(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 February 2016 (04.02.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/018481 A3

(51) International Patent Classification:
G01N 33/48 (2006.01) *G06F 17/00* (2006.01)
G01N 33/50 (2006.01) *C12Q 1/68* (2006.01)

(21) International Application Number:
PCT/US2015/028343

(22) International Filing Date:
29 April 2015 (29.04.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/029,868 28 July 2014 (28.07.2014) US

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(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, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, 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:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

(88) Date of publication of the international search report:
3 March 2016

(54) Title: NETWORK BASED STRATIFICATION OF TUMOR MUTATIONS

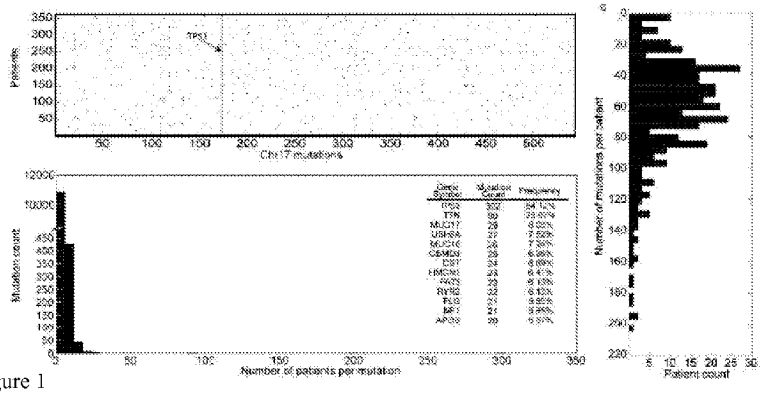

Figure 1

(57) Abstract: The embodiments provide a method of for stratification of cancer into one or more informative subtypes of a subject in need thereof. The embodiments, further provide assigning a subject in need into one or more informative subtypes, including assigning a subject in need into an informative subtype wherein the subtype is an ovarian cancer subtype.

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/48, 33/50; G06F 17/00; C12Q 1/68 (2015.01)
CPC - G06F 19/18, 19/22; C12Q 1/6886; G06N 5/04
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)
CPC: G06F 19/18, 19/22; C12Q 1/6886; G06N 5/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC: G06F 19/18, 19/22; C12Q 1/6886; G06N 5/04 (text search)
USPC: 702/19, 20; 506/8; 706/45; 435/6.14 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PatBase; Google Scholar; Google Patents Search terms: Stratification, network based, tumor mutations, molecular interaction network, exome DNA, genomic DNA, somatic mutations, nonsynonymous, synonymous, cancer subtype classification (e.g. lung, ovarian), TTN (titin or connectin), bioinformatics,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	HOFREE et al. Network-based stratification of tumor mutations. Nature Methods 5 September 2013 Vol 10 No 11 Pages 1108-1115 and Online Supplementary Data. Especially pg 1108 col 2 para 1, pg 1109 col 1 para 2 and col 2 para 2 and fig 1B, pg 1110 col 1 para 1, pg 1111 col 1 para 3, pg 1112 fig 5, pg 1113 fig 6	1, 11/1, 13, 18/13, 19, (24 -27)/1, 28, 30, 35, 36, 37, 43, (46-52)/1 --- 6, 29, 31-34, 38, 42
Y	GenBank AJ277892.2 Homo sapiens partial TTN gene for titin [online] 14 November 2006 [retrieved 15 September 2015]. Available on the internet: <URL: http://www.ncbi.nlm.nih.gov/nuccore/AJ277892>. Especially PDF pg 60, PDF pg 84, PDF pg 85	6, 29, 38, 42
Y	UNIPROT Q8WZ42. Titin human. [online] 9 July 2014 [retrieved 15 September 2015]. Available on the internet: <URL: http://www.uniprot.org/uniprot/Q8WZ42.txt?version=130>. Especially PDF pg 29, PDF pg 33, PDF pg 36	31, 33, 34
Y	Greenman et al. Patterns of somatic mutation in human cancer genomes. Nature 8 March 2007 Vol 446 No 7132 Pages 153-158. Especially pg 5 para 5	32
A	AVESSON et al. "The emerging role of RNA and DNA editing in cancer" [ePub 7 March 2014] Biochem Biophys Acta Vol 1845 No 2 Pages 308-316, pg 311 col 1 para 3 continued to pg 313 col 1 para 5;	1

