

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Title: SYSTEM AND METHOD FOR CLEANING
NOISY GENETIC DATA AND DETERMINING
CHROMOSOME COPY NUMBER
Appl. No.: 17/164,599
Filing Date: 02/01/2021
Examiner: MUMMERT, STEPHANIE KANE
Art Unit: 1637
Confirmation Number: 5317

AMENDMENT AND REPLY UNDER 37 CFR 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This communication is responsive to the non-final Office Action mailed September 21, 2021, concerning the above-referenced patent application.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document.

Remarks begin on page 4 of this document.

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently Amended) A method for preparing a deoxyribonucleic acid (DNA) fraction from a biological sample useful for analyzing genotypes for DNA from cancer cells, the method comprising:
 - (a) extracting cell-free DNA from the biological sample;
 - (b) producing a fraction of the DNA extracted in (a) by amplifying a plurality of target loci from the DNA to obtain amplification products, wherein the amplification comprises targeted amplification to amplify the target loci, wherein the target loci comprise SNP loci;
 - (c) analyzing the fraction of the DNA produced in (b) by
 - (i) sequencing the amplification products by sequencing-by-synthesis to obtain genetic data for the plurality of target loci; and
 - (ii) determining the most likely genotypes for DNA from cancer cells based on allele frequencies at the plurality of target loci in the genetic data.
2. (Original) The method of claim 1, wherein the biological sample is a blood sample.
3. (Cancelled)
4. (Original) The method of claim 1, wherein the amplification further comprises universal amplification.
5. (Original) The method of claim 1, wherein the sequencing-by-synthesis comprises clonal amplification and measurement of sequences of the clonally amplified DNA.
6. (Cancelled)
7. (Original) The method of claim 6, wherein the confidence that each SNP is correctly called is at least 95%.

8. (Original) The method of claim 6, wherein the confidence that each SNP is correctly called is at least 99%.
9. (Original) The method of claim 1, wherein the genetic data obtained is noisy and comprises allele drop out errors.
10. (Original) The method of claim 1, wherein the genetic data obtained is noisy and comprises measurement bias.
11. (Original) The method of claim 1, wherein the genetic data obtained is noisy and comprises incorrect measurements.
12. (Original) The method of claim 1, further comprising normalizing the genetic data for differences in amplification and/or measurement efficiency between the loci.

REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and reasons that follow.

Status of Claims

Claim 1 has been amended to incorporate the limitations of claims 3 and 6. Claims 3 and 6 are cancelled accordingly. These amendments are made without prejudice or disclaimer. Upon entry of this document, claims 1-2, 4-5 and 7-12 will remain pending in this application.

Priority

Applicant thanks the Office for acknowledging that the pending claims are entitled to the filing date of U.S. Prov. Appl. No. 60/817741, filed June 30, 2006. Applicant does not acquiesce to the Office's point of view concerning other priority documents.

Claim Rejections – 35 U.S.C. § 112

Claims 1-12 are rejected under 35 U.S.C. 112 as allegedly lacking enablement for “analyzing genotypes for DNA from cancer cells.” Office Action at page 4. Applicant respectfully disagrees.

In particular, the Office asserts that “there is no specific guidance that would support the steps of the method as applied to ‘analyzing the genotypes from cancer cells.’ Instead, the specification provides Tables which provide a variety of allele calls based on fetal samples where parent genotypes are available. There is neither data nor specific steps which are directed to analysis of cancer cells, at all.” (Office Action, page 6).

