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[Continued on next page]

(54) Title: THROMBOEMOBLIC DISEASE MARKERS

(57) Abstract: The invention relates to a method for a more appropriate thromboembolic event risk assessment based on the presence of different genetic variant. The invention also relates to a method for determining the risk of suffering a thromboembolism disease by combining the absence or presence of one or more polymorphic markers in a sample from the subject with conventional risk factors for thromboembolism as well as computer-implemented means for carrying out said method.

Figure 1a

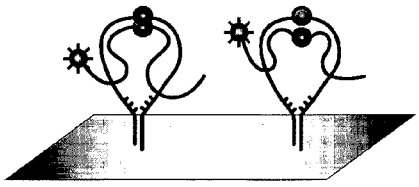
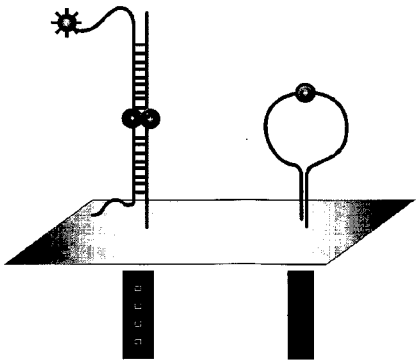


Figure 1b



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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 February 2013

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/061185

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. [X] Claims Nos.: 11, 12(partially)
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 11, 12, 14, 16(all 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/210

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. [X] 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

[X] 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/EP2012/061185

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, COMPENDEX, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	US 2007/054275 A1 (DOGULU CIGDEM F [US] ET AL) 8 March 2007 (2007-03-08) paragraph [0008]; tables 1-3 paragraph [0014] paragraph [0423] paragraph [0478] paragraph [0482] paragraph [0291] - paragraph [0304]; sequences 275-280 paragraph [0505] - paragraph [0511]; example 6 claims 1, 19-20, 30-35 ----- -/--	1-10,12, 13,15 14,16 11

[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
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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	Werner, Andreas

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/020090 A1 (INDAS S A LAB [ES]; PROGENIKA BIOPHARMA S A [ES]; INST ARAGONES DE CIE) 21 February 2008 (2008-02-21)	1-10,12, 13,15
Y	page 9, line 6 - page 10, line 18; claims 1-5; tables 1-2	14,16

X	US 2007/160992 A1 (BORTOLIN SUSAN [CA] ET AL) 12 July 2007 (2007-07-12)	1-10,12, 13,15
Y	abstract paragraph [0017] - paragraph [0030]; figure 5 paragraph [0089] - paragraph [0092]	14,16

X	US 2005/026168 A1 (XIE YA-GANG [CA]) 3 February 2005 (2005-02-03)	1-10,12, 13,15
Y	abstract paragraph [0015] - paragraph [0028]; examples 1-2 paragraph [0088] - paragraph [0090]	14,16

X	EP 1 398 388 A2 (OGHAM GMBH [DE]) 17 March 2004 (2004-03-17)	1-10,12, 13,15
Y	abstract tables 3-4	14,16

A	FRANCO R F ET AL: "GENETIC VARIATIONS OF THE HEMOSTATIC SYSTEM AS RISK FACTORS FOR VENOUS AND ARTERIAL THROMBOTIC DISEASE", CURRENT GENOMICS, BENTHAM SCIENCE PUBLISHERS LTD, NL, vol. 4, no. 4, 1 May 2003 (2003-05-01), pages 309-336, XP009047618, ISSN: 1389-2029, DOI: 10.2174/1389202033490349 abstract; table 3 page 311, column 1, paragraph 3 - column 2, paragraph 2 page 312, column 2, paragraph 3 - paragraph 5 page 313, column 1, paragraph 5 page 313, column 2, paragraph 4 - paragraph 5 page 314, column 1, paragraph 5 - paragraph 6 page 318, column 1, paragraph 4 page 318, column 2, paragraph 2 page 319, column 1, paragraph 1 - paragraph 2	1-10,12

