Abstract: The present invention relates to characterizing changes in mammalian intestinal microbiota associated with associated with high-fat and low-fat diets and with diets containing hydroxypropylmethylcellulose (HPMC) and related methods for diagnosing, preventing and treating obesity and related conditions such as metabolic syndrome and diabetes mellitus. Therapeutic methods of the invention involve the use of probiotics, and/or prebiotics, and/or narrow spectrum antibiotics/anti-bacterial agents that are capable of restoring healthy mammalian bacterial intestinal microbiota.
A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C 12Q 1/04 (2011.01)
USPC - 435/29, 435/34

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)
USPC: 435/29, 435/34
IPC(8): C12Q 1/04 (2011.01)

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)
PubWEST (DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ), Google Scholar, Google Patents

Search Terms Used: diagnostics, obesity, metabolic syndrome, diabetes, Firmicutes, Bacteroidetes, probiotics, ethyl cellulose, methycellulose, methyl ethyl cellulose, hydroxyethyl cellulose, etc., xylose, arabinose, ribose, galactose, etc.

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>
</tr>
</thead>
<tbody>
<tr>
<td>X Y</td>
<td>US 2010/01 72374 A1 (Turnbaugh et al.) 8 July 2010 (08.07.2010) esp: abstract, paras [0041], [0046], [0047], [0052], [0054], [01 16], [0122], [0127].</td>
<td>1, 6, 76</td>
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<td></td>
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<td>72-75</td>
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<td>Y</td>
<td>US 2007/0009577 A1 (Mankovitz) 11 January 2007 (11.01.2007) esp: abstract, paras [0021], [0015], [0043], [0069], [0070], [0077], [0078], [0081].</td>
<td>1, 6, 72-75</td>
</tr>
<tr>
<td>Y</td>
<td>US 2010/0074872 A1 (Blaser et al.) 25 March 2010 (25.03.2010) entire document.</td>
<td>1, 6, 72-75</td>
</tr>
<tr>
<td></td>
<td>Armougom et al. “Monitoring Bacterial Community of Human Gut Microbiota Reveals an Increase in Lactobacillus in Obese Patients and Methanogens in Anorexic Patients” PLoS ONE 2009, 4(9): e7125. doi:10.1371/journal.pone.0007125. entire document, esp: Table 2.</td>
<td>1, 6, 72-75</td>
</tr>
<tr>
<td>A</td>
<td>Li et al. “Symbiotic gut microbes modulate human metabolic phenotypes” PNAS, February 12, 2008, vol. 105, no. 6, 217-2122. entire document.</td>
<td>1, 6, 72-75</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search
28 February 2012 (28.02.2012)

Date of mailing of the international search report
13 MAR 2012

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. 571-273-3201

Authorized officer: Lee W. Young
PCT Helpdesk 571-272-4300
PCT DSP 571-272-7774

Form PCT/ISA/2 10 (second sheet) (July 2009)
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.: 19-26, 31, 41-46, 53, 80 and 113-118 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:

The portions of claims 19-26, 31, 41-46, 53, 80 and 113-118 relating to classifications "Incertae sedis" (EIS and PIS) are deemed to be unsearchable under Article 34(4)(a)(ii) because the subject matter of the claim (or portion thereof) is too unclear with regard to precisely what species are referred to for a proper determination of novelty, inventive step, or industrial applicability to be made.

3. Claims Nos.: 77-79 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

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: claim 1, directed to a method for diagnosing predisposition to a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising:
(a) measuring the populations of Firmicutes and/or Bacteroidetes in the ileal microbiota of the mammal;
(b) measuring the populations of Firmicutes and/or Bacteroidetes in the ileal microbiota of a healthy control;
(c) comparing the populations measured in steps (a) and (b); and
(d) determining that the mammal has a predisposition to the disease if the populations of Firmicutes and/or Bacteroidetes in the ileal microbiota of the mammal are increased as compared to the healthy control.

—continued on extra sheet—

1. All required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. All searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. 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.: Group I claim 1, and Group VI, claims 6 and 72-76.

