

(51) International Patent Classification:  
*G01N 33/574* (2006.01)(21) International Application Number:  
PCT/US2012/022754(22) International Filing Date:  
26 January 2012 (26.01.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
61/441,452 10 February 2011 (10.02.2011) US(71) Applicant (for all designated States except US): **UNIVERSITY OF NORTH DAKOTA [US/US]**; 264 Centennial Drive, Stop 7095, Twamley Hall, Room 102, Grand Forks, North Dakota 58202 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **SAUTER, Edward R.** [US/US]; 1812 Belmont Road, Grand Forks, North Dakota 58201 (US).(74) Agents: **PERDOK SHONKA, Monique M.** et al.; Schwegman, Lundberg & Woessner, P.A., P.O. Box 2938, Minneapolis, Minnesota 55402 (US).

(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, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

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:  
10 April 2014

(54) Title: BREAST CANCER DIAGNOSIS USING NIPPLE DISCHARGE

(57) Abstract: A panel of biomarkers for the prediction of breast cancer using nipple discharge, as well as method and kits for using the same. Nipple discharge may be nipple aspirate fluid or spontaneous discharge. The panel has been selected to optimize predictive ability while minimizing the number of markers to be screened. As observed, the panel approaches one hundred percent accuracy for predicting breast cancer without the need for invasive biopsy.

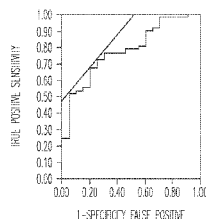


Fig. 1A

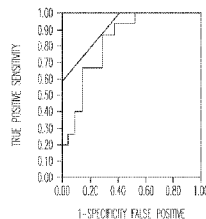


Fig. 1C

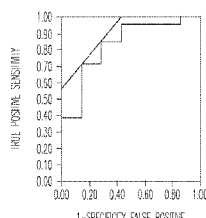


Fig. 1B

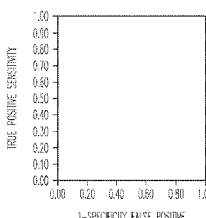


Fig. 1D

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/022754

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC(8) - G01N 33/574 (2012.01)<br>USPC - 435/287.2<br>According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                  |                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC(8) - C12M 3/00; G01N 33/53, 00, 574 (2012.01)<br>USPC - 435/7.1, 287.2; 436/86, 548<br>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched<br>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>PatBase, Google Patents, Google, ProQuest                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                  |                                                                                                     |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                  |                                                                                                     |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                               | Relevant to claim No.                                                                               |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | US 2006/0252097 A1 (DEUTSCHER et al) 09 November 2006 (09.11.2006) entire document                                                                                                                                                                                                                                               | 1-15                                                                                                |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | QIN, W. et al. Nipple Aspirate Fluid Expression of Urokinase-Type Plasminogen Activator, Plasminogen Activator Inhibitor-1, and Urokinase-Type Plasminogen Activator Receptor Predicts Breast Cancer Diagnosis and Advanced Disease. Annals of Surgical Oncology, 2003, Vol. 10, pages 948-953. entire document                  | 1-15                                                                                                |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | US 2003/0211624 A1 (GOLDKNOPF et al) 13 November 2003 (13.11.2003) entire document                                                                                                                                                                                                                                               | 3, 4, 13, 14                                                                                        |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | ZERVOUDIS, S. et al. Nipple Discharge Screening. Medscape Education, Women's Health. 16 December 2009. 23 pages. retrieved from internet. retrieved on [17 May 2012]<br><URL: http://www.medscape.org/viewarticle/713539> entire document                                                                                        | 7, 8, 10                                                                                            |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | AMA Code of Medical Ethics, Opinion 9.095-Reporting Clinical Test Results: General Guidelines. American Medical Association. December 1998. retrieved from internet. retrieved on [18 May 2012]. <URL: http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion8095.page?> entire document | 1-15                                                                                                |
| P, A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | QIN, W. et al. Proteins and carbohydrates in nipple aspirate fluid predict the presence of atypia and cancer in women requiring diagnostic breast biopsy. BMC Cancer, 2012, Vol. 12, pages 52-58. entire document                                                                                                                | 1-15                                                                                                |
| P, A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | TOKUDA, Y. et al. Suspicious Nipple Discharge Diagnostic Evaluation. Imaging of the Breast--Technical Aspects and Clinical Implication, InTech Open Access Publisher, 16 March 2012. 19 pages. retrieved from internet. retrieved on [17 May 2012]<br><URL: http://www.intechopen.com/statistics/32013> entire document          | 1-15                                                                                                |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                  |                                                                                                     |
| * Special categories of cited documents:<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier application or patent but published on or after the international filing date<br>"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)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"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<br>"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<br>"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<br>"&" document member of the same patent family |                                                                                                                                                                                                                                                                                                                                  |                                                                                                     |
| Date of the actual completion of the international search<br>17 May 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                  | Date of mailing of the international search report<br><b>12 JUN 2012</b>                            |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                  | Authorized officer:<br>Blaine R. Copenheaver<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/022754

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                   | Relevant to claim No. |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | DEUTSCHER, S. et al. Carbohydrate antigens in nipple aspirate fluid predict the presence of atypia and cancer in women requiring diagnostic breast biopsy. BMC Cancer, 2010, Vol. 10, pages 519-526. entire document | 1-15                  |
| A         | IMUBIND Tissue PAI-1 ELISA Kit, Product No. 821. American Diagnostica Inc. 13 March 2009. 3 pages. entire document                                                                                                   | 1-15                  |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/022754

## 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:

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 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.