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BUCHHOLZ T ET AL: "INHERITED THROMBOPHOLIA: IMPACT ON HUMAN REPRODUCTION", AMERICAN JOURNAL OF REPRODUCTIVE IMMUNOLOGY, WILEY-BLACKWELL MUNKSGAARD, DK, vol. 50, no. 1, 1 July 2003 (2003-07-01), pages 20-32, XP009047496, ISSN: 1046-7408, DOI: 10.1034/J.1600-0897.2003.00049.X abstract; table I	1-10,12
A	DEBETTE STÉPHANIE ET AL: "Genetics of atherothrombotic and lacunar stroke.", CIRCULATION. CARDIOVASCULAR GENETICS, vol. 2, no. 2, April 2009 (2009-04), pages 191-198, SUPP, XP002666241, ISSN: 1942-3268 abstract; tables 3, 10 (supplement)	1-10,12
X	SATRA MARIA ET AL: "Sequence variations in the FII, FV, F13A1, FGB and PAI-1 genes are associated with differences in myocardial perfusion.", PHARMACOGENOMICS FEB 2011 LNKD-PUBMED:21332313, vol. 12, no. 2, February 2011 (2011-02), pages 195-203, XP009155046, ISSN: 1744-8042	13,15
Y	abstract	14,16
A	page 196, column 1, paragraph 2 - page 197, column 1, paragraph 3; table 1 page 199, column 1, paragraph 3 - column 2, paragraph 2	1-12
X	J. CORRAL ET AL: "A nonsense polymorphism in the protein Z-dependent protease inhibitor increases the risk for venous thrombosis", BLOOD, vol. 108, no. 1, 1 July 2006 (2006-07-01), pages 177-183, XP055015187, ISSN: 0006-4971, DOI: 10.1182/blood-2005-08-3249	13,15
Y	abstract	14,16
A	page 178, column 1, paragraph 4 - paragraph 5; tables 1-2	1-10,12

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	J. CORRAL ET AL: "Antithrombin Cambridge II (A384S): an underestimated genetic risk factor for venous thrombosis", BLOOD, vol. 109, no. 10, 15 May 2007 (2007-05-15) , pages 4258-4263, XP055015332, ISSN: 0006-4971, DOI: 10.1182/blood-2006-08-040774	13,15
Y	abstract	14,16
A	page 4259, column 1, paragraph 5	1-10,12
A	JOHNSON C Y ET AL: "The factor XII -4C>T variant and risk of common thrombotic disorders: A HuGE review and meta-analysis of evidence from observational studies.", AMERICAN JOURNAL OF EPIDEMIOLOGY 15 JAN 2011 LNKD- PUBMED:21071604, vol. 173, no. 2, 15 January 2011 (2011-01-15), pages 136-144, XP002666243, ISSN: 1476-6256 abstract	1-10,12
X	MANNILA M N ET AL: "Epistatic and pleiotropic effects of polymorphisms in the fibrinogen and coagulation factor XIII genes on plasma fibrinogen concentration, fibrin gel structure and risk of myocardial infarction", THROMBOSIS AND HAEMOSTASIS, vol. 95, no. 3, March 2006 (2006-03), pages 420-427, XP009155047, ISSN: 0340-6245	13,15
Y	abstract	14,16
A	page 421, column 2, paragraph 5 - page 422, column 1, paragraph 1	1-10,12

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YE Z ET AL: "Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66@?155 cases and 91@?307 controls", THE LANCET, LANCET LIMITED. LONDON, GB, vol. 367, no. 9511, 25 February 2006 (2006-02-25), pages 651-658, XP025093729, ISSN: 0140-6736, DOI: 10.1016/S0140-6736(06)68263-9 [retrieved on 2006-02-25] abstract	1-10,12