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.
Continuation of Box III: Observations where unity of invention is lacking:

Group 2: claims 2 and 53-71, directed to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the populations of Firmicutes and/or Bacteroidetes in the ileal microbiota of the mammal.

Group 3: claims 3 and 53-71, directed to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the populations of Firmicutes and/or Bacteroidetes in the ileal microbiota of the mammal.

Group 4: claims 4 and 72-76, directed to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the populations of Firmicutes and/or Bacteroidetes in the ileal microbiota of the mammal.

Group 5: claims 5 and 72-76, directed to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the populations of Firmicutes and/or Bacteroidetes in the ileal microbiota of the mammal.

Group 6: claims 6 and 72-76, directed to a method of lowering populations of Firmicutes and/or Bacteroidetes in the ileal microbiota of a mammal comprising administering to the mammal a probiotic composition.

Group 7: claim 7, directed to a method for diagnosing predisposition to a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising:
(a) measuring the populations of Firmicutes in the cecal and/or fecal microbiota of the mammal;
(b) measuring the populations of Firmicutes in the cecal and/or fecal microbiota of a healthy control;
(c) comparing the populations measured in steps (a) and (b), and
(d) determining that the mammal has a predisposition to the disease if the populations of Firmicutes in the cecal and/or fecal microbiota of the mammal are increased as compared to the healthy control.

Group 8: claim 8, directed to a method for diagnosing predisposition to a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising:
(a) measuring the ratio of the populations of Firmicutes to the populations of Eubacteria (F/E ratio) in the cecal and/or fecal microbiota of the mammal;
(b) measuring the F/E ratio in the cecal and/or fecal microbiota of a healthy control;
(c) comparing the F/E ratios measured in steps (a) and (b), and
(d) determining that the mammal has a predisposition to the disease if the F/E ratio is increased in the cecal and/or fecal microbiota of the mammal as compared to the healthy control.

Group 9: claims 9 and 53-71, directed to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the populations of Firmicutes in the cecal and/or fecal microbiota of the mammal.

Group 10: claims 10 and 53-71, directed to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the populations of Firmicutes in the cecal and/or fecal microbiota of the mammal.

Group 11: claims 11 and 72-76, directed to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the populations of Firmicutes in the cecal and/or fecal microbiota of the mammal.

Group 12: claims 12 and 72-76, directed to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the populations of Firmicutes in the cecal and/or fecal microbiota of the mammal.

Group 13: claims 13 and 72-76, directed to a method of lowering the populations of Firmicutes in the cecal and/or fecal microbiota of a mammal comprising administering to the mammal a probiotic composition.

Group 14: claims 14 and 53-71, directed to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the ratio of the populations of Firmicutes to Eubacteria (F/E ratio) in the cecal and/or fecal microbiota of the mammal.

Group 15: claims 15 and 53-71, directed to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition lowers the ratio of the populations of Firmicutes to Eubacteria (F/E ratio) in the cecal and/or fecal microbiota of the mammal.
Group 16: claims 16 and 72-76, directed to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a prebiotic composition, wherein said prebiotic composition lowers the ratio of the populations of Firmicutes to Eubacteria (F/E ratio) in the cecal and/or fecal microbiota of the mammal.

Group 17: claims 17 and 72-76, directed to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a prebiotic composition, wherein said prebiotic composition lowers the ratio of the populations of Firmicutes to Eubacteria (F/E ratio) in the cecal and/or fecal microbiota of the mammal.

Group 18: claims 18 and 72-76 a method of lowering the ratio of the populations of Firmicutes to Eubacteria (F/E ratio) in the cecal and/or fecal microbiota of the mammal comprising administering to the mammal a prebiotic composition.

