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(54) Title: APPARATUS, SYSTEMS, AND METHODS FOR RAPID CANCER DETECTION

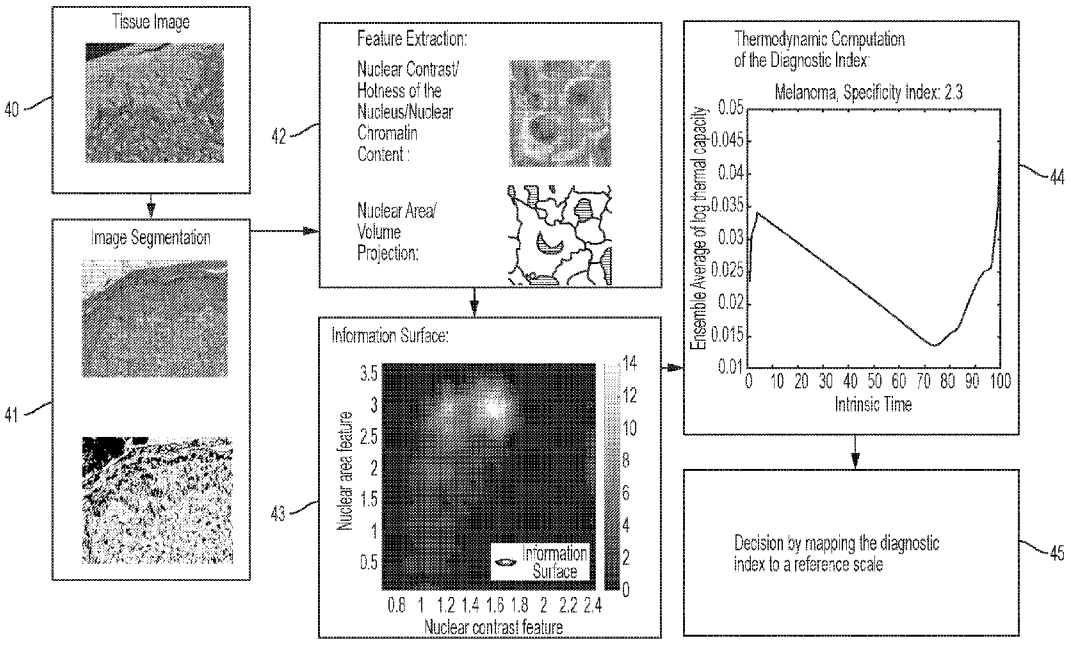

FIG. 7A

(57) Abstract: Presented herein are systems, methods, and apparatus that analyze molecular imprints for detecting cancerous cells. Embodiments of the present disclosure include systems, methods, and apparatus that analyze metabolic imprints of cells for cancer detection. In certain embodiments, the methods/systems comprise extracting thermal and thermodynamic quantities and properties from the molecular imprints. The thermal/thermodynamic quantities and/or further-processed quantities can be mapped on a universal cancer diagnostic scale for disease stratification, thereby providing/determining a normality status of the subject cells.

[Continued on next page]

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GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, 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 applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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))*

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/029995

A. CLASSIFICATION OF SUBJECT MATTER
INV. G16H50/20 G16H30/40 G16H50/30 G16H30/20 G06K9/00 G06T7/00
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)
G16H G06K G06T H04N G01J A61B

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	GIUSEPPE BELLISOLA ET AL: "Infrared spectroscopy and microscopy in cancer research and diagnosis", AMERICAN JOURNAL OF CANCER RESEARCH, vol. 2, no. 1, 1 January 2012 (2012-01-01) , pages 1-21, XP055216511, the whole document ----- -/--	1-33,40

[X] Further documents are listed in the continuation of Box C.