☒ Further documents are listed in the continuation of Box C. ☐

* 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
29 September 2015 (29.09.2015)	26 OCT 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
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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:
------go to Extra Sheet for continuation-------

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.:
Claims 1-54. limited to a nucleic acid sequence encoding the first named gene of Table 2, TTN (1, 6, 11 (in part), 13, 18 (in part), 19, (24-27) (in part), 28-38, 42,43, (46-52) (in part))

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/US 15/28343

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KARVE et al. "Small changes huge impact: the role of protein posttranslational modifications in cellular homeostasis and disease" [ePub 21 June 2011] J Amino Acids Vol 2011 No 207691 Pages 1-13; pg 7 col 1 para 3-4	1

------continuation of Box III (Lack of Unity of Invention)----------

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-54, directed to a method for diagnosing a subject in need thereof as having one or more informative subtypes of a cancer or tumor comprising:
(a) Obtaining nucleic acid sequence, protein sequence, epigenetic modification, RNA modification, or post-translational modification information from the subject;
(b) Determining mutational or modification status from the nucleic acid sequence, protein sequence, epigenetic modification, RNA modification, or post-translational modification information so obtained
(c) Transforming the mutational status or modification status to a transformed profile of the subject based on molecular network(s) of gene, RNA and/or protein interaction or expression;
(d) Comparing the transformed profile of the subject of step (c) with reference transformed profiles corresponding to subjects grouped into one or more informative subtypes of a cancer or tumor, thereby diagnosing the subject with one or more informative subtypes of a cancer or tumor.

The method of treating for diagnosing a subject as having one or more informative subtypes of a cancer or tumor will be searched to the extent that it is the first named invention, where the type of information obtained is from nucleic acid sequence information (claim 1), where the transformed profile in step (c) comprises the first named gene in Table 2 (claim 11), TTN [table 2 begins on pg 87 of the instant application]. It is believed that claims 1, 6, 11 (in part), 13, 18 (in part), 19, (24-27) (in part), 28-38, 42, 43, (46-52) (in part) read on this first named invention and thus these claims will be searched without fee to the extent that they encompass the nucleic acid encoding the TTN gene. Additional types of information (e.g., protein sequence, post-translational modification, etc.) will be searched upon payment of additional fees. Applicant must specify the claims that encompass any additional elected type of information(s). Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be: a post-translation modification (claim 5) of a protein encoded by a specific gene (e.g., TP53) named in Table 4 (instant application pgs. 88-89) (claims 5, 10, 12, 17, 18 (in part), 23, (24-27) (in part), (46-52) (in part)).

Group II+: Claims 55-126, drawn to a method for identifying one or more informative subtypes of a cancer or tumor comprising
(a) Obtaining nucleic acid sequence, protein sequence, epigenetic modification, RNA modification, or post-translational modification information from the subject;
(b) Determining mutational or modification status from the nucleic acid sequence, protein sequence, epigenetic modification, RNA modification, or post-translational modification information so obtained
(c) Transforming the mutational status or modification status to a transformed profile of the subject based on molecular network(s) of gene, RNA and/or protein interaction or expression;
(d) Clustering the transformed profiles for subjects obtained in (c) into one or more clusters so as to obtain one or more subtypes, thereby identifying one or more informative subtypes of a cancer or tumor.