Groups 19+: claim 19, directed to a method for diagnosing predisposition to a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising:
(a) measuring the populations of at least one genus selected from the group consisting of Coprobacillus, Sporacetigenium, Holdemania, Dorea, Blautia, Enterococcus, Erysipelotrichaceae Incertae Sedis (EIS), Clostridium coeleteum, and Peptostepoccaceae IS (PIS) in the intestinal microbiota of the mammal;
(b) comparing the populations measured in steps (a) and (b), and
(c) determining that the mammal has a predisposition to the disease if the populations of at least one genus selected from the group consisting of Coprobacillus, Sporacetigenium, Holdemania, Dorea, Blautia, Enterococcus, Erysipelotrichaceae Incertae Sedis (EIS), Clostridium coeleteum, and Peptostepoccaceae IS (PIS) in the intestinal microbiota of the mammal are decreased as compared to the healthy control; wherein the first invention is limited to measuring the population of coprobacillus (applicants may opt for additional populations to be searched by specifying the genus and paying an additional invention search fee for each elected genus).

Groups 20+: claims 20, 25 and 53-71, directed to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a prebiotic composition, wherein said prebiotic composition stimulates growth or metabolic activity of at least one strain from the genus selected from the group consisting of Coprobacillus, Sporacetigenium, Holdemania, Dorea, Blautia, Enterococcus, Erysipelotrichaceae Incertae Sedis (EIS), Clostridium coeleteum, and Peptostepoccaceae IS (PIS) in the intestinal microbiota of the mammal; wherein the first invention is limited to stimulation of the growth or metabolic activity of Coprobacillus (applicants may opt for additional populations to be searched by specifying the genus and paying an additional invention search fee for each elected genus).

Groups 21+: claims 21, 26, and 53-71, directed to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a prebiotic composition, wherein said prebiotic composition stimulates growth or metabolic activity of at least one strain from the genus selected from the group consisting of Coprobacillus, Sporacetigenium, Holdemania, Dorea, Blautia, Enterococcus, Erysipelotrichaceae Incertae Sedis (EIS), Clostridium coeleteum, and Peptostepoccaceae IS (PIS) in the intestinal microbiota of the mammal; wherein the first invention is limited to stimulation of the growth or metabolic activity of Coprobacillus (applicants may opt for additional populations to be searched by specifying the genus and paying an additional invention search fee for each elected genus).

Groups 22+: claims 22, 25 and 72-76, directed to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a prebiotic composition, wherein said prebiotic composition stimulates growth or metabolic activity of at least one strain from the genus selected from the group consisting of Coprobacillus, Sporacetigenium, Holdemania, Dorea, Blautia, Enterococcus, Erysipelotrichaceae Incertae Sedis (EIS), Clostridium coeleteum, and Peptostepoccaceae IS (PIS) in the intestinal microbiota of the mammal; wherein the first invention is limited to stimulation of the growth or metabolic activity of Coprobacillus (applicants may opt for additional populations to be searched by specifying the genus and paying an additional invention search fee for each elected genus).

Groups 23+: claims 23, 26, and 72-76, directed to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a prebiotic composition, wherein said prebiotic composition stimulates growth or metabolic activity of at least one strain from the genus selected from the group consisting of Coprobacillus, Sporacetigenium, Holdemania, Dorea, Blautia, Enterococcus, Erysipelotrichaceae Incertae Sedis (EIS), Clostridium coeleteum, and Peptostepoccaceae IS (PIS) in the intestinal microbiota of the mammal; wherein the first invention is limited to stimulation of the growth or metabolic activity of Coprobacillus (applicants may opt for additional populations to be searched by specifying the genus and paying an additional invention search fee for each elected genus).

Groups 24+: claims 24 and 72-76, directed to a method of stimulating growth or metabolic activity of at least one strain from the genus selected from the group consisting of Coprobacillus, Sporacetigenium, Holdemania, Dorea, Blautia, Enterococcus, Erysipelotrichaceae Incertae Sedis (EIS), Clostridium coeleteum, and Peptostepoccaceae IS (PIS) in the intestinal microbiota of a mammal comprising administering to the mammal a prebiotic composition; wherein the first invention is limited to stimulation of the growth or metabolic activity of Coprobacillus (applicants may opt for additional populations to be searched by specifying the genus and paying an additional invention search fee for each elected genus).

