PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 6,440,706	)	Docket No. 001107.00989
	)	
Control No. 90/012,894	)	Confirmation No: 8442
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

RESPONSIVE AMENDMENT TO FINAL OFFICE ACTION

U.S. Patent and Trademark Office
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

This paper is in response to the final Office Action mailed May 9, 2014.

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 9 of this paper.

IN THE CLAIMS

Please amend the following claims as indicated by the status identifier. Patent claims under reexamination but not amended are indicated as "original." Patent claims not subject to reexamination are not shown.

1. (Amended) A method for determining the ratio of a selected genetic sequence in a population of genetic sequences, comprising the steps of:

diluting isolated nucleic acid template molecules [in] isolated from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain the selected genetic sequence and a second number of assay samples which contain a reference genetic sequence;

comparing the first number to the second number to ascertain a ratio which reflects the composition of the biological sample.

2. (Original) The method of claim 1 wherein the step of diluting is performed until at least one-tenth of the assay samples in the set comprise a number (N) of molecules such that 1/N is larger than the ratio of selected genetic sequences to total genetic sequences required for the step of analyzing to determine the presence of the selected genetic sequence.

3. (Amended) The method of claim 1 wherein the step of diluting is performed until between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the selected and reference genetic sequences when subjected to a polymerase chain reaction.

4. (Original) The method of claim 1 wherein the step of diluting is performed until all of the assay samples yield an amplification product when subjected to a polymerase chain reaction and each assay sample contains less than 10 nucleic acid template molecules containing the reference genetic sequence.

5. (Original) The method of claim 1 wherein the step of diluting is performed until all of the assay samples yield an amplification product when subjected to a polymerase chain reaction and each assay sample contains less than 100 nucleic acid template molecules containing the reference genetic sequence.

6. (Original) The method of claim 1 wherein the biological sample is cell-free.

7. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 10.

8. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 50.

9. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 100.

10. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 500.

11. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 1000.

12. (Original) The method of claim 1 wherein the step of amplifying and the step of analyzing are performed on assay samples in the same receptacle.

13. (Not subject to reexamination)

14. (Original) The method of claim 1 wherein the step of analyzing employs gel electrophoresis.

15. (Original) The method of claim 1 wherein the step of analyzing employs hybridization to at least one nucleic acid probe.

16. (Original) The method of claim 1 wherein the step of analyzing employs hybridization to at least two nucleic acid probe.

17-18. (Not subject to reexamination)

19. (Original) The method of claim 1 wherein the step of amplifying employs a single pair of primers.

20. (Original) The method of claim 1 wherein the step of amplifying employs a polymerase which is activated only after heating.

21. (Original) The method of claim 1 wherein the step of amplifying employs at least 40 cycles of heating and cooling.

22. (Original) The method of claim 1 wherein the step of amplifying employs at least 50 cycles of heating and cooling.

23. (Original) The method of claim 1 wherein the step of amplifying employs at least 60 cycles of heating and cooling.

24. (Original) The method of claim 1 wherein the biological sample is selected from the group consisting of stool, blood, and lymph nodes.

25. (Original) The method of claim 1 wherein the biological sample is blood or bone marrow of a leukemia or lymphoma patient who has received anti-cancer therapy.

26. (Original) The method of claim 1 wherein the selected genetic sequence is a

translocated allele.

27. (Original) The method of claim 1 wherein the selected genetic sequence is a wild-type allele.

28. (Original) The method of claim 1 wherein the selected genetic sequence is within an amplicon which is amplified during neoplastic development.

29. (Original) The method of claim 1 wherein the selected genetic sequence is a rare exon sequence.

30. (Original) The method of claim 1 wherein the nucleic acid template molecules comprise cDNA of RNA transcripts and the selected genetic sequence is present on a cDNA of a first transcript and the reference genetic sequence is present on a cDNA of a second transcript.

31. (Original) The method of claim 1 wherein the selected genetic sequence comprises a first mutation and the reference genetic sequence comprises a second mutation.

32. (Original) The method of claim 1 wherein the selected genetic sequence and the reference genetic sequence are on distinct chromosomes.

33-37. (Not subject to reexamination)

38. (Twice amended) A method for determining the ratio of a selected genetic sequence in a population of genetic sequences, comprising the steps of:

distributing cell-free nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the nucleic acid template molecules [within a set comprising a plurality of assay samples] to form a population of amplified molecules in [each of the] individual assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first

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