Group II+ will be searched upon payment of additional fee(s). The method for identifying one or more informative subtypes of a cancer or tumor may be searched, for example, to the extent that the information obtained is nucleic acid information (claim 55), where the transformed profile in step (c) comprises (claim 65) a gene shown in Table 2 (instant application pg 87-88) (e.g., MUC17) for an additional fee and election as such. It is believed that claims 55, 60, 65(in part), 67, 72(in part), 73, (78-80) (in part), 81-91, 94-98, (99-105)(in part), 108-125 read on this exemplary invention. Additional types of information (e.g., protein sequence, post-translational modification, etc.) will be searched upon payment of additional fees Applicants must indicate, if applicable, which claims read on this named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the named invention to be searched/examined. An exemplary election would be: a post-translation modification (claim 59) of a protein encoded by a specific gene (e.g., TP53) named in Table 4 (instant application pgs. 88-89) (claims 59, 64, 66(in part), 71, 72 (in part), 77, (78-80)(in part), (99-105)(in part), 111, (112-120, 122-125) (in part)).

The inventions listed as Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ has the special technical feature of diagnosing a subject as having a subtype of cancer, not required by Group II+.

Group I+ has the special technical feature of comparing the transformed profile with reference transformed profiles corresponding to subjects grouped into one or more informative subtypes of a cancer or tumor, not required by Group II+.

Group II+ has the special technical feature of using only subjects who have already been diagnosed with cancer and have a tumor, not required by Group I+.

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Group II+ has the special technical feature of clustering transformed profiles into one or more clusters, where the obtained clusters defined the subtype, not required by Group I+.

Group II+ has the special technical feature of using a supervised learning approach to derive a subtype classifier and to assign a subject to a subtype (e.g., claims 108-109), not required by Group I+

Group II+ has the special technical feature of characterizing the subject of interest by determining one or more measurable or quantifiable biological parameter(s) (e.g., claims 110-111), not required by Group II+.

Among the inventions listed as Groups I+ and II+ are the specific genes recited therein (i.e. instant application Tables 2, 3 and 4 and Figures 19, 25, 31, 32, 33, 37, 38, 39, 40, 41, 42, and 43).The inventions do not share a special technical feature, because no significant structural similarities can readily be ascertained among the genes.

Common Technical Features:

Groups I+ and II+ share the common technical features of:

1. Obtaining nucleic acid sequence, protein sequence, epigenetic modification, RNA modification, or post-translational modification information from the subject

2. Determining mutational or modification status from the nucleic acid sequence, protein sequence, epigenetic modification, RNA modification, or post-translational modification information so obtained.

3. Transforming the mutational status or modification status to a transformed profile of the subject based on molecular network(s) of gene, RNA and/or protein interaction or expression.

However, said common technical features do not represent a contribution over the prior art, and are obvious over the publication titled "Network-based stratification of tumor mutations" by HOFREE et al. (hereinafter "Hofree") [published 15 September 2013 in Nature Methods Vol 10 No 11 Pages 1108-1115], in view of the publication titled "The emerging role of RNA and DNA editing in cancer" by AVESSON et al. (hereinafter "Avesson") [ePub 7 March 2014 in Biochem Biophys Acta Vol 1845 No 2 Pages 308-316], in further view of the publication titled "Small changes huge impact: the role of protein posttranslational modifications in cellular homeostasis and disease" by KARVE et al. (hereinafter "Karve")[ePub 21 June 2011 in J Amino Acids Vol 2011 No 207691 Pages 1-13].

Concerning common technical feature #1, Hofree teaches obtaining nucleic acid sequence information from the subject (pg 1108 col 2 para 2; "A promising new source of data for tumor stratification is the somatic mutation profile, in which high-throughput sequencing is used to compare the genome or exome of a patient's tumor to that of the germ line to identify mutations that have become enriched in the tumor cell population").

Concerning common technical feature #2, Hofree teaches determining mutational status from the nucleic acid sequence information so obtained (pg 1109 col 1 para 2; "Briefly, somatic mutations for each patient are represented as a profile of binary (1, 0) states on genes, in which a "1" indicates a gene for which mutation (a single-nucleotide base change or the insertion or deletion of bases) has occurred in the tumor relative to germ line")

Concerning common technical feature #3, Hofree teaches transforming the mutational to a transformed profile of the subject based on molecular network(s) of gene (s)(pg 1109 col 1 para 2; " NBS [i.e. network based stratification] combines genome-scale somatic mutation profiles with a gene interaction network to produce a robust subdivision of patients into subtypes (Fig. 1a). Briefly, somatic mutations for each patient are represented as a profile of binary (1, 0) states on genes, in which a "1" indicates a gene for which mutation (a single-nucleotide base change or the insertion or deletion of bases) has occurred in the tumor relative to germ line. For each patient, we project the mutation profile onto a human gene interaction network obtained from public database"; pg 1112 fig 5).