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Form: PCT/SA/2 10 (extra sheet) (July 2009)
Groups 25+: claim 27, directed to a method for diagnosing predisposition to a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising:
(a) measuring the populations of at least one taxon selected from the group consisting of Johnsonella, Oscillibacter, Lachnospiraceae, Ruminococcaceae, and Clostridiales in the intestinal microbiota of the mammal;
(b) measuring the populations of the same taxon in the intestinal microbiota of a healthy control; and
(c) comparing the populations measured in steps (a) and (b), and
determining that the mammal has a predisposition to the disease if the populations of at least one taxon selected from the group consisting of Johnsonella, Oscillibacter, Lachnospiraceae, Ruminococcaceae, and Clostridiales in the intestinal microbiota of the mammal is increased as compared to the healthy control; wherein the first invention is limited to measuring and determining an increase in Johnsonella (applicants may opt for additional populations to be searched by specifying the taxon and paying an additional invention search fee for each elected taxon).

Groups 26+: claims 28, 30, 31 and 33, directed to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a composition or a compound, wherein said composition or compound inhibits growth or metabolic activity of at least one strain from the taxon selected from the group consisting of Johnsonella, Oscillibacter, Lachnospiraceae, Ruminococcaceae, and Clostridiales in the intestinal microbiota of the mammal; wherein the first invention is limited to wherein the compound inhibits Johnsonella (applicants may opt for additional populations to be searched by specifying the taxon and paying an additional invention search fee for each elected taxon).

Groups 27+: claims 29-31 and 34, directed to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a composition or a compound, wherein said composition or compound inhibits growth or activity of at least one strain from the taxon selected from the group consisting of Johnsonella, Oscillibacter, Lachnospiraceae, Ruminococcaceae, and Clostridiales in the intestinal microbiota of the mammal; wherein the first invention is limited to wherein the composition or compound inhibits Johnsonella (applicants may opt for additional populations to be searched by specifying the taxon and paying an additional invention search fee for each elected taxon).

Groups 28+: claims 32 and 72-76, directed to a method of inhibiting growth or metabolic activity of at least one strain from the taxon selected from the group consisting of Johnsonella, Oscillibacter, Lachnospiraceae, Ruminococcaceae, and Clostridiales in the intestinal microbiota of a mammal comprising administering to the mammal a prebiotic composition; wherein the first invention is limited to inhibiting Johnsonella (applicants may opt for additional populations to be searched by specifying the taxon and paying an additional invention search fee for each elected taxon).

Group 29: Claims 35-40 and 53-76, directed to methods relating to a ratio of the population of at least one genus selected from the group consisting of Coprobacillus (C), Sporacetigenium (S), and Holdemania (H), in the intestinal microbiota of the mammal to the population of at least one genus selected from Johnsonella (J) and Oscillibacter (O) in the intestinal microbiota of the mammal.

Group 30: claims 41-46 and 53-76, directed to methods relating to a ratio of the populations of at least one genus selected from the group consisting of: Coprobacillus (C), Sporacetigenium (S), Holdemania (H), Erysipelotrichaceae Incertae Sedis (EIS), Peptostreptococcaceae Incertae Sedis (PIS), and Clostridium cocleatum (Cc) in the intestinal microbiota of the mammal to the populations of Firmicutes (F) in the intestinal microbiota of the mammal.

Group 31: claims 47-76, directed to a method methods relating to a ratio of the populations of at least one family selected from Erysipelotrichaceae and Peptostreptococcaceae, in the intestinal microbiota of the mammal to the populations of at least one family selected from Lachnospiraceae and Ruminococcaceae in the intestinal microbiota of the mammal.

Group 32+: claims 80-95 and 119, directed to a probiotic composition comprising one or more strains from the genus selected from the group consisting of: Coprobacillus, Sporacetigenium, Holdemania, Dorea, Blautia, Enterococcus, Erysipelotrichaceae Incertae Sedis (EIS), Clostridium cocleatum, and Peptostreptococcaceae – IS (PIS); wherein the first invention is limited to a probiotic composition comprising coprobacillus (applicants may opt for additional strains to be searched by specifying the genus and paying an additional invention search fee for each elected genus).

Group 33: claims 96-112, directed to methods relating to Butyryl CoA transferase (BCoAT) - encoding genes in the intestinal microbiota of the mammal, and the product of BCoAT, butyrate.