X	DELLUC AURÉLIEN ET AL: "Association of common genetic variations and idiopathic venous thromboembolism. Results from EDITh, a hospital-based case-control study.", THROMBOSIS AND HAEMOSTASIS JUN 2010 LNKD-PUBMED:20352152, vol. 103, no. 6, June 2010 (2010-06), pages 1161-1169, XP009155048, ISSN: 0340-6245	13,15
Y	abstract; tables 1, 3, 4	14,16
A	page 1162, column 2, paragraph 4 - page 1164, column 1, paragraph 2; table 1	1-10,12

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X	K. L. WIGGINS ET AL: "ABO genotype and risk of thrombotic events and hemorrhagic stroke", JOURNAL OF THROMBOSIS AND HAEMOSTASIS, vol. 7, no. 2, 1 February 2009 (2009-02-01), pages 263-269, XP055015151, ISSN: 1538-7933, DOI: 10.1111/j.1538-7836.2008.03243.x	13,15
Y	abstract; table 2	14,16
A	page 264, column 1, paragraph 4 - column 2, paragraph 1	1-10,12

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	V. M. MORELLI ET AL: "ABO blood group genotypes and the risk of venous thrombosis: effect of factor V Leiden", JOURNAL OF THROMBOSIS AND HAEMOSTASIS, vol. 3, no. 1, 1 January 2005 (2005-01-01) , pages 183-185, XP055015150, ISSN: 1538-7933, DOI: 10.1111/j.1538-7836.2004.01071.x	13,15
Y	abstract	14,16
A	page 183, column 1, paragraph 4 - column 2, paragraph 1	1-10,12

A	GORDON D. O. LOWE: "Common risk factors for both arterial and venous thrombosis", BRITISH JOURNAL OF HAEMATOLOGY, vol. 140, no. 5, 1 March 2008 (2008-03-01) , pages 488-495, XP055015148, ISSN: 0007-1048, DOI: 10.1111/j.1365-2141.2007.06973.x the whole document	5

T	M. L. OLSSON ET AL: "Polymorphism and recombination events at the ABO locus: a major challenge for genomic ABO blood grouping strategies", TRANSFUSION MEDICINE, vol. 11, no. 4, 1 August 2001 (2001-08-01) , pages 295-313, XP055015274, ISSN: 0958-7578, DOI: 10.1046/j.1365-3148.2001.00320.x abstract; figures 3, 7; table 1	1-10,12

T	YIP S P: "Sequence variation at the human ABO locus", ANNALS OF HUMAN GENETICS, PUBLISHED FOR THE GALTON LABORATORY BY CAMBRIDGE UNIVERSITY PRESS, vol. 66, no. 1, 1 January 2002 (2002-01-01), pages 1-27, XP008088608, ISSN: 0003-4800, DOI: 10.1017/S0003480001008995 abstract; figures 1-3	1-10,12

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAY JOEL G ET AL: "Genetics University of Toronto Thrombophilia Study in Women (GUTTSI): genetic and other risk factors for venous thromboembolism in women", CURRENT CONTROL TRIALS. CASRDIOVASCULAR MEDICINE, CURRENT CONTROLLED TRIALS, LONDON, GB, vol. 2, no. 3, 18 May 2001 (2001-05-18), pages 141-149, XP021020992, ISSN: 1468-6708, DOI: 10.1186/CVM-2-3-141 abstract page 142, column 2, paragraph 4 - page 1431, column 1, paragraph 1 -----	11,12
X	SZOLNOKI Z ET AL: "Evaluation of the modifying effects of unfavourable genotypes on classical clinical risk factors for ischaemic stroke.", JOURNAL OF NEUROLOGY NEUROSURGERY & PSYCHIATRY, vol. 74, no. 12, December 2003 (2003-12), pages 1615-1620, XP002686926, ISSN: 0022-3050 abstract page 1616, column 1, paragraph 5 - column 2, paragraph 3 -----	11,12
X	CHARLES J. GLUECK ET AL: "Estrogen replacement therapy, thrombophilia, and atherothrombosis", METABOLISM, vol. 51, no. 6, 1 June 2002 (2002-06-01), pages 724-732, XP055043826, ISSN: 0026-0495, DOI: 10.1053/meta.2002.32729 abstract page 725, column 2, paragraph 6 - page 726, column 2, paragraph 1; tables 5-6 -----	11,12
X	EP 1 684 202 A1 (SIGNPOST CORP [JP]) 26 July 2006 (2006-07-26) paragraph [0009] - paragraph [0010] paragraph [0150] - paragraph [0152] paragraph [0003] - paragraph [0005] page 12, line 7; example 1 ----- -/--	11,12

