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C12Q 1/68 (2006.01)

(52) Prior Art References:

(54) Title: PREDICTIVE OUTCOME ASSESSMENT FOR CHEMOTHERAPY WITH NEOADJUVANT BEVACIZUMAB

(57) Abstract: In a predictive outcome assessment test for predicting whether a patient undergoing a breast cancer treatment regimen will achieve pathological complete response (pCR), differential gene expression level information are generated for an input set of genes belonging to the TGF-β signaling pathway. The differential gene expression level information compares baseline gene expression level information from a baseline sample (70) of a breast tumor of a patient acquired before initiating (71) a breast cancer therapy regimen to the patient and response gene expression level information from a response sample (72) of the breast tumor acquired after initiating the breast cancer therapy regimen by administering a first dose of bevacizumab to the patient. A pCR prediction for the patient is computed based on the differential gene expression level information for the input set of genes belonging to the TGF-β signaling pathway. Related predictive outcome assessment test development methods are also disclosed.

FIG. 5
Date of publication of the international search report:
16 October 2014
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

**INV.** C12Q1/68

**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

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, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>SARA M. TOLANEY ET AL.: &quot;A phase II study of preoperative (preop) bevacizumab (bev) followed by dose-dense (dd) doxorubicin/cyclophosphamide (C)/paclitaxel (T) in combination with bevacizumab in HER2-negative operable breast cancer (BC)&quot;. JOURNAL OF CLINICAL ONCOLOGY, vol. 30, no. 15_supp1, 20 May 2012 (2012-05-20), page 1026, XP008167699, abstract</td>
<td>1-6,8-22</td>
</tr>
</tbody>
</table>

* Further documents are listed in the continuation of Box C.  
* See patent family annex.

**Date of the actual completion of the international search**

7 March 2014

**Date of mailing of the international search report**

07/07/2014

**Name and mailing address of the ISA/**

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**Authorized officer**

Agui lera, Miguel

Form PCT/ISA/2/10 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
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<td>A</td>
<td>WO 2012/106559 AI (TRANSLATIONAL GENOMICS RES INST [US]; CRAIG DAVID [US]; VON HOFF DANIEL) 9 August 2012 (2012-08-09) claims 8, 15</td>
<td>1-22</td>
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<td>A</td>
<td>WO 2011/153224 A2 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH]; HEGDE PRITI [US]; CHEN DAN) 8 December 2011 (2011-12-08) claims 1-5</td>
<td>1-22</td>
</tr>
<tr>
<td>A</td>
<td>JUBB A M ET AL: &quot;Biomarkers to predict clinical efficacy of bevacizumab in cancer&quot; , LANCET ONCOLOGY, LANCET PUBLISHING GROUP, LONDON, GB, vol. 11, no. 12, 1 December 2010 (2010-12-01) , pages 1172-1183 , XP027580490, ISSN: 1470-2045 [retrieved on 2010-12-01] page 1179 - page 1180; table 3</td>
<td>1-22</td>
</tr>
<tr>
<td>A</td>
<td>RAKESH K. JAIN ET AL: &quot;Biomarkers of response and resistance to antiangiogenic therapy&quot; , NATURE REVIEWS CLINICAL ONCOLOGY, vol. 6, no. 6, 1 June 2009 (2009-06-01) , pages 327-338 , XP055000425, ISSN: 1759-4774, DOI: 10.1038/nrclinonc.2009.63 the whole document</td>
<td>1-22</td>
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<tr>
<td>X, P</td>
<td>V VARADAN ET AL: &quot;RNA-seq identifies unique transcriptomic changes after brief exposure to preoperative nab-paclitaxel (N), bevacizumab (B) or trastuzumab (T) and reveals down-regulation of TGF-(beta) signaling associated with response to bevacizumab&quot; , CANCER RESEARCH, vol. 72, no. 24, suppl ement 3, 15 December 2012 (2012-12-15) , XP055104270, abstract</td>
<td>1-22</td>
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<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
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<tr>
<td>WO 2012106559 A1</td>
<td>09-08-2012</td>
<td>NONE</td>
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<tr>
<td>WO 2011153224 A2</td>
<td>08-12-2011</td>
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</table>
INTERNATIONAL SEARCH REPORT

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. X claims NOB.: 1-22 (partially) 
   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:
   
   see FURTHER INFORMATION sheet PCT/ISA/21Q

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. X 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.:

   1-22

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

1. claims: 1-22

Method for predicting pathological complete response in a breast cancer patient comprising analyzing differential gene expression for an input set of genes belonging to the TGF-beta signaling pathway or including the first 10 genes of Table 1 by comparing: (i) baseline gene expression before initiating breast cancer therapy regime; and (ii) response gene expression after initiating said therapy with a first dose of bevacizumab.

2. claims: 23-33

Method to generate a trained expression classifier comprising analyzing differential gene expression for at least 1000 genes by comparing gene expression before and after initiating breast cancer therapy with a first dose of neoadjuvant and using the information generated in training a classifier that outputs a prediction of pathological complete response.
Continuation of Box 11.2

Claims Nos.: 1-22 (partially)

Claims 1-22 relate to an extremely large number of possible methods. Each one of the possible combinations of at least two expression markers selected from the list of 20 recited in the claims gives rise to a particular embodiment of the invention claimed.

However, support and disclosure is to be found for only a very small proportion of the them, namely those combinations of markers explicitly disclosed in the claims or in the description and examples:

(a) the 61-gene signature of Figure 7/Table 1.
(b) the 20-gene list of "most informative genes" of said table recited in page 19, lines 29-31, and claim 1
(c) the 10-gene list of "most informative genes" of said table recited in page 20, lines 12-13, and claim 5.

In the present case, the claims do lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search and opinion has been carried out only for those parts of claims 1-14 which appear to be supported and disclosed, namely the methods based on the combinations of expression markers listed above (a), (b), (c) (see also below, Lack of Unity).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examination Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.