Group 34: claims 113-118, directed to methods relating to a ratio of the populations of Clostridium cocleatum (Cc) in the intestinal microbiota of a mammal to the populations of Johnsonella in the intestinal microbiota of the mammal. (see unsearchable claims, below, for an explanation of the elimination of EIS and PIS from this Group).

The groups of inventions listed above 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 technical features for the following reasons:

The only common technical element shared by all of the above groups is that they are related to microbial organisms that may be present in or presented to the gastrointestinal tract of a mammal. Groups 1, 7, 8, 19+, 25+, 29-31, 33 and 34, share a further common technical element of being related to a method for diagnosing predisposition to a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis comprising: a) comparing the population of a microbe in a healthy reference to the population of a subject, wherein an increase in the population in the subject indicates a predisposition to the disease state (Groups 1, 7, 8, 25+ and 33); b) comparing the population of a microbe in a healthy reference to the population a subject, wherein a decrease in the population in the subject indicates a predisposition to the disease state (Groups 19+); or c) comparing two populations of microbes in a subject and determining a predisposition to the disease state based on the ratio (Groups 29-31, 33 and 34). Groups 1-6 also share a common technical element of being related to ileal microbiota, and bacteroidetes.

—continued—
These common technical elements do not represent an improvement over the prior art of US 2010/0172674 A1 to Turnbaugh et al., which teaches the gut microbiome as an immunomarker and therapeutic target for energy metabolism, weight loss and/or obesity in a subject, in particular methods of altering and monitoring the relative abundance of Bacteroides and Firmicutes in the gut microbiome (abstract); wherein "diet-induced obesity is linked to a change in gut microbial ecology, resulting in an increased capacity of the distal gut microbiota (distal - specifically refers to ileal) to promote host adiposity..." (a) is associated with a marked reduction in the overall diversity of the cecal bacterial community... (b) is linked to a bloom of Mollicutes class within the Firmicutes division (para [0018]), wherein the measure used may be a ratio of populations (including the increased ratio of Firmicutes to Bacteroidites; para [0127]) although Turnbaugh does not explicitly recite wherein the diagnosis is based on a decrease in a population, Turnbaugh does teach wherein the relative abundances of Firmicutes and Bacteriodes is relevant (abstract), as well as wherein a decrease in Bacteriodes is correlated with an increase in body fat and weight (para [0044]), and comparison of the populations in a subject to reference populations "a method for selecting a compound for treating obesity or an obesity-related disorder in a host, comprising providing a microbe or microbe population from the host and a plurality of reference microbiome profiles...predicting risk by microbiome profile vs reference profiles (para [0034])." it would have been obvious to a person skilled in the art to make a diagnosis as taught by Turnbaugh based on any of an increase in Firmicutes, a decrease in Bacteriodes in order to change the ratio of the two.

Groups 2, 3, 5, 10, 12, 15, 17, 21+, 23+, 29-31+, 33 and 34 share a common technical element of being related to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a probiotic composition, a prebiotic composition, or a compound, wherein said probiotic composition, prebiotic composition or compound: a) lowers the populations of specific intestinal microbes; b) increases the populations of specific intestinal microbes; c) changes the ratio of specific intestinal microbes. Turnbaugh teaches a composition comprising an antibiosis having efficacy against Firmicutes but not against Bacteriodes, and a prebiotic comprising Bacteriodes (para [0031]), but does not further teach a prebiotic capable of having the same effect. However, in a related disclosure, US 2010/0074872 A1 to Blaser et al. discloses the use of the B/F (bacteriodes/Firmicutes) ratio, which is decreased in mammalian GI microbiota upon sub-therapeutic antibiotic doses, and which is associated with increased body fat and adipose tissue deposition (para [0033]). As well as a method for treating obesity and associated disorders, including type II diabetes, metabolic syndrome, hypertension, cardiac pathology and non-alcoholic fatty liver by restoring GI microbiota to the composition observed in healthy subjects (para [0076]) administration of a therapeutically effective amount of a prebiotic agent or a combination of such agents that (i) increase the number and/or activity of one or more bacteria which are under-represented in a disease and/or (ii) decrease the number and/or activity of one or more bacteria which are over-represented in a disease (para [0044]), it would have been obvious to a person skilled in the art to make a diagnosis as taught by Blaser in the art that the probiotics taught by Blaser, through increasing a desired species, decreasing an undesired species, would have had the effect of altering a ratio of populations including at least said species.

