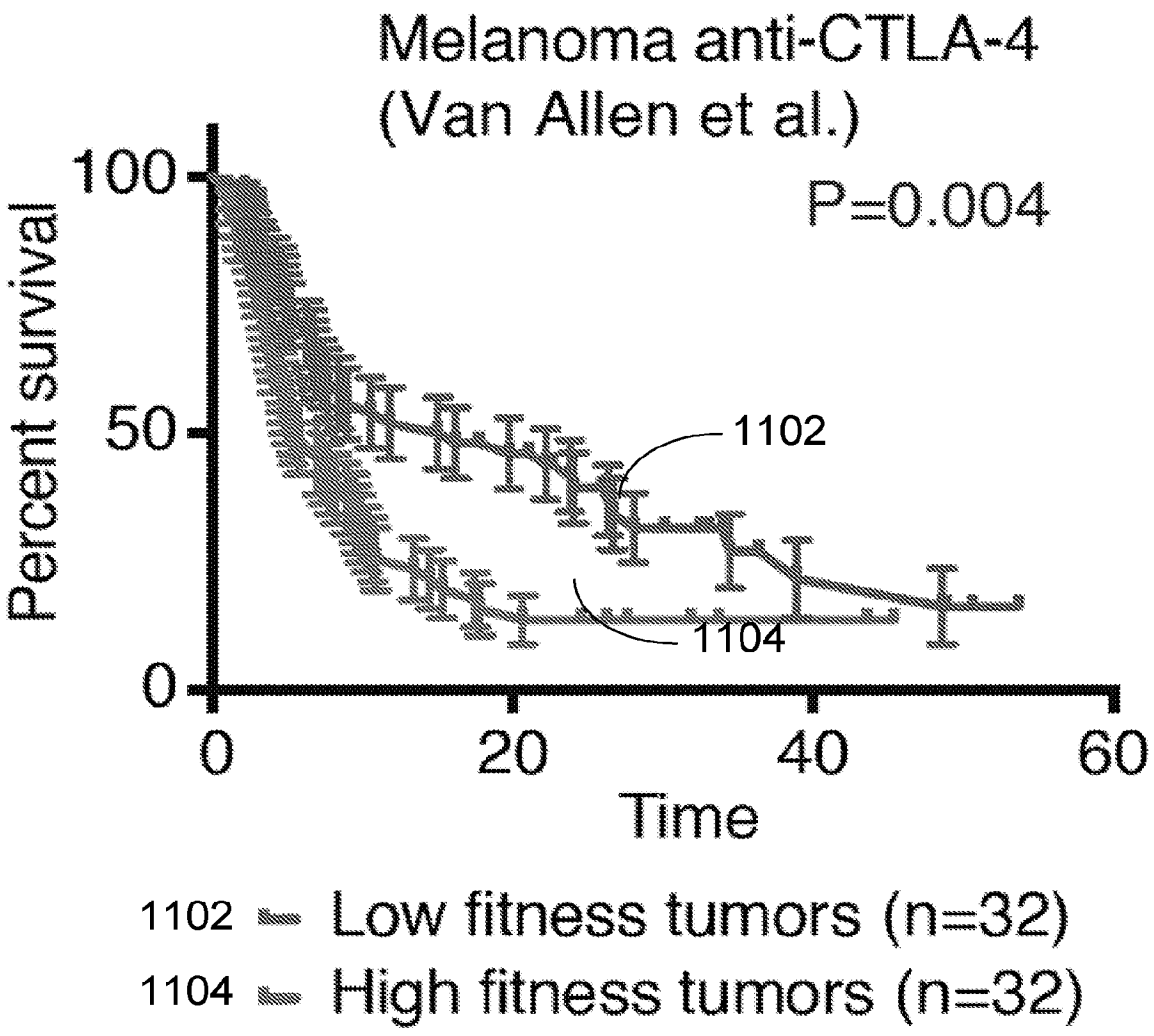

Melanoma anti-CTLA-4
(Van Allen et al.)
P=0.004
Percent survival
100
50
0
0
20
40
60
Time
1102
1104
1102 Low fitness tumors (n=32)
1104 High fitness tumors (n=32)

Fig. 11

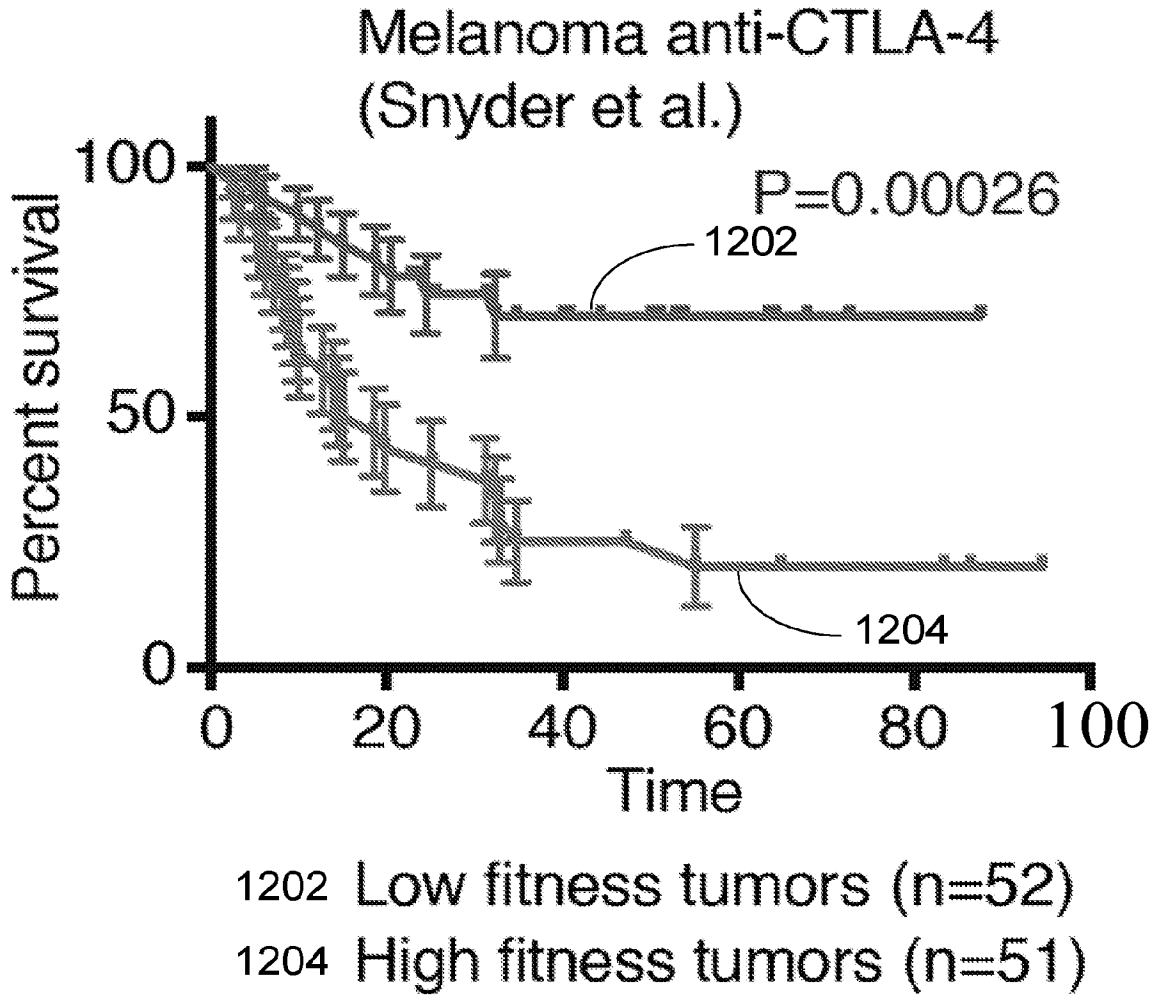

Melanoma anti-CTLA-4
(Snyder et al.)
P=0.00026
1202
1204
Percent survival
100
50
0
0
20
40
60
80
100
Time
1202 Low fitness tumors (n=52)
1204 High fitness tumors (n=51)

Fig. 12

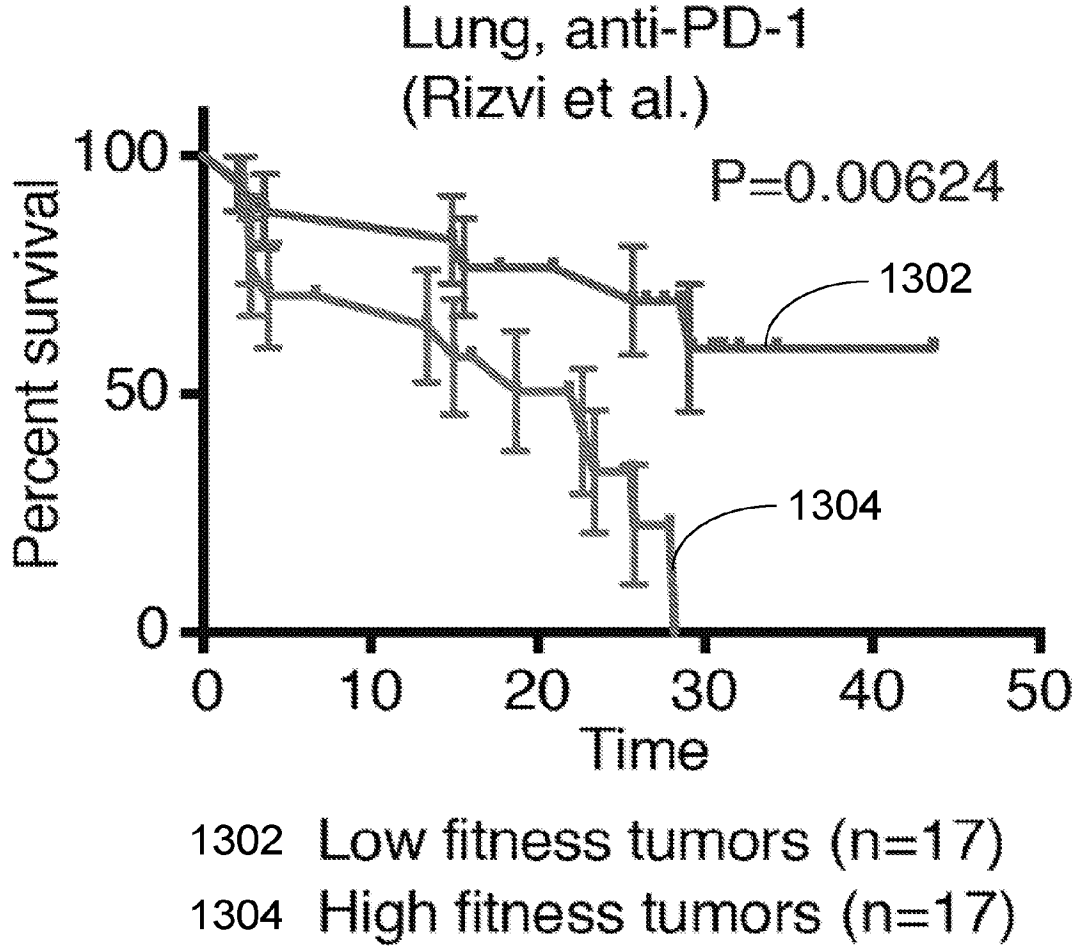

Lung, anti-PD-1
(Rizvi et al.)
P=0.00624
Percent survival
100
50
0
0
10
20
30
40
50
Time
1302
1304
1302 Low fitness tumors (n=17)
1304 High fitness tumors (n=17)

Fig. 13

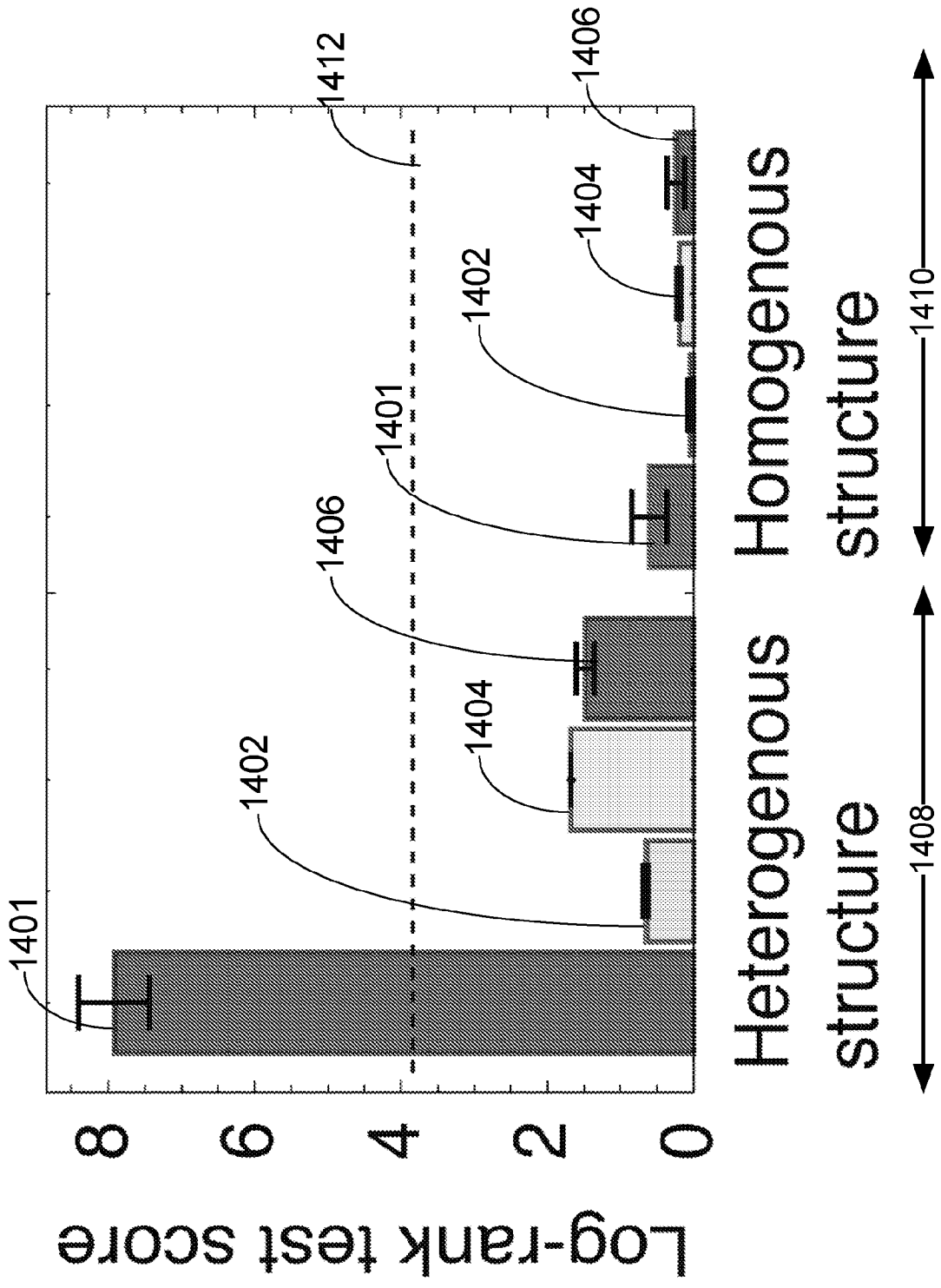

Log-rank test score
0
2
4
6
8
1401
1402
1404
1406
1412
1406
1404
1402
1401
Heterogenous structure
Homogenous structure
1408
1410

Fig. 14

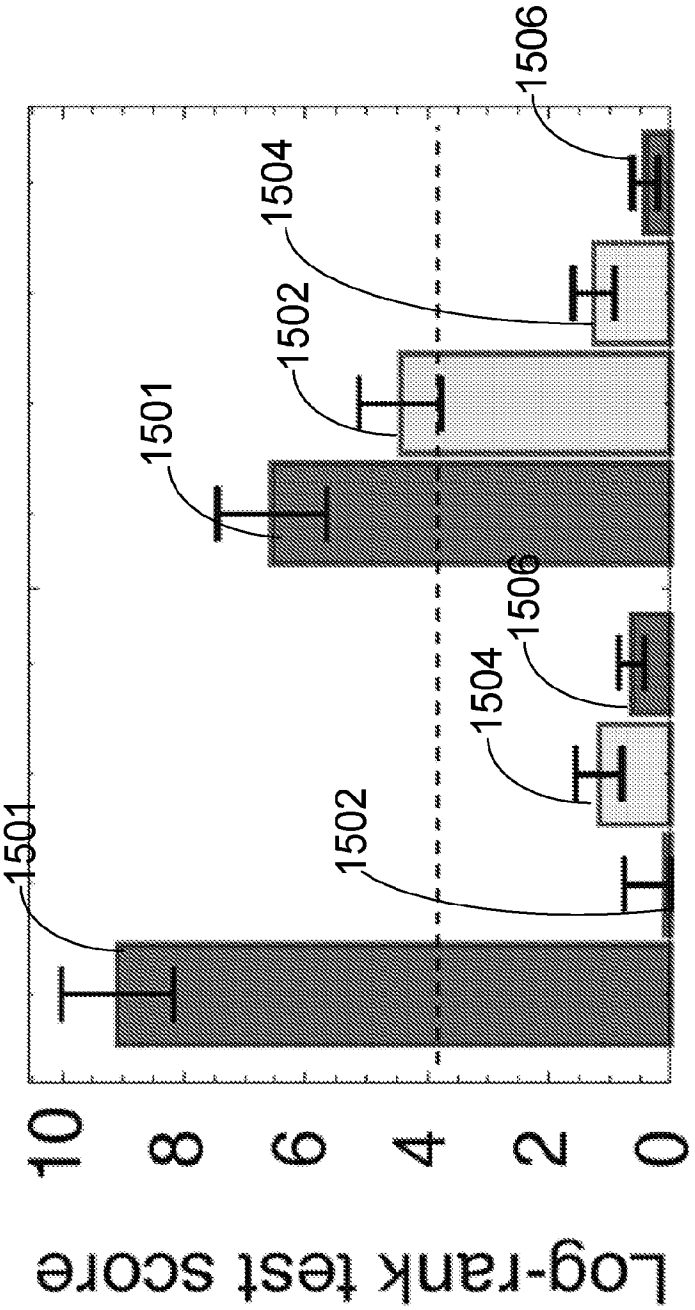

Log-rank test score
10
8
6
4
2
0
1501
1502
1504
1506
1501
1502
1504
1506
Heterogenous structure
Homogenous structure
1508
1510

Fig. 15

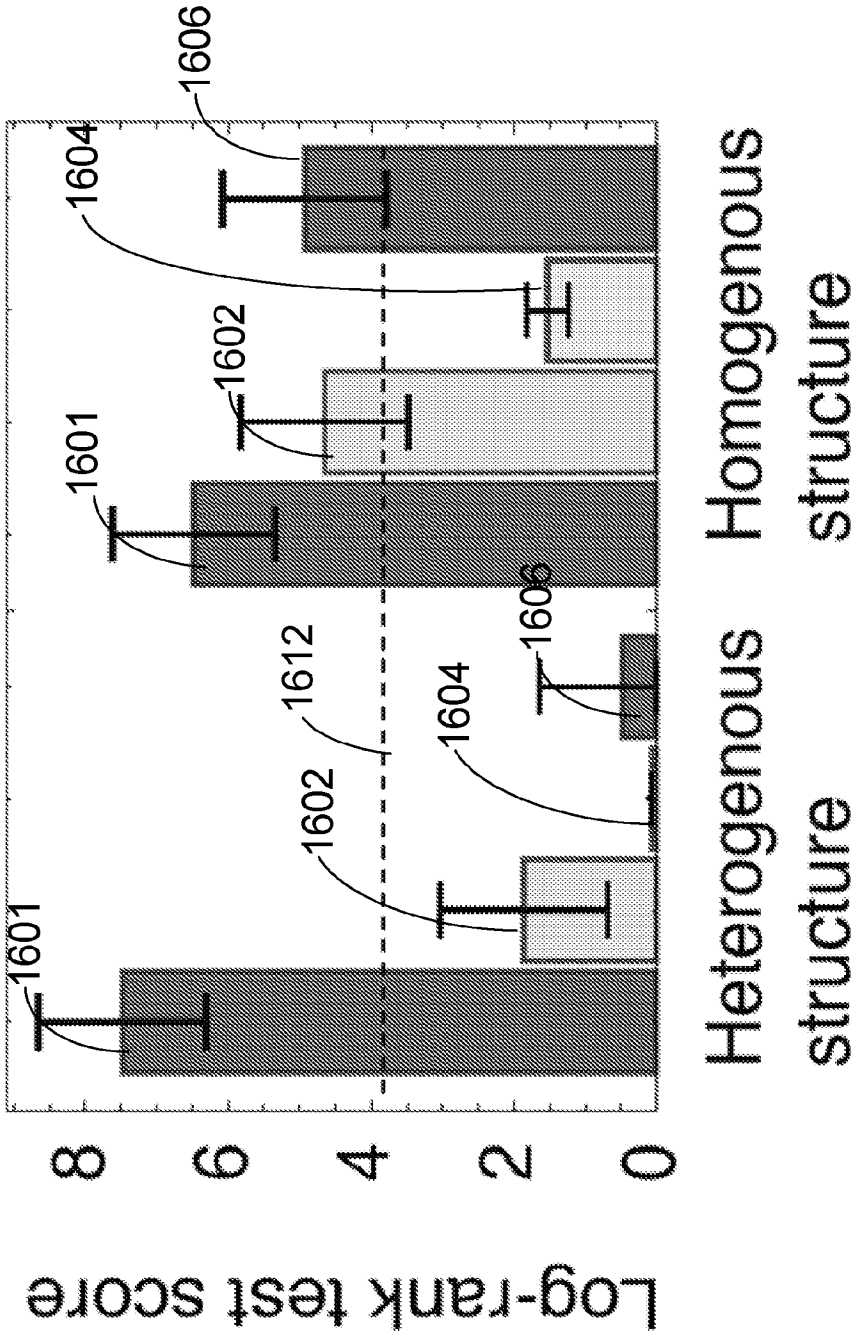

Log-rank test score
0
2
4
6
8
1601
1602
1604
1606
1612
Heterogenous structure
Homogenous structure
1608
1610

Fig. 16

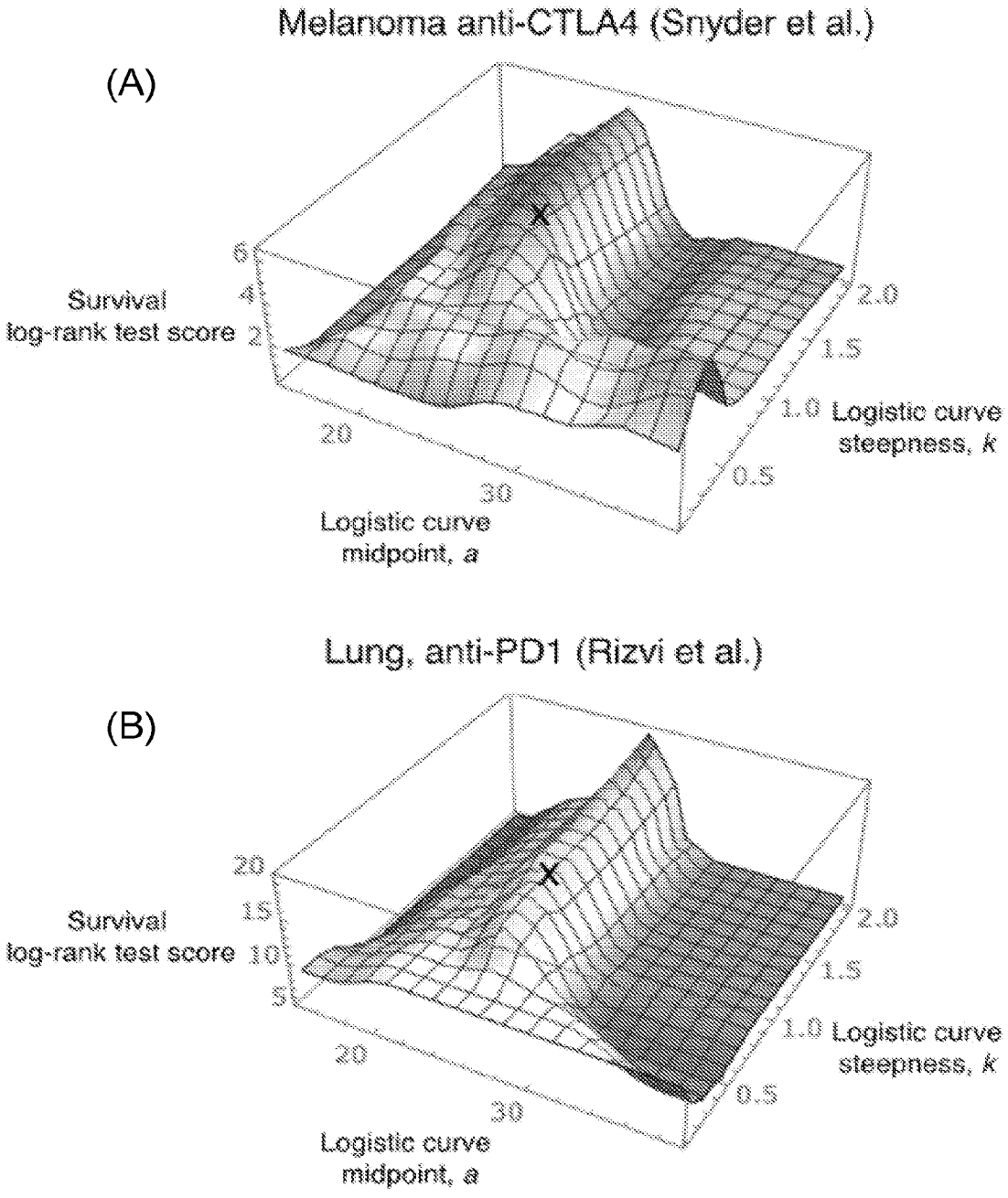

Melanoma anti-CTLA4 (Snyder et al.)
(A)
Survival
log-rank test score
6
4
2
20
30
Logistic curve
midpoint, a
2.0
1.5
1.0
0.5
Logistic curve
steepness, k
Lung, anti-PD1 (Rizvi et al.)
(B)
Survival
log-rank test score
20
15
10
5
20
30
Logistic curve
midpoint, a
2.0
1.5
1.0
0.5
Logistic curve
steepness, k

Fig. 17

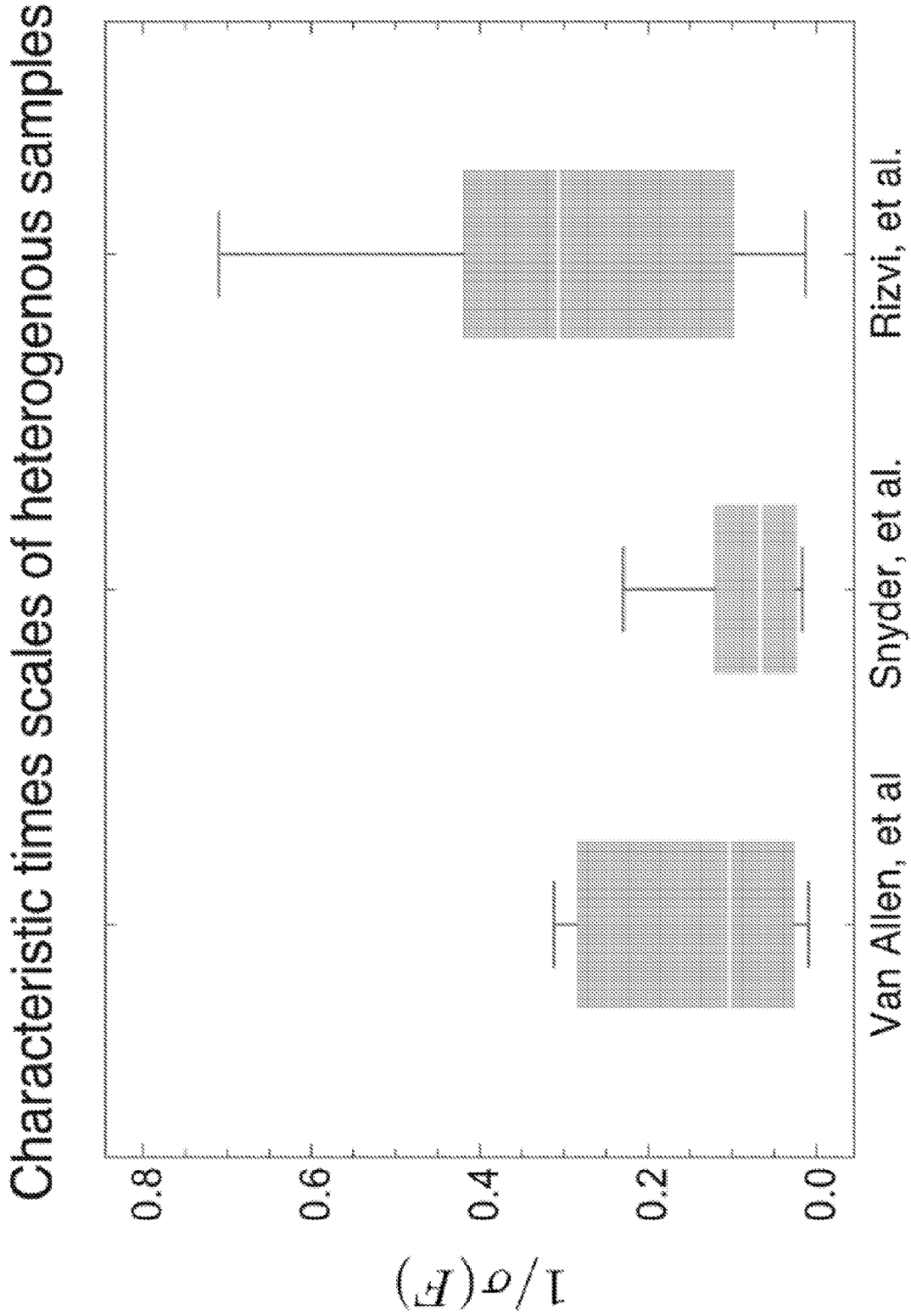

Characteristic times scales of heterogenous samples
0.8
0.6
0.4
0.2
0.0
$1/\sigma(F)$
Van Allen, et al
Snyder, et al.
Rizvi, et al.

Fig. 18

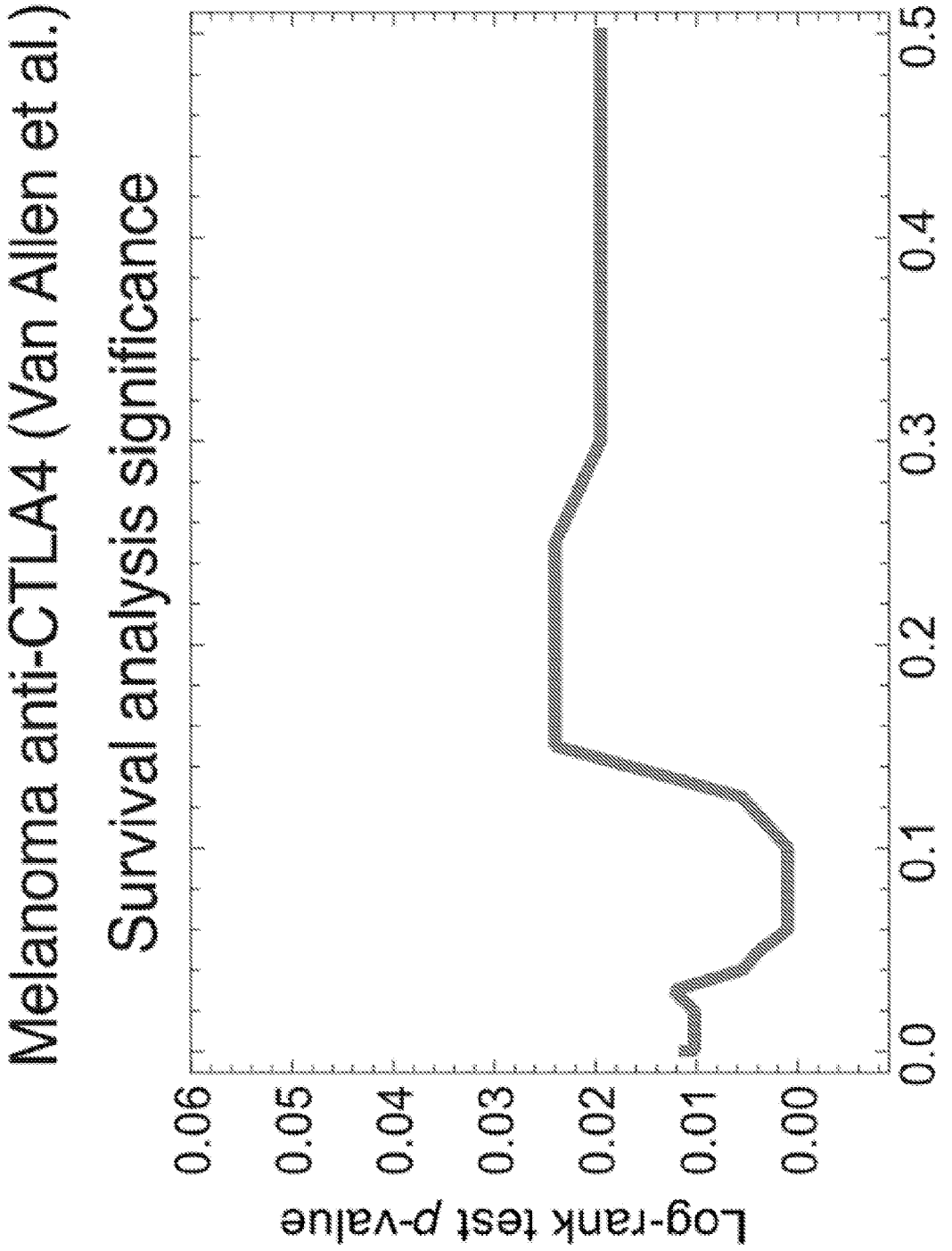

Melanoma anti-CTLA4 (Van Allen et al.)
Survival analysis significance
Log-rank test p-value
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0.0
0.1
0.2
0.3
0.4
0.5
T

Fig. 19

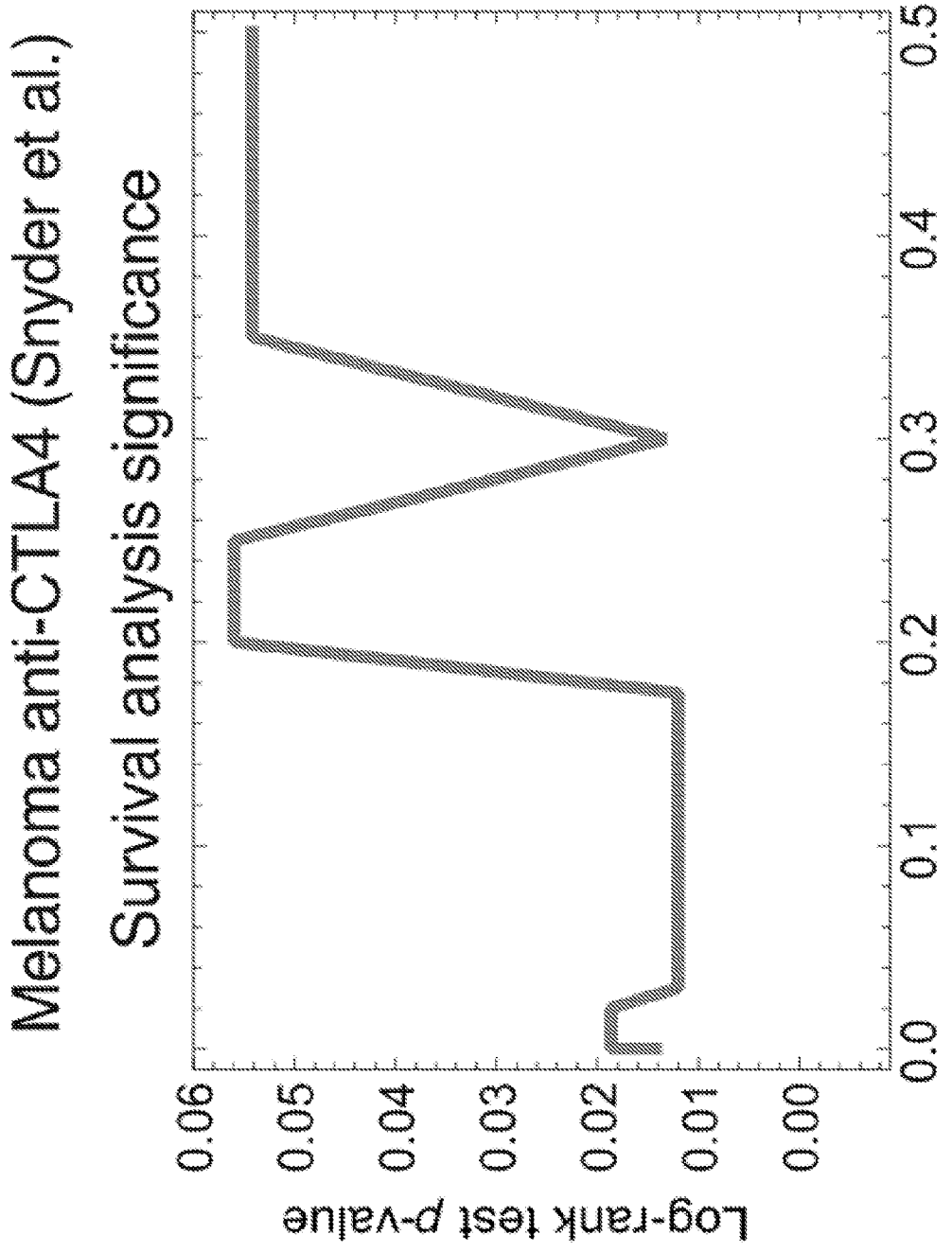

Melanoma anti-CTLA4 (Snyder et al.)
Survival analysis significance
Log-rank test p-value
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0.0
0.1
0.2
0.3
0.4
0.5
τ

Fig. 20

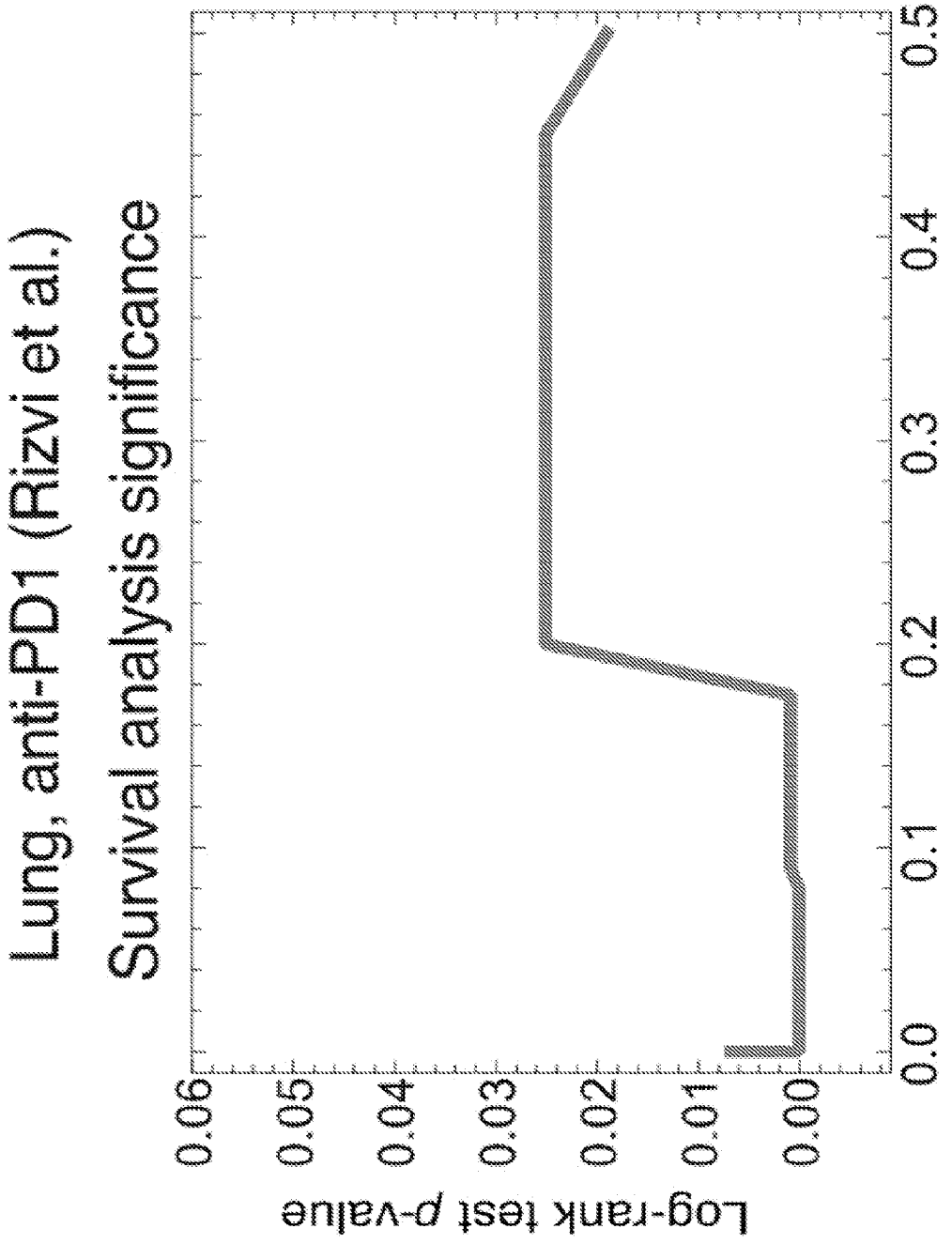

Lung, anti-PD1 (Rizvi et al.)
Survival analysis significance
Log-rank test p-value
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0.0
0.1
0.2
0.3
0.4
0.5
τ

Fig. 21

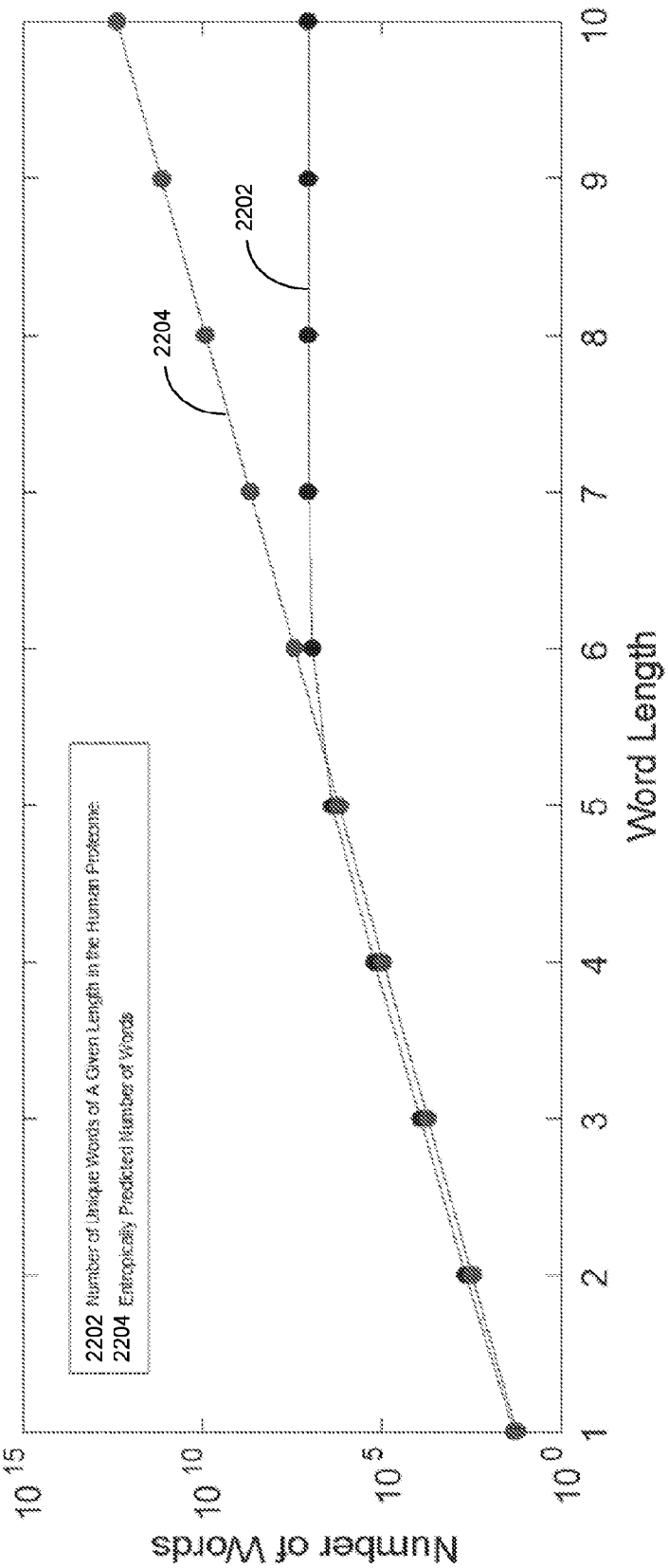

Number of Words
Word Length
2202
2204
2202 Number of Unique Words of A Given Length in the Human Proteome
2204 Entropically Predicted Number of Words

Fig. 22

Van Allen et al., Melanoma anti-CTLA-4	Parameters trained on Snyder						Log-rank test			
Models	τ		a		k		Score		Significance	Equation
	Mean	Std	Mean	Std	Mean	Std	Mean	Std		
A x R	0.09003	±0.077	26	±2.988	4.19761	±0.01	7.92	±0.49	0.00489 ***	(2)
Partial models:										
A	0.00131	±0.0001	-	-	-	-	0.65	±0.03		(12)
R	12.33338	±1.827	12.5	±1.074	1.89795	±24.161	1.68	±0.01		(13)
1/kdM x R	0.03851	±1.711	21.3	±0.353	1.50243	±0.02	2.01	±0.45		(14)
1/kdM	0.3388	±0.0001	-	-	-	-	1.46	±0.23		(14)
kdW x R	0.00048	±0.0001	31	±2.911	6.26907	±0.001	0.09	±0.25		(15)
kdW	0.00307	±0.0001	-	-	-	-	0.04	±0.2		(15)
Alternative models:										
Neoantigen load	16.39039	±0.0001	-	-	-	-	1.48	±0.12		(17)
A x R, sum over neoantigens	18.3366	±0.471	38.3	±0.001	10.1531	±29.105	0.21	±0.08		(16)
A x R, alignments at positions 3-8	0.0716	±1.011	22.3	±0.273	0.46591	±0.022	0.94	±0.13		(2)
A x R, negative IEDB assays	0.00091	±0.58	15.8	±0.056	0.45236	±0.001	0.98	±0.03		(2)
A x R, all neoantigens	0.01602	±0.559	34.9	±0.051	0.53933	±0.834	0.13	±0.03		(2)
A x R, average fitness	-	-	26.3	±0.252	1.06061	±0.001	4.03	±0.84	0.04476 *	(2) and (19)

Fig. 23

Snyder et al., Melanoma anti-CTLA-4	Parameters trained on Van Allen						Log-rank test			
Models	τ		a		k		Score		Significance	Equation
	Mean	Std	Mean	Std	Mean	Std	Mean	Std		
A x R	0.02326	±0.479	26	±3.835	3.44101	±0.088	9.1	±0.92	0.00256 ***	(2)
Partial models:										
A	0.1007	±0.0001	-	-	-	-	0.09	±0.68		(12)
R	1.3483	±17.017	21.2	±5.133	5.57735	±27.093	1.17	±0.38		(13)
1/kdM x R	0.0786	±5.21	22	±0.445	1.4779	±0.065	0.41	±0.65		(14)
1/kdM	0.06196	±0.0001	-	-	-	-	0.63	±0.61		(14)
kdW x R	0.00096	±15.302	27	±4.14	5.53499	±0.001	0.53	±0.22		(15)
kdW	13.33274	±0.0001	-	-	-	-	1.21	±0.75		(15)
Alternative models:										
Neoantigen load	0.10065	±0.0001	-	-	-	-	0.64	±0.21		(17)
A x R, sum over neoantigens	0.08928	±27.215	27	±8.827	5.01647	±34.399	0.09	±0.53		(16)
A x R, alignments at positions 3-8	1.82771	±11.104	24.9	±8.066	8.08455	±1.826	5.33	±1.05	0.021 *	(2)
A x R, negative IEDB assays	0.16414	±10.716	11.7	±0.768	0.89312	±0.164	1.83	±0.97		(2)
A x R, all neoantigens	0.00772	±23.665	25.7	±7.145	7.16555	±0.834	2.63	±0.92		(2)
A x R, average fitness	-	-	26	±3.158	3.34043	±0.001	8.03	±0.92	0.00459 ***	(2) and (19)

Fig. 24

Rizvi et al., Lung anti-PD-1	Parameters trained on Van Allen and Snyder						Log-rank test		
Models	τ		a		k		Score	Significance	Equation
	Mean	Std	Mean	Std	Mean	Std	Mean Std		
A x R	0.08958	±0.458	26	±1.679	4.8714	±0.014	7.48 ±1.17	0.00624 ***	(2)
Partial models:									
A	0.09278	±0.0001	-	-	-	-	1.86 ±1.17		(12)
R	1.9744	±13.288	18.4	±4.897	5.36039	±27.055	0.07 ±0.01		(13)
1/kdM x R	1.50385	±6.017	22.2	±0.74	1.71159	±1.503	0.1 ±0.16		(14)
1/kdM	3.42166	±0.0001	-	-	-	-	0.52 ±0.13		(14)
kdW x R	0.78791	±5.582	30.5	±4.853	4.92212	±0.788	1.62 ±0.54		(15)
kdW	7.31748	±0.0001	-	-	-	-	0.62 ±0.75		(15)
Alternative models:									
Neoantigen load	3.89326	±0.0001	-	-	-	-	0.49 ±1.15		(17)
A x R, sum over neoantigens	22.06719	±1.493	38.4	±0.004	10.1531	±26.389	0 ±0.11		(16)
A x R, alignments at positions 3-8	0.06281	±6.254	21.4	±0.34	0.63805	±0.041	2.55 ±0.59		(2)
A x R, negative IEDB assays	0.01993	±5.485	16.8	±0.485	0.66568	±0.02	3.39 ±0.51		(2)
A x R, all neoantigens	0.44272	±9.226	33.7	±0.464	0.71345	±0.707	0.88 ±0.84		(2)
A x R, average fitness	-	-	28	±1.502	1.85617	±0.001	4.49 ±1.17	0.03402 *	(2) and (19)

Fig. 25

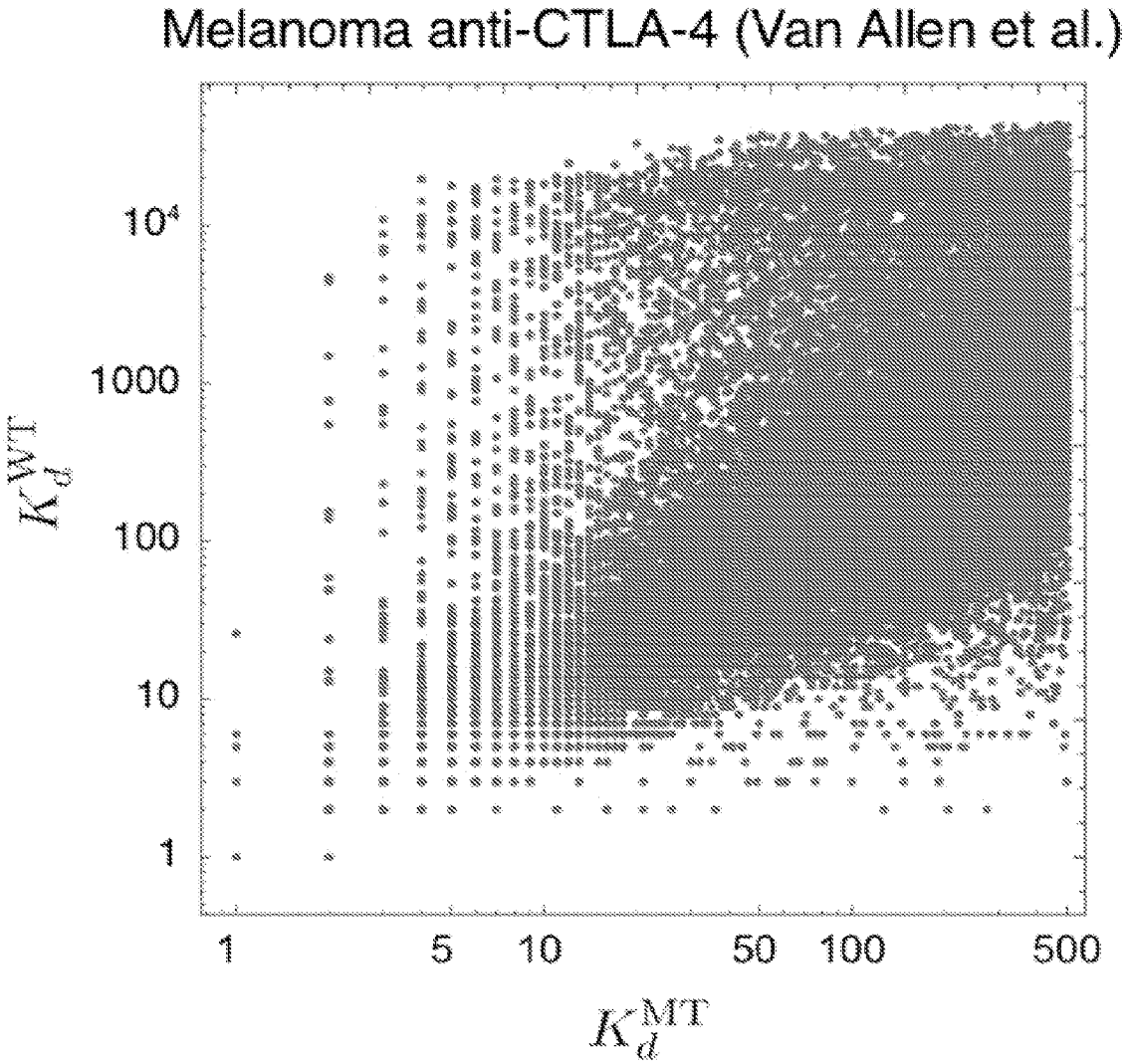

Melanoma anti-CTLA-4 (Van Allen et al.)
10^4
1000
100
10
1
K_d^{WT}
1
5
10
50
100
500
K_d^{MT}

Fig. 26

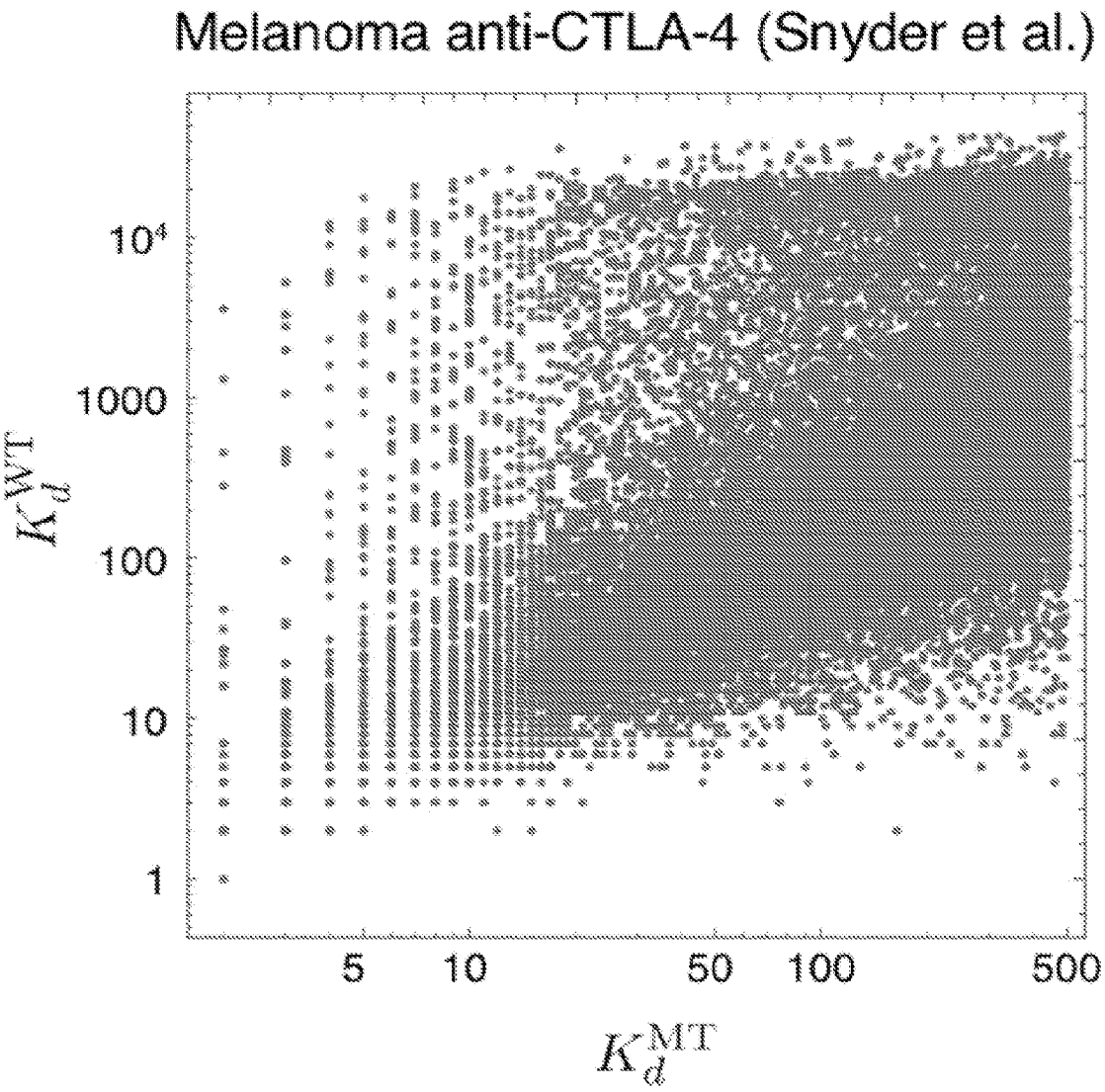

Melanoma anti-CTLA-4 (Snyder et al.)
10^4
1000
100
10
1
K_d^{WT}
5
10
50
100
500
K_d^{MT}

Fig. 27

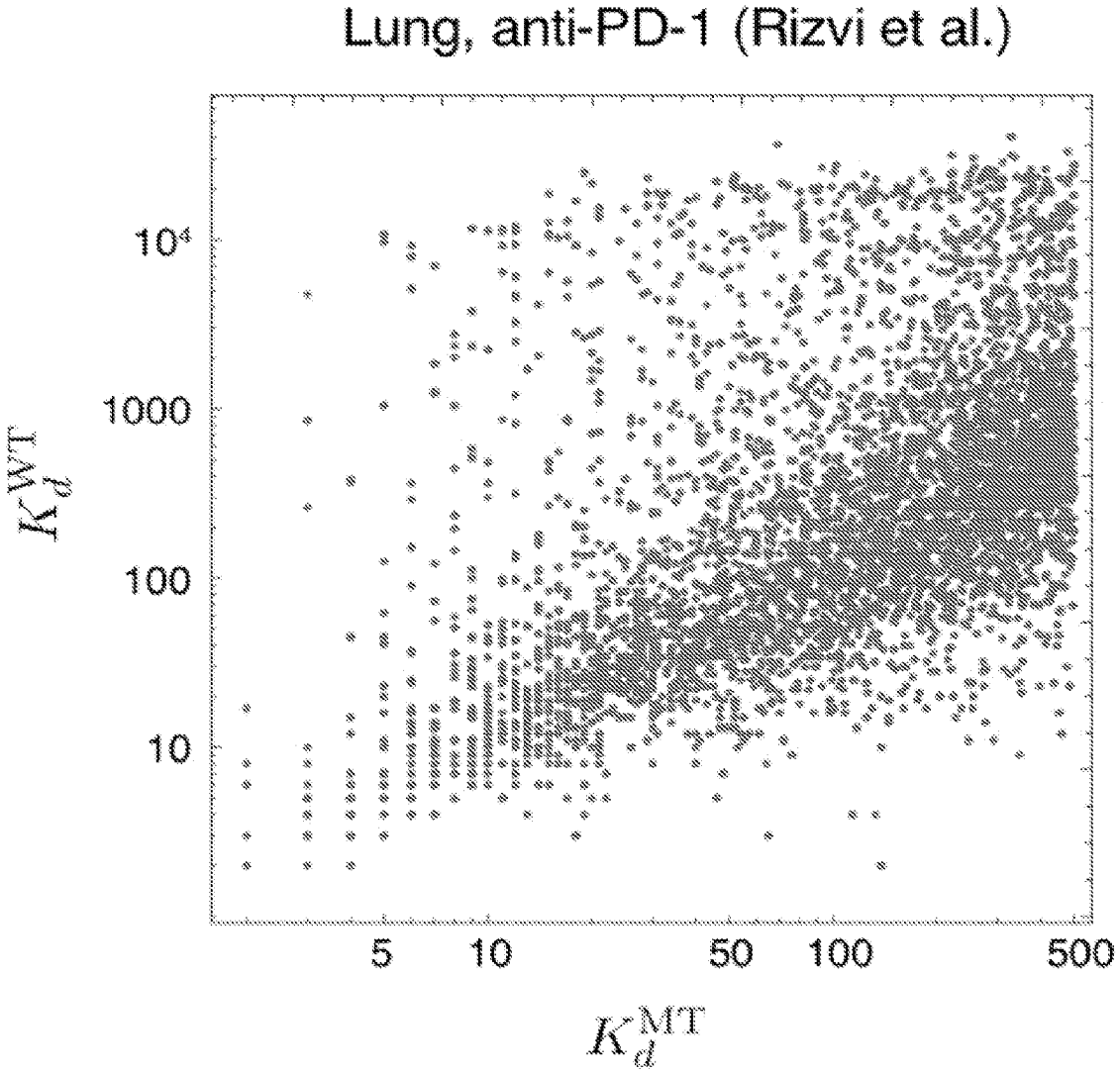

Lung, anti-PD-1 (Rizvi et al.)
10^4
1000
100
10
K_d^{WT}
5
10
50
100
500
K_d^{MT}

Fig. 28

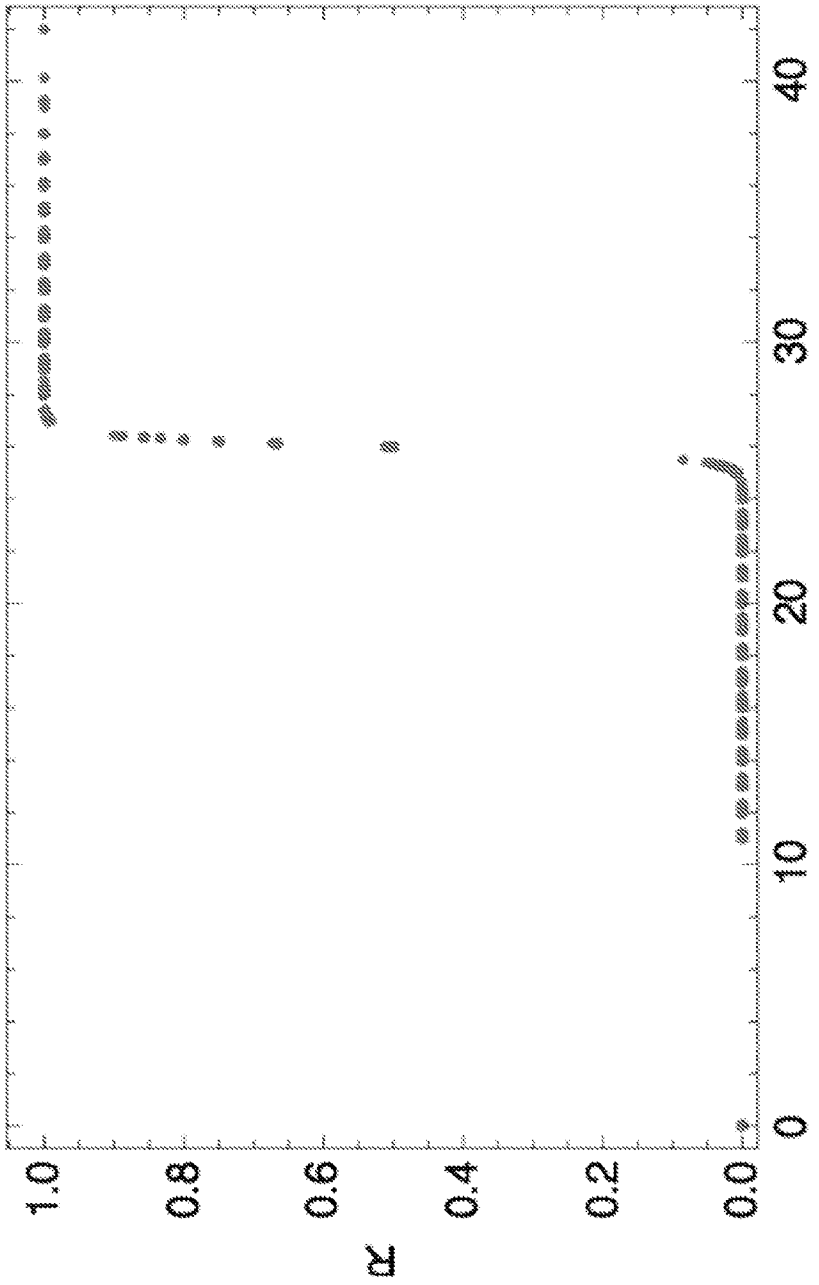


Fig. 29

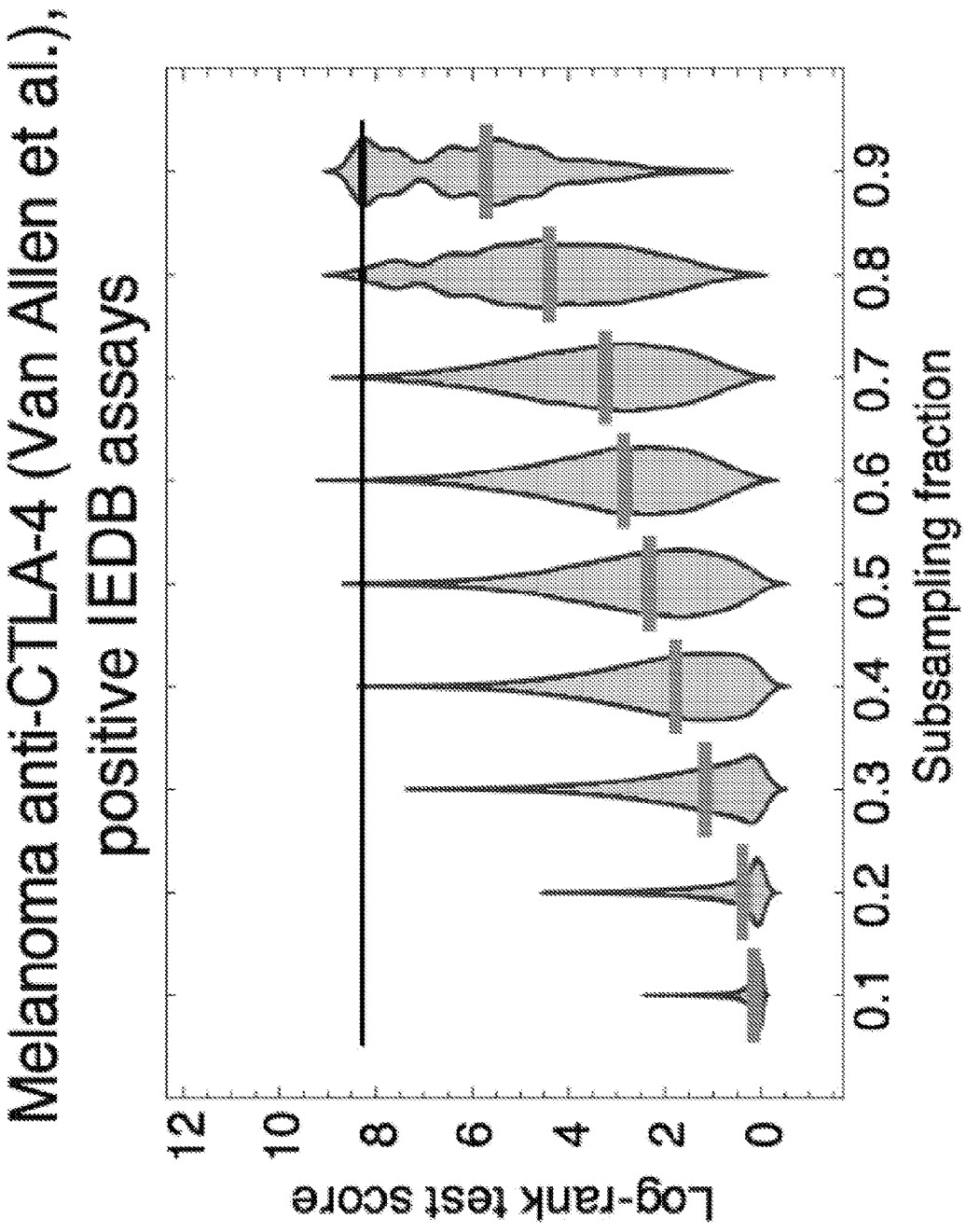

Melanoma anti-CTLA-4 (Van Allen et al.),
positive IEDB assays
Log-rank test score
0
2
4
6
8
10
12
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
Subsampling fraction

Fig. 30A

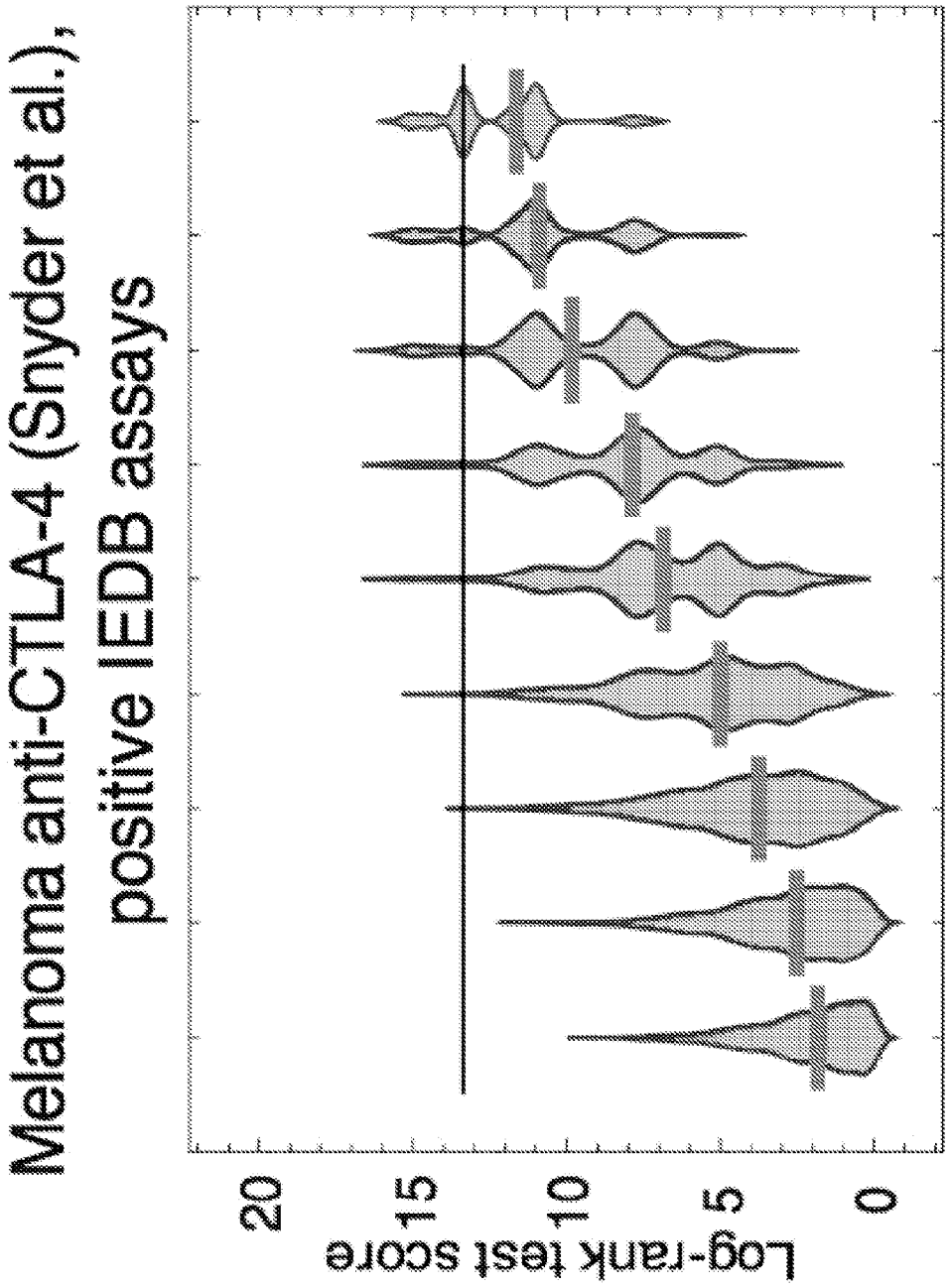

Melanoma anti-CTLA-4 (Snyder et al.),
positive IEDB assays
Log-rank test score
0
5
10
15
20
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
Subsampling fraction

Fig. 30B

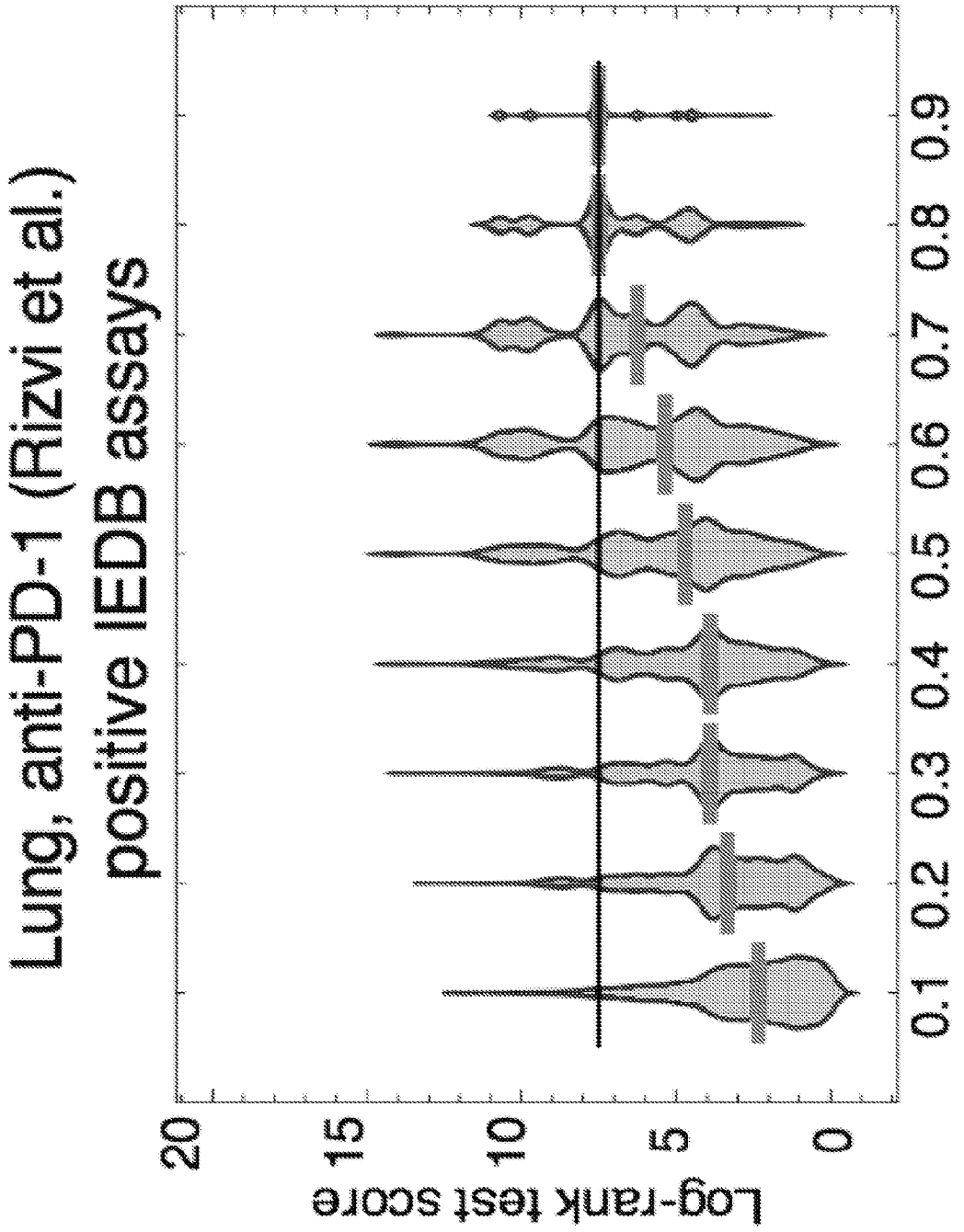

Lung, anti-PD-1 (Rizvi et al.)
positive IEDB assays
Log-rank test score
20
15
10
5
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
Subsampling fraction

Fig. 30C

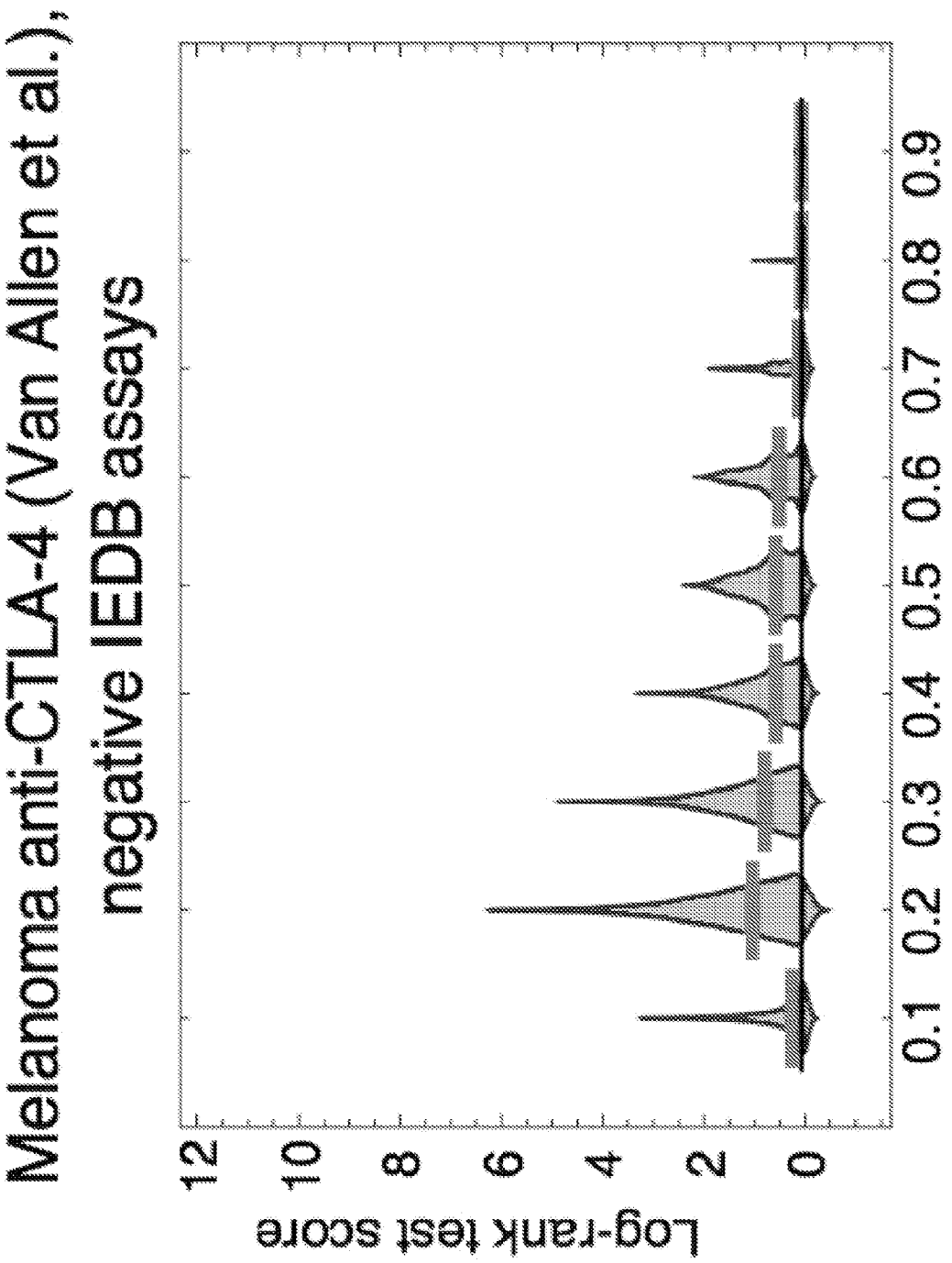

Melanoma anti-CTLA-4 (Van Allen et al.),
negative IEDB assays
Log-rank test score
0
2
4
6
8
10
12
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
Subsampling fraction

Fig. 30D

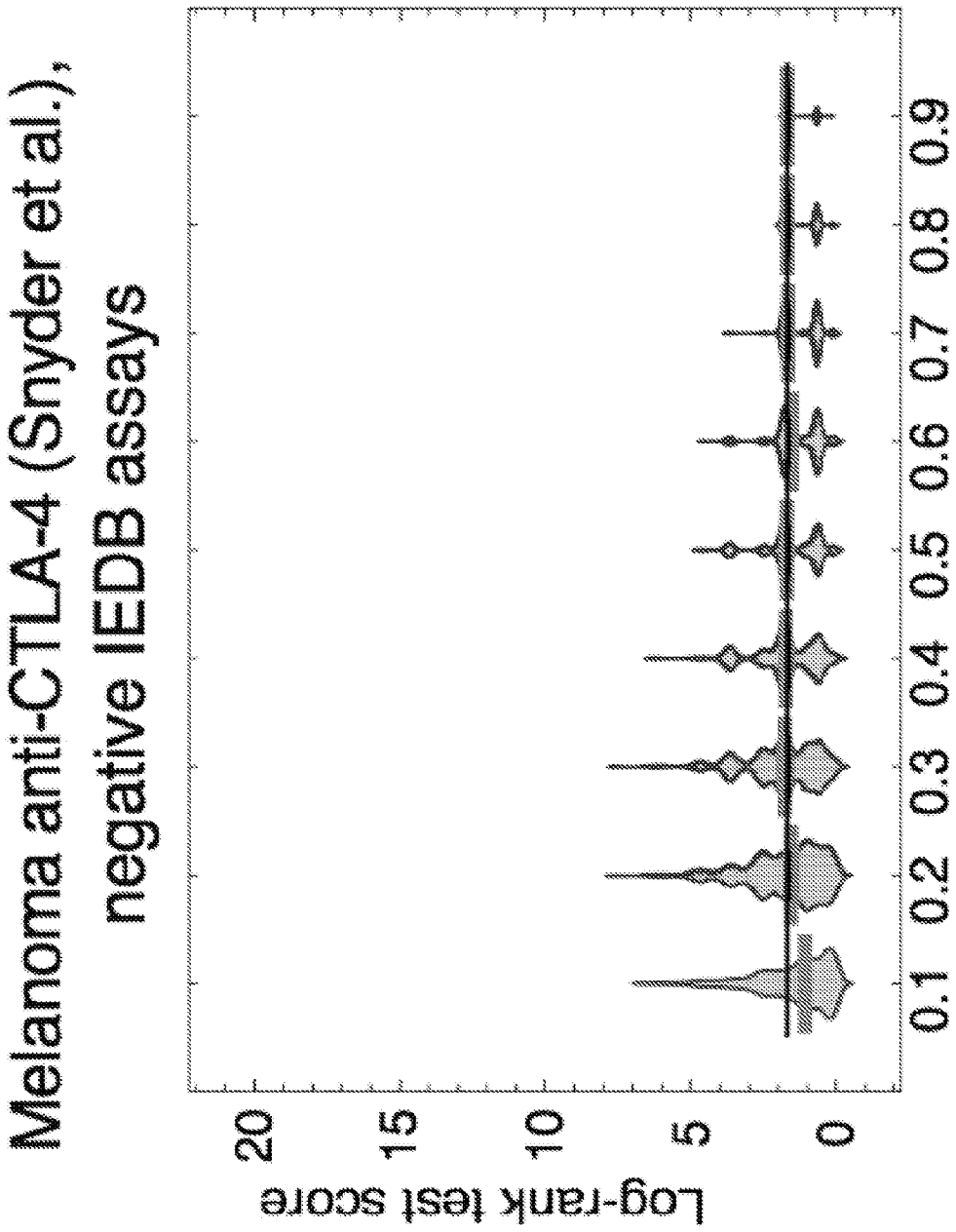

Melanoma anti-CTLA-4 (Snyder et al.), negative IEDB assays
Log-rank test score
0
5
10
15
20
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
Subsampling fraction

Fig. 30E

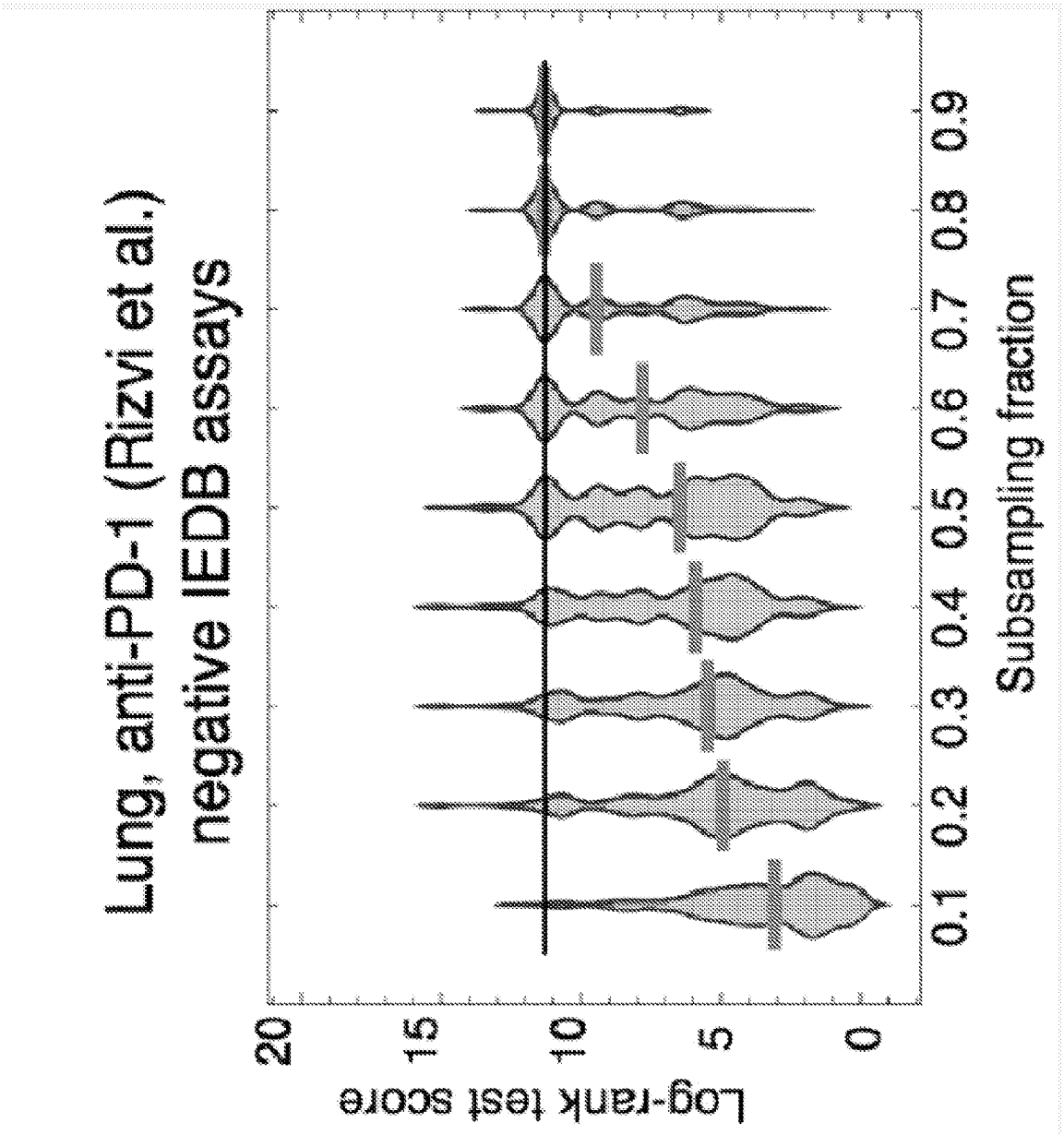

Lung, anti-PD-1 (Rizvi et al.)
negative IEDB assays
Log-rank test score
0
5
10
15
20
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
Subsampling fraction

