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(54) Title: METHODS AND SYSTEMS FOR METABOLITE AND/OR LIPID-BASED DETECTION OF COLORECTAL CANCER AND/OR ADENOMATOUS POLYPS

(57) Abstract: Described herein are sets of metabolite and lipid (e.g., fatty acid) markers that can be used in the detection of early stage colorectal cancer and/or early development of adenomatous polyps. Presented herein are illustrative pathology-linked panels. In certain embodiments, the markers presented herein (or subsets thereof) are used as a panel for detecting either colorectal cancer or adenomatous polyps at the same time. The markers presented herein include metabolites and lipids (e.g., fatty acid) freely detectable and accurately quantifiable in human serum. In certain embodiments, the sample may be plasma, urine, saliva, whole blood, dried blood spot or dried serum spot.



INTERNATIONAL SEARCH REPORT

International application No PCT/EP2017/063058

A. CLASSIFICATION OF SUBJECT MATTER INV. G01N33/574 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) G01N				
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, BIOSIS, WPI Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
E	WO 2017/114955 A2 (UNIVERSAL DIAGNOSTICS S L [ES]) 6 July 2017 (2017-07-06) claims -----	1-17		
X	WO 2014/116833 A2 (US HEALTH [US]) 31 July 2014 (2014-07-31) page 22 - page 25; claims -----	1,12-14		
X	WO 2015/109263 A2 (UNIV WASHINGTON [US]) 23 July 2015 (2015-07-23) paragraph [0053]; claims -----	1,12-14		
X	WO 2011/011882 A1 (PHENOMENOME DISCOVERIES INC [CA]; RITCHIE SHAWN [CA]; GOODENOWE DAYAN) 3 February 2011 (2011-02-03) claims 32-37 -----	1,12-14		
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<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			
16 November 2017	27/11/2017			
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 Vogt, Titus			

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/063058

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	D. C. MONTROSE ET AL: "Metabolic Profiling, a Noninvasive Approach for the Detection of Experimental Colorectal Neoplasia", CANCER PREVENTION RESEARCH, vol. 5, no. 12, 1 December 2012 (2012-12-01), pages 1358-1367, XP055118574, ISSN: 1940-6207, DOI: 10.1158/1940-6207.CAPR-12-0160 Abstract + Discussion; figure 4	1-17
Y	----- WO 2011/143779 A1 (UNIV ALBERTA [CA]; FEDORAK RICHARD NEIL [CA]; WANG HAILI [CA]) 24 November 2011 (2011-11-24) claims; tables 2,4,6	1-17
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X	----- YOSHIFUMI NAKAYAMA: "The clinical usefulness of urinary N1,N12-diacetylspermine (DiAcSpm) levels as a tumor marker in patients with colorectal cancer", ONCOLOGY LETTERS, vol. 2, 29 February 2012 (2012-02-29), pages 970-974, XP55424172, GR ISSN: 1792-1074, DOI: 10.3892/ol.2012.625 abstract	1
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/063058

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>UMEMORI Y ET AL: "Evaluating the utility of N<1>,N<12>-diacetylspermine and N<1>,N<8>-diacetylspermidine in urine as tumor markers for breast and colorectal cancers", CLINICA CHIMICA ACTA, ELSEVIER BV, AMSTERDAM, NL, vol. 411, no. 23-24, 14 December 2010 (2010-12-14), pages 1894-1899, XP027406760, ISSN: 0009-8981 [retrieved on 2010-07-23] abstract</p>	1
X	<p>-----</p> <p>Hao Yue ET AL: "A METABONOMICS STUDY OF COLORECTAL CANCER BY RRLC-QTOF/MS", Journal of Liquid Chromatography & Related Technologies, vol. 36, no. 4 24 August 2012 (2012-08-24), 2012, pages 428-438, XP055424606, Abingdon DOI: 10.1080/10826076.2012.657738 Retrieved from the Internet: URL:http://www.tandfonline.com/doi/pdf/10.1080/10826076.2012.657738 abstract; table 1</p>	1,12,13
X	<p>-----</p> <p>YUAN TIAN ET AL: "Tissue Metabonomic Phenotyping for Diagnosis and Prognosis of Human Colorectal Cancer", SCIENTIFIC REPORTS, vol. 6, 15 February 2016 (2016-02-15), page 20790, XP55424057, DOI: 10.1038/srep20790 table 1</p>	1,12,13
X	<p>-----</p> <p>JIANGJIANG ZHU ET AL: "Colorectal Cancer Detection Using Targeted Serum Metabolic Profiling", JOURNAL OF PROTEOME RESEARCH., vol. 13, no. 9, 5 September 2014 (2014-09-05), pages 4120-4130, XP55424393, US ISSN: 1535-3893, DOI: 10.1021/pr500494u table 2</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1,12,13

