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(81) Designated States (unless otherwise indicated, for every kind of national protection available):

AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

(54) Title: DETECTING CANCER DRIVER GENES AND PATHWAYS

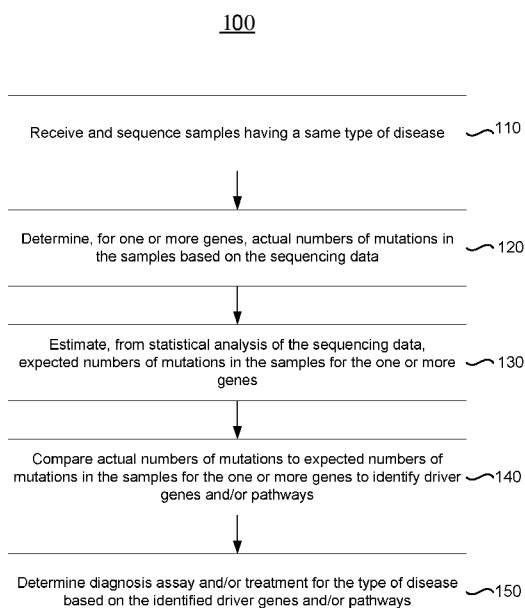


FIG. 1

(57) Abstract: Described herein are methods, systems, and apparatuses for detecting significantly mutated genes/pathways in a cancer cohort. A driver gene detection technique taking into account the heterogeneous mutational context in a cancer cohort is disclosed. A statistical model of a gene-specific mutation rate distribution (e.g., using an optimized gene specific mean estimation and/or a gene-specific dispersion estimation) is used to model a sample/gene-specific background mutation rate. The statistical model may then be used to detect gene/pathway enrichment and distinguish tumor suppressors and oncogenes based on the spatial distribution of non-silent mutations, loss-of-function mutations, and/or gain-of-function mutations.



TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(in))*

**Published:**

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

**(88) Date of publication of the international search report:**

21 December 2017 (21.12.2017)

INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2017/027794

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C12Q1/68 G06F19/18  
ADD.  
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)  
C12Q 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)  
EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KR 2015 0102468 A (ASAN FOUNDATION [KR] ) 7 September 2015 (2015-09-07) claim 17 -----	1
A	CN 103 305 625 A (GUANGDONG GENERAL HOSPITAL) 18 September 2013 (2013-09-18) claim 1 -----	1
X	A. YOUN ET AL: "Identi fyi ng cancer dri ver genes in tumor genome sequenci ng studi es" , BIOINFORMATICS, vol . 27, no. 2, 17 December 2010 (2010-12-17) , pages 175-181 , XP055155001 , ISSN: 1367-4803 , DOI : 10.1093/bi oi nformati cs/btq630 cited in the appl icati on the whole document ----- -/- .	1-20

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	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search  18 September 2017	Date of mailing of the international search report  23/11/2017
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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  Cornel is, Karen
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2017/027794

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	<p>COLLIN J. TOKHEIM ET AL: "Eval uati ng the eval uati on of cancer dri ver genes" , PROCEEDINGS NATIONAL ACADEMY OF SCI ENCES PNAS, vol . 113 , no. 50, 22 November 2016 (2016-11-22) , pages 14330-14335 , XP055406786, US ISSN: 0027-8424, DOI : 10. 1073/pnas . 1616440113 -----</p>	1-20
A	<p>XIUYING XIAO ET AL: "Role of MUC20 overexpressi on as a predi ctor of recurrence and poor outcome i n col orectal cancer" , JOURNAL OF TRANSLATIONAL MEDICINE, BIOMED CENTRAL, vol . 11, no. 1, 20 June 2013 (2013-06-20) , page 151 , XP021155521 , ISSN: 1479-5876, DOI : 10. 1186/1479-5876-11-151 -----</p>	13
A	<p>K. D. KORTHAUER ET AL: "MADGi C: a model -based approach for i denti fyi ng dri ver genes i n cancer" , BIOINFORMATICS, vol . 31, no. 10, 15 May 2015 (2015-05-15) , pages 1526-1535 , XP055217196, ISSN: 1367-4803 , DOI : 10 . 1093/bi oi nformati cs/btu858 -----</p>	1-20

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2017/027794

## 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 additional 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 an 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. :

1-20

### 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.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims : 1-20

A method to identify candidate driver genes, a computer product and a system for doing so.

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2-35 . claims : 21-30(parti ally)

A method of diagnosing lung cancer by detecting a mutation in at least one gene wherein the gene is one of ELP2, RBM10, KIAA1324L, STXBP5L, STK11, LARPI, ABI3BP, KRAS, CCAR1, EGFR, BRAF, CMTR2, ASMTL, SMARCA4, RBL1, KEAP1, ARID1A, TP53, CDKN2A, MUC20, PTEN, NFE2L2, RYR2, KMT2D, PIK3CA, RASA1, RBL1, FAT1, MS4A14, DPPA4, CEP89, NRD1, KLHL4, and PIP5K2

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/027794

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 20150102468	A	07-09 -20 15	NON E
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CN 103305625	A	18-09 -20 13	NON E
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