Fig. 30F

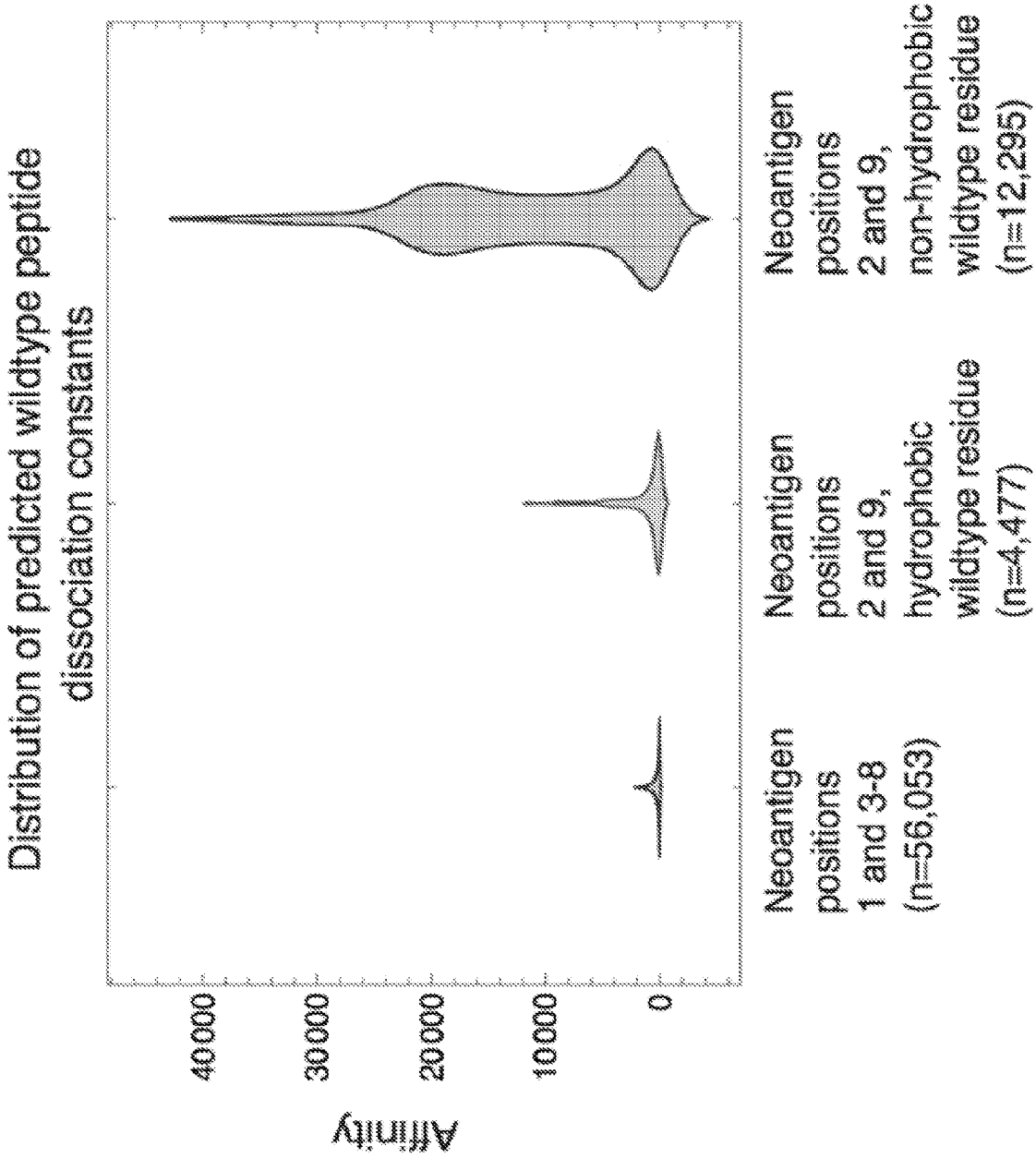

Distribution of predicted wildtype peptide dissociation constants
Affinity
40000
30000
20000
10000
0
Neoantigen positions 1 and 3-8 (n=56,053)
Neoantigen positions 2 and 9, hydrophobic wildtype residue (n=4,477)
Neoantigen positions 2 and 9, non-hydrophobic wildtype residue (n=12,295)

Fig. 31A

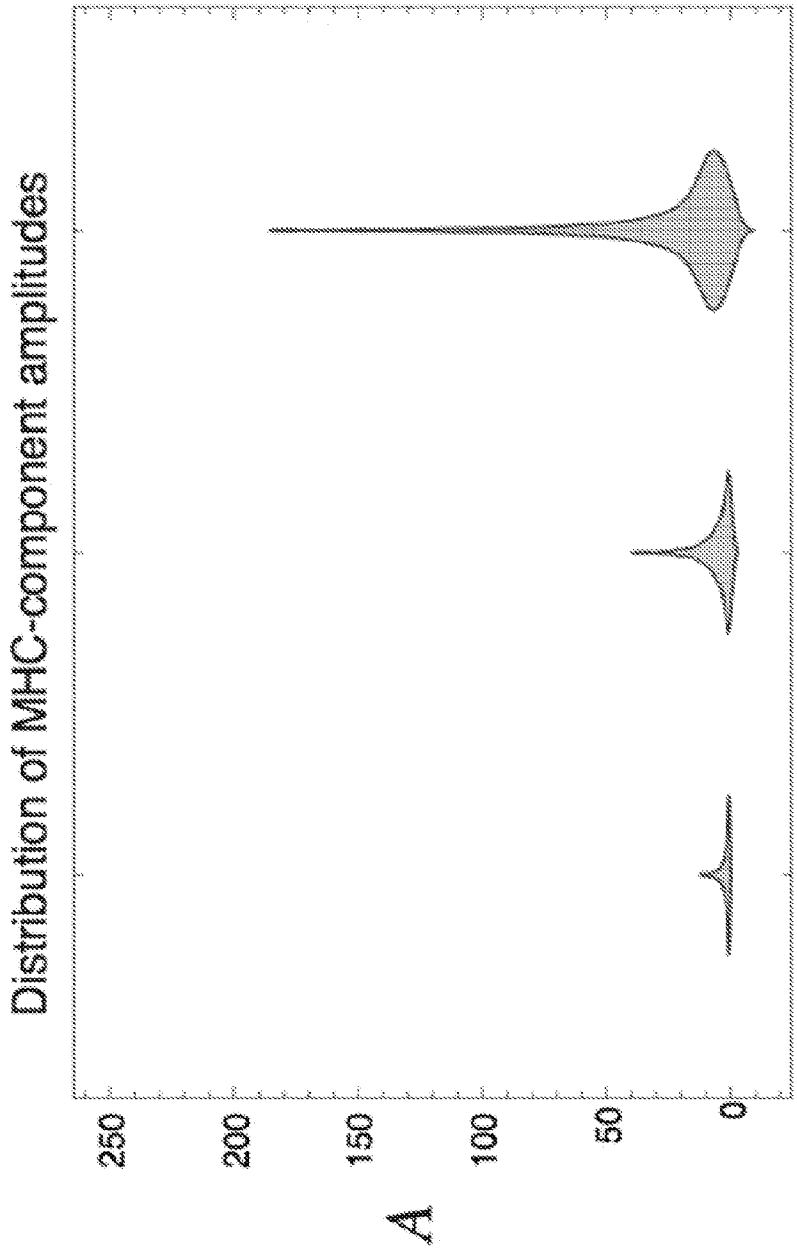

Distribution of MHC-component amplitudes
A
250
200
150
100
50
0
Neoantigen positions 1 and 3-8 (n=56,053)
Neoantigen positions 2 and 9, hydrophobic residue (n=4,477)
Neoantigen positions 2 and 9, non-hydrophobic residue (n=12,295)

Fig. 31B

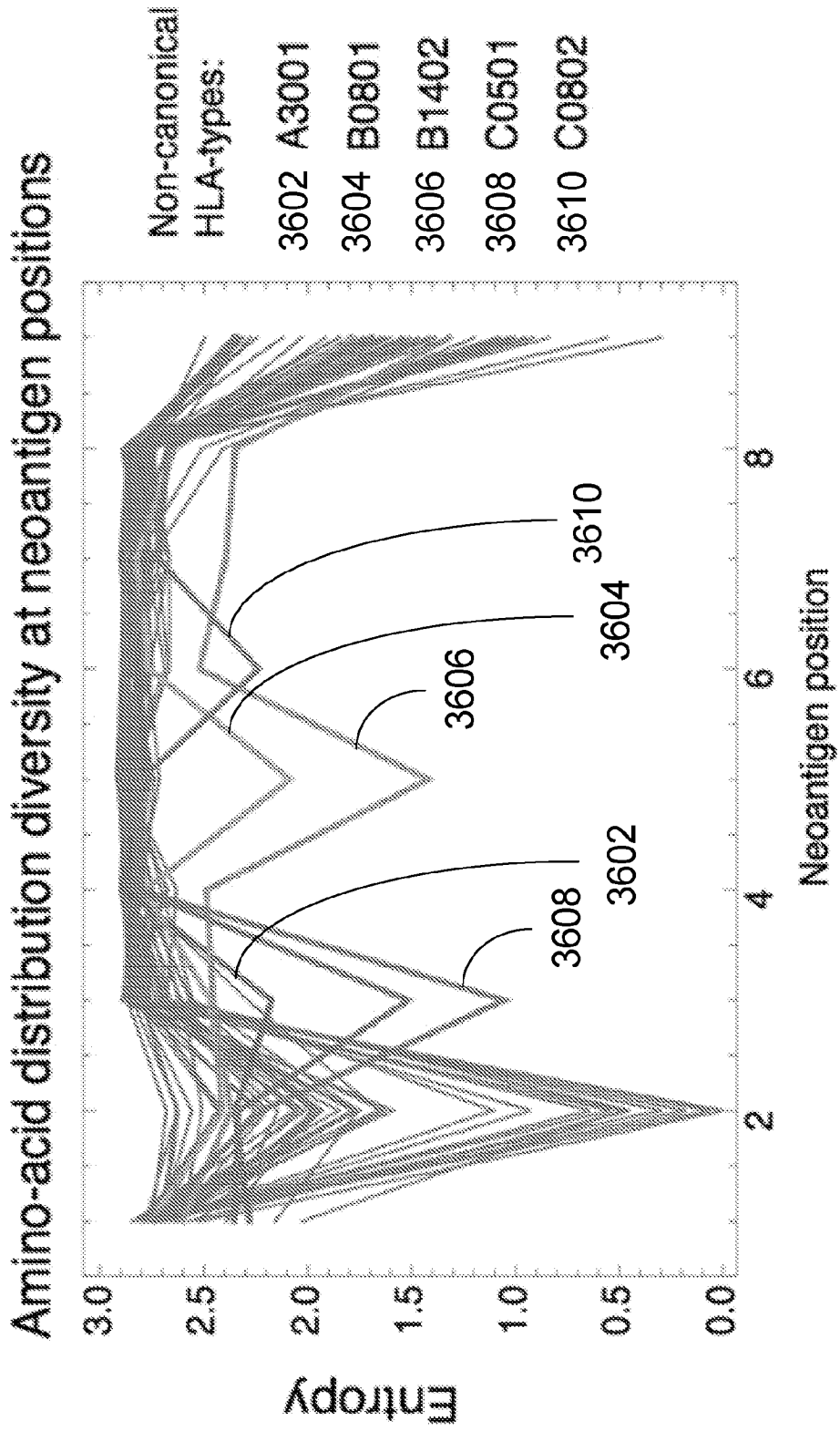

Amino-acid distribution diversity at neoantigen positions
Non-canonical HLA-types:
3602 A3001
3604 B0801
3606 B1402
3608 C0501
3610 C0802
Entropy
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2
4
6
8
Neoantigen position
3608
3602
3606
3604
3610

Fig. 31C

Van Allen et al., Melanoma anti-CTLA-4	Parameters trained on Snyder et al. dataset				Log-rank test			
Models	*a*		*k*		Score		Significance	Equation
	Mean	Std	Mean	Std	Mean	Std		
A x R	18.5	±0.152	0.59845	±0.001	0.61	±0.24		(2)
Partial models:								
A	-	-	-	-	0.05	±0.03		(12)
R	18.2	±2.995	4.54981	±0.001	0.2	±0.03		(13)
1/kdM x R	26.6	±1.609	1.34421	±0.001	1.41	±0.61		(14)
1/kdM	-	-	-	-	0.69	±0.23		(14)
kdW x R	23.7	±2.593	3.83397	±0.001	1.35	±0.34		(15)
kdW	-	-	-	-	0.46	±0.2		(15)
Alternative models:								
Neoantigen load	-	-	-	-	0.24	±0.12		(17)
A x R, sum over neoantigens	25.1	±3.308	4.89176	±0.001	1.57	±0.39		(16)
A x R, alignments at positions 3-8	21.9	±2.871	3.1276	±0.001	0.35	±0.36		(2)
A x R, negative IEDB assays	14.4	±2.58	2.20223	±0.001	0.04	±0.03		(2)
A x R, all neoantigens	29.2	±2.892	3.88642	±0.001	0.24	±0.19		(2)

Fig. 32A

Snyder et al., Melanoma anti-CTLA-4	Parameters trained on Van Allen et al. dataset				Log-rank test			
Models	*a*		*k*		Score		Significance	Equation
	Mean	Std	Mean	Std	Mean	Std		
A x R	26.4	±0.892	1.0851	±0.001	6.55	±0.9	0.01047 *	(2)
Partial models:								
A	-	-	-	-	4.44	±0.68	0.03507 *	(12)
R	29.7	±4.829	2.51962	±0.001	1.26	±0.34		(13)
1/kdM x R	26	±1.929	0.82074	±0.001	3.65	±0.81		(14)
1/kdM	-	-	-	-	3.44	±0.61		(14)
kdW x R	26.9	±2.735	3.73387	±0.001	1.67	±0.22		(15)
kdW	-	-	-	-	3.11	±0.75		(15)
Alternative models:								
Neoantigen load	-	-	-	-	0.42	±0.21		(17)
A x R, sum over neoantigens	27	±3.005	5.08369	±0.001	1.63	±0.53		(16)
A x R, alignments at positions 3-8	30	±4.023	1.35553	±0.001	2.73	±0.65		(2)
A x R, negative IEDB assays	36	±9.57	10.1531	±0.001	0.23	±0.65		(2)
A x R, all neoantigens	26	±1.95	5.22216	±0.001	0.59	±0.92		(2)

Fig. 32B

Rizvi et al., Lung anti-PD-1	Parameters trained on Van Allen et al. and Snyder et al. datasets				Log-rank test			
Models	*a*		*k*		Score		Significance	Equation
	Mean	Std	Mean	Std	Mean	Std		
A x R	27	±0.787	1.00032	±0.001	6.48	±1.14	0.01047 *	(2)
Partial models:								
A	-	-	-	-	4.65	±1.17	0.03507 *	(12)
R	19.6	±3.355	4.29127	±0.001	1.53	±0.29		(13)
1/kdM x R	21	±2.027	0.53498	±0.001	0.02	±0.07		(14)
1/kdM	-	-	-	-	0.17	±0.13		(14)
kdW x R	23	±2.737	5.37707	±0.001	10.48	±1.71	0.00121 ***	(15)
kdW	-	-	-	-	4.49	±0.75	0.03416 *	(15)
Alternative models:								
Neoantigen load	-	-	-	-	4.93	±1.15	0.023639 *	(17)
A x R, sum over neoantigens	25	±4.316	4.03113	±0.001	3.09	±1.09		(16)
A x R, alignments at positions 3-8	22	±3.042	5.2228	±0.001	2.3	±0.82		(2)
A x R, negative IEDB assays	14.5	±2.806	1.90577	±0.001	1	±0.45		(2)
A x R, all neoantigens	29	±4.469	1.87092	±0.001	0.75	±0.62		(2)

Fig. 32C

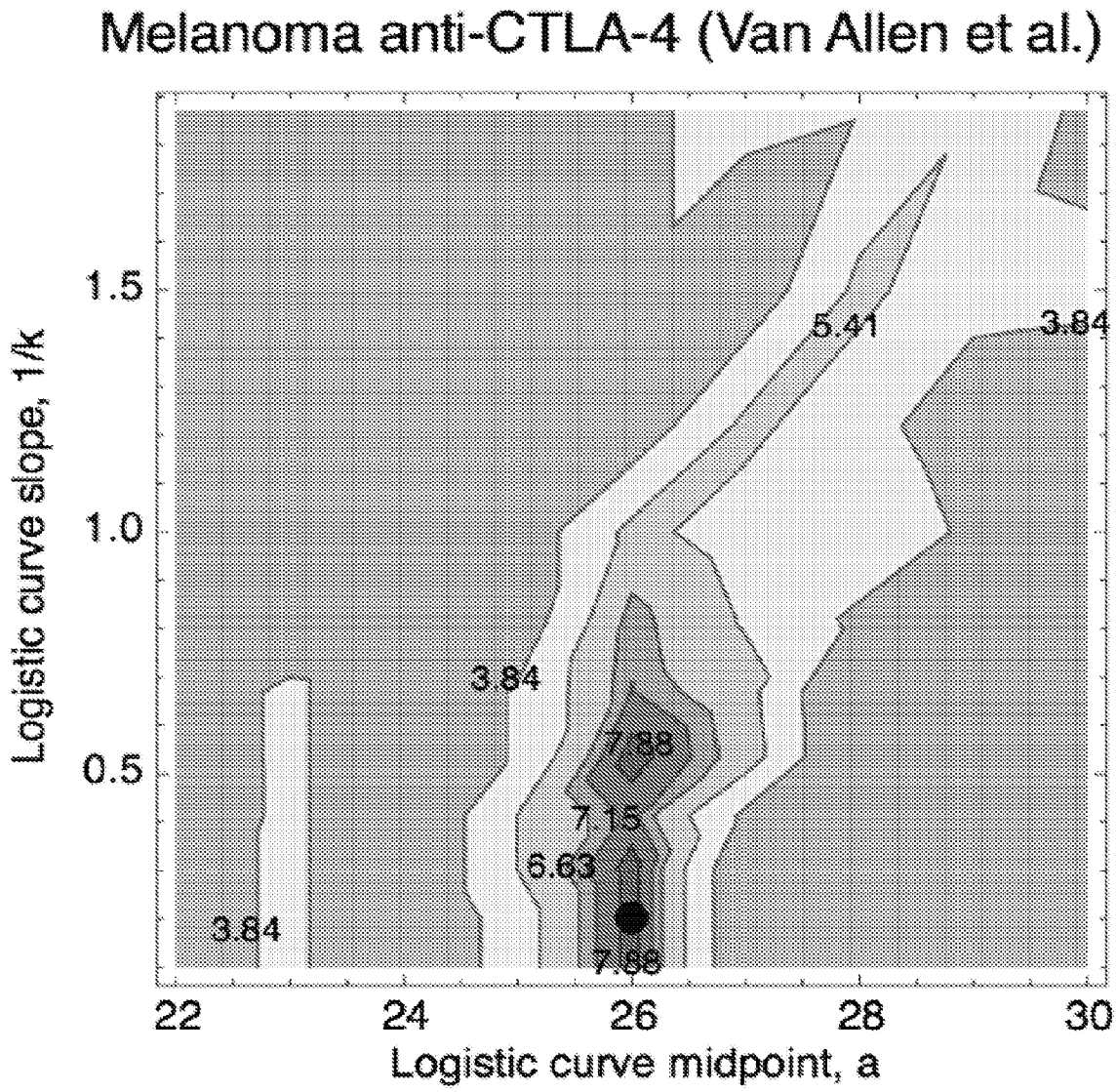

Melanoma anti-CTLA-4 (Van Allen et al.)
Logistic curve slope, 1/k
1.5
1.0
0.5
22
24
26
28
30
Logistic curve midpoint, a
5.41
3.84
3.84
7.88
7.15
6.63
3.84
7.68

Fig. 33A

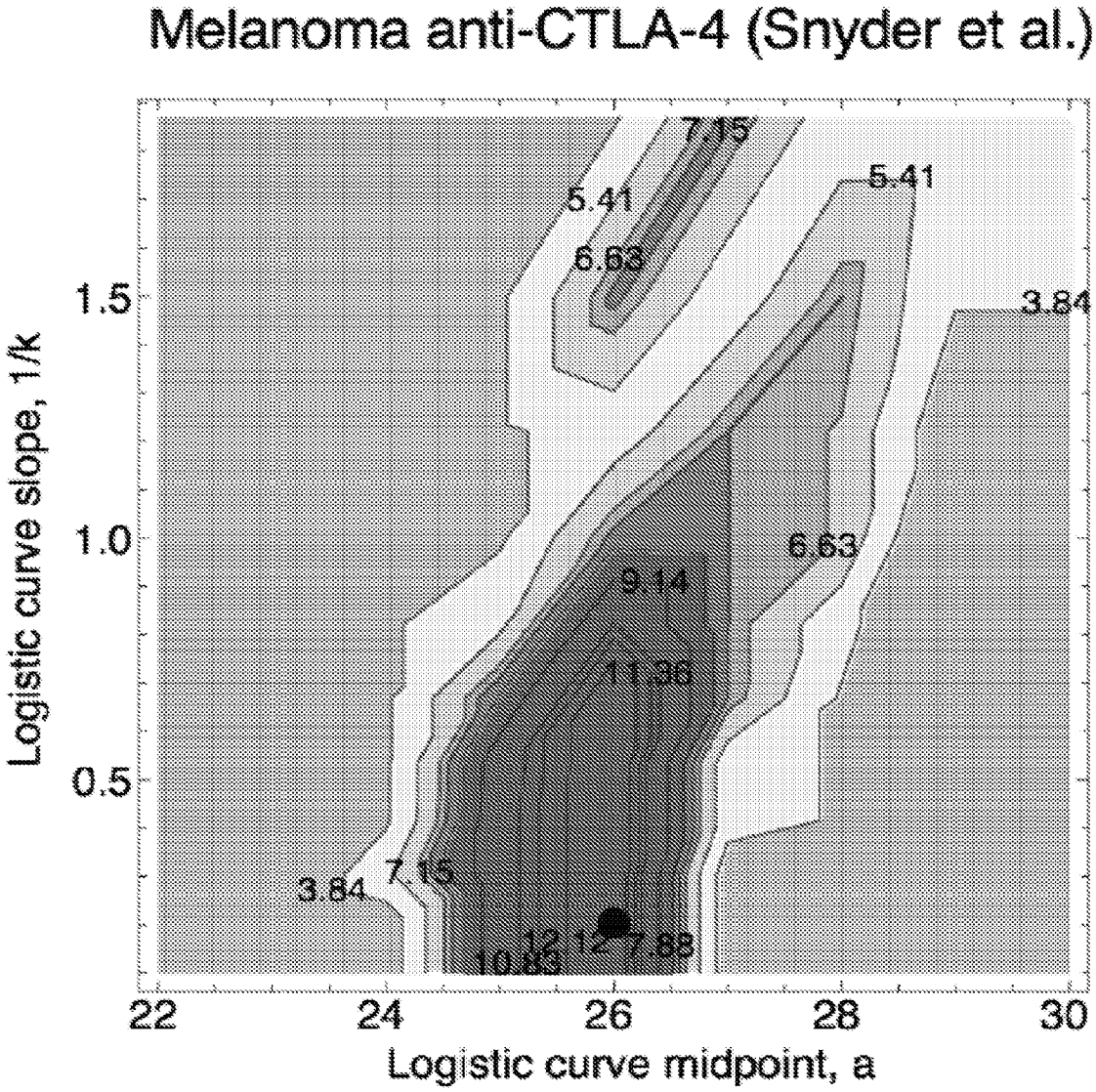

Melanoma anti-CTLA-4 (Snyder et al.)
7.15
5.41
5.41
6.63
3.84
6.63
9.14
11.36
3.84
7.15
12.12
7.88
10.83
1.5
1.0
0.5
Logistic curve slope, 1/k
22
24
26
28
30
Logistic curve midpoint, a

Fig. 33B

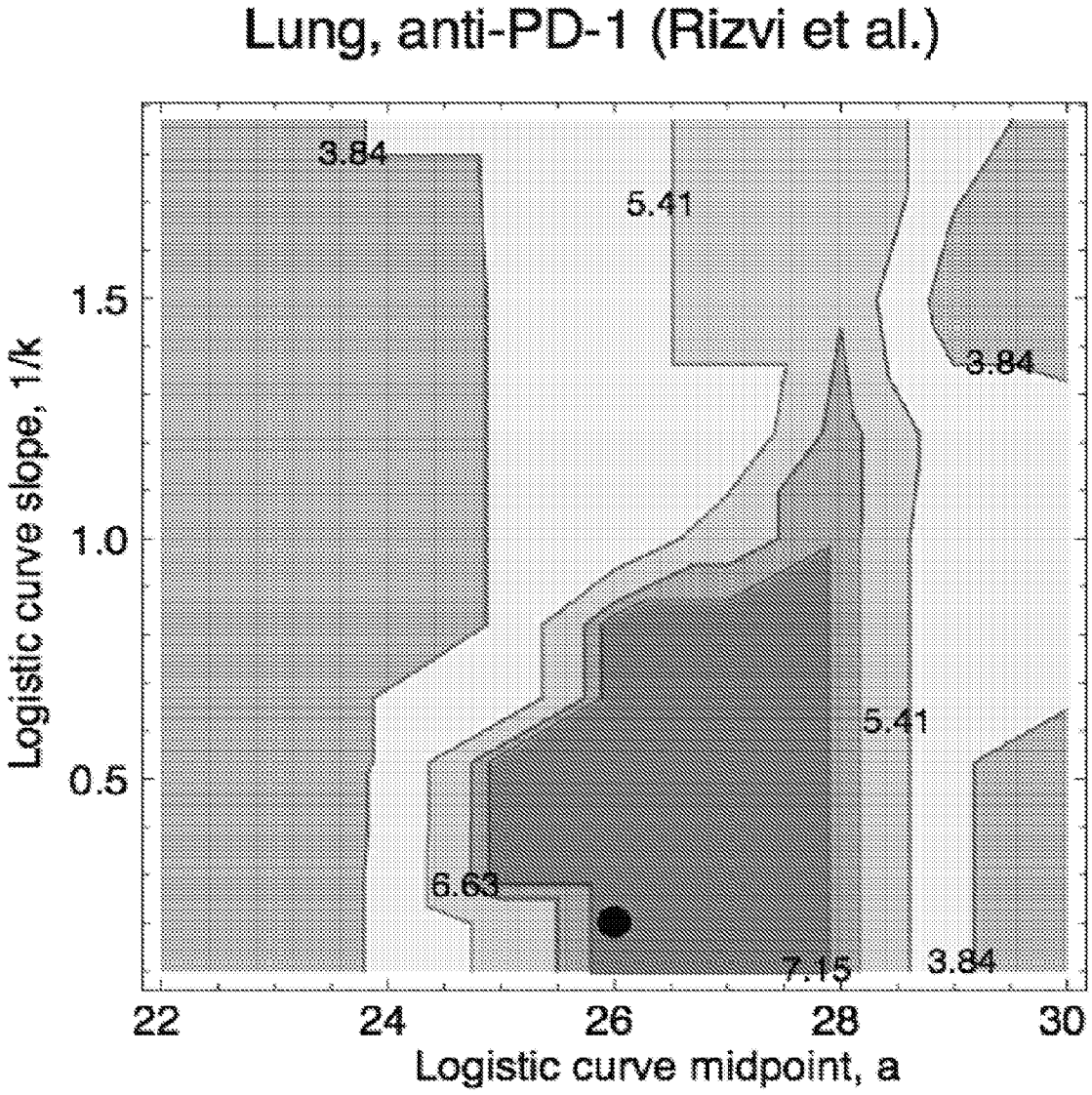

Lung, anti-PD-1 (Rizvi et al.)
3.84
5.41
3.84
5.41
6.63
7.15
3.84
1.5
1.0
0.5
Logistic curve slope, 1/k
22
24
26
28
30
Logistic curve midpoint, a

Fig. 33C

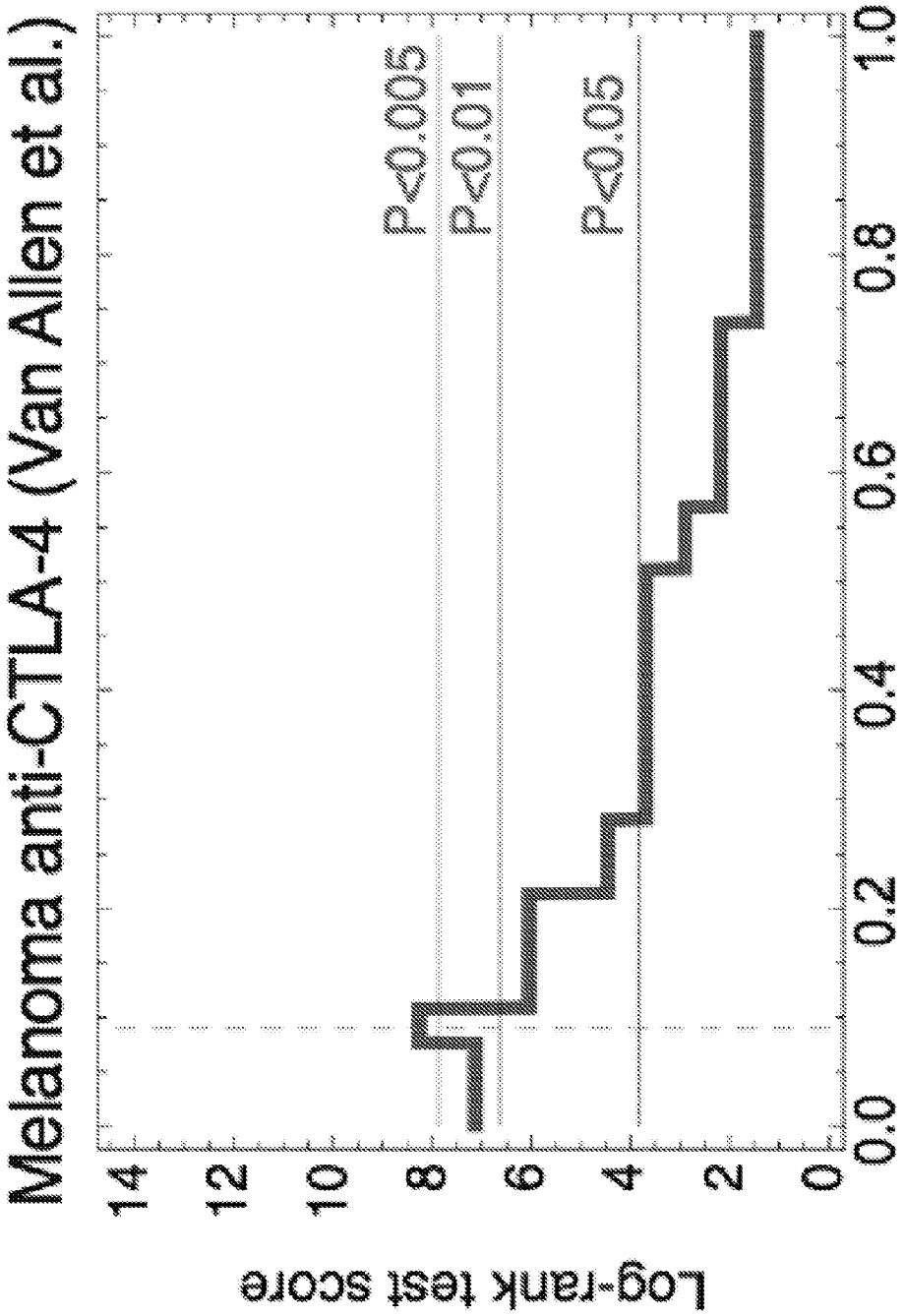

Melanoma anti-CTLA-4 (Van Allen et al.)
P<0.005
P<0.01
P<0.05
Log-rank test score
τ
0
2
4
6
8
10
12
14
0.0
0.2
0.4
0.6
0.8
1.0

Fig. 33D

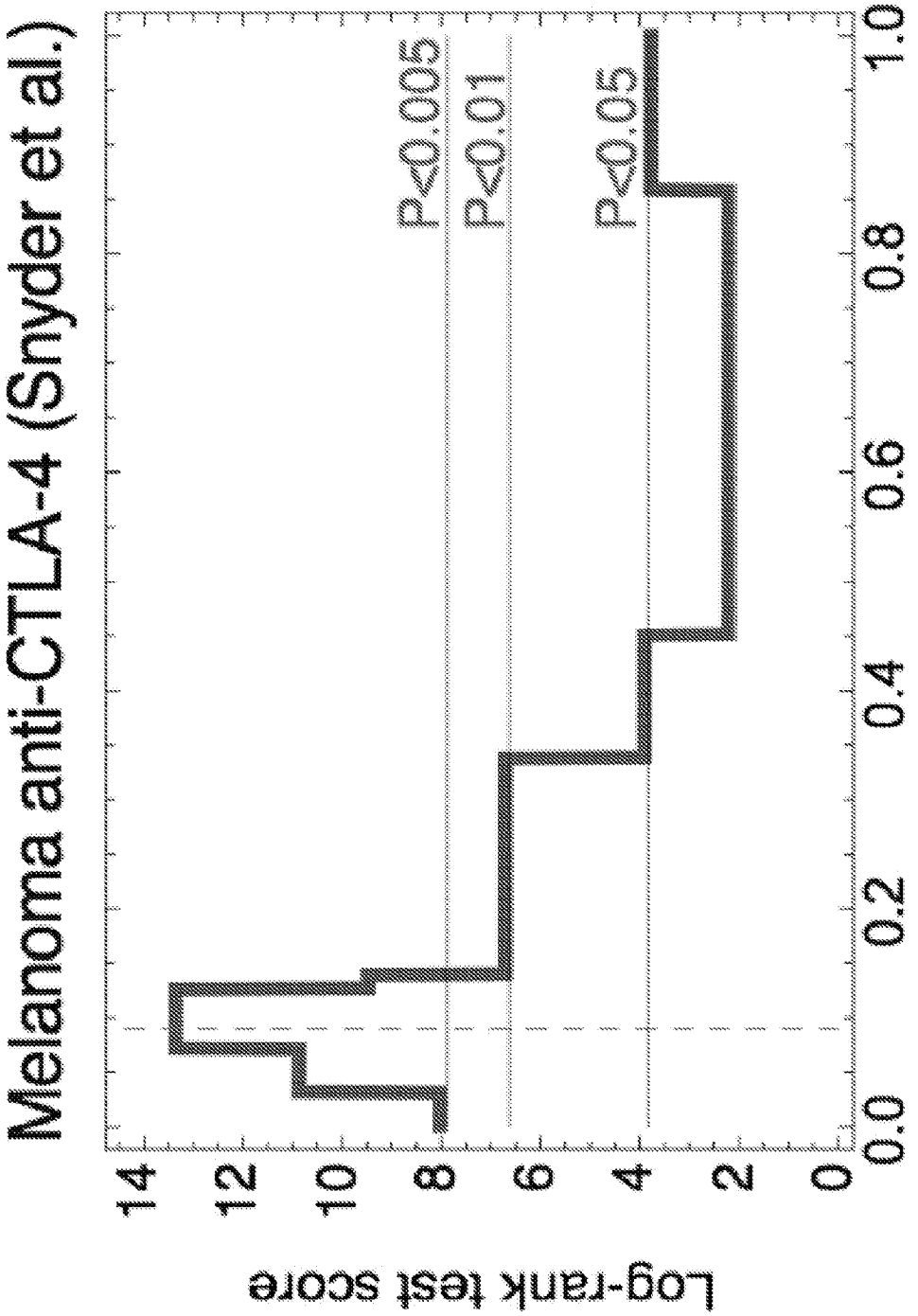

Melanoma anti-CTLA-4 (Snyder et al.)
P≤0.005
P≤0.01
P≤0.05
Log-rank test score
τ
0
2
4
6
8
10
12
14
0.0
0.2
0.4
0.6
0.8
1.0

Fig. 33E

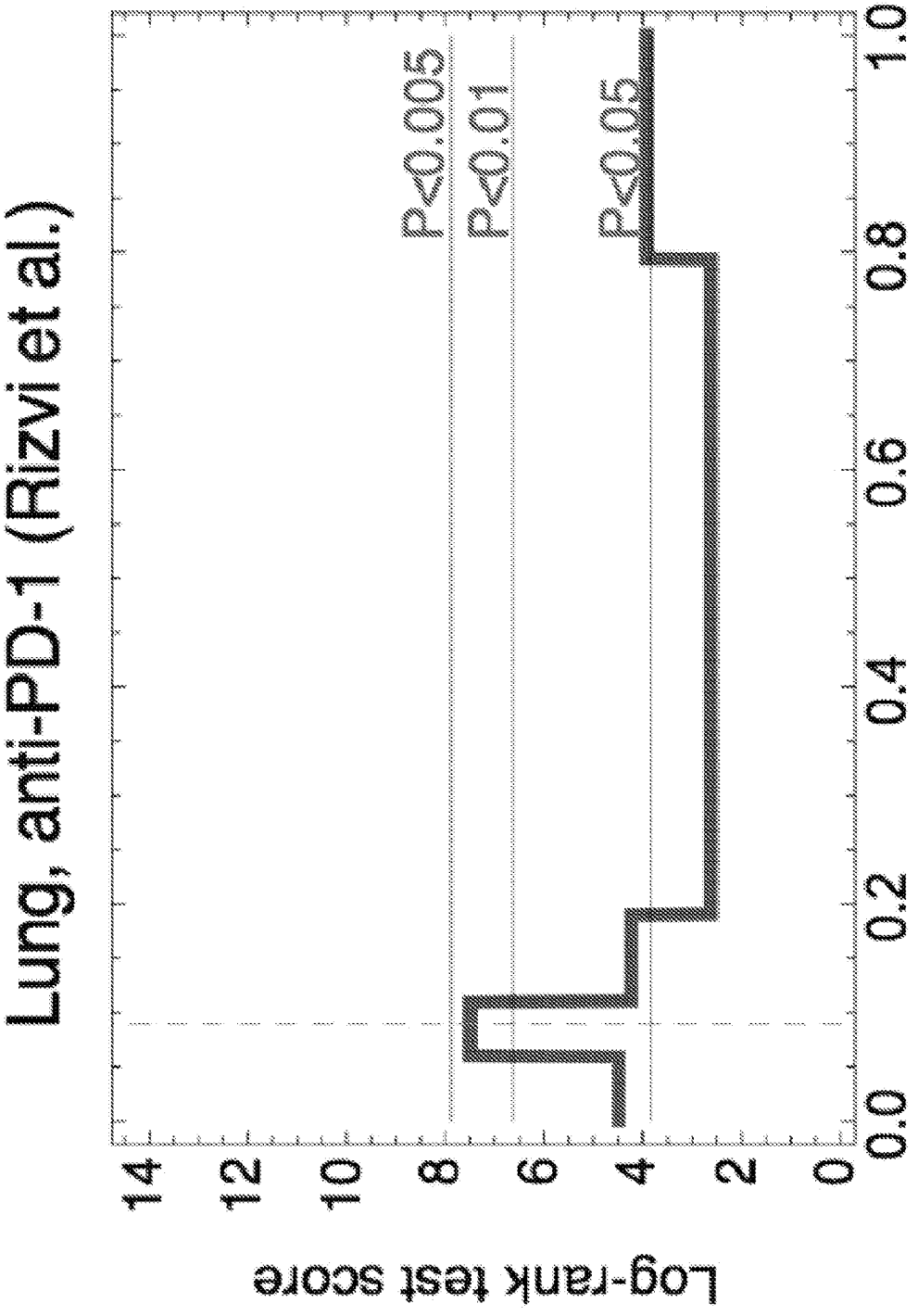

Lung, anti-PD-1 (Rizvi et al.)
Log-rank test score
τ
P<0.005
P<0.01
P<0.05
0
2
4
6
8
10
12
14
0.0
0.2
0.4
0.6
0.8
1.0

Fig. 33F

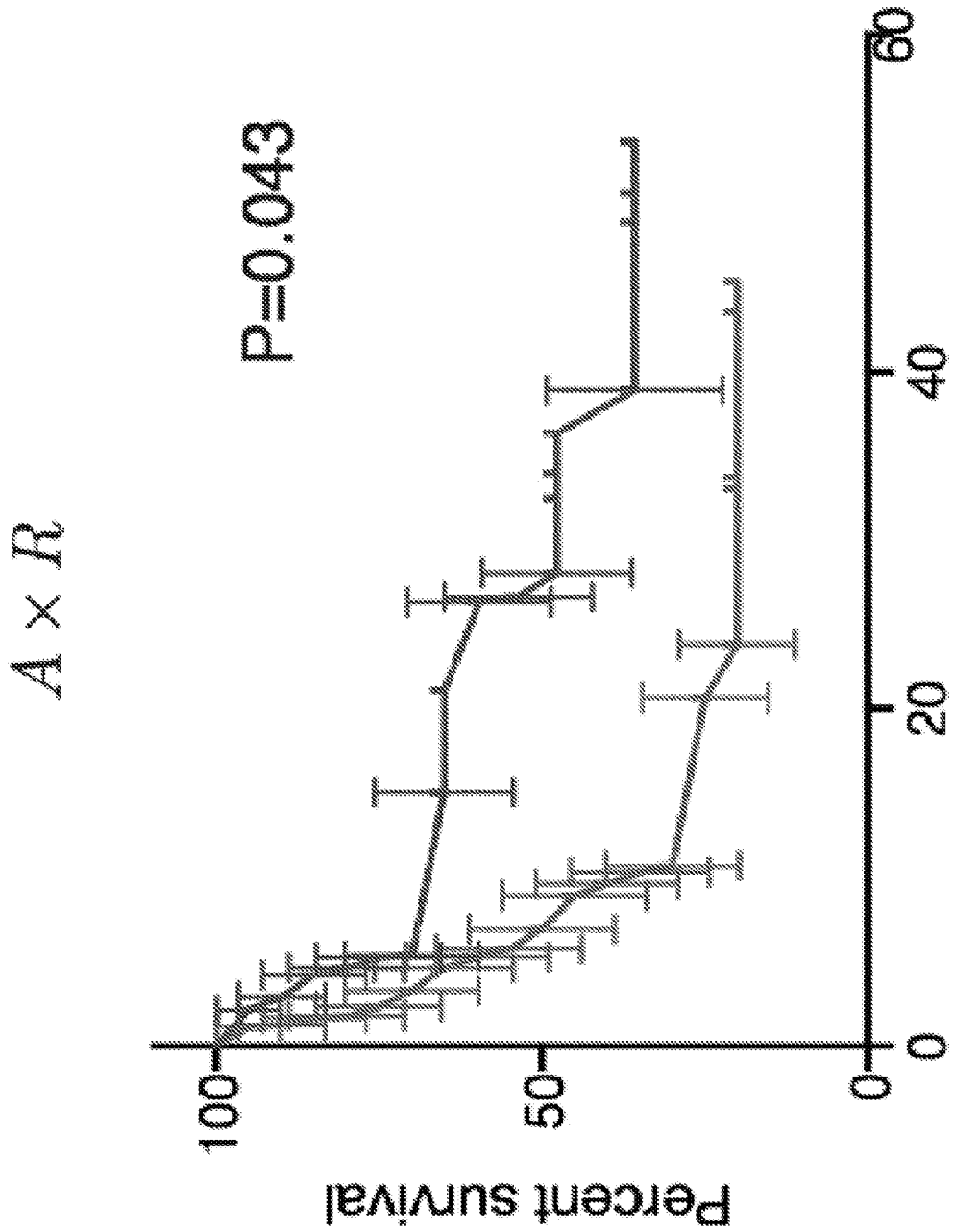


Fig. 34A

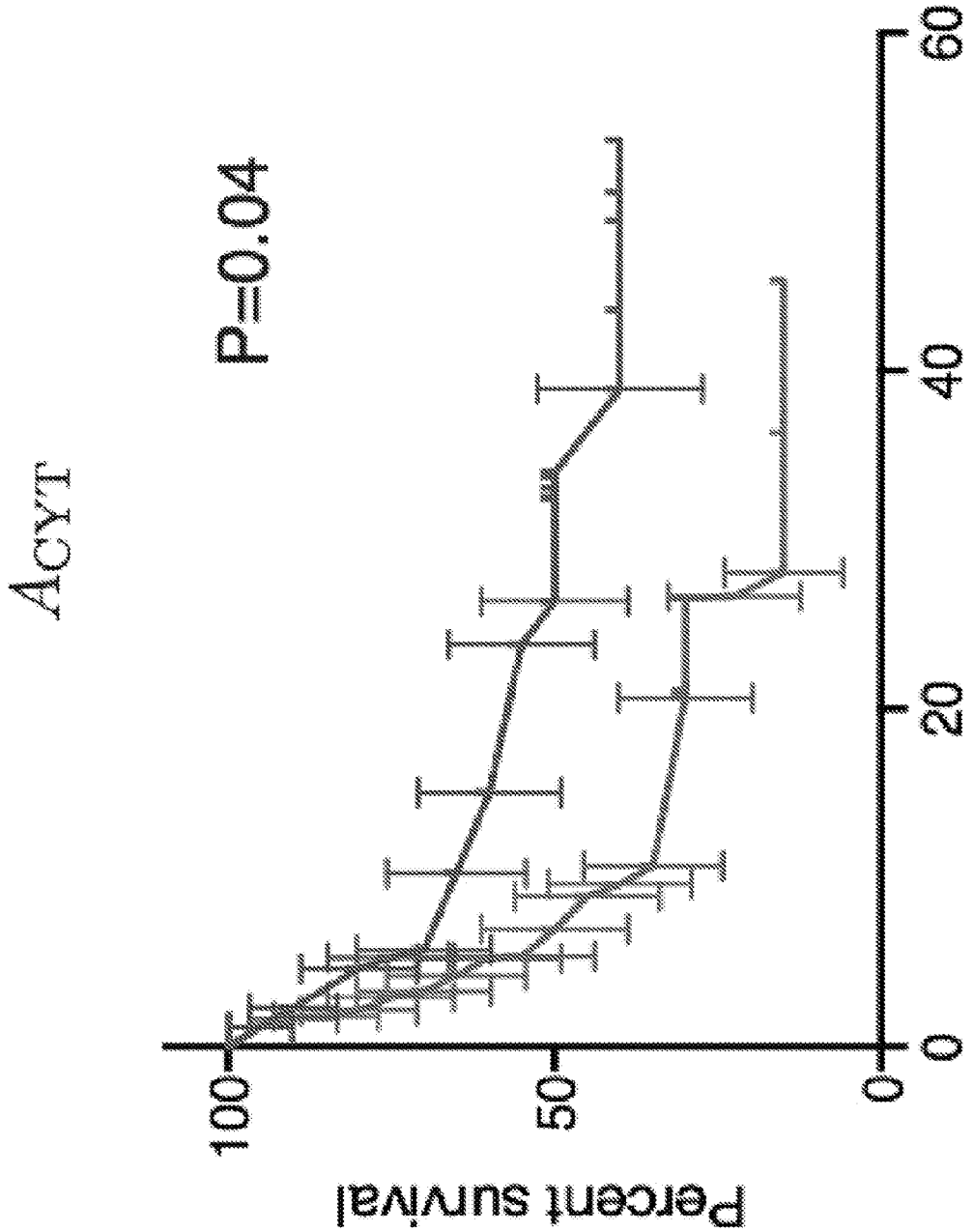


Fig. 34B

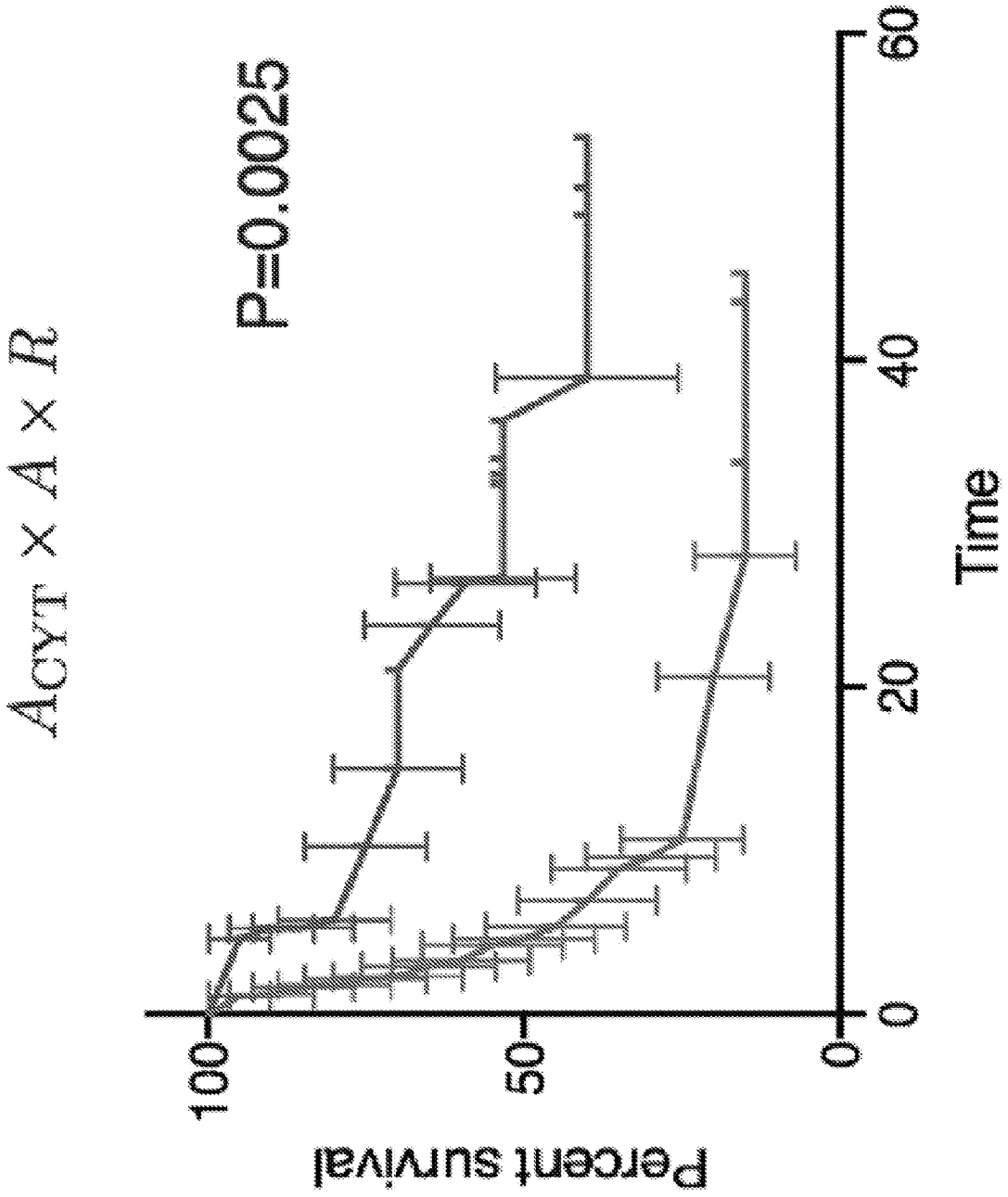

$A_{CYT} \times A \times R$
P=0.0025
Percent survival
100
50
0
0
20
40
60
Time

Fig. 34C

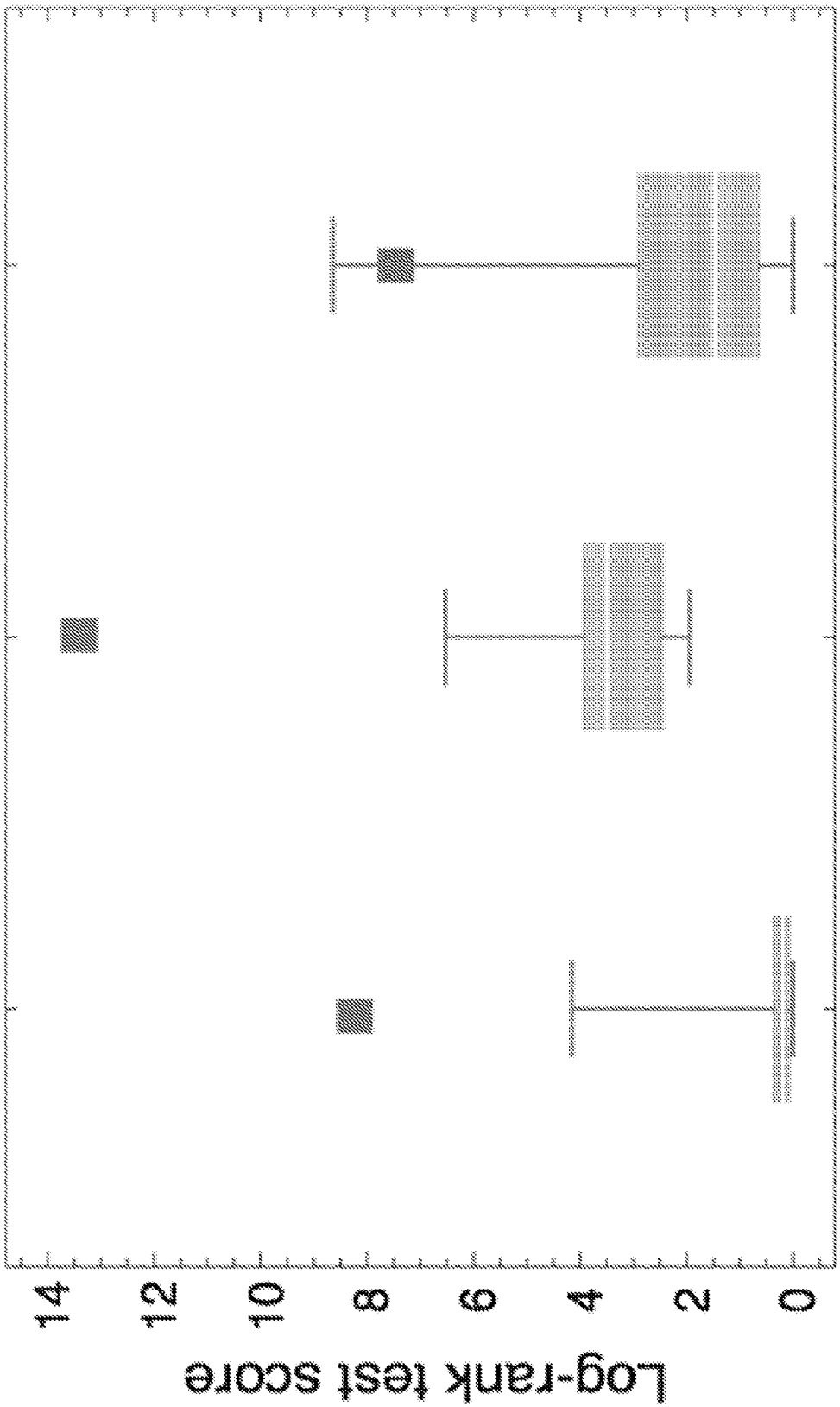

Log-rank test score
14
12
10
8
6
4
2
0
Van Allen et al.
Snyder et al.
Rizvi et al.

Fig. 35

Variable	Snyder HR	Snyder 95% CI	Snyder p-value	Van Allen HR	Van Allen 95% CI	Van Allen p-value
n(τ) > Median	3.88	1.72 -- 8.75	0.001	1.99	1.25 -- 3.15	0.004
Stage M1b	1.36	0.3 -- 6.15	0.69	0.8	0.27 -- 2.40	0.703
Stage M1c	2.41	0.69 -- 8.40	0.168	1.52	0.60 -- 3.88	0.372
Age	1	0.98 -- 1.03	0.802	1	0.99 -- 1.02	0.43
Gender (Male)	0.82	0.40 -- 1.69	0.59	0.72	0.43 -- 1.21	0.218

Variable	Rizvi HR	Rizvi 95% CI	Rizvi p-value
n(τ) > Median	4.85	1.34 -- 17.45	0.016
Age	1	0.95 -- 1.05	0.962
Gender (Male)	1.61	0.61 -- 4.25	0.339
Pack-Years Smoked	1	0.98 -- 1.03	0.534

Fig. 36

```
#################################################################################################
# Compute neoantigen fitness cost (recognition potential)
#
# Directory structure:
#
# InputData:
# 1. neoantigen-data files for 3 cohorts (Van Allen et al., Snyder et al. and Rizvi et al.)
# 2. iedb.fasta: fasta file with IEDB epitope sequences
# 3. neoantigen alignment folders with precomputed blastp alignments for all neoantigens, split into files for each sample.
# eg. run as
# blastp -query <InputData/neoantigen_alignments_Rizvi/neoantigens_AL4602.fasta> -db
#     InputData/iedb.fasta -outfmt 5 -evalue 100000000 -gapopen 11 -gapextend 1 >
#       <InputData/neoantigen_alignments_Rizvi/neoantigens_AL4602.xml>
#
# src:
# source code folder
#
# Output:
# source code output folder: neoantigens with computed fitness cost
#################################################################################################
#
# fitness model parameters
a=26.
k=4.86936
python src/main.py InputData/neoantigens_VanAllen.txt InputData/neoantigen_alignments_VanAllen $a $k Output/neoantigen_fitness_VanAllen.txt
python src/main.py InputData/neoantigens_Snyder.txt InputData/neoantigen_alignments_Snyder $a $k Output/neoantigen_fitness_Snyder.txt
python src/main.py InputData/neoantigens_Rizvi.txt InputData/neoantigen_alignments_Rizvi $a $k Output/neoantigen_fitness_Rizvi.txt
```

Fig. 37

```
'''
@author: Karta Lukza, wlukszal@as.edu
'''
from Bio.Blast import NCBIXML
from Bio import pairwise2
from Bio.SubsMat import MatrixInfo as matlist
from math import log, exp

class Aligner(object):
    '''
    Class to compute alignment score of neoantigens with IEDB epitopes and compute TCR-recognition
    probabilities.
    '''
    INF = float("inf")

    @staticmethod
    def align(seq1,seq2):
        '''
        Smith-Waterman alignment with default parameters.
        '''
        matrix = matlist.blosum62
        gap_open = -11
        gap_extend = -1
        aln = pairwise2.align.localds(seq1.upper(), seq2.upper(), matrix,gap_open,gap_extend)
        return aln

    @staticmethod
    def logSum(v):
        '''
        compute the logarithm of a sum of exponentials
        '''
        if len(v)==0:
            return -Aligner.INF
        ma = max(v)
        if ma==-Aligner.INF:
            return -Aligner.INF
        return log(sum(map(lambda x: exp(x-ma),v)))+ma

    def __init__(self):
```

Fig. 38A

```
        #dictionary of computed RI-values mapped to neoantigen identifiers
        self.RI={}
        #dictionary of IEDB epitope alignments mapped to neoantigen identifiers
        self.alignments={}
        #dictionary of the highest scoring alignments mapped to neoantigen identifiers
        self.maximum_alignment={}

    def readAllBlastAlignments(self,xmlpath):
        '''
        Read precomputed blastp alignments from xml files,
        compute alignment scores,
        find the highest scoring alignment for each neoantigen.
        '''
        f = open(xmlpath)
        blast_records = NCBIXML.parse(f)
        maxscore={}
        try:
            for brecord in blast_records:
                tab=str(brecord.query).split("|")
                ptype=tab[1]
                nid=int(tab[2])
                if ptype=="MUT":
                    if not nid in maxscore:
                        maxscore[nid]=0
                    for alignment in brecord.alignments:
                        if not nid in self.alignments:
                            self.alignments[nid]={}
                            self.maximum_alignment[nid]=None
                            self.maximum_alignment[nid]=0
                            maxscore[nid]=0
                        species=" ".join((str(alignment).split())[1:-3])
                        for hsp in alignment.hsps:
                            if not "_" in hsp.query and not "_" in hsp.sbjct:
                                al=Aligner.align(hsp.query, hsp.sbjct)
                                if len(al)>0:
                                    al=al[0]
                                    self.alignments[nid][species]=al
                                    if al[2]>maxscore[nid]:
                                        self.maximum_alignment[nid]=species
                                        maxscore[nid]=al[2]
```

Fig. 38B

```
            except ValueError:
                print "error"
                pass
            f.close()

        def computeR(self,a=26,k=4.86936):
            '''
            Compute TCR-recognition probabilities for each neoantigen.
            '''
            #iterate over all neoantigens
            for i in self.alignments:
                #energies of all bound states of neoantigen i
                bindingEnergies=map(lambda el: -k*(a-el[2]), self.alignments[i].values())
                #partition function, over all bound states and an unbound state
                lZ=Aligner.logSum(bindingEnergies+[0])
                lGb=Aligner.logSum(bindingEnergies)
                R=exp(lGb-lZ)
                self.Ri[i]=R

        def getR(self,i):
            '''
            Return precomputed R value for a given neoantigen i.
            '''
            if i in self.Ri:
                return self.Ri[i]
            return 0.
```

Fig. 38C

```
'''
@author: Marta Luksza, mluksza@ias.edu
'''

import sys
from Aligner import Aligner

from Neoantigen import Neoantigen

def readNeoantigens(neofilename):
    neoantigens={}
    f=open(neofilename)
    header=f.readline()
    htab=header.strip().split("\t")
    hdict={}
    for i in range(0,len(htab)):
        hdict[htab[i]]=i

    line=f.readline()
    while line:
        line=line.strip()
        nparams=line.split("\t")
        if nparams[7]=="NA":
            line=f.readline()
            continue
        neoantigen=Neoantigen(nparams)
        neoantigens[neoantigen.id]=neoantigen
        neoantigen.setA()
        line=f.readline()
    f.close()
    samples=set(map(lambda neo: neo.getSampleName(),neoantigens.values()))
    return [neoantigens,samples]

def main(argv):

    '''
    command line parameters:
    neofile - text file with neoantigen data (supplementary data)
    alignmentDirectory - folder with precomputed alignments
    a - midpoint parameter of the logistic function, alignment score threshold
    k - slope parameter of the logistic function
    outfile - path to a file where to output neoantigen fitness computation
    '''
```

Fig. 39A

```
neofile=argv[1]
alignmentDirectory=argv[2]
wtPeptide=argv[3]
wtPeptide=argv[4]
outfile=sys.argv[5]

[neoantigens,samples]=readNeoantigenFile(neofile)
#Compute TCR-recognition probabilities for all neoantigens
aligner=Aligner()
for sample in samples:
    xmlpath=alignmentDirectory+"/neoantigens_"+sample+"_ledb.xml"
    aligner.readAllBlastAlignments(xmlpath)
aligner.computeR(a, b)

#Write neoantigen recognition potential
f=open(outfile,'w')
header=["NeoantigenID","Mutation","Sample","MutatedPeptide","RestoreChangeClass","MutantPeptide","WildtypePeptide","a","b","Excluded","NeoantigenRecognitionPotential"]
header="\t".join(header)
of.write(header+"\n")
for i in neoantigens:
    neoantigen=neoantigens[i]
    #neoantigen.getWeight() #excludes neoantigens that detected from a nonsynonymous residue on position 2 or 8
    A=neoantigens[i].getA() #MHC amplitude A
    mtpeptide=neoantigens[i].mtpeptide #mutant peptide
    wtpeptide=neoantigens[i].wtpeptide
    b=aligner.getB(i)

    # Residue change:
    # RRK: from hydrophobic to hydrophobic,
    # RRH: from non-hydrophobic to non-hydrophobic,
    # RRD: from hydrophobic to non-hydrophobic,
    # RRR: from non-hydrophobic to hydrophobic
    # other (RR, HH, DD, KK, HK, KH, DH, HD) which include mutations without a clear classification
    residueChange=neoantigen.residueChange

    fitnessCost=a*b

    l=[i, neoantigen.mid, neoantigen.sample, neoantigen.position, residueChange, mtpeptide, wtpeptide, A,B, 1-a, fitnessCost, mismatch, epitopealignment, score, excluded]
    l="\t".join(map(lambda x: str(x),l))
    of.write(l+"\n")

if __name__ == '__main__':
    main(sys.argv)
```

Fig. 39B

```
'''
@author: Marta Luksza, mluksza@ias.edu
'''

class Neoantigen(object):
    '''
    classdocs
    '''
    L=1. #default concentration of peptides
    M=1. #default concentration of mutant peptides
    W=1. #default concentration of wildtype peptides

    WEPS=0.0003
    WTCAP=float("inf")


    HYDROPHOBIC_RESIDUES="AILMFWYV"
    WEIRD_RESIDUES="CGP"

    AGGR="MAX"
    KDnormalize=1
    AGGRnum=float("inf")

    @staticmethod
    def residueChangeClass(res1,res2):
        code=""
        if res1 in Neoantigen.HYDROPHOBIC_RESIDUES:
            code+="H"
        elif res2 in Neoantigen.WEIRD_RESIDUES:
            code+="W"
        else:
            code+="N"
        if res2 in Neoantigen.HYDROPHOBIC_RESIDUES:
            code+="H"
        elif res2 in Neoantigen.WEIRD_RESIDUES:
            code+="W"
        else:
            code+="N"
        return code

```

Fig. 40A

```
    def __init__(self, params):
        '''
        Constructor
        '''
        pparams=params
        if len(params)==9:
            pparams.append("1")
        [nid,mid,sample,mtPeptide,allele,mtScore,HLA,chopscore]=pparams
        self.id=int(nid)
        self.mid=mid
        self.sample=sample
        self.mtPeptide=mtPeptide
        self.mtPeptide=mtPeptide

        [res1,res2]=filter(lambda el: el[0]!=el[1],zip(self.wtPeptide,self.mtPeptide))[0]
        self.residueChange=Neoantigen.residueChangeClass(res1, res2)

        self.position=filter(lambda el: el[1], map(lambda i: (i,self.mtPeptide[i]!=self.wtPeptide[i]),range(0,9)))
        self.position=self.position[0][0]+1
        self.allele=allele
        self.HLA=HLA
        self.chopscore=int(chopscore)
        self.potential=-1e10
        try:
            self.wtKD=min(Neoantigen.WTCAP,float(mtScore))
            self.KD=float(mtScore)
            self.setA()
        except:
            self.KD=Neoantigen.IMF
            self.wtKD=Neoantigen.IMF
            self.A=1.

    def getSampleName(self):
        return self.sample

    def correctWT(self):
        '''
        Corrects large wildtype kD dissociation constants
```

Fig. 40B

```
        '''
        kd=self.wtKD
        prb=Neoantigen.W/(Neoantigen.W+kd)
        pru=kd/(Neoantigen.W+kd)
        eps=Neoantigen.WEPS
        prb+=eps
        pru+=eps
        z=1+2*eps
        prb/=z
        pru/=z
        return pru/prb

    def getWeight(self):
        '''
        Returns 0 for neoantigens that mutated from a non-hydrophobic residues on position 2 or 9;
        these are excluded from analysis. Returns 1 for all other neoantigens
        '''
        w=1
        if self.residueChange[0]!="M" and (self.position==2 or self.position==9):
            w=0
        return w

    def setA(self):
        '''
        Computes MHC amplitude A
        '''
        self.A=Neoantigen.M/self.KD*self.correctWT()

    def getA(self):
        '''
        Return MHC amplitude A
        '''
        return self.A
```

Fig. 40C

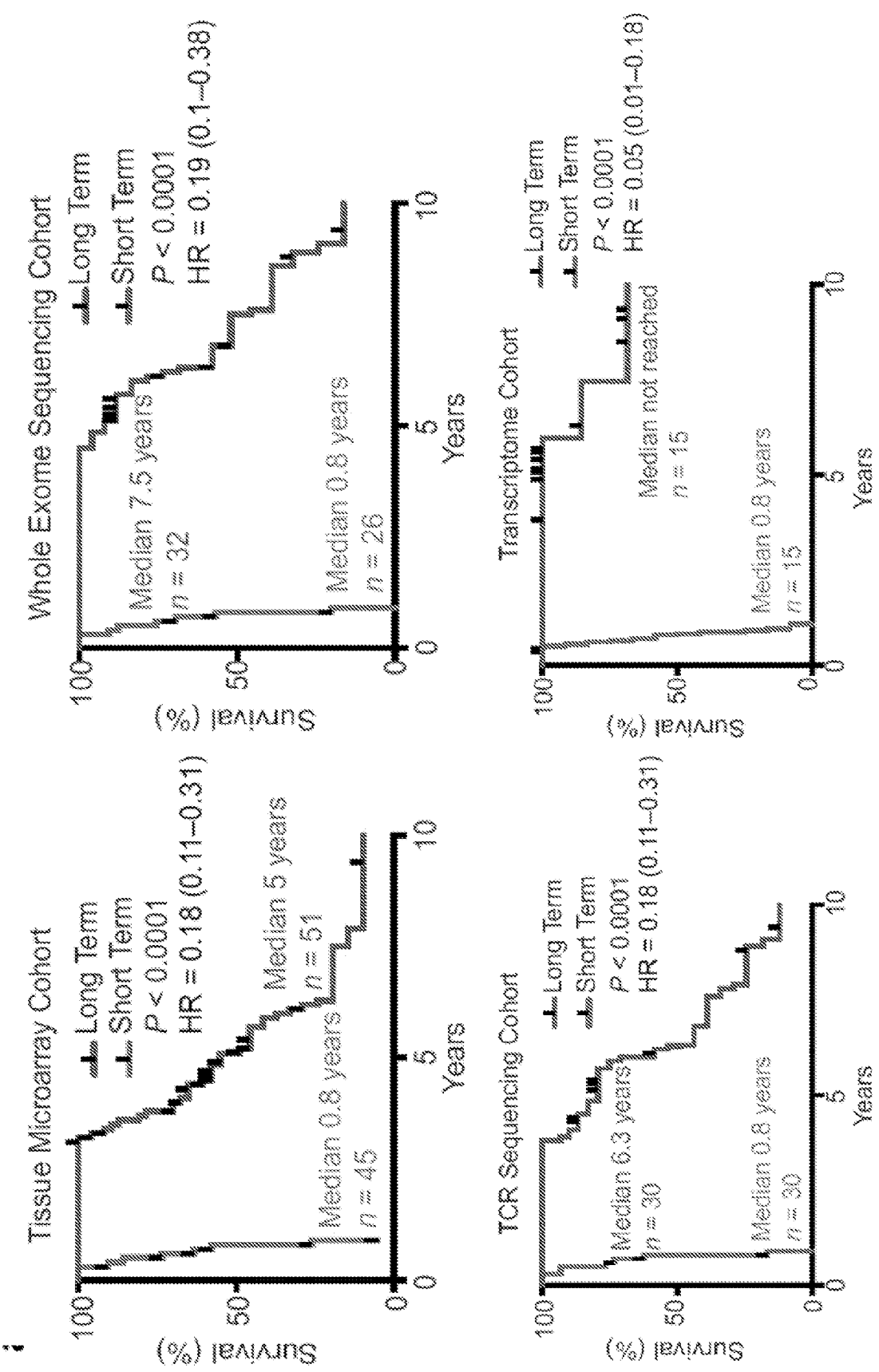

Whole Exome Sequencing Cohort
Long Term
Short Term
P < 0.0001
HR = 0.19 (0.1–0.38)
Median 7.5 years
n = 32
Median 0.8 years
n = 26
Survival (%)
Years
Transcriptome Cohort
Long Term
Short Term
P < 0.0001
HR = 0.05 (0.01–0.18)
Median not reached
n = 15
Median 0.8 years
n = 15
Survival (%)
Years
Tissue Microarray Cohort
Long Term
Short Term
P < 0.0001
HR = 0.18 (0.11–0.31)
Median 5 years
n = 51
Median 0.8 years
n = 45
Survival (%)
Years
TCR Sequencing Cohort
Long Term
Short Term
P < 0.0001
HR = 0.18 (0.11–0.31)
Median 6.3 years
n = 30
Median 0.8 years
n = 30
Survival (%)
Years

Fig. 41A

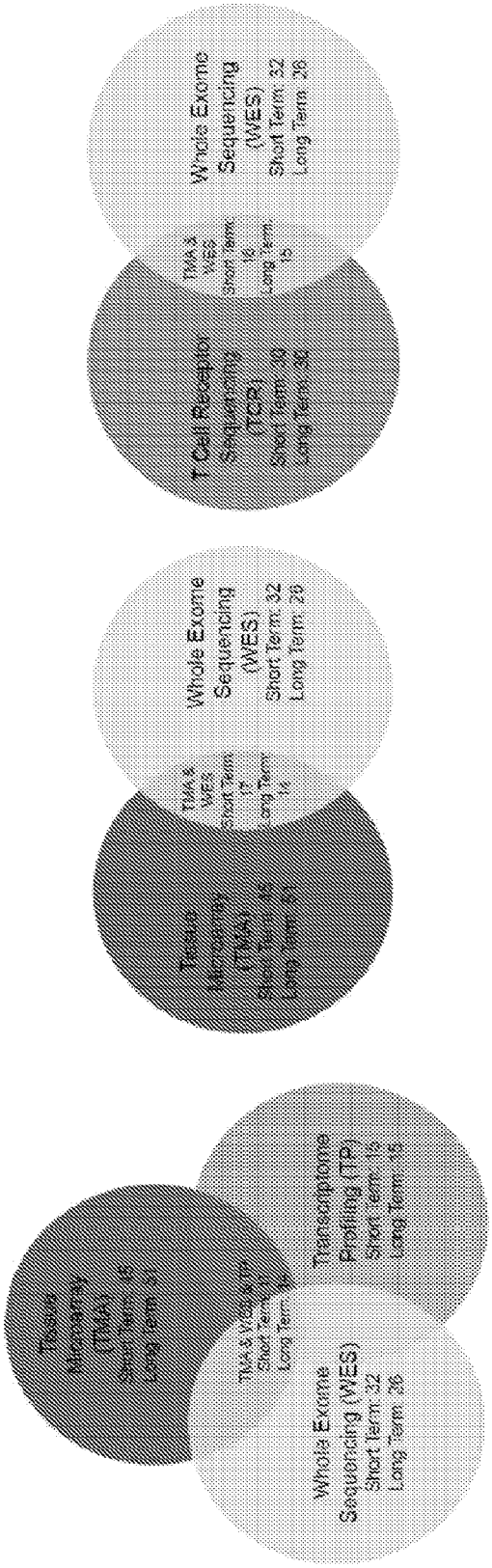

Whole Exome Sequencing (WES)
Short Term 32
Long Term 28
TMA3 WES
Short Term 18
Long Term 15
T Cell Receptor Sequencing (TCR)
Short Term 49
Long Term 30
Whole Exome Sequencing (WES)
Short Term 32
Long Term 28
TMA3 WES
Short Term 17
Long Term 14
Tempus Microarray (TMA) Sequencing
Short Term 49
Long Term 31
Transcriptome Profiling (TP)
Short Term 15
Long Term 13
TMA3 WES
Short Term 17
Long Term 14
Whole Exome Sequencing (WES)
Short Term 32
Long Term 28
Tempus Microarray (TMA) Sequencing
Short Term 49
Long Term 31

Fig. 41B

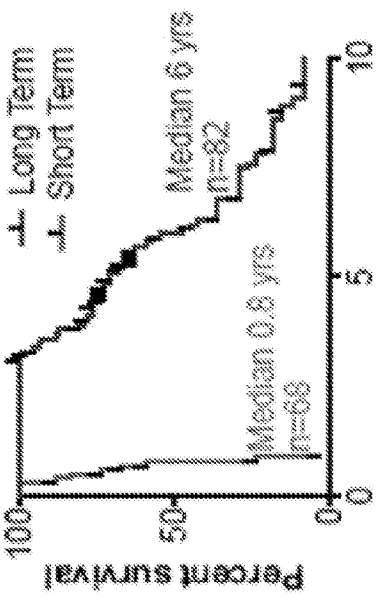


Fig. 42A

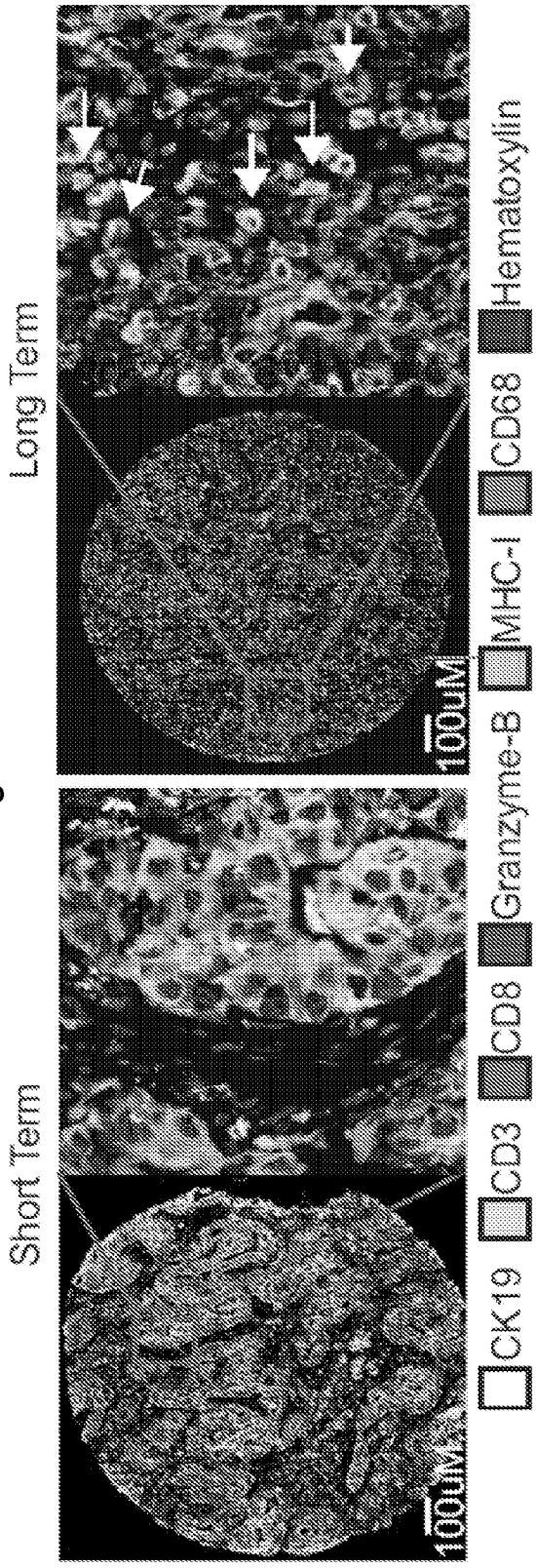


Fig. 42B

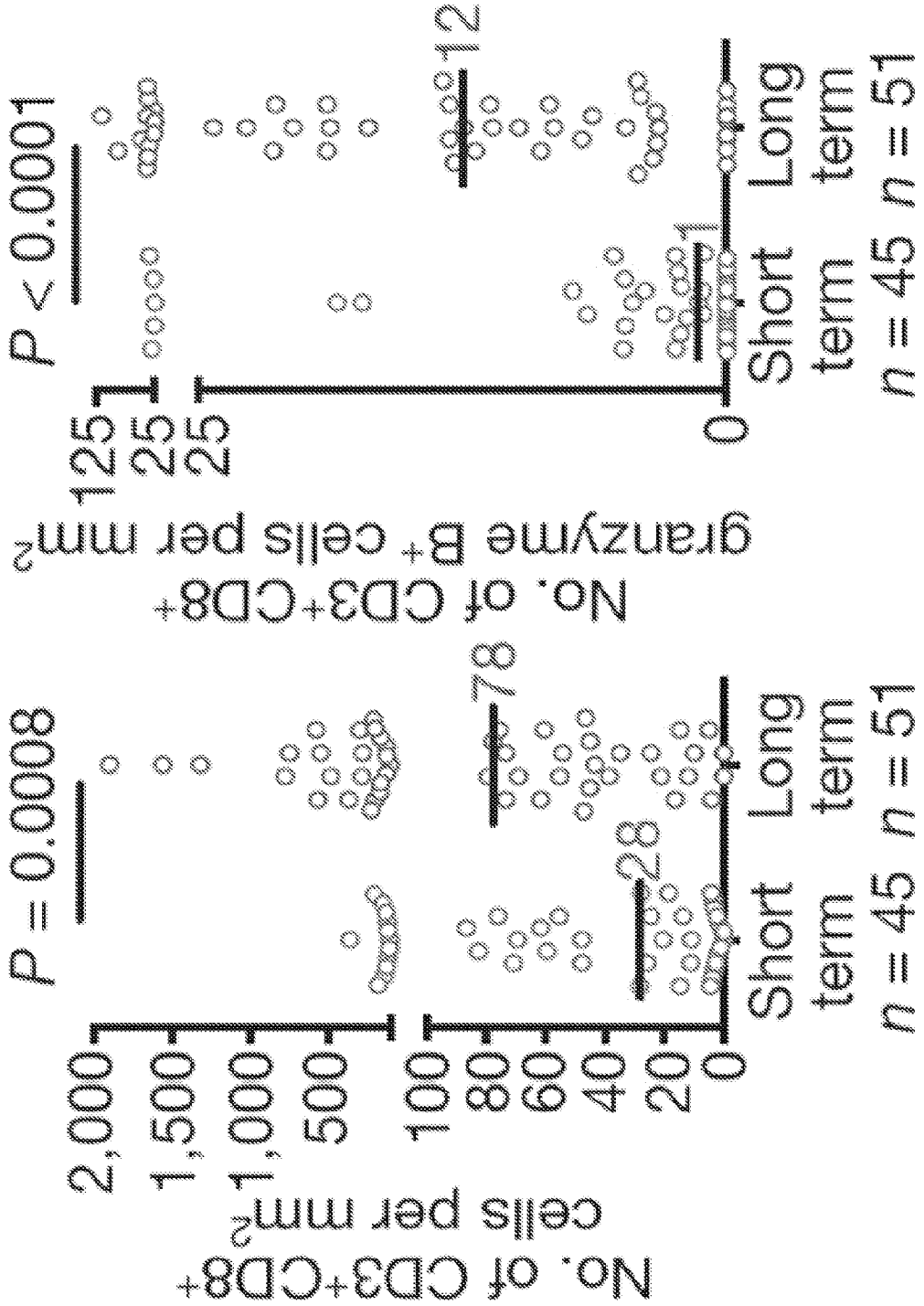

No. of CD3+CD8+ cells per mm2
2,000
1,500
1,000
500
0
P = 0.0008
28
78
Short term
Long term
n = 45
n = 51
No. of CD3+CD8+ granzyme B+ cells per mm2
125
25
25
0
P < 0.0001
1
12
Short term
Long term
n = 45
n = 51

Fig. 42C

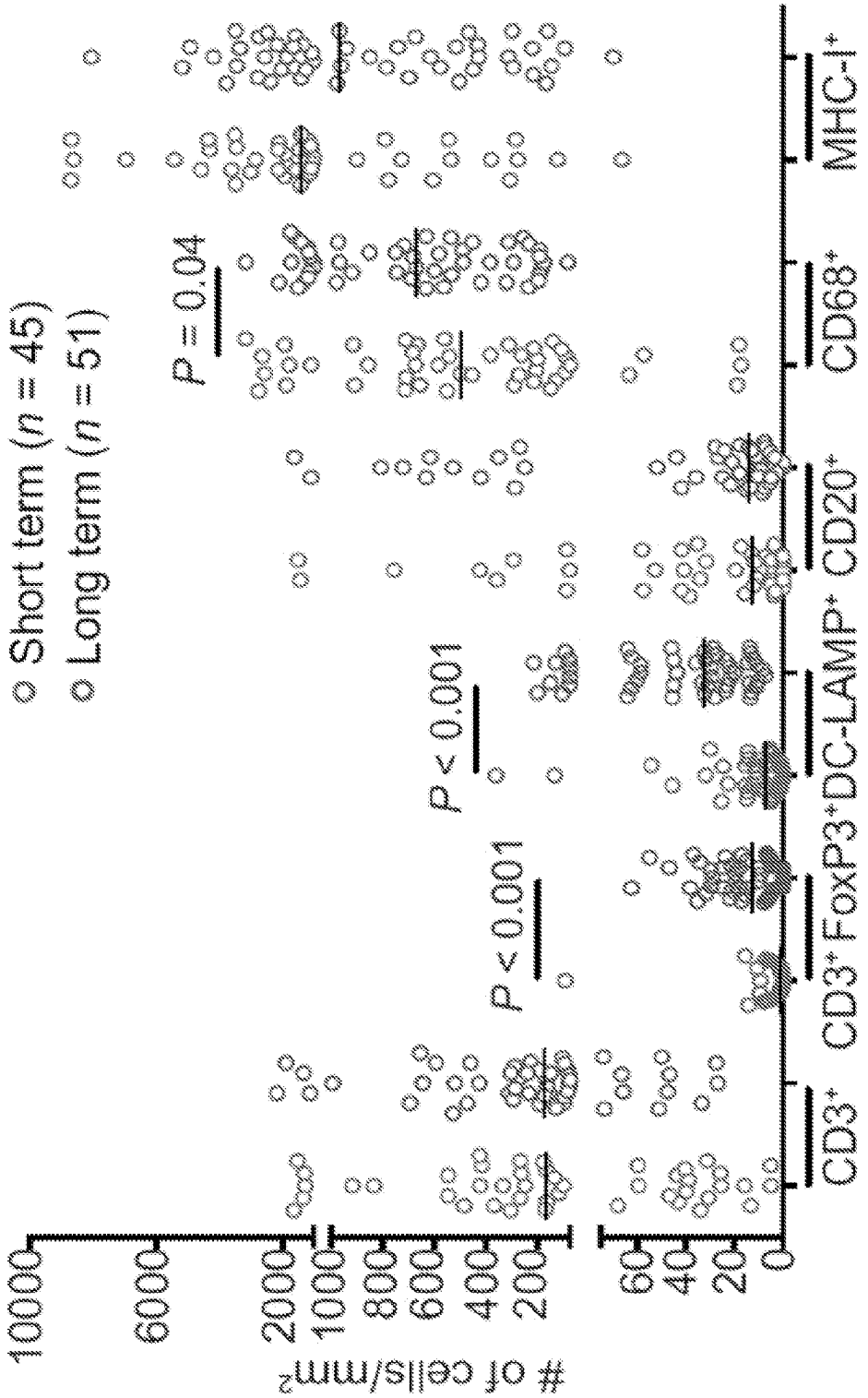

Short term (n = 45)
Long term (n = 51)
P = 0.04
P < 0.001
P < 0.001
of cells/mm²
10000
6000
2000
1000
800
600
400
200
60
40
20
0
CD3⁺
CD3⁺ FoxP3⁺
DC-LAMP⁺
CD20⁺
CD68⁺
MHC-I⁺

Fig. 42D

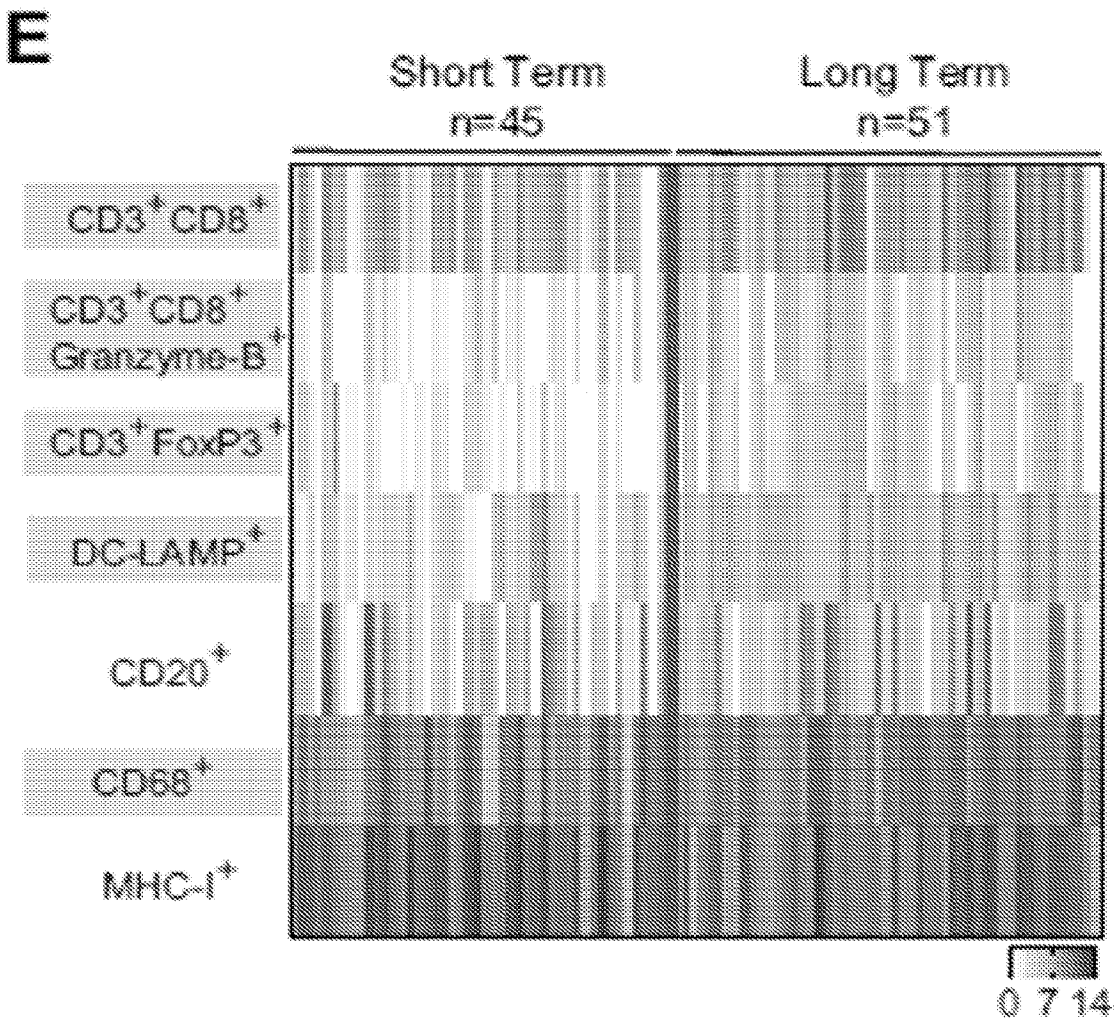

E
Short Term
n=45
Long Term
n=51
CD3+CD8+
CD3+CD8+ Granzyme-B+
CD3+FoxP3+
DC-LAMP+
CD20+
CD68+
MHC-I+
0 7 14