Concerning Group I+ independent claims:

As to claim 1, Hofree teaches a method for diagnosing a subject in need thereof as having one or more informative subtypes of a cancer or tumor comprising:
(a) Obtaining nucleic acid sequence information from the subject [already indicated for common technical feature #1, pg 1108 col 2 para 2].
(b) Determining mutational status from the nucleic acid sequence information so obtained [already indicated for common technical feature #2; pg 1109 col 1 para 2]
(c) Transforming the mutational status to a transformed profile of the subject based on molecular network(s) of gene [already indicated for common technical feature #3; pg 1109 col 1 para 2; pg 1112 fig 5]
(d) Comparing the transformed profile of step (c) with reference transformed profiles corresponding to subjects grouped into one or more informative subtypes of a cancer or tumor (pg 1110 col 1 para 3; We next sought to apply NBS to stratify patients profiled by TCGA [i.e. The Cancer Genome Atlas] full-exome sequencing for uterine, ovarian and lung cancers, thereby diagnosing the subject as having one or more informative subtypes of a cancer or tumor").

As to claim 2, Hofree teaches a method for diagnosing a subject in need thereof as having one or more informative subtypes of a cancer or tumor , and fulfills claim limitations (a), (b), (c), (d) above for claim 1, but does not specifically make a determination mutational status from protein sequence information. However, protein sequence information for cancer types and subtypes was known in the art, as taught by Hofree (pg 1110 col 2 para 2; "We compared these results to subtypes derived from other data types in the TCGA, including protein profiles"). An artisan of ordinary skill in the art would have recognized that since protein profiles in the TCGA were known, as were protein sequences, the method could have been applied specifically using protein sequences (e.g. obtained by mass spectrometry sequencing, etc).
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As to claim 3, Hofree teaches a method for diagnosing a subject in need thereof as having one or more informative subtypes of a cancer or tumor, and fulfills claim limitations (a), (b), (c), (d) as above for claim 1, but does not specifically make a determination of epigenetic modification status from epigenetic modification information. However, epigenetic information for cancer types and subtypes was known in the art, as taught by Hofree (pg 1110 col 2 para 2; "We compared these results to subtypes derived from other data types in the TCGA, including methylation"; pg 1112 fig 4-" Predictive power and overlap of subtypes derived from different TCGA datasets [includes methylation data]"). An artisan of ordinary skill in the art would have recognized that since methylation profiles in the TCGA were known, the method could have been applied specifically using high-throughput methods known in the art to characterize a methylation profile for a particular individual or groups of individuals.

As to claim 4, Hofree teaches method for diagnosing a subject in need thereof as having one or more informative subtypes of a cancer or tumor, and fulfills claim limitations (a), (b), (c), (d), as above for claim 1, but does not specifically make a determination of RNA modification status from RNA modification information. However, Avesson teaches RNA modification status from the RNA modification information (pg 311 col 1 para 3 continued to pg 313 col 1 para 5; Role of RNA editing in cancer: -editing of the RNA of numerous genes implicated in cancer are indicated). An artisan of ordinary skill in the art would have recognized that the editing of numerous RNAs of specific genes, as indicated by Avesson could have been specifically analyzed to obtain one or more subsets for a specific cancer.