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. A. HEIT ET AL: "Genetic variation within the anticoagulant, procoagulant, fibrinolytic and innate immunity pathways as risk factors for venous thromboembolism", JOURNAL OF THROMBOSIS AND HAEMOSTASIS, vol. 9, no. 6, 6 June 2011 (2011-06-06), pages 1133-1142, XP055043858, ISSN: 1538-7933, DOI: 10.1111/j.1538-7836.2011.04272.x abstract page 1135, column 1, paragraph 1	11,12
A	"Chapter 8: Parametric Regression Models" In: Hosmer, D.W.; Lemeshow, S.; May, S.: "Applied Survival Analysis: Regression Modeling of Time to Event Data", 2008, Wiley, XP009164556, ISBN: 9780471754992 pages 244-285, page 273 - page 284	11,12
A	M. L. COTE ET AL: "Tobacco and estrogen metabolic polymorphisms and risk of non-small cell lung cancer in women", CARCINOGENESIS, vol. 30, no. 4, 1 January 2009 (2009-01-01), pages 626-635, XP055043864, ISSN: 0143-3334, DOI: 10.1093/carcin/bgp033 abstract page 627, column 2, paragraph 4 - page 628, column 2, paragraph 1	11,12
X	WO 02/14555 A2 (UNIV UTAH RES FOUND [US]; IDAHO TECHNOLOGY INC [US]) 21 February 2002 (2002-02-21)	13,15
Y	page 3, line 22 - page 7, line 7 figures 6-7; example 8	14,16
X	MARION E. REID ET AL: "DNA-based methods in the immunohematology reference laboratory", TRANSFUSION AND APHERESIS SCIENCE, vol. 44, no. 1, 1 February 2011 (2011-02-01), pages 65-72, XP55015207, ISSN: 1473-0502, DOI: 10.1016/j.transci.2010.12.011	13,15
Y	abstract; table 1 page 66, column 1, paragraph 2	14,16

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	abstract; figure 3; table 1	14,16
Y	WO 2004/083225 A2 (VALAT CHRISTOPHE [FR]; LE DOUGUET CECILE [FR]) 30 September 2004 (2004-09-30) page 4, line 24 - page 11, line 7	14,16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/061185

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2004083225 A2	30-09-2004

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-10(completely); 11, 12(partially)

Method for the thromboembolic event risk assessment in a subject, comprising the steps of determining in a sample isolated from said subject the presence of a group of twelve polymorphisms as listed in claim 1;
Method thereof for the diagnosis of being developing or suffering a thromboembolic disease;
Method thereof for identifying a subject in need of anticoagulant and/or antithrombotic therapy or in need of prophylactic antithrombotic and/or anticoagulant therapy;
Method thereof for the indication of the need for a preventive or treatment with an antithrombotic and/or anticoagulant therapy;
Method of determining the probability of an individual of presenting a thromboembolism disease or event based on the presence of 1 to P classical risk factors and all twelve polymorphisms listed in claim 11, using the mathematical formula and parameters given in claim 11;
Computer program or computer-readable media containing means for carrying out said methods.

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2. claims: 11, 12(partially)

Method of determining the probability of an individual of presenting a thromboembolism disease or event based on the presence of 1 to P classical risk factors and 1 to J polymorphisms selected from the group listed in claim 11 with the exception of all twelve polymorphisms, using the mathematical formula and parameters given in claim 11;
Computer program or computer-readable media containing means for carrying out said method.