Fig. 42E

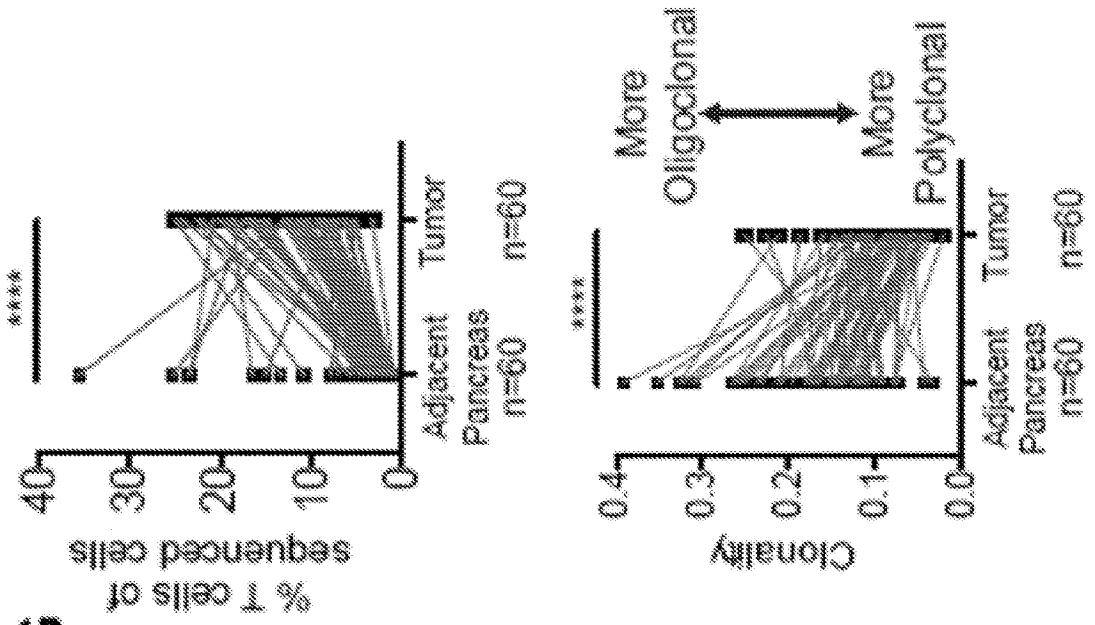


Fig. 42G

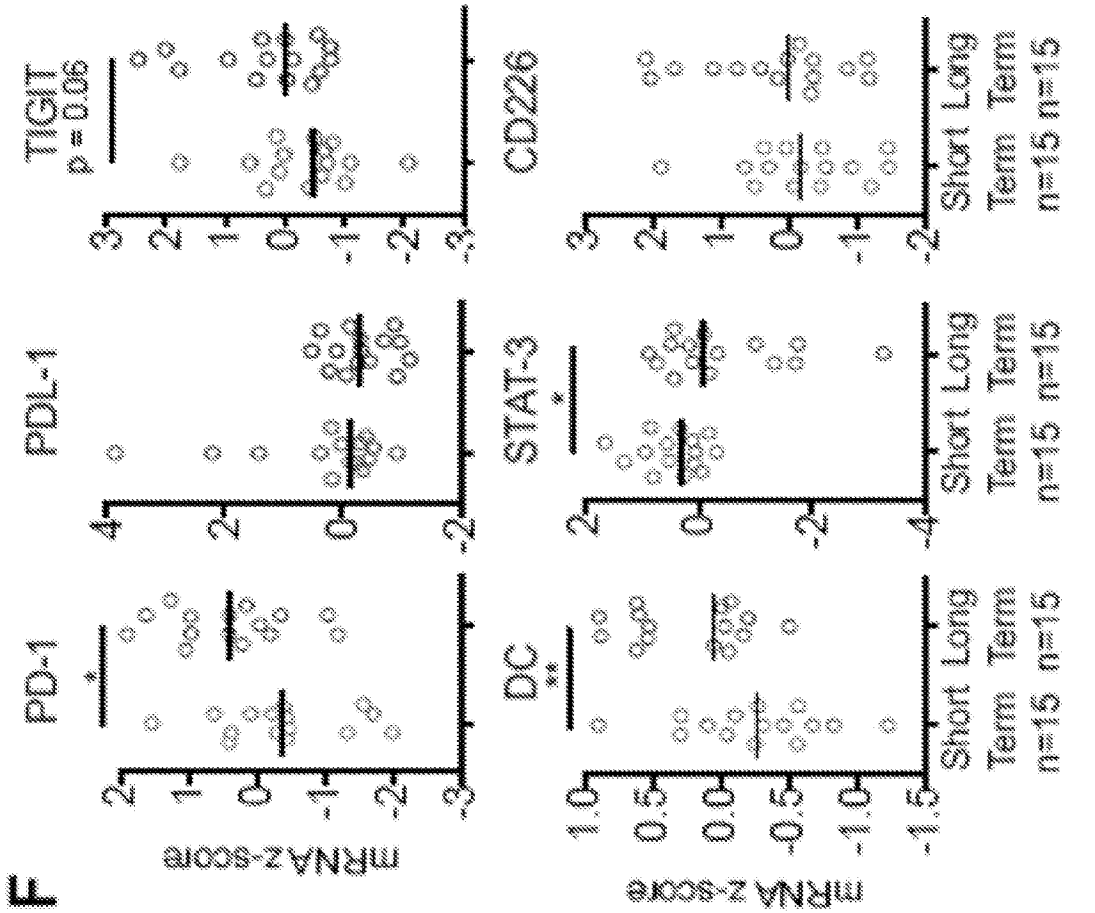


Fig. 42F

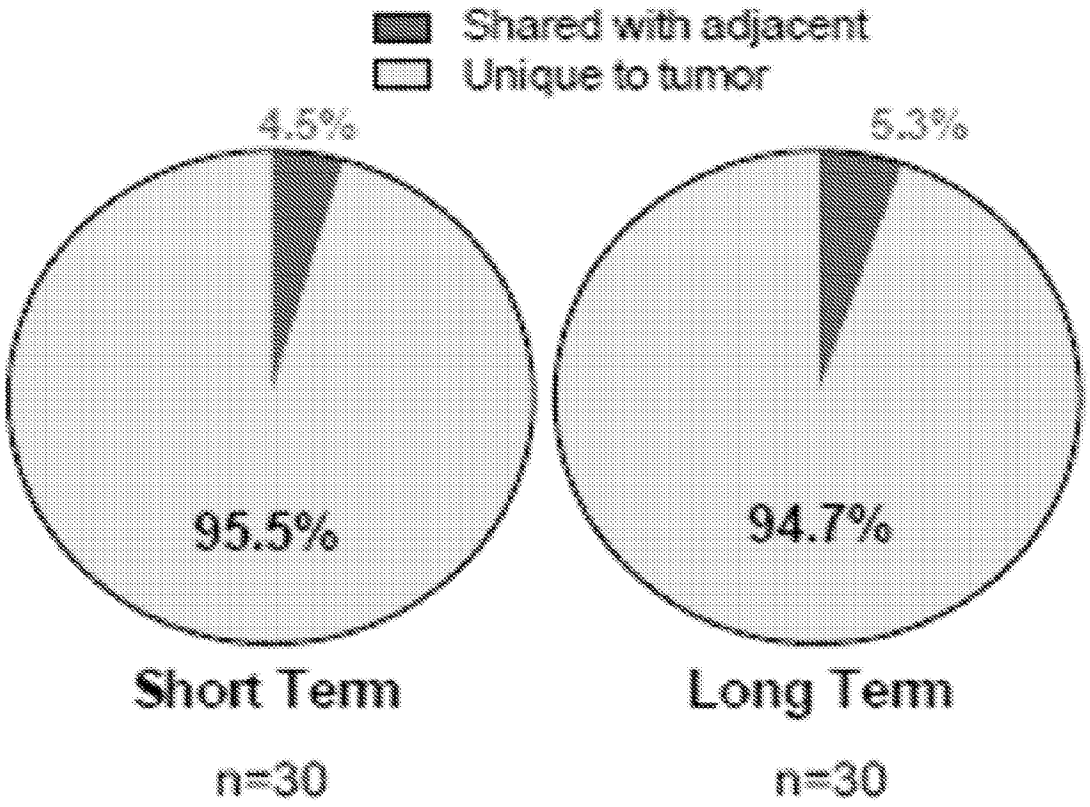

Shared with adjacent
Unique to tumor
4.5%
5.3%
95.5%
94.7%
Short Term
Long Term
n=30
n=30

Fig. 42H

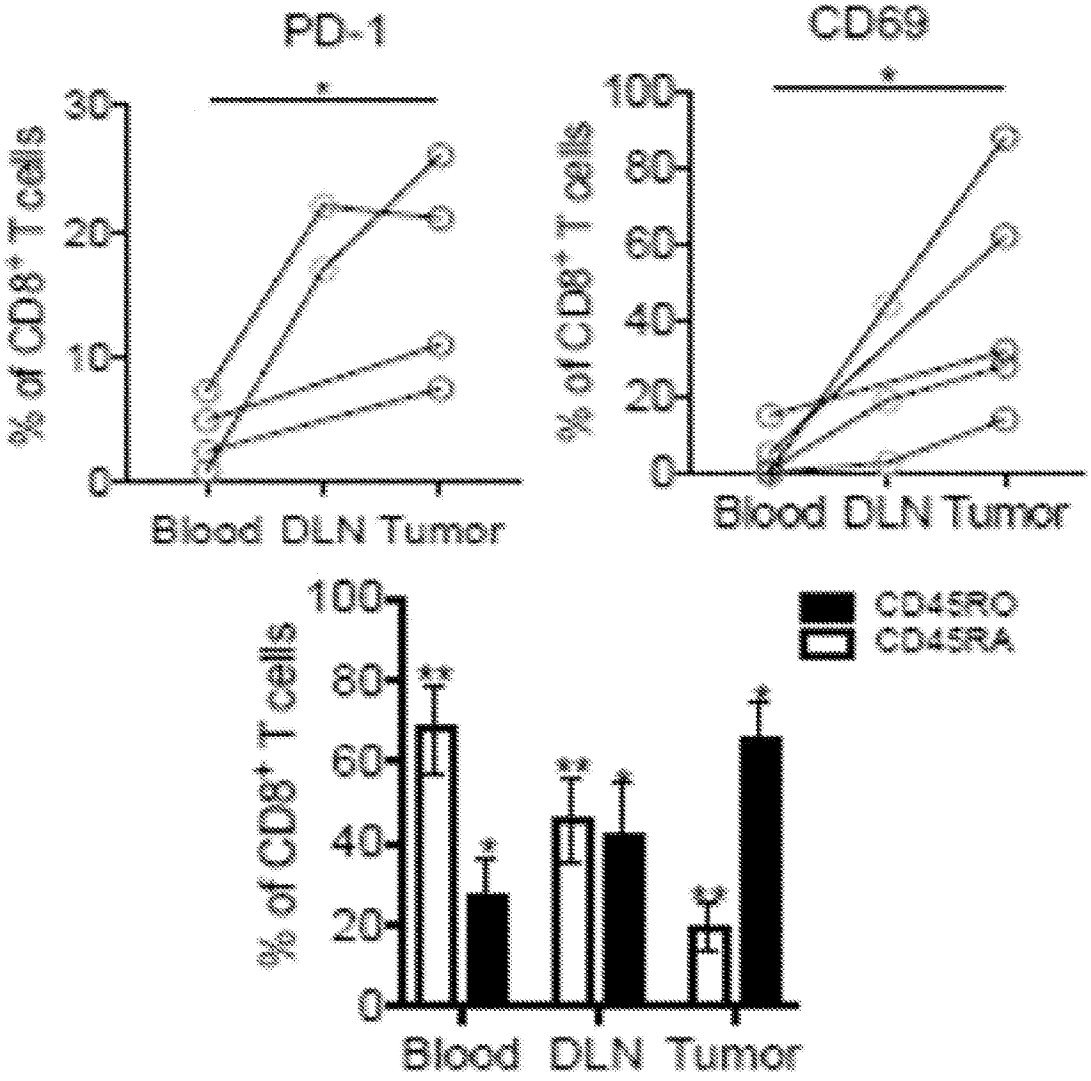


Fig. 42I

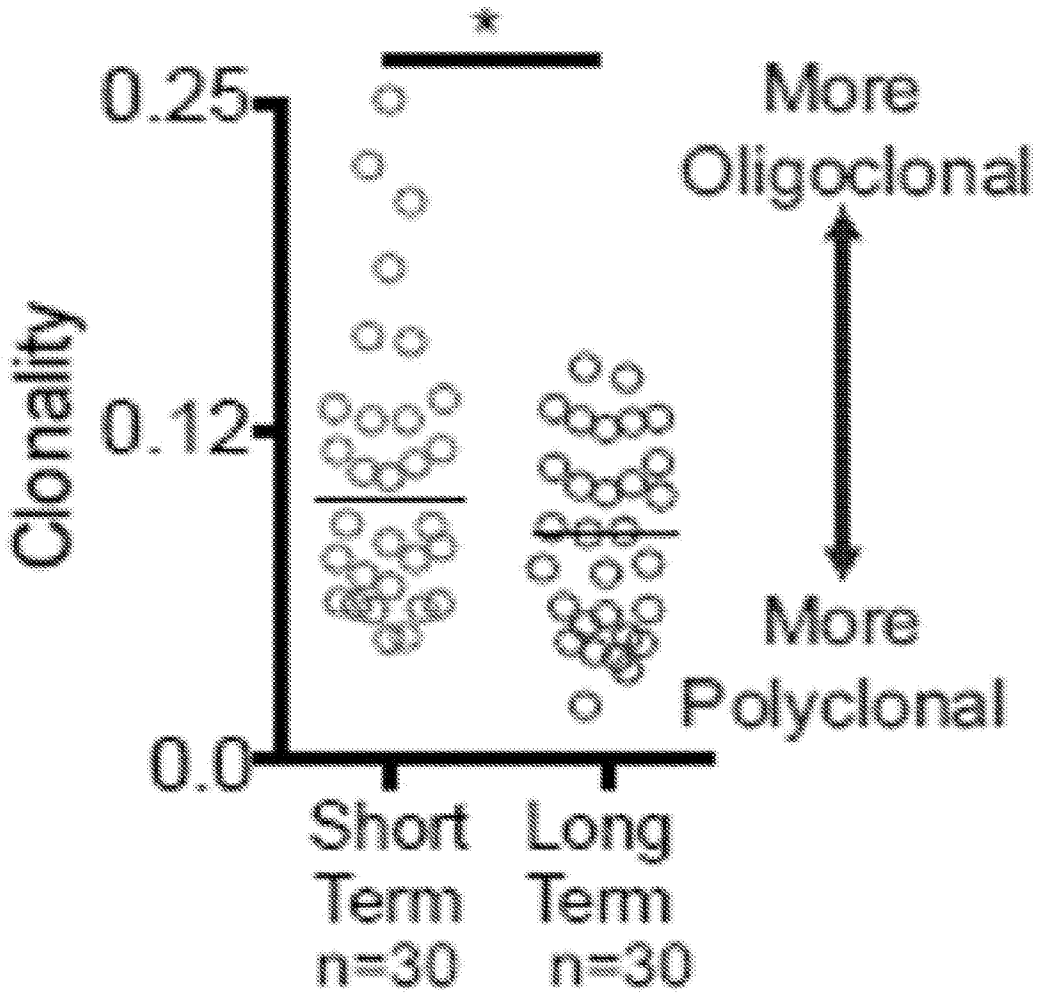

*
0.25
0.12
0.0
Clonality
More
Oligoclonal
More
Polyclonal
Short
Term
n=30
Long
Term
n=30

Fig. 42J

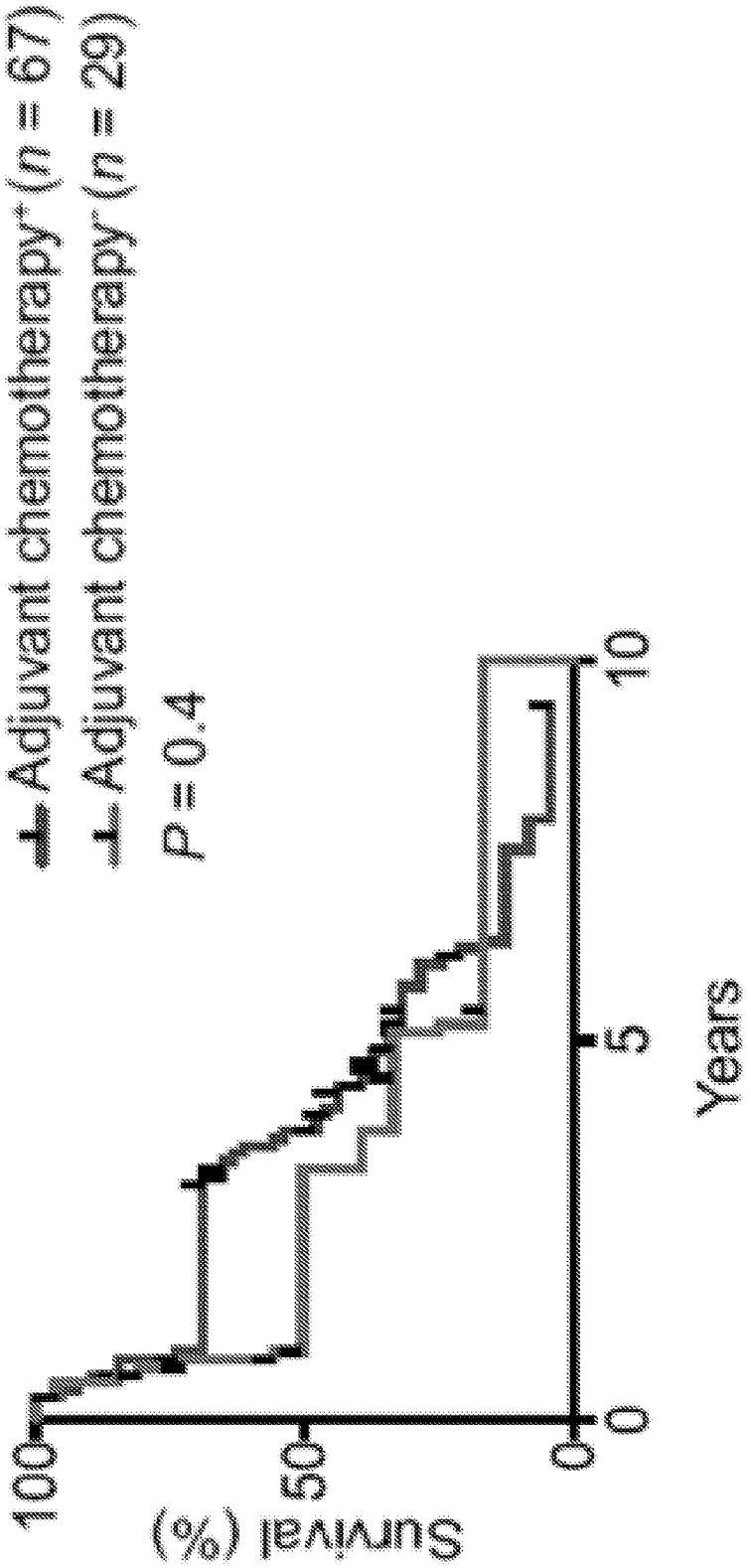

Adjuvant chemotherapy+ (n = 67)
Adjuvant chemotherapy (n = 29)
P = 0.4
Survival (%)
100
50
0
0
5
10
Years

Fig. 42K

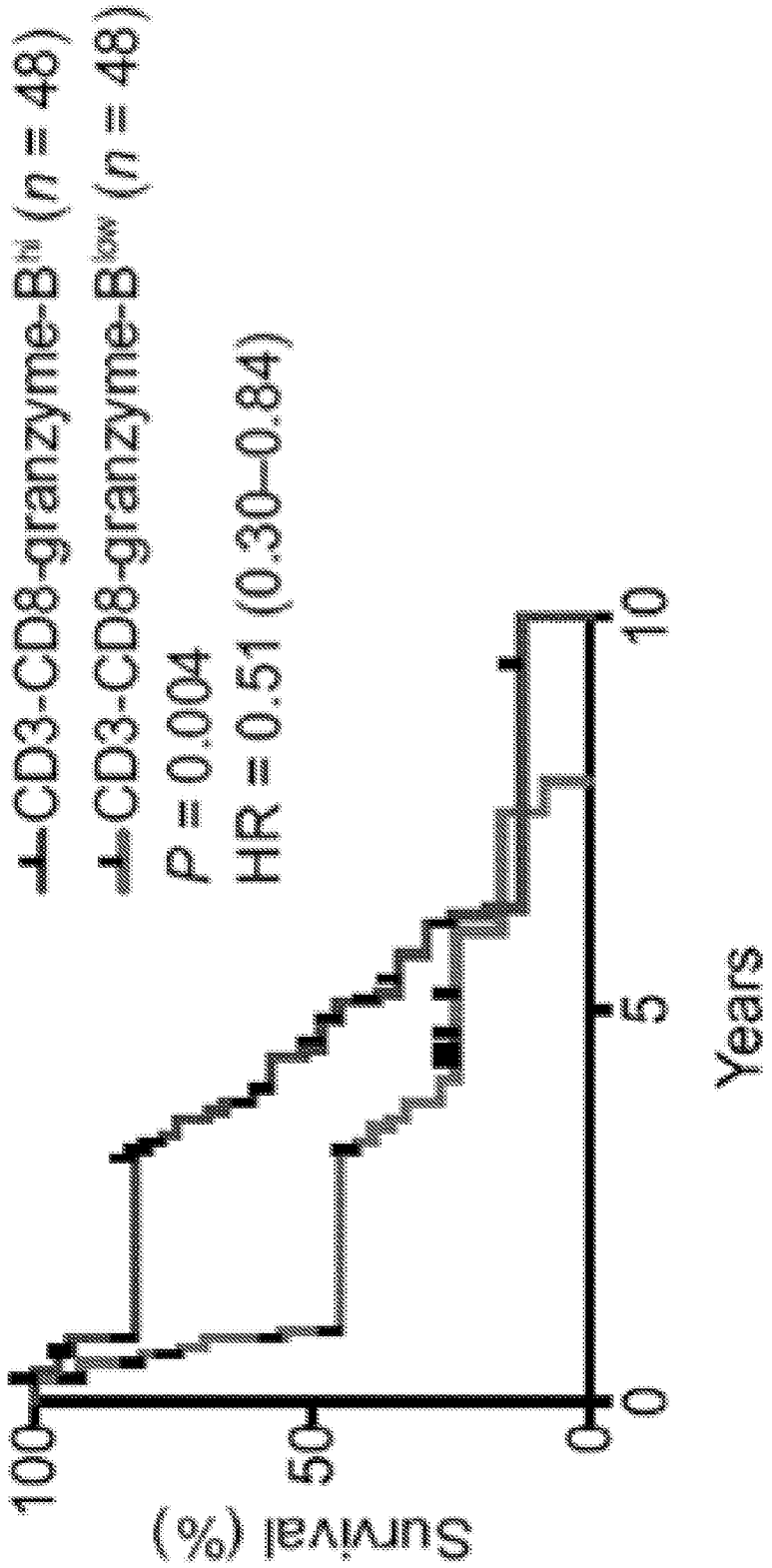
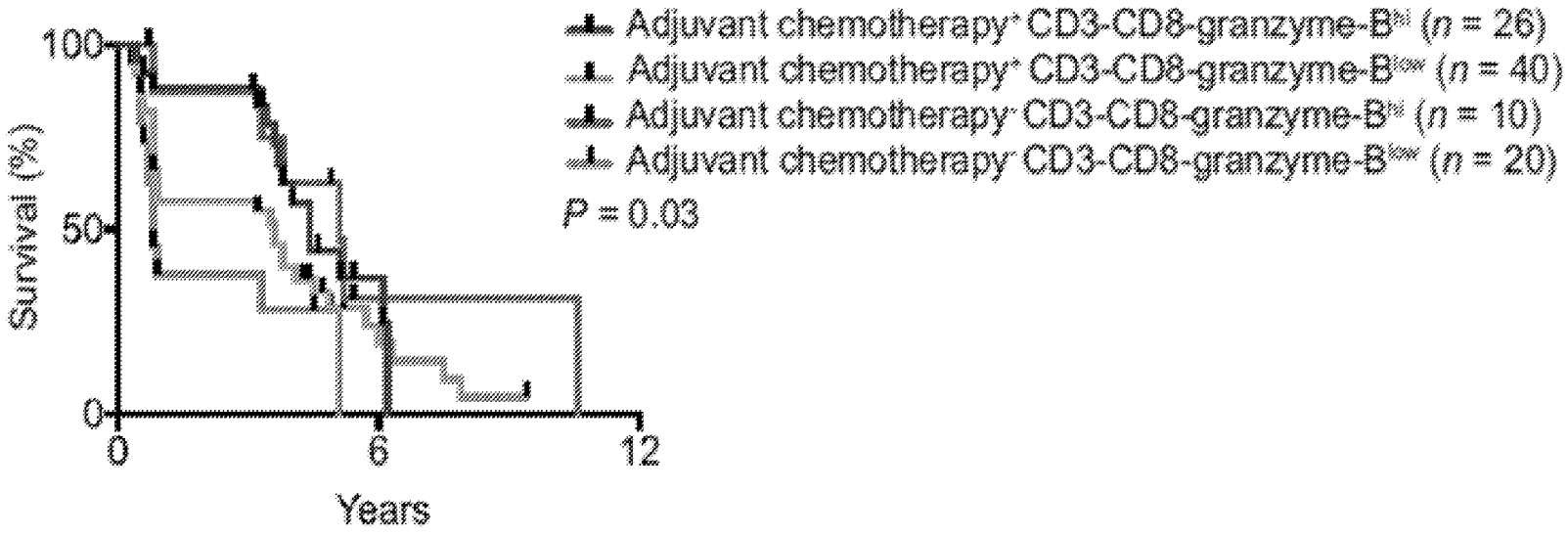

CD3-CD8-granzyme-B^hi (n = 48)
CD3-CD8-granzyme-B^low (n = 48)
P = 0.004
HR = 0.51 (0.30–0.84)
Survival (%)
100
50
0
0
5
10
Years

Fig. 42L



Variable	Univariate			Multivariate		
	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value
Adjuvant chemotherapy	0.7	0.4–1.3	0.4	0.7	0.3–1.3	0.3
Pathologic stage	2.0	0.8–4.7	0.1	-	-	-
Margin	1.6	0.8–3.3	0.1	-	-	-
CD3–CD8-granzyme-B density	0.4	0.2–0.8	0.004	0.4	0.2–0.8	0.007

Fig. 42M

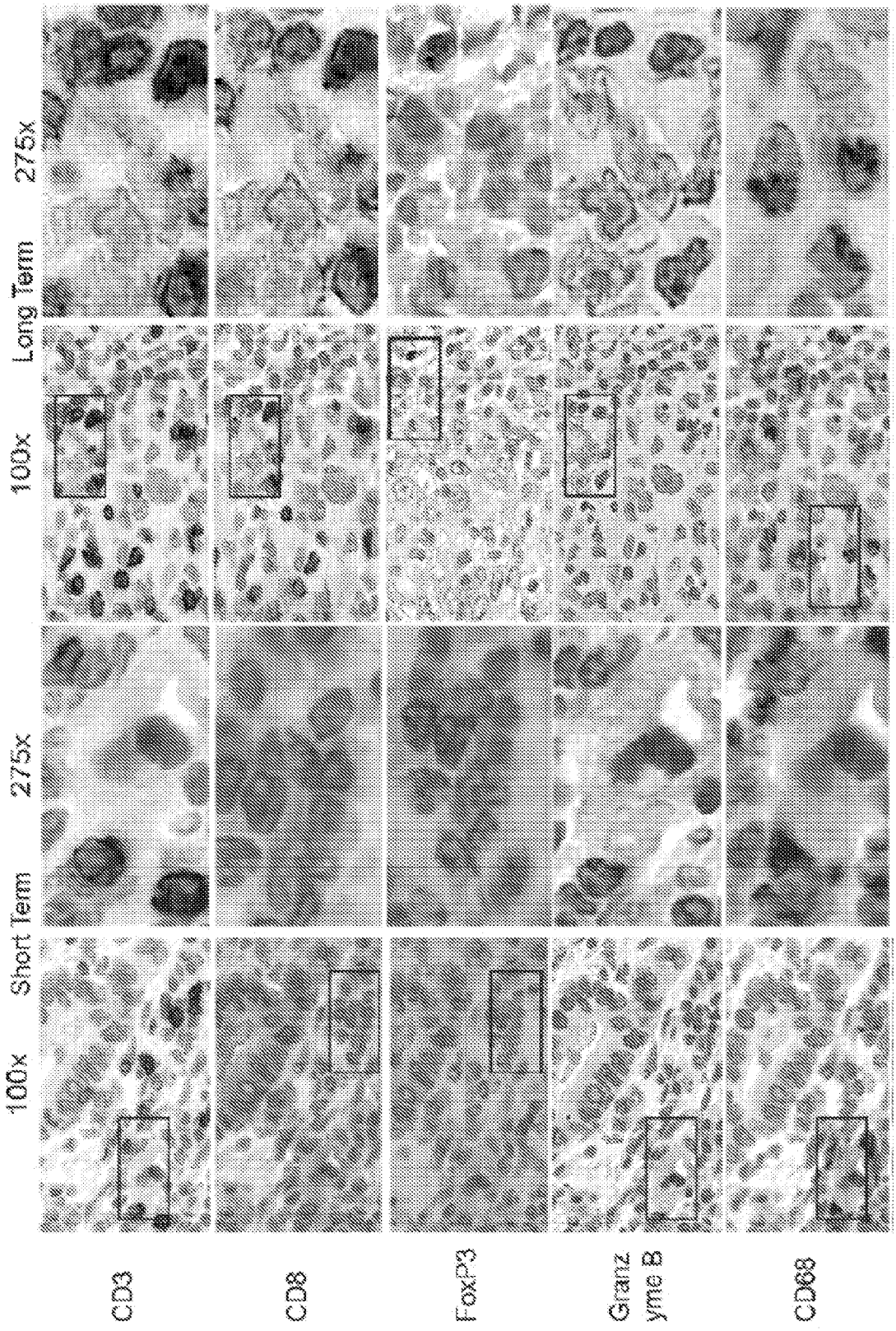

100x
Short Term
275x
100x
Long Term
275x
CD3
CD8
FoxP3
Granzyme B
CD68

Fig. 43A

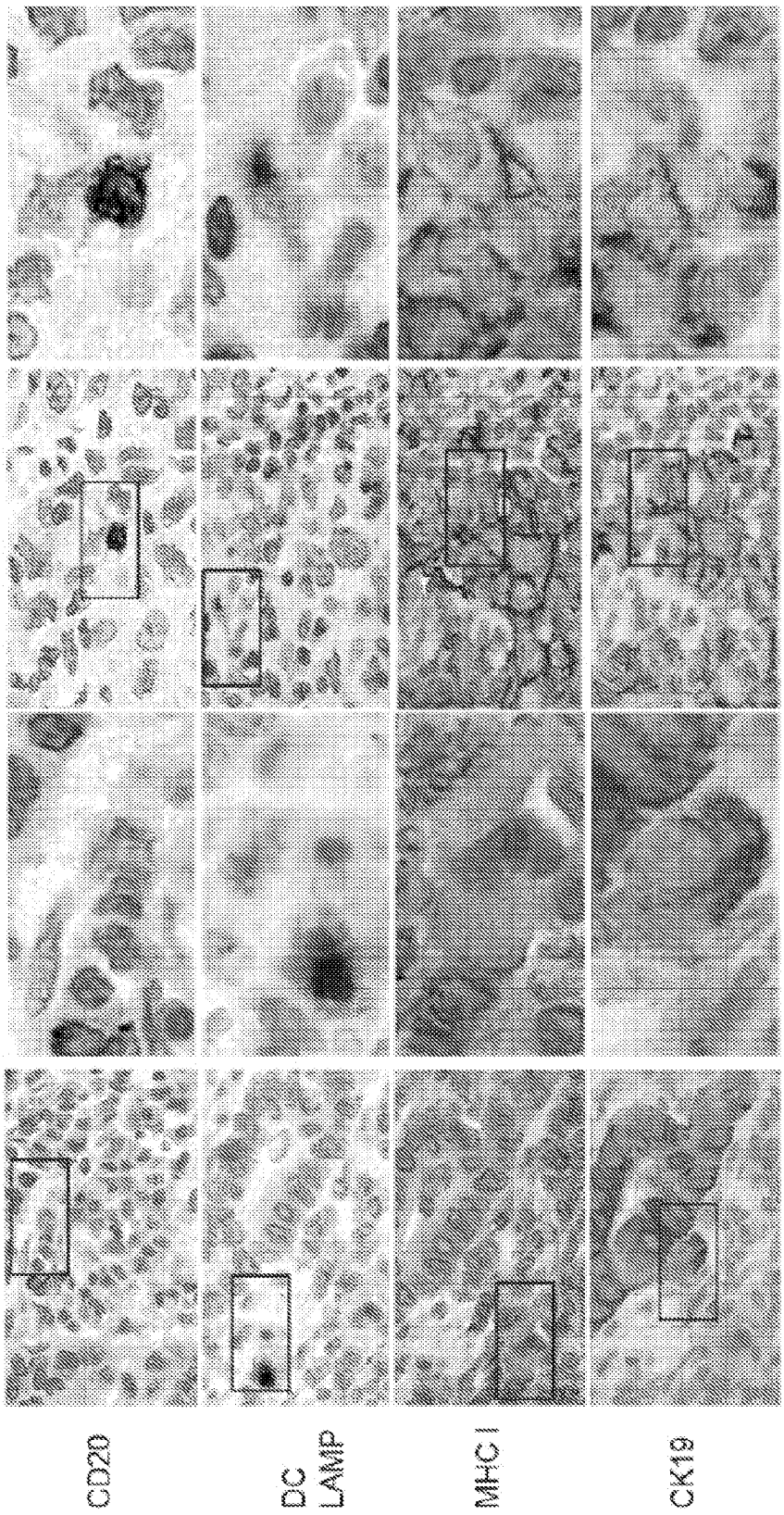


Fig. 43B

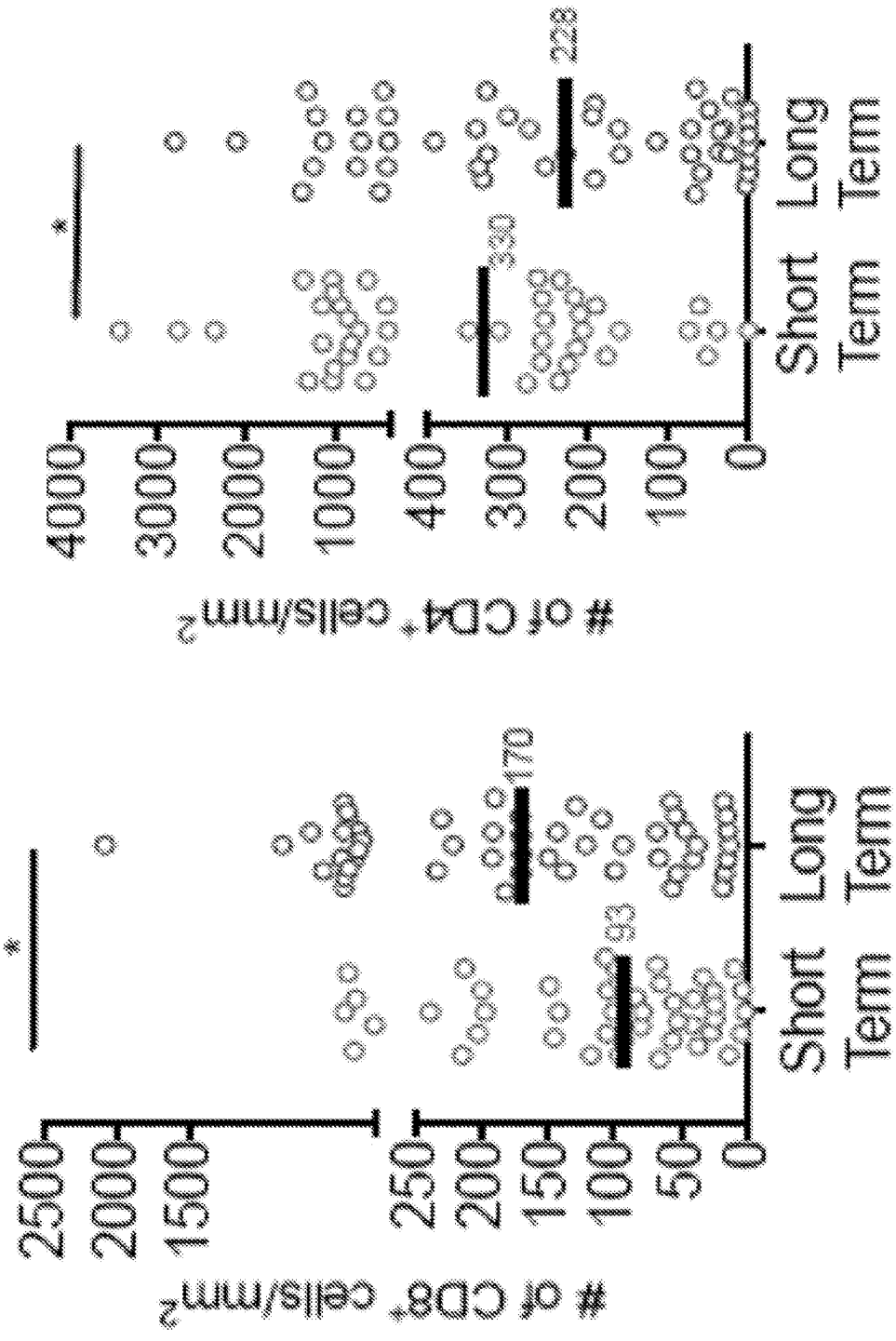

of CD4+ cells/mm2
4000
3000
2000
1000
400
300
200
100
0
330
228
*
Short Term
Long Term
of CD8+ cells/mm2
2500
2000
1500
250
200
150
100
50
0
93
170
*
Short Term
Long Term

Fig. 44

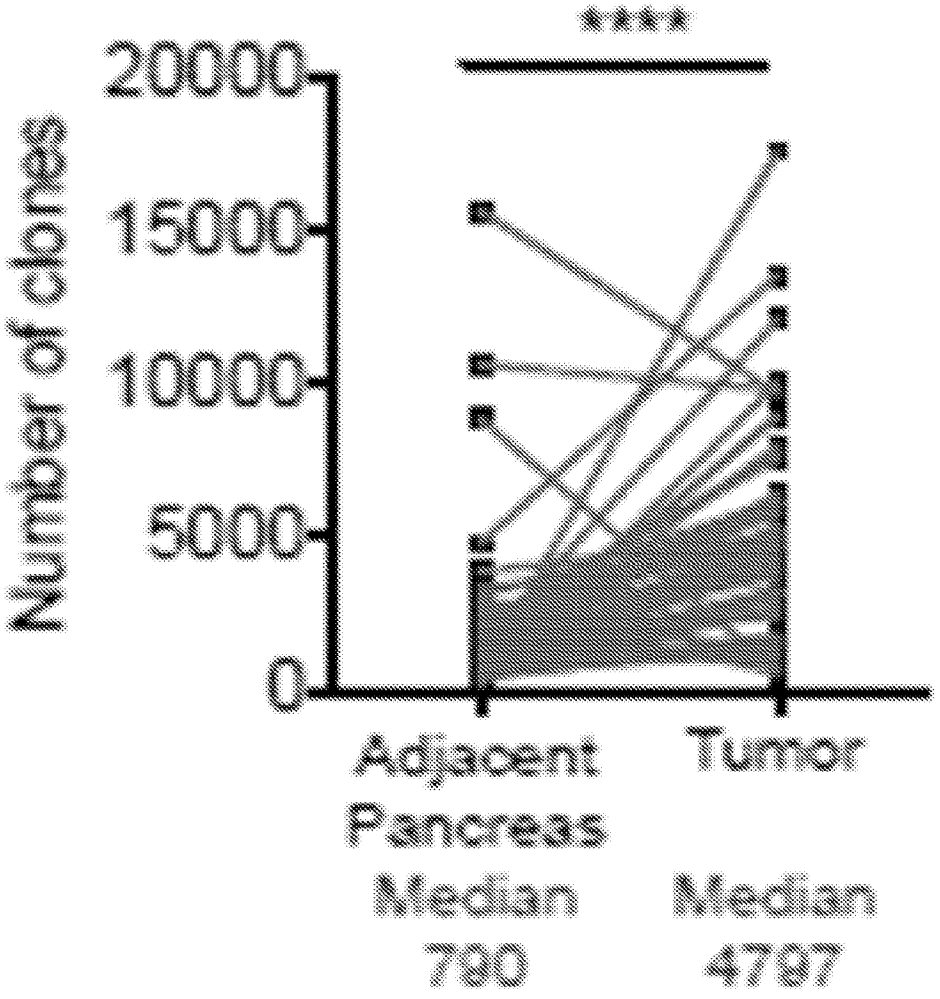

****
20000
15000
10000
5000
0
Number of clones
Adjacent Pancreas
Tumor
Median
780
Median
4787

Fig. 45

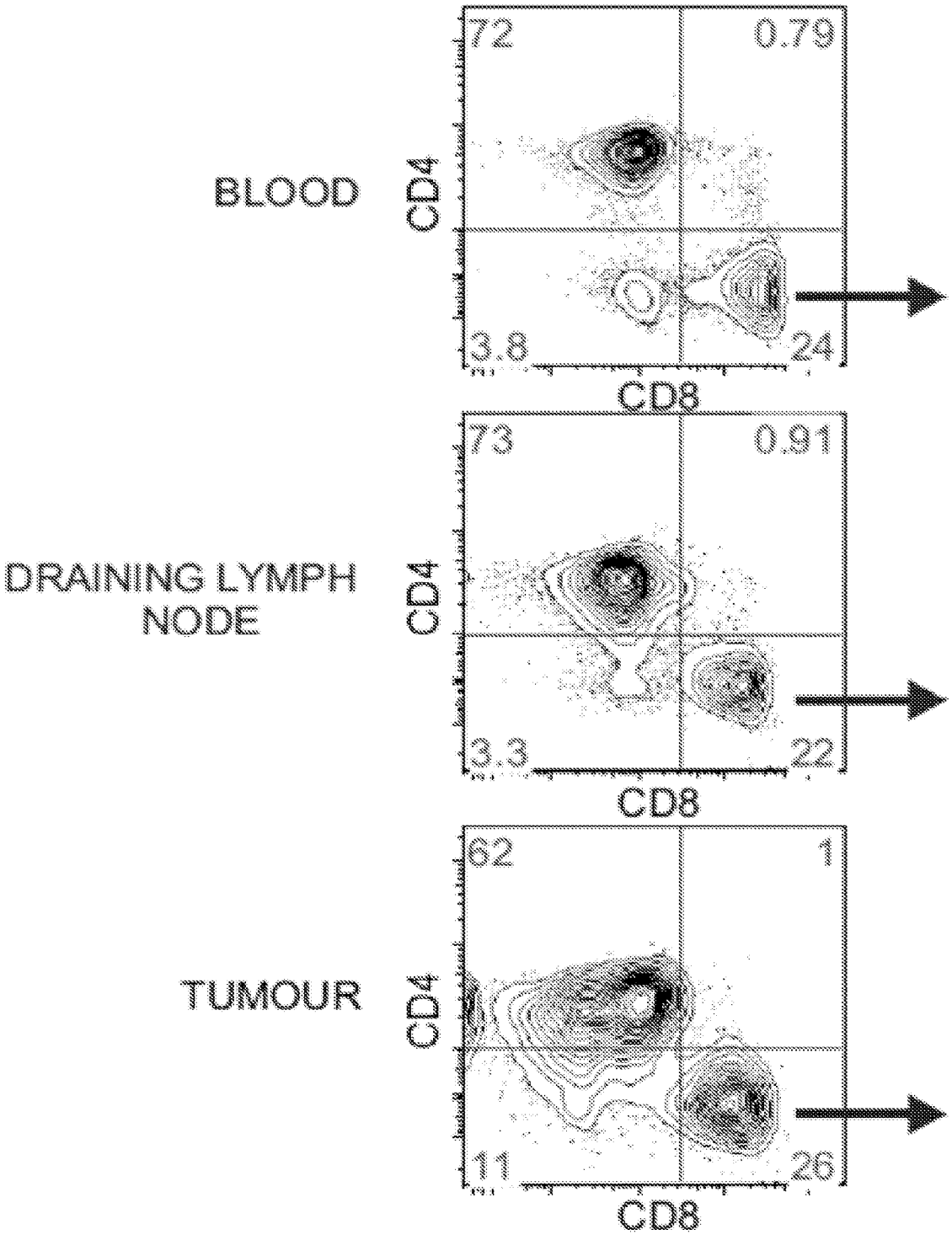

BLOOD
72
0.79
3.8
24
CD4
CD8
DRAINING LYMPH NODE
73
0.91
3.3
22
CD4
CD8
TUMOUR
62
1
11
26
CD4
CD8

Fig. 46A

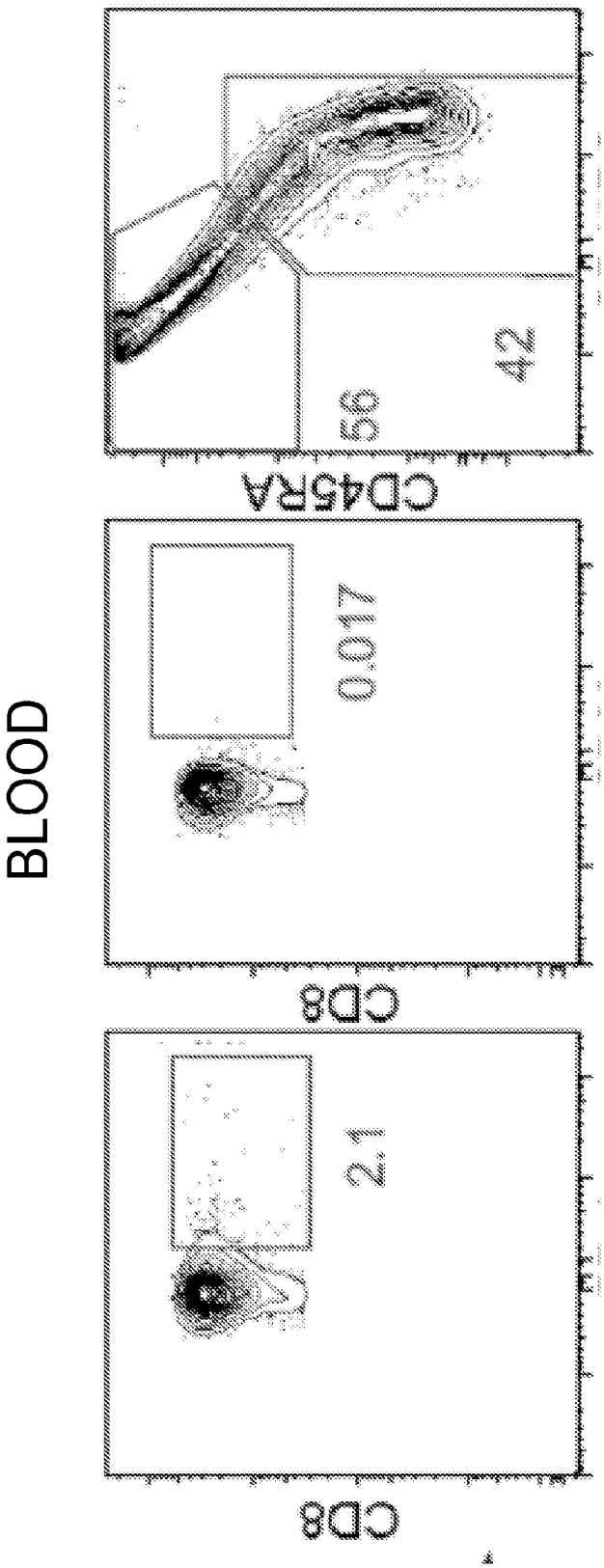


Fig. 46B

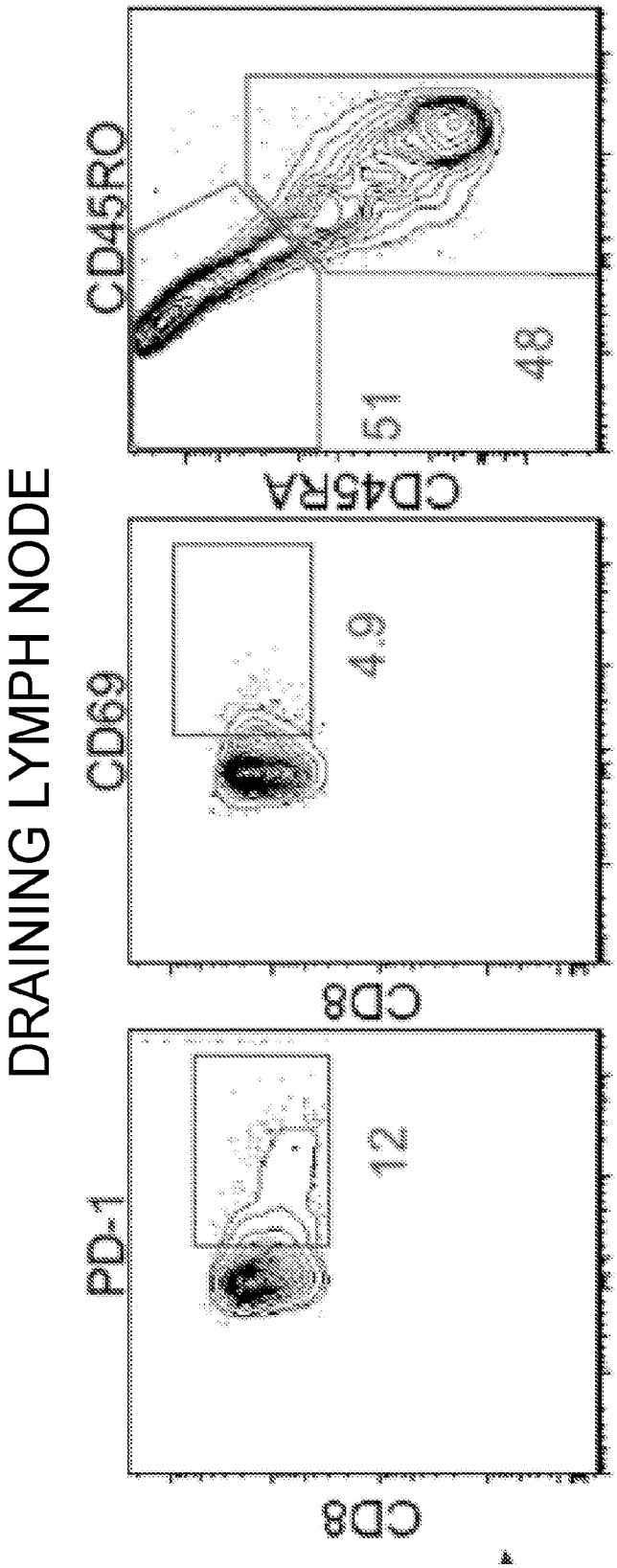

DRAINING LYMPH NODE
PD-1
CD8
12
CD69
CD8
4.9
CD45RO
CD45RA
51
49

Fig. 46C

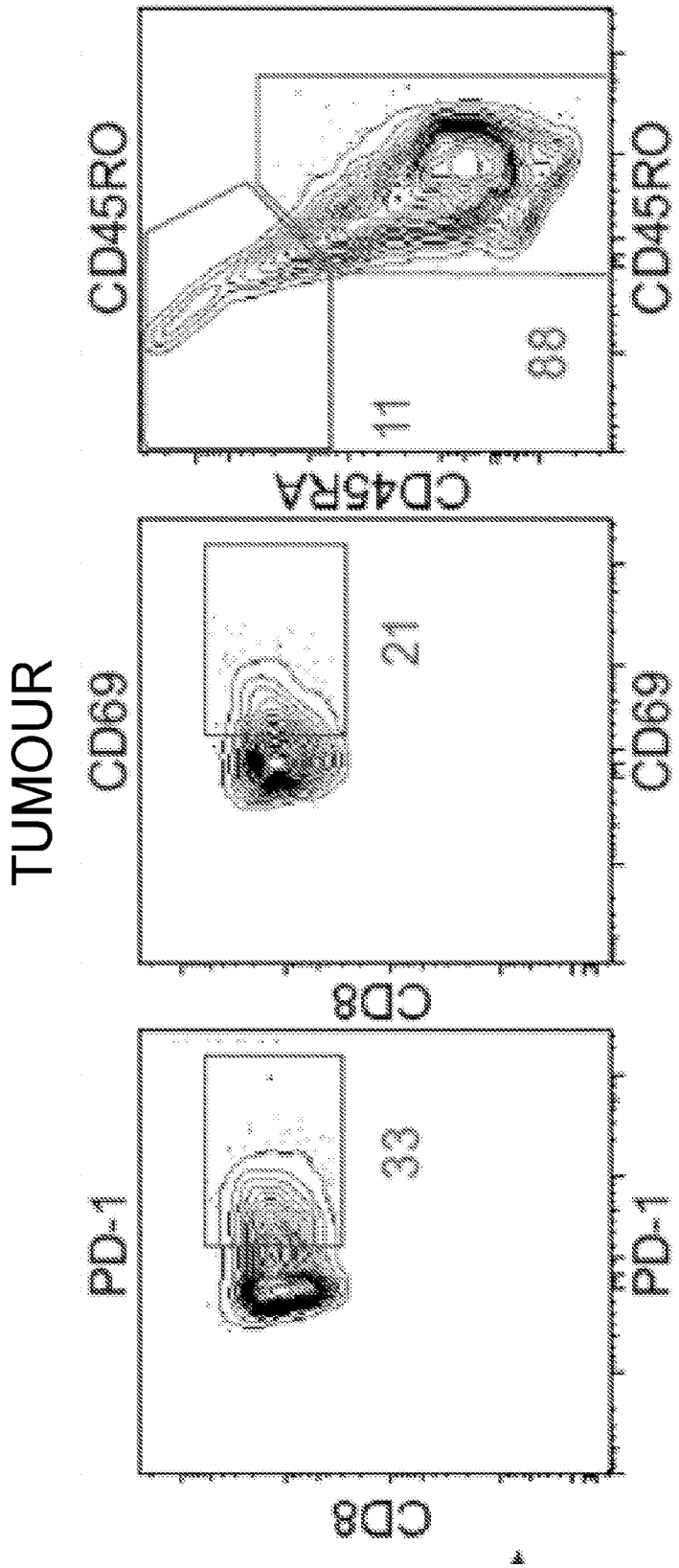


Fig. 46D

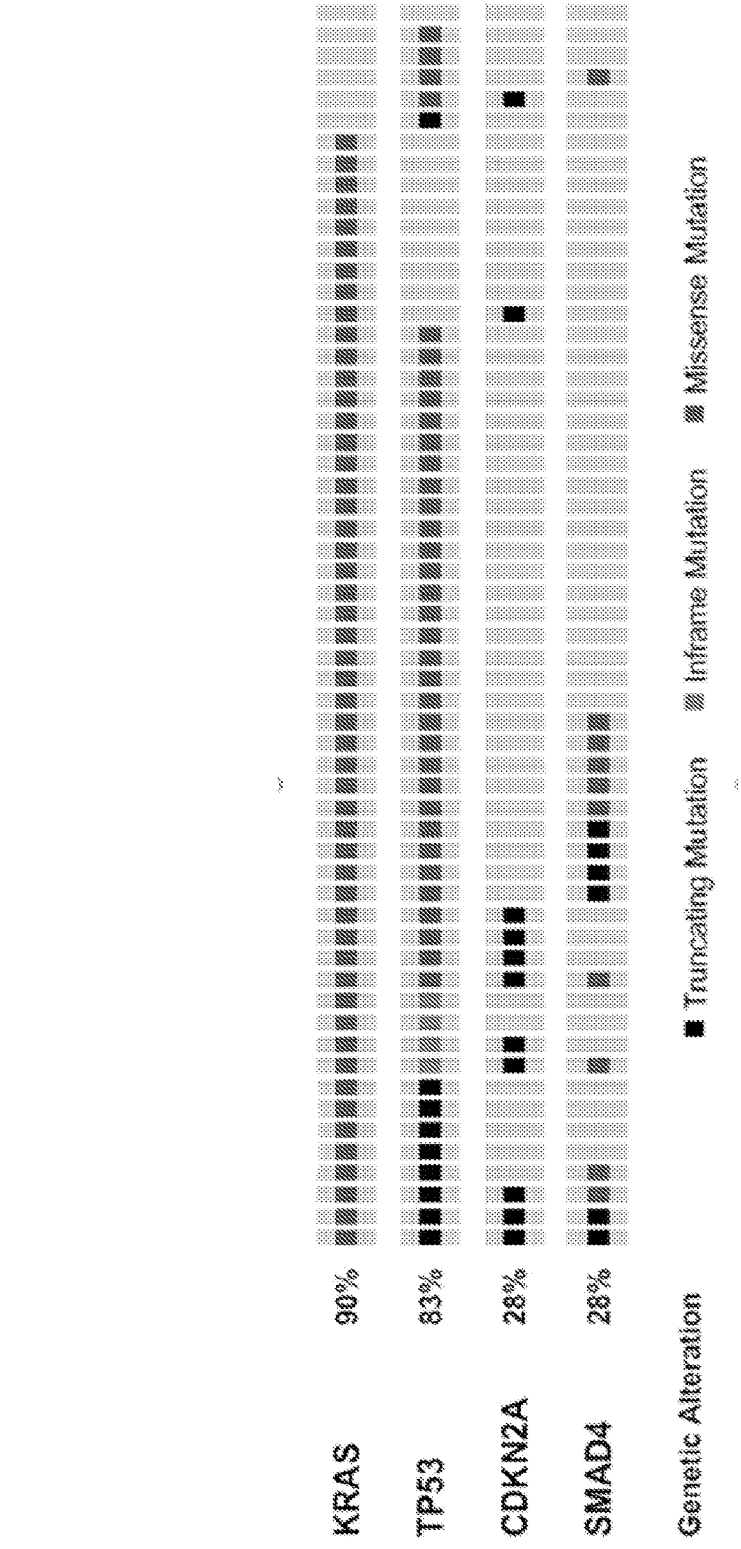

KRAS
90%
TP53
83%
CDKN2A
28%
SMAD4
28%
Genetic Alteration
Truncating Mutation
Inframe Mutation
Missense Mutation

Fig. 47

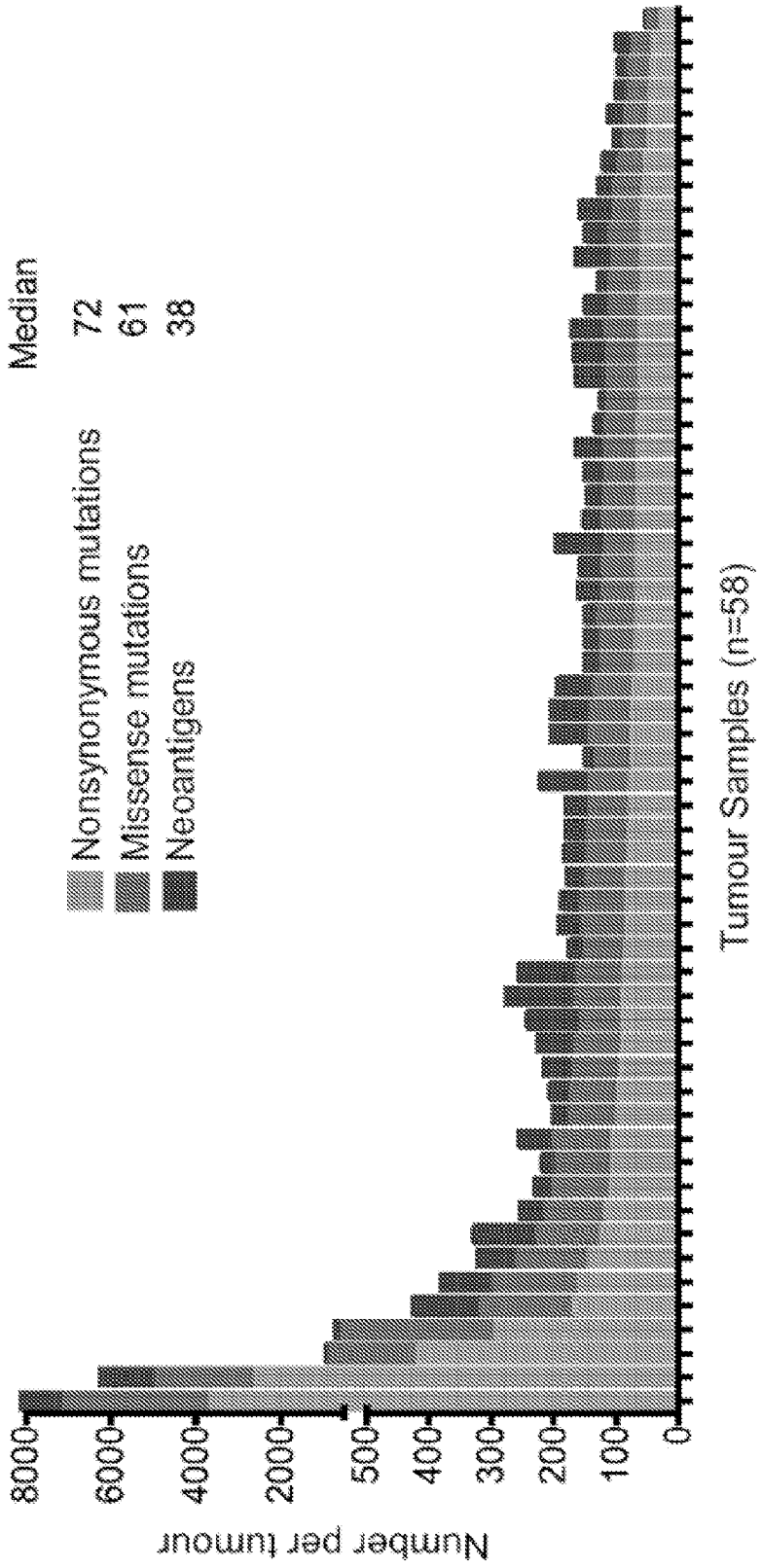

Median
72
61
38
Nonsynonymous mutations
Missense mutations
Neoantigens
8000
6000
4000
2000
500
400
300
200
100
0
Number per tumour
Tumour Samples (n=58)

Fig. 48A

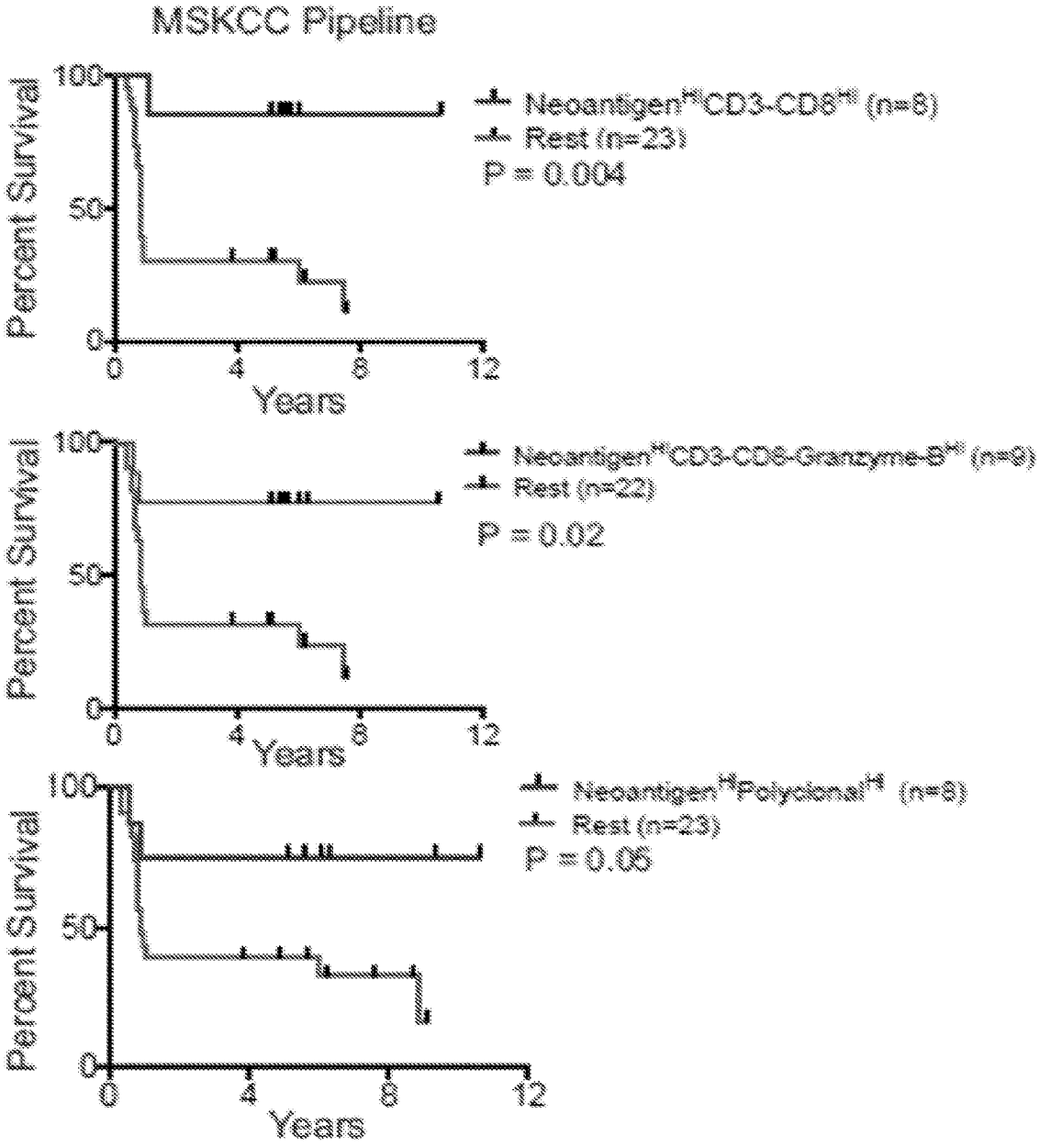

MSKCC Pipeline
Percent Survival
100
50
0
0
4
8
12
Years
Neoantigen^{hi}CD3-CD8^{hi} (n=8)
Rest (n=23)
P = 0.004
Neoantigen^{hi}CD3-CD8-Granzyme-B^{hi} (n=9)
Rest (n=22)
P = 0.02
Neoantigen^{hi}Polyclonal^{hi} (n=8)
Rest (n=23)
P = 0.05

Fig. 48B1

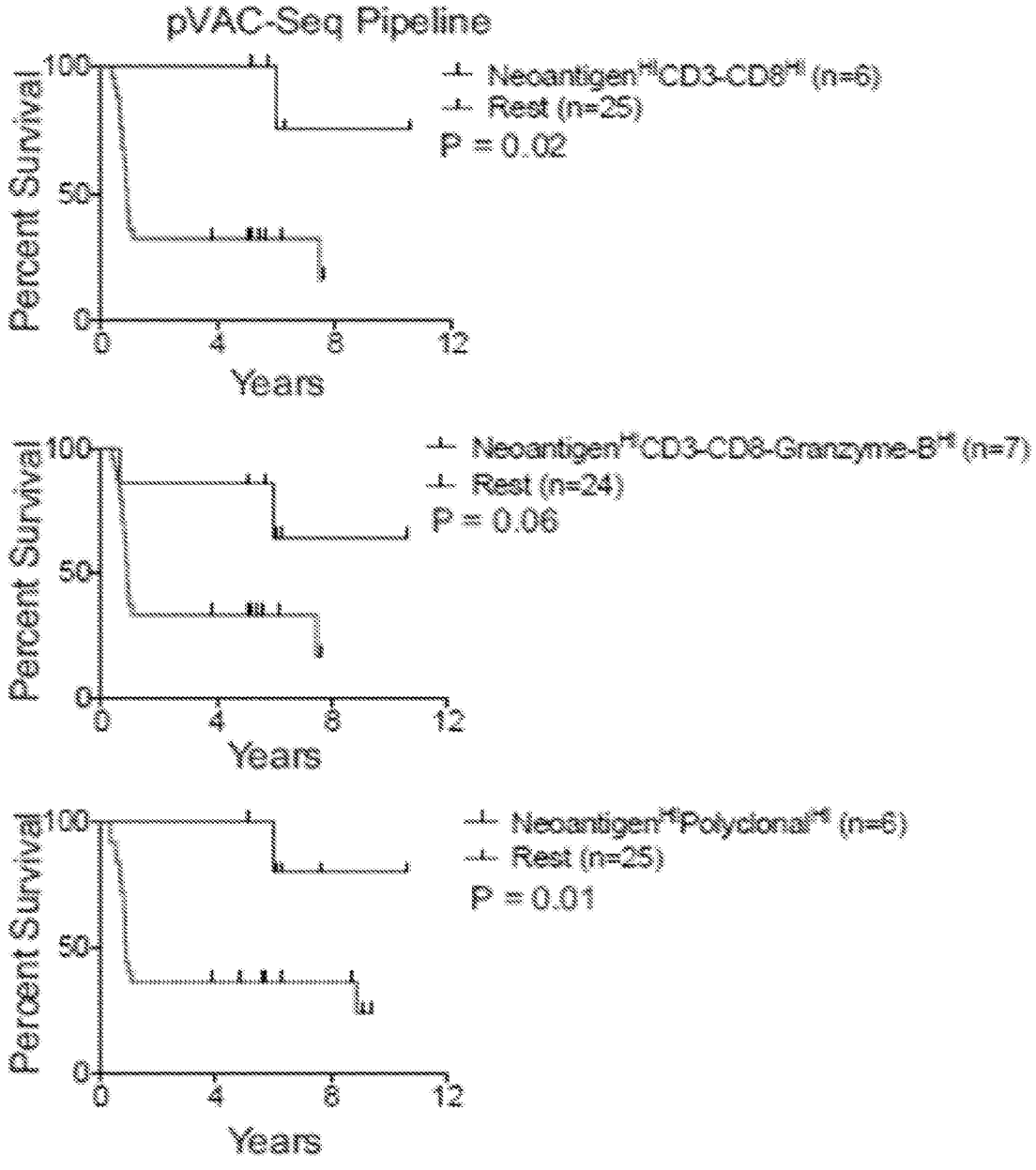

pVAC-Seq Pipeline
Percent Survival
100
50
0
0
4
8
12
Years
Neoantigen+CD3-CD8+ (n=6)
Rest (n=25)
P = 0.02
Neoantigen+CD3-CD8-Granzyme-B+ (n=7)
Rest (n=24)
P = 0.06
Neoantigen+Polyclonal+ (n=6)
Rest (n=25)
P = 0.01

Fig. 48B2

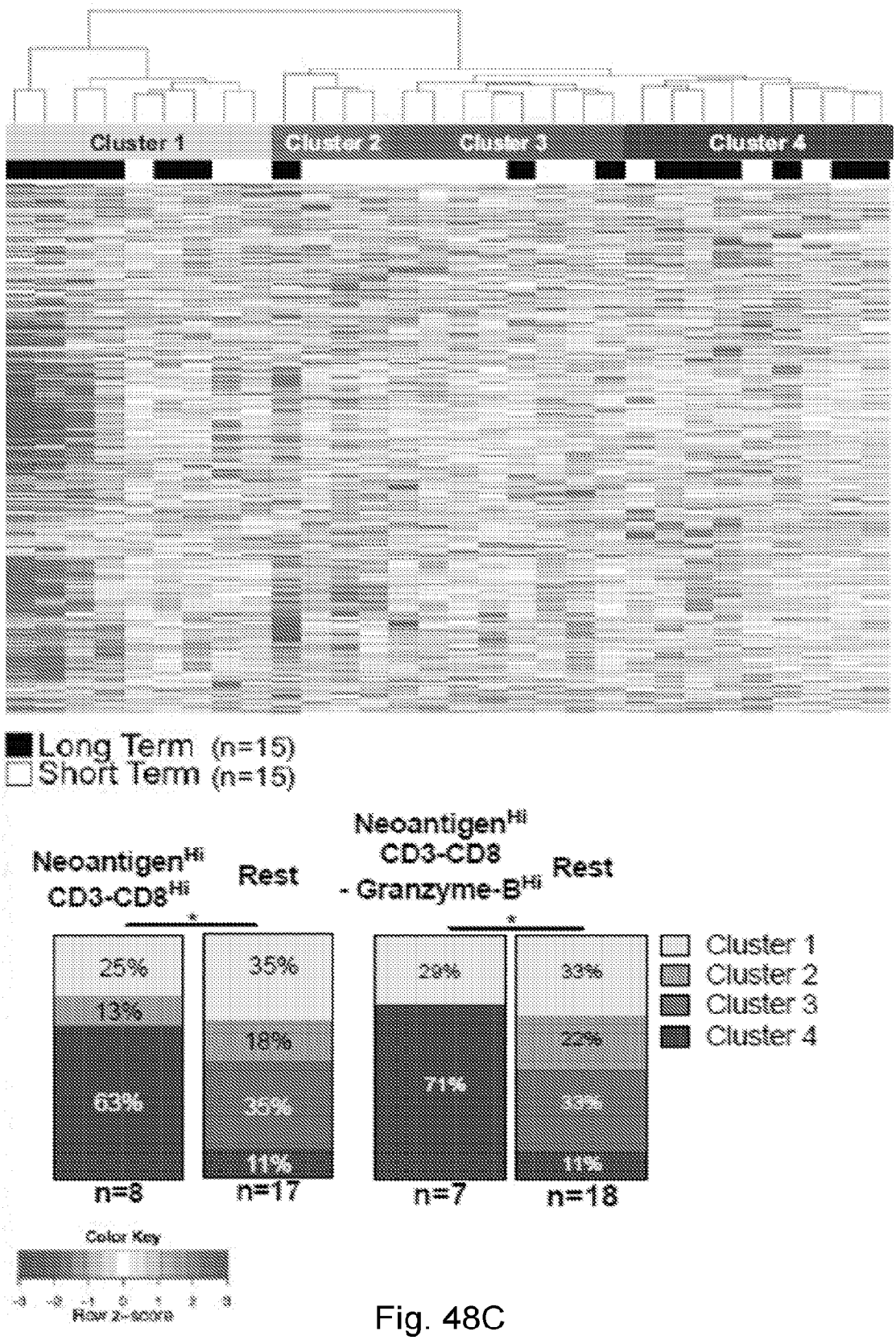

Cluster 1
Cluster 2
Cluster 3
Cluster 4
Long Term (n=15)
Short Term (n=15)
Neoantigen^Hi CD3-CD8^Hi
Rest
Neoantigen^Hi CD3-CD8 - Granzyme-B^Hi
Rest
25%
13%
63%
35%
18%
36%
11%
29%
71%
33%
22%
44%
11%
n=8
n=17
n=7
n=18
Cluster 1
Cluster 2
Cluster 3
Cluster 4
Color Key
Row Z-Score

Fig. 48C

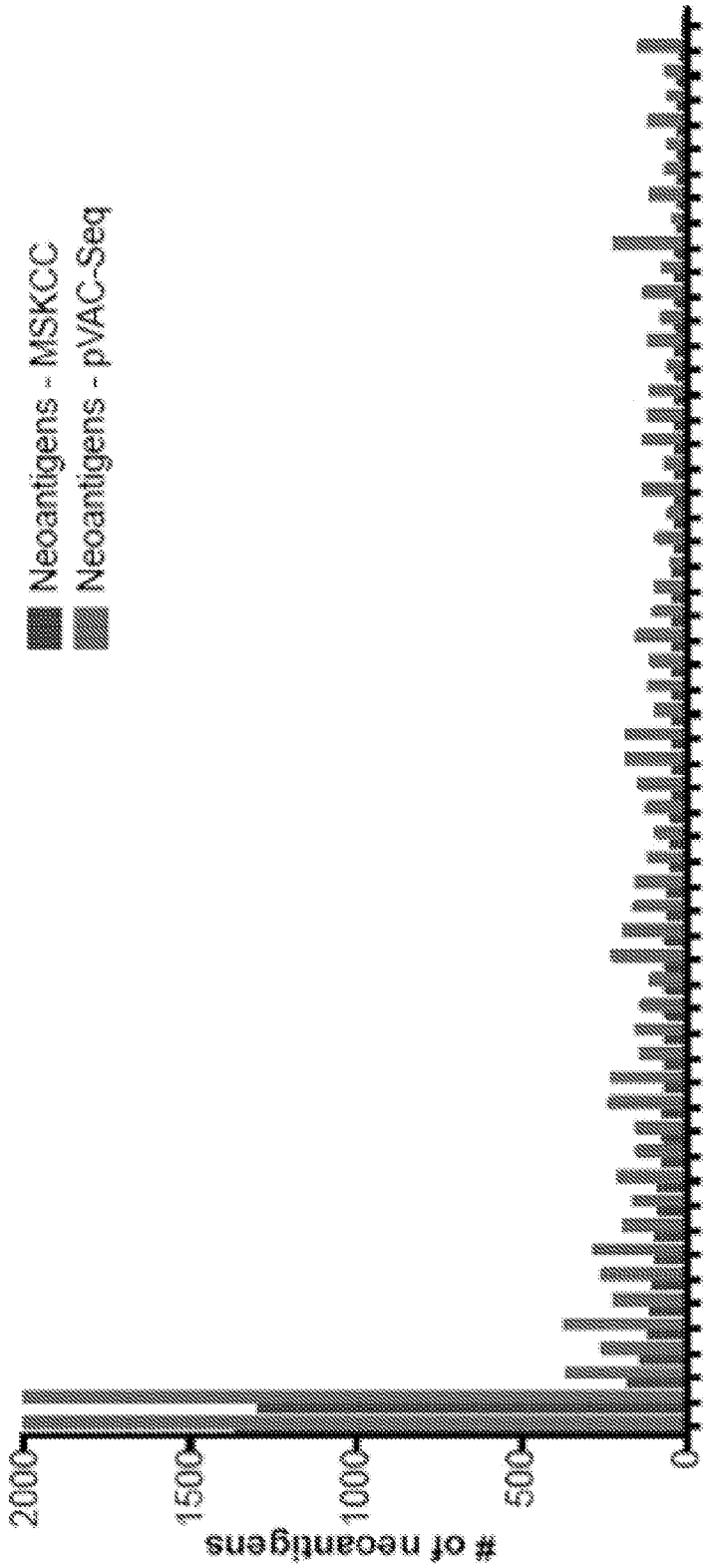

Neoantigens - MSKCC
Neoantigens - pVAC-Seq
of neoantigens
2000
1500
1000
500
0

Fig. 49A

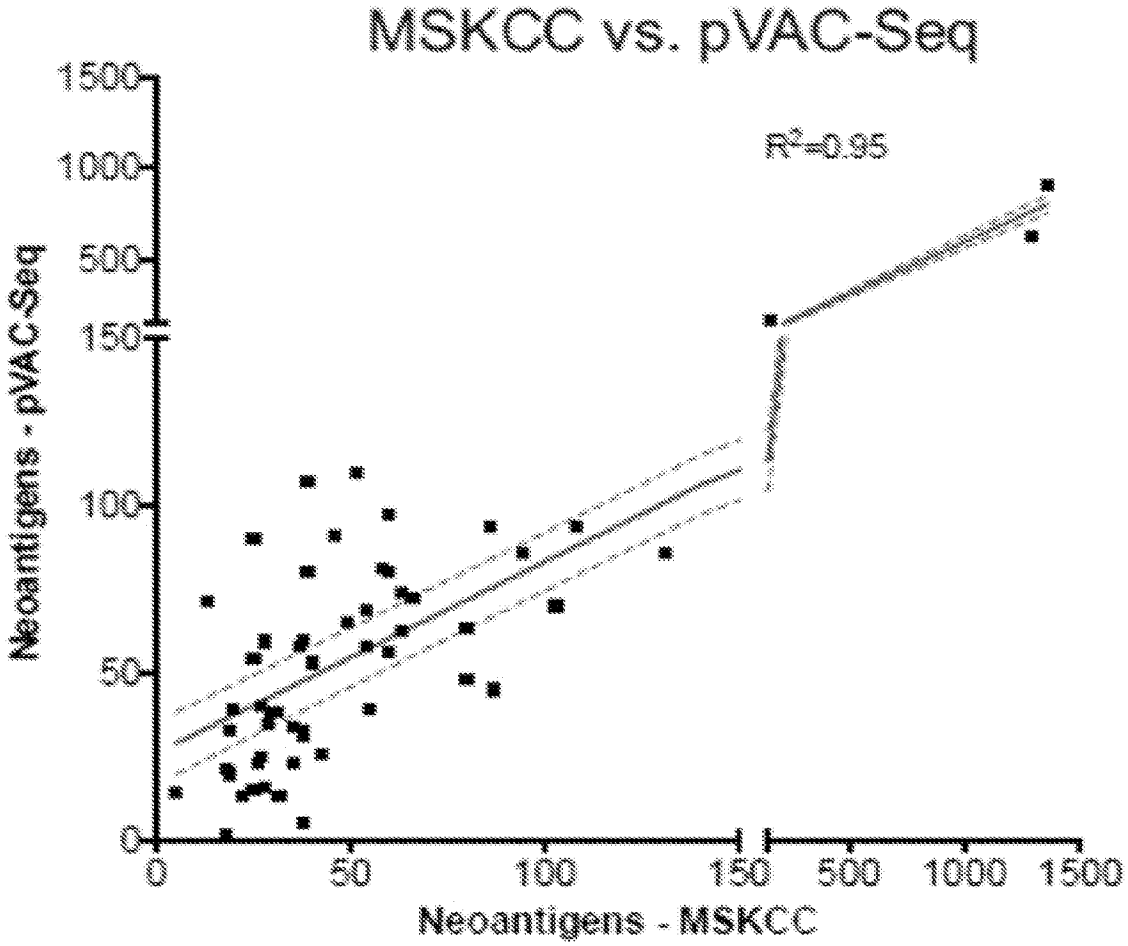

MSKCC vs. pVAC-Seq
R^2=0.95
Neoantigens - pVAC-Seq
Neoantigens - MSKCC
0
50
100
150
500
1000
1500

Fig. 49B

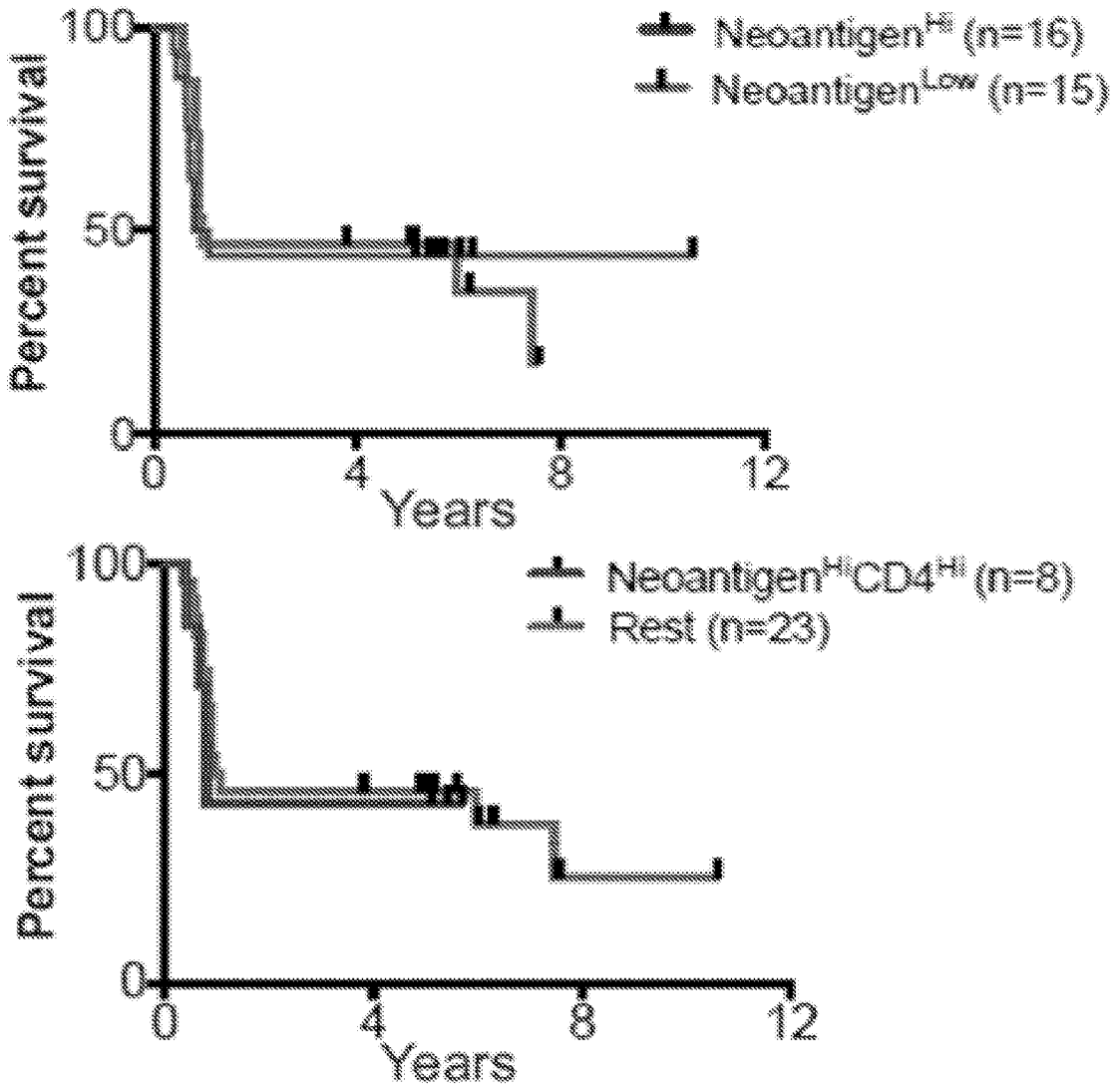

Neoantigen^{Hi} (n=16)
Neoantigen^{Low} (n=15)
Percent survival
100
50
0
0
4
8
12
Years
Neoantigen^{Hi}CD4^{Hi} (n=8)
Rest (n=23)
Percent survival
100
50
0
0
4
8
12
Years

Fig. 50A

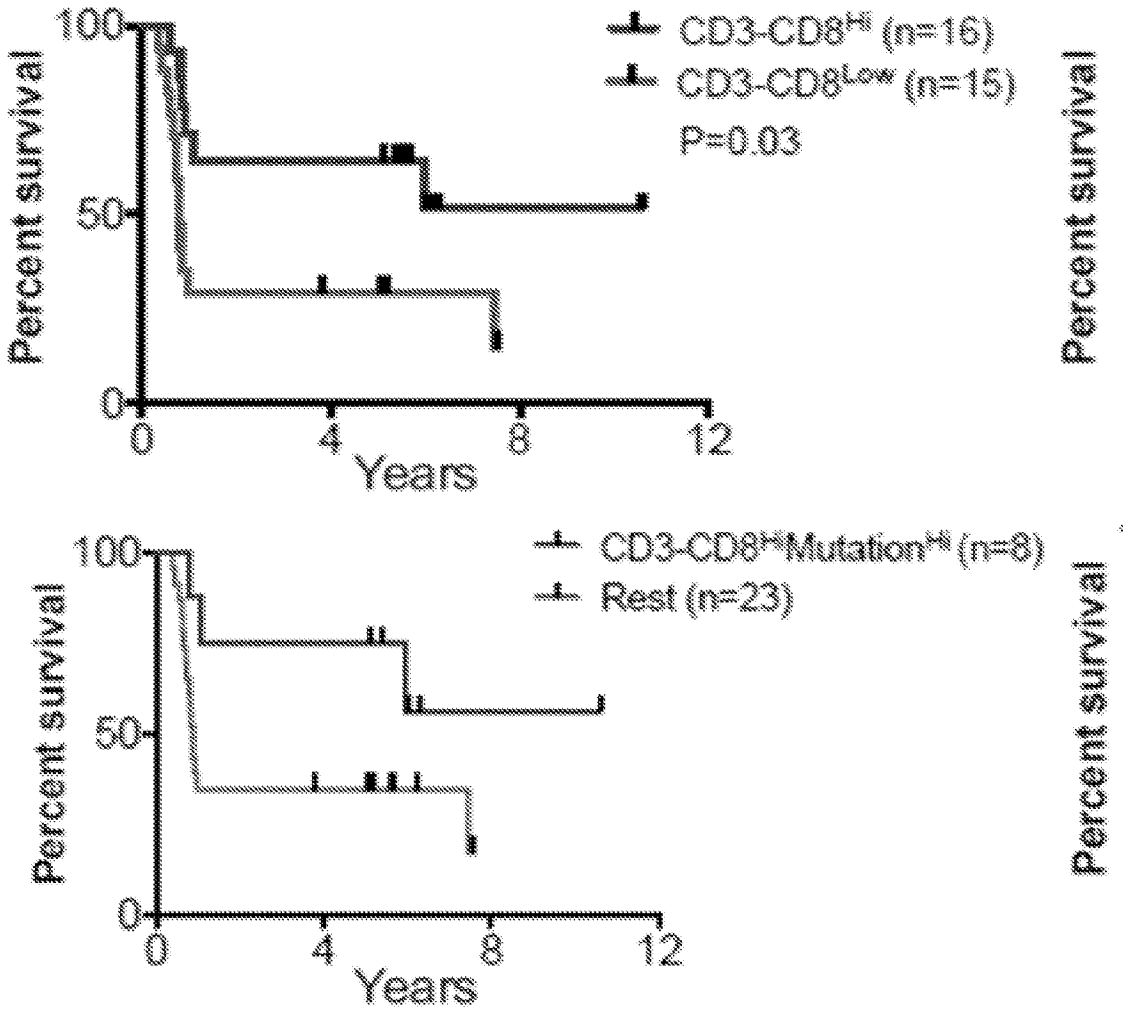

100
50
0
Percent survival
0
4
8
12
Years
CD3-CD8Hi (n=16)
CD3-CD8Low (n=15)
P=0.03
Percent survival
100
50
0
Percent survival
0
4
8
12
Years
CD3-CD8HiMutationHi (n=8)
Rest (n=23)
Percent survival

Fig. 50B

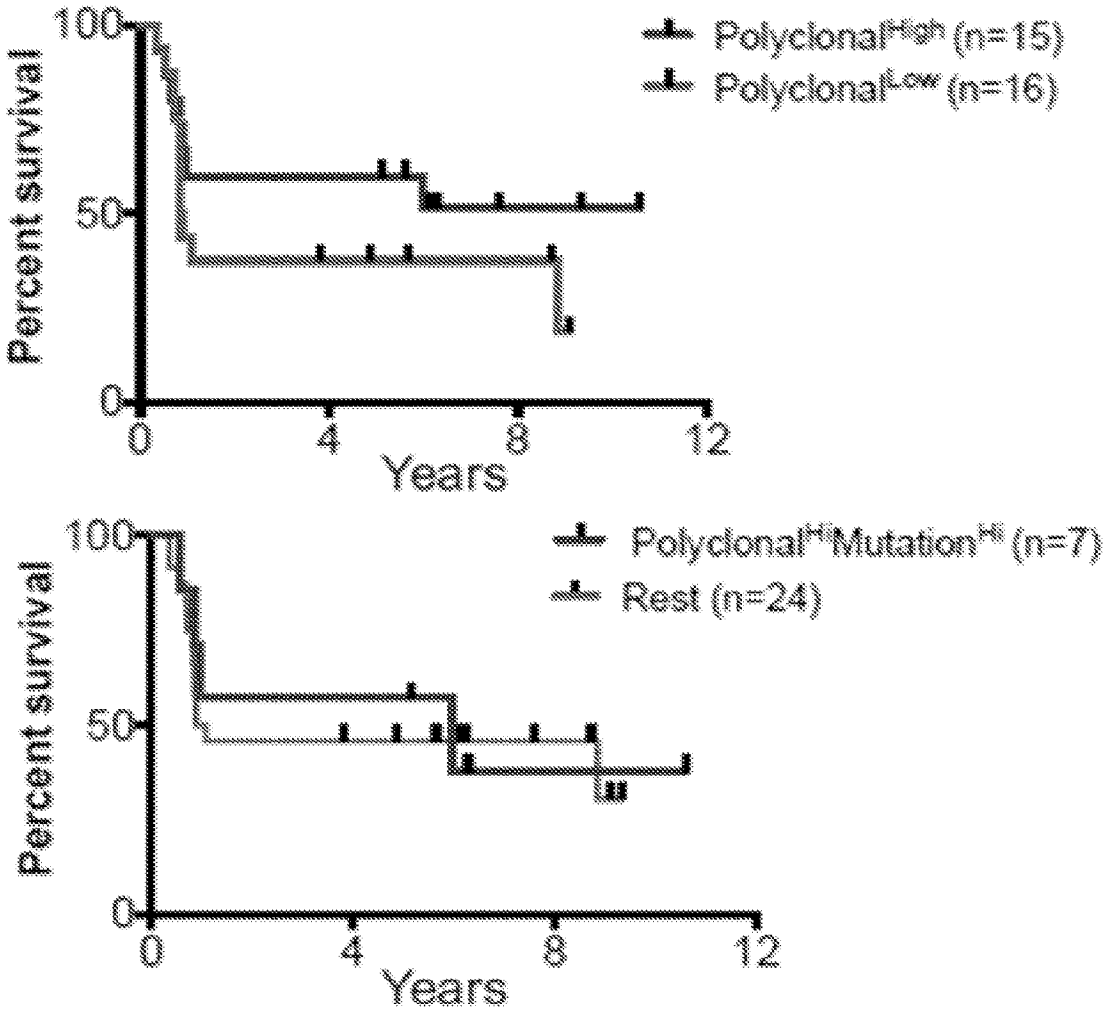

Percent survival
100
50
0
0
4
8
12
Years
Polyclonal^High (n=15)
Polyclonal^Low (n=16)
Percent survival
100
50
0
0
4
8
12
Years
Polyclonal^HiMutation^Hi (n=7)
Rest (n=24)