For the sole purpose of expediting prosecution and without acquiescing to the rejection, Applicant has amended claim 1 to recite that the target loci comprise SNP loci. The present application describes in detail how to analyze genotypes from DNA to determine allele

variations at SNPs. See throughout the specification and in particular, paragraphs [0308] to [0415]. In particular, paragraph [0379] discloses that:

“It is important to note that it is possible to use the method disclosed herein in the context of cancer genotyping and/or karyotyping, where one or more cancer cells is considered the target individual, and the non-cancerous tissue of the individual afflicted with cancer is considered to be the related individual. The non-cancerous tissue of the individual afflicted with the target could provide the set of genotype calls of the related individual that would allow chromosome copy number determination of the cancerous cell or cells using the methods disclosed herein.”
(emphasis added)

Accordingly, the as-filed specification expressly teaches application of the disclosed methods from genotyping of fetal DNA to genotyping of cancer DNA, and a skilled person would not require undue experimentation to apply the disclosed methods from genotyping of fetal DNA to genotyping of cancer DNA. Indeed, the same lab techniques including extraction of cell-free DNA, amplification of targeted loci, and sequencing of the amplicons can be used in both fetal DNA context and cancer DNA context.

Therefore, the present application complies with the enablement requirement. Reconsideration and withdrawal of the subject rejection are therefore respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 103 as allegedly unpatentable over Schwarzenbach et al., *Ann. N.Y. Acad. Sci.* 2004 (“Schwarzenbach”) and Marguiles et al., *Nature* 2005 (“Marguiles”). Applicant respectfully traverses this rejection.

Schwarzenbach is directed to detection and characterization of circulating microsatellite-DNA in blood of patients with breast cancer by using PCR assays for detecting microsatellite instability, and does not use DNA sequencing technology. Accordingly, Schwarzenbach is directed to a completely different methodology than the presently claimed method.

Moreover, Schwarzenbach does not teach or suggest amplification of a plurality of target loci, and sequencing the target loci to obtain genetic data for the plurality of target loci, wherein the target loci comprise SNPs. The Office Action at page 9 refers to Margulies for allegedly teaching that the target loci comprises SNPs as recited by originally filed claim 6, but Margulies does not even mentions SNPs, nor does Margulies provide any methods for determining the most likely genotypes for DNA from cancer cells based on allele frequencies at the plurality of target loci in the genetic data, wherein the target loci comprise SNP loci. Moreover, Margulies does not teach, suggest, or provide any guidance for using its method with cell-free DNA as recited by the present claims.

For the above reasons, even if Schwarzenbach and Margulies are combined, *arguendo*, which one of ordinary skill in the art would not have sufficient guidance/motivated to do so as explained below, the combination of Schwarzenbach and Margulies fails to teach or suggest a method using cell-free DNA that requires targeted amplification of SNP loci, sequencing of the amplification products by sequencing-by-synthesis, obtaining genetic data for SNP loci, and determining the most likely genotypes for DNA from cancer cells based on allele frequencies at the SNP loci.

The Office Action has also not established the required reason or motivation to combine Schwarzenbach and Margulies. As explained above, Schwarzenbach is primarily directed to using a PCR assay to detect microsatellite instability, and there is no reason to use a whole genome sequencing system as disclosed by Margulies to detect microsatellite instability when this purpose can be achieved by the much simpler PCR assay. In addition, Margulies does not mention circulating DNA, and there is no teaching or suggestion in Margulies that its whole genome sequencing system could be used on the circulating DNA fragments isolated from blood as disclosed in Schwarzenbach. Rather, Margulies uses large amounts genomic DNA samples and fragments the genomic DNA under controlled conditions. *See* Margulies, Materials and Methods in the Supplementary Materials. Accordingly, the Office Action has not provided any reason or motivation to modify the PCR assay of Schwarzenbach to detect microsatellite instability in circulating DNA with Margulies' method of whole genome sequencing.

For at least these reasons, the cited references do not provide sufficient teaching or suggestion for a person of ordinary skill in the art to arrive at the presently claimed invention with a reasonable expectation of success. Reconsideration and withdrawal of the subject rejection are therefore respectfully requested.

Concluding Remarks

Applicant believes that the application is in condition for allowance. Favorable reconsideration is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-6075. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 50-6075.

Respectfully submitted,

Date 12-9-2021

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