PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
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Bert VOGELSTEIN et al.	)	Examiner: WOOLWINE, Samuel C.
	)	
Serial No. 13/071,105	)	
	)	Group Art Unit: 1637
	)	
Filed: March 24, 2011	)	Confirmation No. 3361
	)	
For: **DIGITAL AMPLIFICATION**	)	Atty. Dkt. No. 001107.00866

RESPONSE TO OFFICE ACTION

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the office action mailed June 27, 2013, applicants request entry of the amendment and reconsideration of the patentability of the claims in view of the remarks.

A request for consideration under the AFCPP 2.0 accompanies this paper. No petition for extension of time accompanies this submission. The Commissioner is authorized to charge any fees which may be required or credit any overpayment to our Deposit Account 19-0733.

IN THE CLAIMS

Please replace the following claim set for that currently of record.

1. -48. (Cancelled)

49. (Currently amended) A method for detecting quantity of a genetic sequence in a mixed population of human genomic nucleic acid sequences comprising at least a first and a second human genomic sequence, wherein the first sequence is a wild-type sequence of an allele and a second sequence is a mutant sequence of the allele, comprising:

distributing or diluting a mixed population of cell-free, human genomic nucleic acid template molecules from a sample in which the fraction of mutant alleles is less than 20 %, into a set comprising at least ~~ten~~ fifteen assay samples such that said at least ~~ten~~ fifteen assay samples each comprises less than ten template molecules;

amplifying the template molecules in the assay samples, wherein an assay sample with a single template molecule forms homogeneous amplification products in the assay sample;

analyzing by determining nucleic acid sequence of amplification products in the assay samples of the set with homogeneous amplification products to determine a first number of assay samples in the set which contain the first sequence and a second number of assay samples in the set which contain the second sequence;

comparing the first number to the second number to ascertain a ratio which reflects the composition of the mixed population;

identifying a mutation in the mixed population if a statistically significant fraction of assay samples comprises the second sequence.

50. (Previously Presented) The method of claim 49 wherein the assay samples of the set have on average 0.5 molecules of template.

51. (Previously Presented) The method of claim 49 wherein between 0.1 and 0.9 of the assay samples yield an amplification product.

52. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acid sequences is distributed or diluted to a single template molecule level in the assay samples.

53. (Currently amended) The method of claim 49 wherein the mixed population of nucleic acid sequences is from a ~~tissue or~~ body sample.

54. (Currently amended) The method of claim ~~49~~ 53 wherein the mixed population of nucleic acids sequences is from a body sample selected from the group consisting of stool, blood, and lymph nodes.

55. (Cancelled)

56. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least twenty assay samples comprise less than ten template molecules.

57. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least twenty-five assay samples comprise less than ten template molecules.

58. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least thirty assay samples comprise less than ten template molecules.

59. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least forty assay samples comprise less than ten template molecules.

60. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least fifty assay samples comprise less than ten template molecules.

61. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least seventy-five assay samples comprise less than ten template molecules.

62. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least one hundred assay samples comprise less than ten template molecules.

63. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least five hundred assay samples comprise less than ten template molecules.

64. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least one thousand assay samples comprise less than ten template molecules.

65. (Currently amended) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least one thousand assay samples are distributed or diluted to a single template molecule level.

66. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that at least one thousand assay samples has on average 0.5 molecules of template.

67. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that between 0.1 and 0.9 of at least one thousand assay samples yield an amplification product.

68. (Previously Presented) The method of claim 49 wherein the mixed population of nucleic acids sequences is distributed or diluted such that one half of at least one thousand assay samples have one template molecule.

69. (New) The method of claim 49 wherein the mutation is a somatic mutation.

70. (New) The method of claim 49 wherein the mutation is a cancer gene mutation.

71. (New) The method of claim 49 wherein the template molecules are from a population of cells which are not purely tumor cells.

72. (New) The method of claim 49 wherein between 1% and 10 % of the alleles in said human genomic nucleic acid template molecules are the mutant sequence of the allele.

73. (New) The method of claim 49 wherein the mixed population of nucleic acid sequences is from a tissue.

74. (New) A method for detecting quantity of a genetic sequence in a mixed population of human genomic nucleic acid sequences comprising at least a first and a second human genomic sequence, wherein the first sequence is a wild-type sequence of an allele and a second sequence is a mutant sequence of the allele, comprising:

distributing or diluting a mixed population of cell-free, human genomic nucleic acid template molecules into a set comprising at least fifteen assay samples such that said at least fifteen assay samples comprises an average of 0.5 molecules of template.;

amplifying the template molecules in the assay samples, wherein an assay sample with a single template molecule forms homogeneous amplification products in the assay sample;

analyzing by determining nucleic acid sequence of amplification products in the assay samples of the set with homogeneous amplification products to determine a first number of assay samples in the set which contain the first sequence and a second number of assay samples in the set which contain the second sequence;

comparing the first number to the second number to ascertain a ratio which reflects the composition of the mixed population;

identifying a mutation in the mixed population if a statistically significant fraction of assay samples comprises the second sequence.

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