Fig. 50C

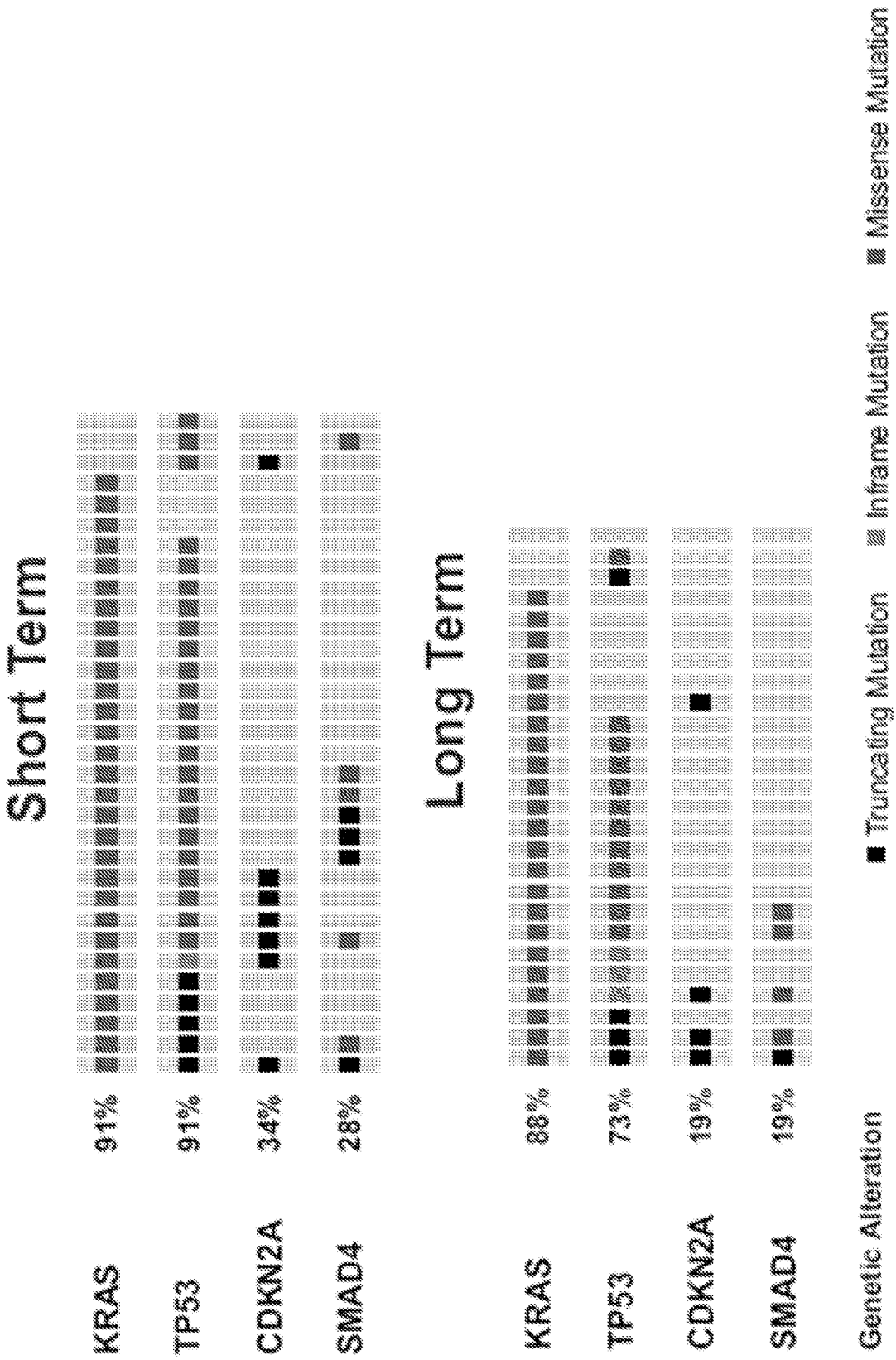

Short Term
KRAS
91%
TP53
91%
CDKN2A
34%
SMAD4
28%
Long Term
KRAS
88%
TP53
73%
CDKN2A
19%
SMAD4
19%
Genetic Alteration
Truncating Mutation
Inframe Mutation
Missense Mutation

Fig. 51

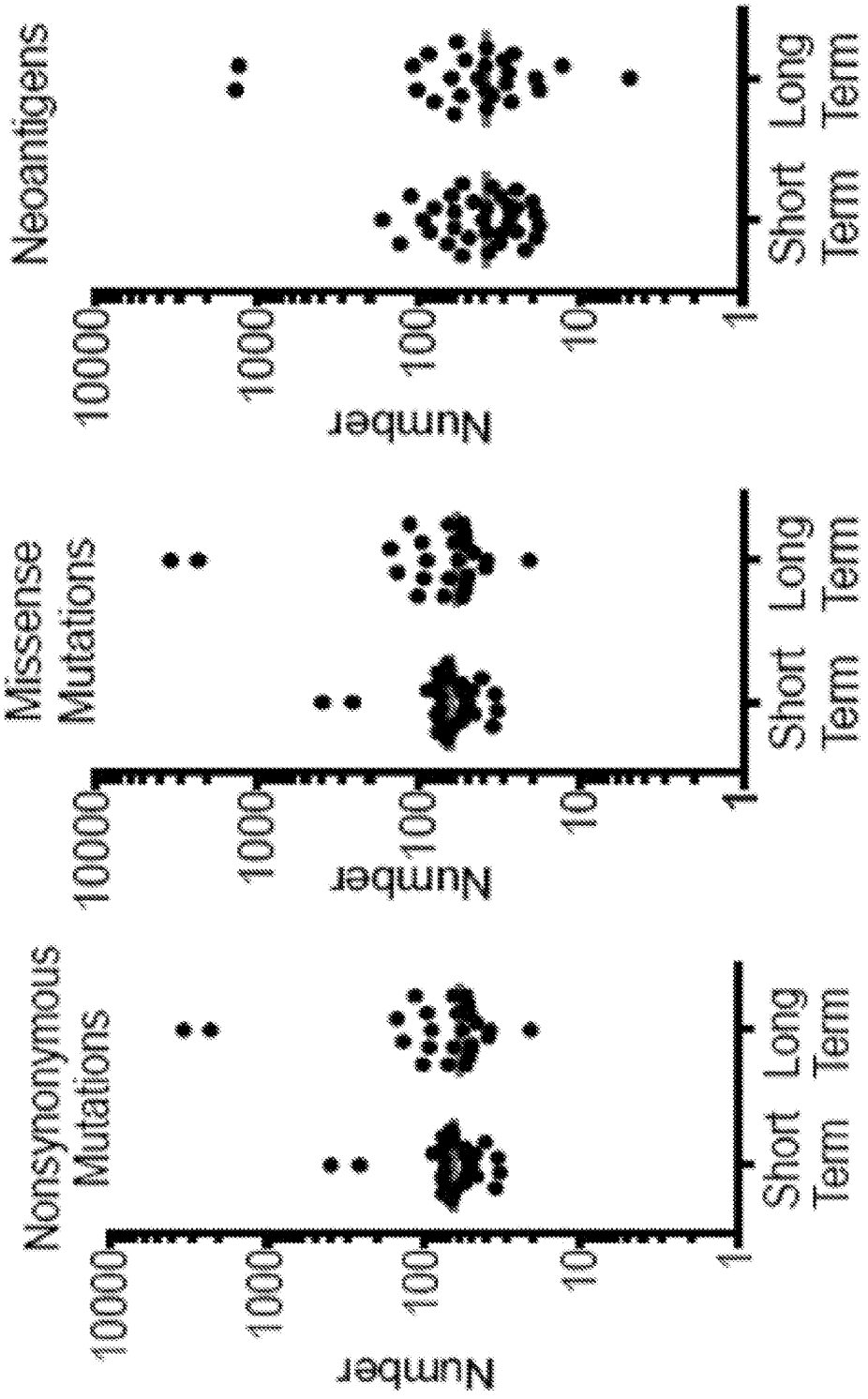

Nonsynonymous Mutations
Missense Mutations
Neoantigens
Number
10000
1000
100
10
1
Short Term
Long Term

Fig. 52

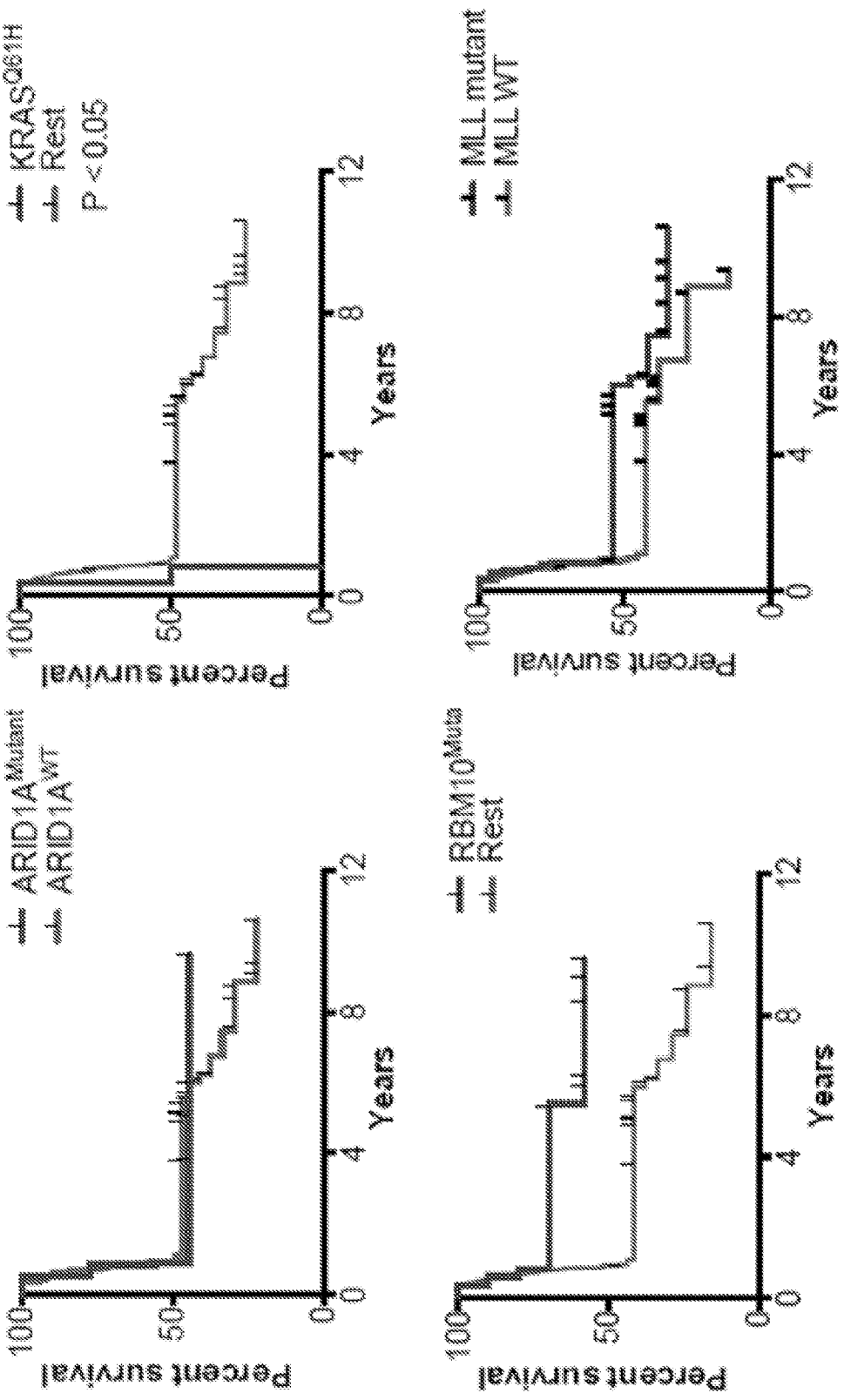

KRAS Q61H
Rest
P < 0.05
Percent survival
100
50
0
0
4
8
12
Years
MLL mutant
MLL WT
Percent survival
100
50
0
0
4
8
12
Years
ARID1A Mutant
ARID1A WT
Percent survival
100
50
0
0
4
8
12
Years
RBM10 Muta
Rest
Percent survival
100
50
0
0
4
8
12
Years

Fig. 53

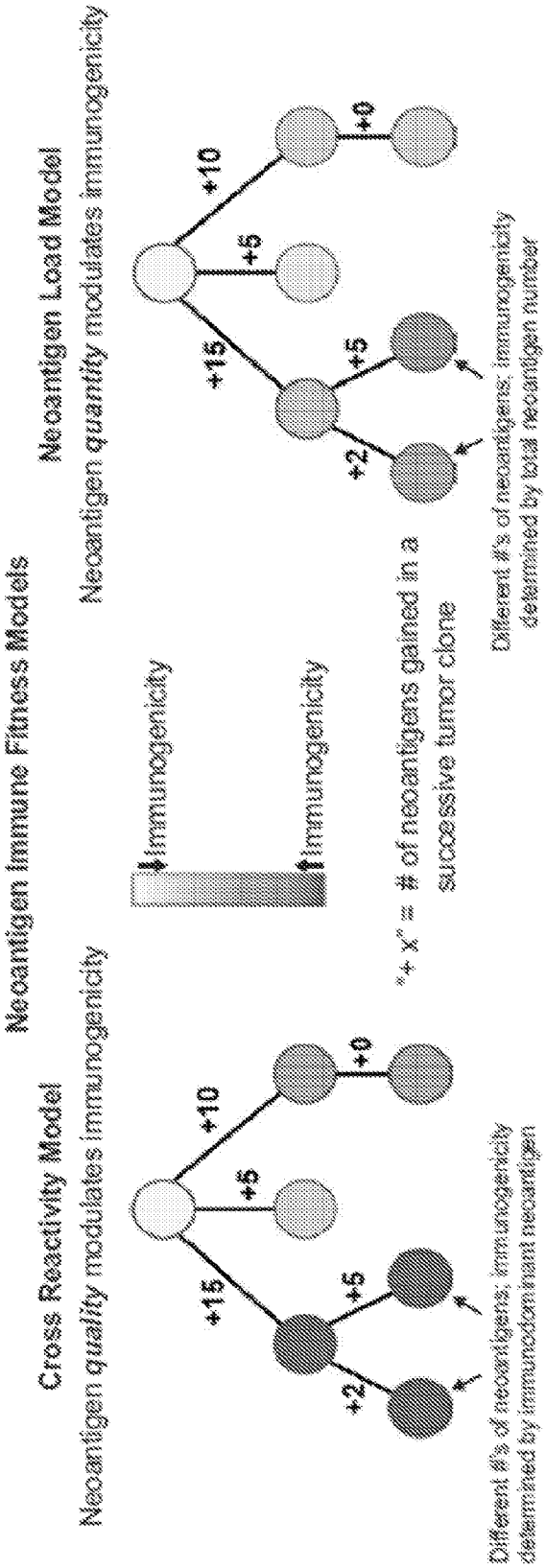

Neoantigen Immune Fitness Models
Cross Reactivity Model
Neoantigen quality modulates immunogenicity
+15
+5
+10
+0
+5
+2
Different #'s of neoantigens; immunogenicity determined by immunodominant neoantigen
Immunogenicity
Immunogenicity
"+ x" = # of neoantigens gained in a successive tumor clone
Neoantigen Load Model
Neoantigen quantity modulates immunogenicity
+15
+5
+10
+0
+5
+2
Different #'s of neoantigens; immunogenicity determined by total neoantigen number

Fig. 54A

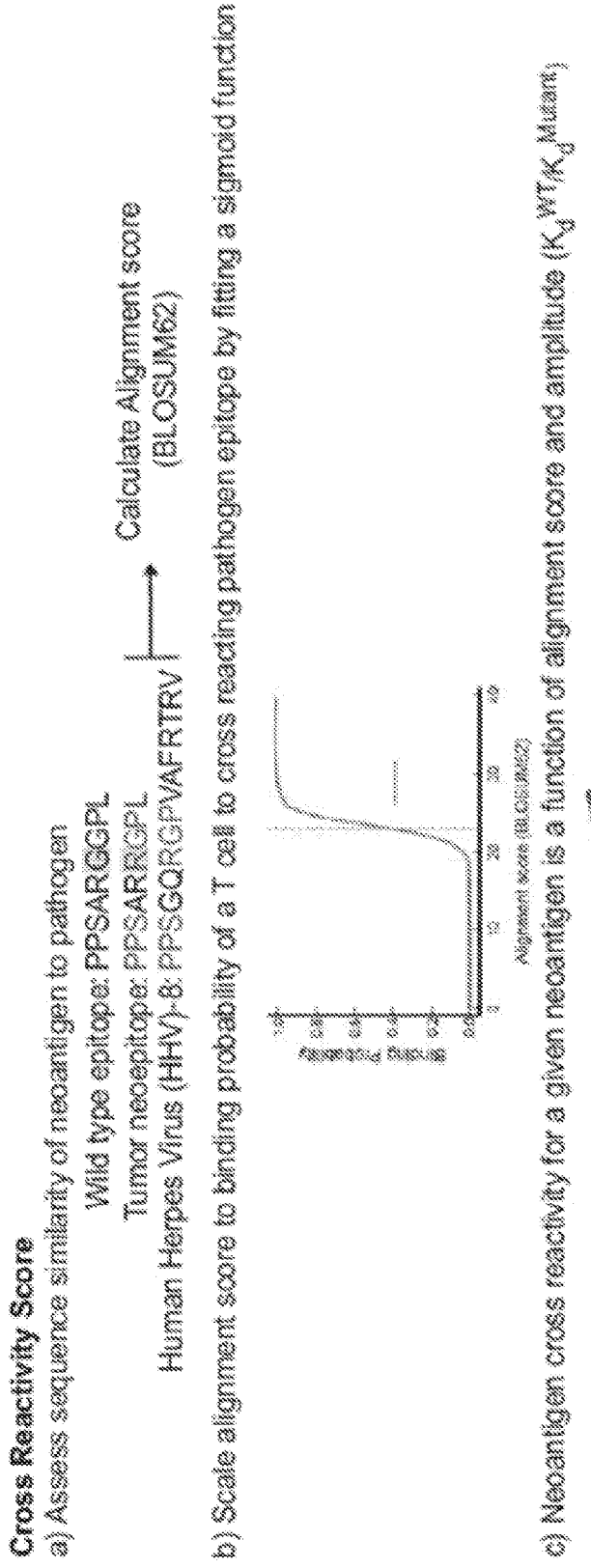

Cross Reactivity Score
a) Assess sequence similarity of neoantigen to pathogen
Wild type epitope: PPSARRGPL
Tumor neoepitope: PPSARRGPL
Human Herpes Virus (HHV)-8: PPSGQRGPVAFRTRV
Calculate Alignment score
(BLOSUM62)
b) Scale alignment score to binding probability of a T cell to cross reacting pathogen epitope by fitting a sigmoid function
c) Neoantigen cross reactivity for a given neoantigen is a function of alignment score and amplitude (K_d^{WT}/K_d^{Mutant})
Amplitude
Alignment score with pathogen
Neoantigen
cross reactivity

Fig. 54B

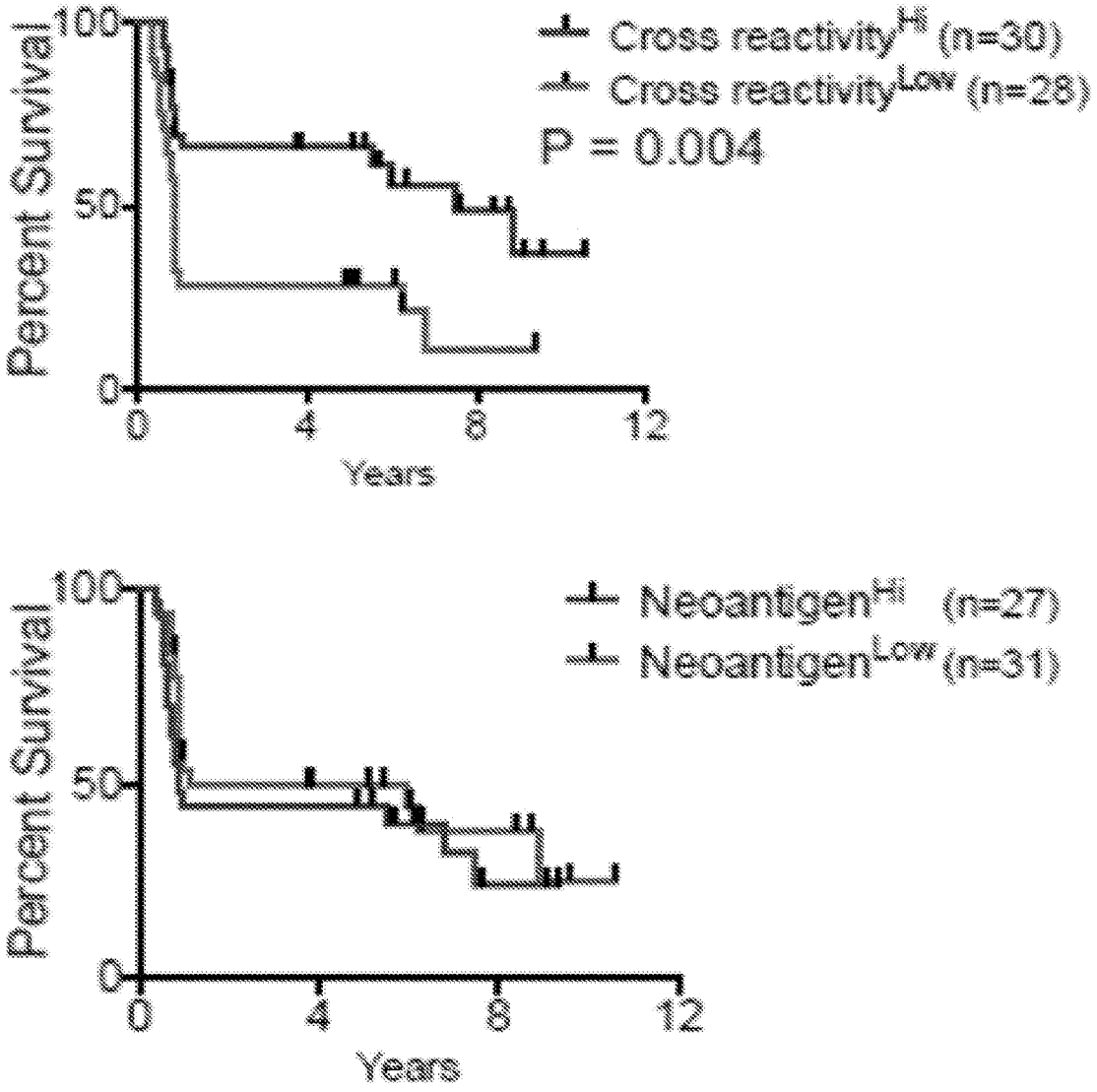

Percent Survival
100
50
0
0
4
8
12
Years
Cross reactivity^{Hi} (n=30)
Cross reactivity^{Low} (n=28)
P = 0.004
Percent Survival
100
50
0
0
4
8
12
Years
Neoantigen^{Hi} (n=27)
Neoantigen^{Low} (n=31)

Fig. 54C

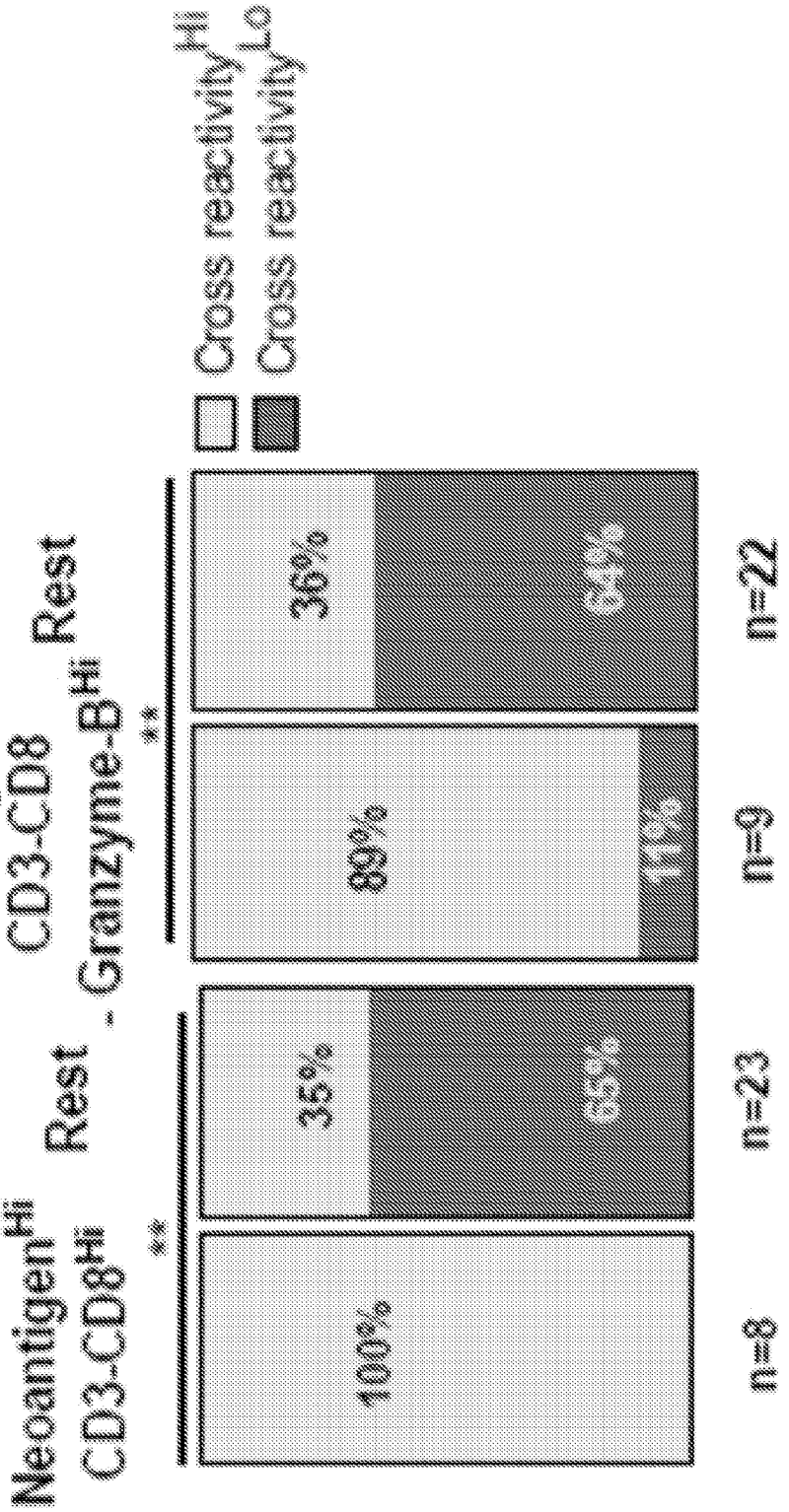

Cross reactivity^Hi
Cross reactivity^Lo
Neoantigen^Hi CD3-CD8^Hi
Rest
Neoantigen^Hi CD3-CD8 - Granzyme-B^Hi
Rest
**
**
100%
35%
65%
89%
11%
36%
64%
n=8
n=23
n=9
n=22

Fig. 54D

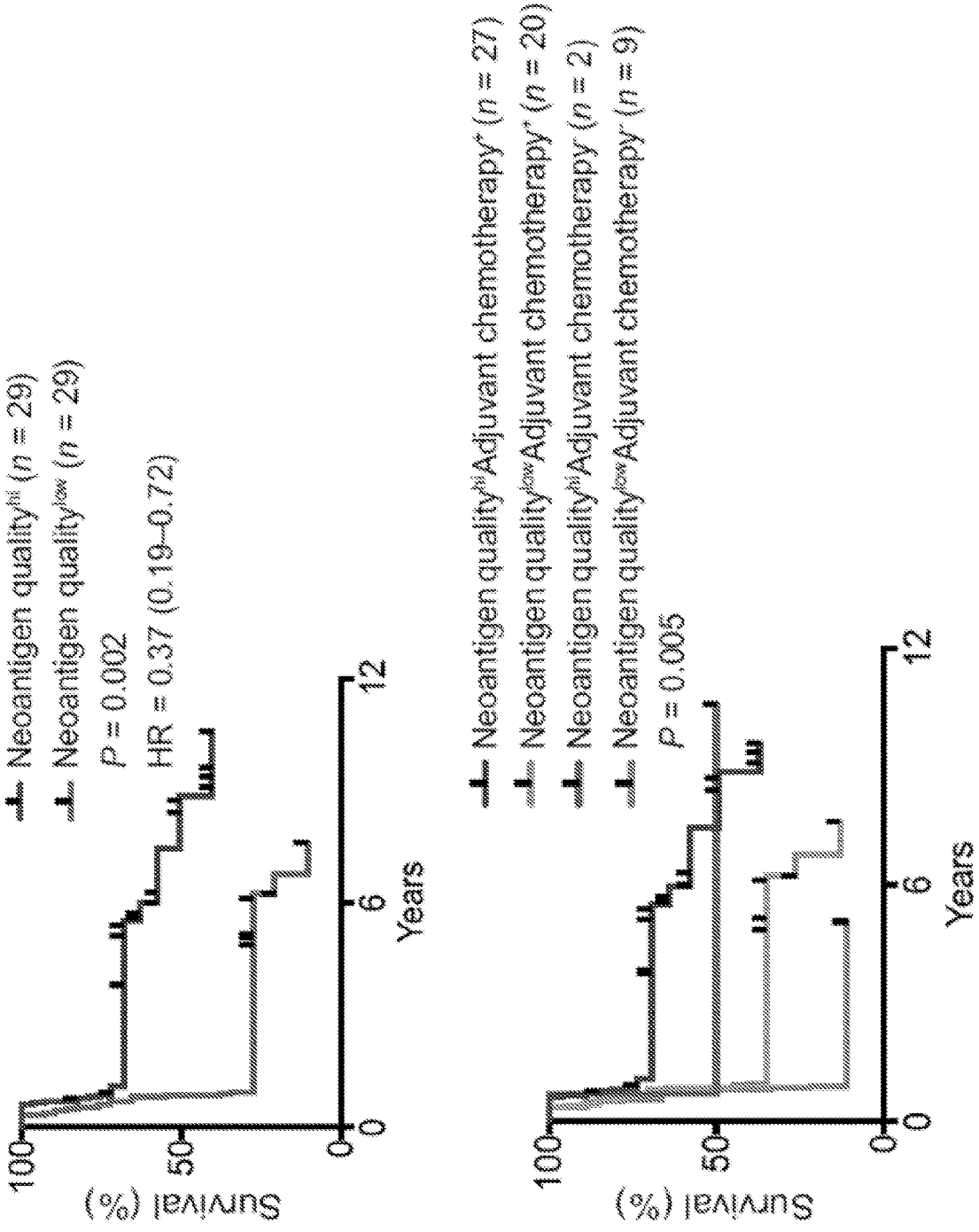

Neoantigen quality^hi (n = 29)
Neoantigen quality^low (n = 29)
P = 0.002
HR = 0.37 (0.19–0.72)
Survival (%)
100
50
0
0
6
12
Years
Neoantigen quality^hi Adjuvant chemotherapy* (n = 27)
Neoantigen quality^low Adjuvant chemotherapy* (n = 20)
Neoantigen quality^hi Adjuvant chemotherapy (n = 2)
Neoantigen quality^low Adjuvant chemotherapy (n = 9)
P = 0.005
Survival (%)
100
50
0
0
6
12
Years

Fig. 54E1

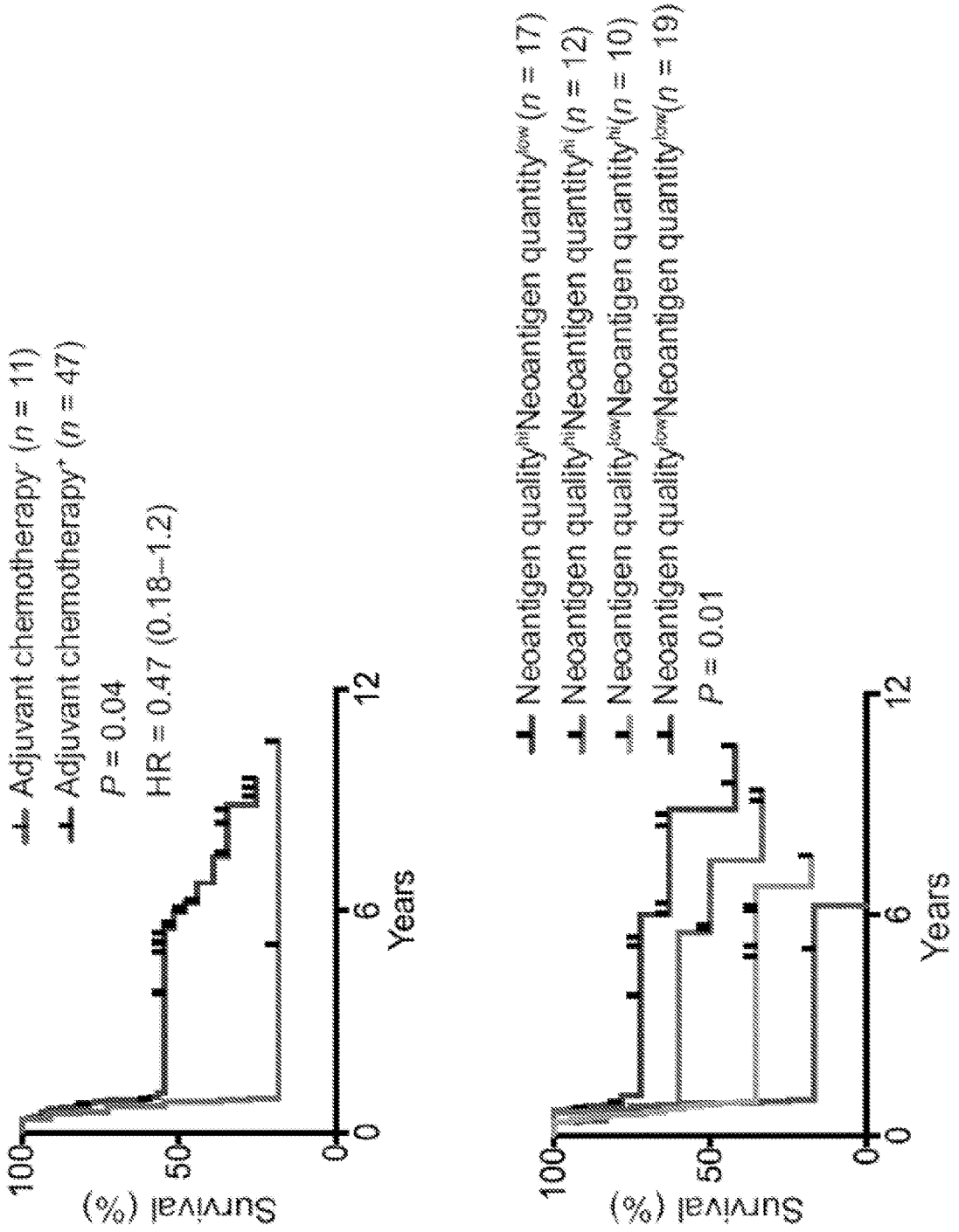

Adjuvant chemotherapy (n = 11)
Adjuvant chemotherapy* (n = 47)
P = 0.04
HR = 0.47 (0.18–1.2)
Survival (%)
100
50
0
0
6
12
Years
Neoantigen quality^high Neoantigen quantity^low (n = 17)
Neoantigen quality^high Neoantigen quantity^high (n = 12)
Neoantigen quality^low Neoantigen quantity^high (n = 10)
Neoantigen quality^low Neoantigen quantity^low (n = 19)
P = 0.01
Survival (%)
100
50
0
0
6
12
Years

Fig. 54E2

Variable	Univariate			Multivariate		
	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value
Adjuvant chemotherapy	0.4	0.1–0.9	0.02	0.5	0.2–1.2	0.1
Pathologic stage	1.4	0.5–4.1	0.4	-	-	-
Margin	1.5	0.7–3.4	0.2	-	-	-
Neoantigen quality	0.3	0.1–0.7	0.003	0.3	0.1–0.7	0.008

Fig. 54E3

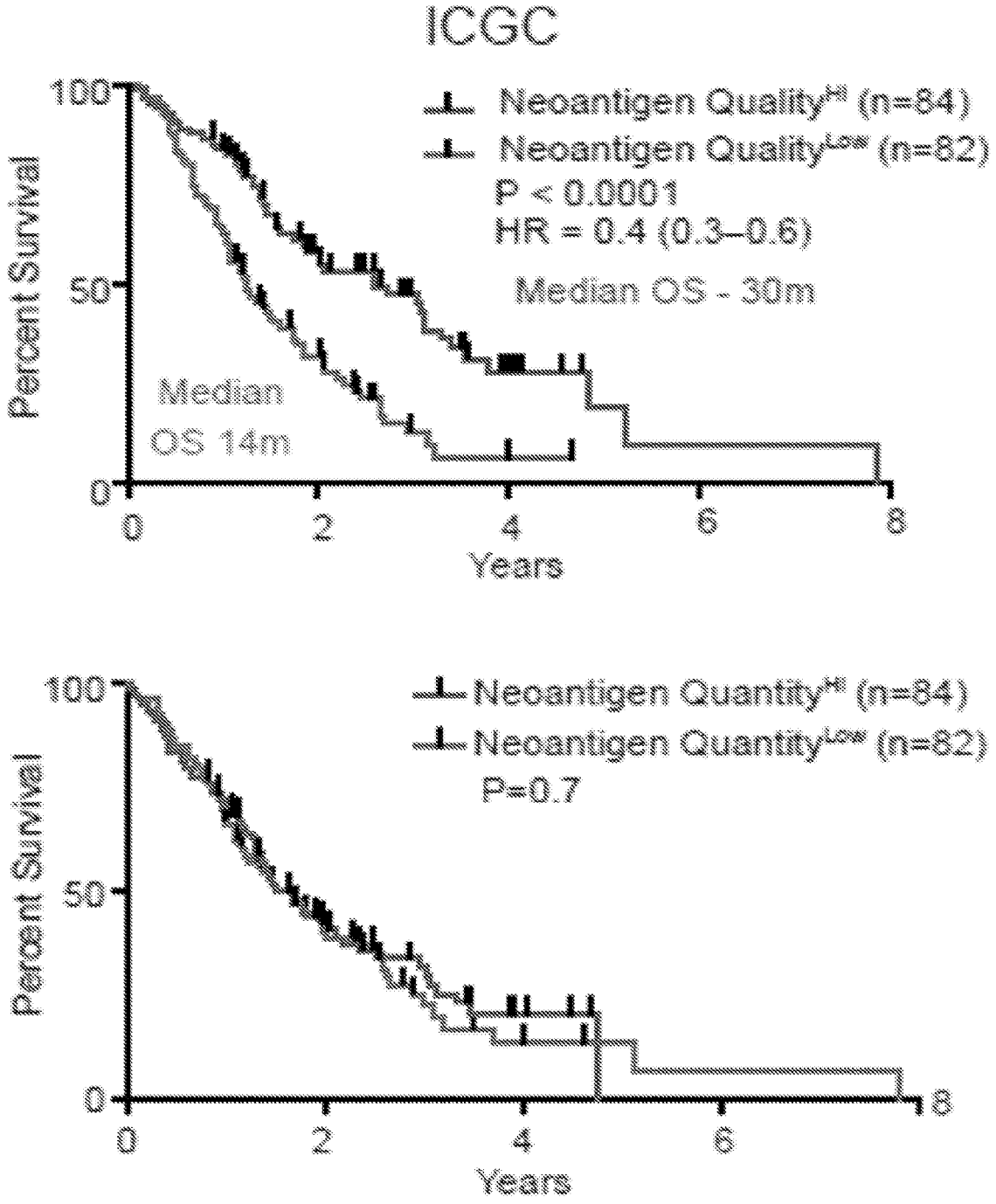

ICGC
Neoantigen Quality^Hi (n=84)
Neoantigen Quality^Low (n=82)
P < 0.0001
HR = 0.4 (0.3–0.6)
Median OS - 30m
Median
OS 14m
Percent Survival
100
50
0
0
2
4
6
8
Years
Neoantigen Quantity^Hi (n=84)
Neoantigen Quantity^Low (n=82)
P=0.7
Percent Survival
100
50
0
0
2
4
6
8
Years

Fig. 54F

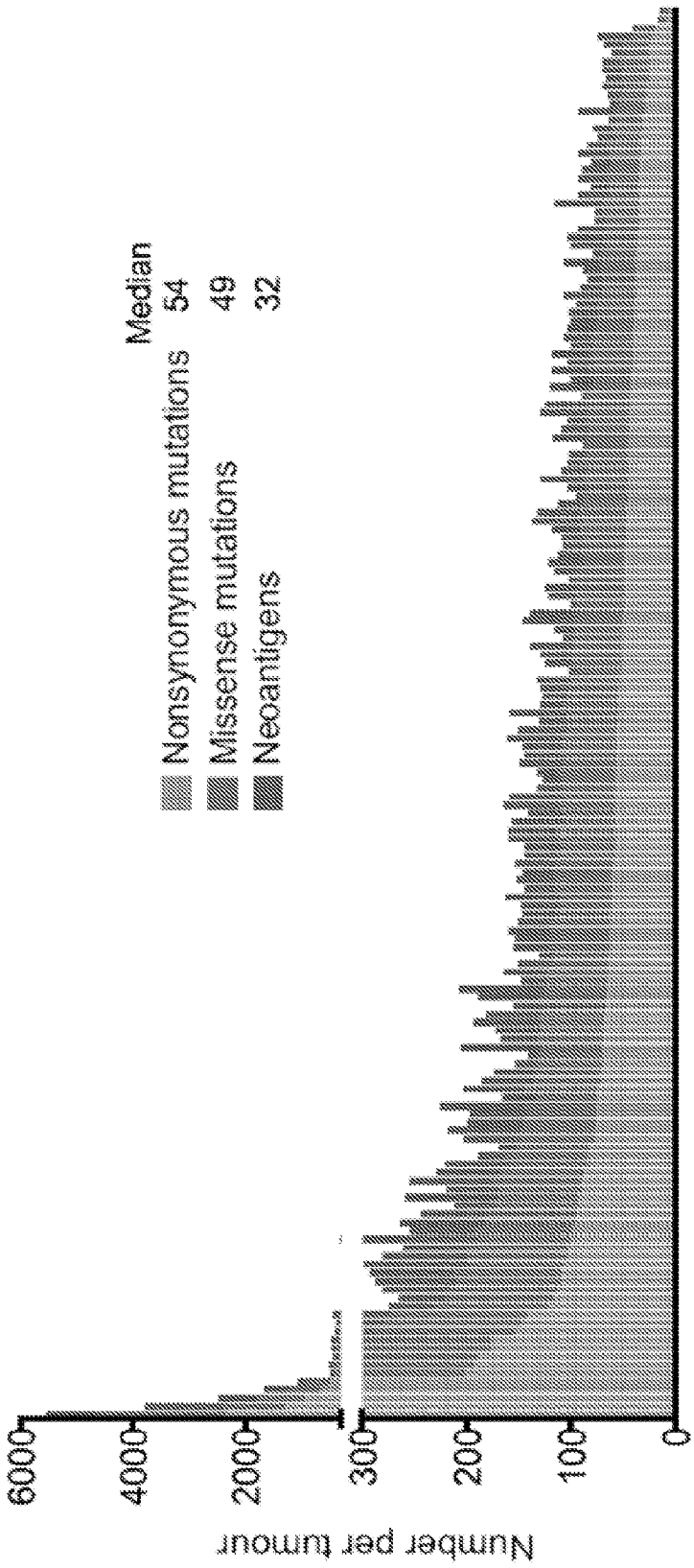

Median
Nonsynonymous mutations 54
Missense mutations 49
Neoantigens 32
Number per tumour
6000
4000
2000
300
200
100
0
Tumour Samples (n=166)

Fig. 54G1

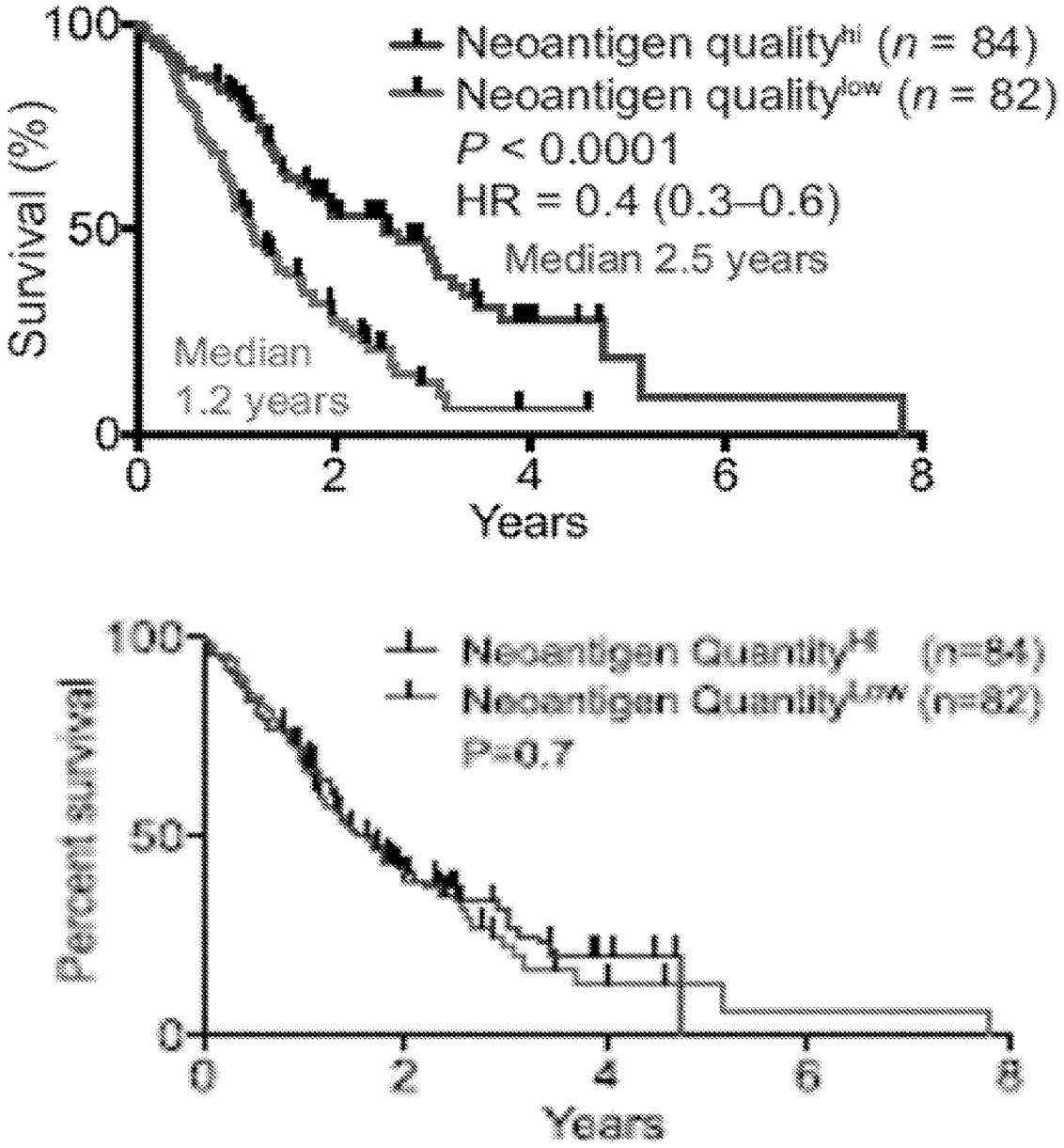

100
50
0
Survival (%)
0
2
4
6
8
Years
Neoantigen quality^hi (n = 84)
Neoantigen quality^low (n = 82)
P < 0.0001
HR = 0.4 (0.3–0.6)
Median 2.5 years
Median
1.2 years
100
50
0
Percent survival
0
2
4
6
8
Years
Neoantigen Quantity^Hi (n=84)
Neoantigen Quantity^Low (n=82)
P=0.7

Fig. 54G2

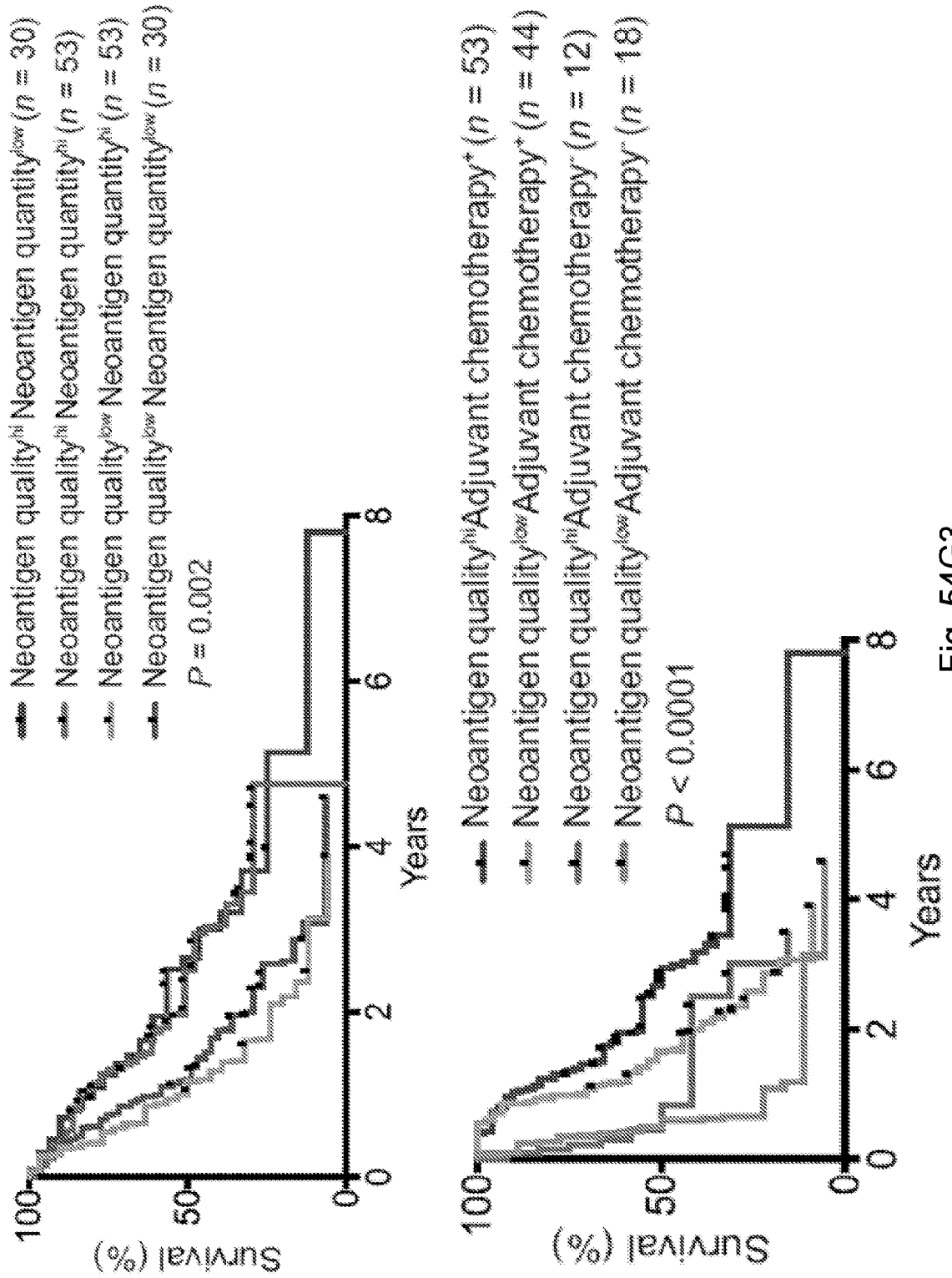

Neoantigen quality^hi Neoantigen quantity^low (n = 30)
Neoantigen quality^hi Neoantigen quantity^hi (n = 53)
Neoantigen quality^low Neoantigen quantity^hi (n = 53)
Neoantigen quality^low Neoantigen quantity^low (n = 30)
P = 0.002
Survival (%)
100
50
0
0
2
4
6
8
Years
Neoantigen quality^hi Adjuvant chemotherapy+ (n = 53)
Neoantigen quality^low Adjuvant chemotherapy+ (n = 44)
Neoantigen quality^hi Adjuvant chemotherapy- (n = 12)
Neoantigen quality^low Adjuvant chemotherapy- (n = 18)
P < 0.0001
Survival (%)
100
50
0
0
2
4
6
8
Years

Fig. 54G3

Variable	Univariate			Multivariate		
	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value
Adjuvant chemotherapy	0.4	0.2–0.5	0.0001	0.4	0.2–0.7	0.001
Pathologic stage						
-Stage I	-	-	-	-	-	-
-Stage II	2.5	0.9–7	0.07	3.7	0.9–15.9	0.07
Stage III/IV	6.8	1.9–24.8	0.004	12.7	1.1–146	0.04
Margin						
-R0	-	-	-	-	-	-
-R1	2.3	1.4–3.7	0.0001	2.7	1.6–4.5	0.001
-R2	3.6	1.6–8	0.001	0.9	0.09–9.5	0.9
Neoantigen Quality	0.4	0.3–0.64	0.0001	0.5	0.3–0.9	0.01

Fig. 54G4

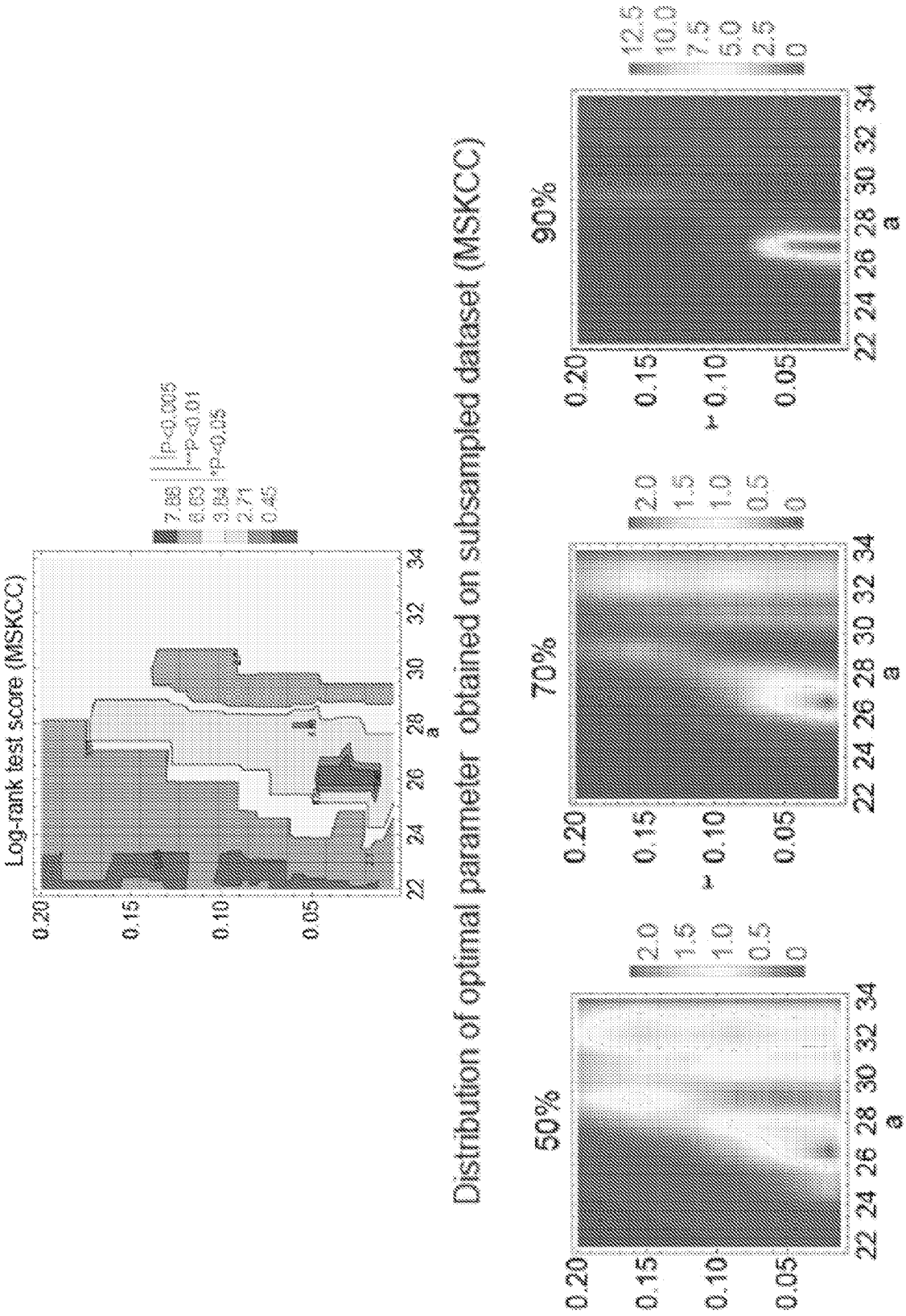

Distribution of optimal parameter obtained on subsampled dataset (MSKCC)
Log-rank test score (MSKCC)
7.88 P<0.005
6.63 **P<0.01
3.84 *P<0.05
2.71
0.45
0.20
0.15
0.10
0.05
22 24 26 28 30 32 34
a
50%
70%
90%
2.0
1.5
1.0
0.5
0
12.5
10.0
7.5
5.0
2.5
0
r 0.10

Fig. 54H1

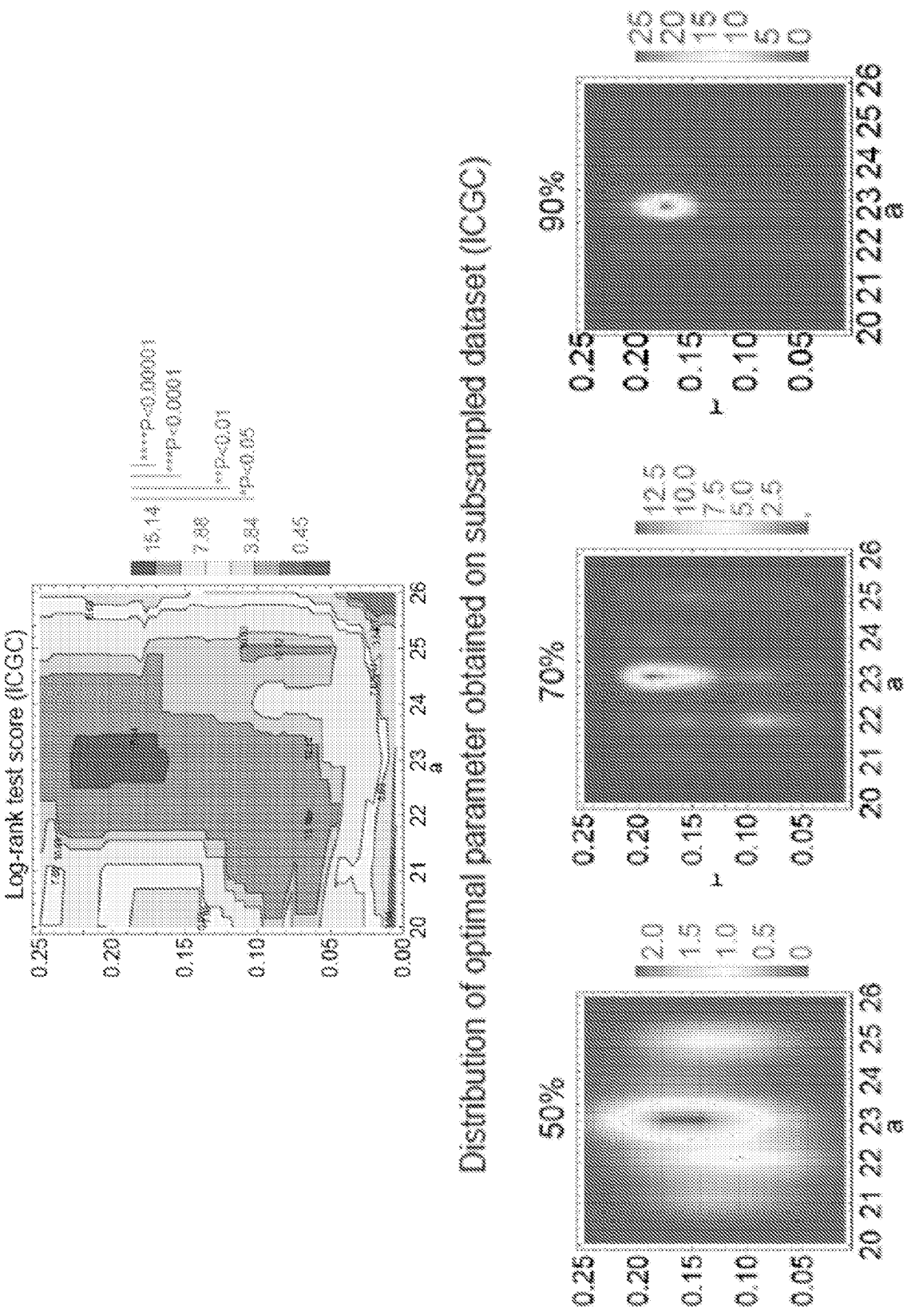

Distribution of optimal parameter obtained on subsampled dataset (ICGC)
Log-rank test score (ICGC)
15.14
7.89
3.84
0.45
***p<0.00001
**p<0.0001
**p<0.01
*p<0.05
0.25
0.20
0.15
0.10
0.05
0.00
20 21 22 23 24 25 26
a
50%
70%
90%
2.0
1.5
1.0
0.5
0
12.5
10.0
7.5
5.0
2.5
25
20
15
10
5
0

Fig. 54H2

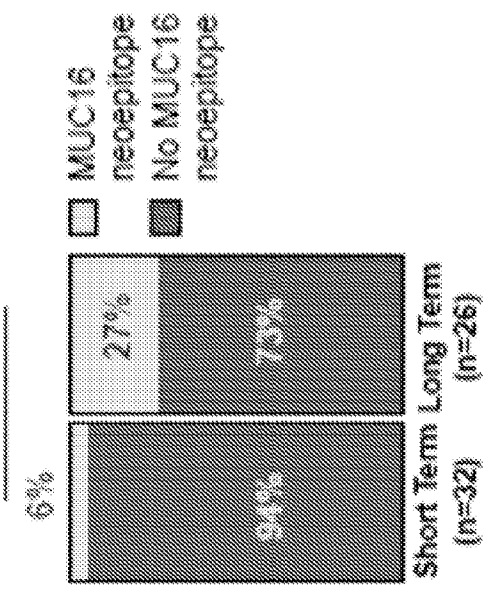


Fig. 55B

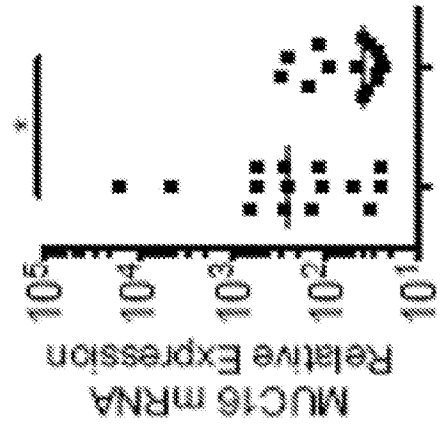


Fig. 55D

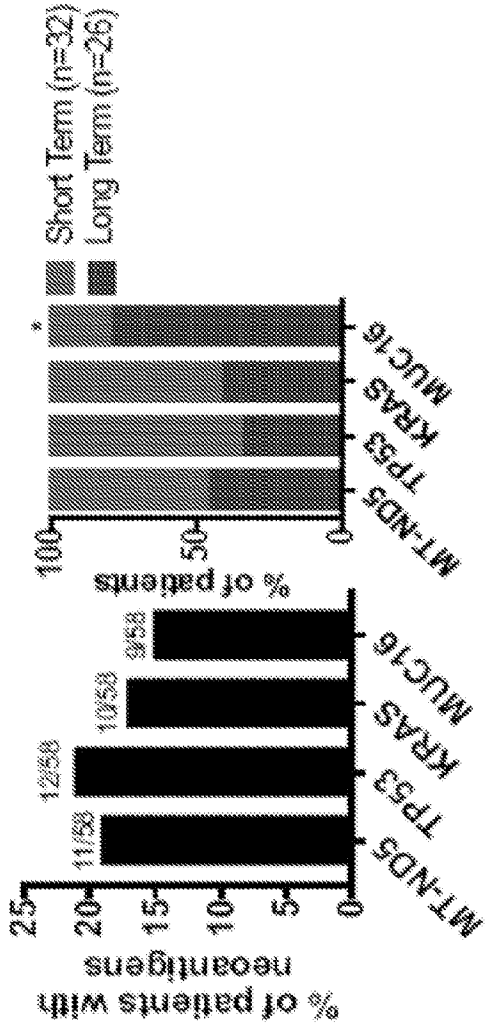


Fig. 55A

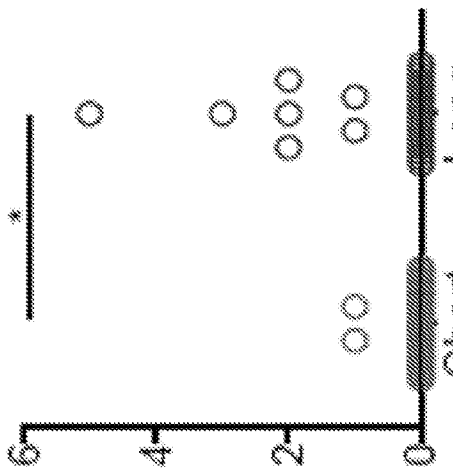


Fig. 55C

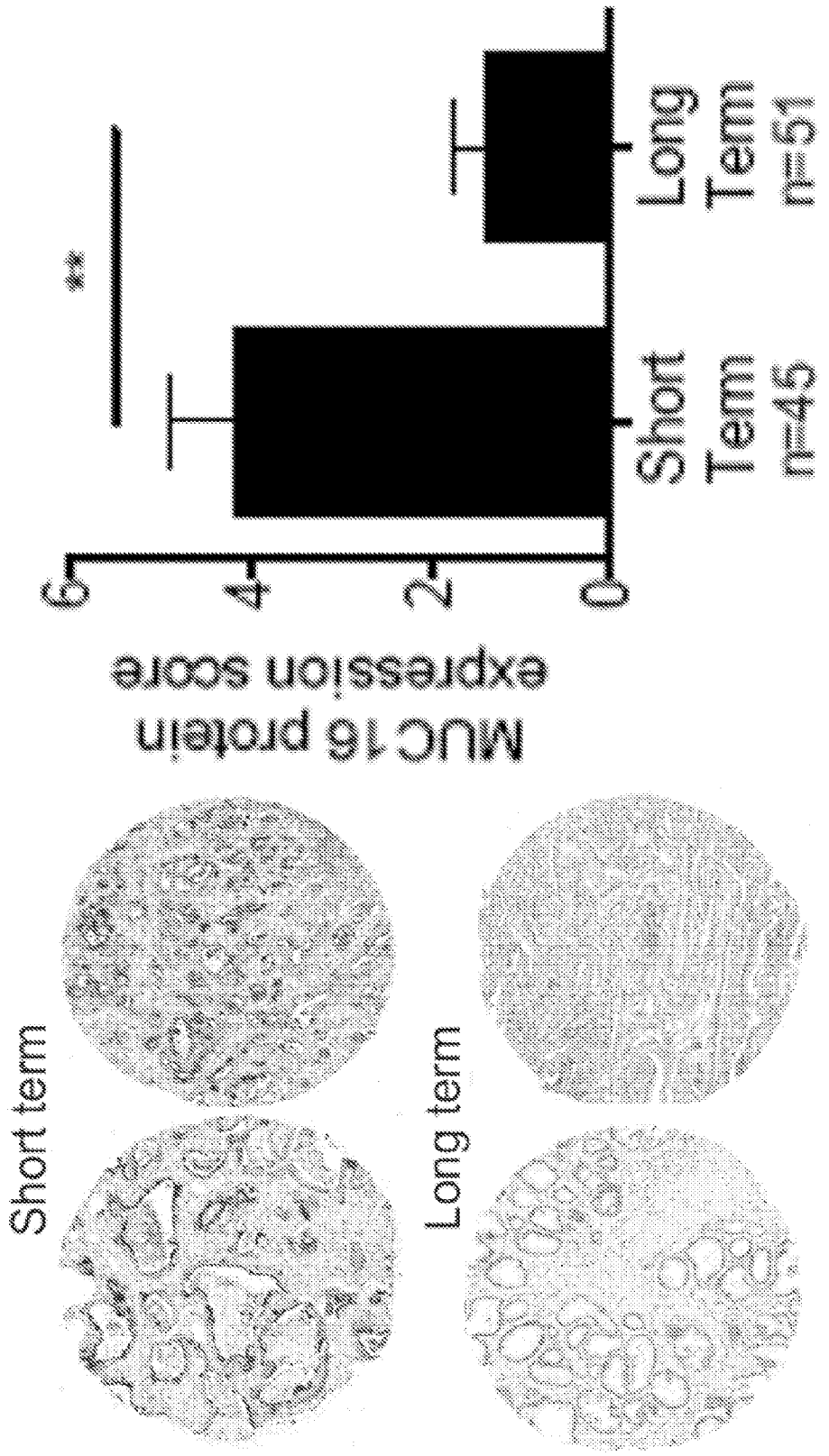

MUC16 protein expression score
0
2
4
6
**
Short Tem n=45
Long Tem n=51
Short term
Long term

Fig. 55E

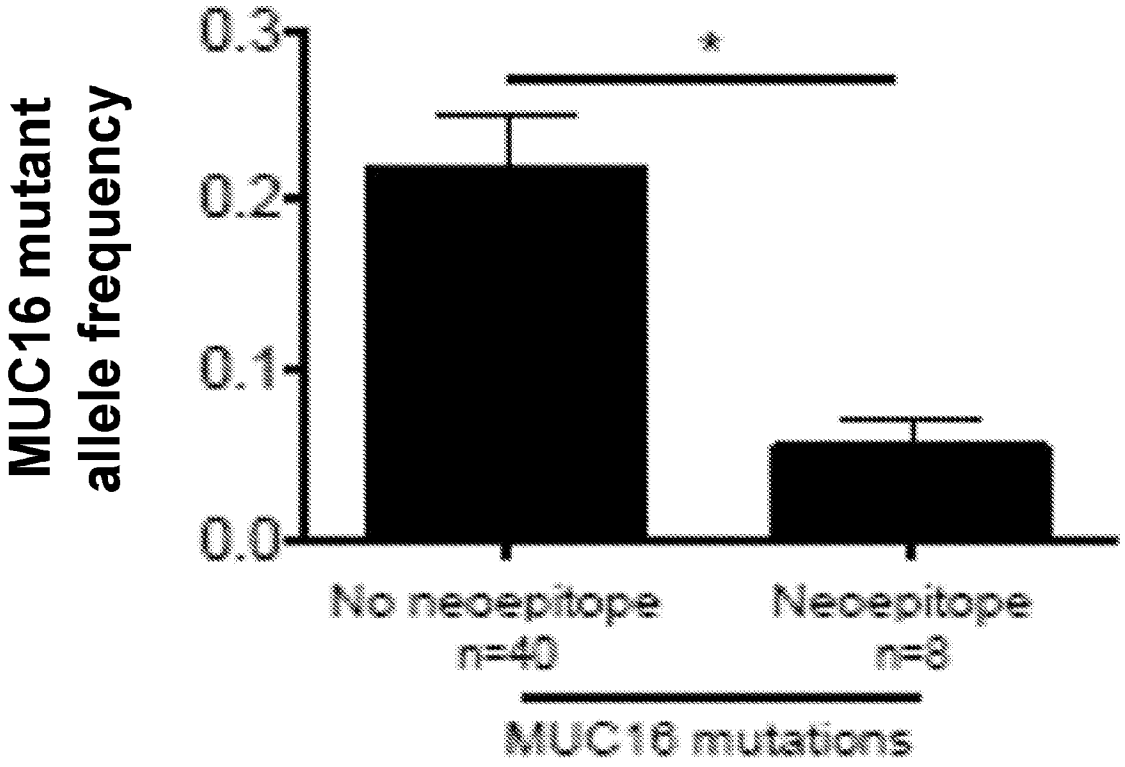


Fig. 55F

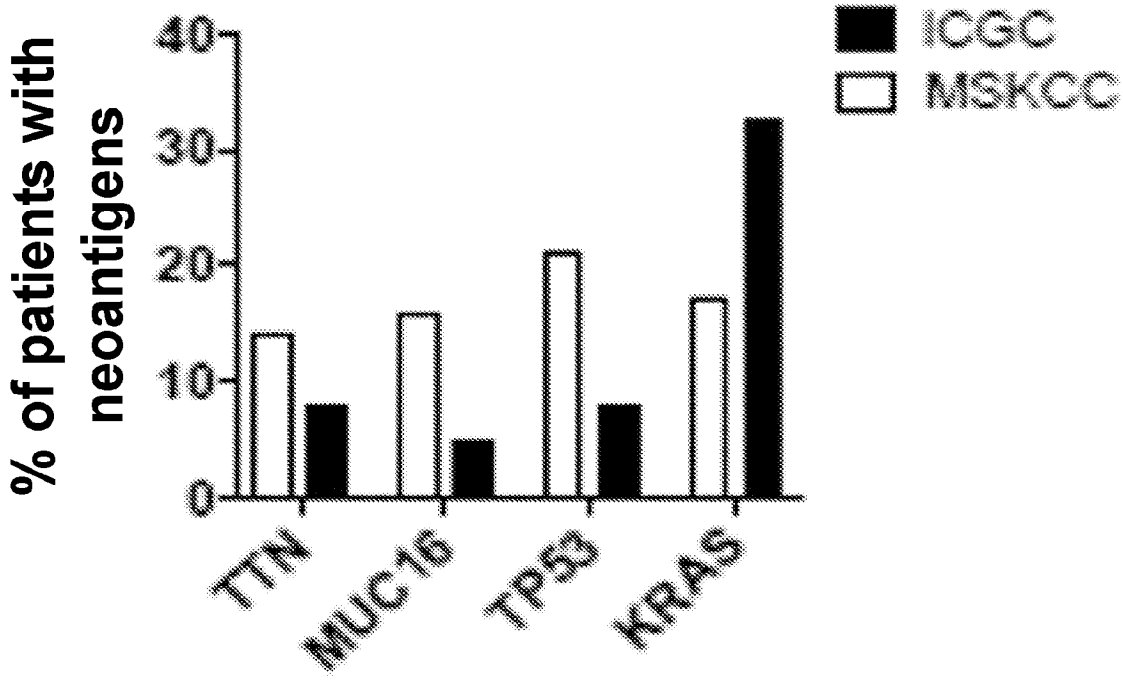


Fig. 55G

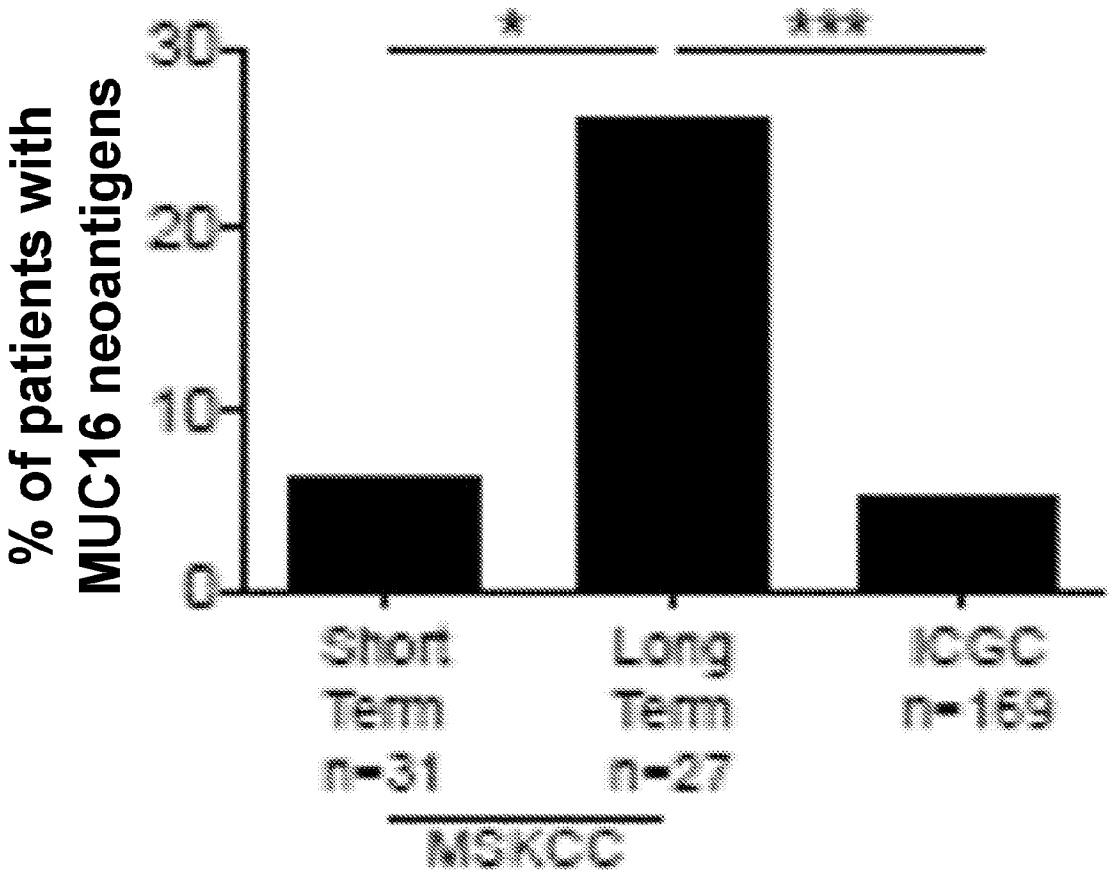

% of patients with MUC16 neoantigens
30
20
10
0
*
***
Short Term n=31
Long Term n=27
ICGC n=169
MSKCC

Fig. 55H

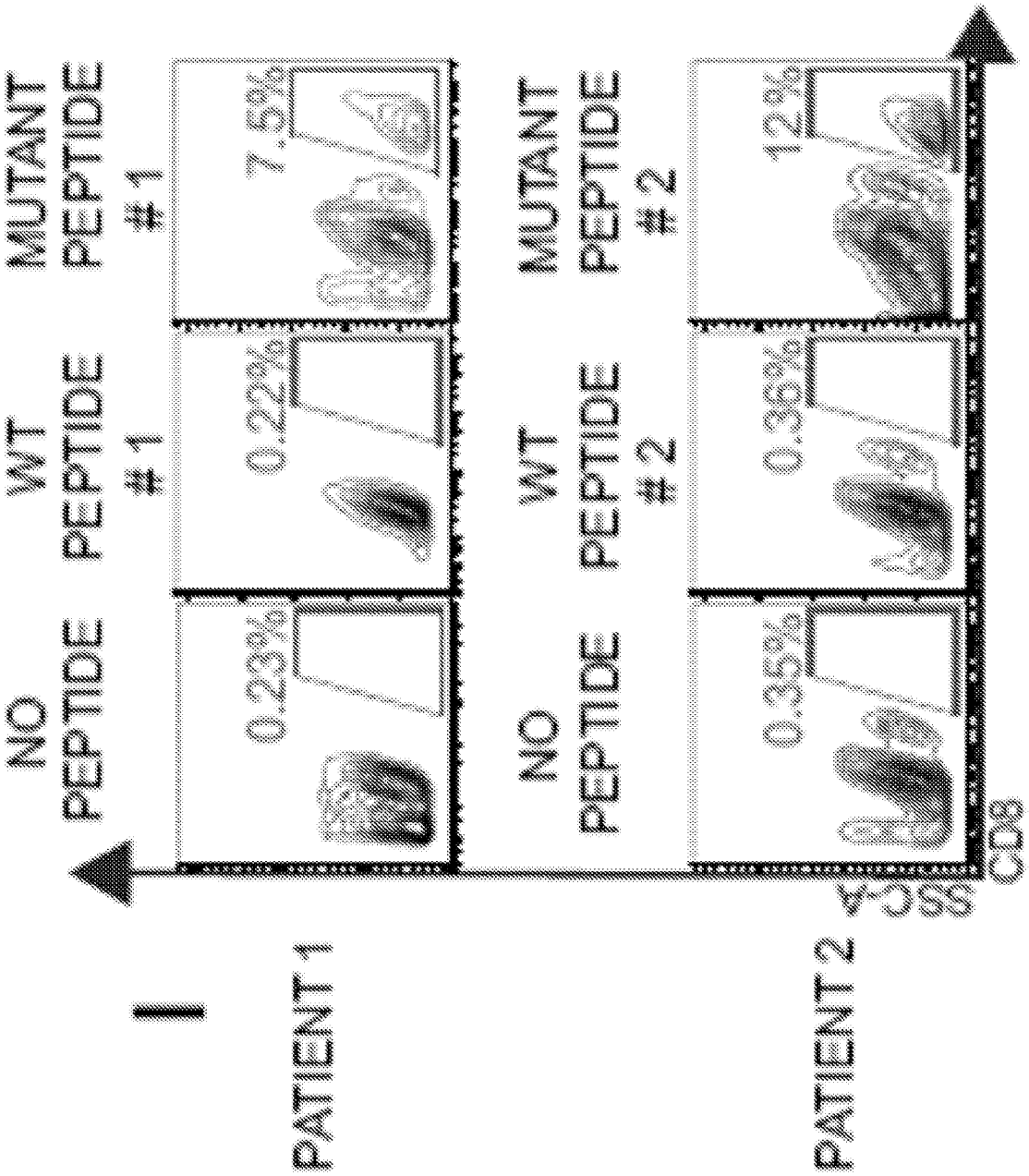

PATIENT 1
PATIENT 2
NO PEPTIDE
WT PEPTIDE #1
MUTANT PEPTIDE #1
NO PEPTIDE
WT PEPTIDE #2
MUTANT PEPTIDE #2
0.23%
0.22%
7.5%
0.35%
0.36%
12%
SSC-A
CD8

Fig. 55I1

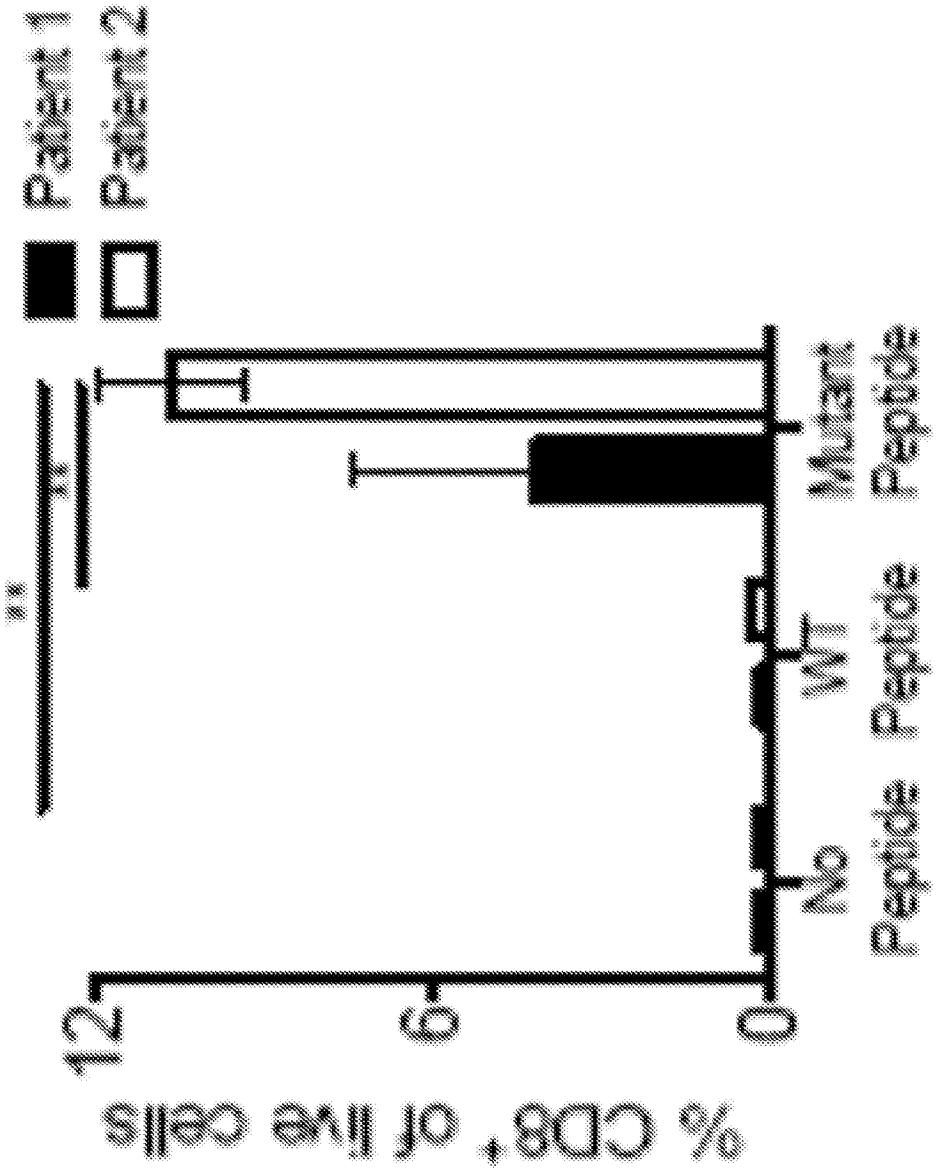

Patient 1
Patient 2
% CD8+ of live cells
12
6
0
No Peptide
WT Peptide
Mutant Peptide