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3. claims: 13-16

Kit comprising reagents for detecting the identity of the nucleotide selected from the group given in claim 13;
Kit comprising a HairLoop(TM) probe selected from SEQ ID NO:1-24.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 11, 12(partially)

Claim 11, and claim 12 with reference thereto, relate to a mathematical method of determining the probability of an individual of presenting a thromboembolism disease or event, and computer implementations thereof. Said method is defined by the use of a mathematical expression calculating a probability P of presenting a thrombosis in an individual, taking account of a linear combination of an unspecified non-variable related risk beta(0); n unspecified predictor variables x(n); unspecified cross product terms x(f)x(g), x(h)x(i); and corresponding regression coefficients which are numerically not specified except for an unclearly defined regression coefficient of predictor variable x(i) being "1,185 with a range of possible values from 0.200 to 2.500". Claims to a mathematical method may be patentable if used in a technical process by some technical means implementing the method, and providing as its result a certain change in that entity, wherein the technical means might include a computer comprising suitable hardware or an appropriately programmed general purpose computer. Contrary to this, the mathematical method or algorithm in claim 11 is only an abstract concept prescribing how to operate on the numbers, but no direct technical result is produced by the method as such. Said method does not process tangible data representing technical or physical entities and providing a technical effect of allowing risk prediction of a thromboembolism disease, but merely presents a mathematical formalism of calculating a probability from a number of unspecified predictor variables and regression coefficients. No search is required for subject-matter relating to purely scientific and mathematical theories (Art. 34(4)(a)(i) PCT and Rule 39.1(i) PCT/Rule 67.1(i) PCT). Therefore claims 11-12 were only searched partially to the extent that said mathematical expression is implemented to produce a practical application and has technical character (PCT GL 9.05), i.e. the particular embodiments of the description integrating classical risk factors and polymorphic markers for thromboembolism disease as set out in Table 5 (p.32-33).

Continuation of Box II.2

Claims Nos.: 11, 12, 14, 16(all partially)

Claim 11, and claim 12 with reference thereto, refer to an indeterminable number of possible combinations of an undetermined list of 1 to P "classical risk factors" in combination with 1 to J polymorphisms selected from twelve different SNPs. The parameters P and J are not defined, leading to a lack of clarity (Art. 6 PCT). It is ambiguous and unclear what subject-matter would fall under the term "classical risk factors", because the description (tables 1-2 and p.17 par.3-4) speaks of "conventional risk factors" or "sociodemographic and clinical characteristics" which may also be considered classical risk factors.

Furthermore, it is unclear if and how the 1 to P classical risk factors and the 1 to J polymorphisms enter the provided mathematical expression, which only refers to "predictor variables" in general but makes no reference to either classical risk factors or SNPs. The possible combinations of any combination of twelve genetic markers with an indeterminable number or arbitrary diagnostic set of classical risk factors is neither sufficiently disclosed nor supported contrary to the requirements of Art. 5 and 6 PCT. In fact, the claims contain so many options that a lack of clarity within the meaning of Art. 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, a search of claims 11-12 could only be carried out for those parts of the application which do appear to be clear and which are sufficiently disclosed and supported, namely the particular embodiments of the description integrating classical risk factors and polymorphic markers for thromboembolism disease as set out in Table 5 (p.32-33). Independent claim 14, and claim 16 dependent thereon, refer to "detecting the identity of the nucleotide of risk within a nucleic acid sequence selected from the group of SEQ ID NO:1 to 24", yet without specifying what risk and which nucleotide this refers to. This extremely broad claim is unclear and lacks support and disclosure over part of its scope (Art. 5, 6 PCT) to the extent that search of claims 14 and 16 had to be restricted (Art. 34(4)(ii) PCT and Rule 66.2(a)(i) PCT) to those parts of the application which are clear and sufficiently disclosed and supported, namely the particular HairLoop(TM) probe sequences identified on p.28-29 and Table 4.

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 Examining 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 Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.