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/063058

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	<p>LINGLI DENG ET AL: "Combining NMR and LC/MS Using Backward Variable Elimination: Metabolomics Analysis of Colorectal Cancer, Polyps, and Healthy Controls", ANALYTICAL CHEMISTRY, vol. 88, no. 16, 1 August 2016 (2016-08-01), pages 7975-7983, XP55424080, US ISSN: 0003-2700, DOI: 10.1021/acs.analchem.6b00885 the whole document</p> <p style="text-align: center;">-----</p>	1-17
X,P	<p>YU JING ET AL: "Rapid differentiating colorectal cancer and colorectal polyp using dried blood spot mass spectrometry metabolomic approach : DIFFERENTIATING COLORECTAL CANCER AND COLORECTAL POLYP", IUBMB LIFE, vol. 69, no. 5, 20 March 2017 (2017-03-20), pages 347-354, XP55424070, GB ISSN: 1521-6543, DOI: 10.1002/iub.1617 the whole document</p> <p style="text-align: center;">-----</p>	1-17

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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.:

3-8, 11(completely); 1, 2, 9, 10, 12-17(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 3-8, 11(completely); 1, 2, 9, 10, 12-17(partially)

This international search report was only completed for the subject matter of inventions 1-7 as defined herein.

1.1. claims: 3-6(completely); 1, 2, 12-17(partially)

Invention 1: A method of diagnosing colorectal cancer, comprising: detecting PUFA 446 and/or methyl-glutaroyl-carnitine (S192).

1.2. claims: 7(completely); 1, 2, 12-17(partially)

Invention 2: A method of diagnosing colorectal cancer, comprising: detecting S49 and/or S236

1.3. claims: 8(completely); 1, 2, 9, 10, 12-17(partially)

Invention 3: A method of diagnosing adenomatous polyps, comprising: detecting s69 and S153

1.4. claims: 1, 2, 12-17(all partially)

Invention 4: A method of determining at least one of a presence of, a stage of, and a risk of colorectal cancer and/or adenomatous polyps, comprising measuring by mass spectrometry the level of: the marker combination PUFA 468/S192 of Table 12.

1.5. claims: 1, 2, 12-17(all partially)

Invention 5: A method of determining at least one of a presence of, a stage of, and a risk of colorectal cancer and/or adenomatous polyps, comprising measuring by mass spectrometry the level of: the marker combination PUFA 446/S103 of Table 12.

1.6. claims: 11(completely); 1, 2, 9, 10, 12-17(partially)

Invention 6: A method of determining at least one of a presence of, a stage of, and a risk of colorectal cancer and/or adenomatous polyps, comprising measuring by mass spectrometry the level of: S153 of Table 13.

1.7. claims: 1, 2, 12-17(all partially)

Invention 7: A method of determining at least one of a presence of, a stage of, and a risk of colorectal cancer and/or adenomatous polyps, comprising measuring by mass spectrometry the level of: the marker combination S109/S153 of Table 13

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

2-88. claims: 1, 2, 12-17(all partially)

A method of diagnosing colorectal cancer, comprising:
detecting any other compound or compound combinations
selected from Tables 1 or 2.

89-178. claims: 1, 2, 9, 10, 12-17(all partially)

A method of diagnosing adenomatous polyps, comprising:
detecting any other compound or compound combinations
selected from Tables 1 or 2.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/EP2017/063058

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017114955 A2	06-07-2017	US 2017192029 A1 WO 2017114955 A2	06-07-2017 06-07-2017

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