Fig. 55I1

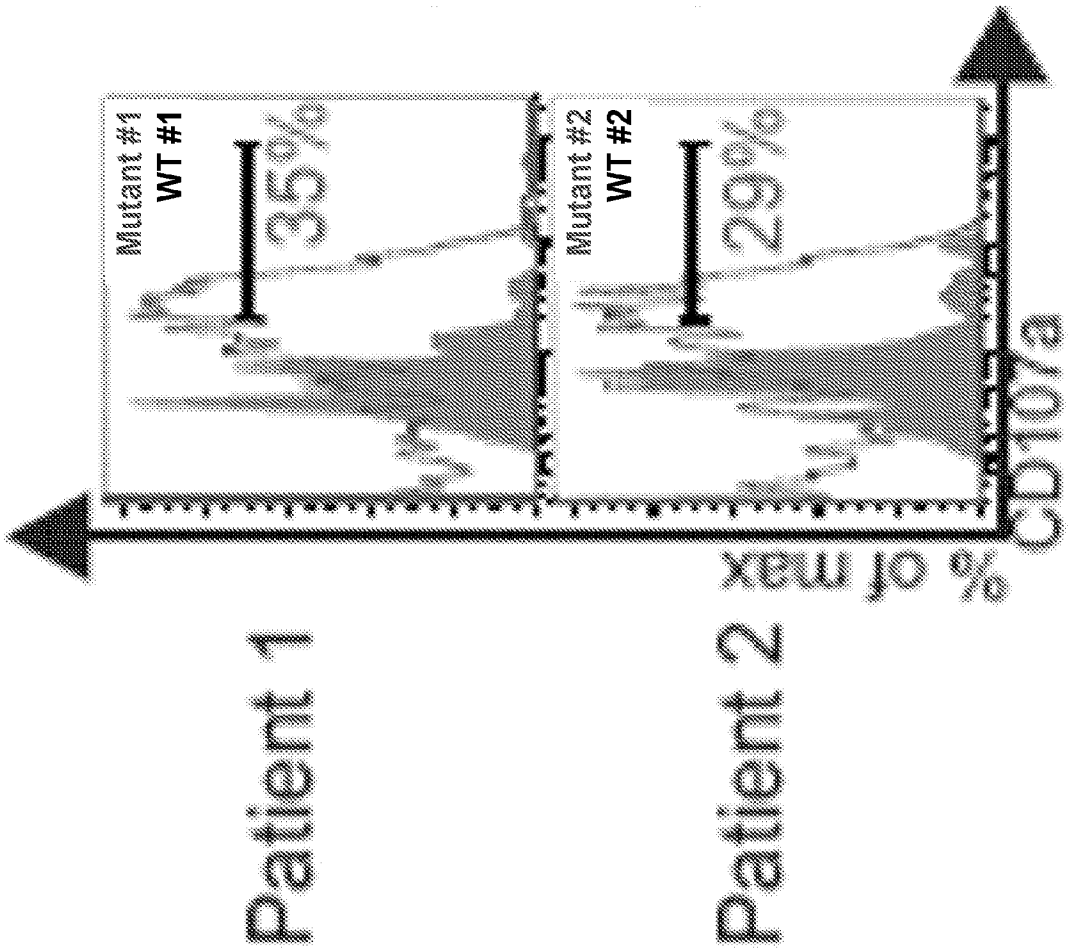

Patient 1
Patient 2
% of max
CD107a
Mutant #1
WT #1
35%
Mutant #2
WT #2
29%

Fig. 55J1

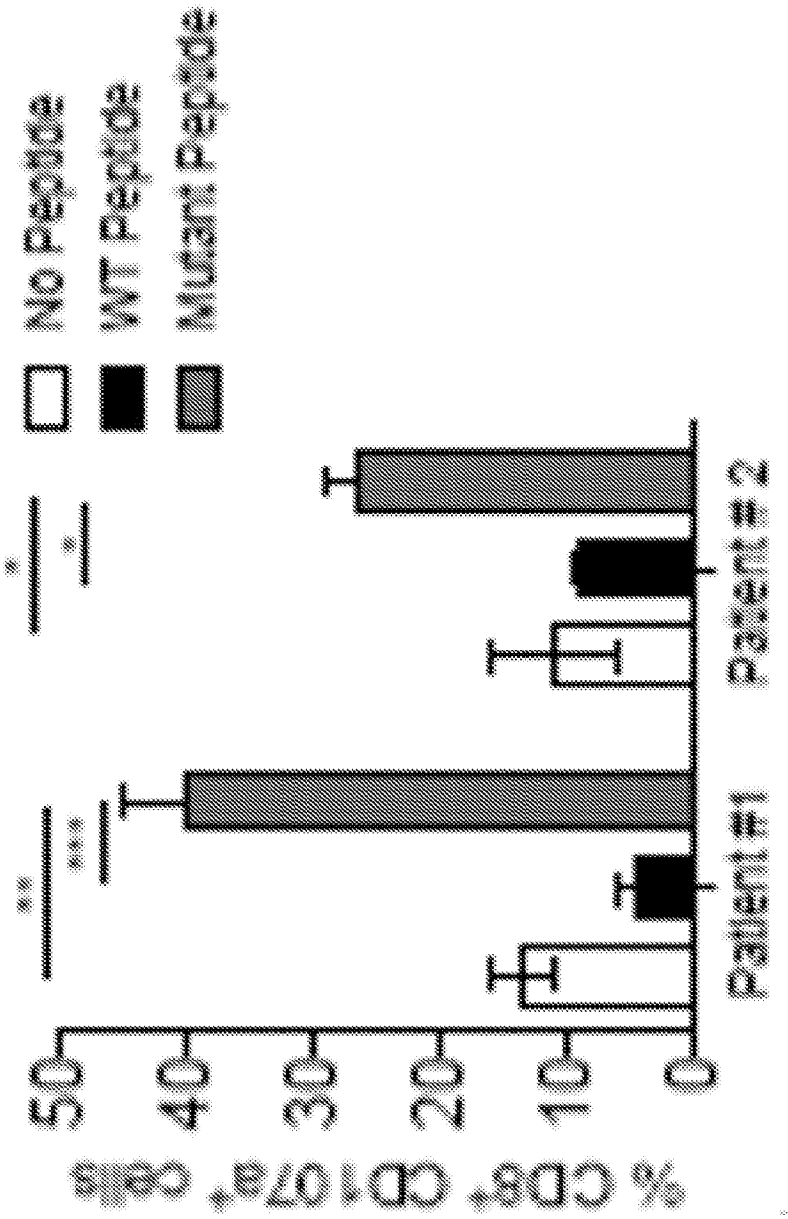

No Peptide
WT Peptide
Mutant Peptide
% CD8+ CD107a+ cells
50
40
30
20
10
0
Patient #1
Patient #2
*
**
***

Fig. 55J2

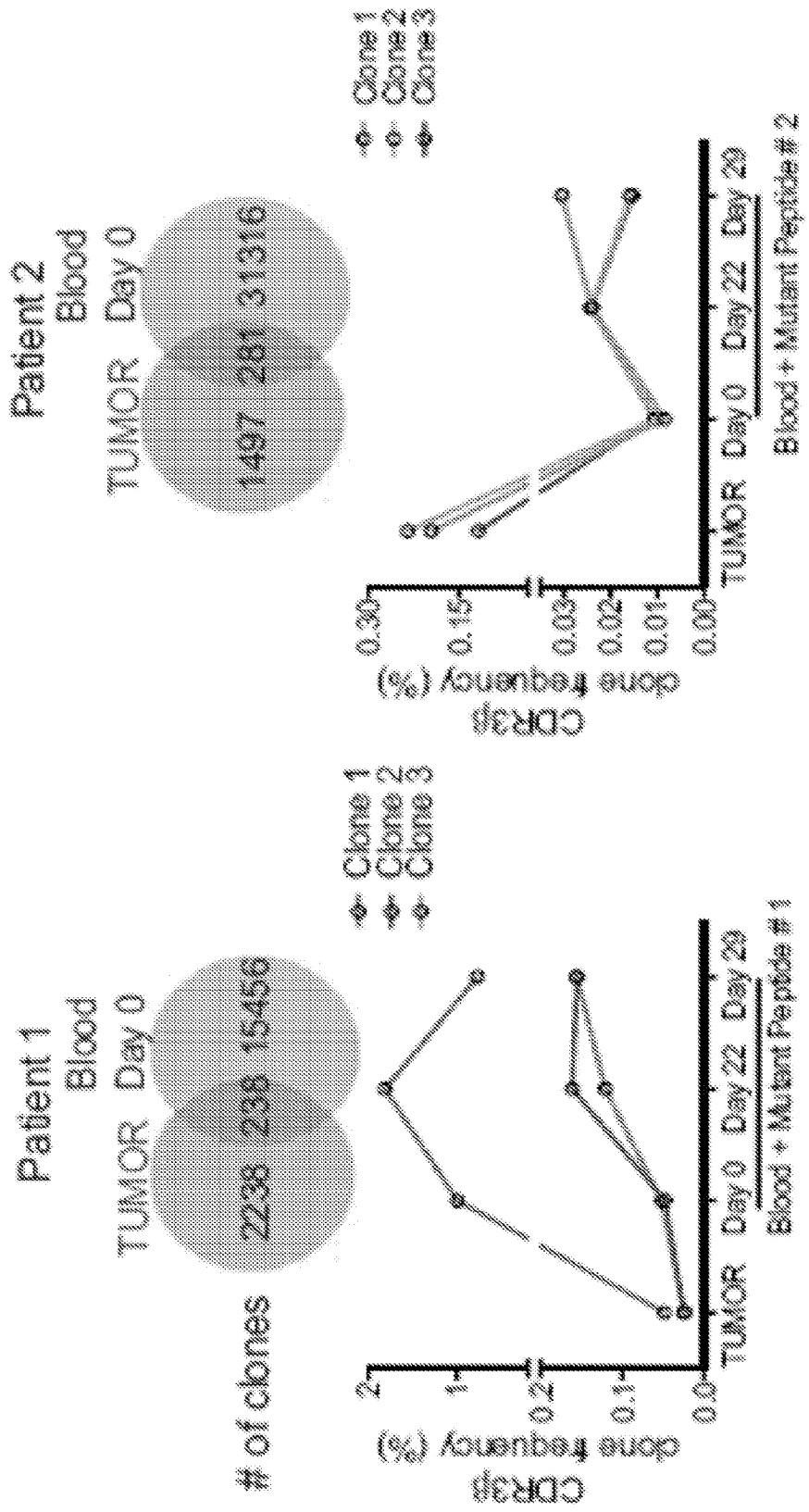

Patient 1
Blood
TUMOR Day 0
2238 238 15456
of clones
CDR3jb
clone frequency (%)
2
1
0.2
0.1
0.0
Clone 1
Clone 2
Clone 3
TUMOR Day 0 Day 22 Day 29
Blood + Mutant Peptide # 1
Patient 2
Blood
TUMOR Day 0
1497 281 31316
CDR3jb
clone frequency (%)
0.30
0.15
0.03
0.02
0.01
0.00
Clone 1
Clone 2
Clone 3
TUMOR Day 0 Day 22 Day 29
Blood + Mutant Peptide # 2

Fig. 55K

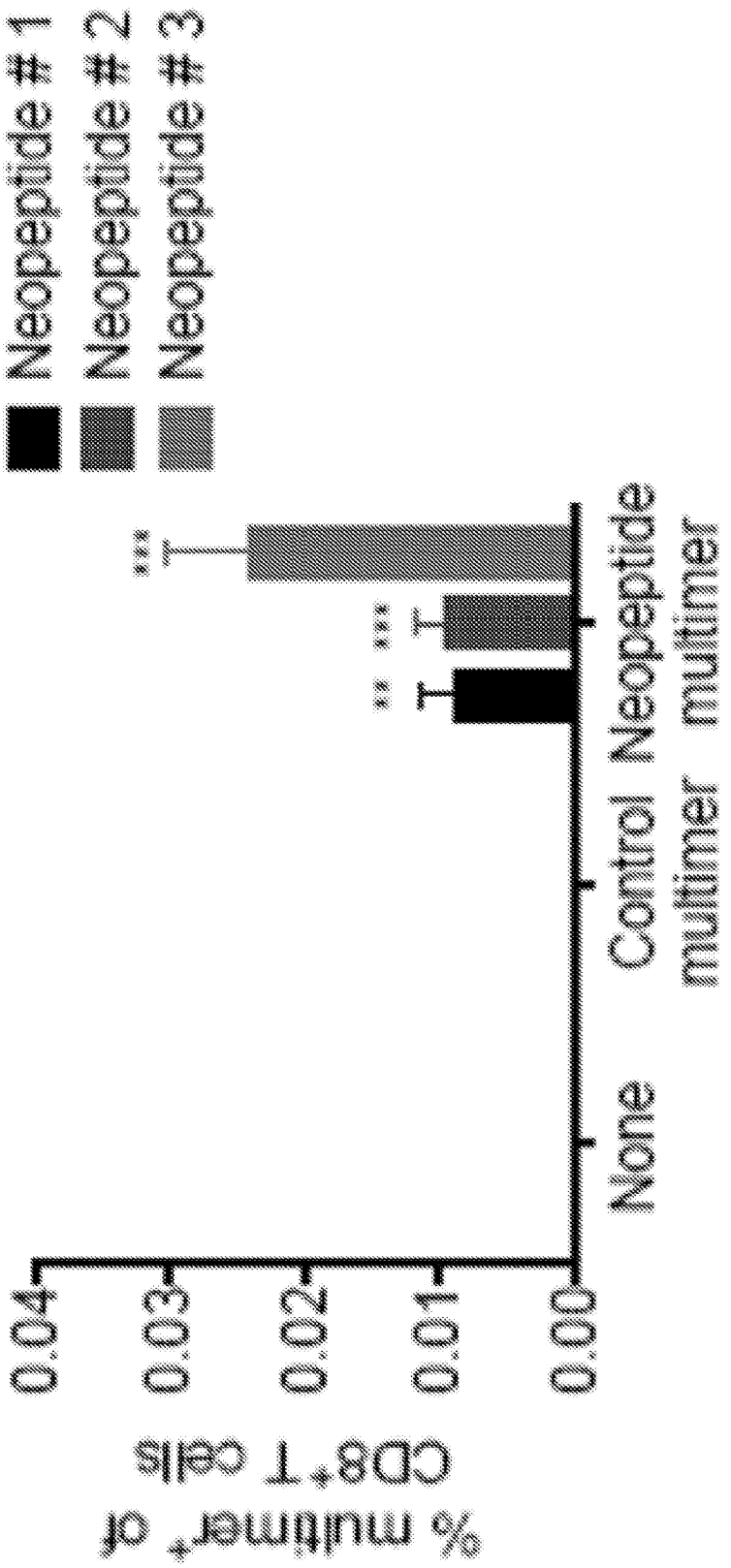
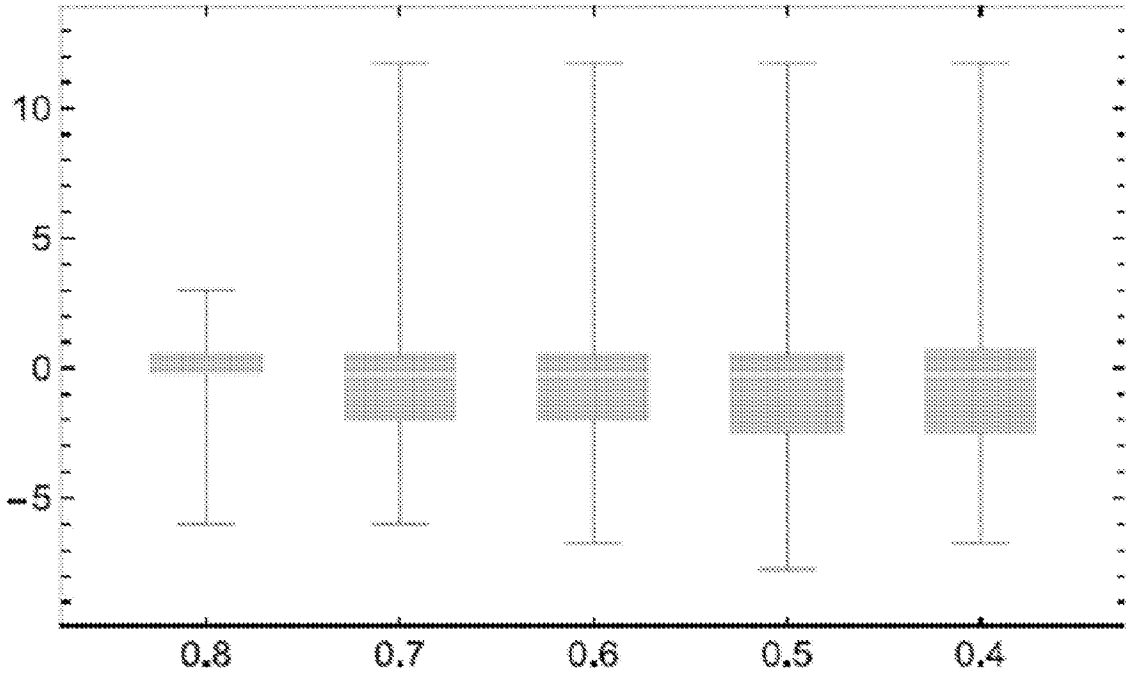

Neopeptide #1
Neopeptide #2
Neopeptide #3
% multimer+ of CD8+T cells
0.04
0.03
0.02
0.01
0.00
None
Control multimer
Neopeptide multimer

Fig. 55L


10
5
0
-5
0.8
0.7
0.6
0.5
0.4

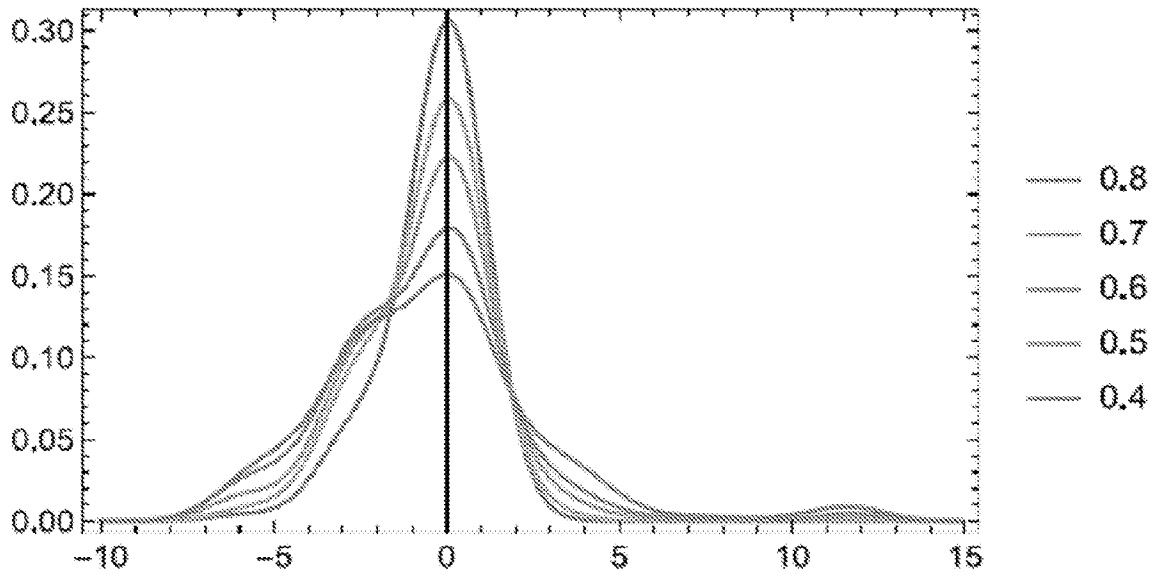

0.30
0.25
0.20
0.15
0.10
0.05
0.00
-10
-5
0
5
10
15
0.8
0.7
0.6
0.5
0.4

Fig. 56

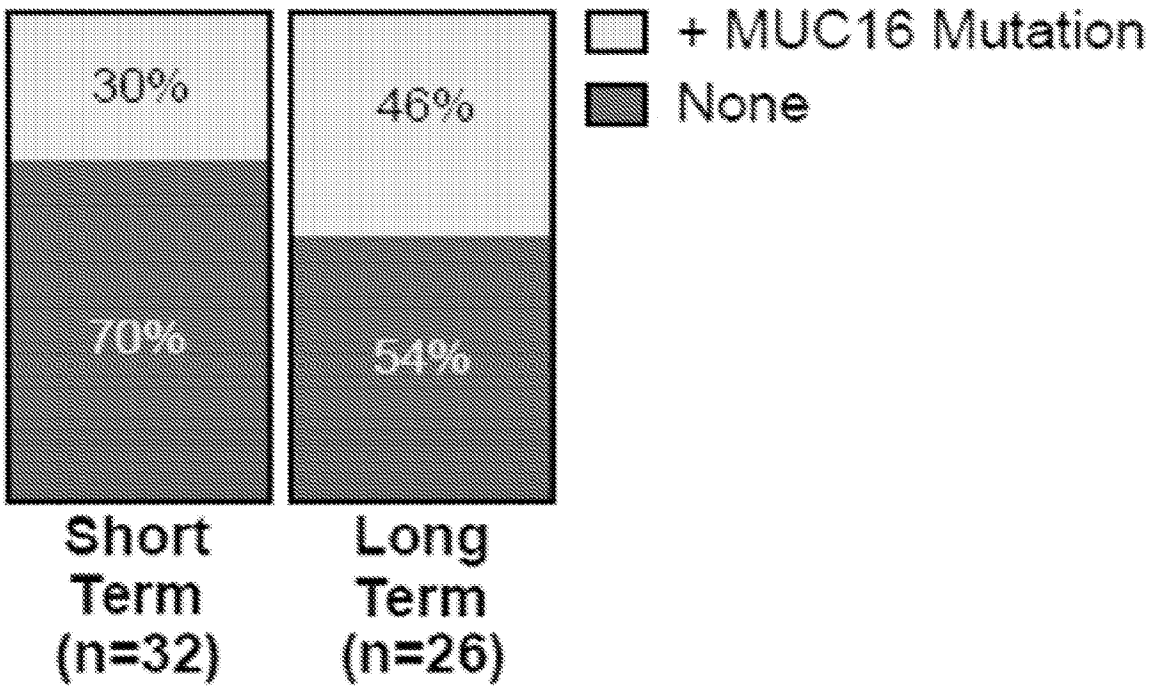


Fig. 57

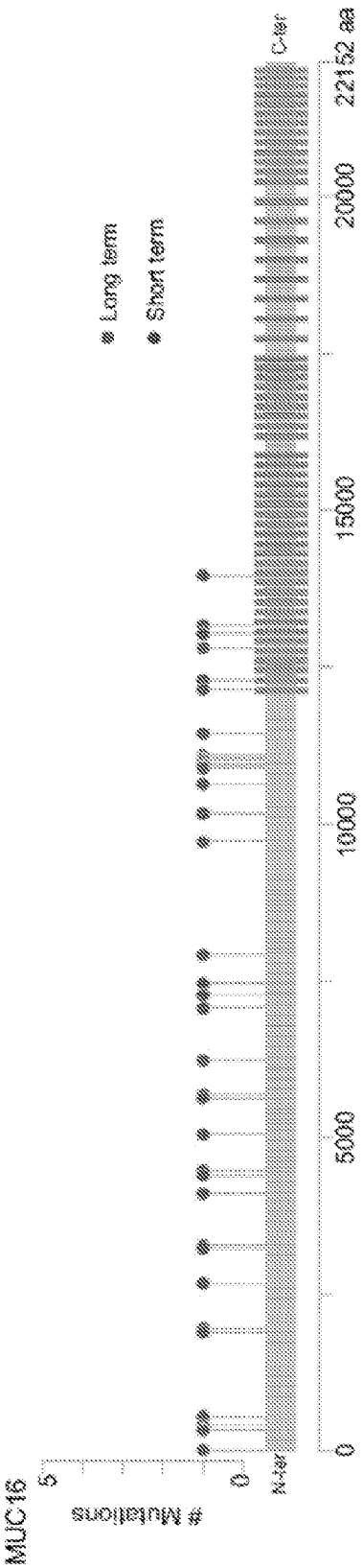

MUC16
Mutations
5
0
N-ter
0
5000
10000
15000
20000
22152 aa
C-ter
Long term
Short term

Fig. 58

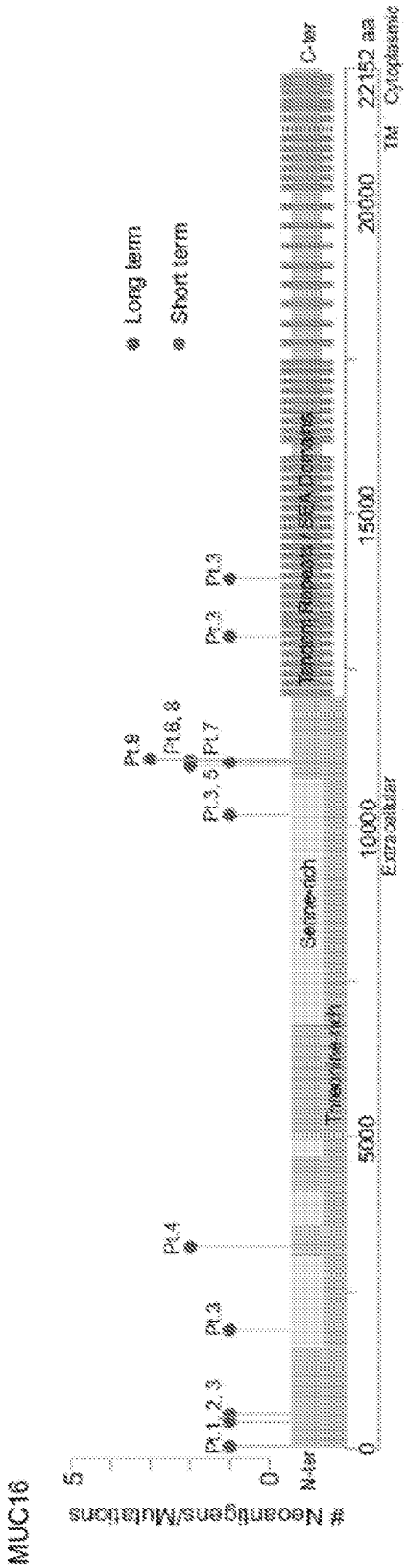

MUC16
Neoantigens/Mutations
5
0
N-ter
Pt 1, 2, 3
Pt 4
Pt 3
Pt 5
Pt 6, 8
Pt 9
Pt 7
Pt 2
Pt 3
Transmembrane
Cytoplasmic
0
5000
10000
15000
20000
22152 aa
C-ter
Long term
Short term

Fig. 59

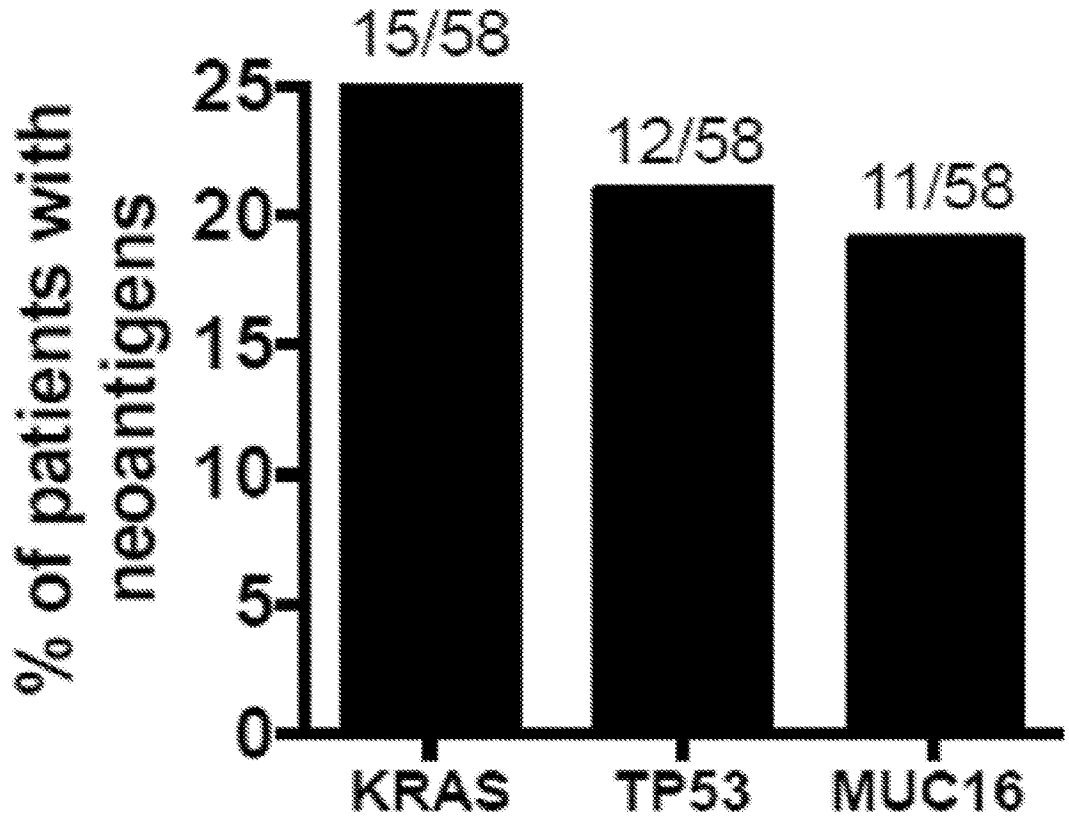

% of patients with neoantigens
25
20
15
10
5
0
15/58
12/58
11/58
KRAS
TP53
MUC16

Fig. 60

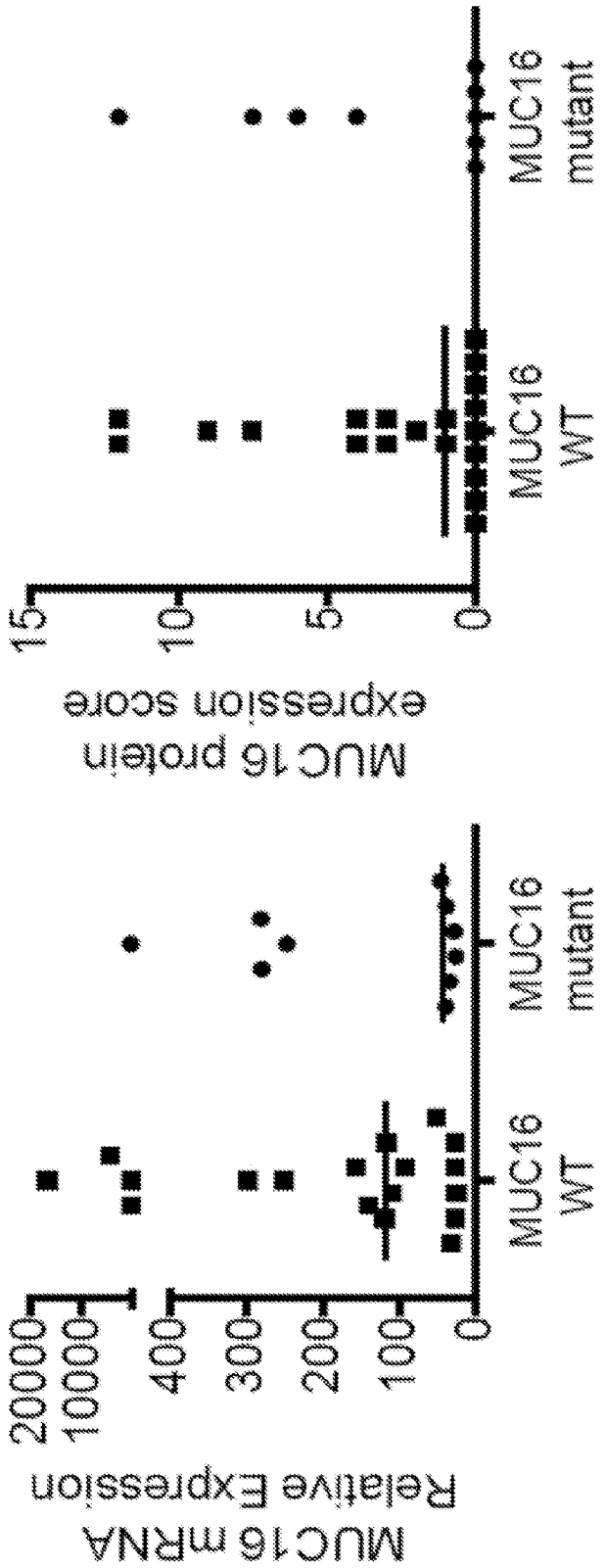

MUC16 mRNA
Relative Expression
20000
10000
400
300
200
100
0
MUC16 WT
MUC16 mutant
MUC 16 protein
expression score
15
10
5
0
MUC16 WT
MUC16 mutant

Fig. 61

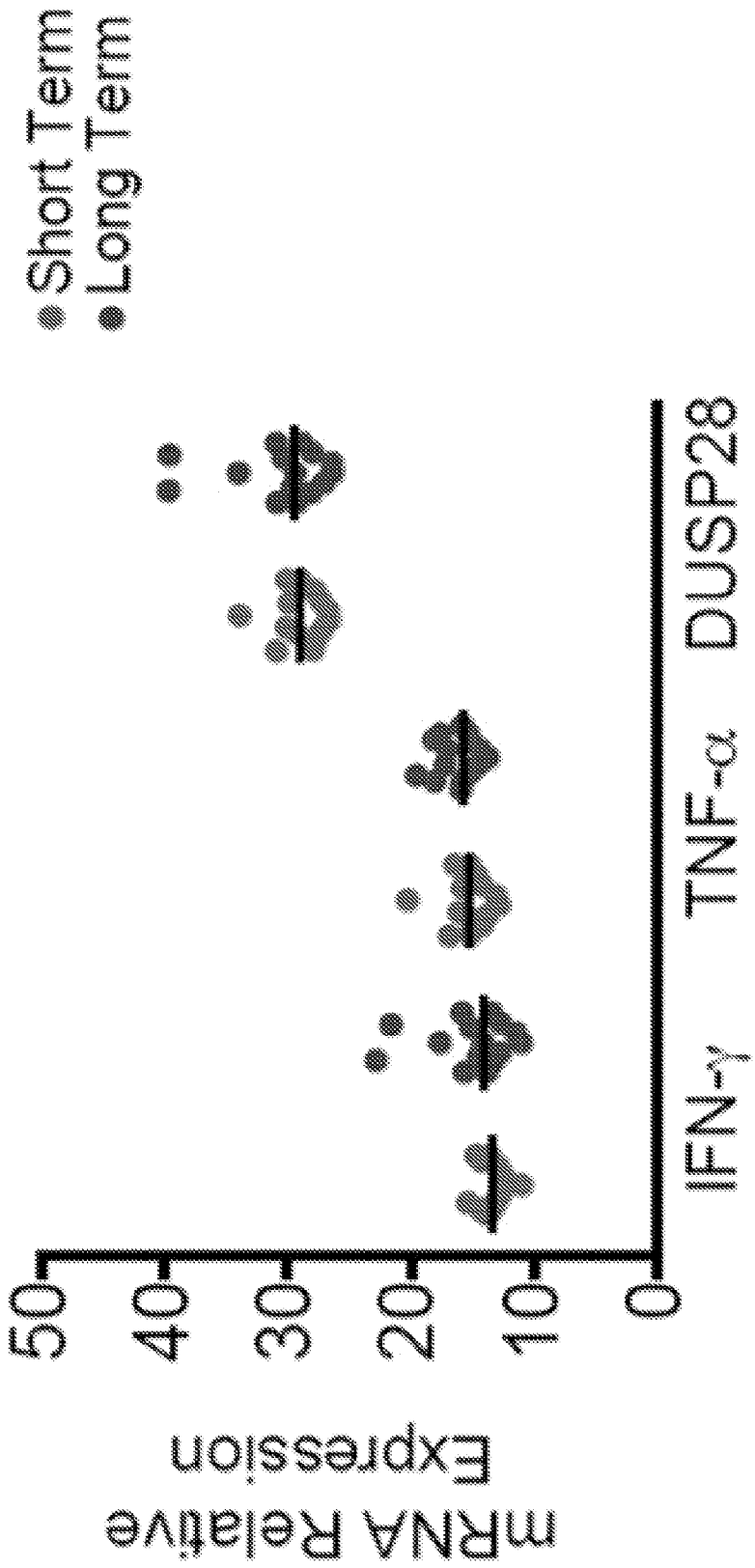

Short Term
Long Term
mRNA Relative Expression
50
40
30
20
10
0
IFN-γ
TNF-α
DUSP28

Fig. 62

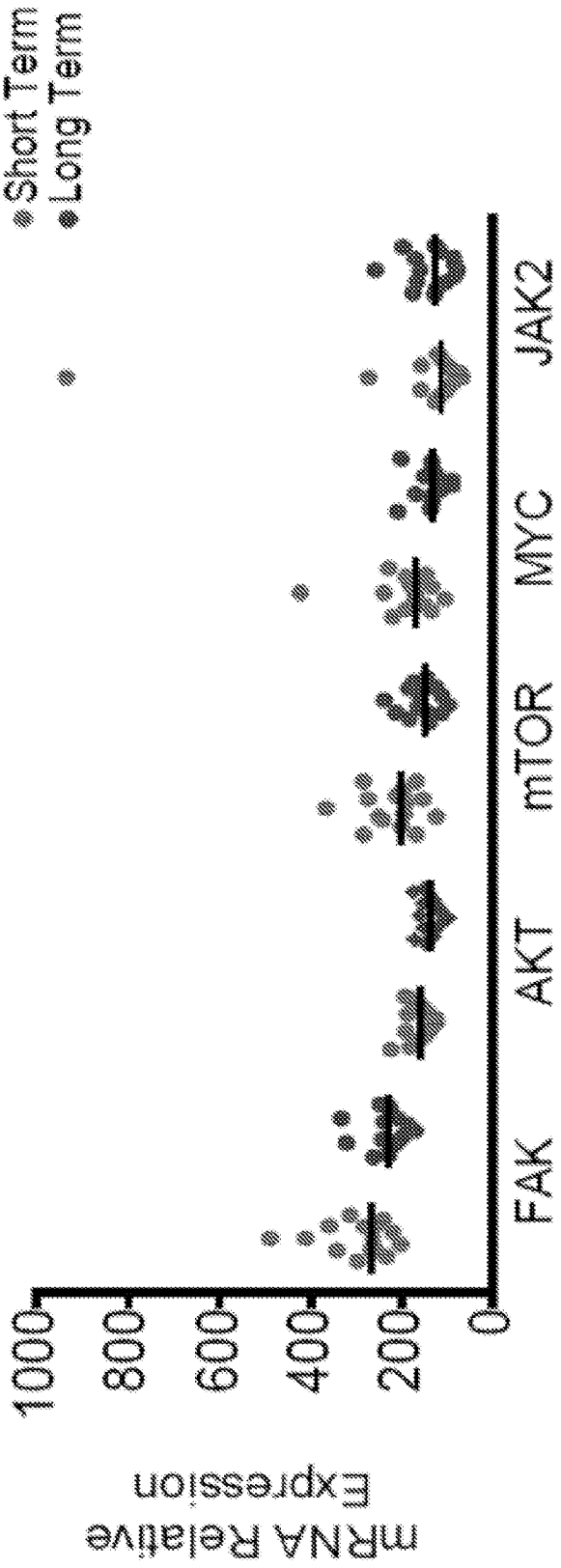

Short Term
Long Term
mRNA Relative Expression
1000
800
600
400
200
0
FAK
AKT
mTOR
MYC
JAK2

Fig. 63

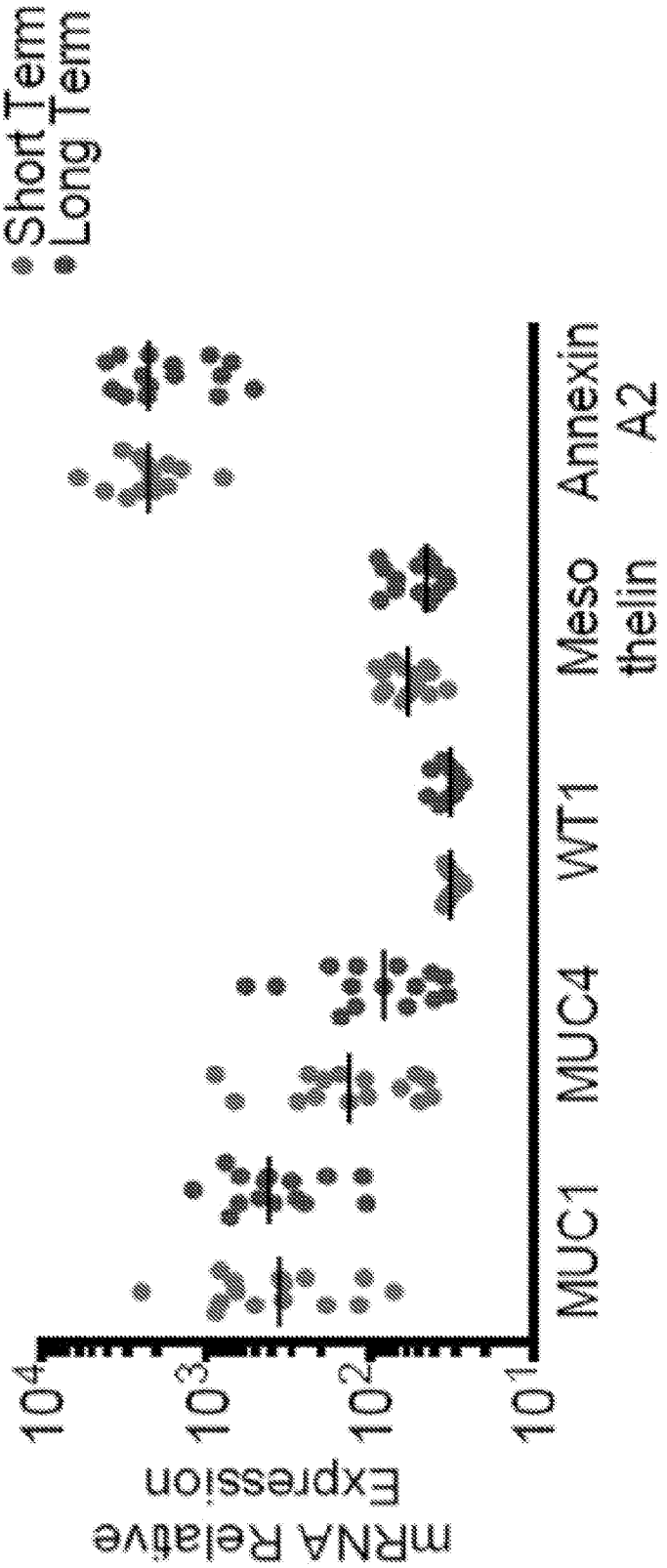

Short Term
Long Term
mRNA Relative Expression
10^4
10^3
10^2
10^1
MUC1
MUC4
WT1
Meso thelin
Annexin A2

Fig. 64

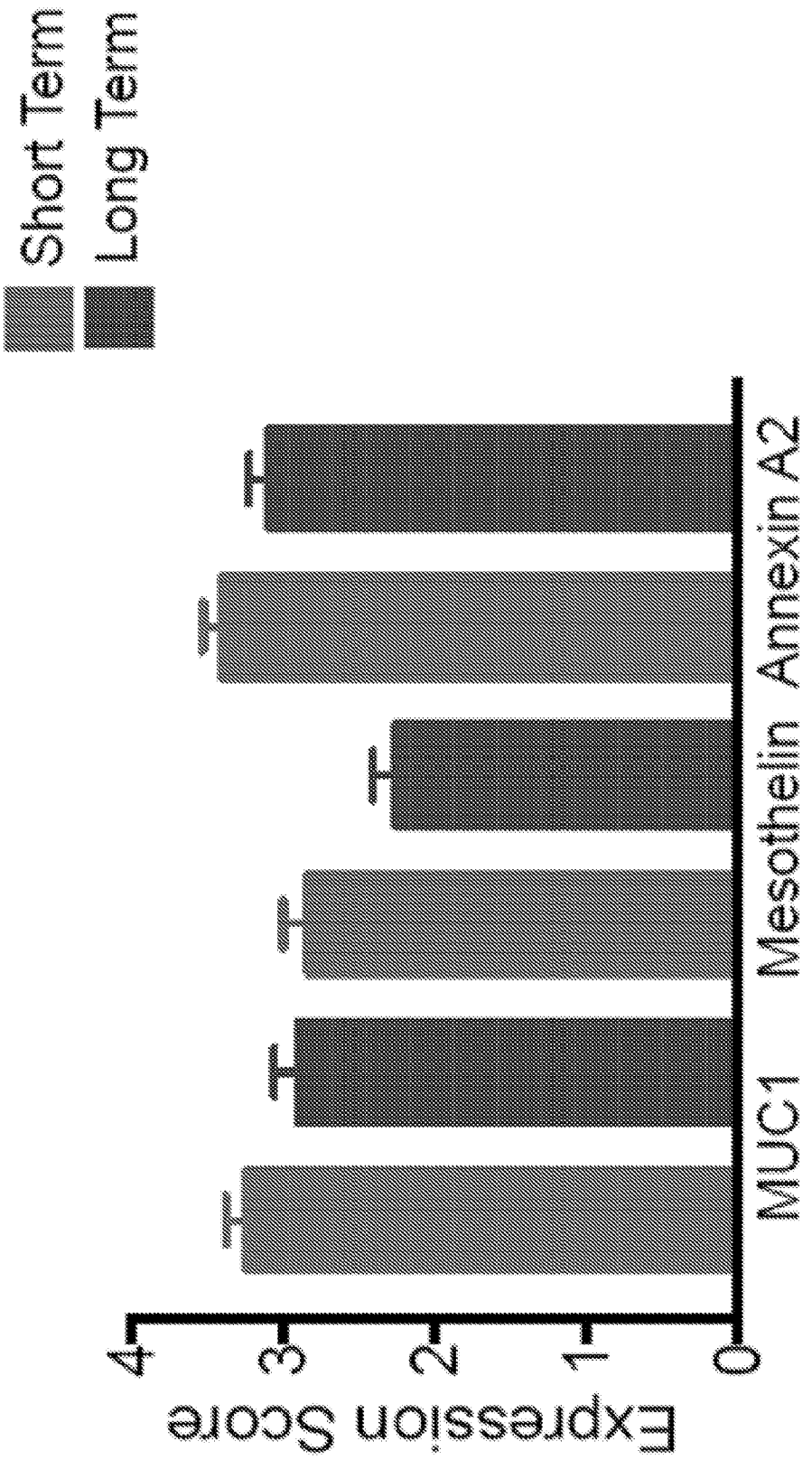

Short Term
Long Term
Expression Score
0
1
2
3
4
MUC1
Mesothelin
Annexin A2

Fig. 65

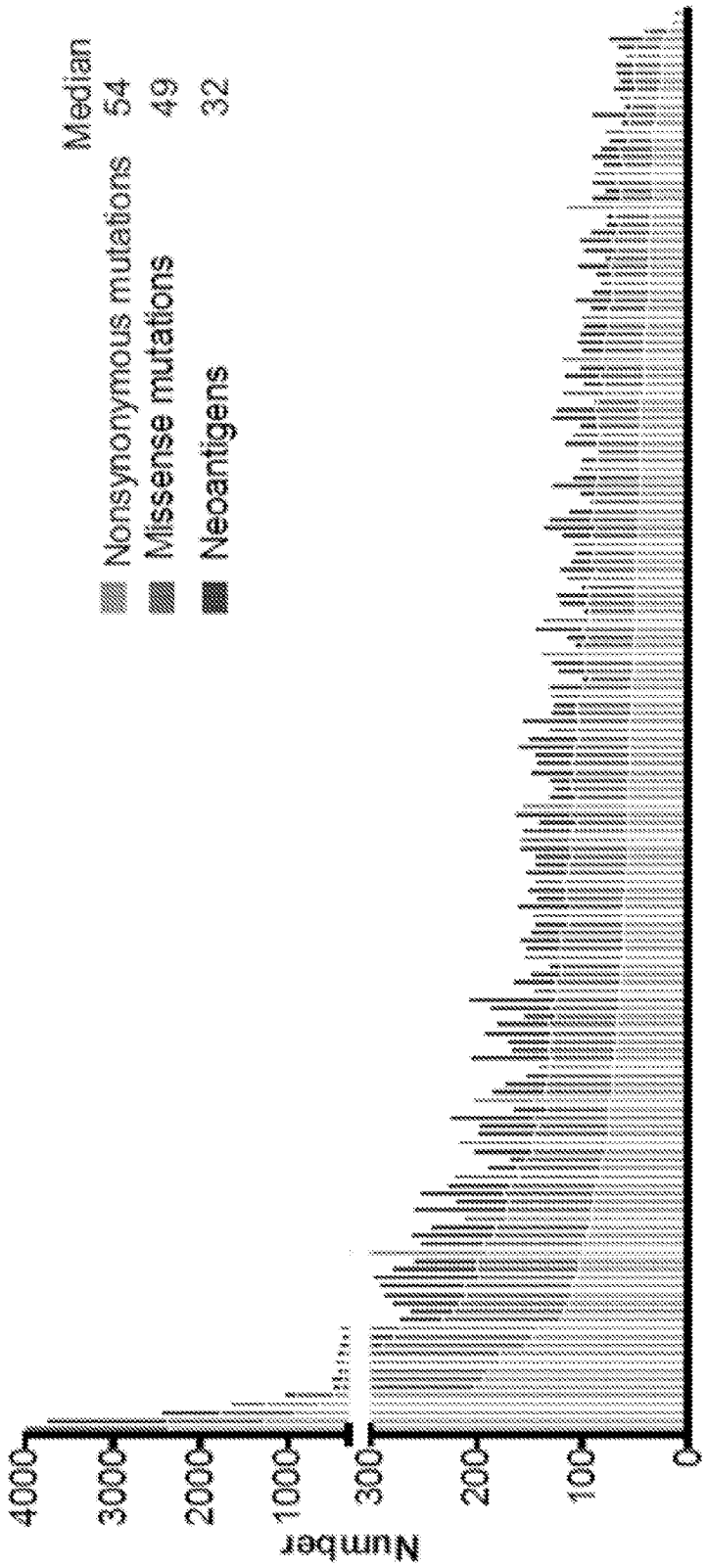

Median
Nonsynonymous mutations 54
Missense mutations 49
Neoantigens 32
Number
4000
3000
2000
1000
300
200
100
0

Fig. 66

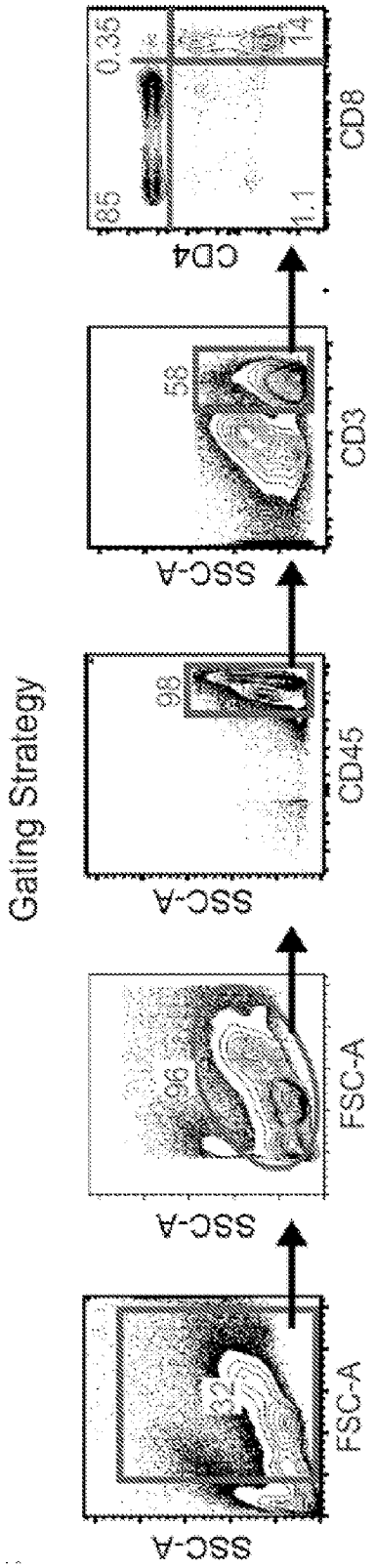

Gating Strategy
SSC-A
FSC-A
32
SSC-A
FSC-A
96
SSC-A
CD45
98
SSC-A
CD3
53
CD4
CD8
85
0.35
1.1
14

Fig. 67A

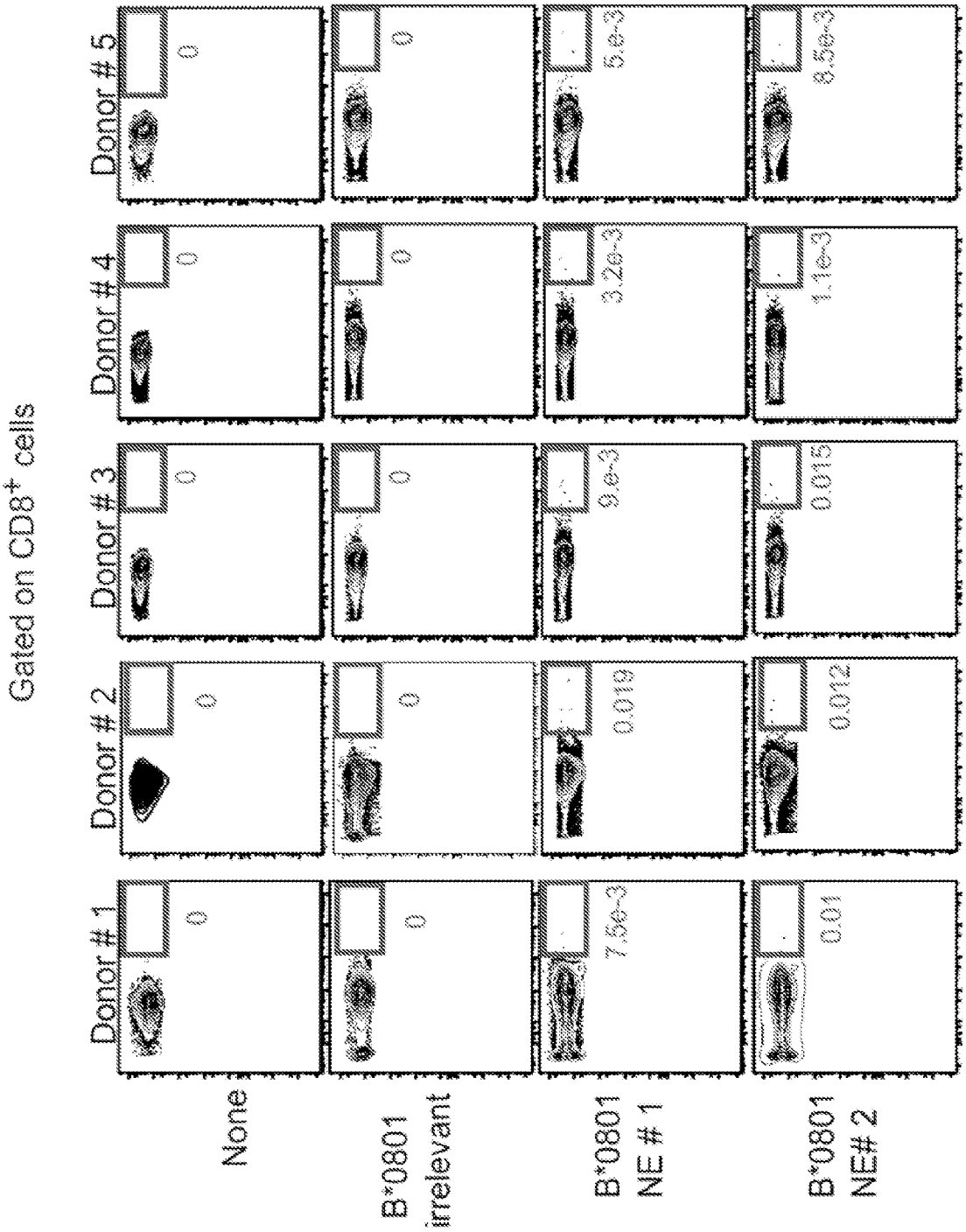

Gated on CD8+ cells
Donor # 1
Donor # 2
Donor # 3
Donor # 4
Donor # 5
None
B*0801 irrelevant
B*0801 NE # 1
B*0801 NE# 2
0
0
0
0
0
0
0
0
0
0
0
0
0
0
0
0
0.019
0.012
9.6e-3
0.015
3.2e-3
1.1e-3
6.8e-3
8.5e-3
7.5e-3
0.01

Fig. 67B

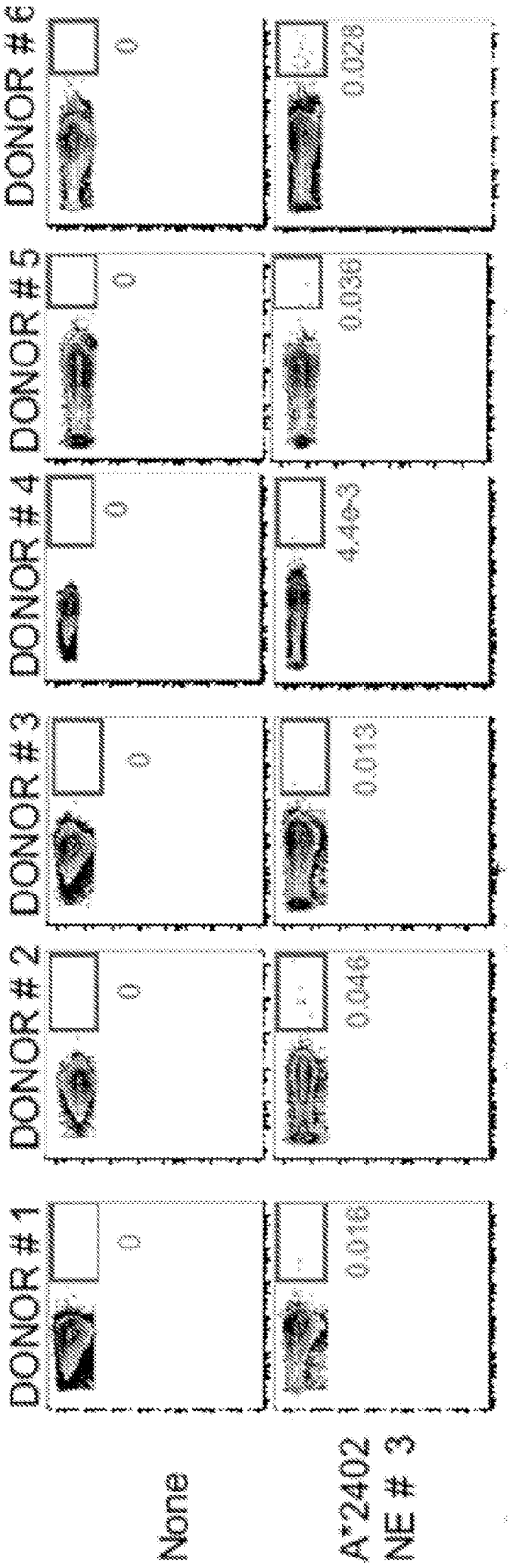

DONOR #1
DONOR #2
DONOR #3
DONOR #4
DONOR #5
DONOR #6
None
A*2402 NE # 3
0
0
0
0
0
0
0.016
0.046
0.013
4.4e-3
0.036
0.028

Fig. 68

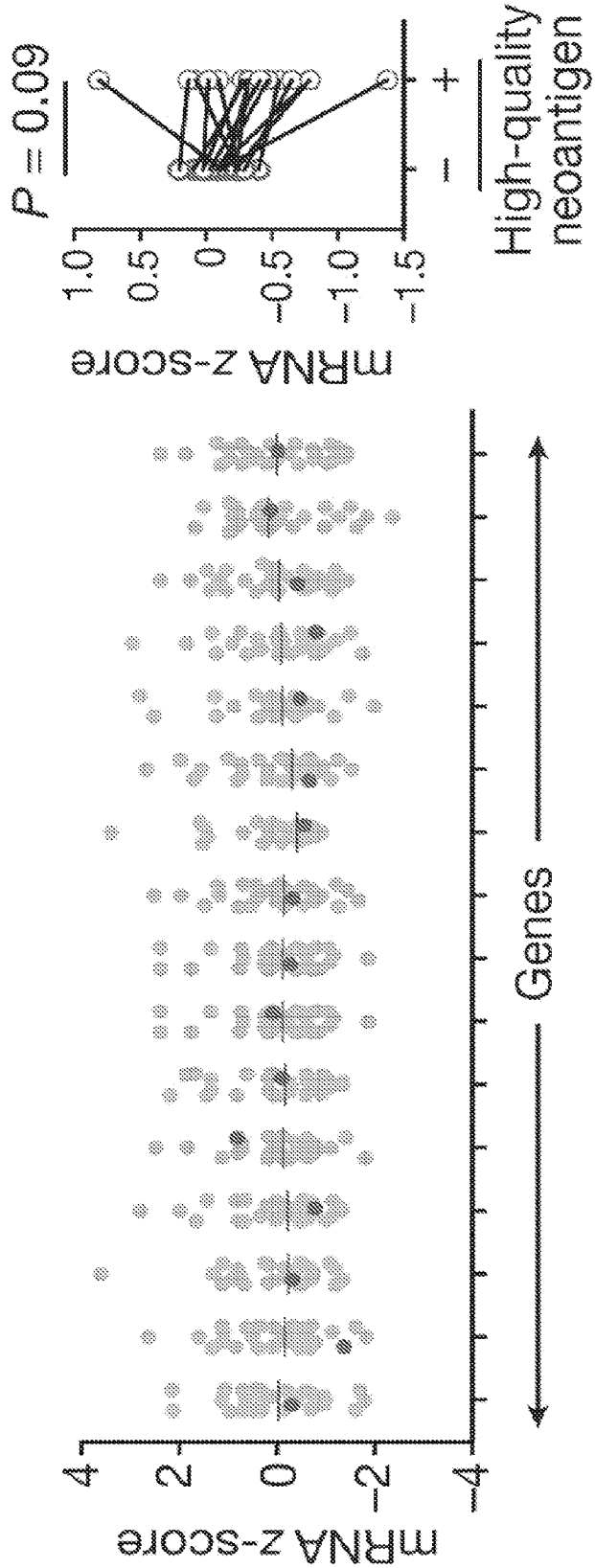

P = 0.09
1.0
0.5
0
−0.5
−1.0
−1.5
mRNA z-score
+
−
High-quality neoantigen
4
2
0
−2
−4
mRNA z-score
Genes

Fig. 69A

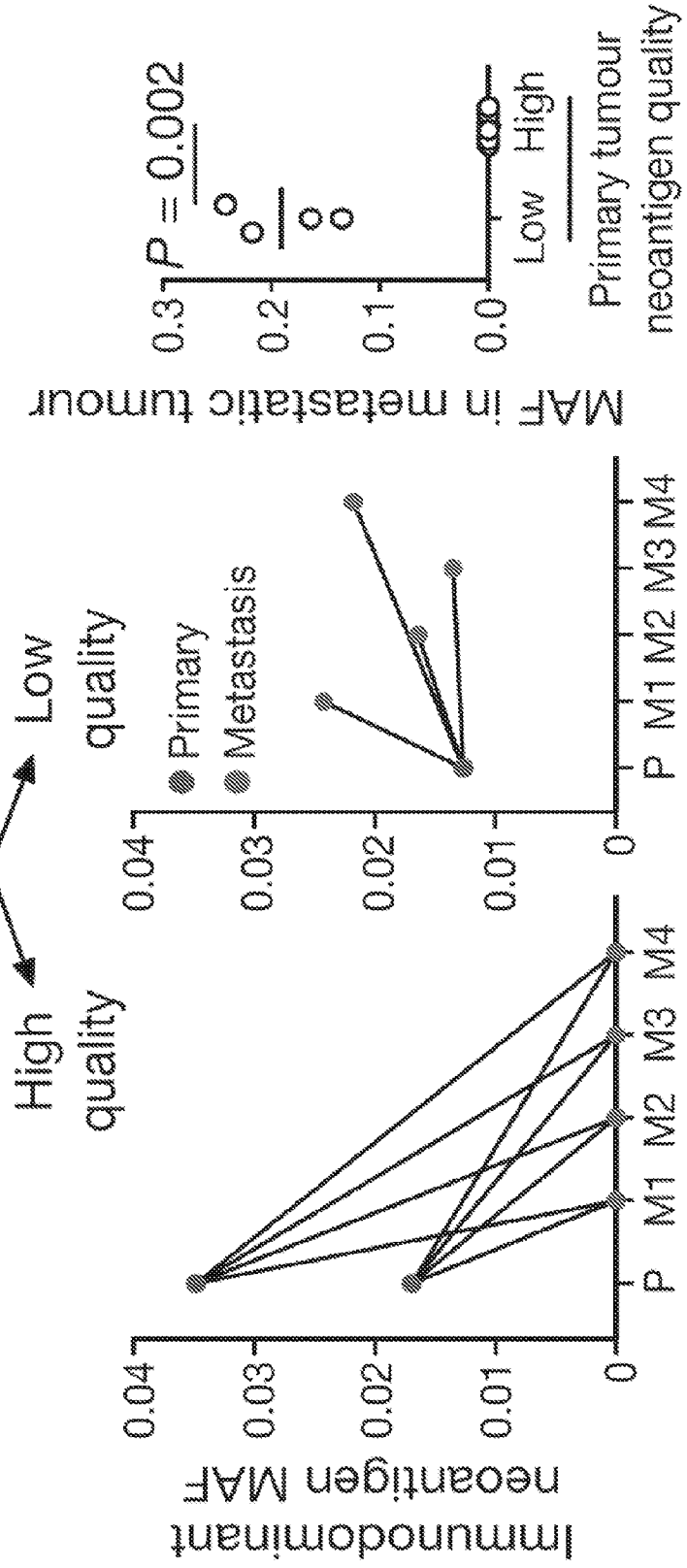

Immunodominant neoantigen MAF
0.04
0.03
0.02
0.01
0
P M1 M2 M3 M4
High quality
Low quality
Primary
Metastasis
MAF in metastatic tumour
P = 0.002
Low High
Primary tumour neoantigen quality

Fig. 69B

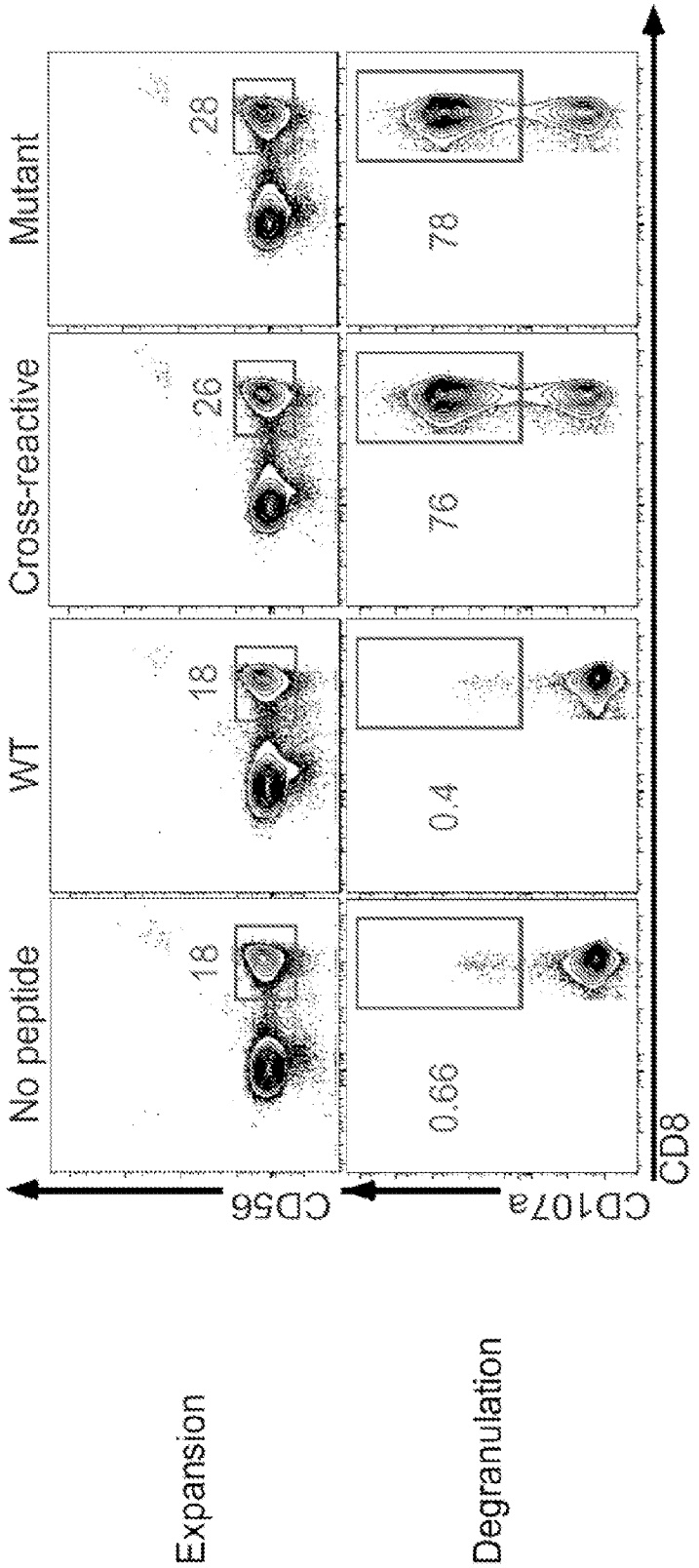

No peptide
WT
Cross-reactive
Mutant
18
18
26
28
0.66
0.4
76
78
CD56
CD107a
CD8
Expansion
Degranulation

Fig. 69C1

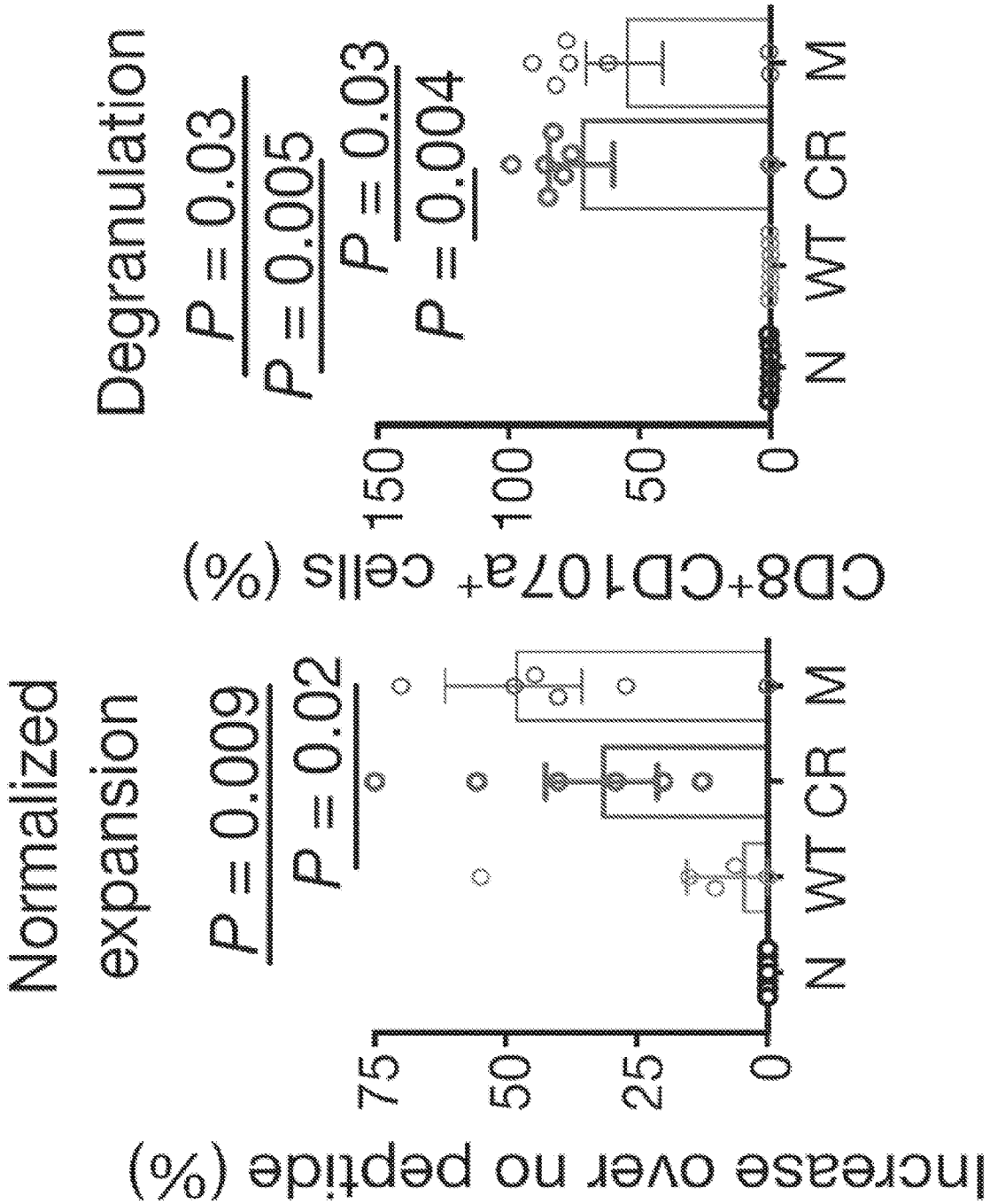

Normalized expansion
P = 0.009
P = 0.02
Increase over no peptide (%)
75
50
25
0
N WT CR M
Degranulation
P = 0.03
P = 0.005
P = 0.03
P = 0.004
CD8+CD107a+ cells (%)
150
100
50
0
N WT CR M

Fig. 69C2

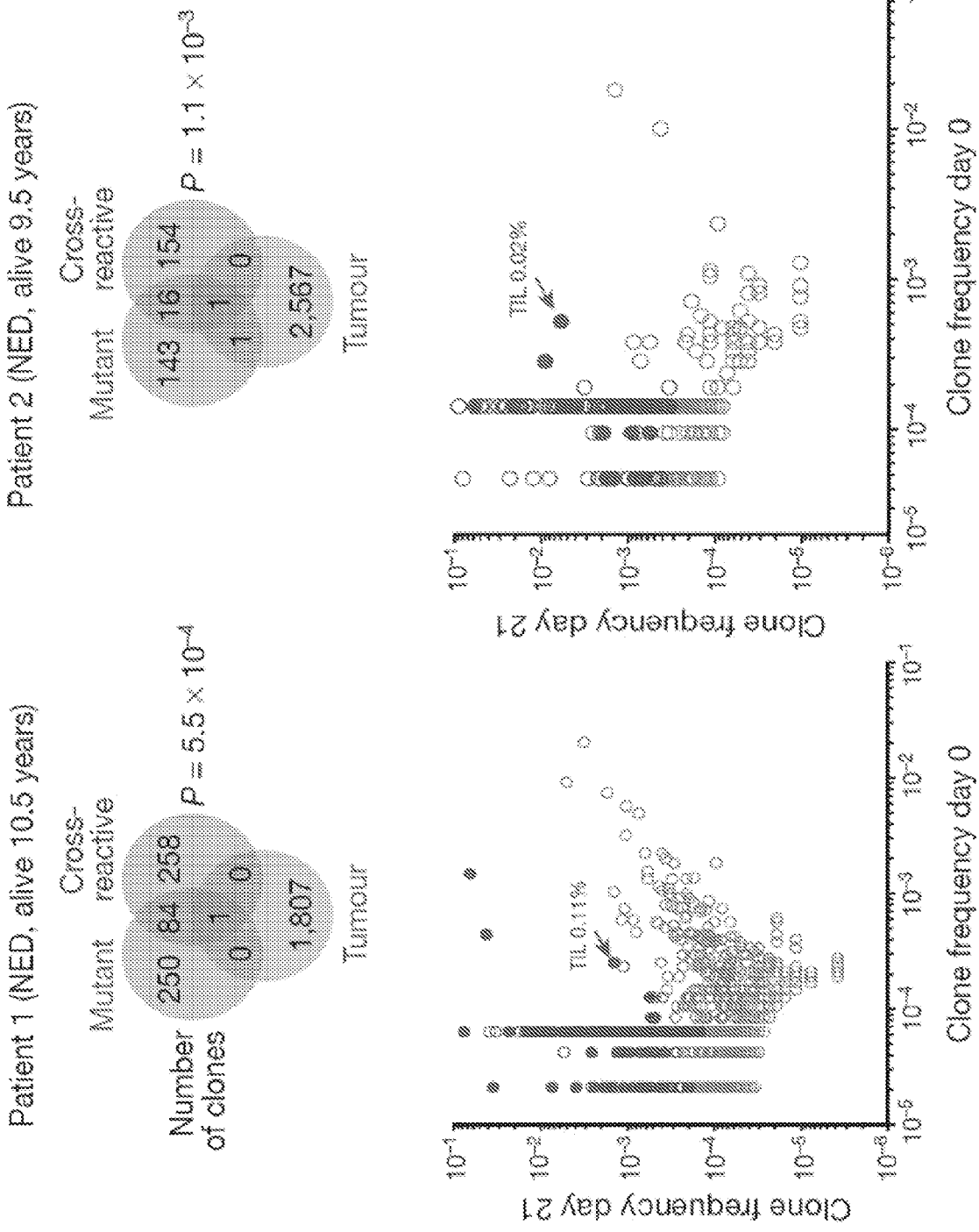

Patient 1 (NED, alive 10.5 years)
Patient 2 (NED, alive 9.5 years)
Number of clones
Mutant
Cross-reactive
Tumour
250
84
258
0
1
0
1,807
$P = 5.5 \times 10^{-4}$
143
16
154
1
1
0
2,567
$P = 1.1 \times 10^{-3}$
TIL 0.11%
TIL 0.02%
Clone frequency day 21
Clone frequency day 0
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}

Fig. 69D1

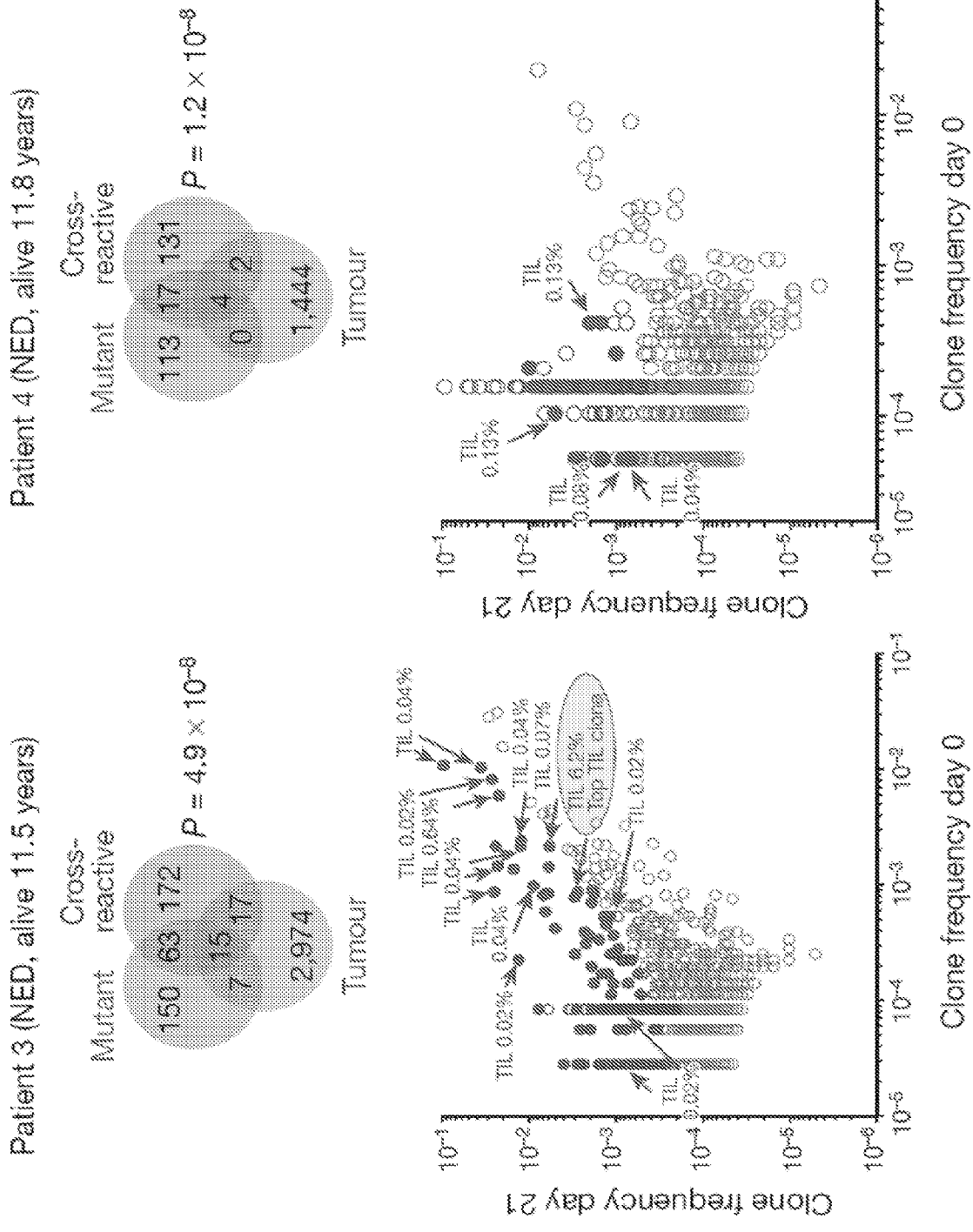

Patient 3 (NED, alive 11.5 years)
Cross-reactive
Mutant
150 63 172
7 15 17
2,974
P = 4.9 × 10⁻⁸
Tumour
Patient 4 (NED, alive 11.8 years)
Cross-reactive
Mutant
113 17 131
0 4 2
1,444
P = 1.2 × 10⁻⁸
Tumour
Clone frequency day 21
Clone frequency day 0
TIL 0.02%
TIL 0.04%
TIL 0.64%
TIL 0.07%
TIL 6.2%
Top TIL clone
TIL 0.13%
TIL 0.08%
TIL 0.04%

Fig. 69D2

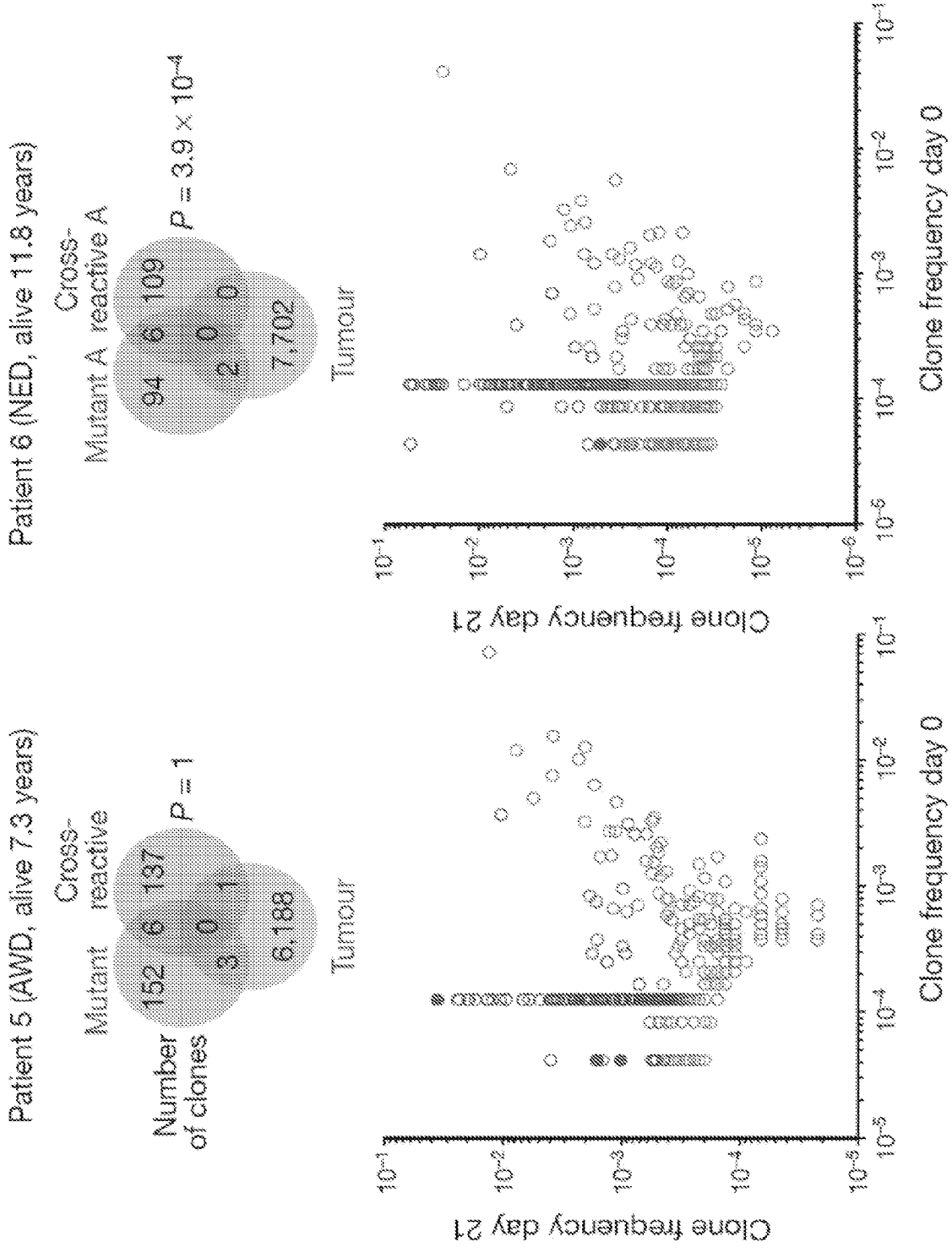

Patient 5 (AWD, alive 7.3 years)
Patient 6 (NED, alive 11.8 years)
Cross-reactive
Mutant
Cross-reactive
Mutant A
Number of clones
152
6
137
3
0
1
6,188
P = 1
94
6
109
2
0
0
7,702
P = 3.9 × 10−4
Tumour
Tumour
Clone frequency day 21
Clone frequency day 0
Clone frequency day 21
Clone frequency day 0

Fig. 69D3

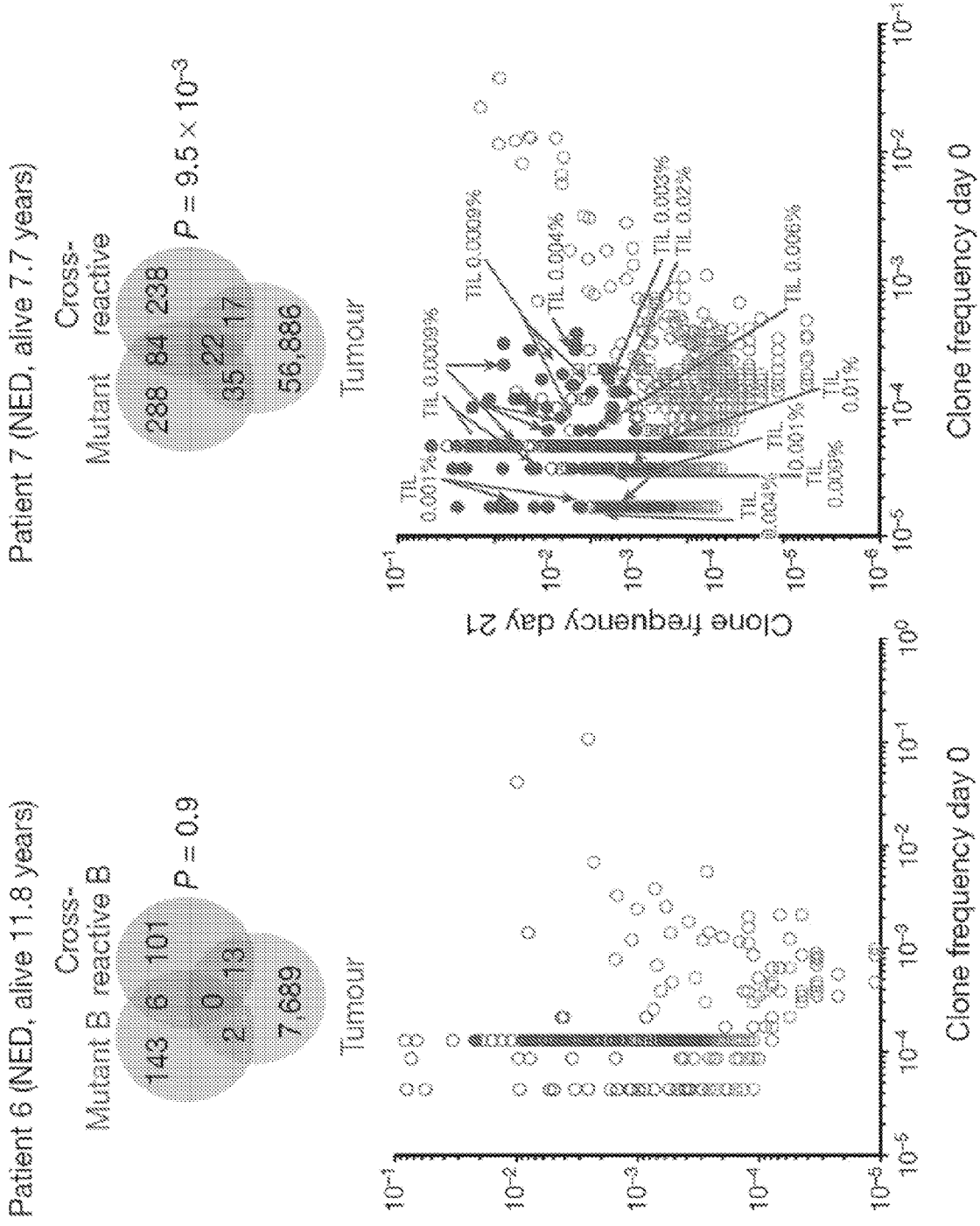

Patient 7 (NED, alive 7.7 years)
Cross-reactive
Mutant
288 84 238
35 22 17
56,886
P = 9.5 × 10−3
Tumour
Clone frequency day 21
Clone frequency day 0
TIL 0.0009%
TIL 0.004%
TIL 0.002%
TIL 0.02%
TIL 0.001%
TIL 0.008%
TIL 0.01%
TIL 0.0003%
Patient 6 (NED, alive 11.8 years)
Cross-reactive B
Mutant B
143 6 101
2 0 13
7,689
P = 0.9
Tumour
Clone frequency day 0

