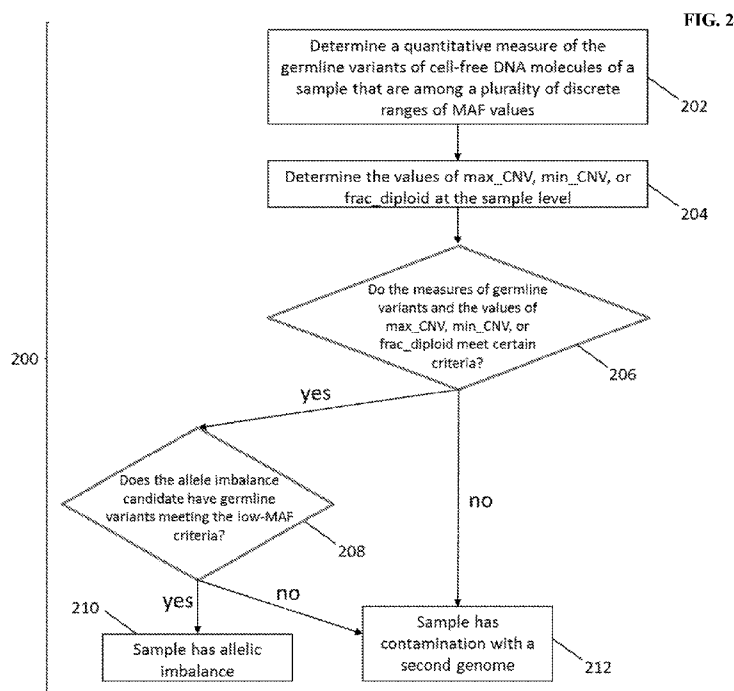




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- (74) Agent: **HOTT, Timothy A.** et al.; 505 Penobscot Drive, Redwood City, California 94063 (US).
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(54) Title: METHODS AND SYSTEMS FOR DETECTING ALLELIC IMBALANCE IN CELL-FREE NUCLEIC ACID SAMPLES



(57) Abstract: The present disclosure provides methods and systems for detecting an allelic imbalance in a sample from a subject, comprising: (a) sequencing cell-free DNA molecules from the sample to generate sequence reads; (b) aligning at least a portion of the sequence reads to a reference sequence to produce aligned sequence reads; (c) for at least a portion of the plurality of aligned sequence reads, identifying a germline variant present at a mutant allele fraction (MAF) in the sample, thereby identifying a set of germline variants in the sample, wherein individual germline variants in the set of germline variants have corresponding MAF values; (d) determining a quantitative measure of the set of germline variants that are among a plurality of discrete ranges of MAF values; and (e) detecting the allelic imbalance based on a predetermined criterion by filtering the set of germline variants based on at least the quantitative measure.

SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
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B. FIELDS SEARCHED				
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C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	WO 2012/174378 A2 (MYRIAD GENETICS INC [US]; GUTIN ALEXANDER [US] ET AL.) 20 December 2012 (2012-12-20) paragraph [0021] - paragraph [0025]; claims 1-8,17 -----	1-53		
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X	WO 2018/144782 A1 (TRANSLATIONAL GENOMICS RES INST) 9 August 2018 (2018-08-09) claim 1 -----	1-53		
-/--				
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.				
* Special categories of cited documents : <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> </tr> </table>			"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
"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 May 2020	09/06/2020			
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Gabriels, Jan			

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ESER KIRKIZLAR ET AL: "Detection of Clonal and Subclonal Copy-Number Variants in Cell-Free DNA from Patients with Breast Cancer Using a Massively Multiplexed PCR Methodology", TRANSLATIONAL ONCOLOGY, vol. 8, no. 5, 1 October 2015 (2015-10-01) , pages 407-416, XP055441218, United States ISSN: 1936-5233, DOI: 10.1016/j.tranon.2015.08.004 the whole document</p> <p align="center">-----</p>	1-53

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