Groups 3, 5, 10, 12, 15, 17, 21+, 23+, 29-31, 33 and 34 share a common technical element of being related to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of: a) a probiotic composition; b) a prebiotic composition; or c) a compound; wherein said agent: i) lowers the amount of a specific microbial population in the gastrointestinal tract; ii) increases the amount of a specific microbial population in a mammal; iii) alters the ratio of microbial populations in a mammal. As indicated above, Turnbaugh teaches preventing or treating at least one of said diseases (para [0030]) using a probiotic or compound that may increase or decrease specific cell populations (para [0031]), and Blaser discloses the use of a prebiotic for similar therapeutic treatments (para [0044]).

Groups 6, 13, 18, 24+, 27+, 29-31, 33 and 34 share a common technical element of being related to a method of: a) lowering: b) increasing or c) changing the ratio of specific microbial populations in a mammal, comprising administering to the mammal a prebiotic composition. As above, Blaser discloses the use of a prebiotic to effect an increase or decrease in desired microbial populations (para [0044]). Although Blaser does not explicitly disclose wherein the probiotic alters the ratios of populations of particular microbes in a mammal's intestinal microbiota, it would have been obvious to a person skilled in the art that the probiotics taught by Blaser through increasing a desired species, decreasing an undesired species, would have had the effect of altering a ratio of populations including at least said species.

Groups 7-18 share a common technical element of being related to populations in the cecal and/or fecal microbiota of a mammal. This common technical element does not represent an improvement over the prior art of Turnbaugh (para [0007]).

Groups 8 and 14-18 share a common technical element of being related to the ratio of the populations of Firmicutes to the populations of Eubacteria (F/E ratio) microbiota of the mammal. This common technical element does not improve upon the prior art of Blaser (para [0068]).

Groups 1-18 share a common technical element of being related to populations of Firmicutes. As above, this common technical element does not improve upon the prior art of Turnbaugh (abstract).

Groups 20+ share a common technical element of being related to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition stimulates growth or metabolic activity of at least one microbe population in the mammal. This common technical element, as above, does not improve upon the prior art of Turnbaugh (para [0030], [0031]).

Groups 21+ share a common technical element of being related to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a probiotic composition, wherein said probiotic composition stimulates growth or metabolic activity of at least one strain of microbe in the mammal. This common technical element, as above, does not improve upon the prior art of Turnbaugh (para [0030], [0031]).
Continuation of: Lack of Unity of Invention:

Groups 22+ share a common technical element of being related to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a prebiotic composition, wherein said prebiotic composition stimulates growth or metabolic activity of at least one strain in the mammal. As above, this common technical element does not improve upon the prior art of Blaser (para [0044]).

Groups 23+ share a common technical element of being related to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a prebiotic composition, wherein said prebiotic composition stimulates growth or metabolic activity of at least one strain in the mammal. As above, this common technical element does not improve upon the prior art of Blaser (para [0044]).

Groups 19+ to 24+ and 32+ share a common technical element of being related to populations of Coprobacillus, Sporacetigenium, Holdemania, Dorea, Enterococcus, or Clostridium cocleatum. (see note below regarding searchability of EIS and PIS). This common technical element does not represent an improvement over the prior art of the article entitled "Revised road map to the phylum Firmicutes" by Ludwig et al., which teaches wherein coprobacillus (pg. 6, col 2, para 3), sporacetigenium (pg. 10, col 1, para 2), Holdemania (pg 12, col 1, para 4), Dorea (pg 6, col 2, para 3), Enterococcus (pg 6, col 1, para 2) and Clostridium cocleatum (pg. 12, col 1, para 4) are members of the phylum Firmicutes (title).