Fig. 69D4

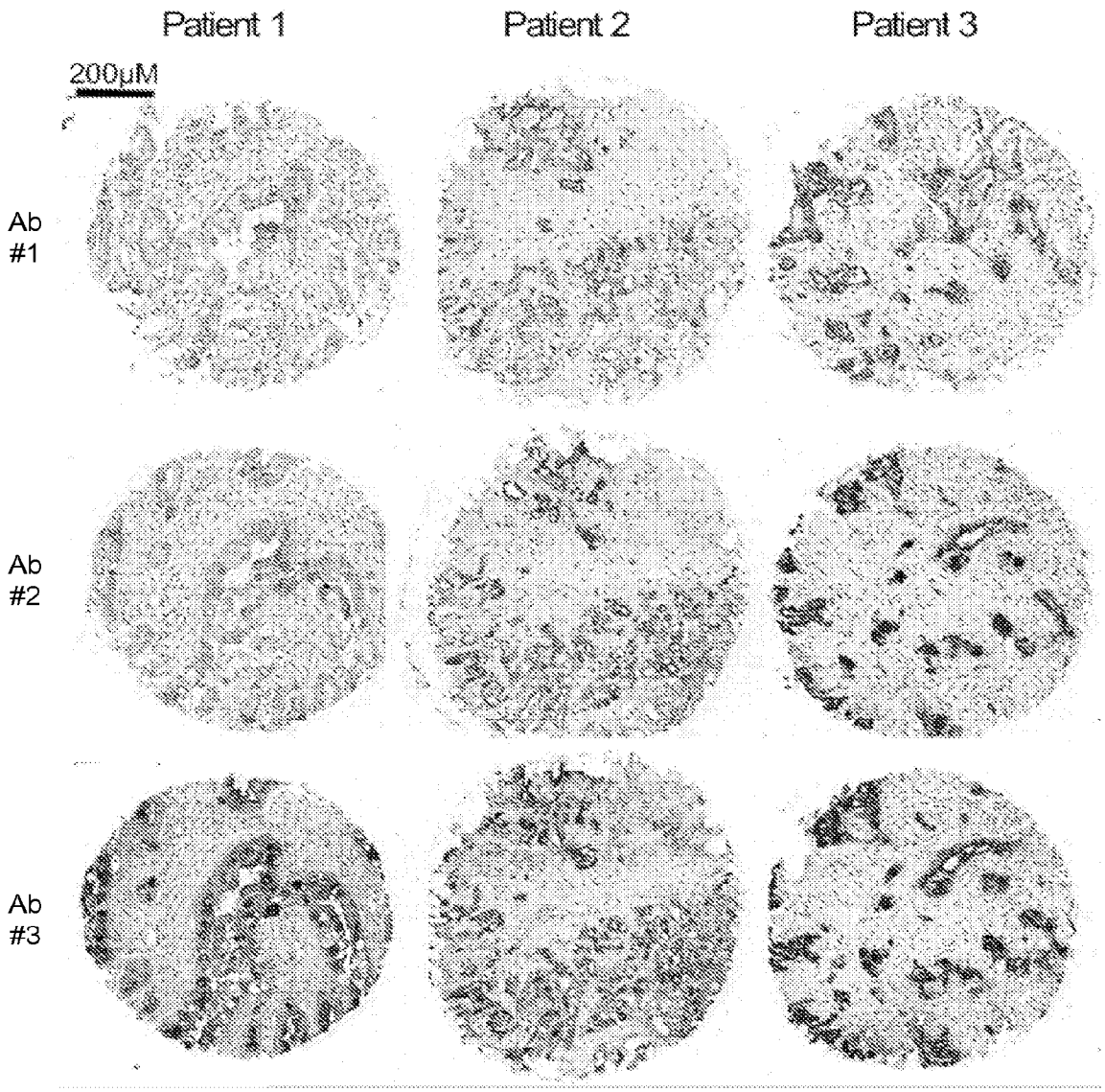


Fig. 70A1

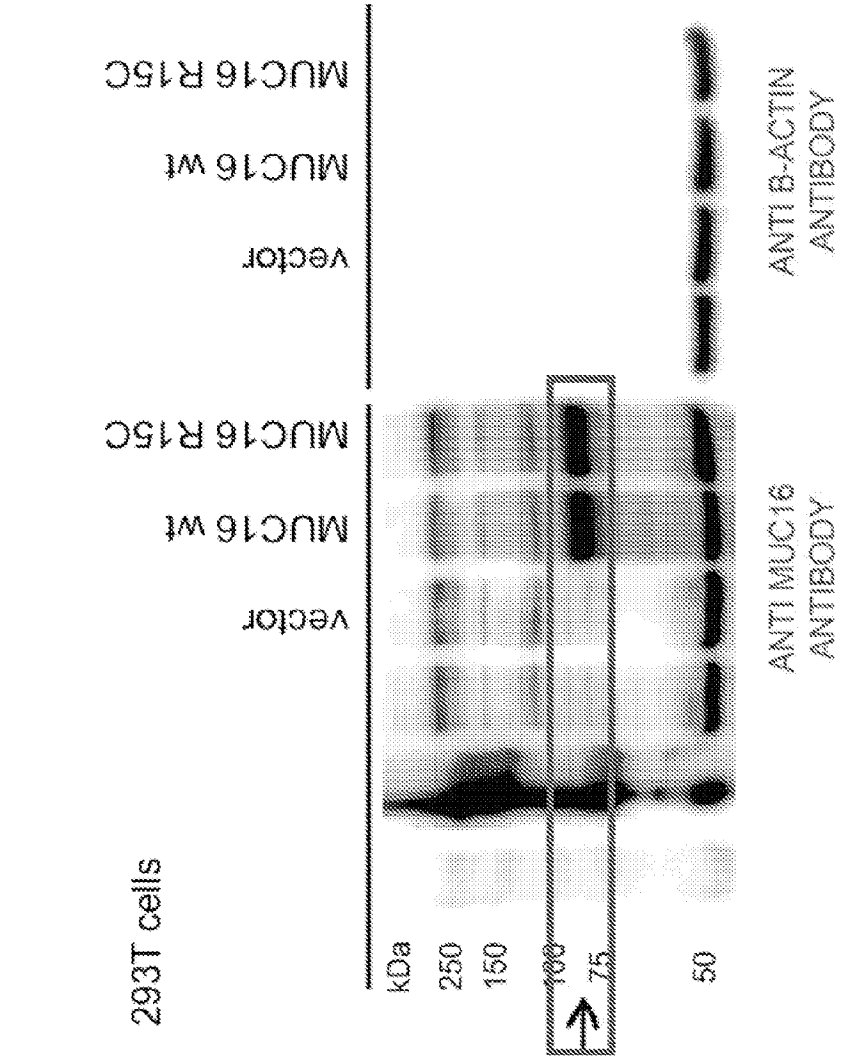


Fig. 70B

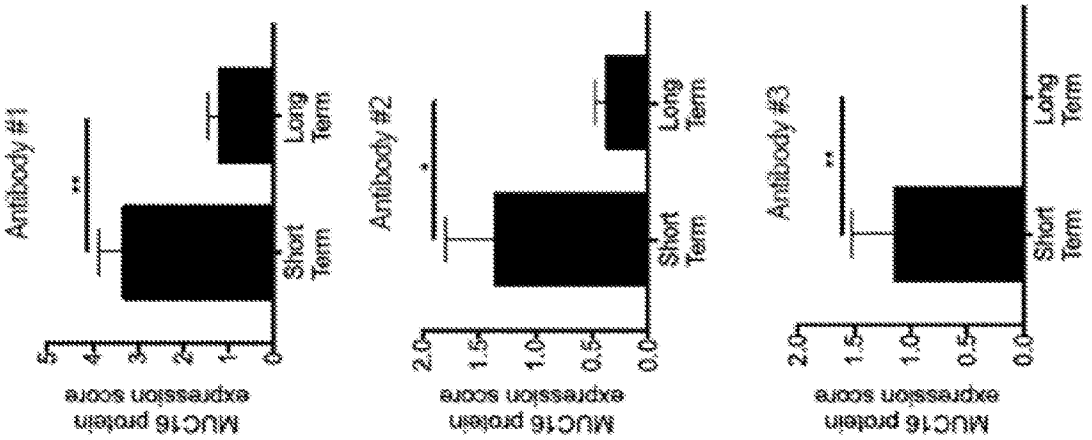


Fig. 70A2

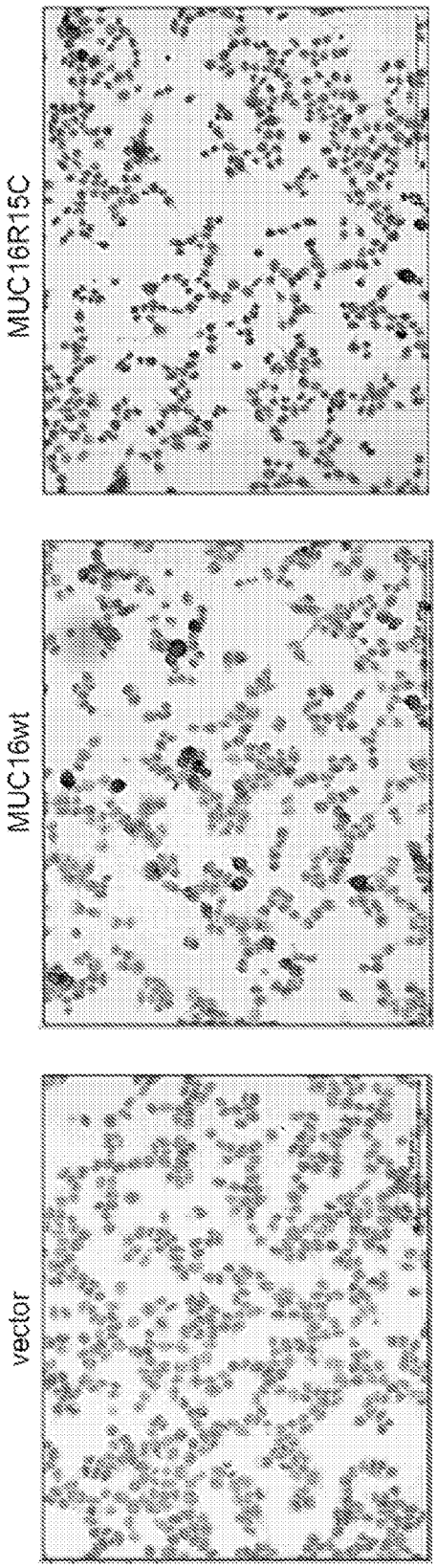


Fig. 70B2

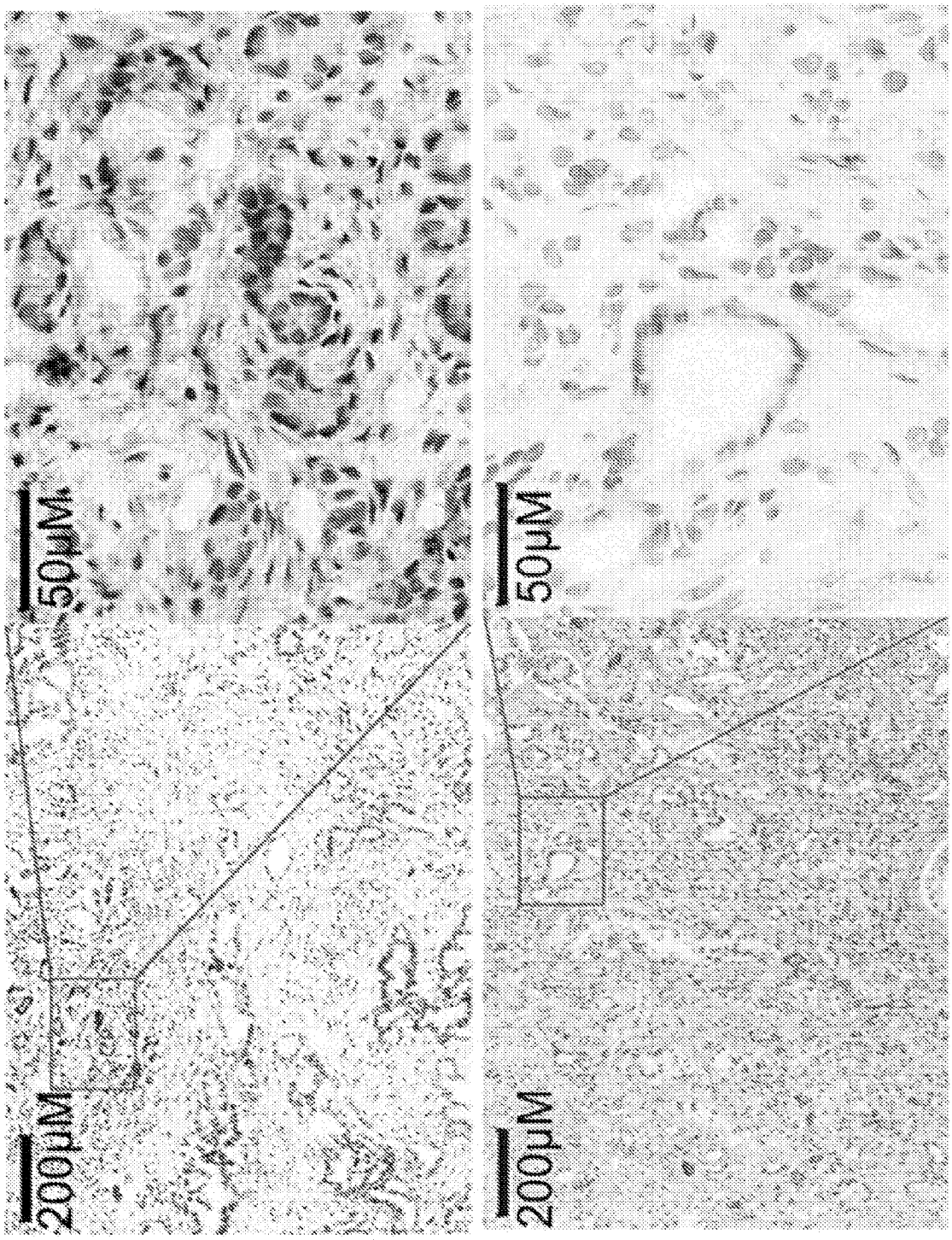


Fig. 70C

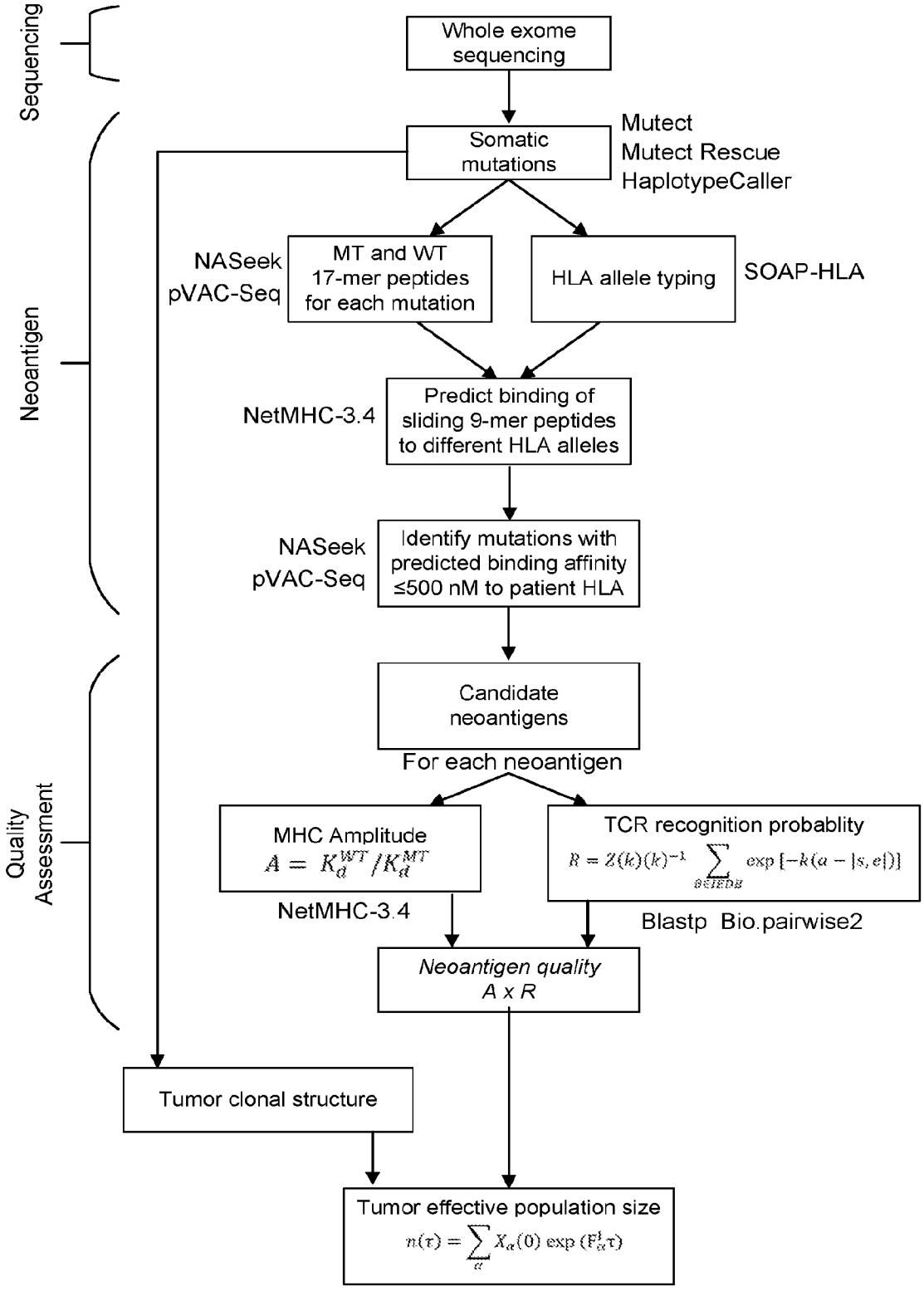

Sequencing
Neoantigen
Quality Assessment
Whole exome sequencing
Somatic mutations
Mutect
Mutect Rescue
HaplotypeCaller
NASeek
pVAC-Seq
MT and WT 17-mer peptides for each mutation
HLA allele typing
SOAP-HLA
NetMHC-3.4
Predict binding of sliding 9-mer peptides to different HLA alleles
NASeek
pVAC-Seq
Identify mutations with predicted binding affinity ≤500 nM to patient HLA
Candidate neoantigens
For each neoantigen
MHC Amplitude
$A = K_d^{WT}/K_d^{MT}$
NetMHC-3.4
TCR recognition probablity
$R = Z(k)(k)^{-1} \sum_{s \in IEDB} \exp[-k(a - |s,e|)]$
Blastp Bio.pairwise2
Neoantigen quality
A x R
Tumor clonal structure
Tumor effective population size
$n(\tau) = \sum_{\alpha} X_{\alpha}(0) \exp(F_{\alpha}^{1}\tau)$

Fig. 71

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/014282

A. CLASSIFICATION OF SUBJECT MATTER
See extra sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (2018.01) A61K, A61P, C12Q, G01N, G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See extra sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017106638 A1 GRITSTONE ONCOLOGY INC [US] 22 Jun 2017 (2017/06/22) Abstract, para. 00247, Figure 14, Example 6, Sections VIII-X	1-74,97-101,106,107, 112,124-163
X	Rubinsteyn, Alexander, et al. "Computational pipeline for the PGV-001 neoantigen vaccine trial." bioRxiv (10.08.2017): 174516. URL: https://www.biorxiv.org/content/biorxiv/early/2017/08/10/174516.full.pdf Retrieved from the internet on: 18.04.2018 10 Aug 2017 (2017/08/10) Abstract, Figure 5	1-74,97-101,106,107, 112,124-163
X	Hundal, Jasreet, et al. "pVAC-Seq: A genome-guided in silico approach to identifying tumor neoantigens." Genome medicine 8.1 (29.01.2016): 11. URL: https://genomemedicine.biomedcentral.com/track/pdf/10.1186/s13073-016-0264-5 Retrieved from the internet on: 18.04.2018 29 Jan 2016 (2016/01/29) Figure 1	1-74,97-101,106,107, 112,124-163

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 Apr 2018	26 Apr 2018
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	Authorized officer HERMAN Karin Telephone No. 972-2-5651749

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/014282

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Bjerregaard, Anne-Mette, et al. "MuPeXI: prediction of neo-epitopes from tumor sequencing data." Cancer Immunology, Immunotherapy 66.9 (20.04.2017): 1123-1130. --- URL: https://www.ncbi.nlm.nih.gov/pubmed/28429069 Retrieved from the internet on: 18.04.2018 20 Apr 2017 (2017/04/20) Abstract, section: "Calculation of priority score", Figure 1	1-74,97-101,106,107, 112,124-163
X	Nathanson, Tavi, et al. "Somatic mutations and neoepitope homology in melanomas treated with CTLA-4 blockade." Cancer immunology research 5.1 (12.12.2016): 84-91. --- URL: http://cancerimmunolres.aacrjournals.org/content/5/1/84.long Retrieved from the internet on: 18.04.2018 12 Dec 2016 (2016/12/12) Abstract; Figures 1, 3; Discussion	1-84,97-101,104,106, 107,109,112,122, 124-163
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Information on patent family members

International application No.
PCT/US2018/014282

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/014282

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (2018.01) A61K 39/00, G01N 33/574, C12Q 1/68, G06F 19/22, A61P 35/00, A61K 35/15, A61K 35/17, G01N 33/68, A61K 39/395

B. FIELDS SEARCHED:

* Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases consulted: BLAST, PATENTSCOPE, Esp@cenet, Google Patents, CAPLUS, BIOSIS, PubMed, Google Scholar, PatBase, Derwent Innovation, Orbit

Search terms used: immunotherapy, checkpoint, T cells, cancer, tumor, pancreas, neoantigen, neoepitope, microb*, homology, IEDB, MUC16, CA125, burden, HLA, MHC, affinity, epitopes,clone, reads, score, computer, algorithm, in silico, quality

Electronic Acknowledgement Receipt

EFS ID:	39885003
Application Number:	16732242
International Application Number:	
Confirmation Number:	7185
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Customer Number:	4743
Filer:	Paul Bryan Stephens/Audrey Nagelberg
Filer Authorized By:	Paul Bryan Stephens
Attorney Docket Number:	32830/58872A
Receipt Date:	01-JUL-2020
Filing Date:	31-DEC-2019
Time Stamp:	13:40:25
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	no

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EFS ID:	39885228
Application Number:	16732242
International Application Number:	
Confirmation Number:	7185
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Customer Number:	4743
Filer:	Paul Bryan Stephens/Audrey Nagelberg
Filer Authorized By:	Paul Bryan Stephens
Attorney Docket Number:	32830/58872A
Receipt Date:	01-JUL-2020
Filing Date:	31-DEC-2019
Time Stamp:	13:41:17
Application Type:	Utility under 35 USC 111(a)

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38	Non Patent Literature	52_Gutmane75_354976.pdf	4416404 82150aea95d6b81ee05c247489a0985c127229ad	no	5
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39	Non Patent Literature	53_Hause1342_354977.pdf	889489 f842caf1e1e2871e90248e97388c0a1cdb8d3aba	no	12
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41	Non Patent Literature	55_Microenvironmen_433207.pdf	1610534 1beaa743d0421245f762edfa78f71956418f8dc	no	14
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42	Non Patent Literature	56_Herbst1_433240.pdf	250882 b50a03aefd07238f8a302202fe9c5d32fae711c0	no	12
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43	Non Patent Literature	57_Herbst563_433224.pdf	4647798 823de8e40fdfcf05b76f39fcd798e3e0b257bfd1	no	38
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44	Non Patent Literature	58_ilse18a_433232.pdf	924377 a8a5ce7af5b1b3cf55ba07e928cd5c52e74ce1ea	no	10
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45	Non Patent Literature	59_Ing1_433216.pdf	1604497 99e5334041bae80d22bc76409c7f7eefdb8b831a	no	10
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46	Non Patent Literature	5_Adeyi183_433228.pdf	81049 18eba69a240b0db2d52be9752b930ac3fa2293b7	no	4
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47	Non Patent Literature	60_WO2019222289ISR_433615.pdf	391009 a7357c50b144d0c5a8a9bda7df903c59f2fee8d7	no	9
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Information:					

51	Non Patent Literature	64_Janzic357_433200.pdf	434027 18b6753a94d3c1552e0d29c956d718f693c2e344	no	6
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58	Non Patent Literature	70_Landscape_of_Mi_354982.pdf	2177890 62ad8931e5e8f14cb6f770721e6b7d3893b366b7	no	21
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			Total Files Size (in bytes):	215233464	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/732,242	12/31/2019	Stephen Yip	32830/58872A

CONFIRMATION NO. 7185

4743
MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

PUBLICATION NOTICE

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Title:ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES

Publication No.US-2020-0211189-A1
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NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/732,242	12/31/2019	Stephen Yip	32830/58872A	7185

4743 7590 07/24/2020

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EXAMINER
VARNDELL, ROSS E

ART UNIT	PAPER NUMBER
2666	

NOTIFICATION DATE	DELIVERY MODE
07/24/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mgbdocket@marshallip.com

Office Action Summary	Application No. 16/732,242	Applicant(s) Yip et al.	
	Examiner Ross Varndell	Art Unit 2666	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 12/31/2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 12/31/2019 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Information Disclosure Statement

2. The IDSs have been considered and placed in the application file.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.
> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

4. Claim(s) 1, 2, 4, 6, and 8 is/are rejected under 35 U.S.C. 102(a)(1) and 35 U.S.C. 102(a)(2) as being anticipated by Tunstall et al. (US 2016/0063724 A1 hereinafter "Tunstall" referred to as "Pathxl" on the written opinion for PCT/US2019/069164 filed on 9/4/2020).

Claim 1:

Tunstall discloses a method for creating an overlay map **(¶43 discloses a color map overlaid with the smoothed boundary data, to provide a user with an estimate of the location of**

tumour and non-tumour regions in the image) on a digital image of a slide, the method comprising:

receiving the digital image **(¶29 discloses Fig. 3, 1000)**;

separating the digital image into a plurality of tiles (**Fig. 3, 1004 and ¶33 discloses partitioning the image into tiles)**;

identifying the majority class of tissue visible within each tile in the plurality of tiles **(¶¶36-38 discloses a tile with feature vectors (tumour type) from the, classification data, the second plurality of feature vectors (non-tumour type) from the classification data; ¶42 discloses a probability estimate based on comparing the feature vectors of tiles in tissue regions of the image with the selected subset of model image data to assign a probability to each tile)**, based on a multi-tile analysis **(¶¶39 discloses tiles comprises image data classified as belonging to one of two states –tumour or non-tumour; ¶40 discloses combining 1012 the tiles to provide a two state map to provide a spatial map of the image data which classifies regions of the image into background, tumour tissue, and non-tumour tissue.)**.

Claim 2:

Tunstall discloses the method of claim 1, further comprising: generating a digital overlay drawing of an outer edge of each cell in the image **(¶25 discloses at 204 a boundary of the region to enable identification of a tumour boundary in a sequential tissue section and data representing the identified boundary is output to the controller 30; ¶43 discloses a colour map, overlaid with the smoothed boundary data, to provide a user with an estimate of the location of tumour and non-tumour regions in the image)**.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

8. Claims 3, 7, 11-14, and 16 is/are rejected under 35 U.S.C. 103 as being unpatentable over Tunstall et al. (US 2016/0063724 A1 hereinafter "Tunstall" referred to as "Pathxl" on the written opinion for PCT/US2019/069164 filed on 9/4/2020).

Claim 3:

Tunstall discloses the method of claim 2, wherein the digital overlay drawing is prepared at the resolution level of an individual pixel. **(¶33 discloses each tile comprises image data relating to that tile at a series of different resolutions, and different resolutions comprises a plurality of blocks each representing at least a portion of the tile at a different effective magnification; where, different magnifications may be achieved by providing equivalent pixel numbers for different sized spatial regions, or a different number of pixels for equally sized spatial regions).**

However, Tunstall does not specifically disclose: wherein the digital overlay drawing is prepared at the resolution level of an individual pixel.

It would have been obvious to a person with ordinary skill in the art to arrive by routine experimentation to prepare the overlay drawing at different magnification levels such as resolution level of an individual pixel since it will provide the utmost accuracy in segmenting the image of the slide **(See ¶¶33 and 34)**.

Claim 4:

Tunstall discloses a method for tissue classification **(¶¶36-38 discloses tumour tissues and with non-tumour tissue)** of a digital image of a slide **(FIG. 3 and ¶¶28-29 discloses a flow chart**

illustrating a computer implemented method of processing an image to guide dissection of a tissue sample suspected of comprising tumour; where, the processor 22 obtains 1000 from memory 24 an image of a section through the tissue sample; and, the section can be imaged from a microscope slide stained using Haemotoxylin and Eosin), the method comprising:

receiving the digital image **(1000, Fig. 3)**;

generating a digital overlay drawing of a tissue region in the digital image **(¶43 discloses displaying the resulting probability estimate as a colour map, overlaid with the smoothed boundary data, to provide a user with an estimate of the location of tumour and non-tumour regions in the image)**; and

displaying, in the digital overlay drawing, tiles over the tissue region and visually identifying predicted content of each tile **(¶42 discloses the processor then obtains a probability estimate based on comparing the feature vectors of tiles in tissue regions of the image with the selected subset of model image data to assign a probability to each tile)**, to generate a classification map classifying the digital image **(¶43 discloses the processor then displays the resulting probability estimate as a colour map, overlaid with the smoothed boundary data, to provide a user with an estimate of the location of tumour and non-tumour regions in the image)**.

9. Claim 5 is/are rejected under 35 U.S.C. 103 as being unpatentable over Tunstall in view of Bergado et al. ("Recurrent Multiresolution Convolutional Networks for VHR Image Classification" hereinafter "Bergado").

Claim 5:

Tunstall discloses the method of claim 4, the method further comprising:

~~determining the predicted content for each tile using a classification model configured as a multi-resolution fully convolutional network, the multi-resolution fully convolution network configured to~~ perform classification on digital images of different zoom levels **(¶33 discloses different effective magnifications)**

However, Tunstall does not disclose: the method further comprising: determining the predicted content for each tile using a classification model configured as a multi-resolution fully convolutional network, the multi-resolution fully convolution network configured to perform classification on digital images of different zoom levels. Bergado discloses a multi-resolution fully convolutional network to performs classification on digital images **(pp 4 col left, ¶1 discloses "In this paper, we propose a multiresolution convolutional network, called FuseNet, and its recurrent version, called ReuseNet, to perform an end-to-end fusion, classification, and map regularization of a multi-resolution VHR image. ReuseNet is built on top of a fully convolutional network architecture learning to: 1) fuse PAN and MS bands of a VHR image, 2) perform land cover classification on the fused images, and 3) spatially regularize the resulting classification.")**.

It would have been obvious to a person with ordinary skill in the art to arrive by routine experimentation lo use the multi-resolution fully convolutional network of Bergado to classify each tile of Tunstall on different zoom levels since multi-resolution fully convolutional networks allow classification of at several levels of resolution and pixels and it is beneficial to analyze histological images at very high resolution levels for higher accuracy **(pp 2 col left, ¶2)**.

Claim 6:

Tunstall discloses the method of claim 4, the method further comprising: using a classification model **(¶¶36-38)**, for each tile, determining a classification from a plurality of classifications **(¶39 disclose classifying the tiles as belonging to one of two states tumour or non-tumour)**.

Claim 7:

Tunstall discloses the method of claim 6, wherein the plurality of classifications include tumor epithelium, normal epithelium, immune, stroma, necrosis, blood, and fat **(¶39 discloses tumour or non-tumour)**.

However, Tunstall does not specifically disclose: immune, stroma, necrosis, blood, and fat classifications.

It would have been obvious to a person with ordinary skill in the art to arrive by routine experimentation to classify image data as immune, stroma, necrosis, blood, and fat classifications to identify tissue type for image metrics **(¶75 disclose descriptor data for identifier of a tissue type for image metrics to be retrieved from memory for the analysis of any given tissue type (as identified by the descriptor data); where, each item of descriptor data is also associated with at least one as classification data; the descriptor data may identify tissue types such as breast tissue, prostate tissue, lung tissue, pancreatic tissue and other types of tissue; ¶93 discloses data associated with structures known or expected to be found in the tissue type from which the image data was obtained such as glands, nuclei, stroma, vessels, lumen, muscle and other structures)**.

Claim 8:

Tunstall discloses a method for cell detection **(¶68 discloses maps of tissue, in which areas in an image of a tissue sample are classified as belonging to particular types of structures or objects including a multitude of normal components and/or structures, such as cells – such as precancerous and/or cancerous cells)** in a digital image of a slide **(Fig. 3, ¶¶28-29 shows a flow chart illustrating a computer implemented method of processing an image from a microscope slide stained using Haemotoxylin and Eosin)**, the method comprising:

receiving the digital image **(1000, Fig. 3)**;

identifying cell objects in the digital image **(¶¶36-38 disclose classification as tumour tissues or non-tumour tissue)**;

generating a digital overlay drawing for the digital image **(¶43 discloes a colour map, overlaid with the smoothed boundary data, to provide a user with an estimate of the location of tumour and non-tumour regions in the image)**; and

displaying, in the digital overlay drawing, a polygon outlining each of the identified cell objects **(¶43 discloses a smoothed boundary data, to provide a user with an estimate of the location of tumour and non-tumour regions in the image)**.

10. Claims 9-10 is/are rejected under 35 U.S.C. 103 as being unpatentable over Tunstall in view of Erjefalt (US 2014/0140607 A1 hereinafter "Erjefalt").

Claim 9:

Tunstall discloses the method of claim 8, wherein the cell objects **(Tunstall ¶¶36-38)** ~~include lymphocyte cells and not lymphocyte cells~~.

Tunstall disclose all of the subject matter as described above except for specifically teaching include lymphocyte cells and not lymphocyte cells. However, Erjefalt in the same field of endeavor teaches include lymphocyte cells and not lymphocyte cells **(¶190 discloses a choice box 76 for providing a choice between different alternatives such as "B lymphocytes" and a group of a plurality of cell types).**

Therefore, it would have been obvious to one of ordinary skill in the art to combine Tunstall and Erjefalt before the effective filing date of the claimed invention. The motivation for this combination of references would have been to show a reviewer of the overlay a clear delineation between lymphocyte and non-lymphocyte cells since the detection of lymphocyte and non-lymphocyte cells is an important aspect of histological analysis **(See Erjefalt ¶¶5-6)**. This motivation for the combination of Tunstall and Erjefalt is supported by KSR exemplary rationale (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Claim 10:

The combination of Tunstall and Erjefalt discloses the method of claim 8, wherein the cell objects comprise CD3, CD8, CD20, pancytokeratin, and smooth muscle actin **(¶78 and Table 1 discloses immune cell markers CD20 B-lymphocytes and CD8 T lymphocytes ECP (EG2).**

It would have been obvious to one of ordinary skill in the art to combine Tunstall and Erjefalt before the effective filing date of the claimed invention. The motivation for this combination of references would have been identify CD20 and/or CD8 by training the classification model of Tunstall with the data about CD20 and/or CD8 since CD20 and/or CD8 is/are an important aspect(s) of histological analysis **(See Erjefalt ¶¶5-6).** This motivation for the combination of Tunstall and Erjefalt is supported by KSR exemplary rationale (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Claim 11:

Tunstall discloses a method for tissue classification **(¶¶36-38 discloses the classification data comprises a first set of model image feature vectors associated with tumour tissues and a second set of model image feature vectors associated with non-tumour tissue)** of a digital image of a slide **(FIG. 3 and ¶¶28-29 disclose a microscope slide stained using Haemotoxylin and Eosin)**, the method comprising:

receiving the digital image **(1000, Fig. 3)**;

segmenting the digital image into a plurality of tiles **(1004, Fig. 3; ¶33 disclose partitioning 1004 the first group of image data relating to tissue, into tiles)**;

determining a predicted class for each tile **(¶42 discloses obtaining a probability estimate based on comparing the feature vectors of tiles in tissue regions of the image with the selected subset or model image data to assign a probability to each tile)**;

identifying a plurality of cell objects in the digital image **(¶68 discloses precancerous and/or cancerous cells)**;

determining a predicted class for each of the plurality of cell objects **(¶43 discloses a probability estimate as a colour map for an estimate of the location of tumour and nontumour regions in the image)**; and

for each of the plurality of tiles that corresponds to one of the plurality of cell objects, assigning the tile the predicted class of the corresponding cell object **(¶40 discloses combining 1012 the tiles to provide a two state map (e.g. binary) identifying tumour, and non-tumour regions of the tissue with the tissue/non-tissue mask generated by the segmentation 1002 to provide a spatial map of the image data which classifies regions of the image into one of three states e.g. background, tumour tissue. and nontumour tissue.")**. ~~in place of the predicted class of the tile.~~

However Tunstall does not disclose: assigning in place of the predicted class of the tile.

It would have been obvious to a person with ordinary skill in the art to arrive by routine experimentation to replace the predicted class of each tile with the predicted class of cell object formed by combining the tiles in the method of Tunstall since it will allow visualizing the predicted class of the entire cell object rather than individual tiles on the overlay, making it to possible segments on tissue-level **(See ¶¶39, 40)**.

Claim 12:

Tunstall discloses the method of claim 11, further comprising: ~~storing, in a first file, for each tile, a tile position~~ and the predicted class of the tile; and ~~storing, in a second file, for each cell object~~, a polygon outlining the cell object and the predicted class of the cell object **(¶26**

discloses data representing the region and the boundary are stored to non-volatile memory for later user reference and/or for updating the classification data using a learning method; ¶47 disclose the memory 24 of the computer 20 of FIG. 1 maybe configured to store data received from the imager 50, results generated by the processor 22, and classification data for classifying tumour and non-tumour regions. Non-volatile memory may be provided for storing the classification data. Further non-volatile memory may be provided for storing the image data so that the image data for a plurality of tissue samples may be uploaded and stored in memory until such time as the processor 22 has capability or an instruction to process ii. The memory 24 may comprise a buffer or an on-chip cache. Further non-volatile memory may be provided for storing results of the image processing method for later user reference and/or for updating the classification data using a learning method).

However, Tunstall does not specifically disclose: storing, in a first file, for each tile, a tile position; and storing, in a second file, for each cell object.

It would have been obvious for a person with ordinary skill in the art to arrive by routine experimentation to store the position as well as the classification data for each tile and for each cell object in the method of Tunstall since it allows for providing an efficient computer implemented image processing method which selects various data from memory **(See ¶118)**.

Claim 13:

Tunstall discloses the method of claim 11, further comprising: generating a digital overlay drawing for the digital image, where the digital overlay drawing is a cell mask displaying a polygon around each cell object **(¶43 discloses a smoothed boundary data)**.

Claim 14:

Tunstall discloses the method of claim 11, further comprising: generating a digital overlay drawing for the digital image, where the digital overlay drawing is a histology mask displaying the plurality of tiles **(¶40 discloses "The processor is configured to combine 1012 the tiles to provide a two state map (e.g. binary) identifying tumour, and non-tumour regions of the tissue with the tissue/non-tissue mask generated by the segmentation 1002 to provide a spatial map of the image data which classifies regions of the image into one of three states e.g. background, tumour tissue, and non-tumour tissue."; ¶43 discloses "The processor then displays the resulting probability estimate as a colour map, overlaid with the smoothed boundary data, to provide a user with an estimate of the location of tumour and non-tumour regions in the image.")** and the predict class for each tile **(¶42 discloses "The processor then obtains a probability estimate based on comparing the feature vectors of tiles in tissue regions of the image with the selected subset of model image data to assign a probability to each tile.")**.

However, Tunstall does not specifically disclose: displaying the predicted class for each tile.

It would have been obvious to a person with ordinary skill in the art to arrive by routine experimentation to display the predicted class for each tile on the digital overlay in the method of Tunstall since method already can estimate the class of each tile and displaying them on the overlay will provide a more detailed classification map **(See ¶¶39-42)**.

11. Claims 15 is/are rejected under 35 U.S.C. 103 as being unpatentable over Tunstall in view of Wenzel et al. (US 2018/0137394 A1 hereinafter "Wenzel").

Claim 15:

Tunstall discloses the method of claim 11, further comprising: generating a digital overlay drawing for the digital image **(¶43)**; and

~~displaying~~, in the digital overlay drawing, ~~the plurality of tiles and the predicted class for each tile that does not correspond to a cell object~~

and displaying, the plurality of cell objects and the predicted class of each cell object **(¶68 discloses the image data may include a multitude of normal components and/or structures. such as cells, ducts, and/or the like, and a number of non-normal components and/or structures which, for example, may include precancerous and/or cancerous cells)**.

Tunstall disclose all of the subject matter as described above except for specifically teaching: displaying, the plurality of tiles and the predicted class for each tile that does not correspond to a cell object. However, Wenzel in the same field of endeavor teaches displaying, the plurality of tiles and the predicted class for each tile that does not correspond to a cell object **(¶¶7-10 discloses misclassification using an automated tissue classification technique providing as output a tissue classification map of the brain of the patient with a user interaction subsystem comprising a user device operable by a user, wherein the input commands represent user feedback which is indicative of (a) an area of misclassification in the tissue classification map and (b) a correction of the misclassification; and, (j) adjusting the prior probability map based on the user feedback , thereby obtaining an adjusted prior**

probability map to re-apply the automated tissue classification technique to the image based on the adjusted prior probability map).

Therefore, it would have been obvious to one of ordinary skill in the art to combine Tunstall and Wenzel before the effective filing date of the claimed invention. The motivation for this combination of references would have been to display the tiles and the predicted class of each tile that does not belong to the cell object in the digital overlay of the method of Tunstall since it would show misclassified tiles, which would allow for the tile to be correctly classified (See Wenzel ¶5). This motivation for the combination of Tunstall and Wenzel is supported by KSR exemplary rationale (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Claim 16:

Tunstall discloses the method of claim 11, further comprising: generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes the digital image; and displaying the digital overlay drawing **(¶43)**.

However, Tunstall does not disclose: wherein the digital overlay drawing includes the digital image.

It would have been obvious to a person with ordinary skill in the art to arrive by routine experimentation to display the digital image of the slide of Tunstall in the digital overlay of Tunstall since the original image can be used for comparison and reference **(See ¶103)**.

12. Claims 17 and 18 is/are rejected under 35 U.S.C. 103 as being unpatentable over Tunstall in view of Everett et al. (US 2007/0216909 A1 hereinafter "Everett").

Claim 17:

Tunstall discloses the method of claim 11, further comprising: generating a digital overlay drawing for the digital image **(¶43 discloses a probability estimate as a colour map, overlaid with the smoothed boundary data, to provide a user-with an estimate of the location of tumour and non-tumour regions in the image)**, ~~wherein the digital overlay drawing includes a generated version of the digital image~~; and displaying the digital overlay drawing **(¶43)**.

Tunstall disclose all of the subject matter as described above except for specifically teaching wherein the digital overlay drawing includes a generated version of the digital image. However, Everett in the same field of endeavor teaches wherein the digital overlay drawing includes a generated version of the digital image **(¶69 discloses] "In the illustrated embodiment, the overlay is an en face integrated image derived from optical coherence tomography (OCT) data (i.e. generated version) and the underlying image is from the ophthalmoscope).**

Therefore, it would have been obvious to one of ordinary skill in the art to combine Tunstall and Everett before the effective filing date of the claimed invention. The motivation for this combination of references would have been to display a generated version of the digital image of the histological slide of Tunstall in the digital overlay of Tunstall to provide context or location cues for the higher resolution scans since images sampled in different resolutions may provide different information (See Everett ¶9). This motivation for the combination of Tunstall and Everett is supported by KSR exemplary rationale (G) Some

teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Claim 18:

Tunstall discloses the method of claim 11, further comprising: generating ~~a plurality of~~ digital overlay drawing[[s]] for the digital image **(¶43)**, where each digital overlay drawing corresponds to a different predicted class **(¶¶61, 63-64 discloses a posterior probability of corresponding to a tumour region or non-tumour region; where classification data comprises data (e.g. feature vectors) relating to known tissue types and/or known tumour types)**; and ~~selectively displaying one of the plurality of digital overlay drawings~~.

Tunstall disclose all of the subject matter as described above except for specifically teaching – selectively displaying one of a plurality of digital overlay drawings where each digital overlay drawing corresponds to a different predicted class; and selectively displaying one of the plurality of digital overlay drawings. However, Everett in the same field of endeavor teaches selectively displaying **(Fig.3 disclose a currently selected overlay of "ILM to RPE")** one of a plurality of digital overlay drawings **(¶71 discloses various colors can be used in overlays so that when bright regions align, the red and green add to make a new color, like yellow; similarly, when dark regions align they create a darker region because, when they were misaligned, the misaligned color creeps into and brightens the region).**

Therefore, it would have been obvious to one of ordinary skill in the art to combine Tunstall and Everett before the effective filing date of the claimed invention. The motivation for this combination of references would have been to have multiple digital overlays for the

digital image of Tunstall and select one out of the multiple digital overlays since it would provide additional visualization options where each overlay helps visualize different aspects of the image such as how a lower resolution scan can provide context or location cues for the higher resolution scans (See Everett ¶9). This motivation for the combination of Tunstall and Everett is supported by KSR exemplary rationale (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

13. Claims 19 and 20 is/are rejected under 35 U.S.C. 103 as being unpatentable over Tunstall in view of Dolan (US 2020/0105417 A1 hereinafter "Dolan").

Claim 19:

Tunstall discloses the method of claim 11, further comprising: generating a digital overlay drawing for the digital image **(¶43)**, ~~where the digital overlay drawing comprises percentages~~ of predict classes **(¶¶61, 63-64 discloses a posterior probability of corresponding to a tumour region or non-tumour region)** ~~corresponding to the digital image~~.

Tunstall discloses all of the subject matter as described above except for specifically teaching where the digital overlay drawing comprises percentages corresponding to the digital image. However, Dolan in the same field of endeavor teaches where the digital overlay drawing comprises percentages corresponding to the digital image **(¶¶17, 142 discloses overlaying, the population percentage map onto the mortality or adverse outcome rate map thereby generating an overlap map).**

Therefore, it would have been obvious to one of ordinary skill in the art to combine Tunstall and Dolan before the effective filing date of the claimed invention. The motivation for this combination of references would have been to create a visual representation of a percentage of a particular class of tissue for the evaluating the health of an individual (Dolan ¶¶2-4). This motivation for the combination of Tunstall and Dolan is supported by KSR exemplary rationale (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Claim 20:

The combination of Tunstall and Dolan discloses the method of claim 11, further comprising: generating a digital overlay drawing for the digital image **(Tunstall ¶43)**, where the digital overlay drawing comprises total counts of predict classes **(Tunstall ¶¶61, 63-64 discloses a posterior probability of corresponding to a tumour region or non-tumour region)** corresponding to the digital image **(Dolan ¶¶17, 142 discloses overlaying, the population percentage map onto the mortality or adverse outcome rate map thereby generating an overlap map; ¶¶19, 68-72 and the Figures discloses an overlap is present between the distribution of the plurality of joint risk parameters and the adverse outcome data)**. The motivation for this combination of references is the same as for claim 19.

Conclusion

14. The prior art made of record and not relied upon is considered pertinent to the applicant's disclosure: See the PTO-892 mailed with this office action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ross Varndell whose telephone number is (571)270-1922. The examiner can normally be reached on M-F, 9-5 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kim Vu can be reached on (571)272-3859. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ross Varndell/
Primary Examiner, Art Unit 2666

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	Examiner Ross Varndell	Art Unit 2666	Page 1 of 1

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	Examiner	Art Unit
	Ross Varndell	2666

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Symbol	Date	Examiner
G06T7/0012, G06T2207/30096, G06T2207/20084, G06K9/00147, G06K9/00523, G06K9/00536, G06N20/00	07/20/2020	RV

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
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Search Notes		
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Performed double patenting, inventor, and prior art searches.	07/20/2020	RV

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
G06T	7/0012, 2207/30096, 2207/20084	07/20/2020	RV
G06K	9/00147, 9/00523, 9/00536	07/20/2020	RV
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Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2667
Examiner Name	BELLA, MATTHEW C
Attorney Docket Number	32830/58872A

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Foreign Priority claimed: ○ Yes ◉ No

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/RV/	44	YUAN et al., Supplementary materials for quantitative image analysis of cellular heterogeneity in breast tumors complements genomic profiling, (2012), doi:10.1126/scitranslmed.3004330.	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /RV/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2667
Examiner Name	BELLA, MATTHEW C
Attorney Docket Number	32830/58872A

/RV/	45	ZHANG et al., Adversarial deep learning for microsatellite instability prediction from histopathology, slides, First Conference on Medical Imaging with Deep Learning (MIDL, 2018), Amsterdam, The Netherlands.	☐
/RV/	46	ZHU et al., Deciphering genomic underpinnings of quantitative MRI-based radiomic phenotypes of invasive breast carcinoma, Sci. Rep., 5:17787 (2016).	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/Ross Varndell/	Date Considered	07/20/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /RV/

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	0	"16830186"	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 08:53
S2	215	((("YIP") near3 ("Stephen")) OR (("HO") near3 ("Irvin")) OR (("SHA") near3 ("Lingdao")) OR (("OSINSKI") near3 ("Boleslaw")) OR (("KHAN") near3 ("Aly")) OR (("KRUGER") near3 ("Andrew")) OR (("CARLSON") near3 ("Michael")) OR (("GREENWALD") near3 ("Abel")) OR (("WILLIS") near3 ("Caleb"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	AND	OFF	2020/07/07 08:54
S3	1	"20160063724".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 10:28
S4	410,720	(hematoxylin near4 eosin) or h?e	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:51
S5	23,422	tile$2 near4 image$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:51
S6	26,378	(deep$4 near4 learn$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:51
S7	1,971	biomarker$4 near4 classifi$6	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:52
S8	452,847	overlay$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:52

S9	0	S4 S5 S6 S7 S8	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:52
S10	83,955	biomarker$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:53
S11	8	S4 S5 S6 S10 S8	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:53
S12	49,001	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:57
S25	1,305,469	deep$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/08 09:13
S26	1	"20160063724".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/08 09:13
S27	0	S26 deep$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/08 09:13
S28	1	S26 learning$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/08 09:13
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S32	1,612	biomarker$4 near4 classif$6	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:46
S33	38	S31 S32	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:46
S34	0	S29 S31 S32	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:47
S35	0	S30 S31 S32	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:47
S36	13	("20200184643" "10646156" "20190244348" "20190180153" "20190244347" "20190159737" "20190180438" "20190172197" "20190156159" "10426442" "20200005901" "20190087532" "10395366").did.	US-PGPUB; USPAT	OR	OFF	2020/07/08 09:49
S37	33,654	biomarker$4 classif$6	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:49
S38	596	S31 S37	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:49
S39	1	S29 S31 S37	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:49
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S43	0	S42 multiscal$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:30
S44	0	S36 multiscal$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:30
S45	1	S29 multiscal$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:30
S46	12	(multiscal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:31
S47	1	(S40 or S42) (til$4 same mask$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:33
S48	1	(S40 or S42) (til$4 same siz$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:36
S49	0	(S40 or S42) (til$4 same rectangl$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:38
S50	0	(S40 or S42) (til$4 same squar$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:38
S51	0	(S40 or S42) fcn	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:40
S52	0	(S40 or S42) convoluat$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:40
S53	0	(S40 or S42) (UNet or U near2 net)	US-PGPUB; USPAT	AND	ON	2020/07/08 10:41
S54	1	(S40 or S42) (PD-L1)	US-PGPUB; USPAT	AND	ON	2020/07/08 10:42
S55	0	(S40 or S42) (tils)	US-PGPUB; USPAT	AND	ON	2020/07/08 10:43
S56	0	(S40 or S42) (nc near4 ratio$4)	US-PGPUB; USPAT	AND	ON	2020/07/08 10:43
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S58	0	(multiscal$4 with (deep near4 learn$4)) (single near2 scal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:44

S59	0	(multiscal$4 with (deep near4 learn$4)) (singl$4 near4 scal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:45
S60	0	(multiscal$4 with (deep near4 learn$4)) (single with scal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:22
S61	1,534	(scal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:29
S62	408	(scal$4 near4 (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:29
S63	20	("20030215936" | "20060064248" | "20070216909" | "20100111396" | "20140073922" | "20140140607" | "20140337052" | "20150100246" | "20160063724" | "20160103973" | "20160253466" | "20170076046" | "20170337682" | "20180005136" | "20180089373" | "20180121759" | "20180129911" | "20180137394" | "20190169685" | "6463438").PN.	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:49
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S66	1	(US-20180089373-$).did.	US-PGPUB	AND	OFF	2020/07/08 13:51
S67	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/08 13:51
S68	0	(S66 or S67) ResNet$4	US-PGPUB; USPAT	AND	ON	2020/07/08 13:51
S69	0	(S66 or S67) (convolution$4 near4 neural near4 network$4)	US-PGPUB; USPAT	AND	ON	2020/07/08 13:52
S70	0	(S66 or S67) (Inception-v3$4)	US-PGPUB; USPAT	AND	ON	2020/07/08 13:52
S71	1,129	ResNet$4 or (Inception-v3$4)	US-PGPUB; USPAT	AND	ON	2020/07/08 13:53
S72	8	(S64 or S63) S71	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:53
S73	1	(S64 or S63) ((consensus$4 near4 molecular$4 near4 subtype) or (CMS) or (homologous$4 near4 recombination$4 near4 deficienc$4) or (HRD))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:55
S74	0	(S66 or S67) ((consensus$4 near4 molecular$4 near4 subtype) or (CMS) or (homologous$4 near4 recombination$4 near4 deficienc$4) or (HRD))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:56
S75	1	(S66 or S67) (gpu or tpu or cpu)	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:57
S76	0	(S66 or S67) (scanner$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:58
S77	2	(S66 or S67) (scan$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:58
S78	1	(US-20180089373-$).did.	US-PGPUB	AND	OFF	2020/07/09 08:30
S79	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/09 08:30

S80	2	(S78 or S79) (network$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:30
S81	0	(S78 or S79) (pathology$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:32
S82	2	(S78 or S79) (disease$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:32
S83	0	(S78 or S79) (adversar$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:38
S84	20	("20030215936" | "20060064248" | "20070216909" | "20100111396" | "20140073922" | "20140140607" | "20140337052" | "20150100246" | "20160063724" | "20160103973" | "20160253466" | "20170076046" | "20170337682" | "20180005136" | "20180089373" | "20180121759" | "20180129911" | "20180137394" | "20190169685" | "6463438").PN.	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:39
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S87	4	(S85 or S84) adversar$4	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:39
S88	0	(S78 or S79) (overlay$4 same tumor$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:45
S89	0	(S78 or S79) (overlay$4 same2 tumor$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:45
S90	0	(S78 or S79) (overlay$4 same4 tumor$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:45
S91	0	(S78 or S79) (overlay$4 tumor$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:45
S92	2	(S85 or S84) adversar$4 resnet	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:48
S93	2	adversar$4 resnet (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:49
S94	1	"20190392580".did.	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:54
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S96	0	S94 resnet (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:54
S97	0	S94 (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:54
S98	1	S94 biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:54
S99	0	S94 (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:55
S100	1	S94 adversar$4 biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:55
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S103	0	S101 (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57

S104	0	S101 biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S105	0	S101 biomarker$4 (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S106	1	S101 biomarker$4	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S107	1	S101 (u near2 net) biomarker	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S108	1	S101 (u near2 net) resnet biomarker	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S109	1	S101 (u near2 net) resnet biomarker gan	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:58
S110	1	S101 (u near2 net) resnet biomarker gan deep	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:58
S111	0	S101 (u near2 net) resnet biomarker gan deep (multi$4 near4 scal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:00
S112	0	S101 (u near2 net) resnet biomarker gan deep (multiscal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:01
S113	0	S101 ((multi$4 near4 scal$4) or multiscal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:01
S114	7	"15360742"	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:03
S115	3	S114 ((multi$4 near4 scal$4) or multiscal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:04
S116	1	S101 (u near2 net) resnet biomarker gan deep (scal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:09
S117	1	(S78 or S79) (scal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:13
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S121	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/09 12:20
S122	2	(S120 or S121) (train$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 12:20
S123	1	(S120 or S121) (cluster$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 12:25
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S129	0	S127 muliscal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:15
S130	0	S127 mulipl$4 scal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:15
S131	1	S127 scal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:15

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S137	6	S134 ((different$4 or multipl$4) same scal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:20
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S139	8	S138 ((different$4 or multipl$4) same scal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:27
S140	12	S138 (scal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:29
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S144	879	S143 (multiscal$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:34
S145	15	S143 (multiscal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:35
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S148	1	S146 nnf	US-PGPUB	AND	OFF	2020/07/10 13:54
S149	1	S146 cnn	US-PGPUB	AND	OFF	2020/07/10 13:55
S150	1	S146 cnn deep	US-PGPUB	AND	OFF	2020/07/10 13:55
S151	1	S146 (multiscal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:56
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S153	1	S152 scal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 14:16
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S155	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/10 14:24
S156	2	(S154 or S155) (learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/10 14:24

S157	2	(S154 or S155) (class$4)	US-PGPUB; USPAT	AND	OFF	2020/07/10 14:26
S158	0	(S154 or S155) (class$4) discard$4	US-PGPUB; USPAT	AND	OFF	2020/07/10 14:26
S159	1	(S154 or S155) (class$4) delet$4	US-PGPUB; USPAT	AND	OFF	2020/07/10 14:26
S160	1	S152 resnet$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 14:29
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S165	1	S161 tumour$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/11 16:04
S166	0	S161 tumour$4 same4 overlay	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/11 16:05
S167	1	S161 tumour$4 same4 overla$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/11 16:05
S168	2	"16732242"	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/12 23:20
S169	1	(US-20200211189-$).did.	US-PGPUB	AND	OFF	2020/07/12 23:21
S170	1	S169 classif$6 near4 map$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/12 23:21
S171	1	"20140140607".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/14 14:59
S172	1	"20180137394".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/14 15:19
S173	1	"20070216909".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/15 11:48

S174	1	"20070216909".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:37
S175	1	S174 overlay	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:37
S176	1	S174 overlay ((en near2 fac$4) or enfac$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:39
S177	1	S174 overlay ((en near2 fac$4) or enfac$4) oct	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:41
S178	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/16 07:53
S179	0	S174 overlay ((en near2 fac$4) or enfac$4) oct (irl same rpe)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:56
S180	1	S174 overlay ((en near2 fac$4) or enfac$4) oct (ilm same rpe)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:56
S181	1	S178 (tumour$4)	US-PGPUB	AND	OFF	2020/07/16 08:55
S182	1	"20140073922".did.	US-PGPUB	AND	OFF	2020/07/16 09:02
S183	1	"20140073922".did.	US-PGPUB	AND	OFF	2020/07/16 12:47
S184	1	S183 percent$4	US-PGPUB	AND	OFF	2020/07/16 12:47
S185	0	S183 lv	US-PGPUB	AND	OFF	2020/07/16 12:48
S186	1	S183 likelihood$4	US-PGPUB	AND	OFF	2020/07/16 12:48
S187	161	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC. (overlay$4 same percentage$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 12:52

S188	74	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC. (overlay$4 with percentage$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 12:53
S190	1	(US-20200105417-$).did.	US-PGPUB	AND	OFF	2020/07/20 09:25
S191	1	S190 overla$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/20 09:25
S192	474,337	tile	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/20 09:54
S193	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/20 09:54
S194	1	S193 tile$2	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/20 09:54

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S13	16,074	((hematoxylin near4 eosin) or h?e).clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55
S14	3,652	(tile$2 near4 image$4).clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55
S16	2,860	(deep$4 near4 learn$4).clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55
S17	72,913	overlay$4.clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55

S18	0	S13 S14 S16 S17	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55
S19	48,980	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:57
S21	292	S13 S17	US-PGPUB; USPAT	AND	OFF	2020/07/07 14:01
S22	1	S13 S14 S17	US-PGPUB; USPAT	AND	OFF	2020/07/07 14:01
S23	305	((hematoxylin near4 eosin)).clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 14:01
S24	11	S23 S17	US-PGPUB; USPAT	AND	OFF	2020/07/07 14:02
S189	161	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC. (overlay$4 same percentage$4)	US-PGPUB; USPAT	AND	OFF	2020/07/16 12:52

7/20/2020 10:43:31 AM
C:\Users\rvarndell\Documents\EAST\Workspaces\16732242-2.wsp

Docket No.: 32830/58872A
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Yip et al.

Application No.: 16/732,242 | Confirmation No.: 7185

Filed: December 31, 2019 | Art Unit: 2631

For: ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES | Examiner: R. E. Varndell

SUBMISSION OF EXECUTED DECLARATIONS

MS Sequence
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants submit herewith the executed declarations of Stephen Yip, Irvin Ho, Lingdao Sha and Boleslaw Osinski.

The late declaration fee was paid on December 31, 2019. As such, no additional fees are believed to be due.

Dated: August 3, 2020

Respectfully submitted,

Electronic signature: _/Paul B. Stephens/_
Paul B. Stephens
Registration No.: 47,970
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive
6300 Willis Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant

DocuSign Envelope ID: 9CDDED2E-ED5A-4C28-9213-0EED62F2449B

Attorney Docket No.: 32830/58872A 01
(modified)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number 16/732,242 filed on 12/31/2019 .
  - ☐ As Amended on _____ (if applicable)

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by an amendment, if any, specifically referred to herein. I acknowledge the duty to disclose information that is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information that became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Stephen Yip Date (Optional): 7/15/2020

Signature: /Stephen Yip/

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

DocuSign Envelope ID: 9CDDED2E-ED5A-4C28-9213-0EED62F2449B

Attorney Docket No.: 32830/58872A 01
(modified)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

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  - ☐ As Amended on _____ (if applicable)

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I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Irvin Ho Date (Optional): 7/7/2020

Signature: /Irvin Ho/

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

DocuSign Envelope ID: 9CDDED2E-ED5A-4C28-9213-0EED62F2449B

Attorney Docket No.: 32830/58872A 01
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LEGAL NAME OF INVENTOR

Inventor: Lingdao Sha Date (Optional): 7/7/2020

Signature: /Lingdao Sha/

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

DocuSign Envelope ID: 9CDDED2E-ED5A-4C28-9213-0EED62F2449B

Attorney Docket No.: 32830/58872A 01
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- ☒ United States application or PCT international application number 16/732,242 filed on 12/31/2019 .
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The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Boleslaw Osinski Date (Optional): 7/7/2020

Signature: /Boleslaw Osinski/

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Electronic Acknowledgement Receipt

EFS ID:	40181086
Application Number:	16732242
International Application Number:	
Confirmation Number:	7185
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Customer Number:	4743
Filer:	Paul Bryan Stephens/Jennie Mackowiak
Filer Authorized By:	Paul Bryan Stephens
Attorney Docket Number:	32830/58872A
Receipt Date:	03-AUG-2020
Filing Date:	31-DEC-2019
Time Stamp:	17:53:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	Submission_of_executed_declarations.PDF	13672 9bb301e5e33f4eb7e591b5ea23d632e44f249bd5	no	1

Warnings:

Information:					
2	Oath or Declaration filed	Executed_declarations.PDF	105965 b6877137e6575f0c330b617a39b892a4879ca0e6	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	119637		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16732242
	Filing Date	2019-12-31
	First Named Inventor	Stephen Yip
	Art Unit	2666
	Examiner Name	VARNDELL, ROSS E
	Attorney Docket Number	32830/58872A

	1	PELLEGRINO et al., "Controversies in oncology: are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making?," ESMO Open 4(2) (2018)	☐
	2	ULYANOV et al., Instance normalization: the missing ingredient for fast stylization, arXiv:1607.08022, 1-6 (2017).	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	_/Paul B. Stephens/_	Date (YYYY-MM-DD)	2020-08-19
Name/Print	Paul B. Stephens	Registration Number	47,970

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16732242
Filing Date:	31-Dec-2019
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Filer:	Paul Bryan Stephens/Brian Roche
Attorney Docket Number:	32830/58872A

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	40277274
Application Number:	16732242
International Application Number:	
Confirmation Number:	7185
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Customer Number:	4743
Filer:	Paul Bryan Stephens/Audrey Nagelberg
Filer Authorized By:	Paul Bryan Stephens
Attorney Docket Number:	32830/58872A
Receipt Date:	19-AUG-2020
Filing Date:	31-DEC-2019
Time Stamp:	13:45:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	E20208ID45519393
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	1_Pellegrino_B_Ma_465322.pdf	877853 42815c03be6a341aa6862da8654302cdd255d7b3	no	15
Warnings:					
Information:					
2	Non Patent Literature	2_160708022_473295.pdf	7299094 49292d09e5b672cd999d0516f1b04fa0acfb38e1	no	6
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	IDS_16732242_2.pdf	80737 9813fd31872a1e77cd6e45d2e019229a905447d1	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Fee Worksheet (SB06)	fee-info.pdf	30455 d306c485f5a3eee53d87597ab1446b5273bebd56	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	8288139		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20180239949	A1	2018-08-23	CHANDER et al.	
	2	20180340870	A1	2018-11-29	GUSTAFSON et al.	
	3	20190087532	A1	2019-03-21	MADABHUSHI et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2018/165103	WO	A1	2018-09-13	UNIV SOUTHERN CALIFORNIA		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	International Application No. PCT/US2020/024748, International Search Report and Written Opinion, mailed August 03, 2020.	☐
	2	International Application No. PCT/US2020/024748, Invitation to Pay Additional Fees, mailed June 10, 2020.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	_/Paul B. Stephens/_	Date (YYYY-MM-DD)	2020-08-19
Name/Print	Paul B. Stephens	Registration Number	47,970

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	40325066
Application Number:	16732242
International Application Number:	
Confirmation Number:	7185
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Customer Number:	4743
Filer:	Paul Bryan Stephens/Audrey Nagelberg
Filer Authorized By:	Paul Bryan Stephens
Attorney Docket Number:	32830/58872A
Receipt Date:	19-AUG-2020
Filing Date:	31-DEC-2019
Time Stamp:	13:47:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	1_Scan_From_PTO_N_476604.pdf	1622332 9c060f138db2bc54ea8b1acea19a4a7d79a10d37	no	17

Warnings:

Information:					
2	Non Patent Literature	2_51326_476605.pdf	220114 638887a338666f6a68ae6a406fec4507a284129b	no	3
Warnings:					
Information:					
3	Foreign Reference	1_WO2018165103A1_476606.pdf	2691557 ff7b42823bd208b66740d7d70f9d050611c34805	no	48
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	IDS_16732242_1.pdf	80855 21d301ab07ae0967e48b7b6db3e4a827be6419b4	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
		Total Files Size (in bytes):	4614858		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

RECEIVED
AUG 07 2020
PCT MARSHALL GERSTEIN

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: PAUL B. STEPHENS
MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference 32830/55304/PC	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No PCT/US 20/24748	International filing date *(day/month/year)* 25 March 2020 (25.03.2020)
Applicant TEMPUS LABS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34, chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: PAUL B. STEPHENS
MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 03 AUG 2020
Applicant's or agent's file reference 32830/55304/PC	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 20/24748	International filing date *(day/month/year)* 25 March 2020 (25.03.2020)
Applicant TEMPUS LABS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34, chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ this protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The international Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/220 (revised January 2020)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION
32630/55304/PC	see Form PCT/ISA/220 as well as, where applicable, item 5 below.

International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 20/24748	25 March 2020 (25.03.2020)	26 March 2019 (26.03.2019)

Applicant
TEMPUS LABS, INC.

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 3

☐ as suggested by the applicant.

☒ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/24748

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

--see extra sheet--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:
1-29 and 71-84

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/24748

A. CLASSIFICATION OF SUBJECT MATTER
IPC - G06F 19/00 (2020.01)
CPC - G06K 9/4628, G06T 2207/30061, G06K 9/6273, G06K 9/6286

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2019/0087532 A1 (Case Western Reserve University) 21 March 2019 (21.03.2019) entire document (especially para [0022], [0050], [0059], [0109]-[0113], [0124]-[0125]).	1-29, 71-84
Y	WO 2018/165103 A1 (UNIVERSITY OF SOUTHERN CALIFORNIA) 13 September 2018 (13.09.2018) entire document (especially para [0058]-[0060], [0063]-[0066], [0069]-[0072], [0076], [00113])	1-29, 71-84
A	US 2018/0239949 A1 (CELLANYX DIAGNOSTICS, LLC) 23 August 2018 (23.08.2018) entire document	1-29, 71-84
A	US 2018/0340870 A1 (Ventana Medical Systems, Inc.) 29 November 2018 (29.11.2018) entire document	1-29, 71-84

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 July 2020 (20.07.2020)	03 AUG 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/24748

Continuation of Box III: Lack of Unity

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-29 and 71-84 are drawn to training deep learning multiscale classifier models to classify tiled images of tissue and identify cells and based on the tissue classifications and cells identifying a predicted presence of a biomarker.

Group II: Claims 30-40 and 85-95 are drawn to clustering the received molecular training dataset to identify the different biomarkers and using the generated biomarker classifier model on the received subsequent digital image to identifying a predicted presence of biomarkers in the subsequent tissue sample.

Group III: Claims 41-70 and 96-116 are drawn to a deep learning framework to classify different biomarkers, predicting a biomarker classification for each tiled image and using the prediction to generate a report including the image and digital overlay visualizing the determined predict presence of biomarkers in the tissue.

The inventions listed as Groups I through III do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Special Technical Features:
The special technical feature of Group I is training deep learning multiscale classifier models to classify tiled images of tissue and identify cells and based on the tissue classifications and cells identifying a predicted presence of a biomarker, not present in any other group.

The special technical feature of Group II is clustering the received molecular training dataset to identify the different biomarkers and using the generated biomarker classifier model on the received subsequent digital image to identifying a predicted presence of biomarkers in the subsequent tissue sample, not present in any other group.

The special technical feature of Group III is a deep learningframework to classify different biomarkers, predicting a biomarker classification for each tiled image and using the prediction to generate a report including the image and digital overlay visualizing the determined predict presence of biomarkers in the tissue, not present in any other group.

Common Technical Features:

-Groups I through III, share the technical feature computer-implemented method/computing device of identifying biomarkers in a digital image of a hematoxylin and eosin (H&E) stained slide of target tissue, comprising: the trained imagebased biomarker/cell classifier model and identifying a predicted presence of one or more biomarkers for the tissue sample. However, this shared technical features does not represent a contribution over

US 2018/0239949 A1 (CELLANYX DIAGNOSTICS, LLC) (hereinafter Cellanyx) 23 August 2018 (23.08.2018) in view of

US 2018/0340870 A1 (Ventana Medical Systems, Inc.) (hereinafter Ventana) 29 November 2018 (29.11.2018)

Cellanyx teaches a computer-implemented method/computing device of identifying biomarkers in a digital image of a stained slide of target tissue (para [0013], [0023], [0153], [0157], [0172], [0227], [0232]), comprising:
the trained imagebased biomarker/cell classifier model and identifying a predicted presence of one or more biomarkers for the tissue sample (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs (i.e., cells identified during the cell tracking process), and the columns include the individual biomarkers measured for each of those cells, para [0172]; e.g. Results from imaging abnormal cells may then be fed through a classifying algorithm that correlates each biomarker characteristics of the cell with clinically relevant pathological indicators. The classifying algorithm being frequently previously trained with a training set of samples with known pathological indicators or biomarker, para [0189]-[0191]; e.g. supervised learning techniques that may be employed include (in addition to others discussed herein) at least the following techniques: averaged one-dependence estimators (AODE), artificial neural network (e.g., backpropagation, autoencoders, Hopfield networks, Boltzmann machines, Restricted Boltzmann Machines, Spiking neural networks), para [0185]-[0187]);
Cellanyx fails to teach hematoxylin and eosin (H&E). However, Ventana in an analogous art, teaches hematoxylin and eosin (H&E) (para [0028], [0047]). It would have been obvious to one of ordinary skill in the art to have modified the system of Cellanyx by including hematoxylin and eosin (H&E) as taught by Ventana because the modification would permits in a manner that permits microscopic detection of the biomarker or other structures in the context of the cross-sectional relationship between the structures of the tissue sample (Ventana, para [0028]).

Group I and III share the technical feature a computer-implemented method/computing device of identifying biomarkers in digital image of a hematoxylin and eosin (H&E) stained slide of target tissue, the method comprising: receiving the digital image to an image-based biomarker prediction system having one or more processors ; performing an image tiling process, using the one or more processors, on the digital image by separating the digital image into a plurality of tile images, where each of the plurality of tile images contains a different portion of the digital image); classify tissue/biomarker; the plurality of tile images to a deep learning framework comprising one or more trained deep learning classifier models; identifying a predicted presence of one or more biomarkers associated with the digital image (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs.. However, this shared technical features does not represent a contribution over Cellanyx in view of Ventana.

-see extra sheet-

-see preceding sheet-

Cellanyx teaches a computer-implemented method/computing device of identifying biomarkers in digital image of a stained slide of target tissue (para [0013], [0023], [0153], [0157], [0172], [0227], [0232]), the method comprising:
receiving the digital image to an image-based biomarker prediction system having one or more processors (e.g. The cells are then analyzed on the chip using, for example, automated light/fluorescent microscopy, and images are uploaded to, or accessed in a database by, a program that utilizes machine vision image analysis to calculate and return LAPP and MAPP values, para [0147]));
performing an image tiling process, using the one or more processors, on the digital image by separating the digital image into a plurality of tile images, where each of the plurality of tile images contains a different portion of the digital image (e.g. divided into coordinates to provide for imaging of multiple sectors (i.e., imaging spots) that can be montaged to create an image of the whole imaging chamber or selected area of the chamber, para [0166]-[0167]));
classify tissue/biomarker (e.g. For each sample, biomarker data from each single cell is fed into a trained random forest classifier. Each random forest classifier is trained based on study data to predict one of six different adverse pathologies related to prostate cancer. Therefore the likelihood of each of the adverse pathologies is predicted independently. The output from this random forest classifier is a predictor score for each cell in the sample, para [0232]);
the plurality of tile images to a deep learning framework comprising one or more trained deep learning classifier models (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs (i.e., cells identified during the cell tracking process), and the columns include the individual biomarkers measured for each of those cells, para [0172]; e.g. Results from imaging abnormal cells may then be fed through a classifying algorithm that correlates each biomarker characteristics of the cell with clinically relevant pathological indicators. The classifying algorithm being frequently previously trained with a training set of samples with known pathological indicators or biomarker, para [0189]-[0191]; e.g. supervised learning techniques that may be employed include (in addition to others discussed herein) at least the following techniques: averaged one-dependence estimators (AODE), artificial neural network (e.g., backpropagation, autoencoders, Hopfield networks, Boltzmann machines, Restricted Boltzmann Machines, Spiking neural networks), para [0185]-[0187]);
identifying a predicted presence of one or more biomarkers associated with the digital image (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs (i.e., cells identified during the cell tracking process), and the columns include the individual biomarkers measured for each of those cells, para [0172]).
Cellanyx fails to teach hematoxylin and eosin (H&E). However, Ventana in an analogous art, teaches hematoxylin and eosin (H&E) (para [0028], [0047]). It would have been obvious to one of ordinary skill in the art to have modified the system of Cellanyx by including hematoxylin and eosin (H&E) as taught by Ventana because the modification would permits in a manner that permits microscopic detection of the biomarker or other structures in the context of the cross-sectional relationship between the structures of the tissue sample (Ventana, para [0028]).

Thus, unity of invention is lacking under PCT Rule 13.1 because Groups I through III do not share a same or corresponding special technical feature that would provide a unifying contribution over the prior art. None of these special technical features are common to the other groups.

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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: PAUL B. STEPHENS
MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	03 AUG 2020
Applicant's or agent's file reference 32830/55304/PC	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 20/24748	25 March 2020 (25.03.2020)	26 March 2019 (26.03.2019)

International Patent Classification (IPC) or both national classification and IPC
IPC - G06F 19/00 (2020.01)
CPC - G06K 9/4628, G06T 2207/30061, G06K 9/6273, G06K 9/6286

Applicant TEMPUS LABS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [x] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	20 July 2020 (20.07.2020)	Lee Young PCT Help Desk Telephone No. 571-272-4300

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/24748

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(b)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

a. ☐ forming part of the international application as filed:

☐ in the form of an Annex C/ST.25 text file.

☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/24748

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-29 and 71-84 are drawn to training deep learning multiscale classifier models to classify tiled images of tissue and identify cells and based on the tissue classifications and cells identifying a predicted presence of a biomarker.

Group II: Claims 30-40 and 85-95 are drawn to clustering the received molecular training dataset to identify the different biomarkers and using the generated biomarker classifier model on the received subsequent digital image to identifying a predicted presence of biomarkers in the subsequent tissue sample.

Group III: Claims 41-70 and 96-118 are drawn to a deep learning framework to classify different biomarkers, predicting a biomarker classification for each tiled image and using the prediction to generate a report including the image and digital overlay visualizing the determined predict presence of biomarkers in the tissue.

The inventions listed as Groups I through III do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Special Technical Features:
The special technical feature of Group I is training deep learning multiscale classifier models to classify tiled images of tissue and identify cells and based on the tissue classifications and cells identifying a predicted presence of a biomarker, not present in any other group.

The special technical feature of Group II is clustering the received molecular training dataset to identify the different biomarkers and using the generated biomarker classifier model on the received subsequent digital image to identifying a predicted presence of biomarkers in the subsequent tissue sample, not present in any other group.

The special technical feature of Group III is a deep learningframework to classify different biomarkers, predicting a biomarker classification for each tiled image and using the prediction to generate a report including the image and digital overlay visualizing the determined predict presence of biomarkers in the tissue, not present in any other group.

Common Technical Features:

-Groups I through III, share the technical feature computer-implemented method/computing device of identifying biomarkers in a digital image of a hematoxylin and eosin (H&E) stained slide of target tissue, comprising: the trained imagebased biomarker/cell classifier model and identifying a predicted presence of one or more biomarkers for the tissue sample. However, this shared technical features does not represent a contribution over

US 2018/0239949 A1 (CELLANYX DIAGNOSTICS, LLC) (hereinafter Cellanyx) 23 August 2018 (23.08.2018) in view of

US 2018/0340870 A1 (Ventana Medical Systems, Inc.) (hereinafter Ventana) 29 November 2018 (29.11.2018)

-See supplemental box-

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-29 and 71-84

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/24748

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-29 and 71-84	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-29 and 71-84	NO
Industrial applicability (IA)	Claims	1-29 and 71-84	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-29 and 71-84 lack an inventive step under PCT Article 33(3) as being obvious over US 2019/0087532 A1 to Case Western Reserve University (hereinafter Case) in view of WO 2018/165103 A1 to UNIVERSITY OF SOUTHERN CALIFORNIA (hereinafter California).

As per claims 1 and 71, Case teaches a computer-implemented method of identifying biomarkers in digital image of a hematoxylin and eosin (H&E) stained slide of target tissue (para [0022], [0050], [0059]), the method comprising (A computing device configured to identifying biomarkers in digital image of a Hematoxylin and eosin (H&E) stained slide of target tissue, the computing device (para [0101]-[0107]) comprising: one or more memories (para [0022], [0050], [0059], [0101]-[0107]); and one or more processors configured to (para [0022], [0050], [0059], [0101]-[0107])):
receiving the digital image to an image-based biomarker prediction system having one or more processors (e.g. A processor(s) may include any combination of general-purpose processors and dedicated processors (e.g., graphics processors, application processors, etc.). The processors may be coupled with or may include memory or storage...the pathology image is a digitized H&E stained image scanned at 20 times. magnification. In another embodiment, the image may be acquired using other, different imaging parameters, including different sizes, staining techniques, or scanning magnification levels, para [0058]- [0059]; para para [0022], [0050]);
performing an image tiling process, using the one or more processors, on the digital image by separating the digital image into a plurality of tile images, where each of the plurality of tile images contains a different portion of the digital image (e.g. divide the annotated pathomic image into a plurality of patches. In one embodiment, pathomic features are extracted from ten randomly selected patches from the tumoral region, a patch having dimensions of 1000 pixels by 1000 pixels. In another embodiment, other numbers of patches may be randomly selected. In another embodiment, a patch may have different dimensions (e.g., 750 pixels by 750 pixels, 2000 pixels by 2000 pixels), para [0032]; para [0039]);
applying, using the one or more processors, the plurality of tile images to a deep learning framework comprising one or more trained deep learning classifier models, each trained deep learning classifier models being trained to classify a different tissue classification for each tile image and determining a tissue classification for each of the plurality of tile
images, using the deep learning framework (e.g. the machine learning classifier is trained on a set of training images. In another embodiment, combined radiomic-pathomic classification circuit 1155 may be configured as another type of machine learning or deep learning classifier, including as a QDA classifier, an RF classifier, or a CNN classifier, para [0097]; e.g. generating a classification of the region of tissue as recurrent or non-recurrent based, at least in part, on the probability. In another embodiment, other classification schemes may be employed. For example, the region of tissue may be classified as recurrent, unknown, or non-recurrent, based on the probability, para [0121]));
identifying, using the one or more processors, cells within the digital image using a trained cell segmentation model (e.g. identifying a plurality of cellular nuclei represented in the tumor region. Identifying the plurality of cellular nuclei may include using automated segmentation techniques, including watershed segmentation, or other techniques, including deep learning segmentation techniques, para [0109]).
Case fails to teach multiscale deep learning framework; from the tissue classification determined for each tile image and from the identified cells within the digital image, identifying a predicted presence of one or more biomarkers associated with the digital image.
However, California, in an analogous art, teaches multiscale deep learning framework (para [00110]-[00111]); from the tissue classification determined for each tile image and from the identified cells within the digital image, identifying a predicted presence of one or more biomarkers associated with the digital image (para [0052]-[0056]). It would have been obvious to one of ordinary skill in the art to have modified the system of Case by including multiscale deep learning framework ; from the tissue classification determined for each tile image and from the identified cells within the digital image, identifying a predicted presence of one or more biomarkers associated with the digital image as taught by California because the modification would predict the status of a diagnostic feature in stained tissue samples (California, abstract).

As per claims 2 and 72, Case teaches wherein performing the image tiling process on the digital image comprises applying a tiling mask to the digital image, to separate the digital image into the plurality of tile images (para [0032], [0039]).

As per claim 3, Case teaches wherein the tiling mask comprises tiles of the same size (para [0032], [0039]).

As per claim 4, Case teaches wherein the tiling mask comprises tiles of differing size (para [0032], [0039]).

As per claim 5, Case teaches wherein the tiling mask comprises tiles having a rectangular shape (para [0032], [0039]).

-Continuation in supplemental box-

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V, 2: Citations and Explanations

As per claim 6, Case teaches wherein the tiling mask comprises tiles characterized by topology and/or morphology of pixels or groups of pixels (para [0032], [0039]).

As per claim 7, California teaches wherein receiving the digital image comprises, using the one or more processors: retrieving the digital image at a first image resolution (para [0086]); downsampling the digital image to a second image resolution (para [00104], [0086]-[0098]); performing a brightness normalization on pixels in the digital image (para [0086]-[0090]); and removing non-tissue objects from the digital image (para [0086]-[0090]).

As per claims 8 and 73, California teaches further comprising training the one or more trained deep learning multiscale classifier models by:
receiving, at the multiscale deep learning framework, a plurality of H&E slide training images from a training images dataset, each H&E slide training image having a label corresponding to a biomarker to be trained (para [0020]-[0022], [0044]-[0045]); performing tile-based tissue classification analysis on each of the H&E slide training images (para [0020], [0045],[0052]-[0056]); performing a pixel-based cell segmentation analysis on each of the H&E slide training images (para [0020], [0045], [0052]-[0056]); optionally performing a tile-based biomarker classification analysis on each of the H&E slide training images (para [0020], [0045], [0052]-[0056]); and
in response, generating the one or more trained deep learning multiscale classifier models (para [0020]-[0022], [0045]).

As per claims 9 and 74, California teaches wherein each H&E slide training image comprises a plurality of tile images each having a tile-level label (para [0020]-[0022], [0076], [00113]).

As per claim 10, California teaches further comprising, for each H&E slide training image, imputing a tile-level label for each of a plurality of tile images of the H&E slide training image (para [0020]-[0022], [0076], [00113]).

As per claim 11 and 75, California teaches further comprising: for each H&E slide training image, performing a tile selection process that infers a class status for each tile image in the H&E slide training image (para [0020]-[0022], [0076], [00113]); based on inferred class status, discarding tile images not corresponding to a desired class, before performing the tile-based tissue classification analysis on each of the H&E slide training images, such that the tile-based tissue classification analysis is performed on only selected tile images of the H&E slide training image (para [0020]-[0022], [0045], [0076], [00113]).

As per claims 12 and 76, California teaches further comprising training the one or more trained deep learning multiscale classifier models by: receiving a molecular training dataset for a plurality of training tissue samples, the molecular training dataset comprising RNA transcriptome counts from sequencing of a substantially similar sample associated with each training tissue sample (para [0076]-[0081]); performing a clustering process on the molecular training dataset to identify one or more molecular data subsets each corresponding to a different biomarker (para [0052]-[0056], [0076]-[0081]); for each of the one or more molecular data subsets identifying a plurality of digital images of H&E stained training slides of training tissue samples corresponding to the respective biomarker to an image-based biomarker prediction system having one or more processors (para [0052]-[0056], [0076]-[0081]); performing tile-based tissue classification analysis on each of the H&E slide training images (para [0020], [0045],[0052]-[0056]); performing a pixel-based cell segmentation analysis on each of the H&E slide training images (para [0020], [0045], [0052]-[0056]); optionally performing a tile-based biomarker classification analysis on each of the H&E slide training images (para [0020], [0045], [0052]-[0056]); and in response, generating the one or more trained deep learning multiscale classifier models (para [0020], [0045], [0052]-[0056]).

As per claim 13, California teaches wherein the one of the one or more trained deep learning multiscale classifier models are each configured as a tile-resolution Fully Convolutional Network (FCN) classification model (para [0050], [00108]-[00110]).

As per claim 14, California teaches wherein the trained deep learning multiscale classifier models are each trained to classify tissue as corresponding to a classification selected from the group consisting of tumor, stroma, normal, lymphocyte, fat, muscle, blood vessel, immune cluster, necrosis, hyperplasia/dysplasia, and red blood cells (para [0059], [0079]-[0081]).

As per claim 15, Case teaches wherein identifying cells within the digital image tile using the trained cell segmentation model comprises: applying, using the one or more processors, each of the plurality of tile images to the cell segmentation model and, for each tile, assigning a cell classification to one or more pixels within the tile image (para [0124]-[0125]).

As per claim 16, Case teaches wherein assigning the cell classification to one or more pixels within the tile image comprises: identifying, using the one or more processors, the one or more pixels as a cell interior, a cell border, or a cell exterior and classifying the one or more pixels as the cell interior, the cell border, or the cell exterior (para [0109]-[0113]).

As per claim 17, Case teaches wherein the trained cell segmentation model is a pixelresolution three-dimensional UNet classification model trained to classify a cell interior, a cell border, and a cell exterior (para [0109]-[0113]).

As per claim 18, Case teaches wherein identifying cells within the digital image tile using the trained cell segmentation model comprises: applying, using the one or more processors, each of the plurality of tile images to the cell segmentation model (para [0109]-[0113], [0124]-[0125]); and performing, using the one or more processors, a registration on segmented cells in each of the tile images by determining a cell border of each cell, determining a centroid of each cell, and shifting coordinates of centroids to a universal coordinate space for the digital image (para [0109]-[0113], [0124]-[0125]).

-Continuation in next supplemental box-

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
-Continuation in preceding supplemental box-

As per claim 19, Case teaches wherein the trained cell segmentation model is trained using a set of H&E slide training images annotated identifying cell borders, cell interiors, and cell exteriors (para [0032], [0039]; para [0109]-[0113], [0124]-[0126]).

As per claim 20, California teaches wherein the digital image is an unlabeled digital image or a slide-level labeled image (para [0020]-[0022], [0076], [00113]).

As per claim 21, California teaches wherein the digital image is a tile-level labeled image (para [0020]-[0022], [0076], [00113]).

As per claim 22 and 77, California teaches wherein the one or more biomarkers are selected from the group consisting of tumor-infiltrating lymphocytes (TI Ls), nucleus-to-cytyoplasm (NC) ratio, ploidy, signet ring morphology, and programmed death-ligand 1 (PD-Ll) (para [0058]-[0060], [0063]-[0066]).

As per claim 23 and 78, California teaches wherein the one or more biomarkers is TI Ls, the method further comprising:
identifying, using the one or more processors, lymphocyte cells within the digital image using a trained lymphocyte segmentation model, by integrating, using the one or more processors, the cell borders identified using the cell segmentation model with the lymphocytes identified using the lymphocyte segmentation model and generating, using the one or more processors, a nested classification of each cell (para [0058]-[0060], [0063]-[0066], [0069]-[0072]).

As per claims 24 and 79, California teaches wherein the one or more biomarkers is TI Ls, the method further comprising: identifying, using the one or more processors, lymphocyte cells within the digital image using a trained lymphocyte segmentation model, by applying each of a plurality of tile images to a trained lymphocyte segmentation model and, for each tile image, assigning a lymphocyte classification to one or more pixels within the tile image (para [0058]-[0060], [0063]-[0066], [0069]-[0072]).

As per claims 25 and 80, California teaches wherein the one or more biomarkers is TI Ls, the method further comprising identifying, using the one or more processors, lymphocyte cells within the digital image using a trained lymphocyte segmentation model, wherein the lymphocyte segmentation model is a pixel-resolution two-dimensional UNet classification model trained to identify a lymphocyte cell classification within a cell border and a non-lymphocyte cell classification within a cell border (para [0058]-[0060], [0063]-[0066], [0069]-[0072]).

As per claims 26 and 81, Case teaches wherein the one or more processors are one or more graphics processing units (GPUs), tensor processing units (TPUs), and/or central processing units (CPUs) (para [0058]).

As per claims 27 and 82, Case teaches wherein the image-based biomarker prediction system is communicatively coupled to a pathology slide scanner system through a communication network, such that the image-based biomarker prediction system receives the digital image from the pathology slide scanner system over the communication network (para [0101]-[0106]; para [0022]).

As per claim 28, Case teaches wherein the image-based biomarker prediction system is contained within a pathology slide scanner system (para [0101]-[0106]; para [0022]).

As per claim 29, Case teaches wherein at least one of the one or more processors of the image-based biomarker prediction system is contained within a pathology slide scanner system (para [0101]-[0106]; para [0022]).

As per claim 83, Case teaches wherein the computing device is contained within a pathology slide scanner system (para [0101]-[0106]; para [0022]).

As per claim 84, Case teaches wherein at least one of the one or more processors of the computing device is contained within a pathology slide scanner system (para [0101]-[0106]; para [0022]).

Claims 1-29 and 71-84 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/24748

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box IV: Lack of Unity

Cellanyx teaches a computer-implemented method/computing device of identifying biomarkers in a digital image of a stained slide of target tissue (para [0013], [0023], [0153], [0157], [0172], [0227], [0232]), comprising:
the trained imagebased biomarker/cell classifier model and identifying a predicted presence of one or more biomarkers for the tissue sample (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs (i.e., cells identified during the cell tracking process), and the columns include the individual biomarkers measured for each of those cells, para [0172]; e.g. Results from imaging abnormal cells may then be fed through a classifying algorithm that correlates each biomarker characteristics of the cell with clinically relevant pathological indicators. The classifying algorithm being frequently previously trained with a training set of samples with known pathological indicators or biomarker, para [0189]-[0191]; e.g. supervised learning techniques that may be employed include (in addition to others discussed herein) at least the following techniques: averaged one-dependence estimators (AODE), artificial neural network (e.g., backpropagation, autoencoders, Hopfield networks, Boltzmann machines, Restricted Boltzmann Machines, Spiking neural networks), para [0185]-[0187]);
Cellanyx fails to teach hematoxylin and eosin (H&E). However, Ventana in an analogous art, teaches hematoxylin and eosin (H&E) (para [0028], [0047]). It would have been obvious to one of ordinary skill in the art to have modified the system of Cellanyx by including hematoxylin and eosin (H&E) as taught by Ventana because the modification would permits in a manner that permits microscopic detection of the biomarker or other structures in the context of the cross-sectional relationship between the structures of the tissue sample (Ventana, para [0028]).

Group I and III shares the technical feature a computer-implemented method/computing device of identifying biomarkers in digital image of a hematoxylin and eosin (H&E) stained slide of target tissue, the method comprising: receiving the digital image to an image-based biomarker prediction system having one or more processors ; performing an image tiling process, using the one or more processors, on the digital image by separating the digital image into a plurality of tile images, where each of the plurality of tile images contains a different portion of the digital image); classify tissue/biomarker; the plurality of tile images to a deep learning framework comprising one or more trained deep learning classifier models; identifying a predicted presence of one or more biomarkers associated with the digital image (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs.. However, this shared technical features does not represent a contribution over Cellanyx in view of Ventana.