[X] 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

"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
30 October 2018	16/11/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Van der Haegen, D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/029995

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.:

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/029995

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GURCAN M N ET AL: "Histopathological Image Analysis: A Review", IEEE REVIEWS IN BIOMEDICAL ENGINEERING, IEEE, USA, vol. 2, 30 October 2009 (2009-10-30), pages 147-171, XP011507549, ISSN: 1937-3333, DOI: 10.1109/RBME.2009.2034865 the whole document; in particular page 150 to 152, section "Spectroscopic Imaging Modalities for Histopathology"	1-33,40
A	DANIEL C FERNANDEZ ET AL: "Infrared spectroscopic imaging for histopathologic recognition", NATURE BIOTECHNOLOGY, vol. 23, no. 4, 27 March 2005 (2005-03-27) , pages 469-474, XP055487606, US ISSN: 1087-0156, DOI: 10.1038/nbt1080 the whole document	1-33,40
X	Spagnolo M. Daniel ET AL: "Pointwise mutual information quantifies intratumor heterogeneity in tissue sections labeled with multiple fluorescent biomarkers", Journal of Pathology Informatics, 29 November 2016 (2016-11-29), XP055488358, DOI: 10.4103/2153-3539.194839 Retrieved from the Internet: URL:http://www.jpathinformatics.org/temp/JPatholInform7147-2857576_075615.pdf [retrieved on 2018-06-27]	1-14, 16-29, 31-33,40
Y	Abstract, sub-section "Methods" Abstract, sub-section "Results" Page 5, section "Methods", sub-section "Image Processing and Cell Quantification" Page 6, section "Methods", sub-section "Learning Dominant Biomarker Intensity Pattern Set from Each Cell Subpopulation" Page 9, section "Methods", sub-section "Software" Page 9, section "Methods", sub-section "Using Pointwise Mutual Information to Quantify Spatial Biomarker Pattern Relationships" Page 14 to , section "Results", sub-section "Pointwise Mutual Information Maps as Potential Diagnostic Biomarkers"	15,30

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/029995

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Phillip Isola ET AL: "Crisp Boundary Detection Using Pointwise Mutual Information" In: "Medical image computing and computer-assisted intervention - MICCAI 2015 : 18th international conference, Munich, Germany, October 5-9, 2015; proceedings", 9 October 2014 (2014-10-09), Springer International Publishing, Cham 032548, XP055333209, ISSN: 0302-9743 ISBN: 978-3-642-38287-1 vol. 8691, pages 799-814, DOI: 10.1007/978-3-319-10578-9_52, the whole document	15,30
A	Albert Gough ET AL: "Biologically Relevant Heterogeneity: Metrics and Practical Insights", SLAS Discovery, 1 March 2017 (2017-03-01), pages 213-237, XP055488365, Retrieved from the Internet: URL:http://journals.sagepub.com/doi/pdf/10.1177/2472555216682725 [retrieved on 2018-06-27] the whole document	1-33,40
A	FLORENCE DRAUX ET AL: "IR spectroscopy reveals effect of non-cytotoxic doses of anti-tumour drug on cancer cells", ANALYTICAL AND BIOANALYTICAL CHEMISTRY, SPRINGER, BERLIN, DE, vol. 395, no. 7, 2 October 2009 (2009-10-02), pages 2293-2301, XP019798633, ISSN: 1618-2650 the whole document	16,17, 31,32
X	US 2004/119020 A1 (BODKIN ANDREW [US]) 24 June 2004 (2004-06-24)	34,35, 38-40
Y	abstract paragraph [0004] - paragraph [0005] paragraph [0036] - paragraph [0047] figures 1,3,4	36,37
Y	US 2012/223804 A1 (GAITAS ANGELO [US]) 6 September 2012 (2012-09-06) abstract paragraph [0003] - paragraph [0004] paragraph [0007] paragraph [0053] paragraph [0078]	36,37

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/029995

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004119020 A1	24-06-2004	US 2004119020 A1	24-06-2004
		US 2006208193 A1	21-09-2006
US 2012223804 A1	06-09-2012	US 8297837 B1	30-10-2012
		US 2012223804 A1	06-09-2012

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-33(completely); 40(partially)

   A method and corresponding system for detecting one or more types of cancer

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2. claims: 34-39(completely); 40(partially)

   An apparatus for creating a long wavelength infrared image.