Additionally, the article entitled "Recapitulation of Clostridium coccoides, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus luti, Ruminococcus productus and Ruminococcus schinkii as Blautia coccoides gen. nov., comb. nov., Blautia hansenii comb. nov., Blautia hydrogenotrophica comb. nov., Blautia luti comb. nov., Blautia producta comb. nov., Blautia schinkii comb. nov. and description of Blautia wexleri sp. nov., isolated from human faeces" by Liu et al., discloses a number of proposed Blautia species which were subsequently recorded by post-published Ludwig as being in their original Firmicutes genera (pg. 9, col 1, para 1), and not Blautia. It would have been obvious to a person skilled in the art to measure populations within Firmicutes, as taught by the combination of Ludwig and Liu, under the most recent designation of their genus and genera for the method as taught by Turnbaugh, in order to account for all Firmicutes in a sample.

Groups 25+ share a common technical element of being related to a method for diagnosing predisposition to a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis comprising comparing the population of a microbe in a healthy reference to a subject, wherein an increase in the population in the subject indicates a predisposition to the disease state. As above, this common technical element does not improve upon the prior art of Turnbaugh (abstract, para [0018], [0034], [0127]).

Groups 26+ share a common technical element of being related to a method for promoting weight loss in a mammal comprising administering to the mammal a therapeutically effective amount of a composition or a compound, wherein said composition or compound inhibits growth or metabolic activity of at least one strain of microbe in the mammal. As above, this common technical element does not improve upon the prior art of Turnbaugh (para [0030], [0031]).

Groups 27+ share a common technical element of being related to a method for preventing or treating a disease in a mammal selected from the group consisting of obesity, metabolic syndrome, diabetes mellitus, insulin-deficiency related disorders, insulin-resistance related disorders, glucose intolerance, non-alcoholic fatty liver, abnormal lipid metabolism, and atherosclerosis, said method comprising administering to the mammal a therapeutically effective amount of a composition or a compound, wherein said composition or compound inhibits growth or activity of at least one strain of microbe in the mammal. As above, this common technical element does not improve upon the prior art of Turnbaugh (para [0030], [0031]).

Groups 28+ share a common technical element of being related to a method of inhibiting growth or metabolic activity of at least one strain in the intestinal microbiota of a mammal comprising administering to the mammal a prebiotic composition. As above, this common technical element does not improve upon the prior art of Blaser (para [0044]).

Groups 32+ share a common technical element of being related to a probiotic composition comprising a member of the Firmicutes phylum. This common technical element does not improve upon the prior art of US 2004/0028639 A1 to Borody, which teaches a probiotic comprising a non-pathogenic Clostridium species (para [0023]-[0025]).

Therefore, the inventions of Groups 1 - 34 lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

-------See supplemental page-------

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Continuation of: Lack of Unity of Invention:

NOTES:
Claims 77-79 are not formed according to the second and third sentences of Rule 6.4(a) regarding multiply dependent claims.

Additionally, in the article entitled "Revised road map to the phylum Firmicutes" Ludwig discloses wherein "incertae sedis" families are those which are inserted into different orders, based on a high degree of similarity to other order members, without specifically being well-defined members of an order ("a number of genera were also moved to families incertae sedis in recognition of the ambiguity of their phylogeny and taxonomic assignments"); pg. 3, col 2, para 1). In fact, the latin translation of "incertae sedis" is "of uncertain placement". As such, as the taxonomic record evolves, species present in said families at one point in time may be re-organized to another genera, order or genus at a later point in time, making the specific determination of the specific species claimed as EIS and PIS species obscure. Ludwig further teaches that, although the genera Erysipelotrichaceae (pg 12, col 1, para 4), and Peptostreptococcaceae (pg. 10, col 1, para 2) are present in the Firmicutes phylum, the incertae sedis families for these genera do not exist (are null sets) for the 2009 reorganization of the Firmicutes. Therefore, the portions of claims 19-26, 31, 41-46, 53, 80 and 113-118 relating to classifications "Incetae sedis" (EIS and PIS) are deemed to be unsearchable under Article 34(4)(a)(ii) because the subject matter of the claim (or portion thereof) is too unclear with regard to precisely what species are referred to for a proper determination of novelty, inventive step, or industrial applicability to be made.