Cellanyx teaches a computer-implemented method/computing device of identifying biomarkers in digital image of a stained slide of target tissue (para [0013], [0023], [0153], [0157], [0172], [0227], [0232]), the method comprising:
receiving the digital image to an image-based biomarker prediction system having one or more processors. (e.g. The cells are then analyzed on the chip using, for example, automated light/fluorescent microscopy, and images are uploaded to, or accessed in a database by, a program that utilizes machine vision image analysis to calculate and return LAPP and MAPP values, para [0147]));
performing an image tiling process, using the one or more processors, on the digital image by separating the digital image into a plurality of tile images, where each of the plurality of tile images contains a different portion of the digital image (e.g. divided into coordinates to provide for imaging of multiple sectors (i.e., imaging spots) that can be montaged to create an image of the whole imaging chamber or selected area of the chamber, para [0166]-[0167]));
classify tissue/biomarker (e.g. For each sample, biomarker data from each single cell is fed into a trained random forest classifier. Each random forest classifier is trained based on study data to predict one of six different adverse pathologies related to prostate cancer. Therefore the likelihood of each of the adverse pathologies is predicted independently. The output from this random forest classifier is a predictor score for each cell in the sample, para [0232]);
the plurality of tile images to a deep learning framework comprising one or more trained deep learning classifier models (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs (i.e., cells identified during the cell tracking process), and the columns include the individual biomarkers measured for each of those cells, para [0172]; e.g. Results from imaging abnormal cells may then be fed through a classifying algorithm that correlates each biomarker characteristics of the cell with clinically relevant pathological indicators. The classifying algorithm being frequently previously trained with a training set of samples with known pathological indicators or biomarker, para [0189]-[0191]; e.g. supervised learning techniques that may be employed include (in addition to others discussed herein) at least the following techniques: averaged one-dependence estimators (AODE), artificial neural network (e.g., backpropagation, autoencoders, Hopfield networks, Boltzmann machines, Restricted Boltzmann Machines, Spiking neural networks), para [0185]-[0187]);
identifying a predicted presence of one or more biomarkers associated with the digital image (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs (i.e., cells identified during the cell tracking process), and the columns include the individual biomarkers measured for each of those cells, para [0172]).
Cellanyx fails to teach hematoxylin and eosin (H&E). However, Ventana in an analogous art, teaches hematoxylin and eosin (H&E) (para [0028], [0047]). It would have been obvious to one of ordinary skill in the art to have modified the system of Cellanyx by including hematoxylin and eosin (H&E) as taught by Ventana because the modification would permits in a manner that permits microscopic detection of the biomarker or other structures in the context of the cross-sectional relationship between the structures of the tissue sample (Ventana, para [0028]).

Thus, unity of invention is lacking under PCT Rule 13.1 because Groups I through III do not share a same or corresponding special technical feature that would provide a unifying contribution over the prior art. None of these special technical features are common to the other groups.

SEARCH HISTORY

Application Number	PCT/US 20/24748
Search Conducted By	RLP
Search Approved By	RLP

CPC/IPC Classifications Searched	IPC(8): G06F 19/00 (2020.01) CPC: G06K 9/4628, G06T 2207/30061, G06K 9/6273, G06K 9/6286
Date Conducted	19 July 2020 (19.07.2020)

Documentation Searched	IPC(8): G06F 19/00 (2020.01) CPC: G06K 9/4628, G06T 2207/30061, G06K 9/6273, G06K 9/6286
Search Terms Used	predict biomarker images tile OR segment OR slice OR block classification multiscale cell tissue
Date Conducted	19 July 2020 (19.07.2020)

Electronic Database Searched	Patbase
Files Searched	Full-text: AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO Bibliographic: (Europe) AT BA BE BG CH CS CY CZ DD DK EE ES FI GE GR HR HU IE IS IT LT LU LV MC MD MT NL NO PL PT RO RS SE SI SK SM TR UA YU (Asia) EA GC HK ID IL IN KZ MN MY PH RU SG SU TH TJ TW UZ VN (North America) CA CR CU DO GT HN MX NI PA SV TT (South America) AR BR CL CO EC PE UY (Australasia) AU NZ (Africa) AP DZ EG KE MA MW OA ZA ZM ZW
Date Conducted	19 July 2020 (19.07.2020)

Search Logic:

Search 1: IC=(G06F19/00) or CPC=(G06K9/4628 or G06T2207/30061 or G06K9/6273 or G06K9/6286) (Results 157265)
Search 2: 1 and FT=((imag* or photo* or picture* or xray* or x-ray) w9 (tile* or tiling or divid* or separat* or

segment* or split*)) (Results 10071)
Search 3: 2 and FT=((classif* or "deep learn*" or "Fully Convolutional Network" or FCN) w9 (tile* or tiling or divid* or separat* or segment* or split*)) (Results 1174)
Search 4: 3 and FT=((predict* or forecast* or foresee*) w9 (biomarker* or bio-marker* or "bio marker*")) (Results 39)
Search 5: 3 and FT=((classif* or "deep learn*" or "Fully Convolutional Network" or FCN) w9 (tissue* or cell or cells)) (Results 272)
Search 6: 3 and FT=((hematoxylin and eosin) w12 stain*) (Results 65)
Search 7: 3 and FT=(multiscale* or multi-scale* or "multi scale*") (Results 133)
Search 8: 3 and FT=(classif* w9 (tissue* or cell or cells)) (Results 265)
Search 9: 8 not 5 (Results 0)
Search 10: 8 and FT=((hematoxylin and eosin)) (Results 58)

Search 1: FT=((imag* or photo* or picture* or xray* or x-ray) w9 (tile* or tiling or divid* or separat* or segment*)) (Results 584162)
Search 2: FT=((imag* or photo* or picture* or xray* or x-ray) w9 (tile* or tiling or divid* or separat* or segment* or split*)) (Results 625511)
Search 3: 2 and FT=((classif* or "deep learn*" or "Fully Convolutional Network" or FCN) w9 (tile* or tiling or divid* or separat* or segment* or split*)) (Results 14754)
Search 4: 3 and FT=((predict* or forecast* or foresee*) w9 (biomarker* or bio-marker* or "bio marker*")) (Results 114)
Search 5: 4 and PN=(US2019087532) (Results 1)
Search 6: 4 and FT=(TIL) (Results 7)
Search 7: FT=((predict* or forecast* or foresee*) w9 (biomarker* or bio-marker* or "bio marker*")) (Results 8492)
Search 8: 7 and FT=((classif* or "deep learn*" or "Fully Convolutional Network" or FCN) w9 (tissue* or cell or cells)) (Results 1331)
Search 9: 8 and FT=((imag* or photo* or picture* or xray* or x-ray) w9 (tissue* or cell or cells)) (Results 555)
Search 10: 9 and FT=((hematoxylin and eosin) w12 stain*) (Results 140)
Search 11: 10 and FT=((imag* or photo* or picture* or xray* or x-ray) w9 (tile* or tiling or divid* or separat* or segment* or split* or slice* or slic*)) (Results 61)
Search 12: PN=(US2017084021 or US2017352157 or WO18017355 or WO18075873 or US2019087532) (Results 5)
Search 13: 9 and FT=(multiscale* or multi-scale* or "multi scale*") (Results 17)
Search 14: 9 and FT=(" "Fully Convolutional Network" or FCN") (Results 11)
Search 1: FT=(full* convolutional network) (Results 609)
Search 2: 1 and FT=(predict* w12 biomarker*) (Results 13)

Search 1: FT=(classif* w9 (biomarker* or bio-marker*)) (Results 2230)
Search 2: 1 and FT=((til* or segment* or separat* or divid*) w9 (imag* or slide* or photo* or picture* or scan*)) (Results 270)
Search 3: 2 and FT=(predict* w9 (biomarker* or bio-marker*)) (Results 126)
Search 4: 3 and FT=(hematoxylin and eosin) (Results 22)
Search 5: 4 and FT=((deep learn*) or deep-learn*) (Results 5)
Search 6: 3 and FT=((deep learn*) or deep-learn*) (Results 15)
Search 7: 1 and FT=(identif* w9 (biomarker* or bio-marker*)) (Results 1671)
Search 8: 7 and FT=(predict* w9 (biomarker* or bio-marker*)) (Results 1101)
Search 9: 8 and FT=((predict* w9 (biomarker* or bio-marker*)) w9 image*) (Results 3)
Search 10: FT=((predict* w9 (biomarker* or bio-marker*)) w9 image*) (Results 19)

]

Search 1: FT=(image* w9 tile*) (Results 15645)
Search 2: 1 and FT=(predict* w9 biomarker*) (Results 31)
Search 3: 2 and FT=(tile* w9 ((deep learn*) or deep-lear*)) (Results 0)
Search 4: 3 and FT=((deep learn*) or deep-lear*) (Results 0)
Search 5: 2 and FT=((deep learn*) or deep-lear*) (Results 5)
Search 1: FT=(predict* w9 biomarker*) (Results 8326)
Search 2: 1 and FT=(imag* w9 biomarker*) (Results 876)
Search 3: 2 and FT=((imag* or tile*) w9 ((deep learn*) or (machine learn*))) (Results 44)
Search 4: 3 and FT=(((analy* or detect* or identif*) w9 predict*) w9 biomarker*) (Results 13)
Search 5: 4 and PN=(US2018239949) (Results 1)
Search 6: PN=(US2018189947 or WO18075873 or WO17173428 or WO19084697 or US2018348226 or US2018239949 or WO18069768 or US2018340870) (Results 8)

Electronic Database Searched	Google
Files Searched	Google Scholar
Date Conducted	19 July 2020 (19.07.2020)

Search Logic:

About 143,000 results (0.07 sec) predict biomarker images

About 113,000 results (0.11 sec) predict biomarker images tile OR segment OR slice OR block

About 47,300 results (0.09 sec) predict biomarker images tile OR segment OR slice OR block classification

About 4,080 results (0.06 sec) predict biomarker images tile OR segment OR slice OR block classification multiscale

About 2,660 results (0.10 sec) predict biomarker images tile OR segment OR slice OR block classification multiscale cell tissue

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: PAUL B. STEPHENS
MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

PCT

INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE

(PCT Article 17(3)(a) and Rules 40.1 and 40.2(e))

Applicant's or agent's file reference 32830/55304/PC	Date of mailing *(day/month/year)* 10 JUN 2020 **PAYMENT DUE** within **ONE MONTH** from the above date of mailing
International application No. PCT/US 20/24748	International filing date *(day/month/year)* 25 March 2020 (25.03.2020)
Applicant TEMPUS LABS, INC.	

1. This International Searching Authority

(i) considers that there are 3 (three) *(number of)* inventions claimed in the international application covered by the claims indicated below/on an extra sheet:
-see extra sheet-

(ii) therefore considers that **the international application does not comply with the requirement of unity of invention** (Rules 13.1, 13.2 and 13.3) for the reasons indicated below/on an extra sheet:
-see extra sheet-

(iii) ☐ has carried out a partial international search (see Annex) ☒ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
Claims 1-29 and 71-84

(iv) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid.

2. Consequently, the applicant is hereby **invited to pay**, within the time limit indicated above, additional fees in the amount indicated below:

$2080 (Fee per additional invention) x 2 (number of additional inventions) = $4160 (See Item 2 of next sheet) (total amount of additional fees/currency)

3. The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fees may be made under protest**, that is, a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fees is excessive, where applicable, subject to the payment of a protest fee.

Where the applicant pays additional fees under protest, the applicant is hereby invited, within the time limit indicated above, to pay a protest fee (Rule 40.2(e)) in the amount of _____ *(amount/currency)*

Where the applicant has not, within the time limit indicated above, paid the required protest fee, the protest will be considered not to have been made and the International Searching Authority will so declare.

4. ☐ Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young PCT Helpdesk: 571-272-4300

INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE

International application No.
PCT/US 20/24748

Item 2 (continued). For International Applications filed on or after 01 January 2014, Applicant is reminded that the search fee per additional invention indicated in item 2 is the undiscounted fee per additional invention. An Applicant may pay the search fee per additional invention fee reduced by 50% (small entity assertion) or 75% (micro entity certification), as appropriate. See 37 CFR 1.27 and 1.29.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-29 and 71-84 are drawn to training deep learning multiscale classifier models to classify tiled images of tissue and identify cells and based on the tissue classifications and cells identifying a predicted presence of a biomarker.

Group II: Claims 30-40 and 85-95 are drawn to clustering the received molecular training dataset to identify the different biomarkers and using the generated biomarker classifier model on the received subsequent digital image to identifying a predicted presence of biomarkers in the subsequent tissue sample.

Group III: Claims 41-70 and 96-118 are drawn to a deep learning framework to classify different biomarkers, predicting a biomarker classification for each tiled image and using the prediction to generate a report including the image and digital overlay visualizing the determined predict presence of biomarkers in the tissue.

The inventions listed as Groups I through III do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Special Technical Features:
The special technical feature of Group I is training deep learning multiscale classifier models to classify tiled images of tissue and identify cells and based on the tissue classifications and cells identifying a predicted presence of a biomarker, not present in any other group.

The special technical feature of Group II is clustering the received molecular training dataset to identify the different biomarkers and using the generated biomarker classifier model on the received subsequent digital image to identifying a predicted presence of biomarkers in the subsequent tissue sample, not present in any other group.

The special technical feature of Group III is a deep learningframework to classify different biomarkers, predicting a biomarker classification for each tiled image and using the prediction to generate a report including the image and digital overlay visualizing the determined predict presence of biomarkers in the tissue, not present in any other group.

Common Technical Features:

-Groups I through III, share the technical feature computer-implemented method/computing device of identifying biomarkers in a digital image of a hematoxylin and eosin (H&E) stained slide of target tissue, comprising: the trained imagebased biomarker/cell classifier model and identifying a predicted presence of one or more biomarkers for the tissue sample. However, this shared technical features does not represent a contribution over

US 2018/0239949 A1 (CELLANYX DIAGNOSTICS, LLC) (hereinafter Cellanyx) 23 August 2018 (23.08.2018) in view of

US 2018/0340870 A1 (Ventana Medical Systems, Inc.) (hereinafter Ventana) 29 November 2018 (29.11.2018)

Cellanyx teaches a computer-implemented method/computing device of identifying biomarkers in a digital image of a stained slide of target tissue (para [0013], [0023], [0153], [0157], [0172], [0227], [0232]), comprising:
the trained imagebased biomarker/cell classifier model and identifying a predicted presence of one or more biomarkers for the tissue sample (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs (i.e., cells identified during the cell tracking process), and the columns include the individual biomarkers measured for each of those cells, para [0172]; e.g. Results from imaging abnormal cells may then be fed through a classifying algorithm that correlates each biomarker characteristics of the cell with clinically relevant pathological indicators. The classifying algorithm being frequently previously trained with a training set of samples with known pathological indicators or biomarker, para [0189]-[0191]; e.g. supervised learning techniques that may be employed include (in addition to others discussed herein) at least the following techniques: averaged one-dependence estimators (AODE), artificial neural network (e.g., backpropagation, autoencoders, Hopfield networks, Boltzmann machines, Restricted Boltzmann Machines, Spiking neural networks), para [0185]-[0187]);
Cellanyx fails to teach hematoxylin and eosin (H&E). However, Ventana in an analogous art, teaches hematoxylin and eosin (H&E) (para [0028], [0047]). It would have been obvious to one of ordinary skill in the art to have modified the system of Cellanyx by including hematoxylin and eosin (H&E) as taught by Ventana because the modification would permits in a manner that permits microscopic detection of the biomarker or other structures in the context of the cross-sectional relationship between the structures of the tissue sample (Ventana, para [0028]).

-see extra sheet-

INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE

International application No.
PCT/US 20/24748

-see preceding sheet-

Group I and III share the technical feature a computer-implemented method/computing device of identifying biomarkers in digital image of a hematoxylin and eosin (H&E) stained slide of target tissue, the method comprising: receiving the digital image to an image-based biomarker prediction system having one or more processors ; performing an image tiling process, using the one or more processors, on the digital image by separating the digital image into a plurality of tile images, where each of the plurality of tile images contains a different portion of the digital image); classify tissue/biomarker; the plurality of tile images to a deep learning framework comprising one or more trained deep learning classifier models; identifying a predicted presence of one or more biomarkers associated with the digital image (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs.. However, this shared technical features does not represent a contribution over Cellanyx in view of Ventana.

Cellanyx teaches a computer-implemented method/computing device of identifying biomarkers in digital image of a stained slide of target tissue (para [0013], [0023], [0153], [0157], [0172], [0227], [0232]), the method comprising:
receiving the digital image to an image-based biomarker prediction system having one or more processors (e.g. The cells are then analyzed on the chip using, for example, automated light/fluorescent microscopy, and images are uploaded to, or accessed in a database by, a program that utilizes machine vision image analysis to calculate and return LAPP and MAPP values, para [0147]));
performing an image tiling process, using the one or more processors, on the digital image by separating the digital image into a plurality of tile images, where each of the plurality of tile images contains a different portion of the digital image (e.g. divided into coordinates to provide for imaging of multiple sectors (i.e., imaging spots) that can be montaged to create an image of the whole imaging chamber or selected area of the chamber, para [0166]-[0167]));
classify tissue/biomarker (e.g. For each sample, biomarker data from each single cell is fed into a trained random forest classifier. Each random forest classifier is trained based on study data to predict one of six different adverse pathologies related to prostate cancer. Therefore the likelihood of each of the adverse pathologies is predicted independently. The output from this random forest classifier is a predictor score for each cell in the sample, para [0232]);
the plurality of tile images to a deep learning framework comprising one or more trained deep learning classifier models (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs (i.e., cells identified during the cell tracking process), and the columns include the individual biomarkers measured for each of those cells, para [0172]; e.g. Results from imaging abnormal cells may then be fed through a classifying algorithm that correlates each biomarker characteristics of the cell with clinically relevant pathological indicators. The classifying algorithm being frequently previously trained with a training set of samples with known pathological indicators or biomarker, para [0189]-[0191]; e.g. supervised learning techniques that may be employed include (in addition to others discussed herein) at least the following techniques: averaged one-dependence estimators (AODE), artificial neural network (e.g., backpropagation, autoencoders, Hopfield networks, Boltzmann machines, Restricted Boltzmann Machines, Spiking neural networks), para [0185]-[0187]);
identifying a predicted presence of one or more biomarkers associated with the digital image (e.g. the output of imaging provides data grouped into the m-by-n array, where the rows include cell IDs (i.e., cells identified during the cell tracking process), and the columns include the individual biomarkers measured for each of those cells, para [0172]).
Cellanyx fails to teach hematoxylin and eosin (H&E). However, Ventana in an analogous art, teaches hematoxylin and eosin (H&E) (para [0028], [0047]). It would have been obvious to one of ordinary skill in the art to have modified the system of Cellanyx by including hematoxylin and eosin (H&E) as taught by Ventana because the modification would permits in a manner that permits microscopic detection of the biomarker or other structures in the context of the cross-sectional relationship between the structures of the tissue sample (Ventana, para [0028]).

Thus, unity of invention is lacking under PCT Rule 13.1 because Groups I through III do not share a same or corresponding special technical feature that would provide a unifying contribution over the prior art. None of these special technical features are common to the other groups.

Publication Number: WO 2018/165103 A1
Publication Date: Sep 13, 2018

Abstract

A method assessing tissue morphology using machine learning includes a step of training a machine learnable device to predict the status of a diagnostic feature in stained tissue samples. The machine learnable device is trained with a characterized set of digital images of stained tissue samples. Each digital image of the characterized set has a known status for the diagnostic feature and an extracted feature map provides values for a extracted feature over an associated 2-dimensional grid of spatial locations. A step of inputting the set of extracted feature maps is inputted into the machine learnable device to form associations therein between the set of extracted feature maps to and the known status for the diagnostic feature to form a trained machine learnable device. The status for the diagnostic feature of a stained tissue sample of unknown status for the diagnostic feature is predicted from the trained machine learnable device.

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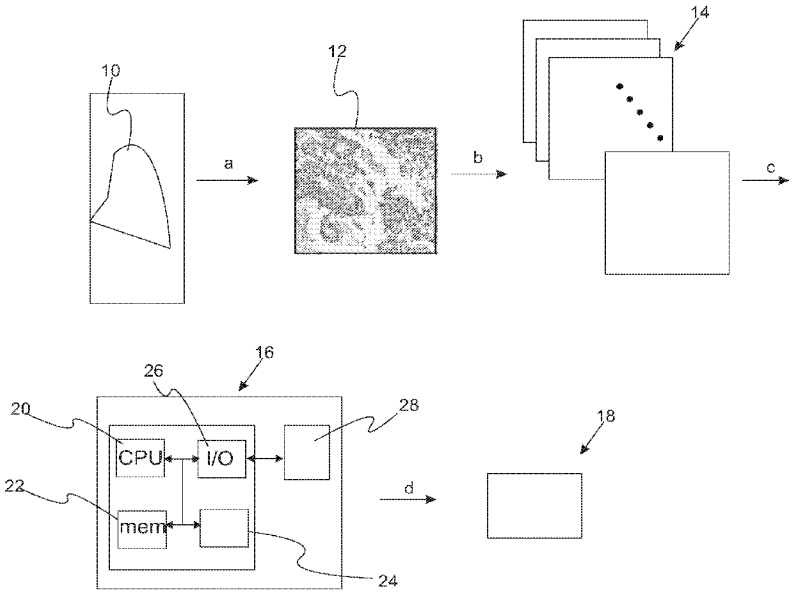


Fig. 1

(57) Abstract: A method assessing tissue morphology using machine learning includes a step of training a machine learnable device to predict the status of a diagnostic feature in stained tissue samples. The machine learnable device is trained with a characterized set of digital images of stained tissue samples. Each digital image of the characterized set has a known status for the diagnostic feature and an extracted feature map provides values for a extracted feature over an associated 2-dimensional grid of spatial locations. A step of inputting the set of extracted feature maps is inputted into the machine learnable device to form associations therein between the set of extracted feature maps to and the known status for the diagnostic feature to form a trained machine learnable device. The status for the diagnostic feature of a stained tissue sample of unknown status for the diagnostic feature is predicted from the trained machine learnable device.

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MACHINE LEARNING FOR DIGITAL PATHOLOGY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional application Serial No. 62/467,579 filed March 6, 2017, the disclosure of which is hereby incorporated in its entirety by reference herein.

TECHNICAL FIELD

[0002] The present invention, in general, relates to machine methods for diagnosing, theragnosing, and classifying types of cancer.

BACKGROUND

[0003] The promise of machine learning in clinical pathology lies in its ability to learn novel, independent patterns that can stratify patients and lead to better clinical decisions. Previous work in digital pathology suggests that hematoxylin and eosin (H&E) images contain a wealth of information that is currently underused in the diagnostic process and may have independent predictive value. For example, computer vision approaches applied to H&E images can detect cancer metastases in lymph nodes[1] and predict survival in lung cancer[2]. Patterns in H&E images may contain diagnostic cues for better diagnosis, stratification and treatment selection. The biology of the cancer is reflected by the patterns and arrangements of the cells, and it has previously been shown by many others that biology of the cancer correlates to clinical outcome and response to therapy. (reference: https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet)

[0004] In the US, the standard of care uses multiple immunohistochemistry (IHC) stains and/or molecular tests for estrogen receptor (ER), progesterone receptor (PR), and HER2 to categorize the breast tumor, determine prognosis and select treatment regimens[3,4]. However, these assays may be inconsistent across laboratories[5], and while marker status is predictive of therapeutic response[3,6], the correlation is far from perfect. For example, only 50% of women with ER-positive tumors and 60%-70% of women with

ER-positive and PR-positive tumors show partial or complete response to tamoxifen therapy[7–9]. Moreover, IHC stains are similarly used in lung, prostate, brain, and other cancer types.

[0005] Accordingly, there is a need for a method of extracting latent information from basic imaging techniques to predict molecular level information that captures the underlying biology of the cancer.

SUMMARY

[0006] The present invention solves one or more problems of the prior art by providing in at least one aspect a method assessing tissue morphology using machine learning. The method includes a step of training a selected (i.e., untrained machine) learnable device to predict the status of a diagnostic feature in stained tissue samples. The machine learnable device is trained with a characterized set of digital images of stained tissue samples. Each digital image of the characterized set has a known status for the diagnostic feature and an associated 2-dimensional grid of spatial locations. The training of the machine learnable device includes steps of identifying a plurality of extracted features in each digital image of the characterized set of digital images associating a value for each extracted feature with each spatial location to form a set of extracted feature maps. Each extracted feature map provides values for an extracted feature over the associated 2-dimensional grid of spatial locations. The training also includes a step of inputting the set of extracted feature maps into the machine learnable device to form associations therein between the set of extracted feature maps and the known status for the diagnostic feature thereby creating a trained machine learnable device. The status for the diagnostic feature of a stained tissue sample of unknown status for the diagnostic feature is predicted by obtaining a sample digital image for the stained tissue sample, the digital image having an associated 2-dimensional grid of spatial locations; associating a value for each extracted feature with each spatial location of the digital image to form a test set of extracted feature maps for the stained tissue sample of unknown status; and inputting the test set of extracted feature maps to the trained machine learnable machine to obtain a predicted status for the status of the diagnostic feature for the stained tissue sample.

[0007] In another embodiment, a trained machine learnable device formed by the methods set forth herein is provided.

[0008] In at least one aspect, the present invention breaks from the current trend in computer vision that incorporates a large number of color, texture and pixel level features. Instead, the present invention focuses on cellular morphology and trained a deep convolutional neural network to learn relationships between nuclear features. Framing the problem in terms of biological units (such as cell nuclei) provides a more natural means to interpret learned patterns than pixel level features, and reduce the impact of noise (such as staining variation) in H&E images.

[0009] The learning pipeline described herein is applied to the task of ER prediction in Breast tumors. ER is an important clinical variable as its presence is a strong indicator of response to endocrine therapy[4]. After testing and training the neural network on independent Invasive Ductal Carcinoma (IDC) and Ductal Carcinoma in Situ (DCIS) datasets, it was found that the pipeline can significantly predict ER status (AUC 0.7-0.8) from H&E images. The approach can be scaled to other critical markers such as HER2, cytokeratin, Ki-67, and molecular phenotypes[5] used in current clinical workflows (luminal A, luminal B, basal, and HER2 positive). The approach can also be applied to predict response or survival variables directly, such as 5Y survival, or days to recurrence following administration of hormonal therapy.

[0010] Aspects of the invention that focus on morphometric features provide a unique way to analyze the trained classifier. Analysis of the trained neural network leads to the conclusion that large pleomorphic nuclei are an important feature for distinguishing between ER positive and negative breast cancer tissue. Refinements to this approach can reveal new patterns that distinguish between tissue types.

[0011] In another aspect, the deep learning pipeline extracts morphometric features (e.g., nuclear, cytoplasmic, and extracellular morphometric features) from H&E images and feeds them into a deep convolutional neural network[10] to learn spatial patterns, and then uses these patterns to predict ER status. After training the network on an H&E image dataset of invasive ductal carcinoma (IDC)[11], it is found that the trained neural network can predict ER status on a test set of independent patient images of IDC[11] (AUC=0.7) and ductal carcinoma *in situ* (DCIS)[12] (AUC=0.8). This result highlights the potential for combining expert-defined features (e.g. nuclear properties) with neural networks to predict the molecular biology of a tumor. This framework can be scaled to larger datasets, additional markers (e.g. HER2, progesterone receptor, Ki-67), and molecular phenotypes[13].

[0012] In another aspect, the variations seek to predict outcome variables, dependent on tumor biology, such as survival, recurrence, and treatment response and duration directly from morphology.

[0013] In another aspect, training the neural network on nuclear morphometric features can provide a way to address the longstanding interpretability challenge of deep neural networks. While deep networks have proven to be remarkably successful at a number of tasks in digital pathology[14], an open problem in artificial intelligence is deconstructing the functions learned by deep networks to determine what the DNN learned. By preprocessing images and extracting expert-defined features (nuclear morphometric properties), the input to the neural network is simplified, and this was found to improve interpretability of the trained network. For example, deconstructing the trained network from this pilot revealed that the DNN learned to correlate large pleomorphic nuclei with ER-negative breast cancer.

[0014] In still another aspect, embodiments directly incorporate domain knowledge into the neural network by learning on relevant, pathology-driven features (morphometric features of identified nuclei), rather than forcing the NN to learn these features from raw pixels. In testing alternative approaches, is found that a neural network could not be built based on raw pixel processing on so few samples.

DRAWING DESCRIPTIONS

[0015] FIGURE 1. Schematic illustration of a method for a method for making diagnosis for stained tissue samples

[0016] FIGURE 2. An idealized schematic illustration of a convolutional neural network

[0017] FIGURES 3A, 3B, and 3C. A) Receiver operating characteristic (ROC) curves for the IDC-Training dataset (AUC=0.70, 95%CI=0.56-0.85), 3B) IDC-Test dataset (AUC=0.72, 95%CI=0.55-0.89), and 3C) DCIS-Test dataset[12] (AUC=0.81, 95%CI=0.70-0.93).

[0018] FIGURES 4A and 4B. Digital stain for regions predicted to be ER-negative. Pixels are enclosed by a dotted line in regions predicted to be ER-negative with probability greater than 50%. Enlarged regions of ER-negative tissue in Figure 4A reveal that the network classifies sub-regions of epithelial tissue as ER negative. For comparison, ER positive tissue is shown in Figure 4B

[0019] FIGURES 5A, 5B, and 5C Correlating nuclear morphometric features with ER predictions from the neural network. Image "patches" were extracted from the IDC-Training dataset, ranked by predicted probability of ER-status, and divided into 15 groups by prediction status. A) Two representative patches classified as ER positive and ER negative are shown. B) The mean of each nuclear feature was calculated within each patch (intra-patch mean); within each group, intra-patch means were averaged to calculate the inter-patch mean. C) The variance of each nuclear feature was calculated in each patch (intra-patch variance); within each group, intra-patch variances were averaged. The x-axis in b indicates group number, higher group numbers correspond to ER negative predictions.

[0020] FIGURES 6A and 6B. Construction of a sparse 12-channel image. A) Hematoxylin and eosin stained tissue are processed by a nuclear segmentation algorithm. Each nuclear feature is measured and represented on a single 2D array, where individual cells are represented as points. Arrays are stacked to form a 12D image. B) Detailed view of 12 individual channels that would be stacked to from a 12-channel image.

[0021] FIGURES 7A and 7B. Schematic of the deep neural network. A) The 12 Channel Image is loaded into a fully convolutional network with six convolutional and max-pooling layers (not shown for simplicity). The output is a 1D map of ER predictions, which is averaged and normalized (not shown) to produce an ER score for the image. The size of the matrix that holds the convolutional weights is indicated by underlining, where a matrix $N \times C \times X \times Y$ has N Kernels that act on a C channel input of size $X \times Y \times C$. B) An example of convolutional and max pooling operations. In convolution, the starting image (left) is convolved by four kernels (middle) to produce four feature maps (right). In max pooling, the maximum value of each 2×2 square is used to produce an output image.

[0022] FIGURES 8A and 8B. The neural network was trained using adadelta gradient descent[1] with binary cross entropy loss. Initially, 20% of the training data were held-out for cross validation during the training process (gray) and 80% of the training data were used for training (black). Starting at epoch 825, all training data were used to train and validate the model (black).

[0023] FIGURE 9. Exemplary over-segmented and well-segmented images. An image is deemed well segmented if it appears to be greater than 70% concordant.

DETAILED DESCRIPTION

[0024] Reference will now be made in detail to presently preferred compositions, embodiments, and methods of the present invention which constitute the best modes of practicing the invention presently known to the inventors. The Figures are not necessarily to scale. However, it is to be understood that the disclosed embodiments are merely exemplary of the invention that may be embodied in various and alternative forms. Therefore, specific details disclosed herein are not to be interpreted as limiting, but merely as a representative basis for any aspect of the invention and/or as a representative basis for teaching one skilled in the art to variously employ the present invention.

[0025] The term "comprising" is synonymous with "including," "having," "containing," or "characterized by." These terms are inclusive and open-ended and do not exclude additional, unrecited elements or method steps.

[0026] The phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. When this phrase appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded from the claim as a whole.

[0027] The phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps, plus those that do not materially affect the basic and novel characteristic(s) of the claimed subject matter.

[0028] It is also to be understood that this invention is not limited to the specific embodiments and methods described below, as specific components and/or conditions may, of course, vary. Furthermore, the terminology used herein is used only for the purpose of describing particular embodiments of the present invention and is not intended to be limiting in any way.

[0029] It must also be noted that, as used in the specification and the appended claims, the singular form "a," "an," and "the" comprise plural referents unless the context clearly indicates otherwise. For example, reference to a component in the singular is intended to comprise a plurality of components.

[0030] Throughout this application, where publications are referenced, the disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

[0031] Abbreviations:

[0032] "AI" means artificial intelligence.

[0033] "AUC" means area under the receiver operating characteristic curve.

[0034] "DCIS" means ductal carcinoma in situ of the breast

[0035] "DNN" means deep convolutional neural network.

[0036] "ER" means estrogen receptor.

[0037] "H&E" means hematoxylin and eosin.

[0038] "IDC" means ductal carcinoma.

[0039] "IHC" means immunohistochemistry.

[0040] "ML" means machine learning.

[0041] "NN" means neural network.

[0042] "PR" means progesterone receptor.

[0043] With reference to Figure 1, a schematic illustration of a method for a method for making diagnosis for stained tissue samples is provided. The method includes a step a) in which a digital image of a stained tissue sample 12 is obtained. Characteristically, each digital image has an associated two-dimensional grid of spatial locations. In step b), a plurality 14 of extracted feature maps are created from the digital image 10 in a pre-processing step. The extracted features can include morphometric, colorimetric, cell classification and traits, and the like. In this context, "extracted features" refers to features of the stained tissue sample that can be identified and/or verified by a trained professional (e.g, a pathologist or other physician). These expert-selected features can be automatically extracted with image

processing algorithms. In step c), machine learnable device 16 receives plurality 14 of extracted feature maps as a pre-processed input. Machine learnable device 16 is trained to predict the status of a diagnostic feature (e.g., ER status, see below for more details) in stained tissue samples. The untrained machine learnable device is trained with a characterized set of digital images of stained tissue samples. Characteristically, each digital image of the characterized set has a "known" status for the diagnostic feature. Machine learnable device 16 executes a machine learning algorithm to determine the diagnostic feature. Examples of such machine learning algorithms include, but are not limited to, neural networks, Bayesian networks, decision tree algorithms, support vector machines, and the like. Particularly useful algorithms for practicing the present invention are neural networks, and in particular, convolutional neural networks. Machine learnable device 16 includes computer processor 20 in communication with random access memory 22. Computer processor 20 executes the machine learning algorithm. Marching learnable device 16 also includes non-transitory memory 24 (e.g., DVD, ROM, hard drive, optical drive, etc.) which can have encoded instruction thereon for producing output 18 from the extracted feature maps using a machine learning algorithm. Typically, the machine learning algorithm instruction will be loaded into random access memory 22 from non-transitory memory 24 and then executed by computer processor 20. Machine learnable device 16 and also include input/output interface 26 that can be connected to displayer 28, keyboard and mouse. When machine learnable device 16 has been trained as set forth below, the status of an unknown sample can be evaluated. In step d), machine learnable device 16 produces output 18 which provides the status for a diagnostic feature of a stained tissue sample. Advantageously, the diagnostic feature can be use make theragnostic, prognostic, and/or diagnostic decisions for a patient.

[0044] With reference to Figure 2, an idealized schematic illustration of a convolutional neural network executed by machine learnable device 16 is provided. It should be appreciated that any deep convolutional neural network that operates on the pre-processed input can be utilized. The convolutional network can include convolutional layers, pooling layers, fully connected layers, normalization layers, a global mean layer, and a batch-normalization layer. An alternative setup to using the global mean layer is to combine convolutional layers with a recurrent neural network layers (for example a "long-short-term memory layer" (LSTM)) . The recurrent neural network layers could perform a similar function to the global mean layer, in that they can aggregate information from an arbitrarily large image into a fixed length vector. An example of using recurrent neural nets is the following paper: www.nature.com/articles/s41598-018-21758-3; the entire disclosure of which is hereby incorporated by

reference. However, the method of this paper acts on raw pixels, unlike ours which acts on pre-extracted features. A global mean layer that takes a feature-wise mean over the entire input matrix results in a fixed-length vector which represents the entire image. Batch normalization, a regularization technique, which may also lead to faster learning. Convolutional neural network layers can be characterized by sparse connectivity where each node in a convolutional layer receives input from only a subset of the nodes in the next lowest neural network layer. The Convolutional neural network layers can have nodes that may or may not share weights with other nodes. In contrast, nodes in fully-connected layers receive input from each node in the next lowest neural network layer. For both convolutional layer and fully connected layers each node calculated its output activation from its inputs, weight, and an optional bias. During training, optimal values for the weight and bias are determined. For example, convolutional neural network 30 receive plurality 14 of extracted feature maps as a multichannel image. Convolutional neural network 30 include convolution layers 32, 34, 36, 38, 40, and 42 as well as pooling layers 44, 46, 48, 50 and 52. The pooling layers can be max pooling layer or a mean pooling layer. Another option is to use convolutional layers with a stride size greater than 1. Figure 2 also depicts a network with global mean layer 54 and batch normalization layer 56. Each of the convolution layer can include multiple internal feature maps which can change from layer to layer via subsampling and convolution. The present embodiment is not limited to by number of convolutional layers, pooling layers, fully connected layers, normalization layers, and sublayers therein.

[0045] The methods set forth herein advantageously uses deep learning to extract information from stained tissue samples. In general, we show that deep learning is powerful and interpretable if it is applied on a matrix of expert-defined medium-level features. In the prior art, the deep learning systems learn medium-order and high-order relationships directly from low-level features such as the actual RGB pixel values. In some cases, this approach of learning directly from RGB pixel values works well because neural networks are good at learning spatial relationships between inputs. In cases where there are enough accurately annotated data, pixel-based deep learning can be a good strategy for building an accurate classifier. However, in medicine/pathology, it is difficult to get enough labeled data of sufficient quality. Moreover, there is a strong desire by physicians to get an intuitive idea of the features that the deep neural network uses to make a classification of diagnosis, prognosis or theragnosis. So instead of traditional approaches which use the raw pixel inputs, embodiments of the present invention perform a pre-processing

step that extracts a set of medium-level features that are defined by humans, and can be verified by humans (e.g. the nuclear morphometric features).

[0046] In this regard, a human can first confirm that the input (the pre-processed features) to the deep neural network meets some minimal quality threshold. For instance, a quality control step can be performed to make sure the quality of the input feature maps (figure 2, item 14) to the deep neural network is sufficient. This is important because a major potential risk in deep learning is that the neural network learns relationships that represent artifacts in the data, rather than real biologic changes. After the preprocessing-step step is done, a human can perform a quality control check to ensure that the data that enters the neural network reflects basic biological assumptions. For instance, it is well known that H&E staining of two consecutive sections can result in images that look vastly different on the color spectrum just by differences in the concentration of dyes used to produce the image. The color variations are an example of noise and may bias neural networks to perform differently on samples processed in different laboratories (due to different stains in different laboratories). Extracting a predefined set of features that are considered robust to common variations in preparation methods such as nuclear morphometry is a way to normalize and regularize the data that are fed into the deep neural network.

[0047] Although it might be suggested that the pre-processing step results in heavy information loss (e.g., discarded color and texture information), such information loss can be alleviated by adding additional morphometric features in the pre-processing step. Practically, any feature that can be identified reproducibly by a pathologist can be encoded into the described sparse matrix representation. Moreover, if enough morphometric features are extracted and included in the feature maps, the information content in the sparse matrix representation should capture a large quantity of the information content present in the original histopathology image. Thus, this approach does not necessarily lead to a loss of information compared to using the raw pixel input.

[0048] Alternatively, it may be useful to purposefully restrict the types of morphometric features that are extracted and utilized to understand the predictive value of these features independent of other features. For instance, comparing the classification results of a deep neural network trained on nuclear morphometric features to a deep neural network trained on cytoplasmic and extracellular morphometric features can provide intuition about which morphometric features are most predictive of an outcome.

[0049] Another benefit of limiting the input data to a subset of pre-extracted morphometric features (e.g., nuclear morphological features) instead of the original RGB pixel value images is that it allowed the deep neural network to learn a function that generalized to the test set with a statistically significant AUC (Invasive Ductal Carcinoma AUC =0.72, 95%CI=0.55-0.89, n=56; Ductal carcinoma *in situ* AUC=0.81, 95%CI=0.70-0.93, n=71). For example, on the same dataset that was tried training on the raw pixel level, it was found that the neural network over-fit the training set and did not generalize to the test set. Thus, performing the morphometric pre-processing step might force the deep neural network to learn biologic relationships rather than spurious relationships.

[0050] The neutral networks that are most useful use the following general design paradigm: a series of convolutional layers, which learn hierarchical spatial relationships (first learn relationships between objects close to each other, then relationships between those objects). The outputs of the convolutions are fed into a fully connected layer (or a fully convolutional layer, which serves a similar purpose), which learns combinations of spatial relationships and outputs a prediction. Importantly, looking at any one portion of an image may not be sufficient to make an accurate prediction. It is important to be able to combine information from multiple parts of an image to make a classification for the patient. Thus, a global pooling layer or pooling mechanism which aggregates outputs from multiple portions of the image is important. Overall, the key elements of the neural network processing used herein include: local computation to capture spatial relationships of cells/nuclei/extracellular matrix components near each other. Then more computation to integrate features from larger areas. Finally, a method to combine information from multiple portions of an image.

[0051] As set forth above, the training of the machine learnable device 18 includes a step of identifying a plurality of extracted features (e.g., morphological features) in each digital image of the characterized set of digital images. In a refinement, the extracted features are morphological features that describe shape, texture, and color of cellular and/or sub-cellular components. Morphological features include nuclear, cytoplasmic, and extracellular (extracellular matrix morphometry descriptors) morphological features. Examples of such cellular and/or sub-cellular components include, but are not limited to, individual cells, mitotic figures, cell nucleus, vacuoles in the cytoplasm, extra cellular space, and nucleolus. In another refinement, the extracted features include colorimetric features within a structured biologic element. A value for each extracted feature is associated with each spatial location to

form a set of extracted feature maps. Therefore, there will be a two-dimensional feature map for each extracted feature used in the present method. For example, if there are 12 extracted features being used, the digital image of a tissue sample being analyzed will have 12 associated feature maps. Each extracted feature map provides feature values for a extracted feature at each point of associated two-dimensional grid of spatial locations. It should be appreciated that these feature values can be a single number, a vector or a matrix. The set of extracted feature maps (i.e., the feature values with associated position coordinates) is inputted to the machine learnable device to form associations therein between the set of extracted feature maps and the known status for the diagnostic feature to form a trained machine learnable device.

[0052] The machine learnable device 18 having been trained in this manner can now be used to make predictions regarding tissue samples with an unknown status for the diagnostic feature. In particular, a status for the diagnostic feature of a stained tissue sample of unknown status for the diagnostic feature is predicted as follows. A sample digital image for the stained tissue sample is obtained. As set forth above, the digital image has an associated 2-dimensional grid of spatial locations. A feature value for each extracted feature is associated with each spatial location of the digital image to form a test set of extracted feature maps for the stained tissue sample of unknown status. The test set of extracted feature maps is inputted to obtain a predicted status for the status of the diagnostic feature for the stained tissue sample.

[0053] As set forth above, the methods of the invention predict the status of a diagnostic feature. Typically, this status of the diagnostic feature will be the presence or absence of a biomarker. In one variation, the stained tissue sample is a putative breast cancer sample with the biomarker being selected from ER, HER2, PR, Ki67, and cytokeratin markers. Advantageously, the biomarker can be ER which alone can be used to determine specific treatments (e.g., hormonal therapy). In another refinement, the biomarkers ER, PR, and HER2 are prognostic. For example, patients with ER+ PR+ HER2- have the best outcomes, followed by patients with ER+ PR- with patient having ER-PR- having the worst prognosis. All three markers (i.e., ER, PR, HER2) can be used to clarify the cancer and make determinations for treatment. In still other refinements, the biomarker can be E-cadherin and/or PIK3CA with the predicted status being used to differentiate between subtypes of breast cancer (e.g., ductal and lobular carcinoma *in situ*).

[0054] In another variation, the stained tissue sample is a putative cancer (e.g. lung cancer) sample. In this variation, the biomarker can be EGFR, KRAS, c-Met, MET, and ALK. In this regard, Alk rearrangements are theragnostic with specific treatments being known for patients with ALK rearrangements.

[0055] In still other variations, the biomarker can be selected from the group consisting of p53 (multiple cancers), Bcl-2 (leukemia), and c-Myc (lymphoma).

[0056] As set forth above, a plurality of extracted features, and in particular, a plurality of morphological features is used to characterize each digital image. In this regard, features describing the shape, texture, and color of sub-nuclear components of a cell are important. Examples of such cellular and/or sub-cellular components include, but are not limited to, individual cells, mitotic figures cell nucleus, vacuoles in the cytoplasm, extra cellular space, and nucleolus. These structures are visible on H&E images and can be quantified by shape and color intensity much like the nucleus. Examples of the morphological features that can be used to characterize these components include, but are not limited to, one or more features selected from the group consisting of area, perimeter, circumference, fractal dimension, Zernike moments, mitotic figure, and combinations thereof. In some circumstances, it may be useful to approximate the cellular and/or subcellular components by an ellipse. When such an approximation is made, the morphological features may include one or more features selected from the group consisting of ellipse area, ellipse major axis length, ellipse minor angle length, ellipse angle from horizontal, and combinations thereof.

[0057] In another variation, the plurality of extracted features includes color parameters. In particular, color information may be used to quantify cellular and subcellular components. These features are calculated from color channels (either RGB channels or a transformation of these channels (e.g. after color deconvolution)). For example, color related features may include: the mean and variance in color channels throughout the nucleus; the mean and variance in color channels within a radius (e.g. 2 μm) about the nucleus (this is a way to quantify the cytoplasm); the mean and variance in color channels outside cells and throughout the stroma. The difference between using the colorimetric parameters in the present variation and using RGB pixels is the

colorimetric parameters describe the colors within a structured biologic element ("cells" or within "nuclei"). They are not raw color pixels of an image.

[0058] In still other variations, the identification of extracted features can include a higher-level classification step which may also lead to useful features for machine learning. For example, a useful feature might be the categorical classification of nuclear cell type: epithelial, fibroblast, lymphocytic, myocontractive, and the like.

[0059] In still other variations, the extracted features can also include the spatial neighborhood of nuclei and cells. Examples of such features include the number of neighbors within a given radius that satisfy some criteria (e.g. nearest neighbors within 50 micrometers that have a radius > 5 micrometers) and the number of white pixels within a radius. It should be appreciated that white pixels may result from various phenomena, such as artifact during tissue processing, fat cells, or spaces between extracellular matrix proteins. Therefore, white pixel quantification contains a wealth of important information about the architecture of a tissue.

[0060] In yet another variation of the methods set forth above, further includes steps of determining treatment for a subject from the subjects' predicted status for the status of the diagnostic feature and then treating the subject. Treatment of cancer patients is dependent on the biology of the cancer. The premise of the current invention is that the biology is described in the tissue morphology. Thus, the tissue morphology as assessed by the machine learning methods, can be used as a theragnostic agent in cancer patients to help chose appropriate treatment. An example would be to segregate hormone receptor positive breast cancer patients by morphology using AI/ML, which would then predict outcome to hormone receptor targeted therapy. A logical extension would be to correlate with clinical outcome to targeted therapy (i.e., duration of response and other parameters) that are not associated just with hormone receptor positivity (but may be correlated to associated morphology). In a refinement, the subject can be treated with an appropriate chemotherapeutic agent specific to (i.e., known for the treatment of) the identified status of the diagnostic feature.

[0061] The following examples illustrate the various embodiments of the present invention. Those skilled in the art will recognize many variations that are within the spirit of the present invention and scope of the claims.

[0062] **Nuclear morphometric features predict ER status in IDC tissue**

[0063] Publicly available H&E images and corresponding clinical ER status (positive/negative, determined by IHC) were obtained for 131 invasive ductal carcinoma (IDC) patients on a tissue microarray[11]. After segmenting nuclei and applying a quality control step to exclude over-segmented images (Figure 8), the images were randomized into a training set ("IDC-Train", 57 patients) and a test set ("IDC-Test", 56 patients). Nuclear morphometric features (shape and orientation) were extracted from each nucleus in the training set. These measurements were fed into a deep convolutional neural network (DNN) to learn spatial patterns that correlate to ER positive or ER negative status. The DNN was designed to produce a spatial heatmap of ER-positive or negative status. When an input image is fed into the DNN, the output is a heatmap of predictions where intense regions correspond to ER-negative status. The overall ER-status prediction for a patient is the average value of the heatmap.

[0064] After training the neural network, the pipeline was evaluated on the test set and measured area under the curve (AUC) scores of 0.70 (95%CI=0.56-0.85) and 0.72 (95%CI=0.55-0.89) on the IDC-Train and IDC-Test datasets, respectively (Figure 3). This result suggests that the pipeline indeed learned to predict ER status from H&E images. Moreover, the similarity between the AUC scores on the training and test sets suggests that the pipeline learned a classification function that generalizes well and does not over fit the training data.

[0065] Trained neural network can also predict ER status in ductal carcinoma in situ

[0066] Studies suggest that ER status may be an important marker for subtypes of DCIS with different outcomes15,16. To characterize how the patterns learned by the network generalize across subtypes of breast disease, a second publicly-available and previously published dataset ("DCIS-Test")12 consisting of H&E images from patients with ductal carcinoma in situ was obtained.

[0067] Following the segmentation and quality control steps, the previously trained network was on images from 71 patients with ductal carcinoma in situ and obtained a statistically significant AUC score of 0.81 (95%CI 0.70-0.93, Figure 3). Together, these findings suggest that the pipeline learned patterns that correlate with ER in both IDC and DCIS

[0068] A correlation between nuclear size, heterogeneity, and ER status

[0069] While deep networks are typically considered to be uninterpretable "black boxes," several techniques were applied to reverse-engineer the system and understand the morphometric patterns the DNN used to classify ER status. The first step was to visualize the heatmap the DNN learned to predict. This analysis is similar to laying an IHC image over an H&E image; however, while an IHC image shows the real protein expression, the DNN heatmap shows regions estimated by the DNN to be ER positive or negative. Because the DNN was trained to predict an accurate patient-level classification (not the spatial pattern of ER-staining), the regions predicted on the heatmap may be different from regions predicted by IHC. However, regions on the DNN heatmap contain information that leads to an accurate ER+/- prediction, and are thus diagnostic regions for ER-assessment.

[0070] For this analysis, several cases were selected that were classified correctly and overlaid the predicted heatmaps on the H&E image to form a "digital stain" where ER-negative regions are enclosed by a dotted line and ER-positive regions are uncolored (Figure 4). By visual inspection, it was observed that a subset of epithelial areas was predicted ER-negative. Thus, it appears that features in epithelial regions are used by the DNN to classify ER status.

[0071] Next, the DNN was used to gain intuition about the specific nuclear features linked to the ER prediction. The training images are divided into small image patches (100 × 100 pixels, 200 × 200 μm, approximately 104 total). The ER score for each patch was predicted and sorted the patches by prediction from ER positive to ER negative. Looking only at the extremes (patches most strongly predicted to be ER positive or ER negative), a difference in nuclear size and the variation in nuclear features was noted (exemplary patches in Figure 5A).

[0072] It is hypothesized that the pipeline learned to predict ER status as a function of nuclear size and pleiomorphism. To formally investigate this pattern, the sorted list of patches was dived into 15 groups ranked by predicted ER score. For each patch, the mean value of each nuclear feature (intra-patch mean) and the variance of the feature (intra-patch variance) was calculated. The inter-patch mean and standard error across all patches in the group was also calculated (Figure 5B). This revealed that several nuclear morphometric quantities, such as mean height, width, area and perimeter were elevated in patches classified as ER negative. Additionally, nuclear heterogeneity (variance of nuclear features) is correlated to an ER negative prediction.

[0073] Based on these observations, it was directly tested if the mean and variance of nuclear features in a patch could predict ER status. 5000 patches were randomly from the IDC-Train dataset, calculated the intra-patch means and variances of nuclei within each patch and trained a logistic regression model on these features. Next, the trained logistic regression model was applied to full-sized images in the IDC-Test dataset. Each image was divided into equally-spaced non-overlapping patches, calculated an ER score for each patch, and averaged the ER score from all patches in each test image. On the IDC-Train dataset, an AUC of 0.648 (95% CI: 0.498-0.799) was obtained. On the IDC-Test dataset, an AUC of 0.6715 (95% CI: 0.494-0.850) was obtained. While these linear classifiers are less accurate than the DNN, the trend suggests that these features capture information about ER status. Analyzing a DNN trained on expert-defined features helped us interpret the DNN in terms of biological relationships.

[0074] Together, these findings suggest that nuclear morphometric features can be used to predict the presence of the estrogen receptor. A neural network trained on IDC images predicted ER status on a held-out IDC dataset (IDC-Test) and an external DCIS dataset (DCIS-Test). Further analysis of the trained neural network suggests a biological difference between ER positive and negative tissue: large, pleomorphic nuclei seem to be correlated with an ER negative prediction.

[0075] Discussion

[0076] Embodiments herein aim to determine whether tissue morphology reflects the biologic state of hormone receptor signaling pathways in breast cancer samples. Using deep

learning and labeled tissue images, a learning pipeline to correlate patterns of nuclei to ER status was trained, based on IHC staining as the reference. Analysis of the trained model revealed that the morphometric-biologic correlation is dependent on the association of large pleomorphic nuclei with ER negative tumors. This is the first work to use deep learning to identify, correlate, and explain how a morphologic pattern in a pathology image correlates to signaling pathways reflecting the underlying molecular biology of a cancer. Future studies will correlate to clinical responsiveness to ER pathway therapeutics.

[0077] A core factor in this work was the development of a hybrid machine-learning approach that combined expert-defined local features with the powerful feature-learning framework of convolutional neural networks. While convolutional neural networks can learn high-order features from the raw image data, training these models typically requires thousands to millions of training images to minimize the impact of noise and color variations. Limited by the quantity of annotated training images, variations of the invention introduced a pre-processing step to extract nuclear morphometric data and developed a novel method for deep learning on these features instead of the raw RGB image pixels, which may be subject to H&E staining variation. Preprocessing effectively compressed each training image into a vector of morphometric data. While this constrains the types of features the neural network could learn, it also prevents it from learning spurious correlations between nonsensical variables (e.g., staining variation). Thus, it is believed believe using expert-defined features as input allowed the network to learn patterns that generalized well between the training and test datasets and between IDC and DCIS images.

[0078] The network's performance on the DCIS dataset was intriguing. While the network was trained on IDC images, the high accuracy on DCIS images may be explained by a several factors. Biologically, it has been noted that there are morphometric similarities between DCIS and IDC17, thus patterns learned on IDC may apply to DCIS. Another explanation is that the co-occurrence of DCIS and IDC in some of the IDC training images allowed the network to learn patterns for DCIS and IDC simultaneously. An alternative explanation is that the higher accuracy on the DCIS dataset was due to the method of dataset preparation. Images in the DCIS dataset were carefully chosen by pathologists and contain little stroma relative to epithelial tissue. On the other hand, images in the IDC datasets were obtained from a commercial tissue microarray supplier. These cores are large,

diverse (containing a mixture of stromal and epithelial tissue), and noisy (exhibiting varying degrees of staining artifact). Thus, biologic or region-selection factors may explain the accuracy on the DCIS dataset.

[0079] The promise of machine learning lies in its ability to learn novel, independent patterns that can stratify patients and lead to better clinical decisions. While previous works in digital pathology have suggested that H&E images contain a wealth of information that is currently underused in the diagnostic process, variations of the invention demonstrate that the information contained in the shapes and arrangements of the nuclei contain information that is correlated to the molecular biology of breast cancer. While this pipeline can be adapted and scaled to classify other subtypes of breast cancer, breast cancer markers, molecular phenotypes13 (luminal A, luminal B, HER2, basal), etc, the power of the inventive approach lies in the ability to extract biological insights from the neural network. The hybrid system is not a "black-box" learning system. It learns high-order features based on lower-order, human-defined features that can be reverse-engineered to gain intution about biology. In embodiments of the present invention, digital staining and patch analysis was used to learn the correlation between large pleomorphic nuclei with ER negative tumors.

[0080] Method

[0081] It is hypothesized that the combination of (1) spatial arrangement of cells combined with (2) nuclear morphometric properties would capture important information about the underlying molecular biology of breast cancer and provide clinically useful predictions. Thus, a learning pipeline was constructed to classify cancers by molecular markers. Here, this hypothesis was tested on the pathological classification of a tumor as ER+ or ER-. The method comprises five steps: (1) data acquisition, (2) image pre-processing, (3) quality control, (4) designing and training the neural network, and (5) testing the neural network.

[0082] Step 1: Data acquisition

[0083] Dataset 1: IDC

[0084] The first set of acquired H&E images were from the website of the tissue microarray supplier, US Biomax, Inc. (Derwood, MD 20855). As a service to customers, US Biomax, Inc. provides JPEG-compressed H&E images of many tissue microarrays along with immunohistochemistry (IHC) staining information, such as ER receptor status. With permission from US Biomax, Inc., the array titled "HBre-Duc140Sur-01" (www.biomax.us/tissue-arrays/Breast/HBre-Duc140Sur-01) was used, which contains 140 tissue cores (1.5mm diameter) from 140 patients diagnosed with invasive ductal carcinoma. This particular microarray was chosen because the H&E images displayed minimal staining artifacts and included molecular marker staining status. To collect the data, the digital slide viewer was used on the US Biomax, Inc. website, zoomed in to 20× resolution (0.5 μm per pixel) with screenshots taken of each core. These images were correlated to ER status (from the US Biomax, Inc. website), and then fed into the pre-processing pipeline. Following a quality control step (described below), 113 tissue cores remained, with one core per patient. These patients were randomly divided into the "Biomax training" (n=57) and "Biomax test" (n=56) datasets.

[0085] Dataset 2: DCIS

[0086] A second dataset (called "DCIS") consisting of H&E images with ER status for patients with ductal carcinoma in situ was used. The DCIS dataset is a subset of a publicly available dataset12 that contains 327 H&E images for 167 patients with either ductal carcinoma in situ or usual ductal hyperplasia (UDH). ER status was not available for patients with UDH. Out of the patients with ductal carcinoma in situ, ER status was available for 84 patients. Out of these 84 patients, 71 patients passed the quality control step (described below) and were included in the DCIS dataset. The original image resolution in the DCIS dataset is 40x (0.25 μm per pixel). These images were rescaled to be the same resolution as the Biomax dataset (0.5 μm per pixel) using bicubic sampling before subsequent processing steps. The DCIS dataset was used as an external validation dataset. Table 1 summarizes the IDC and DCIS datasets.

[0087] Step 2: Image pre-processing

[0088] A fully automated nuclear segmentation pipeline using Python (version 2.7.12) and Fiji18 (version 1.0, a distribution of ImageJ19) was. The steps consist of the following:

[0089] Scale images as necessary to a resolution 0.5 μm per pixel, using bicubic interpolation.

[0090] Transform the RGB image into hue, saturation, brightness channels, retaining only the brightness channel for downstream analysis.

[0091] Apply an automatic, global Otsu threshold20 to roughly identify cellular regions

[0092] Apply a local adaptive threshold with a radius of 20 pixels (10 μm) to provide fine-scale local separation of nuclei.

[0093] Use the built-in Fiji watershed transform to separate overlapping nuclei.

[0094] Calculate the following morphometric parameters for each detected nucleus using the particle analysis functions in ImageJ: center of nucleus (x, y coordinates), major axis length, minor axis length, major axis to minor axis ratio, area, perimeter, and circularity.

[0095] Convert data into a MultiCellDS digital tissue snapshot (a standardized XML representation for spatial multicellular data)21 for storage.

[0096] The pre-processing image scripts are available in the supplementary materials.

[0097] Step 3: Quality Control

[0098] A label-blind quality control step was performed in which 200 × 200 pixel patches were extracted from each H&E image and overlaid with ellipses representing the extracted nuclei. Visually, RR assigned a Boolean value (0 or 1) to each image corresponding to whether the image appeared well segmented (defined as greater than 70% concordant, Supplemental Figure 3). Patients with unknown ER status were excluded from the analysis. As a result of the quality control step, 113 out of 140 cases were used from the IDC dataset and 71 out of 84 ductal carcinoma in situ cases for the DCIS dataset.

[0099] Step 4: Designing and Training the Neural Network

[00100] Each MultiCellDS digital tissue snapshot was converted into a sparse 12 channel image (Figure 6), consisting of zeros everywhere except at the cell centers, which contain information about the nuclei. The first six channels correspond to cellular shape features (major axis, minor axis, major: minor ratio, area, perimeter, circularity). In addition, 6 "binary angle" features from the nuclear angle measurement were constructed, leading to a total of 12 feature channels; if the major axis of cell i has an angle θi ($0 < \theta i < 180$) with the positive x-axis, six orientation features $\varphi i, j$ ($1 \leq j \leq 6$) are defined by

[00101] $\varphi i,j = 1$ if $30 \times (j-1) < \theta\_i \leq 30 \times j$

[00102] $\varphi i,j = 0$ otherwise.

[00103] The rationale for constructing binary features relates to the training process for the neural network. It was desirable that the network learn rotationally invariant features, which are robust to flips and rotations (in the spatial image coordinates) of the 12-D image. Using binary angle channels allowed us to flip or rotate the image while keeping the cell angle information properly oriented.

[00104] The final step before training involved downscaling the sparse images 4× via nearest-neighbor scaling to reduce downstream computation. Thus, the DNN sees cell features at a resolution of 2 μm per pixel. Following down sampling, cells positioned at physical coordinates (x1, y1), are positioned at matrix indices (x2, y2) such that:

[00105] $x2 = \text{floor}(x1/4)$

[00106] $y2 = \text{floor}(y1/4)$

[00107] Network Design

[00108] The overall structure of the neural network was inspired by previous work applying deep learning to image segmentation22 and high-content screening23. The network of the present example has approximately 4.6×105 parameters arranged in six fully convolutional layers, 5 max pooling layers, one global mean layer, and one batch-normalization layer (Figure 7). Through cross-

validation on the training set, it was to use leaky rectifying linear neurons with cross-entropy loss. Importantly, it was that using a batch normalization layer24 was necessary for convergence. Over one batch of training data, a batch normalization layer produces outputs with zero mean and unit variance. In training, this leads to a well-distributed set of output predictions, which accelerates the learning process. In addition, a dropout layer was used, which randomly eliminates 50% of the neurons during each round of training to prevent co-adaptation of neurons (a form of over-fitting)25.

[00109] Using a global mean layer gives us the option of training the network on images of arbitrary size. However, training was performed on small patches extracted from sparse images to increase the relative size of the training set. Thus, during the training process, small patches (100 × 100 pixels, 200 × 200 μm) were randomly extracted from the downscaled feature maps (approx. 750 x 750 pixels, 1500 × 1500 μm) and assigned them the same class as the overall image. At runtime, these patches were randomly flipped and rotated (in multiples of 90 degrees) to augment the dataset and promote the learning of rotationally invariant features. Theoretically, the augmented training set consists of 108 different patches; however only a subset of these images was actually used to train the network.

[00110] Each layer in the neural network combines features from the previous layer, and deeper layers can learn higher order features. The model uses a fully convolutional architecture, which means that it can process images of arbitrary size, producing output in the form of a spatial map that scales with the size of the input image22. Thus, the final classification layer produces a spatial map for ER score over the image, and the average prediction over the map is treated as the score for the image.

[00111] All experiments were conducted on an Nvidia K80 GPU using the Deep Learning libraries Theano26 and Lasagne27.

[00112] Network Training

[00113] 113 patients from the IDC dataset were randomly into training (n = 57) and test (n = 56) datasets. From the training set, 20% data was held out for cross validation during the training

process. From the training set, small patches (100 × 100 pixels, 200 × 200 μm) were subsampled and trained the network using image-level labels (ER+, ER-) for the patches and a cross-entropy loss function. After approximately 450 epochs (corresponding to training on approx. 7 × 104 individual patches), the training loss began to plateau (Figure 9). The loss had plateaued by epoch 825, so the held-out cross-validation data was added back in and trained the net for approximately 1000 epochs to maximize accuracy on the entire training dataset.

[00114] Step 5: Testing the Neural Network

[00115] Following training, all parameters and weights in the neural network were fixed. Full sized images were classified and the predictions were stored in a text file for analysis. The test sets were held out during training and were only evaluated after the network had been trained.

[00116] Data availability

[00117] The nuclear segmentations that were used to train the neural network are freely available under the Creative Commons CC-BY 4.0 license as MultiCellDS digital snapshots, included here as supplementary data21. In addition, the raw H&E images used to generate cell segmentations available from the website of Biomax.us (IDC, www.biomax.us/tissue-arrays/Breast/HBre-Duc140Sur-01), or the Dryad Digital Repository28 (DCIS Dataset).

[00118] While exemplary embodiments are described above, it is not intended that these embodiments describe all possible forms of the invention. Rather, the words used in the specification are words of description rather than limitation, and it is understood that various changes may be made without departing from d spirit and scope of the invention. Additionally, the features of various implementing embodiments may be combined to form further embodiments of the invention.

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WHAT IS CLAIMED IS:

1. A method comprising:

a) training an untrained machine learnable device to predict status of a diagnostic, prognostic, or theragnostic feature in stained tissue samples, the untrained machine learnable device being trained with a characterized set of digital images of stained tissue samples, each digital image of the characterized set having a known status for the diagnostic, prognostic, or theragnostic feature and an associated 2-dimensional grid of spatial locations, training of the untrained machine learnable device including steps of:

identifying a plurality of extracted features in each digital image of the characterized set of digital images;

associating a value for each extracted feature with each spatial location to form a set of feature maps, each extracted feature map providing values for a extracted feature over the associated 2-dimensional grid of spatial locations; and

inputting the set of extracted feature maps to the untrained machine learnable device to form associations therein between the set of extracted feature maps and the known status for the diagnostic, prognostic, or theragnostic feature thereby creating a trained machine learnable device; and

b) predicting a status for the diagnostic, prognostic, or theragnostic feature of a stained tissue sample of unknown status for the diagnostic feature by:

obtaining a sample digital image for the stained tissue sample, the digital image having an associated 2-dimensional grid of spatial locations;

associating a value for each extracted feature with each spatial location of the digital image to form a test set of extracted feature maps for the stained tissue sample of unknown status; and

inputting the test set of extracted feature maps to the trained machine learnable device to obtain a predicted status for the status of the diagnostic, prognostic, or theragnostic feature for the stained tissue sample.

2. The method of claim 1 wherein the extracted features include morphological features.

3. The method of claim 2 wherein the morphological features describe shape, texture, and color of cellular and/or sub-cellular components.

4. The method of claim 3 wherein the cellular and/or sub-cellular components include individual cells, mitotic figures, cell nucleus, vacuoles in the cytoplasm, extra cellular space, and nucleolus.

5. The method of claim 1 wherein the extracted features include colorimetric features and using RGB pixels is that these are "features" that describe the colors within a structured biologic element.,

6. The method of claim 1 wherein the untrained machine learnable device is a computer executing instructions for a neural network.

7. The method of claim 1 wherein the untrained machine learnable device is a computer executing instructions for a convolutional neural network.

8. The method of claim 7 wherein the convolutional neural network includes a plurality of convolutional layers and a plurality of pooling layers.

9. The method of claim 8 wherein the convolutional neural network further includes a global mean layer and a batch-normalization layer.

10. The method of claim 1 further comprising determining treatment for a subject from a subjects' predicted status for the status of the diagnostic feature and then treating the subject.

11. The method of claim 10 wherein the subject is treated with a chemotherapeutic agent.

12. The method of claim 1 wherein the diagnostic feature, prognostic, or theragnostic is presence or absence of a biomarker.

13. The method of claim 12 wherein the stained tissue sample is a putative breast cancer sample.

14. The method of claim 13 wherein the biomarker is selected from ER, HER2, PR, Ki67, and cytokeratin markers

15. The method of claim 14 wherein the biomarker is ER with the predicted status being used to determine specific treatments.

16. The method of claim 12 wherein the biomarker is ER, PR, and HER2 with the predicted status indicating prognosis.

17. The method of claim 12 wherein the biomarker is E-cadherin and PIK3CA with the predicted status being used to differentiate between subtypes of breast cancer.

18. The method of claim 12 wherein the stained tissue sample is a putative cancer sample.

19. The method of claim 12 wherein the stained tissue sample is a putative lung cancer sample.

20. The method of claim 12 wherein the biomarker is EGFR, KRAS, c-Met, MET, and ALK.

21. The method of claim 12 wherein the biomarker is selected from the group consisting of p53, Bcl-2, and c-Myc.

22. The method of claim 1 wherein the plurality of extracted features includes parameters for quantifying shapes of cellular and/or sub-cellular components.

23. The method of claim 22 wherein the cellular and/or sub-cellular components include individual cells, cell nucleus, vacuoles, extra cellular space, and nucleolus,

24. The method of claim 22 wherein the extracted features include one or more features selected from the group consisting of area, perimeter, circumference, fractal dimension, Zernike moments, mitotic figure, and combinations thereof.

25. The method of claim 22 wherein the cellular and/or subcellular components are approximated by an ellipse.

26. The method of claim 22 wherein the extracted features include one or more features selected from the group consisting of ellipse area, ellipse major axis length, ellipse minor angle length, ellipse angle from horizontal

27. The method of claim 1 wherein the plurality of extracted features includes color parameters.

28. A method comprising:

a) predicting a status for the diagnostic, prognostic, or theragnostic feature of a stained tissue sample of unknown status for the diagnostic feature by:

obtaining a sample digital image for the stained tissue sample, the digital image having an associated 2-dimensional grid of spatial locations;

associating a value for each extracted feature with each spatial location of the digital image to form a test set of extracted feature maps for the stained tissue sample of unknown status; and

inputting the test set of extracted feature maps into a trained machine learnable device to obtain a predicted status for the status of the diagnostic feature for the stained tissue sample.

29. The method of claim 28 wherein the trained machine learnable device is formed by training an untrained machine learnable device to predict status of a diagnostic, prognostic, or theragnostic feature in stained tissue samples, the untrained machine learnable device being trained with a characterized set of digital images of stained tissue samples, each digital image of the characterized set having a known status for the diagnostic feature and an associated 2-dimensional grid of spatial locations, training of the untrained machine learnable device including steps of:

identifying a plurality of extracted features in each digital image of the characterized set of digital images;

associating a value for each extracted feature with each spatial location to form a set of extracted feature maps, each extracted feature map providing values for a extracted feature over the associated 2-dimensional grid of spatial locations; and

inputting the set of extracted feature maps to the untrained machine learnable device to form associations therein between the set of extracted feature maps and the known status for the diagnostic feature to form a trained machine learnable device.

29. A trained machine learnable device formed by training an untrained machine learnable device to predict status of a diagnostic feature in stained tissue samples, the untrained machine learnable device being trained with a characterized set of digital images of stained tissue samples, each digital image of the characterized set having a known status for the diagnostic feature and an associated 2-dimensional grid of spatial locations, training of the untrained machine learnable device including steps of:

identifying a plurality of extracted features in each digital image of the characterized set of digital images;

associating a value for each extracted feature with each spatial location to form a set of extracted feature maps, each extracted feature map providing values for a extracted feature over the associated 2-dimensional grid of spatial locations; and

inputting the set of extracted feature maps to the untrained machine learnable device to form associations therein between the set of extracted feature maps and the known status for the diagnostic feature thereby creating a trained machine learnable device.

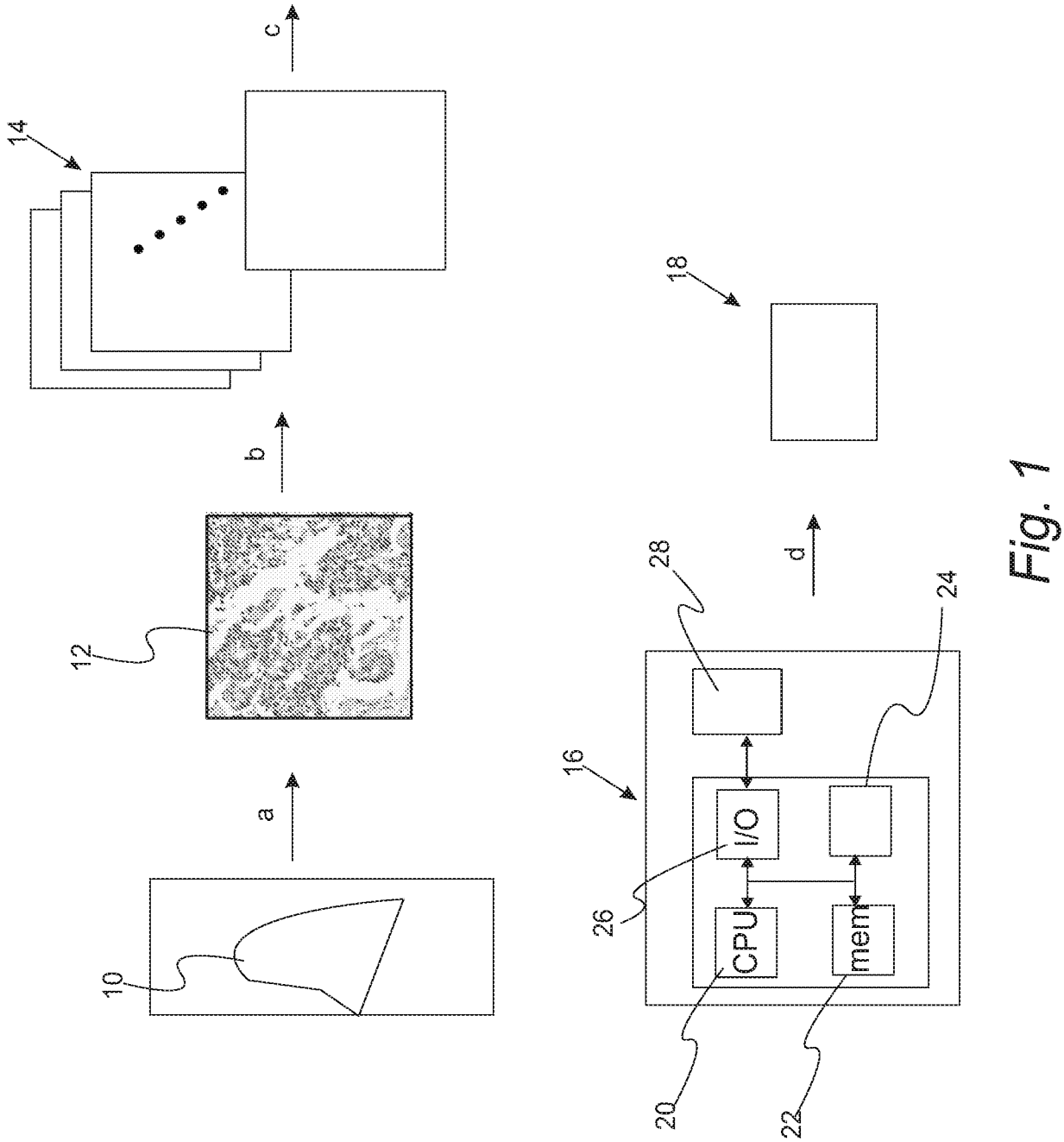


Fig. 1

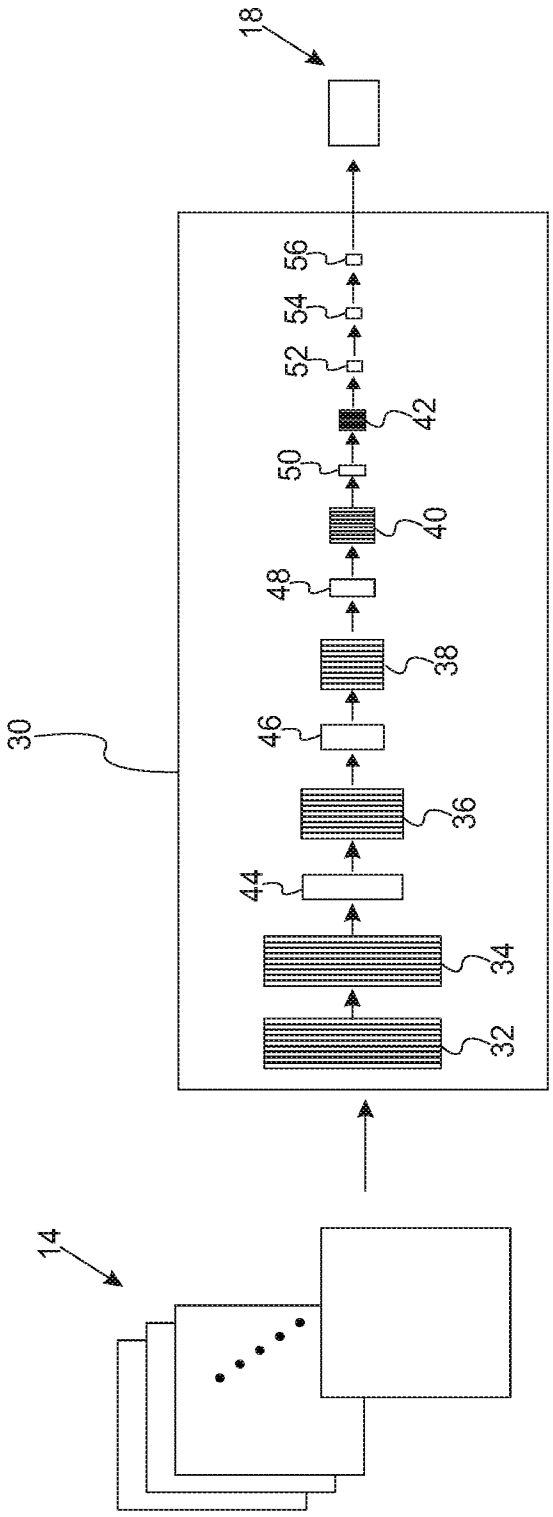


Fig. 2

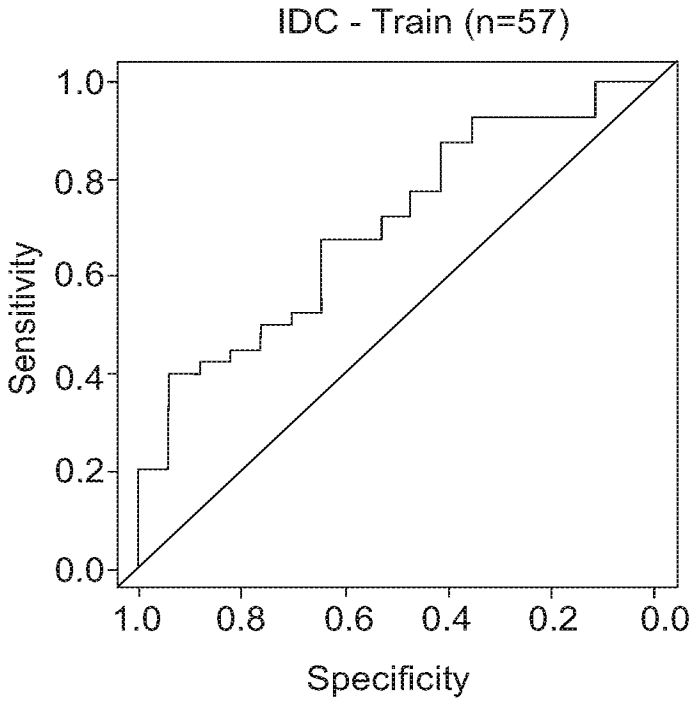

IDC - Train (n=57)
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
1.0
0.8
0.6
0.4
0.2
0.0
Specificity

Fig. 3A

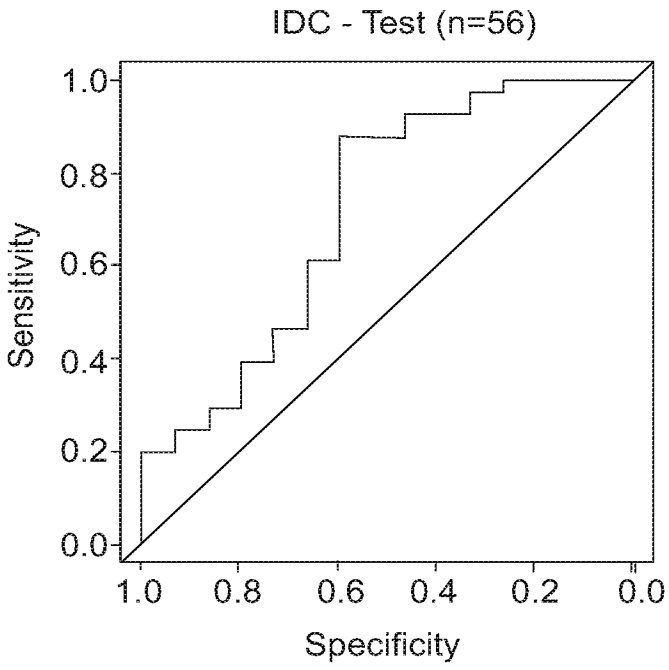

IDC - Test (n=56)
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
1.0
0.8
0.6
0.4
0.2
0.0
Specificity

Fig. 3B

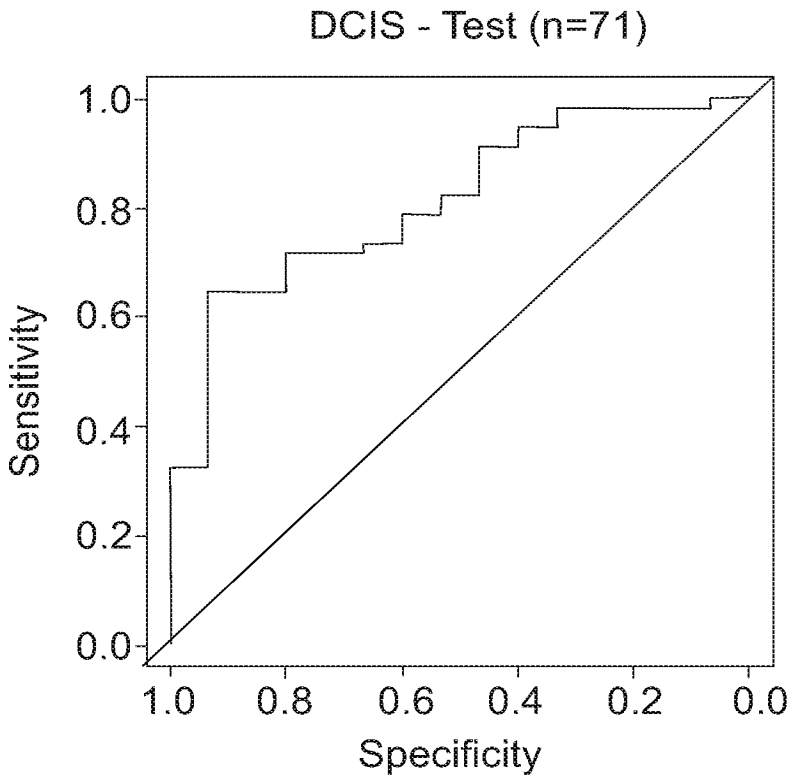

DCIS - Test (n=71)
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
1.0
0.8
0.6
0.4
0.2
0.0
Specificity

Fig. 3C

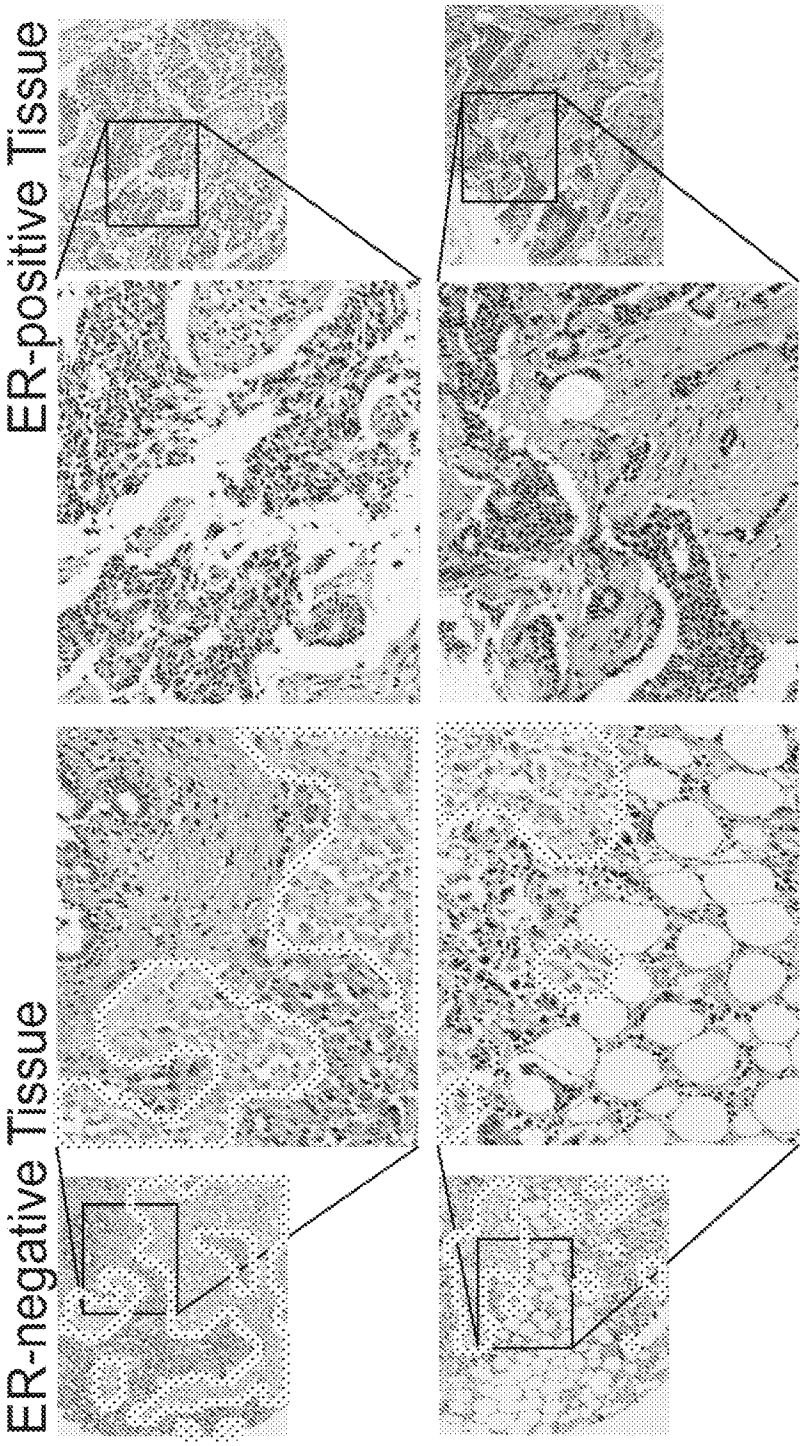


Fig. 4B

Fig. 4A

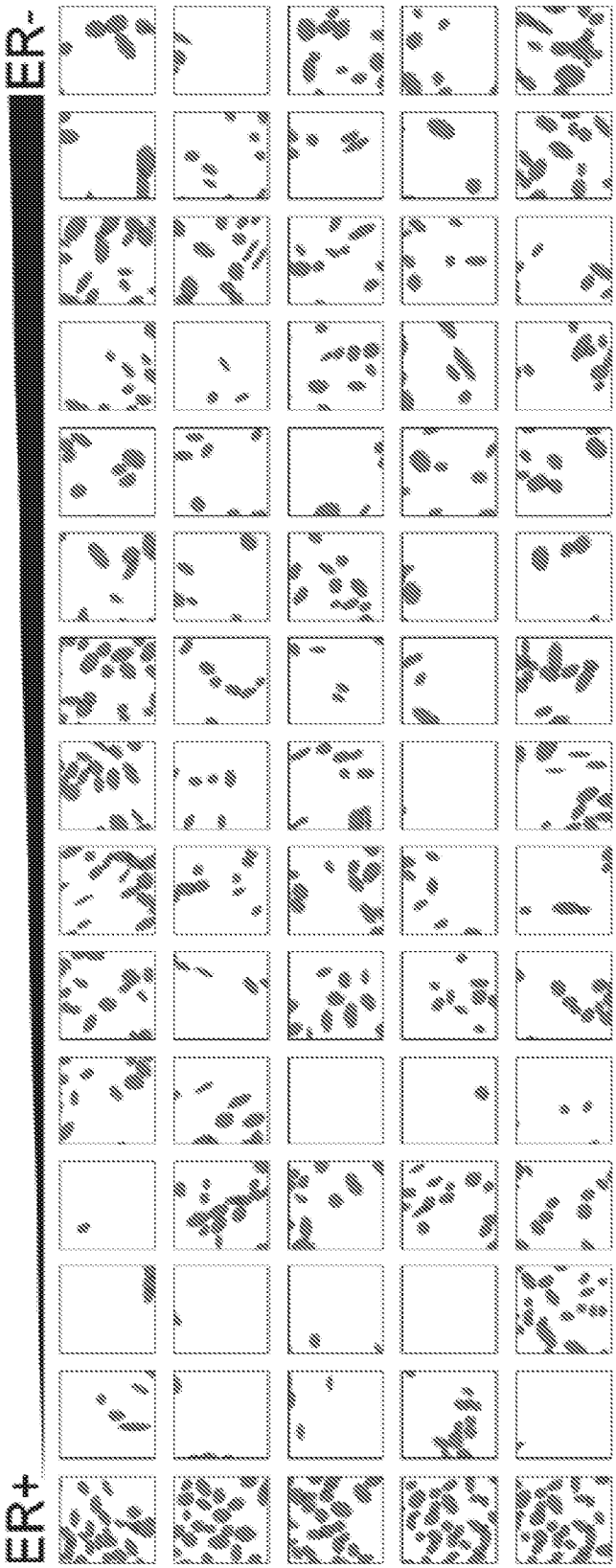


Fig. 5A

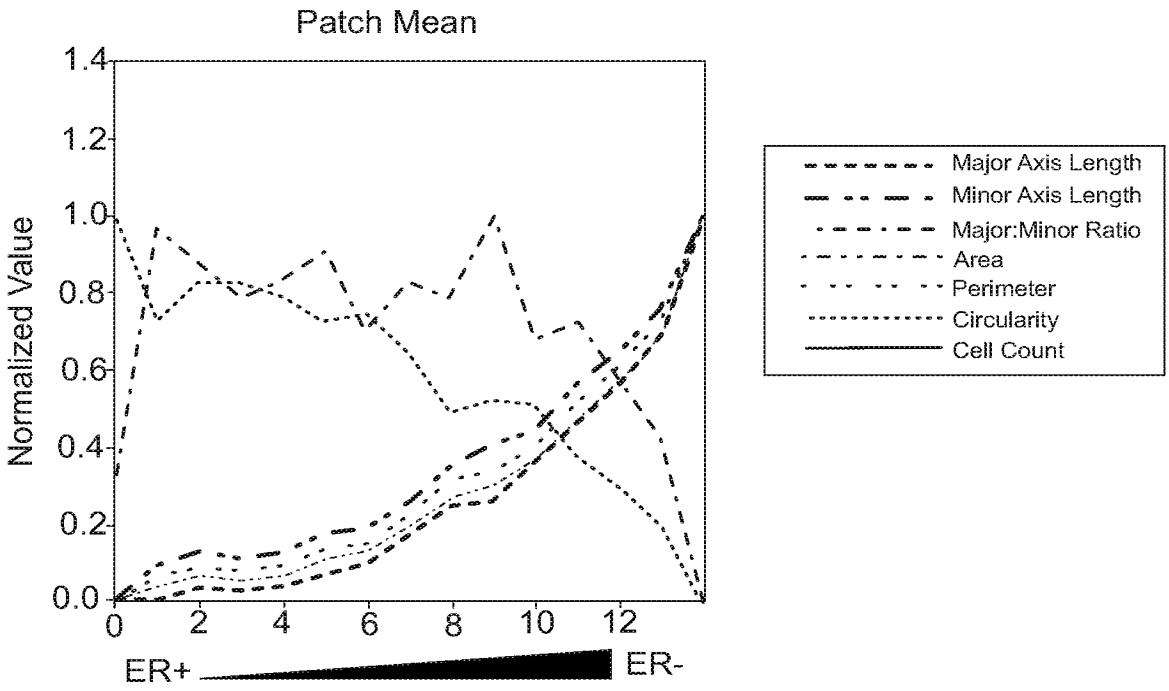

Patch Mean
Normalized Value
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
ER+
ER-
Major Axis Length
Minor Axis Length
Major:Minor Ratio
Area
Perimeter
Circularity
Cell Count

Fig. 5B

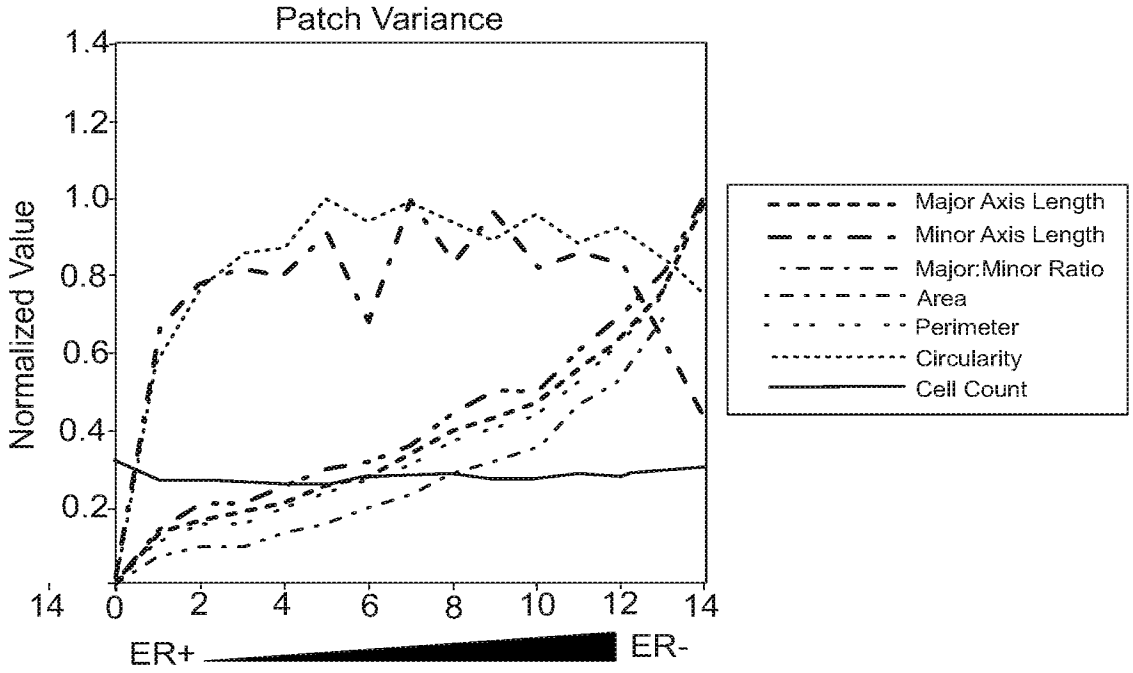

Patch Variance
Normalized Value
1.4
1.2
1.0
0.8
0.6
0.4
0.2
14
0
2
4
6
8
10
12
14
ER+
ER-
Major Axis Length
Minor Axis Length
Major:Minor Ratio
Area
Perimeter
Circularity
Cell Count

Fig. 5C

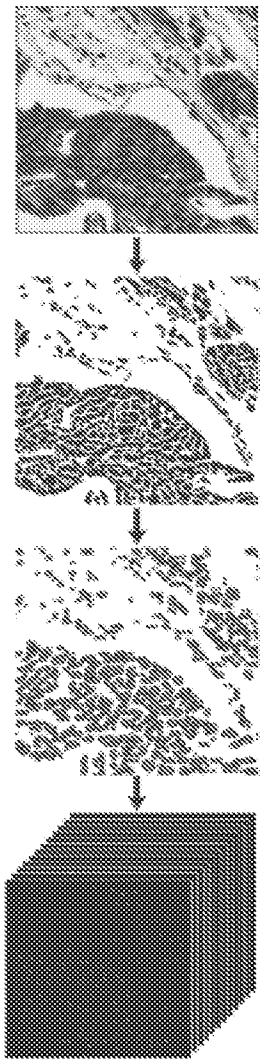


Fig. 6A

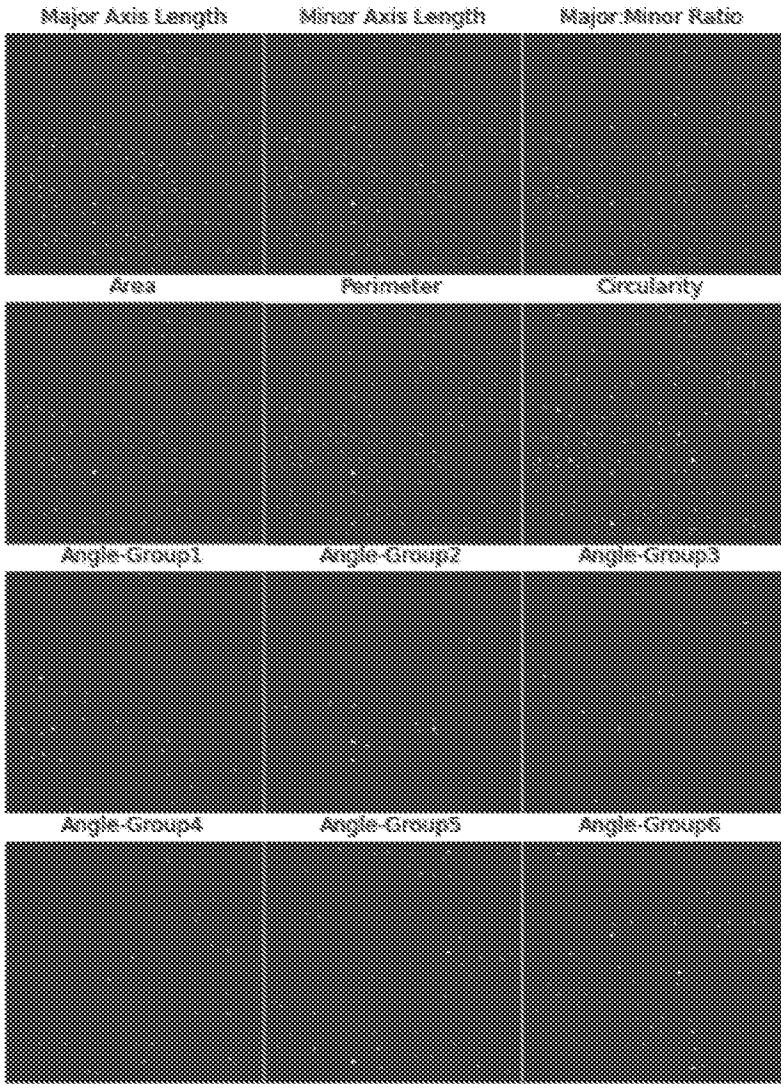

Major Axis Length
Minor Axis Length
Major:Minor Ratio
Area
Perimeter
Circularity
Angle-Group1
Angle-Group2
Angle-Group3
Angle-Group4
Angle-Group5
Angle-Group6

Fig. 6B

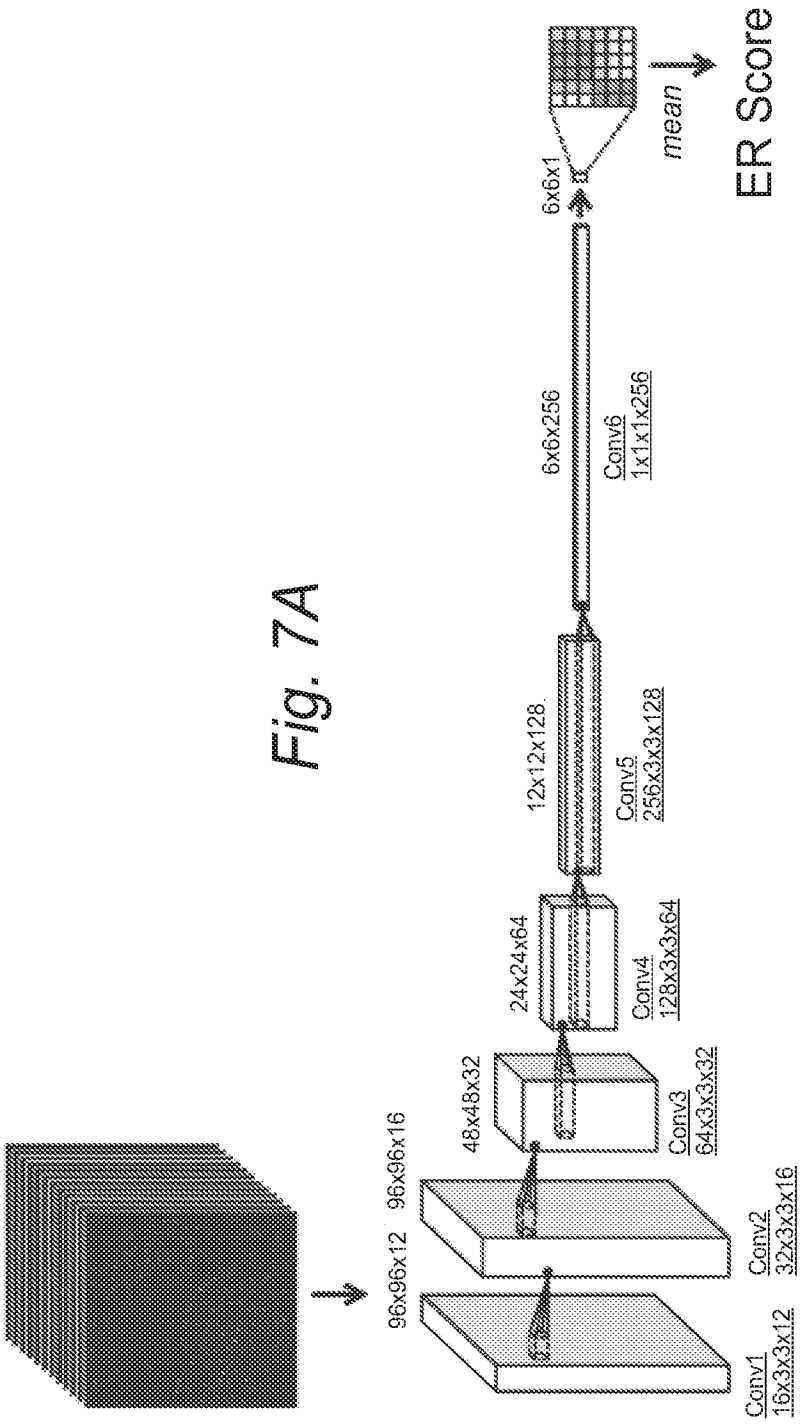

96x96x12
96x96x16
48x48x32
24x24x64
12x12x128
6x6x256
6x6x1
Conv1
16x3x3x12
Conv2
32x3x3x16
Conv3
64x3x3x32
Conv4
128x3x3x64
Conv5
256x3x3x128
Conv6
1x1x1x256
mean
ER Score

Fig. 7A

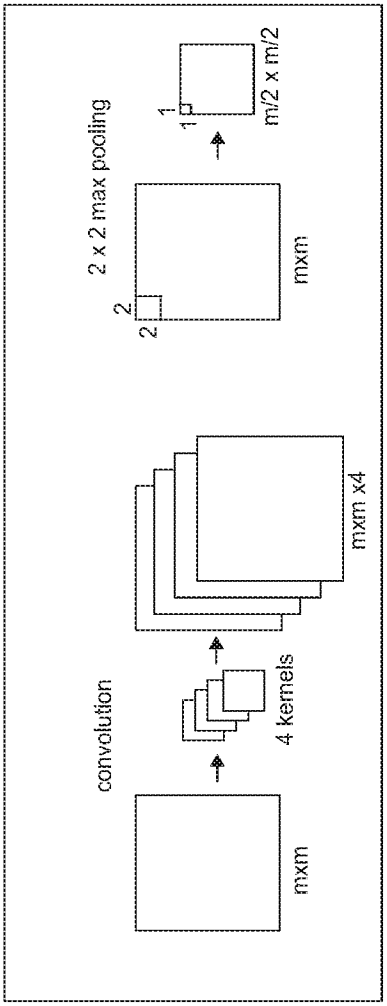

convolution
mxm
4 kernels
mxm x4
2 x 2 max pooling
2
2
mxm
1
1
m/2 x m/2

Fig. 7B

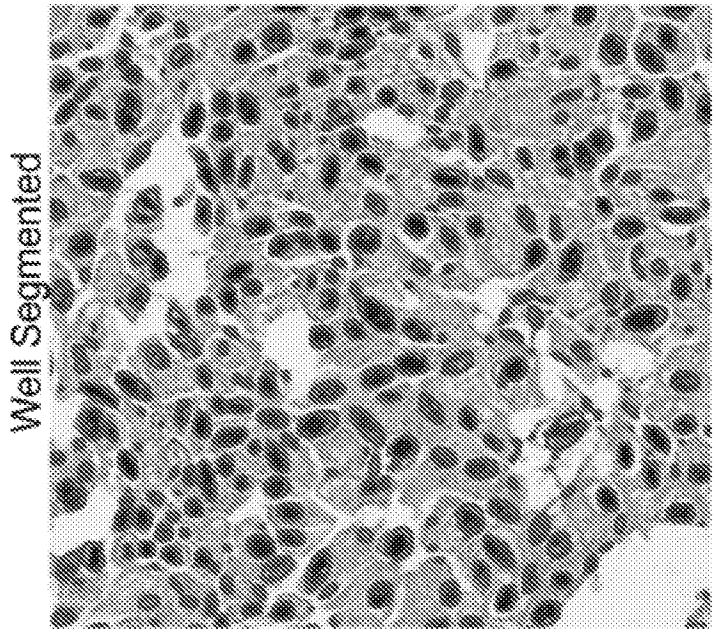


Fig. 8B

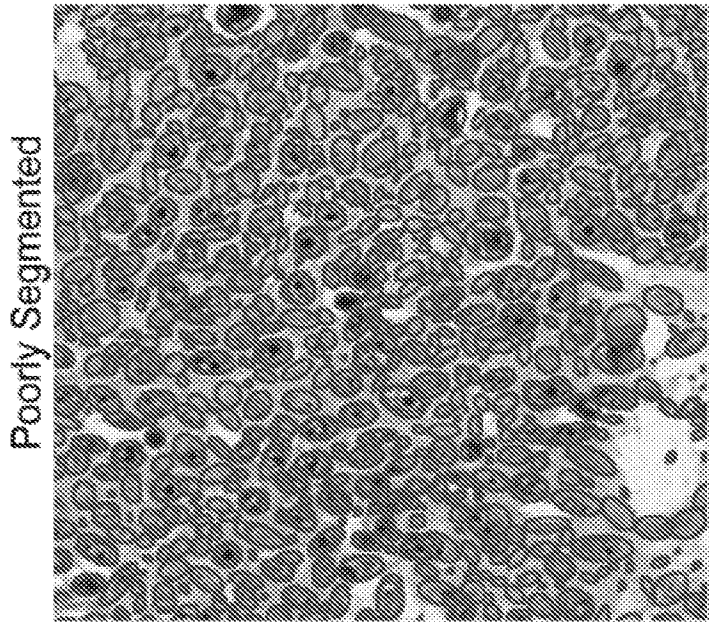


Fig. 8A

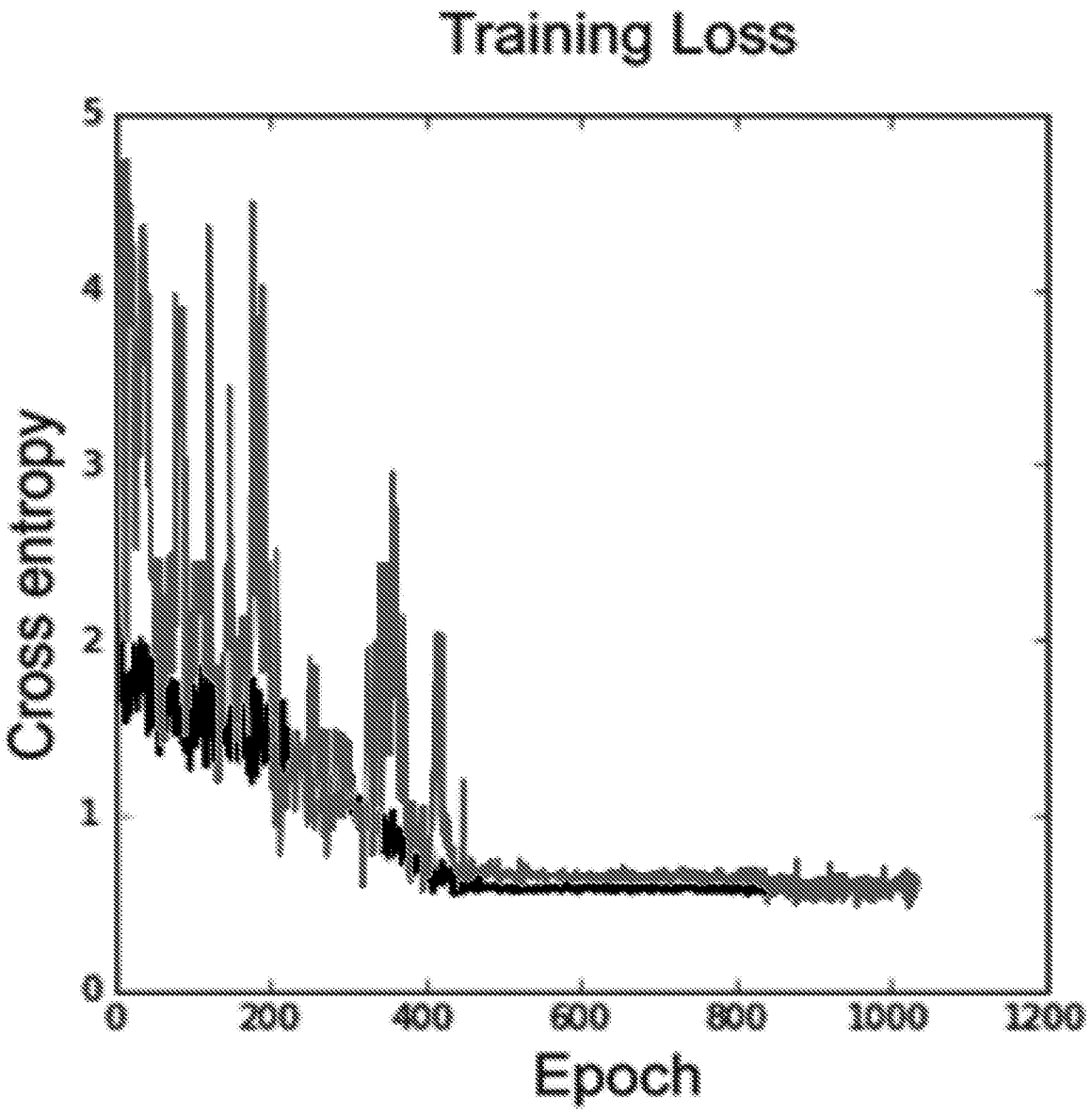

Training Loss
Cross entropy
0
1
2
3
4
5
0
200
400
600
800
1000
1200
Epoch

Fig. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/021060

A. CLASSIFICATION OF SUBJECT MATTER

G16H 50/20(2018.01)i, G16H 50/30(2018.01)i, G06T 7/00(2006.01)i, G01N 33/574(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G16H 50/20; G06F 19/00; G06N 99/00; G06K 9/00; G06K 9/62; G06T 7/00; G16H 50/30; G01N 33/574

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: machine learning, diagnosis, image, 2 dimensional, biomarker, CNN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014-0101080 A1 (SAMSUNG ELECTRONICS CO., LTD.) 10 April 2014 See paragraphs [0043]-[0048], [0062]-[0071]; claim 9; and figures 1-2, 3A.	1-8,10-30
A		9
Y	ANDREW JANOWCZYK et al. Deep learning for digital pathology image analysis: A comprehensive tutorial with selected use cases. 2016 Journal of Pathology Informatics, 26 July 2016, pages 1-18. See pages 1-8, 13-14; and figures 3-4, 6, 9.	1-8,10-30
Y	WO 2015-189264 A1 (VENTANA MEDICAL SYSTEMS, INC. et al.) 17 December 2015 See paragraphs [0020], [0029]; and figures 1-2.	12-21
A	WO 2005-001740 A2 (SIEMENS MEDICAL SOLUTIONS USA, INC.) 06 January 2005 See page 14, line 14 - page 21, line 13; and figure 2.	1-30
A	US 2016-0314580 A1 (H. LEE MOFFITT CANCER CENTER AND RESEARCH INSTITUTE, INC.) 27 October 2016 See paragraphs [0070]-[0081]; and figures 2-4. Note: since claim 29 are found twice, the claim 29, which is written later, is renumbered as claim 30 by this authority.	1-30

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2018 (28.06.2018)	**28 June 2018 (28.06.2018)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
LEE, Myung Jin
Telephone No. +82-42-481-8474

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2018/021060

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014-0101080 A1	10/04/2014	KR 10-2014-0042531 A	07/04/2014
		US 9514416 B2	06/12/2016
WO 2015-189264 A1	17/12/2015	EP 3155592 A1	19/04/2017
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WO 2005-001740 A2	06/01/2005	AU 2004-251359 A1	06/01/2005
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		AU 2004-316027 B2	30/07/2009
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		US 7640051 B2	29/12/2009
		US 7653227 B2	26/01/2010
		US 7693315 B2	06/04/2010
		US 7912528 B2	22/03/2011
		WO 2005-001740 A3	09/06/2005
		WO 2005-001769 A2	06/01/2005
		WO 2005-001769 A3	22/12/2005
		WO 2005-078631 A1	25/08/2005
		WO 2005-081168 A2	01/09/2005
		WO 2005-081168 A3	01/12/2005
US 2016-0314580 A1	27/10/2016	WO 2015-069827 A2	14/05/2015
		WO 2015-069827 A3	05/11/2015

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/732,242	12/31/2019	Stephen Yip	32830/58872A	7185

4743 7590 10/20/2020

MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

EXAMINER
VARNDELL, ROSS E

ART UNIT	PAPER NUMBER
2666	

NOTIFICATION DATE	DELIVERY MODE
10/20/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mgbdocket@marshallip.com

Applicant-Initiated Interview Summary	**Application No.** 16/732,242	**Applicant(s)** Yip et al.	
	Examiner Ross Varndell	**Art Unit** 2666	**AIA (FITF) Status** Yes

All participants (applicant, applicants representative, PTO personnel):

(1) Ross Varndell. (3) _____.

(2) Paul Stephens (Reg. No. 47,970). (4) _____.

Date of Interview: 14 October 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1.

Identification of prior art discussed: Tunstall.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Focusing on Fig. 5B, looking outside of a single tile for information about the tiles. Doing smaller tile analysis in parallel . - Not just classification but looking for tissue structural features in surrounding areas. Look for features within each tile to inform classification. Features in surrounding area inform classification. Specification [0058], [0117], [0171] has some information about these details. No agreement was reached. Differential between feature and a structural tissue feature..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Ross Varndell/ Primary Examiner, Art Unit 2666	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	9996664	B2	2018-06-12	LLOYD et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20110188728	A1	2011-08-04	SAMMAK et al.	
	2	20160217253	A1	2016-07-28	NEWMAN et al.	
	3	20190034591	A1	2019-01-31	MOSSIN et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

If you wish to add additional Foreign Patent Document citation information please click the Add button [Add]

NON-PATENT LITERATURE DOCUMENTS [Remove]

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	ANDERS et al., Differential expression analysis for sequence count data, Genome Biology, 11:R106 (2010).	
	2	BENSCH et al., 89Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer, Nat. Med., 24:1852-1858 (2018).	
	3	CHANG et al., Deep-learning convolutional neural networks accurately classify genetic mutations in gliomas, Am. J. Neuroradiology, (2018).	
	4	CHANG et al., Residual convolution neural network for determination of IDH status in low- and high-grade gliomas from MR imaging, Clin. Cancer Res., 24(5):1073-1081 (2018).	
	5	CHEN et al., Microscope 2.0: An augmented reality microscope with real-time artificial integration, Nat. Med., 25:1453-1457 (2019).	
	6	CHEN et al., Pathomic fusion: An integrated framework for fusing histopathology and genomic features for cancer diagnosis and prognosis, downloaded from the Internet at: <https://arxiv.org/pdf/1912.08937v1.pdf> (December 18, 2019).	
	7	Department of health and human services. Part I. overview information, Integration of imaging and fluid-based tumor monitoring in cancer therapy (R01 Clinical Trial Optional), (February 5, 2018).	
	8	DEY et al., Visualizing the structure of RNA-seq expression data using grade of membership models, PLoS Genetics, 13(5) (2017).	
	9	FDA Summary of safety and effectiveness data (SSED), PD-L1 IHC 22C3 pharmDx, Dako North America, Inc., (October 2, 2015).	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16732242
	Filing Date	2019-12-31
	First Named Inventor	Stephen Yip
	Art Unit	2666
	Examiner Name	VARNDELL, ROSS E
	Attorney Docket Number	32830/58872A

	10	FDA Summary of safety and effectiveness data (SSED), PD-L1 IHC 22C3 pharmDx, Dako North America, Inc., (September 22, 2017).	
	11	KEYTRUDA medication guide, page 46, from prescribing information guide, Merck & Co. Inc., revised (September 2017) (Reference ID: 4156447).	
	12	Letter from U.S. Department of Health & Human Services to Agfa Healthcare N.V., regarding Enterprise Imaging XERO Viewer 8.1, dated (July 3, 2017).	
	13	Letter from U.S. Department of Health & Human Services to Arterys, Inc. regarding Arterys Software v2.0, dated (October 28, 2016).	
	14	Letter from U.S. Department of Health & Human Services to Arterys, Inc. regarding Arterys Viewer, dated (July 18, 2017).	
	15	Letter from U.S. Department of Health & Human Services to Brainlab AG regarding DICOM Viewer, dated (April 13, 2016).	
	16	Letter from U.S. Department of Health & Human Services to Healthmyne Inc. regarding Healthmyne PACS, dated (August 20, 2015).	
	17	Letter from U.S. Department of Health & Human Services to Healthmyne Inc. regarding Healthmyne, dated (January 15, 2016).	
	18	Letter from U.S. Department of Health and Human Services to Philips Medical Systems Nederland B.V. regarding Philips Intellisite Pathology Solution (PIPS), dated (October 13, 2017).	
	19	Letter from U.S. Food & Drug Administration to Arterys, Inc. regarding Arterys Oncology DL, dated (January 25, 2018).	
	20	Letter from U.S. Food & Drug Administration to Dako North America, Inc. regarding PD-L1 IHC 22C3 pharmDx, dated (August 16, 2018).	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	VARNDELL, ROSS E
	Attorney Docket Number	32830/58872A

	21	Letter from U.S. Food & Drug Administration to Dako North America, Inc. regarding PD-L1 IHC 22C3 pharmDx, dated (June 12, 2018).	
	22	MYRONENKO, 3D MRI brain tumor segmentation using autoencoder regularization, downloaded from the Internet at: <https://arxiv.org/pdf/1810.11654.pdf> (published November 19, 2018).	
	23	NEWMAN et al., Determining cell type abundance and expression from bulk tissues with digital cytometry, Nat. Biotec., 37:773-782 (2019).	
	24	NEWMAN et al., Robust enumeration of cell subsets from tissue expression profiles, Nat. Methods, 12:453-457 (2015).	
	25	PD-L1 IHC 28-8 pharmDx Guide, 13 pp. Dako North America Inc. (October 2015 edition).	
	26	RAJPURKAR et al., Deep learning for chest radiograph diagnosis: A retrospective comparison of the CheXNeXt algorithm to practicing radiologists, PLOS Medicine, (2018).	
	27	Redox awarded patent for its electronic medical record integration technology, August 29, 2018.	
	28	SHAH et al., Deep learning assessment of tumor proliferation in breast cancer histological images, Int. Conf. Bioinform. Biomed., (2017).	
	29	Stanford ML Group, CheXNeXt: Deep learning for chest radiograph diagnosis, downloaded from the Internet at: <https://stanfordmlgroup.github.io/projects/chexnext/> (November 2018).	
	30	UZZAN et al., Microvessel density as a prognostic factor in women with breast cancer, Cancer Res., 64(9):2941-55 (2004).	
	31	YALA et al., A deep learning mammography-based model for improved breast cancer risk prediction, Radiology, 292(1):60-66 (2019).	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16732242
	Filing Date	2019-12-31
	First Named Inventor	Stephen Yip
	Art Unit	2666
	Examiner Name	VARNDELL, ROSS E
	Attorney Docket Number	32830/58872A

	32	YOUNG et al., Gene ontology analysis for RNA-seq: accounting for selection bias, Genome. Biol., 11:R14 (2010).
	33	ZHANG et al., Aspect-augmented adversarial network for domain adaptation, Transactions of the Association for Computational Linguistics, 5:515-528 (2017).

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	_/Paul B. Stephens/_	Date (YYYY-MM-DD)	2020-10-27
Name/Print	Paul B. Stephens	Registration Number	47,970

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16732242
Filing Date:	31-Dec-2019
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Filer:	Paul Bryan Stephens/Brian Roche
Attorney Docket Number:	32830/58872A

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**260**

Electronic Acknowledgement Receipt

EFS ID:	40955613
Application Number:	16732242
International Application Number:	
Confirmation Number:	7185
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Customer Number:	4743
Filer:	Paul Bryan Stephens/Audrey Nagelberg
Filer Authorized By:	Paul Bryan Stephens
Attorney Docket Number:	32830/58872A
Receipt Date:	27-OCT-2020
Filing Date:	31-DEC-2019
Time Stamp:	11:44:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$260
RAM confirmation Number	E20200QB45102749
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	10_FDASummary_DAKO_487706.pdf	424043 561475d9ec0c22f9ff20b2eed15c03bce6a5d68b	no	20
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Information:					
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Information:					
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Warnings:					
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35	Information Disclosure Statement (IDS) Form (SB08)	IDS_16732242_1.pdf	1071958 9f62096a3c3419b66fcbc6cd219875d4b70e65c9	no	7
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/732,242	Filing Date 12/31/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	11/24/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 18	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 4	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/ALLYSON PURNELL/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Docket No.: 32830/58872A
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Yip et al.

Application No.: 16/732,242 | Confirmation No.: 7185

Filed: December 31, 2019 | Art Unit: 2666

For: ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES | Examiner: R. E. Varndell

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated July 24, 2020, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

Electronic Patent Application Fee Transmittal

Application Number:	16732242
Filing Date:	31-Dec-2019
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Filer:	Paul Bryan Stephens/Jennie Mackowiak
Attorney Docket Number:	32830/58872A

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	220	220
Miscellaneous:				
			Total in USD ($)	**220**

Electronic Acknowledgement Receipt

EFS ID:	41219003
Application Number:	16732242
International Application Number:	
Confirmation Number:	7185
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Customer Number:	4743
Filer:	Paul Bryan Stephens/Jennie Mackowiak
Filer Authorized By:	Paul Bryan Stephens
Attorney Docket Number:	32830/58872A
Receipt Date:	24-NOV-2020
Filing Date:	31-DEC-2019
Time Stamp:	18:00:01
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$220
RAM confirmation Number	E2020ANI00233170
Deposit Account	
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	One_Month_Request_for_Extension_of_Time_Under_37_CFR_1136a.PDF	22697 eeee93f02bdf0d98717f8281c8da25fe92631074	no	1
Warnings:					
Information:					
2		AMD_in_response_to_NFOA.PDF	50415 31fa137b3d3d58f5d928ed750302d3606d19f9c7	yes	9

Multipart Description/PDF files in .zip description

Document Description	Start	End
Applicant Arguments/Remarks Made in an Amendment	5	9
Claims	2	4
Amendment/Req. Reconsideration-After Non-Final Reject	1	1

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30972 8d61483ac59fb20e8fd3593ba392d38f573bea54	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	104084		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/22 (10-20)
Approved for use through 11/30/2020. OMB 0651-0031
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 32830/58872A
Application Number 16/732,242-Conf. #7185	Filed December 31, 2019
For ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES	
Art Unit 2666	Examiner R. E. Varndell

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
[x] One month (37 CFR 1.17(a)(1))	$220	$110	$55	$ 220.00
[ ] Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$
[ ] Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$
[ ] Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$
[ ] Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$

[ ] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

[ ] A check in the amount of the fee is enclosed.

[x] Payment by credit card.

[ ] The Director has already been authorized to charge fees in this application to a Deposit Account.

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WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

[ ] applicant.

[x] attorney or agent of record. Registration number 47,970 .

[ ] attorney or agent acting under 37 CFR 1.34. Registration number _____ .

/Paul B. Stephens/	November 24, 2020
Signature	Date
Paul B. Stephens	(312) 474-6300
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

[ ] * Total of 1 forms are submitted.

REMARKS

Applicant has not dedicated or abandoned any unclaimed subject matter and has not acquiesced to any rejections made by the U.S. Patent and Trademark Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

This paper is filed in response to the Official Action dated June 24, 2020, in which claims 1-20 are pending and:

(i) claims 1, 2, 4, 6, and 8 stand rejected under 35 U.S.C. §§ 102(a)(1) and 102(a)(2) as anticipated by U.S. Publication No. 2016/0063724 ("*Tunstall et al.*"),

(ii) claims 3, 7, 11-14, and 16 stand rejected as obvious under 35 U.S.C. § 103 based on *Tunstall et al.*,

(iii) claim 5 stands rejected as obvious under 35 U.S.C. § 103 based on a suggested combination of *Tunstall et al.* in view of a "Recurrent Multiresolution Convolutional Networks for VHR Image Classification" ("*Bargado*"),

(iv) claims 9 and 10 stand rejected as obvious under 35 U.S.C. § 103 based on a suggested combination of *Tunstall et al.* in view of U.S. Publication No. 2014/0140607 ("*Erjefalt*"),

(v) claim 15 stands rejected as obvious under 35 U.S.C. § 103 based on a suggested combination of *Tunstall et al.* in view of U.S. Publication No. 2018/0137394 ("*Wenzel*"),

(vi) claims 17 and 18 stand rejected as obvious under 35 U.S.C. § 103 based on a suggested combination of *Tunstall et al.* in view of U.S. Publication No. 2007/0216909 ("*Everett*"), and

(vi) claims 19 and 20 stand rejected as obvious under 35 U.S.C. § 103 based on a suggested combination of *Tunstall et al.* in view of U.S. Publication No. 2020/0105417 ("*Dolan*").

Above, Applicant has amended claims 1 and 11 and canceled claims 4-10. Dependent claims 21-25 have been added. The amendments are supported by the application, as filed. For example, support can be found at paras. [0058] et seq., [0109] et seq., [0116]-[0117], and [0171] - [0173], as well as in the claims as originally filed. No new matter has been added.

Claims 1-3 and 11-25 are pending after amendment.

I. Telephonic Interview & Claim Amendments

Applicant's representatives appreciate Examiner Varndell's time in conducting the October 14, 2020 telephonic interview, in which claim 1 was discussed. As indicated in the October 20, 2020 Applicant-Initiated Interview Summary, Applicant's representatives discussed inventive features described in the application in various locations, including in reference to the example illustrated in FIG. 5B. In particular, it was discussed the ability to classify tissue in a tile by examining not only features within the tile, but also features outside that tile, such as structural tissue features that are typically larger than a tile itself. The ability to look for features within each tile and features in surrounding areas results in a more accurate classification of the tissue within each tile and therefore a more accurate digital overlay, none of which is taught by the primary reference *Tunstall et al*.

In line with the discussion, above Applicant has amended independent claim 1 to recite further features, in particular:

> separating the digital image into a plurality of tiles, each tile of the plurality of tiles containing a respective portion of the digital image of the slide;

and for each tile of the plurality of tiles,

> identifying features of the tile;
>
> identifying structural tissue features of a second portion of the digital image of the slide including at least part of one or more other tiles of the plurality of tiles, wherein the second portion is larger than the respective portion of the digital image contained in the tile; and
>
> identifying the majority class of tissue visible within the tile based at least in part on the features of the tile and the structural tissue features of the second portion of the digital image of the slide.

Support for these amendments is found within the application, as filed, and at least at paras. [0058] et seq., [0109] et seq., [0116]-[0117], and [0171] - [0173]. Applicant has amended independent claim 11 in a similar manner.

II. 35 U.S.C. §§ 102 & 103 Rejections

Claim 1 stands rejected as anticipated, under 35 U.S.C. § 102, by *Tunstall et al.* Applicant respectfully traverses, in light of the foregoing amendments.

In the Official Action, Figure 3, para. [0033], paras. [0036]-[0038], and para. [0042] of *Tunstall et al.* are cited as purportedly teaching "separating the digital image into a plurality of tiles" and "identifying the majority class of tissue visible within each tile." Official Action at page 3. These sections of *Tunstall et al.* simply describe partitioning an image into tiles, determining image components within the tile, and concatenating these components to provide a feature vector for the tile, from which a classification of the tile is performed (*see*, [0034]-[0042]). *Tunstall et al.* nowhere teaches or suggests "identifying features of the tile" and further:

> identifying structural tissue features of a second portion of the digital image of the slide including at least part of one or more other tiles of the plurality of tiles, wherein the second portion is larger than the respective portion of the digital image contained in the tile, and
>
> identifying the majority class of tissue visible within the tile based at least in part on the features of the tile and the structural tissue features of the second portion of the digital image of the slide,

as set forth in amended claim 1.

Tunstall et al. does not teach or suggest each and every element of amended claim 1. For this reason alone, the rejection of claim 1 as anticipated by *Tunstall et al.* is traversed, and claim 1 is in condition for allowance.

Moreover, looking at the remaining cited references, Applicant notes that none overcome the deficiencies of *Tunstall et al.*

Bergado is cited in this rejection for teaching a multiresolution convolutional network to perform classification on digital images. Official Action at page 7 (citing to *Bergado* at page 4 discussing FuseNet for classification and map regularization). As such,

Bergado does not cure the deficiencies of *Tunstall et al.* discussed above, namely the aforementioned features of claim 1.

Erjefalt is cited in this rejection for teaching the inclusion of lymphocyte cells and not lymphocyte cells. Official Action at page 10 (citing *Erjefalt* at para. [0190] describing a dropdown box for selecting between different alternatives such as B lymphocytes and group of a plurality of cell types). As such, *Erjefalt* does not cure the deficiencies of *Tunstall et al.*

Wenzel is cited in this rejection for teaching displaying a plurality of tiles and the predicted class for each tile that does not correspond to a cell object. Official Action at page 15. As such, *Wenzel* does not cure the deficiencies of *Tunstall et al.*

Everett is cited in this rejection for teaching a digital overlay drawing including a generated version of the digital image and selectively displaying one of a plurality of digital overlay drawings. Official Action at pages 17 & 18. As such, *Everett* does not cure the deficiencies of *Tunstall et al.*

Dolan is cited in this rejection for teaching the digital overlay drawing comprises percentages corresponding to the digital image. Official Action at page 19. As such, *Dolan* does not cure the deficiencies of *Tunstall et al.*

As neither *Tunstall et al.* nor any combination thereof with the art of record can be fairly described as teaching the recited subject matter, the rejection of claim 1 is traversed. Claim 1 and dependent claims 2, 3, 24, and 25 are in condition for immediate allowance.

Likewise, for at least the reasons detailed above, the rejection of amended independent claim 11 is traversed. Claim 11 is in condition for immediate allowance, as are claims 12-23 depending therefrom.

III. Conclusion

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections and objections. It

is believed that a full and complete response has been made to the outstanding Official Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested.

Dated: November 24, 2020

Respectfully submitted,

Electronic signature: _/Paul B. Stephens/_
Paul B. Stephens
Registration No.: 47,970
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive
6300 Willis Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A method for creating an overlay map on a digital image of a slide, the method comprising:

receiving the digital image;

separating the digital image into a plurality of tiles, each tile of the plurality of tiles containing a respective portion of the digital image of the slide; and

for each tile of the plurality of tiles:

identifying features of the tile;

identifying structural tissue features of a second portion of the digital image of the slide including at least part of one or more other tiles of the plurality of tiles, wherein the second portion is larger than the respective portion of the digital image contained in the tile; and

identifying the majority class of tissue visible within ~~each tile in the plurality of tiles, based on a multi-tile analysis~~ the tile based at least in part on the features of the tile and the structural tissue features of the second portion of the digital image of the slide.

2. (Original) The method of claim 1, further comprising:

generating a digital overlay drawing of an outer edge of each cell in the image.

3. (Original) The method of claim 2, wherein the digital overlay drawing is prepared at the resolution level of an individual pixel.

4. – 10. (Canceled)

11. (Currently amended) A method for tissue classification of a digital image of a slide, the method comprising:

receiving the digital image;

segmenting the digital image into a plurality of tiles, each tile of the plurality of tiles containing a respective portion of the digital image of the slide;

for each tile of the plurality of tiles:

identifying features of the tile;

identifying structural tissue features of a second portion of the digital image of the slide including at least part of one or more other tiles of the plurality of tiles,

wherein the second portion is larger than the respective portion of the digital image contained in the tile; and

determining a predicted class for each tile based at least in part on the features of the tile and the structural tissue features of the second portion of the digital image of the slide;

identifying a plurality of cell objects in the digital image;

determining a predicted class for each of the plurality of cell objects; and

for each of the plurality of tiles that corresponds to one of the plurality of cell objects, assigning the tile the predicted class of the corresponding cell object in place of the predicted class of the tile.

12. (Original) The method of claim 11, further comprising:

storing, in a first file, for each tile, a tile position and the predicted class of the tile; and

storing, in a second file, for each cell object, a polygon outlining the cell object and the predicted class of the cell object.

13. (Original) The method of claim 11, further comprising:

generating a digital overlay drawing for the digital image, where the digital overlay drawing is a cell mask displaying a polygon around each cell object.

14. (Original) The method of claim 11, further comprising:

generating a digital overlay drawing for the digital image, where the digital overlay drawing is a histology mask displaying the plurality of tiles and the predict class for each tile.

15. (Original) The method of claim 11, further comprising:

generating a digital overlay drawing for the digital image; and

displaying, in the digital overlay drawing, the plurality of tiles and the predicted class for each tile that does not correspond to a cell object, and displaying, the plurality of cell objects and the predicted class of each cell object.

16. (Original) The method of claim 11, further comprising:

generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes the digital image; and

displaying the digital overlay drawing.

17. (Original) The method of claim 11, further comprising:

generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes a generated version of the digital image; and

displaying the digital overlay drawing.

18. (Original) The method of claim 11, further comprising:

generating a plurality of digital overlay drawings for the digital image, where each digital overlay drawing corresponds to a different predicted class; and

selectively displaying one of the plurality of digital overlay drawings.

19. (Original) The method of claim 11, further comprising:

generating a digital overlay drawing for the digital image, where the digital overlay drawing comprises percentages of predict classes corresponding to the digital image.

20. (Original) The method of claim 11, further comprising:

generating a digital overlay drawing for the digital image, where the digital overlay drawing comprises total counts of predict classes corresponding to the digital image.

21. (New) The method of claim 11, wherein the cell objects comprise CD3, CD8, CD20, pancytokeratin, and smooth muscle actin.

22. (New) The method of claim 11, wherein the cell objects include lymphocyte cells and not lymphocyte cells.

23. (New) The method of claim 11, wherein the structural tissue features comprises at least one of glands, ducts, vessels, and immune clusters.

24. (New) The method of claim 1, wherein the majority class of tissue is selected from the group consisting of epithelium, normal epithelium, immune, stroma, necrosis, blood, and fat.

25. (New) The method of claim 1, wherein the structural tissue features comprises at least one of glands, ducts, vessels, and immune clusters.

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NOTICE OF ALLOWANCE AND FEE(S) DUE

4743 7590 12/11/2020

MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

EXAMINER	
VARNDELL, ROSS E	
ART UNIT	PAPER NUMBER
2666	

DATE MAILED: 12/11/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/732,242	12/31/2019	Stephen Yip	32830/58872A	7185

TITLE OF INVENTION: ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	03/11/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

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For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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By fax, send to: (571)-273-2885

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/732,242	12/31/2019	Stephen Yip	32830/58872A	7185

TITLE OF INVENTION: ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	03/11/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
VARNDELL, ROSS E	2666	382-100000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

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❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
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NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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Typed or printed name _____ Registration No. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/732,242	12/31/2019	Stephen Yip	32830/58872A	7185

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EXAMINER	
VARNDELL, ROSS E	
ART UNIT	PAPER NUMBER
2666	

DATE MAILED: 12/11/2020

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/732,242	Applicant(s) Yip et al.	
	Examiner Ross Varndell	Art Unit 2666	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 11/24/2020.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-3 and 11-25 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Ross Varndell/
Primary Examiner, Art Unit 2666

Allowable Subject Matter

1. Claims 1-3 and 11-25 are allowed.

2. The following is an examiner's statement of reasons for allowance: The present invention comprises a generalizable and interpretable deep learning model for predicting biomarker status and biomarker metrics from histopathology slide images. The closest prior art, Tunstall et al. (US 2016/0063724 A1 hereinafter "Tunstall" referred to as "Pathxl" on the written opinion for PCT/US2019/069164 filed on 9/4/2020) shows a similar system which also includes an image of a section of a tissue sample imaged from a microscope slide stained using Haemotoxylin and Eosin, using a learning method with classification data, obtaining a probability estimate based on comparing the feature vectors of tiles in tissue regions of the image, and displaying the resulting probability estimate as a color map. However, Tunstall fails to disclose "each tile of the plurality of tiles containing a respective portion of the digital image of the slide; and for each tile of the plurality of tiles: identifying features of the tile; identifying structural tissue features of a second portion of the digital image of the slide including at least part of one or more other tiles of the plurality of tiles, wherein the second portion is larger than the respective portion of the digital image contained in the tile; and identifying the majority class of tissue visible within the tile based at least in part on the features of the tile and the structural tissue features of the second portion of the digital image of the slide," as claimed. These distinct features have been added to the independent claims 1 and 11; therefore, rendering them allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the

issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ross Varndell whose telephone number is (571)270-1922. The examiner can normally be reached on M-F, 9-5 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kim Vu can be reached on (571)272-3859. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ross Varndell/
Primary Examiner, Art Unit 2666

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/732,242	Yip et al.
	Examiner	Art Unit
	Ross Varndell	2666

CPC - Searched*		
Symbol	Date	Examiner
G06T7/0012, G06T2207/30096, G06T2207/20084, G06K9/00147, G06K9/00523, G06K9/00536, G06N20/00	07/20/2020	RV

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Performed double patenting, inventor, and prior art searches.	07/20/2020	RV
Updated searches.	12/05/2020	RV
Performed ip.com search with NPL.	12/05/2020	RV

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
G06T	7/0012, 2207/30096, 2207/20084	07/20/2020	RV
G06K	9/00147, 9/00523, 9/00536	07/20/2020	RV
G06N	20/00	07/20/2020	RV

/RV/ Primary Examiner, Art Unit 2666	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/732,242	Yip et al.
	Examiner	**Art Unit**
	Ross Varndell	2666

CPC						
Symbol					**Type**	**Version**
G06T	/	7	/	0012	F	2013-01-01
G06T	/	7	/	11	I	2017-01-01
G06T	/	2207	/	30096	A	2013-01-01
G06T	/	2207	/	30024	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	18	
/Ross Varndell/ Primary Examiner, Art Unit 2666	05 December 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	5B

U.S. Patent and Trademark Office — Part of Paper No.: 20201205

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/732,242	Yip et al.
	Examiner	**Art Unit**
	Ross Varndell	2666

INTERNATIONAL CLASSIFICATION				
CLAIMED				
G06T7/00	/	7	/	00
G06T7/11	/	7	/	11

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	18	
/Ross Varndell/ Primary Examiner, Art Unit 2666	05 December 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	5B

U.S. Patent and Trademark Office

Part of Paper No.: 20201205

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/732,242	Yip et al.
	Examiner	**Art Unit**
	Ross Varndell	2666

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1		10	14	19										
2	2	6	11	15	20										
3	3	7	12	16	21										
	4	8	13	17	22										
	5	9	14	18	23										
	6	10	15	4	24										
	7	11	16	5	25										
	8	12	17												
	9	13	18												

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	18	
/Ross Varndell/ Primary Examiner, Art Unit 2666	05 December 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	5B

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	0	"16830186"	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 08:53
S2	215	((("YIP") near3 ("Stephen")) OR (("HO") near3 ("Irvin")) OR (("SHA") near3 ("Lingdao")) OR (("OSINSKI") near3 ("Boleslaw")) OR (("KHAN") near3 ("Aly")) OR (("KRUGER") near3 ("Andrew")) OR (("CARLSON") near3 ("Michael")) OR (("GREENWALD") near3 ("Abel")) OR (("WILLIS") near3 ("Caleb"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	AND	OFF	2020/07/07 08:54
S3	1	"20160063724".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 10:28
S4	410,720	(hematoxylin near4 eosin) or h?e	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:51
S5	23,422	tile$2 near4 image$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:51
S6	26,378	(deep$4 near4 learn$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:51
S7	1,971	biomarker$4 near4 classifi$6	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:52
S8	452,847	overlay$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:52

S9	0	S4 S5 S6 S7 S8	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:52
S10	83,955	biomarker$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:53
S11	8	S4 S5 S6 S10 S8	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:53
S12	49,001	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/07 13:57
S25	1,305,469	deep$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/08 09:13
S26	1	"20160063724".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/08 09:13
S27	0	S26 deep$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/08 09:13
S28	1	S26 learning$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/08 09:13
S29	20	("20030215936" | "20060064248" | "20070216909" | "20100111396" | "20140073922" | "20140140607" | "20140337052" | "20150100246" | "20160063724" | "20160103973" | "20160253466" | "20170076046" | "20170337682" |	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:16

		"20180005136" | "20180089373" | "20180121759" | "20180129911" | "20180137394" | "20190169685" | "6463438").PN.				
S30	1	"20200184643".did.	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:46
S31	26,373	deep$4 near4 learn$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:46
S32	1,612	biomarker$4 near4 classif$6	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:46
S33	38	S31 S32	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:46
S34	0	S29 S31 S32	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:47
S35	0	S30 S31 S32	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:47
S36	13	("20200184643" "10646156" "20190244348" "20190180153" "20190244347" "20190159737" "20190180438" "20190172197" "20190156159" "10426442" "20200005901" "20190087532" "10395366").did.	US-PGPUB; USPAT	OR	OFF	2020/07/08 09:49
S37	33,654	biomarker$4 classif$6	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:49
S38	596	S31 S37	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:49
S39	1	S29 S31 S37	US-PGPUB; USPAT	AND	OFF	2020/07/08 09:49
S40	1	(US-20180089373-$).did.	US-PGPUB	AND	OFF	2020/07/08 10:27

S41	0	S40 multiscal$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:27
S42	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/08 10:30
S43	0	S42 multiscal$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:30
S44	0	S36 multiscal$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:30
S45	1	S29 multiscal$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:30
S46	12	(multiscal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:31
S47	1	(S40 or S42) (til$4 same mask$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:33
S48	1	(S40 or S42) (til$4 same siz$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:36
S49	0	(S40 or S42) (til$4 same rectangl$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:38
S50	0	(S40 or S42) (til$4 same squar$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:38
S51	0	(S40 or S42) fcn	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:40
S52	0	(S40 or S42) convoluat$4	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:40
S53	0	(S40 or S42) (UNet or U near2 net)	US-PGPUB; USPAT	AND	ON	2020/07/08 10:41
S54	1	(S40 or S42) (PD-L1)	US-PGPUB; USPAT	AND	ON	2020/07/08 10:42
S55	0	(S40 or S42) (tils)	US-PGPUB; USPAT	AND	ON	2020/07/08 10:43
S56	0	(S40 or S42) (nc near4 ratio$4)	US-PGPUB; USPAT	AND	ON	2020/07/08 10:43
S57	0	(S40 or S42) (ploidy$4)	US-PGPUB; USPAT	AND	ON	2020/07/08 10:43
S58	0	(multiscal$4 with (deep near4 learn$4)) (single near2 scal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:44

S59	0	(multiscal$4 with (deep near4 learn$4)) (singl$4 near4 scal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 10:45
S60	0	(multiscal$4 with (deep near4 learn$4)) (single with scal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:22
S61	1,534	(scal$4 with (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:29
S62	408	(scal$4 near4 (deep near4 learn$4))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:29
S63	20	("20030215936" | "20060064248" | "20070216909" | "20100111396" | "20140073922" | "20140140607" | "20140337052" | "20150100246" | "20160063724" | "20160103973" | "20160253466" | "20170076046" | "20170337682" | "20180005136" | "20180089373" | "20180121759" | "20180129911" | "20180137394" | "20190169685" | "6463438").PN.	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:49
S64	13	("20200184643" "10646156" "20190244348" "20190180153" "20190244347" "20190159737" "20190180438" "20190172197" "20190156159" "10426442" "20200005901" "20190087532" "10395366").did.	US-PGPUB; USPAT	OR	OFF	2020/07/08 13:49

S65	2	(S64 or S63) S62	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:49
S66	1	(US-20180089373-$).did.	US-PGPUB	AND	OFF	2020/07/08 13:51
S67	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/08 13:51
S68	0	(S66 or S67) ResNet$4	US-PGPUB; USPAT	AND	ON	2020/07/08 13:51
S69	0	(S66 or S67) (convolution$4 near4 neural near4 network$4)	US-PGPUB; USPAT	AND	ON	2020/07/08 13:52
S70	0	(S66 or S67) (Inception-v3$4)	US-PGPUB; USPAT	AND	ON	2020/07/08 13:52
S71	1,129	ResNet$4 or (Inception-v3$4)	US-PGPUB; USPAT	AND	ON	2020/07/08 13:53
S72	8	(S64 or S63) S71	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:53
S73	1	(S64 or S63) ((consensus$4 near4 molecular$4 near4 subtype) or (CMS) or (homologous$4 near4 recombination$4 near4 deficienc$4) or (HRD))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:55
S74	0	(S66 or S67) ((consensus$4 near4 molecular$4 near4 subtype) or (CMS) or (homologous$4 near4 recombination$4 near4 deficienc$4) or (HRD))	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:56
S75	1	(S66 or S67) (gpu or tpu or cpu)	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:57
S76	0	(S66 or S67) (scanner$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:58
S77	2	(S66 or S67) (scan$4)	US-PGPUB; USPAT	AND	OFF	2020/07/08 13:58
S78	1	(US-20180089373-$).did.	US-PGPUB	AND	OFF	2020/07/09 08:30
S79	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/09 08:30

S80	2	(S78 or S79) (network$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:30
S81	0	(S78 or S79) (pathology$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:32
S82	2	(S78 or S79) (disease$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:32
S83	0	(S78 or S79) (adversar$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:38
S84	20	("20030215936" | "20060064248" | "20070216909" | "20100111396" | "20140073922" | "20140140607" | "20140337052" | "20150100246" | "20160063724" | "20160103973" | "20160253466" | "20170076046" | "20170337682" | "20180005136" | "20180089373" | "20180121759" | "20180129911" | "20180137394" | "20190169685" | "6463438").PN.	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:39
S85	13	("20200184643" "10646156" "20190244348" "20190180153" "20190244347" "20190159737" "20190180438" "20190172197" "20190156159" "10426442" "20200005901" "20190087532" "10395366").did.	US-PGPUB; USPAT	OR	OFF	2020/07/09 08:39
S86	33	(S85 or S84)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:39

S87	4	(S85 or S84) adversar$4	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:39
S88	0	(S78 or S79) (overlay$4 same tumor$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:45
S89	0	(S78 or S79) (overlay$4 same2 tumor$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:45
S90	0	(S78 or S79) (overlay$4 same4 tumor$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:45
S91	0	(S78 or S79) (overlay$4 tumor$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:45
S92	2	(S85 or S84) adversar$4 resnet	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:48
S93	2	adversar$4 resnet (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:49
S94	1	"20190392580".did.	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:54
S95	0	S94 GAN resnet (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:54
S96	0	S94 resnet (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:54
S97	0	S94 (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:54
S98	1	S94 biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:54
S99	0	S94 (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:55
S100	1	S94 adversar$4 biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:55
S101	1	"10699163".did.	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:56
S102	0	S101 adversar$4 biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:56
S103	0	S101 (u near2 net) biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57

S104	0	S101 biomarker (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S105	0	S101 biomarker$4 (deep near4 learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S106	1	S101 biomarker$4	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S107	1	S101 (u near2 net) biomarker	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S108	1	S101 (u near2 net) resnet biomarker	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:57
S109	1	S101 (u near2 net) resnet biomarker gan	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:58
S110	1	S101 (u near2 net) resnet biomarker gan deep	US-PGPUB; USPAT	AND	OFF	2020/07/09 08:58
S111	0	S101 (u near2 net) resnet biomarker gan deep (multi$4 near4 scal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:00
S112	0	S101 (u near2 net) resnet biomarker gan deep (multiscal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:01
S113	0	S101 ((multi$4 near4 scal$4) or multiscal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:01
S114	7	"15360742"	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:03
S115	3	S114 ((multi$4 near4 scal$4) or multiscal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:04
S116	1	S101 (u near2 net) resnet biomarker gan deep (scal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:09
S117	1	(S78 or S79) (scal$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:13
S118	6	(US-20160063724-$ or US-20180089373-$ or US-20140337052-$ or US-20190392580-$).did. or (US-10426442-$ or US-10699163-$).did.	US-PGPUB; USPAT	AND	OFF	2020/07/09 09:16

S119	2	S118 tile$2	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/09 09:16
S120	1	(US-20180089373-$).did.	US-PGPUB	AND	OFF	2020/07/09 12:20
S121	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/09 12:20
S122	2	(S120 or S121) (train$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 12:20
S123	1	(S120 or S121) (cluster$4)	US-PGPUB; USPAT	AND	OFF	2020/07/09 12:25
S124	6	(US-20160063724-$ or US-20180089373-$ or US-20140337052-$ or US-20190392580-$).did. or (US-10426442-$ or US-10699163-$).did.	US-PGPUB; USPAT	AND	OFF	2020/07/09 12:27
S125	0	S124 cms hrd	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/09 12:27
S126	1	S124 (cms or hrd)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/09 12:27
S127	1	"20170270666".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:15
S128	0	S127 muliscale	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:15
S129	0	S127 muliscal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:15
S130	0	S127 mulipl$4 scal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:15
S131	1	S127 scal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:15

S132	1	"20140185891".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:16
S133	1	S132 scal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:16
S134	7	("20140185891" "9159129" "20170076442" "9741112" "20100061605" "8139833" "10474874").did.	US-PGPUB; USPAT; USOCR	OR	OFF	2020/07/10 13:18
S136	6	S134 (different$4 or multipl$4) same scal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:18
S137	6	S134 ((different$4 or multipl$4) same scal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:20
S138	19	("20140185891" "9159129" "20170076442" "9741112" "10474874" "20180053033" "9805248" "20160098589" "20160063308" "9740957" "10445557" "20170337415" "20170358079" "10339653" "20160203599" "9721340" "10262189" "9740912" "20100111396").did.	US-PGPUB; USPAT; USOCR	OR	OFF	2020/07/10 13:27
S139	8	S138 ((different$4 or multipl$4) same scal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:27
S140	12	S138 (scal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:29
S141	13	("20160098589" "10474874" "9805248" "20100111396" "8488863" "20190073510" "10614285" "20180053033" "10664722" "9740957" "20160063308" "10445557" "20170270666").did.	US-PGPUB; USPAT; USOCR	OR	OFF	2020/07/10 13:33

S142	4	S141 (multiscal$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:33
S143	49,189	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:34
S144	879	S143 (multiscal$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:34
S145	15	S143 (multiscal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:35
S146	1	(US-20190043242-$).did.	US-PGPUB	AND	OFF	2020/07/10 13:53
S148	1	S146 nnf	US-PGPUB	AND	OFF	2020/07/10 13:54
S149	1	S146 cnn	US-PGPUB	AND	OFF	2020/07/10 13:55
S150	1	S146 cnn deep	US-PGPUB	AND	OFF	2020/07/10 13:55
S151	1	S146 (multiscal$4) ((rectang$4 or squar$4) same til$2)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 13:56
S152	1	(US-10699163-$).did.	USPAT	AND	OFF	2020/07/10 14:16
S153	1	S152 scal$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 14:16
S154	1	(US-20180089373-$).did.	US-PGPUB	AND	OFF	2020/07/10 14:24
S155	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/10 14:24
S156	2	(S154 or S155) (learn$4)	US-PGPUB; USPAT	AND	OFF	2020/07/10 14:24

S157	2	(S154 or S155) (class$4)	US-PGPUB; USPAT	AND	OFF	2020/07/10 14:26
S158	0	(S154 or S155) (class$4) discard$4	US-PGPUB; USPAT	AND	OFF	2020/07/10 14:26
S159	1	(S154 or S155) (class$4) delet$4	US-PGPUB; USPAT	AND	OFF	2020/07/10 14:26
S160	1	S152 resnet$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/10 14:29
S161	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/11 16:02
S165	1	S161 tumour$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/11 16:04
S166	0	S161 tumour$4 same4 overlay	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/11 16:05
S167	1	S161 tumour$4 same4 overla$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/11 16:05
S168	2	"16732242"	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/12 23:20
S169	1	(US-20200211189-$).did.	US-PGPUB	AND	OFF	2020/07/12 23:21
S170	1	S169 classif$6 near4 map$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/12 23:21
S171	1	"20140140607".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/14 14:59
S172	1	"20180137394".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/14 15:19
S173	1	"20070216909".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/15 11:48

S174	1	"20070216909".did.	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:37
S175	1	S174 overlay	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:37
S176	1	S174 overlay ((en near2 fac$4) or enfac$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:39
S177	1	S174 overlay ((en near2 fac$4) or enfac$4) oct	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:41
S178	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/16 07:53
S179	0	S174 overlay ((en near2 fac$4) or enfac$4) oct (irl same rpe)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:56
S180	1	S174 overlay ((en near2 fac$4) or enfac$4) oct (ilm same rpe)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 07:56
S181	1	S178 (tumour$4)	US-PGPUB	AND	OFF	2020/07/16 08:55
S182	1	"20140073922".did.	US-PGPUB	AND	OFF	2020/07/16 09:02
S183	1	"20140073922".did.	US-PGPUB	AND	OFF	2020/07/16 12:47
S184	1	S183 percent$4	US-PGPUB	AND	OFF	2020/07/16 12:47
S185	0	S183 lv	US-PGPUB	AND	OFF	2020/07/16 12:48
S186	1	S183 likelihood$4	US-PGPUB	AND	OFF	2020/07/16 12:48
S187	161	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC. (overlay$4 same percentage$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 12:52

S188	74	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC. (overlay$4 with percentage$4)	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/16 12:53
S190	1	(US-20200105417-$).did.	US-PGPUB	AND	OFF	2020/07/20 09:25
S191	1	S190 overla$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/20 09:25
S192	474,337	tile	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/20 09:54
S193	1	(US-20160063724-$).did.	US-PGPUB	AND	OFF	2020/07/20 09:54
S194	1	S193 tile$2	US-PGPUB; USPAT; USOCR	AND	OFF	2020/07/20 09:54
S195	4	("20110188728" | "20160217253" | "20190034591" | "9996664").PN.	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:14
S196	3	("20180239949" | "20180340870" | "20190087532").PN.	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:15
S197	3	(S195 or S196) tile$2	US-PGPUB; USPAT; USOCR	AND	OFF	2020/12/05 17:15
S198	8,904	(structur$4 with tissu$4 with featur$4)	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:26
S199	2,268,476	second near4 portion$4	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:28
S200	119,989	(second near4 portion$4) with larg$4	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:28
S201	147	S198 S200	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:29

S202	24,290	tile$2 near4 image$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/12/05 17:29
S203	0	S198 S200 S202	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:29
S204	33,865	tile$2 with image$4	US-PGPUB; USPAT; USOCR	AND	OFF	2020/12/05 17:32
S205	0	S198 S200 S204	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:32

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S13	16,074	((hematoxylin near4 eosin) or h?e).clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55
S14	3,652	(tile$2 near4 image$4).clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55
S16	2,860	(deep$4 near4 learn$4).clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55
S17	72,913	overlay$4.clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55
S18	0	S13 S14 S16 S17	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:55
S19	48,980	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC.	US-PGPUB; USPAT	AND	OFF	2020/07/07 13:57
S21	292	S13 S17	US-PGPUB; USPAT	AND	OFF	2020/07/07 14:01

S22	1	S13 S14 S17	US-PGPUB; USPAT	AND	OFF	2020/07/07 14:01
S23	305	((hematoxylin near4 eosin)).clm.	US-PGPUB; USPAT	AND	OFF	2020/07/07 14:01
S24	11	S23 S17	US-PGPUB; USPAT	AND	OFF	2020/07/07 14:02
S189	161	(G06T7/0012 OR G06T2207/30096 OR G06T2207/20084 OR G06K9/00147 OR G06K9/00523 OR G06K9/00536 OR G06N20/00).CPC. (overlay$4 same percentage$4)	US-PGPUB; USPAT	AND	OFF	2020/07/16 12:52
S206	16,537	((hematoxylin near4 eosin) or h?e).clm.	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:30
S207	3,786	(tile$2 near4 image$4).clm.	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:30
S208	75,213	overlay$4.clm.	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:30
S209	2	S206 S207 S208	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:30
S210	8,904	(structur$4 with tissu$4 with featur$4)	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:31
S211	346	(structur$4 with tissu$4 with featur$4).clm.	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:31
S212	43,396	((second near4 portion$4) with larg$4).clm.	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:31
S213	4,853	(tile$2 with image$4).clm.	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:32

S214	0	S211 S212 "17"	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:32
S215	0	S211 S212 S213	US-PGPUB; USPAT	AND	OFF	2020/12/05 17:33

12/5/2020 5:33:25 PM
C:\Users\rvarndell\Documents\EAST\Workspaces\16732242-2.wsp

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

U.S.PATENTS

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /RV/

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Attorney Docket Number	32830/58872A

/RV/	1	PELLEGRINO et al., "Controversies in oncology: are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making?," ESMO Open 4(2) (2018)	☐
/RV/	2	ULYANOV et al., Instance normalization: the missing ingredient for fast stylization, arXiv:1607.08022, 1-6 (2017).	☐

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EXAMINER SIGNATURE

Examiner Signature	/Ross Varndell/	Date Considered	12/05/2020

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
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Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/RV/	1	20180239949	A1	2018-08-23	CHANDER et al.	
/RV/	2	20180340870	A1	2018-11-29	GUSTAFSON et al.	
	3	20190087532	A1	2019-03-21	MADABHUSHI et al.	

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/RV/	1	2018/165103	WO	A1	2018-09-13	UNIV SOUTHERN CALIFORNIA		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/RV/	1	International Application No. PCT/US2020/024748, International Search Report and Written Opinion, mailed August 03, 2020.	☐
/RV/	2	International Application No. PCT/US2020/024748, Invitation to Pay Additional Fees, mailed June 10, 2020.	☐

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Examiner Signature	/Ross Varndell/	Date Considered	12/05/2020

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Main Concept Document
==========
US20200211189
Title: ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES

Concept Modifiers (1)
==========
1. More Like Text: identifying structural tissue features of a second portion of the digital image of the slide including at least part of one or more other tiles of the plurality of tiles, wherein the second portion is larger than the respective portion of the digital image contained in the tile

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Options
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De-dup: None
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PTO/SB/08a (02-18)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/RV/	1	9996664	B2	2018-06-12	LLOYD et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/RV/	1	20110188728	A1	2011-08-04	SAMMAK et al.	
/RV/	2	20160217253	A1	2016-07-28	NEWMAN et al.	
/RV/	3	20190034591	A1	2019-01-31	MOSSIN et al.	

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	1							

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Attorney Docket Number	32830/58872A

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/RV/	1	ANDERS et al., Differential expression analysis for sequence count data, Genome Biology, 11:R106 (2010).	
/RV/	2	BENSCH et al., 89Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer, Nat. Med., 24:1852-1858 (2018).	
/RV/	3	CHANG et al., Deep-learning convolutional neural networks accurately classify genetic mutations in gliomas, Am. J. Neuroradiology, (2018).	
/RV/	4	CHANG et al., Residual convolution neural network for determination of IDH status in low- and high-grade gliomas from MR imaging, Clin. Cancer Res., 24(5):1073-1081 (2018).	
/RV/	5	CHEN et al., Microscope 2.0: An augmented reality microscope with real-time artificial integration, Nat. Med., 25:1453-1457 (2019).	
/RV/	6	CHEN et al., Pathomic fusion: An integrated framework for fusing histopathology and genomic features for cancer diagnosis and prognosis, downloaded from the Internet at: <https://arxiv.org/pdf/1912.08937v1.pdf> (December 18, 2019).	
/RV/	7	Department of health and human services. Part I. overview information, Integration of imaging and fluid-based tumor monitoring in cancer therapy (R01 Clinical Trial Optional), (February 5, 2018).	
/RV/	8	DEY et al., Visualizing the structure of RNA-seq expression data using grade of membership models, PLoS Genetics, 13(5) (2017).	
/RV/	9	FDA Summary of safety and effectiveness data (SSED), PD-L1 IHC 22C3 pharmDx, Dako North America, Inc., (October 2, 2015).	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16732242
	Filing Date	2019-12-31
	First Named Inventor	Stephen Yip
	Art Unit	2666
	Examiner Name	VARNDELL, ROSS E
	Attorney Docket Number	32830/58872A

/RV/	10	FDA Summary of safety and effectiveness data (SSED), PD-L1 IHC 22C3 pharmDx, Dako North America, Inc., (September 22, 2017).	
/RV/	11	KEYTRUDA medication guide, page 46, from prescribing information guide, Merck & Co. Inc., revised (September 2017) (Reference ID: 4156447).	
/RV/	12	Letter from U.S. Department of Health & Human Services to Agfa Healthcare N.V., regarding Enterprise Imaging XERO Viewer 8.1, dated (July 3, 2017).	
/RV/	13	Letter from U.S. Department of Health & Human Services to Arterys, Inc. regarding Arterys Software v2.0, dated (October 28, 2016).	
/RV/	14	Letter from U.S. Department of Health & Human Services to Arterys, Inc. regarding Arterys Viewer, dated (July 18, 2017).	
/RV/	15	Letter from U.S. Department of Health & Human Services to Brainlab AG regarding DICOM Viewer, dated (April 13, 2016).	
/RV/	16	Letter from U.S. Department of Health & Human Services to Healthmyne Inc. regarding Healthmyne PACS, dated (August 20, 2015).	
/RV/	17	Letter from U.S. Department of Health & Human Services to Healthmyne Inc. regarding Healthmyne, dated (January 15, 2016).	
/RV/	18	Letter from U.S. Department of Health and Human Services to Philips Medical Systems Nederland B.V. regarding Philips Intellisite Pathology Solution (PIPS), dated (October 13, 2017).	
/RV/	19	Letter from U.S. Food & Drug Administration to Arterys, Inc. regarding Arterys Oncology DL, dated (January 25, 2018).	
/RV/	20	Letter from U.S. Food & Drug Administration to Dako North America, Inc. regarding PD-L1 IHC 22C3 pharmDx, dated (August 16, 2018).	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Application Number	16732242
Filing Date	2019-12-31
First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

/RV/	21	Letter from U.S. Food & Drug Administration to Dako North America, Inc. regarding PD-L1 IHC 22C3 pharmDx, dated (June 12, 2018).	
/RV/	22	MYRONENKO, 3D MRI brain tumor segmentation using autoencoder regularization, downloaded from the Internet at: <https://arxiv.org/pdf/1810.11654.pdf> (published November 19, 2018).	
/RV/	23	NEWMAN et al., Determining cell type abundance and expression from bulk tissues with digital cytometry, Nat. Biotec., 37:773-782 (2019).	
/RV/	24	NEWMAN et al., Robust enumeration of cell subsets from tissue expression profiles, Nat. Methods, 12:453-457 (2015).	
/RV/	25	PD-L1 IHC 28-8 pharmDx Guide, 13 pp. Dako North America Inc. (October 2015 edition).	
/RV/	26	RAJPURKAR et al., Deep learning for chest radiograph diagnosis: A retrospective comparison of the CheXNeXt algorithm to practicing radiologists, PLOS Medicine, (2018).	
/RV/	27	Redox awarded patent for its electronic medical record integration technology, August 29, 2018.	
/RV/	28	SHAH et al., Deep learning assessment of tumor proliferation in breast cancer histological images, Int. Conf. Bioinform. Biomed., (2017).	
/RV/	29	Stanford ML Group, CheXNeXt: Deep learning for chest radiograph diagnosis, downloaded from the Internet at: <https://stanfordmlgroup.github.io/projects/chexnext/> (November 2018).	
/RV/	30	UZZAN et al., Microvessel density as a prognostic factor in women with breast cancer, Cancer Res., 64(9):2941-55 (2004).	
/RV/	31	YALA et al., A deep learning mammography-based model for improved breast cancer risk prediction, Radiology, 292(1):60-66 (2019).	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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First Named Inventor	Stephen Yip
Art Unit	2666
Examiner Name	VARNDELL, ROSS E
Attorney Docket Number	32830/58872A

/RV/	32	YOUNG et al., Gene ontology analysis for RNA-seq: accounting for selection bias, Genome. Biol., 11:R14 (2010).
/RV/	33	ZHANG et al., Aspect-augmented adversarial network for domain adaptation, Transactions of the Association for Computational Linguistics, 5:515-528 (2017).

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EXAMINER SIGNATURE

Examiner Signature	/Ross Varndell/	Date Considered	12/05/2020

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/732,242	12/31/2019	Stephen Yip	32830-58872A	7185

4743 7590 01/28/2021

MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

EXAMINER	
VARNDELL, ROSS E	

ART UNIT	PAPER NUMBER
2666	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

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Application No. : 16732242
Applicant : Yip
Filing Date : 12/31/2019
Date Mailed : 01/28/2021

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

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/Marsha Palmer-Lee/
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Application No. 16732242 **Drawings filed: 12/31/2019**

IDENTIFICATION OF DRAWING DEFICIENCIES

- [ ] There is a hole or the image thereof within the illustration. FIG(s)
- [ ] The illustration is penetrated or traversed by a solid or broken line that is not intended to be part of the drawing, such as a dark line caused by a flaw in the copying process. FIG(s)
- [ ] An ink stamp or the image thereof obscures part of the illustration. FIG(s)
- [ ] The drawing is marred by black smudges, obliterations, or fax/copier marks (for example, speckles or dots in a substantial portion of the drawing). FIG(s)
- [ ] Figure numbers are duplicated or missing. FIG(s)
- [ ] Drawing sheet or figure is missing. FIG(s)
- [ ] Numbers, letters, or reference characters in the drawing have been crossed out or are illegibly handwritten. FIG(s)
- [ ] The character of the lines, numbers, and letters is poor. FIG(s)
- [ ] The drawing's background shows that the original drawing was made on graph paper or other paper with a pattern or decoration. FIG(s)
- [ ] The FIG. number label is placed in a location that causes the drawing to be read upside down. FIG(s)
- [X] Data, a reference number, or part of the drawing is truncated or missing, or a lead line has no reference number. FIG(s) 5a
- [ ] The drawing and/or the FIG. label contain(s) foreign language. FIG(s)
- [ ] This utility application contains a photograph of a view that is capable of being illustrated as a line drawing. FIG(s)
- [ ] A petition under 37 CFR 1.84(a)(2) to accept color drawings has been granted, but the brief description of the drawings in the specification does not contain (or has not been amended to contain) the paragraph required by 37 CFR 1.84(a)(2)(iii).
- [ ] This reissue application contains added and/or amended drawings that are not labeled as “New” or “Amended” or “Canceled” as required by 37 CFR 1.173(b)(3). FIG(s)
- [ ] This Design reissue application contains a drawing that is labeled as “Canceled” but is not surrounded by brackets, or a drawing that is surrounded by brackets but is not labeled as “Canceled.” See 37 CFR 1.173(b)(3). FIG(s)
- [ ] OTHER:
- [ ] COMMENTS:

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Docket No.: 32830/58872A
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Stephen Yip et al.	Allowed: December 11, 2020
Application No.: 16/732,242	Confirmation No.: 7185
Filed: December 31, 2019	Art Unit: 2666
For: ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES	Examiner: R. E. Varndell

AMENDMENT AFTER ALLOWANCE & RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

MS Issue Fee
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P.O. Box 1450
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Dear Sir:

INTRODUCTORY COMMENTS

Prior to issuance of the patent, applicant respectfully requests entry of this amendment under 37 C.F.R. 1.312 for the above-captioned patent application.

Amendments to the Drawings begin on page 2 of this paper and include an attached replacement sheet .

Remarks begin on page 3 of this paper.

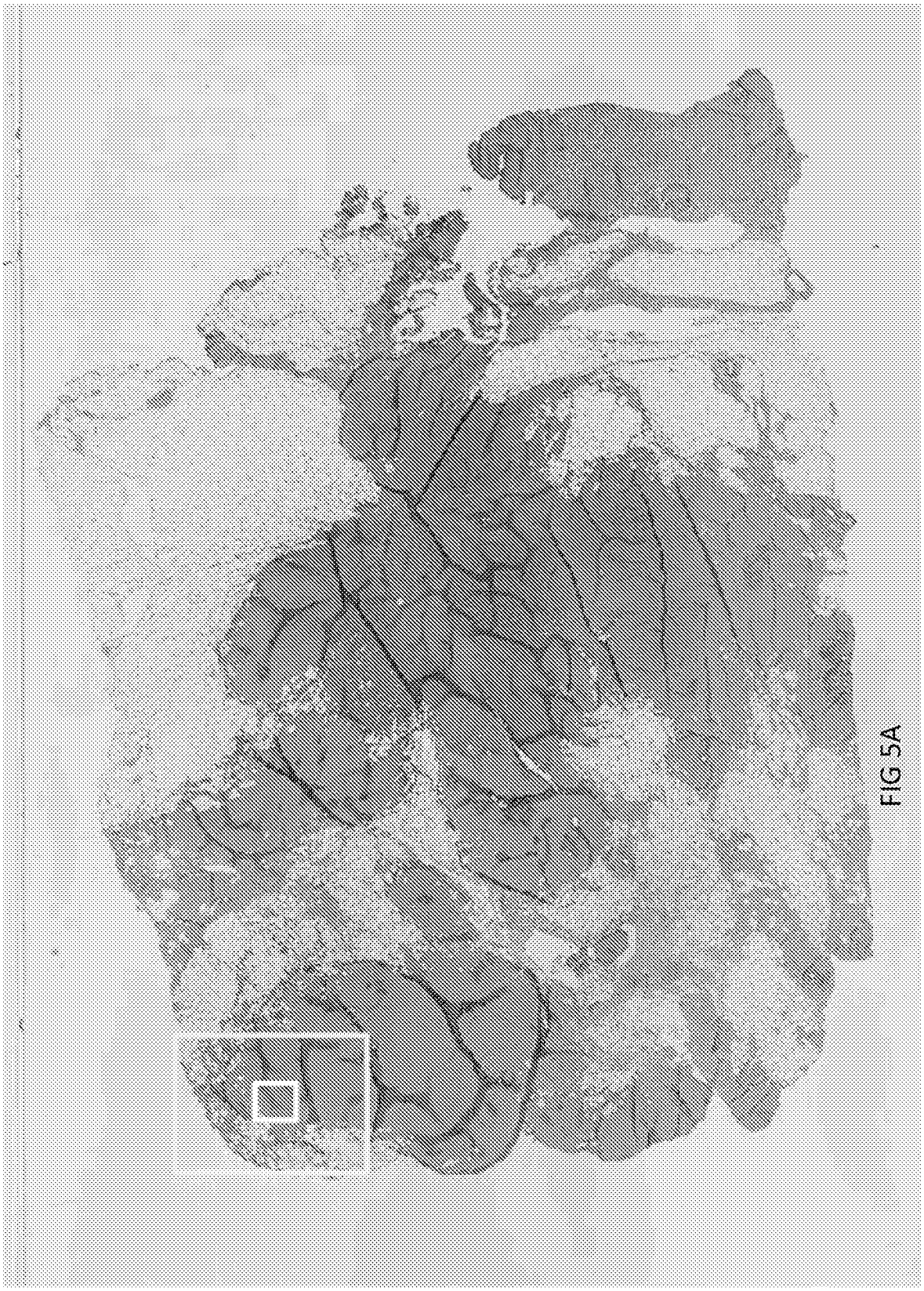


FIG 5A

Electronic Acknowledgement Receipt

EFS ID:	42012144
Application Number:	16732242
International Application Number:	
Confirmation Number:	7185
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Customer Number:	4743
Filer:	Paul Bryan Stephens/Jennie Mackowiak
Filer Authorized By:	Paul Bryan Stephens
Attorney Docket Number:	32830/58872A
Receipt Date:	24-FEB-2021
Filing Date:	31-DEC-2019
Time Stamp:	15:52:41
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		AMD_After_Allow__Response_to_Notice.PDF	17914 4be1a61aaf787a1dbbc1c0af169d372bb76ef3c7	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	3	3
	Drawings-other than black and white line drawings	2	2
	Amendment after Notice of Allowance (Rule 312)	1	1

Warnings:					
Information:					
2	Drawings-other than black and white line drawings	32830-58872A_Replacement_Fig_5A.PDF	2585934 9bc4fe31b8fe74a3ab3e170f4f4d8d578b513e0a	no	1
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Information:					
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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AMENDMENTS TO THE DRAWINGS

The attached drawing sheet includes a change to Figure 5A

Attachment: Replacement sheet

REMARKS

In response to the Notice to File Corrected Application Papers mailed January 28, 2021, Applicants have amended Figure 5A to remove the lead line missing a reference number. The amendment to Figure 5A includes no new matter.

Dated: February 24, 2021

Respectfully submitted,

Electronic signature: _/Paul B. Stephens/_
Paul B. Stephens
Registration No.: 47,970
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive
6300 Willis Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant

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Alexandria, VA 22313-1450

By fax, send to: (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

04743
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive
6300 Willis Tower
Chicago, Illinois 60606-6357

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)

(Signature)

(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
16/732,242	12/31/2019	Stephen Yip	32830/58872A	7185

TITLE OF INVENTION: ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1,200.00			$1,200.00	03/11/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
R. E. Varndell	2666	

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. MARSHALL, GERSTEIN & BORUN LLP
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: TEMPUS LABS, INC.

(B) RESIDENCE: (CITY and STATE or COUNTRY): Chicago, Illinois

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 13-2855

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature: _/Paul B. Stephens/_ Date: March 11, 2021

Typed or printed name: Paul B. Stephens Registration No. 47,970

Electronic Patent Application Fee Transmittal

Application Number:	16732242
Filing Date:	31-Dec-2019
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Filer:	Paul Bryan Stephens/Jennie Mackowiak
Attorney Docket Number:	32830/58872A

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1200**

Electronic Acknowledgement Receipt

EFS ID:	42158607
Application Number:	16732242
International Application Number:	
Confirmation Number:	7185
Title of Invention:	ARTIFICIAL INTELLIGENCE SEGMENTATION OF TISSUE IMAGES
First Named Inventor/Applicant Name:	Stephen Yip
Customer Number:	4743
Filer:	Paul Bryan Stephens/Jennie Mackowiak
Filer Authorized By:	Paul Bryan Stephens
Attorney Docket Number:	32830/58872A
Receipt Date:	11-MAR-2021
Filing Date:	31-DEC-2019
Time Stamp:	17:05:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1200
RAM confirmation Number	E20213AH06190037
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Fee_Transmittal_--_Part_B_PTOL-85.PDF	36276 4ad2ba3adb479a565a15aaf99a18ad4353cdb39d	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30601 39e220345b9451205c65b682e143e2959acf0ea8	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	66877		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/732,242	04/27/2021	10991097	32830/58872A	7185

4743 7590 04/07/2021

MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Stephen Yip, Chicago, IL;
TEMPUS LABS, INC., Chicago, IL;
Irvin Ho, Wilmette, IL;
Lingdao Sha, Chicago, IL;
Boleslaw Osinski, Chicago, IL;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

DocCode - PATENT.GRANT

SCORE Placeholder Sheet for IFW Content

Application Number: 16732242 Document Date: 04/27/2021

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Patent Grant with Color/Grayscale Drawings

At the time of document entry (noted above):

- USPTO employees may access SCORE content via DAV or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: March 1, 2019

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

Assignment ID: PATI16028

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	CHANGE OF NAME

CONVEYING PARTY DATA

Name	Execution Date
TEMPUS LABS, INC.	12/07/2023

RECEIVING PARTY DATA

Company Name:	TEMPUS AI, INC.
Street Address:	600 West Chicago Ave
Internal Address:	Suite 510
City:	Chicago
State/Country:	ILLINOIS
Postal Code:	60654

PROPERTY NUMBERS Total: 52

Property Type	Number
Application Number:	18123959
Application Number:	17829228
Application Number:	18433240
Application Number:	17902558
Application Number:	18091320
Application Number:	63426009
Application Number:	18511998
Application Number:	63460791
Application Number:	63599508
Application Number:	63537458
Application Number:	63599471
Application Number:	17515052
Application Number:	16581706
Application Number:	16533676
Application Number:	16653868
Application Number:	16732229
Application Number:	16888357
Application Number:	17816345
Application Number:	17968509

Property Type	Number
Application Number:	17247510
Application Number:	17243397
Application Number:	17738935
Application Number:	18210449
Application Number:	17684191
Application Number:	17686131
Application Number:	17816395
Application Number:	17207582
Application Number:	16889779
Application Number:	18222324
Application Number:	17837025
Application Number:	18132109
Patent Number:	11741365
Patent Number:	11189029
Patent Number:	11081210
Patent Number:	11475978
Patent Number:	11367004
Patent Number:	10957041
Patent Number:	11610307
Patent Number:	11682098
Patent Number:	11727674
Patent Number:	11348661
Patent Number:	11348239
Patent Number:	11348240
Patent Number:	11263748
Patent Number:	10957433
Patent Number:	11742064
Patent Number:	11373739
Patent Number:	10395772
Patent Number:	10902952
Patent Number:	11532397
Patent Number:	11651442
Patent Number:	10991097

CORRESPONDENCE DATA

Fax Number: 3124740448

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Phone: (312)474-6300

Email:	docket@marshallip.com,gorozco@marshallip.com
Correspondent Name:	Marshall Gerstein & Borun LLP
Address Line 1:	233 SOUTH WACKER DRIVE
Address Line 2:	6300 WILLIS TOWER
Address Line 4:	Chicago, ILLINOIS 60606-6357

NAME OF SUBMITTER:	Gabriela Orozco
SIGNATURE:	Gabriela Orozco
DATE SIGNED:	02/09/2024
	This document serves as an Oath/Declaration (37 CFR 1.63).

Total Attachments: 3

source=TEMPUS LABS, INC. - DE - Department of State_ Division Of Corporations - Restated Certificate Filing - Electronic#page1.tif

source=TEMPUS LABS, INC. - DE - Department of State_ Division Of Corporations - Restated Certificate Filing - Electronic#page2.tif

source=TEMPUS LABS, INC. - DE - Department of State_ Division Of Corporations - Restated Certificate Filing - Electronic#page3.tif

Delaware

The First State

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "TEMPUS LABS, INC.", CHANGING ITS NAME FROM "TEMPUS LABS, INC." TO "TEMPUS AI, INC.", FILED IN THIS OFFICE ON THE SEVENTH DAY OF DECEMBER, A.D. 2023, AT 12:40 O`CLOCK P.M.

Jeffrey W. Bullock, Secretary of State

5810758 8100
SR# 20234161120

Authentication: 204756807
Date: 12-07-23

You may verify this certificate online at corp.delaware.gov/authver.shtml

CERTIFICATE OF AMENDMENT TO ELEVENTH AMENDED AND RESTATED CERTIFICATE OF INCORPORATION OF TEMPUS LABS, INC.

Tempus Labs, Inc., a corporation organized and existing under and by virtue of the provisions of the General Corporation Law of the State of Delaware (the "***General Corporation Law***"), does hereby certify:

ARTICLE I

The name of the corporation is Tempus Labs, Inc. (the "***Corporation***").

ARTICLE II

The Corporation was originally incorporated pursuant to the General Corporation Law on September 21, 2015, under the name Bioin, Inc.

ARTICLE III

Pursuant to Sections 141 and 242 of the General Corporation Law, this Certificate of Amendment to the Eleventh Amended and Restated Certificate of Incorporation (the "***Certificate of Amendment***") amends the Corporation's Eleventh Amended and Restated Certificate of Incorporation (the "***Certificate of Incorporation***") as follows:

Article FIRST of the Certificate of Incorporation is hereby amended and restated in its entirety to read as follows:

"**FIRST:** The name of this corporation is Tempus AI, Inc. (the "***Corporation***")."

ARTICLE IV

This Certificate of Amendment has been duly adopted in accordance with Sections 141 and 242 of the General Corporation Law.

ARTICLE V

All other provisions of the Certificate of Incorporation, as currently on file with the Secretary of State of the State of Delaware, shall remain in full force and effect.

[Remainder of Page Intentionally Left Blank]

State of Delaware
Secretary of State
Division of Corporations
Delivered 12:40 PM 12/07/2023
FILED 12:40 PM 12/07/2023
SR 20234161120 - File Number 5810758

IN WITNESS WHEREOF, the undersigned authorized officer of the Corporation has caused this Certificate of Amendment to be signed on December 4, 2023.

By: /s/ Ryan Fukushima
RYAN FUKUSHIMA
Chief Operating Officer