As to claim 5, Hofree teaches a method for diagnosing a subject in need thereof as having one or more informative subtypes of a cancer or tumor and fulfills claim limitations (a), (b), (c), (d), as above for claim 1, but does not specifically teach determining post-translational modification status from the post-translational modification information. However, Karve teaches post-translational modification status from the post-translational modification information (pg 7 col 1 para 3-4; " "Phosphorylation, addition of a phosphate group to an amino acid, is one of the central reversible, post-translational modifications that regulate cellular metabolism, protein interaction, enzyme reactions, and protein degradation for a myriad of proteins, which results in intracellular signaling cascades [...] Serine/threonine (Ser/Thr) and tyrosine are the most commonly observed phosphorylated amino acid residues and have been frequently implicated in progression of cancers"). An artisan of ordinary skill in the art would have known that constructing a phosphoproteome as it pertains to cancers was well-well known in the art, and could have been specifically applied to obtain one or more subsets for a specific cancer.

Concerning Group II+ independent claims:

As to claim 55, Hofree teaches a method for identifying one or more informative subtypes of a cancer or tumor comprising:
(a) Obtaining nucleic acid sequence information from subjects with a cancer or tumor subject [already indicated for common technical feature #1, pg 1108 col 2 para 2].

(b) Determining mutational status for each subject from the nucleic acid sequence information so obtained [already indicated for common technical feature #2; pg 1109 col 1 para 2]

(c) Transforming the mutational status to a transformed profile of the subject based on molecular network(s) of gene, RNA and/or protein interaction or expression [already indicated for common technical feature #3; pg 1109 col 1 para 2; pg 1112 fig 5]

(d) Clustering the transformed profiles for subjects obtained in (c) into one or more clusters so as to obtain one or more subtypes, thereby identifying one or more informative subtypes of a cancer or tumor (abstract; "Here we introduce network-based stratification (NBS), a method to integrate somatic tumor genomes with gene networks. This approach allows for stratification of cancer into informative subtypes by clustering together patients with mutations in similar network regions").

As to claim 56, Hofree teaches a method for identifying one or more informative subtypes of a cancer or tumor, and fulfills claim limitations (a), (b), (c), (d) above for claim 55, but does not specifically make a determination mutational status from protein sequence information. However, protein sequence information for cancer types and subtypes was known in the art, as taught by Hofree (pg 1110 col 2 para 2), and could have used it for clustering subjects into one or more clusters based on the similarities.

As to claim 57, Hofree teaches a method for identifying one or more informative subtypes of a cancer or tumor, and fulfills claim limitations (a), (b), (c), (d) above for claim 55, but does not specifically make a determination of epigenetic modification status from epigenetic modification information. However, epigenetic information for cancer types and subtypes was known in the art, as taught by Hofree (pg 1110 col 2 para 2; pg 1112 fig 4). An artisan of ordinary skill in the art would have recognized that since methylation profiles in the TCGA were known, for example, the method could have been applied specifically using high-throughput methods known in the art to characterize a methylation profile for a particular individual or groups of individuals, and could have used it for clustering subjects into one or more clusters based on the similarities.

As to claim 58, Hofree teaches method for diagnosing a subject in need thereof as having one or more informative subtypes of a cancer or tumor, and fulfills claim limitations (a), (b), (c), (d), as above for claim 55, but does not specifically make a determination of RNA modification status from RNA modification information. However, Avesson teaches RNA modification status from the RNA modification information (pg 311 col 1 para 3 continued to pg 313 col 1 para 5). An artisan of ordinary skill in the art would have recognized that the editing of numerous RNAs of specific genes, as indicated by Avesson could have been specifically analyzed to obtain one or more subsets for a specific cancer, and could have clustered subjects into one or more clusters based on their similarities.

As to claim 59, Hofree teaches method for diagnosing a subject in need thereof as having one or more informative subtypes of a cancer or tumor, and fulfills claim limitations (a), (b), (c), (d), as above for claim 55, but does not specifically teach determining post-translational modification status from the post-translational modification information. However, Karve teaches post-translational modification status from the post-translational modification information (pg 7 col 1 para 3). An artisan of ordinary skill in the art would have known that constructing a phospho-proteome as it pertains to specific cancers was well-well known in the art, and could have been specifically applied to obtain one or more subsets for a specific cancer, and to cluster profiles from subjects based on their similarities.
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As the common technical features were known in the art at the time of the invention, they cannot be considered common special technical features that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Groups I+ and II+ lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature