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(54) Title: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

(57) Abstract: Provided herein are methods and compositions for the treatment of cancer by modulating the microbiome to enhance the efficacy of immune checkpoint blockade. The microbiome may be modulated by the admimstration of butyrate and/or butyrate-producing bacteria. Also provided herein are methods of determining a response to an immune checkpoint inhibitor by identifying if a subject has a favorable microbial profile.

# DESCRIPTION

# METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

**[0001]** This application claims the benefit of United States Provisional Patent Applications No. 62/400,372, filed September 27, 2016; No. 62/508,885, filed May 19, 2017; and No. 62/557,566, filed September 12, 2017, each of which is incorporated herein by reference in its entirety.

## BACKGROUND OF THE INVENTION

### 1. Field of the Invention

**[0002]** The present invention relates generally to the fields of microbiology, immunology, and medicine. More particularly, it concerns the use of the microbiome to improve the efficacy of immune checkpoint blockade therapy

### 2. Description of Related Art

**[0003]** Within the past decade, major advances have been made in the treatment of melanoma through the use of targeted therapy and immunotherapy. In particular, the use of immune checkpoint inhibitors has shown tremendous promise, leading to the FDA approval of several agents blocking immuno-modulatory molecules on the surface of T lymphocytes *(e.g.,* anti-CTLA-4 antibody Ipilimumab, and anti-PD-1 antibodies Nivolumab, Pembrolizumab). Importantly, treatment with immune checkpoint blockade may result in durable long-term complete responses, though overall response rates are modest *(i.e.,* 15% with CTLA-4 blockade, and 30-40% with PD-1 blockade).

**[0004]** However, immune checkpoint inhibitors can be associated with substantial toxicity and only a subset of patients may benefit. Efforts are underway to better understand variation in responses to immune checkpoint blockade; however, it remains unclear what is contributing to this enhanced response in these patients, and there is a critical need to identify actionable strategies to improve responses to therapy in all patients.

**[0005]** There is an increasing appreciation of the role of the host microbiome in responses to cancer therapy, and studies suggest that bacteria present in the tumor and the gut

may impact therapeutic responses. There is also a growing appreciation of the role of the gastrointestinal microbiome in shaping immune responses in health and disease. However, there is a significant translational knowledge gap, and there is an unmet need for therapeutic strategies to enhance responses to immune checkpoint blockade in melanoma, and other cancers.

## SUMMARY OF THE INVENTION

**[0006]** In one embodiment, the present disclosure provides a composition comprising at least one isolated or purified population of bacteria belonging to of one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae. In other embodiments, the composition comprises at least two isolated or purified populations of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae. In certain embodiments, the composition is a live bacterial product, live biotherapeutic product or a probiotic composition. In still other embodiments, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria are provided as bacterial spores. In another embodiment, the at least one population of bacteria belongs to Clostridiales Family XII and/or Clostridiales Family XIII. In some aspects, the composition comprises at least two isolated or purified populations of bacteria belonging to the family Ruminococcaceae and/or of the family Clostridiaceae. In other embodiments, the composition comprises at least one population belonging to the family Ruminococcaceae and at least one population belonging to the family Clostridiaceae. In some aspects, the two populations of bacteria belonging to the family Ruminococcaceae are further defined as populations of bacteria belonging to the genus *Ruminococcus.* In certain aspects, the at least two isolated or purified populations of bacteria belonging to the family Ruminococcaceae are further defined as populations of bacteria belonging to the genus *Faecalibacterium.* In certain aspects, the population of bacteria belonging to the genus *Faecalibacterium* are further defined as a population of bacteria belonging to the species *Faecalibacterium prausnitzii.* In certain aspects, the population of bacteria belonging to the genus *Ruminococcus* are further defined as a population of bacteria belonging to the species *Ruminococcus bromii.* In some aspects, the at least two isolated or purified populations of bacteria belonging to the family Micrococcaceae are further defined as a population of bacteria belonging to the genus *Rothia.* In additional aspects, the composition further comprises a population of bacteria belonging to the species

*Porphyromonas pasteri,* the species *Clostridium hungatei,* the species *Phascolarctobacterium faecium,* the genus *Peptoniphilus,* and/or the class Mollicutes. In certain aspects, the composition does not comprise populations of bacteria belonging to the order Bacteroidales.

**[0007]** Particular embodiments of the present disclosure provide a method of preventing cancer in a subject comprising administering a composition of the embodiments to the subject. For example, in some aspects, a method is provided for preventing cancer in a subject at risk for developing cancer *(e.g.,* a melanoma) or treating cancer in a subject having a tumor comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium,* wherein administration of the composition results in an increase of $CD8^+$ T lymphocytes in the tumor. In particular embodiments, the T lymphocytes are cytotoxic T lymphocytes. In still other embodiments, the method is a method of treating cancer in a subject comprising administerting a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium,* wherein administration of the composition results in an increase of effector $CD4^+$, $CD8^+$ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject. In some embodiments, the method is a method of treating cancer in a subject comprising administerting a composition comprising at least one isolated or purified population of bacteria belonging one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium* and/or *Ruminococcus,* wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject. In other aspects, the method is a method of treating cancer in a subject having a tumor comprising administering a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium,* wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate. In still other aspects, the method is a method of treating cancer in a subject having a tumor comprising administering a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus

*Faecalibacterium*, wherein administration of the composition to the subject results in an decrease in RORγT expression in a tumor immune infiltrate. Also described are methods of treating a tumor in a subject diagnosed with or suspected of having cancer comprising administering a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*, wherein administration of the composition to the subject results in an increase in $CD45^+$, $CD3^+/CD20^+/CD56^+$, $CD68^+$ and/or $HLA\text{-}DR^+$ cells in the tumor. In some aspects, a composition of the embodiments is administered in a sufficient amount to increase the level of innate effector cells in the subject. In other aspects, administration of the composition to the subject results in an increase in the level of innate effector cells in the subject. For example, administration of the composition can increase innate effector cells such as $CD45^+CDllb^+Ly6G^+$ cells. In some aspects, a composition of the embodiments is administered in a sufficient amount to decrease the level of suppressive myeloid cells in the subject. In additional aspects, administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject. For example, administration of the composition can decrease the level of suppressive myeloid cells such as $CD45^+CDllb^+CDllc^+$ cells. In particular embodiments, the composition comprises the bacteria *Faecalibacterium prausnitzii*.

**[0008]** Another embodiment provides a method of treating cancer in a subject comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject, wherein the subject has been determined to have a favorable microbial profile in the gut microbiome. In some aspects, a favorable microbial profile is further defined as having one or more of the bacterial populations of the probiotic or live bacterial product compositions of the embodiments. In a further embodiment, there is provided a method of predicting a response *(e.g.,* predicting survival) to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises one or more of the bacterial populations of the probiotic or live bacterial product compositions of the embodiments, the response is favorable. In particular embodiments, a patient is administered an immune checkpoint inhibitor if the patient is predicted to have a favorable response to the immune checkpoint inhibitor. In certain embodiments, the favorable microbial profile is a favorable gut microbial profile.

**[0009]** In some embodiments, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to one or more of the species, subspecies or bacterial strains selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5, 0.6, 0.7, 0.8 or 0.9. In particular embodiments, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria are selected from the group consisting of the species in Table 1 with an "ei" equal to 1.

**[0010]** In certain aspects, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the species, subspecies or bacterial strains identified by NCBI Taxonomy IDs selected from the group consisting of NCBI Taxonomy ID: 717959, 587, 758823, 649756, 44749, 671218, 1264, 1122135, 853, 484018, 46503, 54565, 290052, 216931, 575978, 433321, 1796646, 213810, 228924, 290054, 1509, 1462919, 29375, 337097, 1298596, 487174, 642492, 1735, 1297424, 742766, 46680, 132925, 411467, 1318465, 1852367, 1841857, 169679, 1175296, 259063, 172901, 39488, 57172, 28118, 166486, 28133, 1529, 694434, 1007096, 84030, 56774, 102148, 626947, 216933, 1348613, 1472417, 100176, 824, 1471761, 1297617, 288966, 1317125, 28197, 358743, 264639, 1265, 1335, 66219, 69473, 115117, 341220, 1732, 873513, 396504, 1796619, 45851, 2741, 105841, 86332, 1349822, 84037, 180311, 54291, 1217282, 762984, 1185412, 154046, 663278, 1543, 398512, 69825, 1841867, 1535, 1510, 84026, 1502, 1619234, 39497, 1544, 29343, 649762, 332095, 536633, 1033731, 574930, 742818, 177412, 1121308, 419208, 1673717, 55779, 28117, 626937, 180332, 1776382, 40519, 34062, 40518, 74426, 1216062, 293826, 850, 645466, 474960, 36835, 115544, 1515, 88431, 216932, 1417852, 39492, 1583, 420247, 118967, 169435, 37658, 138595, 31971, 100886, 1197717, 234908, 537007, 319644, 168384, 915173, 95159, 1816678, 626940, 501571, 1796620, 888727, 1147123, 376806, 1274356, 1267, 39495, 404403, 1348, 253314, 258515, 33033, 1118061, 357276, 214851, 320502, 217731, 246787, 29371, 649764, 901, 29374, 33043, 39778, 682400, 871665, 160404, 745368, 408, 1584, 333367, 47246, 1096246, 53342, 438033, 351091, 1796622, 1776384, 817, 48256, 720554, 500632, 36849, 301302, 879970, 655811, 264463, 1532, 285, 995, 242750, 29539, 1432052, 622312, 1796636, 1337051, 328814, 28446, 1492, 820, 39496, 52786, 1549, 1796618, 582, 46507, 109327, 1531, 1382, 33039, 311460, 230143, 216935, 539, 35519, 1681, 328813, 214853, 89014, 1121115, 1585974, 29466, 1363, 292800, 270498, 214856, 142877, 133926, 209880, 179628, 1121102, 105612, 1796615, 39777, 29353, 1579, 163665, 53443, 261299, 1302, 1150298, 938289, 358742, 471875, 938278, 1796613, 1118057, 1077144,

1737, 218205, 1121298, 684066, 433659, 52699, 204516, 706562, 253257, 328812, 1280, 147802, 58134, 1335613, 891, 585394, 1582, 235931, 308994, 1589, 1682, 1736, 28129, 178001, 551788, 2051, 856, 118562, 101070, 515619, 40215, 187979, 82979, 29363, 1776391, 1285191, 84112, 157688, 38304, 36850, 341694, 287, 75612, 818, 371674, 338188, 88164, 588581, 676965, 546271, 1236512, 178338, 862517, 157687, 158, 51048, 1583331, 529, 888745, 394340, 40545, 855, 553973, 938293, 93063, 708634, 179995, 1351, 476652, 1464038, 555088, 237576, 879566, 1852371, 742727, 1377, 35830, 997353, 218538, 83771, 1605, 28111, 131109, 46609, 690567, 46206, 155615, 51616, 40542, 203, 294, 1034346, 156456, 80866, 554406, 796942, 1002367, 29347, 796944, 61592, 487175, 1050201, 762948, 137732, 1211819, 1019, 272548, 1717, 384636, 216940, 2087, 45634, 466107, 1689, 47678, 575, 979627, 840, 1660, 1236517, 617123, 546, 28135, 82171, 483, 501496, 99656, 1379, 84032, 39483, 1107316, 584, 28124, 1033744, 657309, 536441, 76123, 1118060, 89152, 76122, 303, 1541, 507751, 515620, 38302, 53419, 726, 40324, 1796610, 988946, 1852370, 1017, 1168289, 76936, 94869, 1161098, 215580, 1125779, 327575, 549, 1450648 and 478. In specific aspects, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria are closely related to the species, subspecies or bacterial strains identified by NCBI Taxonomy IDs listed above. For example, in some aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria belong to species, subspecies or strains comprises a 16S ribosomal RNA (rRNA) nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the 16S rRNA nucleotide sequence of one of the bacteria listed above *(i.e.,* the Set 1 bacteria from Table 1) or bacteria listed in Table 1 and having an ei greater that 0.5 or equal to 1.

**[0011]** In still other aspects, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the species, subspecies or bacterial strains selected from the group consisting of *Bacteroides coagulans, Clostridium aldenense, Clostridium aldrichii, Clostridium alkalicellulosi, Clostridium amygdalinum, Clostridium asparagiforme, Clostridium cellulosi, Clostridium citroniae, Clostridium clariflavum DSM 19732, Clostridium clostridioforme, Clostridium colinum, Clostridium fimetarium, Clostridium hiranonis, Clostridium hungatei, Clostridium hylemonae DSM 15053, Clostridium indolis, Clostridium lactatifermentans, Clostridium leptum, Clostridium methylpentosum, Clostridium oroticum, Clostridium papyrosolvens DSM 2782, Clostridium populeti, Clostridium propionicum, Clostridium saccharolyticum, Clostridium scindens,*

*Clostridium sporosphaeroides, Clostridium stercorarium, Clostridium straminisolvens, Clostridium sufflavum, Clostridium termitidis, Clostridium thermosuccinogenes, Clostridium viride, Clostridium xylanolyticum, Desuljotomaculum guttoideum, Eubacterium rectale ATCC 33656, Eubacterium dolichum, Eubacterium eligens ATCC 27750, Eubacterium hallii, Eubacterium infirmum, Eubacterium siraeum, Eubacterium tenue, Ruminococcus torques, Acetanaerobacterium elongatum, Acetatifactor muris, Acetivibrio cellulolyticus, Acetivibrio ethanolgignens, Acholeplasma brassicae 0502, Acholeplasma parvum, Acholeplasma vituli, Acinetobacter junii, Actinobacillus porcinus, Actinomyces bowdenii, Actinomyces dentalis, Actinomyces odontolyticus, Acutalibacter muris, Aerococcus viridans, Aeromicrobium fastidiosum, Alistipes finegoldii, Alistipes obesi, Alistipes onderdonkii, Alistipes putredinis, Alistipes shahii, Alistipes shahii WAL 8301, Alistipes timonensis JC136, Alkalibacter saccharofermentans, Alkaliphilus metalliredigens QYMF, Allisonella histaminiformans, Allobaculum stercoricanis DSM 13633, Alloprevotella rava, Alloprevotella tannerae, Anaerobacterium chartisolvens, Anaerobiospirillum thomasii, Anaerobium acetethylicum, Anaerococcus octavius NCTC 9810, Anaerococcus provenciensis, Anaerococcus vaginalis ATCC 51170, Anaerocolumna jejuensis, Anaerofilum agile, Anaerofustis stercorihominis, Anaeroglobus geminatus, Anaeromassilibacillus senegalensis, Anaeroplasma abactoclasticum, Anaerorhabdus furcosa, Anaerosporobacter mobilis, Anaerostipes butyraticus, Anaerostipes caccae, Anaerostipes hadrus, Anaerotruncus colihominis, Anaerovorax odorimutans, Anoxybacillus rupiensis, Aquabacterium limnoticum, Arcobacter butzleri, Arthrospira platensis, Asaccharobacter celatus, Atopobium parvulum, Bacteroides caccae, Bacteroides caecimuris, Bacteroides cellulosilyticus, Bacteroides clarus YIT 12056, Bacteroides dorei, Bacteroides eggerthii, Bacteroides finegoldii, Bacteroides fragilis, Bacteroides gallinarum, Bacteroides massiliensis, Bacteroides oleiciplenus YIT 12058, Bacteroides plebeius DSM 17135, Bacteroides rodentium JCM 16496, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides xylanisolvens XB1A, Bacteroides xylanolyticus, Barnesiella intestinihominis, Beduini massiliensis, Bifidobacterium bifidum, Bifidobacterium dentium, Bifidobacterium longum subsp. infantis, Blautia caecimuris, Blautia coccoides, Blautia faecis, Blautia glucerasea, Blautia hansenii DSM 20583, Blautia hydrogenotrophica, Blautia luti, Blautia luti DSM 14534, Blautia wexlerae DSM 19850, Budvicia aquatica, Butyricicoccus pullicaecorum, Butyricimonas paravirosa, Butyrivibrio crossotus, Caldicoprobacter oshimai, Caloramator coolhaasii, Caloramator proteoclasticus, Caloramator quimbayensis, Campylobacter gracilis, Campylobacter rectus, Campylobacter ureolyticus DSM 20703, Capnocytophaga gingivalis, Capnocytophaga leadbetteri,*

*Capnocytophaga sputigena, Casaltella massiliensis, Catabacter hongkongensis, Catenibacterium mitsuokai, Christensenella minuta, Christensenella timonensis, Chryseobacterium taklimakanense, Citrobacter freundii, Cloacibacillus porcorum, Clostridioides difficile ATCC 9689 = DSM 1296, Clostridium amylolyticum, Clostridium bowmanii, Clostridium butyricum, Clostridium cadaveris, Clostridium colicanis, Clostridium gasigenes, Clostridium lentocellum DSM 5427, Clostridium oceanicum, Clostridium oryzae, Clostridium paraputrificum, Clostridium pascui, Clostridium perfringens, Clostridium quinii, Clostridium saccharobutylicum, Clostridium sporogenes, Clostridium ventriculi, Collinsella aerofaciens, Comamonas testosteroni, Coprobacter fastidiosus NSB1, Coprococcus eutactus, Corynebacterium diphtheriae, Corynebacterium durum, Corynebacterium mycetoides, Corynebacterium pyruviciproducens ATCC BAA-1742, Corynebacterium tuberculostearicum, Culturomica massiliensis, Cuneatibacter caecimuris, Defluviitalea saccharophila, Delftia acidovorans, Desulfitobacterium chlororespirans, Desulfitobacterium metallireducens, Desulfosporosinus acididurans, Desulfotomaculum halophilum, Desulfotomaculum intricatum, Desulfotomaculum tongense, Desulfovibrio desulfuricans subsp. desulfuricans, Desulfovibrio idahonensis, Desulfovibrio litoralis, Desulfovibrio piger, Desulfovibrio simplex, Desulfovibrio zosterae, Desulfuromonas acetoxidans, Dethiobacter alkaliphilus AHT 1, Dethiosulfatibacter aminovorans, Dialister invisus, Dialister propionicifaciens, Dielma fastidiosa, Dietzia alimentaria 72, Dorea longicatena, Dysgonomonas gadei ATCC BAA-286, Dysgonomonas mossii, Eggerthella lenta, Eikenella corrodens, Eisenbergiella tayi, Emergencia timonensis, Enorma massiliensis phi, Enterococcus faecalis, Enterorhabdus muris, Ethanoligenens harbinense YUAN-3, Eubacterium coprostanoligenes, Eubacterium limosum, Eubacterium oxidoreducens, Eubacterium sulci ATCC 35585, Eubacterium uniforme, Eubacterium ventriosum, Eubacterium xylanophilum, Extibacter muris, Ezakiella peruensis, Faecalibacterium prausnitzii, Faecalicoccus acidiformans, Faecalitalea cylindroides, Filifactor villosus, Flavonifractor plautii, Flintibacter butyricus, Frisingicoccus caecimuris, Fucophilus fucoidanolyticus, Fusicatenibacter saccharivorans, Fusobacterium mortiferum, Fusobacterium nucleatum subsp. vincentii, Fusobacterium simiae, Fusobacterium varium, Garciella nitratireducens, Gemella haemolysans, Gemmiger formicilis, Gordonibacter urolithinfaciens, Gracilibacter thermotolerans JW/YJL-S1, Granulicatella elegans, Guggenheimella bovis, Haemophilus haemolyticus, Helicobacter typhlonius, Hespellia stercorisuis, Holdemanella biformis, Holdemania massiliensis AP2, Howardella ureilytica, Hungatella effluvii, Hungatella hathewayi, Hydrogenoanaerobacterium saccharovorans, Ihubacter massiliensis, Intestinibacter bartlettii, Intestinimonas*

*butyriciproducens, Irregularibacter muris, Kiloniella laminariae DSM 19542, Kroppenstedtia guangzhouensis, Lachnoanaerobaculum orale, Lachnoanaerobaculum umeaense, Lachnoclostridium phytofermentans, Lactobacillus acidophilus, Lactobacillus algidus, Lactobacillus animalis, Lactobacillus casei, Lactobacillus delbrueckii, Lactobacillus jornicalis, Lactobacillus iners, Lactobacillus pentosus, Lactobacillus rogosae, Lactococcus garvieae, Lactonifactor longoviformis, Leptotrichia buccalis, Leptotrichia hofstadii, Leptotrichia hongkongensis, Leptotrichia wadei, Leuconostoc inhae, Levyella massiliensis, Loriellopsis cavernicola, Lutispora thermophila, Marinilabilia salmonicolor JCM 21150, Marvinbryantia formatexigens, Mesoplasma photuris, Methanobrevibacter smithii ATCC 35061, Methanomassiliicoccus luminyensis BIO, Methylobacterium extorquens, Mitsuokella jalaludinii, Mobilitalea sibirica, Mobiluncus curtisii, Mogibacterium pumilum, Mogibacterium timidum, Moorella glycerini, Moorella humiferrea, Moraxella nonliquefaciens, Moraxella osloensis, Morganella morganii, Moryella indoligenes, Muribaculum intestinale, Murimonas intestini, Natranaerovirga pectinivora, Neglecta timonensis, Neisseria cinerea, Neisseria oralis, Nocardioides mesophilus, Novibacillus thermophilus, Ochrobactrum anthropi, Odoribacter splanchnicus, Olsenella profusa, Olsenella uli, Oribacterium asaccharolyticum ACB7, Oribacterium sinus, Oscillibacter ruminantium GH1, Oscillibacter valericigenes, Oxobacter pfennigii, Pantoea agglomerans, Papillibacter cinnamivorans, Parabacteroides faecis, Parabacteroides goldsteinii, Parabacteroides gordonii, Parabacteroides merdae, Parasporobacterium paucivorans, Parasutterella excrementihominis, Parasutterella secunda, Parvimonas micra, Peptococcus niger, Peptoniphilus duerdenii ATCC BAA-1640, Peptoniphilus grossensis ph5, Peptoniphilus koenoeneniae , Peptoniphilus senegalensis JC140, Peptostreptococcus stomatis, Phascolarctobacterium succinatutens, Phocea massiliensis, Pontibacter indicus, Porphyromonas bennonis, Porphyromonas endodontalis, Porphyromonas pasteri, Prevotella bergensis, Prevotella buccae ATCC 33574, Prevotella denticola, Prevotella enoeca, Prevotella fusca JCM 17724, Prevotella loescheii, Prevotella nigrescens, Prevotella oris, Prevotella pollens ATCC 700821, Prevotella stercorea DSM 18206, Prevotellamassilia timonensis, Propionispira arcuata, Proteus mirabilis, Providencia rettgeri, Pseudobacteroides cellulosolvens ATCC 35603 = DSM 2933, Pseudobutyrivibrio ruminis, Pseudoflavonifr actor capillosus ATCC 29799, Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas mandelii, Pseudomonas nitroreducens, Pseudomonas putida, Raoultella ornithinolytica, Raoultella planticola, Raoultibacter massiliensis, Robinsoniella peoriensis, Romboutsia timonensis, Roseburia faecis, Roseburia hominis A2-183, Roseburia intestinalis, Roseburia inulinivorans DSM 16841, Rothia dentocariosa ATCC 17931, Ruminiclostridium*

*thermocellum, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus champanellensis 18P13 = JCM 17042, Ruminococcus faecis JCM 15917, Ruminococcus flavefaciens, Ruminococcus gauvreauii, Ruminococcus lactaris ATCC 29176, Rummeliibacillus pycnus, Saccharofermentans acetigenes, Scardovia wiggsiae, Schlegelella thermodepolymerans, Sedimentibacter hongkongensis, Selenomonas sputigena ATCC 35185, Slackia exigua ATCC 700122, Slackia piriformis YIT 12062, Solitalea canadensis, Solobacterium moorei, Sphingomonas aquatilis, Spiroplasma alleghenense, Spiroplasma chinense, Spiroplasma chrysopicola, Spiroplasma culicicola, Spiroplasma lampyridicola, Sporobacter termitidis, Staphylococcus aureus, Stenotrophomonas maltophilia, Stomatobaculum longum, Streptococcus agalactiae ATCC 13813, Streptococcus cristatus, Streptococcus equinus, Streptococcus gordonii, Streptococcus lactarius, Streptococcus parauberis, Subdoligranulum variabile, Succinivibrio dextrinosolvens, Sutterella stercoricanis, Sutterella wadsworthensis, Syntrophococcus sucromutans, Syntrophomonas zehnderi OL-4, Terrisporobacter mayombei, Thermoleophilum album, Treponema denticola, Treponema socranskii, Tyzzerella nexilis DSM 1787, Vallitalea guaymasensis, Vallitalea pronyensis, Vampirovibrio chlorellavorus, Veillonella atypica, Veillonella denticariosi, Veillonella dispar, Veillonella parvula, Victivallis vadensis, Vulcanibacillus modesticaldus and Weissella confusa.*

**[0012]** In certain aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations belong to species of bacteria selected from the species in Table 2 designated with a response status of responder (R). In still further aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria belong to species, subspecies or strains comprising a 16S ribosomal RNA (rRNA) nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the 16S rRNA nucleotide sequence of bacteria selected from the species in Table 2 designated with a response status of responder (R). In particular aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria comprises a 16S ribosomal RNA (rRNA) nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the 16S rRNA nucleotide sequence of bacteria selected from the group consisting of the species in Table 2 designated with a response status of responder (R) and having an unadjusted p-value less than 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, or 0.01.

**[0013]** In certain aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria comprises a 16S ribosomal RNA (rRNA) nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the 16S rRNA nucleotide sequence of bacteria selected from the group consisting of the species in Table 1 designated with a response status of responder (R) and having an unadjusted p-value less than 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, or 0.01. In particular embodiments, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria are a species, subspecies or bacterial strains comprising a 16S rRNA gene sequence at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 1-876.

**[0014]** In some aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations belong to species of bacteria selected from the species in Table 2 designated with a response status of responder (R). In particular aspects, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to species of bacteria selected from the group consisting of the species in Table 2 designated with a response status of responder (R) and having an unadjusted p-value less than 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, or 0.01. In still other aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria belong to species, subspecies or strains comprising nucleotide sequences with at least 60%, 65%, 70%, 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% percent identity to the co-abundance gene group (CAG) sequences (see, Table 2A) selected from the group consisting of SEQ ID NO: 877-926, SEQ ID NO: 927-976, SEQ ID NO: 977-1026, SEQ ID NO: 1027-1076, SEQ ID NO: 1077-1126, SEQ ID NO: 1127-1176, SEQ ID NO: 1177-1226, SEQ ID NO: 1227-1276, SEQ ID NO: 1277-1326, SEQ ID NO: 1327-1376, SEQ ID NO: 1377-1426, SEQ ID NO: 1427-1476, SEQ ID NO: 1477-1526, SEQ ID NO: 1527-1576, SEQ ID NO: 1577-1626, SEQ ID NO: 1627-1676, SEQ ID NO: 1677-1726, SEQ ID NO: 1727-1776, SEQ ID NO: 1777-1826, SEQ ID NO: 1827-1876, SEQ ID NO: 1877-1926, SEQ ID NO: 1927-1976, SEQ ID NO: 1977-2026, SEQ ID NO: 2027-2076, SEQ ID NO: 2077-2126, SEQ ID NO: 2127-2176, SEQ ID NO: 2177-2226, SEQ ID NO: 2227-2276, SEQ ID NO: 2277-2326, SEQ ID NO: 2327-2376, SEQ ID NO: 2377-2426, SEQ ID NO: 2427-2476, SEQ ID NO: 2477-2526, SEQ ID NO: 2527-2576, SEQ ID NO: 2577-2626 and SEQ ID NO: 2627-2676.

| CAG ID | Sequence Identifiers |
|---|---|
| CAG00327 | SEQ ID NO: 877-926 |
| CAG00659 | SEQ ID NO: 927-976 |
| CAG00492 | SEQ ID NO: 977-1026 |
| CAG00518 | SEQ ID NO: 1027-1076 |
| CAG01146 | SEQ ID NO: 1077-1126 |
| CAG00079 | SEQ ID NO: 1127-1176 |
| CAG00393 | SEQ ID NO: 1177-1226 |
| CAG00766 | SEQ ID NO: 1227-1276 |
| CAG00095 | SEQ ID NO: 1277-1326 |
| CAG00010_1 | SEQ ID NO: 1327-1376 |
| CAG00342 | SEQ ID NO: 1377-1426 |
| CAG00303 | SEQ ID NO: 1427-1476 |
| CAG00337 | SEQ ID NO: 1477-1526 |
| CAG00381 | SEQ ID NO: 1527-1576 |
| CAG00559 | SEQ ID NO: 1577-1626 |
| CAG00570 | SEQ ID NO: 1627-1676 |
| CAG00635 | SEQ ID NO: 1677-1726 |
| CAG00636 | SEQ ID NO: 1727-1776 |
| CAG00660 | SEQ ID NO: 1777-1826 |
| CAG00669 | SEQ ID NO: 1827-1876 |
| CAG00708 | SEQ ID NO: 1877-1926 |
| CAG00773 | SEQ ID NO: 1927-1976 |
| CAG00807 | SEQ ID NO: 1977-2026 |
| CAG00880 | SEQ ID NO: 2027-2076 |
| CAG00907 | SEQ ID NO: 2077-2126 |
| CAG01086 | SEQ ID NO: 2127-2176 |
| CAG01215 | SEQ ID NO: 2177-2226 |
| CAG01277 | SEQ ID NO: 2227-2276 |
| CAG01308 | SEQ ID NO: 2277-2326 |
| CAG00577 | SEQ ID NO: 2327-2376 |
| CAG00506 | SEQ ID NO: 2377-2426 |
| CAG00852 | SEQ ID NO: 2427-2476 |
| CAG01046 | SEQ ID NO: 2477-2526 |
| CAG00320 | SEQ ID NO: 2527-2576 |
| CAG00619 | SEQ ID NO: 2577-2626 |
| CAG01366 | SEQ ID NO: 2627-2676 |

**[0015]** In certain aspects, the at least one isolated or purified population of bacteria or the two populations of bacteria are selected from the group consisting of species, subspecies or strains comprising nucleotide sequences with at least 29% identity to SEQ ID NO: 877-926, at least 16.5% identity to SEQ ID NO: 927-976, at least 48.5% identity to SEQ ID NO: 977-1026,

at least 28% identity to SEQ ID NO: 1027-1076, at least 93.5% identity to SEQ ID NO: 1077-1126, at least 99.5% identity to SEQ ID NO: 1127-1176, at least 99.5% identity to SEQ ID NO: 1177-1226, at least 99% identity to SEQ ID NO: 1227-1276, 100% identity to SEQ ID NO: 1277-1326, at least 21.5% identity to SEQ ID NO: 1327-1376, 100% identity to SEQ ID NO: 1377-1426, at least 97% identity to SEQ ID NO: 1427-1476, at least 55.5% identity to SEQ ID NO: 1477-1526, 100% identity to SEQ ID NO: 1527-1576, at least 34% identity to SEQ ID NO: 1577-1626, at least 14% identity to SEQ ID NO: 1627-1676, 100% identity to SEQ ID NO: 1677-1726, at least 93% identity to SEQ ID NO: 1727-1776, 100% identity to SEQ ID NO: 1777-1826, at least 45% identity to SEQ ID NO: 1827-1876, at least 99% identity to SEQ ID NO: 1877-1926, at least 74% identity to SEQ ID NO: 1927-1976, 100% identity to SEQ ID NO: 1977-2026, 100% identity to SEQ ID NO: 2027-2076, at least 20% identity to SEQ ID NO: 2077-2126, at least 84% identity to SEQ ID NO: 2127-2176, at least 35.5% identity to SEQ ID NO: 2177-2226, at least 32.5% identity to SEQ ID NO: 2227-2276, at least 70% identity to SEQ ID NO: 2277-2326, 100% identity to SEQ ID NO: 2327-2376, at least 70.5% identity to SEQ ID NO: 2377-2426, at least 99.5% identity to SEQ ID NO: 2427-2476, at least 68.5% identity to SEQ ID NO: 2477-2526, 100% identity to SEQ ID NO: 2527-2576, at least 97.5% identity to SEQ ID NO: 2577-2626 or 100% identity to SEQ ID NO: 2627-2676.

**[0016]** In certain aspects, the at least one isolated or purified population of bacteria or the two populations of bacteria are selected from the group consisting of species, subspecies or strains comprising nucleotide sequences with at least 29% identity to genes of *Faecalibacterium sp.* CAG:74 corresponding to SEQ ID NO: 877-926, at least 16.5% identity to genes of *Clostridiales bacterium* NK3B98 corresponding to SEQ ID NO: 927-976, at least 48.5% identity to genes of Subdoligranulum sp. 4_3_54A2FAA corresponding to SEQ ID NO: 977-1026, at least 28% identity to genes of *Faecalibacterium sp.* CAG:74 corresponding to genes of corresponding to SEQ ID NO: 1027-1076, at least 93.5% identity to genes of *Oscillibacter sp.* CAG:155 corresponding to SEQ ID NO: 1077-1126, at least 99.5% identity to genes of *Clostridium sp.* CAG:7 corresponding to SEQ ID NO: 1127-1176, at least 99.5% identity to genes of *Eubacterium sp.* CAG:86 corresponding to SEQ ID NO: 1177-1226, at least 99% identity to genes of *Firmicutes bacterium* CAG:176 corresponding to SEQ ID NO: 1227-1276, 100% identity to genes of *Akkermansia sp.* CAG:344 corresponding to SEQ ID NO: 1277-1326, at least 21.5% identity to genes of *Faecalibacterium sp.* CAG:74 corresponding to SEQ ID NO: 1327-1376, 100% identity to genes of *Bifidobacterium pseudocatenulatum* DSM 20438 = JCM 1200 = LMG 10505 corresponding to SEQ ID NO:

1377-1426, at least 97% identity to genes of *Clostridium sp.* JCC corresponding to SEQ ID NO: 1427-1476, at least 55.5% identity to genes of *Faecalibacterium prausnitzii* SL3/3 corresponding to SEQ ID NO: 1477-1526, 100% identity to genes of *Clostridium sp.* CAG:242 corresponding to SEQ ID NO: 1527-1576, at least 34% identity to genes of *Clostridium sp.* CAG:226 corresponding to SEQ ID NO: 1577-1626 , at least 14% identity to genes of *Ruminococcus sp.* CAG:382 corresponding to SEQ ID NO: 1627-1676, 100% identity to genes of *Bifidobacterium bifidum* S17 corresponding to SEQ ID NO: 1677-1726, at least 93% identity to genes of *Roseburia sp.* CAG:309 corresponding to SEQ ID NO: 1727-1776, 100% identity to genes of *Alistipes timonensis* JC136 corresponding to SEQ ID NO: 1777-1826, at least 45% identity to genes of *Firmicutes bacterium* CAG:103 corresponding to SEQ ID NO: 1827-1876, at least 99% identity to genes of *Alistipes senegalensis* JC50 corresponding to SEQ ID NO: 1877-1926, at least 74% identity to genes of *Firmicutes bacterium* CAG:176 corresponding to SEQ ID NO: 1927-1976, 100% identity to genes of *Holdemanella biformis* DSM 3989 corresponding to SEQ ID NO: 1977-2026, 100% identity to genes of *Subdoligranulum sp.* CAG:314 corresponding to SEQ ID NO: 2027-2076, at least 20% identity to genes of *Clostridium sp.* CAG:226 corresponding to SEQ ID NO: 2077-2126, at least 84% identity to genes of *Firmicutes bacterium* CAG:124 corresponding to SEQ ID NO: 2127-2176, at least 35.5% identity to genes of *lntestinimonas butyriciproducens* corresponding to SEQ ID NO: 2177-2226, at least 32.5% identity to genes of *Clostridium sp.* CAG:226 corresponding to SEQ ID NO: 2227-2276, at least 70% identity to genes of *Firmicutes bacterium* CAG:124 corresponding to SEQ ID NO: 2277-2326, 100% identity to genes of *Faecalibacterium prausnitzii* L2-6 corresponding to SEQ ID NO: 2327-2376, at least 70.5% identity to genes of *Ruminococcaceae bacterium* D16 corresponding to SEQ ID NO: 2377-2426, at least 99.5% identity to genes of *Clostridium spiroforme* DSM 1552 corresponding to SEQ ID NO: 2427-2476, at least 68.5% identity to genes of *lntestinimonas butyriciproducens* corresponding to SEQ ID NO: 2477-2526, 100% identity to genes of *Phascolarctobacterium sp.* CAG:207 corresponding to SEQ ID NO: 2527-2576, at least 97.5% identity to genes of *Faecalibacterium prausnitzii* L2-6 corresponding to SEQ ID NO: 2577-2626 of or 100% identity to genes of *Streptococcus parasanguinis* ATCC 15912 corresponding to SEQ ID NO: 2627-2676.

**[0017]** In some aspects, the bacteria are lyophilized or freeze dried. In particular aspects, the composition is formulated for oral delivery. For example, the composition formulated for oral delivery is a tablet or capsule. In particular aspects, the tablet or capsule comprises an acid-resistant enteric coating. In certain aspects the composition comprising the

at least one isolated or purified population of bacteria or the at least two isolated or purified populationss of bacteria is formulated for administration rectally, via colonoscopy, sigmoidoscopy by nasogastric tube, or enema. In some aspects, the composition is lyophilized or is frozen. In certain aspects, the composition is capable of being re-formulated for final delivery as comprising a liquid, a suspension, a gel, a geltab, a semisolid, a tablet, a sachet, a lozenge, a capsule, or as an enteral formulation. In some aspects, the composition is formulated for multiple administrations. In some aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria comprises an antibiotic resistance gene. In some aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria is a short-chain fatty acid-producing population of bacteria. In certain aspects, the short-chain fatty acid-producing population of bacteria is a butyrate-producing population of bacteria. In particular aspects, at least one immune checkpoint inhibitor is administered intravenously and the butyrate-producing population of bacteria is administered orally.

**[0018]** Embodiments of the present disclosure provide a method of treating cancer in a subject comprising administering a therapeutically effective amount of a short-chain fatty acid, such as butyrate, and/or a short-chain fatty acid-producing bacterial population, such as a butyrate-producing bacterial population, to said subject, wherein the subject has been administered an immune checkpoint inhibitor. In some aspects, the method further comprises administering at least one immune checkpoint inhibitor. In certain aspects, more than one checkpoint inhibitor is administered. In some aspects, the method further comprises administering a prebiotic or probiotic.

**[0019]** In some aspects, the short-chain fatty acid-producing bacterial population comprises bacteria comprising an antibiotic resistance gene. In some aspects, the butyrate-producing bacterial population comprises bacteria comprising an antibiotic resistance gene. In some embodiments, the method further comprises a step of administering such short-chain fatty acid-producing antibiotic resistant bacterial population, for example, such butyrate-producing antibiotic resistant bacterial population, to a subject having cancer. In some embodiments, the method further comprises administering the antibiotic to which the short-chain fatty acid-producing antibiotic resistant bacterial population, such as the butyrate-producing antibiotic resistant bacterial population, are resistant to the subject, wherein the antibiotic resistance gene confers resistance to the antibiotic.

**[0020]** In some aspects, the butyrate-producing bacterial population comprises one or more bacterial species of the order Clostridiales. In certain aspects, the one or more bacterial species are from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriaceae. In particular aspects, the one or more bacterial species are selected from the group consisting of *Faecalibacterium prausnitzii, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus flavefaciens, Ruminococcus champanellensis, Ruminococcus faecis, Ruminococcus gauvreauii, Ruminococcus gnavus, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus lactaris, Ruminococcus luti, Ruminococcus obeum, Ruminococcus palustris, Ruminococcus pasteurii, Ruminococcus productus, Ruminococcus schinkii, Ruminococcus torques, Subdoligranulum variabile, Butyrivibrio fibrisolvens, Roseburia intestinalis, Anaerostipes caccae, Blautia obeum, Eubacterium nodatum,* and *Eubacterium oxidoreducens.* In one specific aspect, the one or more bacterial species is *Faecalibacterium prausnitzii.* In particular aspects, the butyrate-producing bacterial population does not comprise bacterial species of the family Prevotellaceae or the order Bacteriodales.

**[0021]** In certain aspects, administering the butyrate comprises administering a butyrate prodrug or salt. In particular aspects, administering butyrate comprises administering sodium butyrate, arginine butyrate, ethylbutyryl lactate, tributyrin, 4-phenyl butyrate, pivaloyloxymethyl butyrate (AN-9) or butylidenedi-butyrate (AN-10).

**[0022]** In some aspects, the butyrate or butyrate-producing bacterial population, are administered orally, rectally, via colonoscopy, sigmoidoscopy, enema or by direct injection. In particular aspects, the at least one immune checkpoint inhibitor is administered intravenously, and the butyrate and/or the butyrate-producing bacterial population is administered orally.

**[0023]** In some aspects, the at least one checkpoint inhibitor is selected from an inhibitor of CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, BTLA, B7H3, B7H4, TIM3, KIR, or A2aR. In certain aspects, the at least one immune checkpoint inhibitor is a human programmed cell death 1 (PD-1) axis-binding antagonist. In some aspects, the PD-1 axis-binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PDLl -binding antagonist and a PDL2-binding antagonist. In certain aspects, the PD-1 axis-binding antagonist is a PD-1-binding antagonist. In some aspects, the PD-l-binding antagonist inhibits the binding of PD-1 to PDLl and/or PDL2. In particular aspects, the PD-l-binding antagonist is a monoclonal antibody or antigen binding fragment thereof. In specific aspects, the PD-l-binding antagonist

is nivolumab, pembrolizumab, pidillizumab, KEYTRUDA®, AMP-514, REGN2810, CT-011, BMS 936559, MPDL3280A or AMP-224. In some aspects, the at least one immune checkpoint inhibitor is an anti-CTLA-4 antibody. In particular aspects, the anti-CTLA-4 antibody is tremelimumab, YERVOY®, or ipilimumab. In certain aspects, the at least one immune checkpoint inhibitor is an anti-killer-cell immunoglobulin-like receptor (KIR) antibody. In some aspects, the anti-KIR antibody is lirilumab.

**[0024]** In certain aspects, the cancer is a skin cancer, such as basal-cell skin cancer, squamous-cell skin cancer or melanoma. In other aspects the skin cancer is a skin cancer selected from the group consisting of dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, and angiosarcoma. In particular aspects, the melanoma is metastatic melanoma. In other aspects, the melanoma is Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

**[0025]** In certain aspects, the method further comprises administering at least one additional anticancer treatment. In some aspects, the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy. In some aspects, the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

**[0026]** In some aspects, the at least one immune checkpoint inhibitor and/or at least one additional anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion. In particular aspects, the at least one immune checkpoint inhibitor is administered intravenously, and the butyrate and/or the butyrate-producing bacterial population is administered orally.

**[0027]** Another embodiment provides a method of treating cancer in a subject comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject, wherein the subject has been determined to have a favorable microbial

profile in the gut microbiome. In some aspects, a favorable microbial profile is further defined as having: (a) high alpha-diversity of the gut microbiome; (b) a high abundance of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, in the gut microbiome; (c) one or more *(e.g.,* 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) bacteria selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5, 0.6, 0.7, 0.8 or 0.9 or equal to 1 in the gut microbiome; (d) one or more *(e.g.,* 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) of the bacteria species in Table 2 designated with a response status of responder (R) in the gut microbiome; and/or (e) clusters centered around R-centroid by beta-diversity (by *e.g.,* weighted unifrac distances).

**[0028]** In some aspects, a favorable microbial profile is further defined as the presence or high abundance of bacteria of the phylum Firmicutes, class Clostridia, order Clostridiales, family Ruminococcaceae, genus *Ruminococcus,* genus *Faecalibacterium,* genus *Hydrogenoanaerobacterium,* phylum Actinobacteria, class Coriobacteriia, order Coriobacteriales, family Coriobacteriaceae, domain Archaea, phylum Cyanobacteria, phylum Euryarchaeota, or family Christensenellaceae. In certain aspects, a favorable microbial profile is further defined as the absence or low abundance of bacteria of the species *Escherichia coli,* species *Anerotruncus colihominis,* genus *Dialister,* family Veillonellaceae, phylum Bacteroidetes, class Bacteroidia, order Bacteroidales or family Prevotellaceae. In particular aspects, a favorable microbial profiles is defined as the presence or high abundance of bacteria of the class Clostridiales and the absence or low abundance of bacteria of the order Bacteroidales. In some aspects, a favorable microbial profile is further defined as a high abundance of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria. In certain aspects, the butyrate-producing bacteria comprises one or more species is from the genus *Ruminococcus* or *Faecalibacterium.*

**[0029]** In some aspects, the subject was determined to comprise a favorable microbial profile or favorable gut microbiome by analyzing the microbiome in a patient sample. In certain aspects, the patient sample is a fecal sample or buccal sample. In some aspects, analyzing comprises performing 16S ribosomal sequencing and/or metagenomics whole genome sequencing.

**[0030]** In a further embodiment, there is provided a method of predicting a response *(e.g.,* patient survival) to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the

microbial profile comprises: (a) high alpha-diversity; (b) a high abundance of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria; (c) one or more *(e.g.,* 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) bacteria selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5, 0.6, 0.7, 0.8 or 0.9 or equal to 1; (d) one or more *(e.g., 2,* 3, 4, 5, 6, 7, 8, 9, 10 or more) of the bacteria species in Table 2 designated with a response status of responder (R); (e) a low abundance of Bacteriodales; and/or (f) distinct clusters by beta-diversity weighted unifrac distances, then the patient is predicted to have a favorable response to the immune checkpoint inhibitor. In particular embodiments, a patient is administered an immune checkpoint inhibitor if the patient is predicted to have a favorable response to the immune checkpoint inhibitor. In certain embodiments, a patient is administered a second immune checkpoint inhibitor. In certain embodiments the favorable microbial profile is a favorable gut microbial profile.

**[0031]** In certain aspects, the cancer is a skin cancer, such as basal-cell skin cancer, squamous-cell skin cancer or melanoma. In other aspects the skin cancer is a skin cancer selected from the group consisting of dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, and angiosarcoma. In other aspects, the melanoma is Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma. In particular aspects, the immune checkpoint inhibitor is an anti-PDl monoclonal antibody or an anti-CTLA4 monoclonal antibody.

**[0032]** In some aspects, the short-chain fatty acid-producing bacteria, such as butyrate-producing bacterial population, comprises one or more bacterial species of the order Clostridiales. In certain aspects, the one or more species is from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriacease. In particular aspects, the one or more species are selected from the group consisting of *Faecalibacterium prausnitzii, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus flavefaciens, Ruminococcus champanellensis, Ruminococcus faecis, Ruminococcus gauvreauii, Ruminococcus gnavus, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus lactaris, Ruminococcus luti , Ruminococcus obeum, Ruminococcus palustris , Ruminococcus pasteurii,*

*Ruminococcus productus, Ruminococcus schinkii, Ruminococcus torques, Subdoligranulum variabile, Butyrivibrio fibrisolvens, Roseburia intestinalis, Anaerostipes caccae, Blautia obeum, Eubacterium nodatum, and Eubacterium oxidoreducens.* In certain aspects, the one or more species is *Faecalibacterium prausnitzii.*

**[0033]** In additional aspects, the method further comprises administering an immune checkpoint inhibitor to a subject predicted to have a favorable response to the immune checkpoint inhibitor. In some aspects, the immune checkpoint inhibitor is an anti-PDl monoclonal antibody or an anti-CTLA4 monoclonal antibody.

**[0034]** In some aspects, the method further comprises administering at least one additional anticancer treatment. In certain aspects, the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy. In particular aspects, the at least one additional anticancer treatment is a short-chain fatty acid, such as butyrate, and/or a short-chain fatty acid-producing bacterial population, such as a butyrate-producing bacterial population. In specific aspects, the at least one anticancer treatment is a composition of the embodiments. In some aspects, the method further comprises administering a prebiotic or probiotic.

**[0035]** In another embodiment, there is provided a method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises: (a) a low abundance of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria; (b) one or more of the bacteria species in Table 2 designated with a response status of non responder (NR); (c) low alpha diversity; and/or (d) a high amount of the order Bacteriodales, then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. In further aspects, the method further comprises administering to the patient a probiotic or live bacterial product composition of the embodiments if the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. In still further aspects, a patient predicted to not have a favorable response to an immune checkpoint inhibitor is administered an immune checkpoint inhibitor after administration of a prebiotic or live bacterial product composition of the embodiments.

**[0036]** In additional aspects, the method further comprises administering at least one non-immune checkpoint inhibitor additional anticancer treatment to a subject predicted to not have a favorable response to the immune checkpoint inhibitor.

**[0037]** In further aspects, the method comprises administering at least one anticancer treatment to the subject. In some aspects, the at least one anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy, an immune checkpoint inhibitor, a second immune checkpoint inhibitor or a biological therapy. In particular aspects, the at least one additional anticancer treatment is a short-chain fatty acid, such as butyrate and/or a short-chain fatty acid-producing bacterial population, such as a butyrate-producing bacterial population. In some aspects, the anti-cancer therapy is a prebiotic or probiotic. In specific aspects, the probiotic is a probiotic composition of the embodiments.

**[0038]** In certain aspects, the cancer is a skin cancer, such as basal-cell skin cancer, squamous-cell skin cancer or melanoma. In other aspects the skin cancer is a skin cancer selected from the group consisting of dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, and angiosarcoma. In other aspects, the melanoma is Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

**[0039]** In some aspects, if the microbial profile comprises one or more of the bacteria species in Table 2 designated with a response status of non responder (NR) or a high amount of the order Bacteriodales, then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. In some aspects, if the microbial profile comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the bacteria species in Table 2 designated with a response status of non responder (NR), then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. In further aspects, the method comprises administering to the patient a probiotic or live bacterial product composition of the embodiments.

**[0040]** Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the

detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0041]** The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

**[0042] FIGS. 1A-G: Increased diversity of the gut microbiome is associated with enhanced responses to PD-1 blockade in patients with metastatic melanoma.** (A) Schema of sample collection and analyses. (B) Stacked bar plot of phylogenetic composition of common bacterial taxa (>0.1% abundance) at the order level in oral (n=109, top) and fecal (n=53, bottom) samples by 16S rRNA sequencing. (C) Bipartite network diagram of matched oral and fecal samples from 48 anti-PD-1-treated patients. Edges connect species level OTUs to sample nodes in which they are found. (D) Inverse Simpson diversity scores of the gut microbiome in R (n=30) and NR (n=13) to anti-PD-1 therapy by Mann-Whitney (MW) test. (E) Phylogenetic composition of 39 fecal samples at the family level (>0.1% abundance) at baseline. High (>1 1.63, n=13), intermediate (7.46-11.63, n=13) and low (<7.46, n=13) diversity groups were determined using tertiles of Inverse Simpson scores. (F) Kaplan-Meier (KM) plot of progression-free survival (PFS) by fecal diversity; high (median PFS undefined), intermediate (median PFS=232 days), and low (median PFS=188 days). High vs intermediate diversity (HR=3.60, 95% C.I.=1.02- 12.74) and high vs low (Low HR=3.57, 95% C.I.=1.02-12.52) by univariate Cox model. *p<0.05, **p<0.01. (G) Principal coordinate analysis of fecal samples (n=43) by response using Weighted UniFrac distances.

**[0043] FIGS. 2A-F: Compositional differences in the gut microbiome are associated with responses to PD-1 blockade. (A)** Heatmap of OTU abundances in R (n=30) and NR (n=13). Columns denote patients and rows denote bacterial species grouped according to their enrichment in R versus NR into 3 sets. **(B)** Phylogenetic composition of OTUs within each set at the order level. **(C)** Taxonomic cladogram from LEfSe showing differences in fecal taxa. Dot size is proportional to the abundance of the taxon. **(D)** LDA scores computed for

differentially-abundant taxa in the fecal microbiomes of R and NR, as indicated. Length indicates effect size associated with a taxon. $p$ =0.05 for the Kruskal-Wallis test; LDA score > 3. **(E)** Differentially-abundant gut bacteria in R vs NR by MW test (FDR-adjusted) within all taxonomic levels. **(F)** Pairwise comparisons of abundances of bacterial species identified by metagenomic WGS in 25 fecal samples: R (n=14), NR (n=l 1). *$p<0.05$, **$p<0.01$.

**[0044] FIGS. 3A-F: Abundance of crOTUs within the gut microbiome is predictive of response to PD-1 blockade. (A)** Unsupervised hierarchical clustering by complete linkage of crOTU abundances in 43 fecal samples. **(B)** Association of crOTU clusters with response to anti-PD-1 by Fisher's exact test. crOTU Cluster 1 (n=14: R=14, NR=0); Cluster 2 (n=29: R=16, NR=13). **(C)** KM plot of PFS by crOTU cluster. crOTU cluster 1 (median PFS undefined), crOTU cluster 2 (median PFS=242 days). **(D)** Differentially-abundant fecal taxa in crOTU cluster 1 vs crOTU cluster 2, by MW test (FDR-adjusted) within all taxonomic levels. **(E)** PFS in patients with high (n=19, median PFS undefined) or low (n=20, median PFS=242 days) abundance of *F. prausnitzii* (top) or high (n=20, median PFS=188 days) or low (n=19, median PFS=393 days) abundance of Bacteroidales (bottom). **(F)** Unsupervised hierarchical clustering of pathway class abundances inferred from MetaCyc pathways predicted in 28 fecal samples from 25 patients (R=14, NR=11). Regular type: biosynthetic pathways, Bold type: degradative pathways. *$p$<0.05.

**[0045] FIGS. 4A-G: A favorable gut microbiome is associated with systemic anti-tumor immunity. (A)** Quantification by IHC of the CD8+ infiltrate at pre-treatment in counts/mm$^2$ in R (n=15) and NR (n=6) by one-sided MW test. *p=0.04. **(B)** Pairwise Spearman rank correlation heatmap of significantly different taxa in fecal samples (n=15) at baseline and CD3, CD8, PD-1, FoxP3, GzmB and RORγT density in counts/mm$^2$ and PD-L1 by H-score in matched tumors. **(C)** Univariate linear regression between CD8+ counts/mm$^2$ in the tumor versus *Faecalibacterium* (open circles and dashed line; $r^2$=0.42, /?=0.0067) and Bacteroidales (solid circles and solid line; $r^2$=0.056, $p$=0.38) abundance in the gut. **(D)** Pairwise Spearman rank correlation heatmap between significantly different fecal taxa and frequency of CD4$^+$ effector T cells, CD8$^+$ T cells, myeloid dendritic cells, monocytes, B cells, Tregs, and MDSCs by flow cytometry in peripheral blood at baseline. **(E)** Multiplex IHC showing representative images and **(F)** frequency of immune cells, lymphoid cells, myeloid cells, and MHC II in patients having high *Faecalibacterium* or high Bacteroidales in the gut. **(G)** Proposed

mechanism of action of the gut microbiome on tumor immunity in favorable and unfavorable conditions.

**[0046] FIGS. 5A-B. No differences are observed in the mutational landscape of R and NR to PD-1 blockade. (A)** Number of mutations per megabase and landscape of driver mutations in tumors of patients with matched fecal microbiome samples (n=7R vs 3NR). **(B)** Total non-synonymous mutational burden in available tumors (n=8R vs 4NR, /?=0.683), by two-sided Mann-Whitney (MW) test.

**[0047] FIG. 6: Differences in community structure between the oral and fecal microbiomes.** Bipartite network diagram of bacterial 16S rRNA derived operational taxonomic units (OTU) from 109 buccal and 53 fecal samples. Edges connect species-level OTUs (diamonds) to sample nodes from oral (open circles) and fecal (filled circles) in which they are found.

**[0048] FIGS. 7A-C: Diversity of the fecal microbiome is increased in R to anti-PD-1 therapy.** Comparison of alpha-diversity scores in R (n=30, open cirles) and NR (n=13, filled cirles) using the **(A)** Shannon, **(B)** Simpson and **(C)** Chaol indices by two-sided MW test. *$p<0.05$, **$p<0.01$.

**[0049] FIGS. 8A-D: No differences are observed in the diversity of the oral microbiome between R and NR to anti-PD-1 therapy.** Comparison of alpha-diversity scores in R (n=54, open cirles) and NR (n=32, filled cirles) using the **(A)** Inverse Simpson (/?=0.107), **(B)** Shannon (/?=0.139), **(C)** Simpson (/?=0.136) and **(D)** Chaol (p=0.826) indices, by two-sided MW test.

**[0050] FIGS. 9A-B: High diversity of the fecal microbiome is associated with longer PFS.** Gut microbiota at baseline and subsequent treatment course by subject (n=39). **(A)** Horizontal bars represent alpha diversity scores measured by Inverse Simpson index in each patient. **(B)** Timeline plots showing days elapsed on therapy. x=progressed, o=not progressed at last follow-up.

**[0051] FIGS. 10A-D: Diversity of the oral microbiome is not associated with PFS.** Oral microbiota and subsequent treatment course by patient (n=86). **(A)** Stacked bars represent the phylogenetic composition of each sample at the family level at baseline. All patients were classified into high (>6.17), intermediate (3.26- 6.17) and low (<3.26) diversity groups, as

indicated, based on tertiles of Inverse Simpson scores. **(B)** Kaplan-Meier plot of progression-free survival by oral diversity tertiles: high (n=29, median PFS=279 days), intermediate (n=28, median PFS undefined), low (n=29, median PFS=348 days), as indicated. High vs intermediate, $p$=0.34; high vs low, $p=0.54$ by log-rank test. **(C)** Horizontal bars represent alpha-diversity scores measured by Inverse Simpson index. **(D)** Timeline plots showing days elapsed on therapy. x=progressed, o=not progressed at last follow-up.

**[0052] FIGS. 11A-D: Thresholds for enrichment index *(ei)* scores and relative abundances for OTUs in 86 oral and 43 fecal microbiome samples.** Distribution of enrichment scores for bacterial OTUs at the species level in **(A)** fecal and **(B)** oral microbiome samples by Set. The boundaries for each set are indicated. Distribution of logio relative abundance of species in **(C)** fecal and **(D)** oral microbiome samples. The range for each abundance category is indicated.

**[0053] FIGS. 12A-B: No significant differences in oral microbiome OTUs between R and NR to anti- PD-1 therapy by enrichment index *(ei)* score. (A)** Heatmap of species abundance in R (n=52) and NR (n=34), as indicated, by set of bacterial OTUs based on *ei* scores. Each column denotes a patient and each row denotes a bacterial OTU. High, intermediate, and low are indicated. **(B)** Phylogenetic composition of bacterial OTUs within each set at the order level.

**[0054] FIGS. 13A-B: High-dimensional class comparisons using LEfSe reveal increased abundance of Bacteroidales in the oral microbiome of NR to anti-PD-1 therapy. (A)** Taxonomic Cladogram from LEfSe showing differences in the oral taxa. Taxa enriched in R and NR, respectively, are indciated with size of the dot proportional to abundance of the taxon. **(B)** Histogram of LDA scores computed for differentially abundant taxa between the oral microbiomes of R and NR, where the length of the bar indicates the effect size associated with a taxon. $p$=0.05 for Kruskal-Wallis test; LDA score > 3.

**[0055] FIGS. 14A-C: The diversity and composition of the gut microbiome is stable over time. (A)** Alpha-diversity of the gut microbiome by Inverse Simpson over time in 3 patients (R) with longitudinal collections. **(B)** Principal component analysis using unweighted UniFrac distances. **(C)** Stacked bars showing the composition of the gut microbiome in patients over time at the order level.

**[0056] FIGS. 15A-B: Clustering by relative OTU abundances shows no association with response to anti-PD-1 therapy.** Unsupervised hierarchical by complete linkage using Euclidean distances based on OTU abundance in **(A)** 43 fecal and **(B)** 86 oral microbiome samples. Each column represent a unique microbiome sample whereas each row represents a unique OTU.

**[0057] FIGS. 16A-B: Clusters based on oral microbiome crOTU abundances are not associated with response to PD-1 blockade. (A)** Unsupervised hierarchical clustering by complete linkage of 86 oral microbiome samples based on crOTU abundances. **(B)** Comparison of clusters by response showing crOTU cluster 1 (n=ll, R=9 and NR=2) and Cluster 2 (n=75, R=45 and NR=30). $p$ =0.20 by two-sided Fisher's exact test.

**[0058] FIG. 17: Metabolic profiles based on KEGG-orthologs differ in the gut microbiome of R vs NR to PD-1 blockade.** Unsupervised hierarchical clustering of common functional pathways (found in at least 20 samples) in 28 fecal samples obtained from 25 patients (n=14R and 11NR) according to KEGGortholog relative abundances.

**[0059] FIGS. 18A-F: Responders to PD-1 blockade present an enriched tumor immune infiltrate at baseline.** Immunohistochemical quantification and representative images at 40X magnification of **(A)** CD3, **(B)** PD-1, **(C)** FoxP3, **(D)** GzmB, **(E)** PD-Ll and **(F)** RORyT as counts/mm2or H-Score in responders (R) and non-responders (NR) to anti-PD-1.

**[0060] FIG. 19: Patients with a high abundance of *Faecalibacterium* present a favorable antitumor immune infiltrate prior to anti-PD-1 therapy.** Spearman rank correlation heatmap of GzmB, CD3, CD8, PD-1, FoxP3, RORyT by counts/mni2, PD-Ll by H-Score by IHC and abundance of all genera within the Ruminococcaceae family in the fecal microbiome (n=15). Positive correlation, negative correlation and no correlation are indicated.

**[0061] FIGS. 20A-F: *Faecalibacterium* and Bacteroidales abundance in the fecal microbiome have distinct associations with the tumor immune infiltrate prior to PD-1 blockade.** Linear regression between *Faecalibacterium* abundance, Bacteroidales abundance, and density by counts/mni2 or H-score of **(A)** CD3, **(B)** GzmB, **(C)** PD-1, **(D)** PD-Ll, **(E)** FoxP3, and **(F)** RORyT by IHC in tumors of patients treated with anti-PD-1 at baseline. Lines show regression for *Faecalibacterium* (thin line, normal type values) and Bacteroidales (thick line, bold type values) with the associated $n$ and p-values.

**[0062] FIG. 21: Gating strategy for flow cytometric analysis of peripheral blood in patients treated with anti-PD-1 therapy.** PBMC at baseline in patients treated with anti-PD-1 were analyzed by gating for CD19+ B cells, CD3+CD8+ T cells, CD3+CD4+ T cells (CD3+CD4+FoxP3+ regulatory and CD3+CD4+FoxP3- effector), monocytes (based on CD14/HLA-DR), and MDSC (CD3-CD19-HLADRCD33+ CDllb+).

**[0063] FIGS. 22A-D: Patients with high *Faecalibacterium* abundance display a peripheral cytokine profile favorable for response to PD-1 blockade at baseline and enhanced cytokine responses over the course of therapy. (A)** Spearman rank correlation heatmap between Clostridiales, *Faecalibacterium,* Ruminococcaceae, and Bacteroidales abundance and peripheral concentration of cytokines in pg/mL by multiplex bead assay. Positive correlation, negative correlation and no correlation is indicated. Change in production of cytokines in serum of responders (n=2) and non-responders (n=2) to anti-PD-1 therapy for **(B)** IP-10 (p=0.042 and $p$=0.344, respectively), **(C)** MIP-1β (p=0.043 and $p$=0.898, respectively), and **(D)** IL-17A ($p$=0.072 and $p$=0.862, respectively) in fold-change from baseline by ratio paired t-test.

**[0064] FIG. 23: Gating strategy for myeloid multiplex IHC in the tumors of patients treated with PD-1 blockade at baseline.** Myeloid multiplex immunohistochemistry gating strategy showing immune cells (CD45+), lymphoid cells (CD45+CD3+CD20+CD56+), myeloid cells (CD45+CD3-CD20-CD56-), mast cells (CD45+CD3-CD20-CD56-HLADR-Tryptase+), granulocytes (CD45+CD3-CD20-CD56-HLADRCD66b+), M1 tumor-associated macrophages (CD45+CD3-CD20-CD56-HLADR+CSF1R+CD163-), M2 tumor-associated macrophages (CD45+CD3-CD20-CD56-HLADR+CSF1R+CD 163+), mature dendritic cells (CD45+CD3-CD20-CD56-HLADR+CSF1R-DCSIGN-) and immature dendritic cells (CD45+CD3-CD20- CD56-HLADR+CSF1R-DCSIGN+).

**[0065] FIGS. 24A-C: High *Faecalibacterium* abundance at baseline is associated with an increased immune infiltrate prior to PD-1 blockade. (A)** Multiplex immunohistochemistry showing representative myeloid immune cell staining at 40X magnification. **(B)** Quantification of CD45, CD3/CD20/CD56, CD68, CD66b, Tryptase, HLA-DR, CD163, and DC-SIGN as counts/mrm. **(C)** Quantification of myeloid cells, lymphoid cells, mast cells, granulocytes, M1 and M2 tumor-associated macrophages, immature dendritic cells, and mature dendritic cells as a percentage of total CD45+ immune cells in patients with a high *Faecalibacterium* (n=2) or high Bacteroidales (n=2) abundance.

**[0066] FIGS. 25A-B: Fecal Microbiota Transplantation (FMT) of a favorable gut microbiome in germ-free (GF) mice reduces tumor growth. (A)** Experimental design of FMTl experiment in germ-free (GF) mice. Time is indicated in days (D) relative to the day of tumor injection ($8xl0^{-5}$ tumor cells). **(B)** Difference in size of tumors implanted in responder (R)-FMT and non-responder (NR)-FMT mice, or control mice. Tumor volumes on day 14 post-tumor implantation are plotted, each value representing a single mouse.

**[0067] FIGS. 26A-C: Favorable FMT promotes innate effector and reduced myeloid suppressor infiltration in the spleen of GF mice. (A)** Flow cytometry quantification showing the frequency of $CD45^+$ immune cells in R-FMT (R), NR-FMT (NR), and control mice (C) in the spleen. **(B)** Flow cytometry quantification showing the frequency of $CD45^+CDllb^+Ly6G^+$ innate effector cells in R-FMT (R), NR-FMT (NR), and control mice (C) in the spleen. **(C)** Flow cytometry quantification showing the frequency of $CD45^+CDllb^+CDllc^+$ suppressive cells in R-FMT (R), NR-FMT (NR), and control mice (C) in the spleen.

**[0068] FIGS. 27A-C: Favorable FMT increases CD45+ and CD8+ in the gut and tumor of GF mice.** Representative immunofluorescent staining of **(A)** tumor and **(B)** gut from Control (left), NR-FMT (middle), and R-FMT (right) in the tumor of GF mice post-FMT for CD45, CD8, and nuclei (DAPI). **(C)** Quantification of CD8+ density in tumor (top) of R-FMT (n=2, median=433.5 cells/HPF across 12 regions), NR-FMT (NR-FMT n=2, median=325 cells/HPF across 12 regions) and Control mice (n=2, median=412 cells/HPF across 9 regions). p=0.30 (R-FMT vs Control) and gut (bottom) (R-FMT n=2, median=67 cells/HPF across 7 regions, NR-FMT n=2, median=24 cells/HPF across in 5 regions, Control n=2, median=47 cells/HPF across 10 regions). p=0.17 (R-FMT vs Control).

**[0069] FIGS. 28A-C: FMT of a favorable gut microbiome in GF mice reduces tumor growth and enhances response to a-PD-Ll therapy. (A)** Experimental design of FMT2 experiment in germ-free (GF) mice. Time is indicated in days (D) relative to the day of tumor injection ($2.5xl0^{-5}$ tumor cells). **(B)** Difference in size of tumors implanted in R-FMT (R, squares) and NR-FMT mice (NR, triangles), or control mice (circles). Tumor volumes on day 14 post-tumor implantation are plotted, each value representing a single mouse. **(C)** Tumor growth curves for each GF mouse from a-PD-Ll treated (3xl00 μg ip every 3 days) R-FMT (squares, n=2, median tumor volume=403.7 $mm^3$), NR-FMT (triangles, n=2, median tumor volume= 2301 $mm^3$), and Control (cirlces, n=2, median tumor volume=771.35 $mm^3$) mice.

p=0.20 (R-FMT vs NR-FMT), p=0.33 (NR-FMT vs Control by two-sided MW test). Dotted black line marks the tumor size cutoff for a-PD-Ll treatment (500$mm^3$).

**[0070] FIGS. 29A-E: Enhanced therapeutic response upon favorable FMT correlates with increased innate effector and reduced myeloid suppressor infiltration in tumors in GF mice. (A)** Flow cytometry quantification showing the frequency of $CD45^+$ immune cells in R-FMT, NR-FMT, and control mice infiltrating the tumor, as indicated. **(B)** Flow cytometry representative plots of $CD45^+CDllb^+Ly6G^+$ innate effector cells and **(D)** $CDllb^+CDllc^+$ suppressive myeloid cells in Control (left), NR-FMT (middle), and R-FMT (right) mice. **(C)** Flow cytometry quantification showing the frequency of $CD45^+CD1lb^+Ly6G^+$ innate effector cells and **(E)** $CD45^+CD1lb^+CDllc^+$ suppressive cells in R-FMT, NR-FMT, and control mice infiltrating the tumor, as indicated.

**[0071] FIGS. 30A-D: GF mice receiving FMT from NR-donor have highly activated Thl7 compartment. (A)** Representative images of IHC staining for Retinoic acid-related orphan receptor gamma t (RORyT) nuclear receptor on tumors from R-FMT (right), NR-FMT (middle), and control (left) mice. Arrows point to RORyT-positive cells. **(B)** IHC quantification showing the number of RORyT+ Thl7 cells in R-FMT (R), NR-FMT (NR), and control mice (C) in tumor as counts/$mm^2$. **(C)** Flow cytometry quantification showing the frequency of CD4+FoxP3+ regulatory T cells in R-FMT (R), NR-FMT (NR), and control mice (C) in spleen. **(D)** Flow cytometry quantification showing the frequency of CD4+IL17+ Thl7 cells in R-FMT (R), NR-FMT (NR), and control mice (C) in spleen.

**[0072] FIGS. 31A-B: Up-regulation of PD-L1 in the tumor microenvironment of mice receiving R-FMT versus NR-FMT by mass cytometry (CyTOF). (A)** t-SNE plot of total live cells (left) isolated from tumors derived from control, NR-, and R- colonized mice, as indicated, by mass cytometry. t-SNE plot of total live cells overlaid with the expression of CD45 (middle) and PD-L1 (right). Equal numbers of cells are displayed from each group. **(B) (top left)** t-SNE plot of total $CD45^+$ cells isolated from tumors derived from control, NR-FMT, and R-FMT mice, as indicated, by CyTOF. **(top right)** Density plots of total $CD45^+$ cells isolated from tumors derived from the indicated experimental groups. **(bottom)** t-SNE plot of total $CD45^+$ cells overlaid with the expression of indicated markers.

**[0073] FIGS. 32A-C: FMT from another R-donor in GF mice confirms the impact of a favorable gut microbiome on tumor growth. (A)** Experimental design of FMT2

experiment in germ-free (GF) mice. Time is indicated in days (D) relative to the day of tumor injection (2.5xl0 $^{5}$ tumor cells). **(B)** Difference in size of tumors implanted in R-FMT (squares) and NR-FMT mice (triangles), or control mice (circles). Tumor volumes on day 14 post-tumor implantation are plotted, each value representing a single mouse. **(C)** Tumor growth curves for each GF mouse from R-FMT (square, tumor volume=414.3 $mm^3$), NR-FMT (triangle, tumor volume= 1909.1 $mm^3$), and Control (circle, n=3, median tumor volume=1049.3 $mm^3$) mice.

**[0074] FIGs. 33A-33F:** Genetically-identical C57/BL6 mice from Jackson and Taconic exhibit differential tumor growth (earlier in Jackson) **(A),** survival (higher in Taconic) **(B-C),** and microbiome composition (Taconic single-housed upper right; Jackson single-housed lower right) **(D)** after implantation of murine melanoma tumors (BRAF-mutant, PTEN-null). Co-housing of Taconic and Jackson mice resulted in similar tumor outgrowth **(C)** and increased microbiome similarity was observed by principal coordinate analysis **(D).** Differential abundance at the genus level was observed in singly-housed mice from Jackson and Taconic, but no differences were noted after co-housing **(E).** Oral administration of butyrate significantly delayed tumor outgrowth in mice implanted with melanoma tumors **(F).**

**[0075] FIGs. 34A-C: 16S analysis of fecal samples from R and NR donors and germ-free recipient mice.** Relative abundance comparisons of **(A)** *Faecalibacterium*, **(B)** *Ruminococcaceae* and **(C)** *Bacteroidales* on day 14 post tumor injection. Data from 2 independent experiments are presented. ** $p<0.01$.

## DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

**[0076]** Tremendous advances have been made in cancer therapy through the use of molecularly targeted therapy and immunotherapy, however responses are variable and are not always durable. Treatment with immune checkpoint inhibitors is associated with response rates of 15-40% in patients with widespread melanoma, and efforts are underway to identify strategies to enhance responses to checkpoint inhibitor therapy. Thus, methods to improve therapeutic responses as well as increase the number of responders are critically needed.

**[0077]** The present disclosure overcomes problems with current technologies by providing methods to modulate the microbiome to improve immune response to cancer and therapeutic response to immune checkpoint inhibitors in cancer patients. Studies in the present disclosure used a large cohort of patients with metastatic melanoma undergoing systemic treatment (n=233), a subset of whom were treated with PD-l-based immunotherapy (n=112).

Oral and gut microbiome samples were characterized in these patients via 16S rRNA gene sequencing and metagenomic whole genome shotgun sequencing. In these analyses, significant differences were observed in the diversity and composition of the gut microbiome in responders versus non-responders to immune checkpoint blockade therapy *(e.g.,* to PD-l-based therapy), with a significantly higher diversity and increased abundance of specific bacteria *(e.g.,* within the order Clostridiales and family Ruminococcaceae) in the gut microbiome of responders versus non-responders. In particular, the species *Faecalibacteriumprausnitzii* was found to be more abundant in responders. These bacteria are known to produce short chain fatty acids such as butyrate, which help sustain the integrity of specific cells within the gut *(i.e.,* enterocytes) and may enhance immunity.

**[0078]** Interestingly, non-responders to therapy were noted to have low levels of these bacteria and significantly higher levels of bacteria of the order Bacteroidales, which has been shown in some studies to down-regulate systemic immune responses. Metagenomic analysis via whole genome shotgun sequencing was performed in a subset of these patients validating these findings, and further demonstrated differences in metabolic processes in bacteria of responders versus non-responders. Furthermore, it was demonstrated that modulation of the gut microbiome by co-housing Taconic and Jackson mice and by oral administration of short chain fatty acids *(e.g.,* butyrate) resulted in delayed tumor outgrowth in mice with a less favorable gut microbiome (Jackson mice). These results from human and murine studies have potentially far-reaching implications to enhance responses to immune checkpoint blockade via modulation of the gut microbiome.

**[0079]** Importantly, the present studies show that patients with a "favorable" gut microbiome (with high diversity and high relative abundance of bacteria of the order Clostridiales and/or family Ruminococcaceae) have enhanced systemic and anti-tumor immune responses mediated by enhanced antigen presentation at the level of the lymph node and tumor, as well as preserved effector T cell function in the periphery and the tumor microenvironment. In contrast, patients with an "unfavorable" gut microbiome (with low diversity and high relative abundance of bacteria of the order Bacteroidales) have impaired systemic and anti-tumor immune responses mediated by limited intratumoral infiltration of both lymphoid and myeloid elements, weakened antigen presentation capacity, and skewing towards immunoregulatory cellular and humoral elements in the periphery, including Treg and MDSC.

**[0080]** Further studies were also undertaken in a mouse melanoma model system. These studies showed mice that received fecal microbiota transplantation from a responder population had decreased tumor growth and increased response to anti-PDL1 therapy. Moreover, mice that received transplantation of a responder microbial popultion had higher percentages of innate effector cells (expressing $CD45^+CD11b^+Ly6G^+$) and lower frequency of suppressive myeloid cells (expressing $CDllb^+CDllc^+$) in the spleen as well as an increased the number of $CD45^+$ immune and $CD8^+$ T cells in the gut. These findings highlight the potential for parallel modulation of the gut microbiome to significantly enhance checkpoint blockade efficacy, warranting prompt evaluation in clinical trials.

**[0081]** Based on these findings, methods of cancer treatment and diagnosis are provided herein. In one method, short-chain fatty acids, such as butyrate and/or a population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, are administered to patients during treatment with immune checkpoint blockade to enhance therapeutic responses. Also provided herein are methods to use the diversity and composition of the gut microbiome as a predictive biomarker to identify patients who will have a favorable response to immune checkpoint blockade.

## I. Definitions

**[0082]** As used herein, "essentially free," in terms of a specified component, is used herein to mean that none of the specified component has been purposefully formulated into a composition and/or is present only as a contaminant or in trace amounts. The total amount of the specified component resulting from any unintended contamination of a composition is therefore well below 0.01%. Most preferred is a composition in which no amount of the specified component can be detected with standard analytical methods.

**[0083]** As used herein, "a" or "an" may mean one or more than one.

**[0084]** The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." As used herein, the term "another" may mean at least a second or more.

**[0085]** Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

**[0086]** The phrase "effective amount" or "therapeutically effective amount" or "sufficient amount" means a dosage of a drug or agent sufficient to produce a desired result. The desired result can be a decrease in tumor size, a decrease in the rate of growth of cancer cells, a decrease in metastasis, increase in CD8+ T lymphocytes in the tumor or tumor immune infiltrate, an increase in CD45+, CD3+/CD20+/CD56+, CD68+ and/or HLA-DR+ cells in the tumor, an increase in CD3, CD8, PDl, FoxP3, Granzyme B and/or PD-Ll expression in a tumor immune infiltrate, a decrease in RORγT expression in a tumor immune infiltrate, an increase of effector CD4+, CD8+ T, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood, a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject or any combination of the above.

**[0087]** The term "tumor cell" or "cancer cell" denotes a cell that demonstrates inappropriate, unregulated proliferation. A "human" tumor is comprised of cells that have human chromosomes. Such tumors include those in a human patient, and tumors resulting from the introduction into a non-human host animal of a malignant cell line having human chromosomes.

**[0088]** As used herein, the term "antibody" refers to an immunoglobulin, derivatives thereof which maintain specific binding ability, and proteins having a binding domain which is homologous or largely homologous to an immunoglobulin binding domain. These proteins may be derived from natural sources, or partly or wholly synthetically produced. An antibody may be monoclonal or polyclonal. The antibody may be a member of any immunoglobulin class, including any of the human classes: IgG, IgM, IgA, IgD, and IgE. Antibodies used with the methods and compositions described herein are generally derivatives of the IgG class. The term antibody also refers to antigen-binding antibody fragments. Examples of such antibody fragments include, but are not limited to, Fab, Fab', F(ab')2, scFv, Fv, dsFv diabody, and Fd fragments. Antibody fragments may be produced by any means. For instance, the antibody fragment may be enzymatically or chemically produced by fragmentation of an intact antibody, it may be recombinantly produced from a gene encoding the partial antibody sequence, or it may be wholly or partially synthetically produced. The antibody fragment may optionally be

a single chain antibody fragment. Alternatively, the fragment may comprise multiple chains which are linked together, for instance, by disulfide linkages. The fragment may also optionally be a multimolecular complex. A functional antibody fragment retains the ability to bind its cognate antigen at comparable affinity to the full antibody.

**[0089]** The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *e.g.*, the individual antibodies comprising the population are identical except for possible mutations, *e.g.*, naturally occurring mutations, that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies. In certain embodiments, such a monoclonal antibody typically includes an antibody comprising a polypeptide sequence that binds a target, wherein the target-binding polypeptide sequence was obtained by a process that includes the selection of a single target binding polypeptide sequence from a plurality of polypeptide sequences. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones, or recombinant DNA clones. It should be understood that a selected target binding sequence can be further altered, for example, to improve affinity for the target, to humanize the target binding sequence, to improve its production in cell culture, to reduce its immunogenicity *in vivo*, to create a multispecific antibody, *etc.*, and that an antibody comprising the altered target binding sequence is also a monoclonal antibody of this disclosure. In contrast to polyclonal antibody preparations, which typically include several different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. In addition to their specificity, monoclonal antibody preparations are advantageous in that they are typically uncontaminated by other immunoglobulins.

**[0090]** The phrases "pharmaceutical composition" or "pharmacologically acceptable compisition" refers to molecular entities and compositions that do not produce an adverse, allergic, or other untoward reaction when administered to an animal, such as a human, as appropriate. The preparation of a pharmaceutical composition comprising an antibody or additional active ingredient will be known to those of skill in the art in light of the present disclosure. Moreover, for animal *(e.g.*, human) administration, it will be understood that preparations should meet sterility, pyrogenicity, general safety, and purity standards as required by FDA Office of Biological Standards.

**[0091]** As used herein, "pharmaceutically acceptable carrier" includes any and all aqueous solvents *(e.g.,* water, alcoholic/aqueous solutions, saline solutions, parenteral vehicles, such as sodium chloride, and Ringer's dextrose), non-aqueous solvents *(e.g.,* propylene glycol, polyethylene glycol, vegetable oil, and injectable organic esters, such as ethyloleate), dispersion media, coatings, surfactants, antioxidants, preservatives *(e.g.,* antibacterial or antifungal agents, anti-oxidants, chelating agents, and inert gases), isotonic agents, absorption delaying agents, salts, drugs, drug stabilizers, gels, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, fluid and nutrient replenishers, such like materials and combinations thereof, as would be known to one of ordinary skill in the art. The pH and exact concentration of the various components in a pharmaceutical composition may be adjusted according to well-known parameters.

**[0092]** The term "unit dose" or "dosage" refers to physically discrete units suitable for use in a subject, each unit containing a predetermined quantity of the therapeutic composition calculated to produce the desired responses discussed herein in association with its administration, *i.e.,* the appropriate route and treatment regimen. The quantity to be administered, both according to number of treatments and unit dose, depends on the effect desired. The actual dosage amount of a composition of the present embodiments administered to a patient or subject can be determined by physical and physiological factors, such as body weight, the age, health, and sex of the subject, the type of disease being treated, the extent of disease penetration, previous or concurrent therapeutic interventions, idiopathy of the patient, the route of administration, and the potency, stability, and toxicity of the particular therapeutic substance. For example, a dose may also comprise from about 1 μg/kg/body weight to about 1000 mg/kg/body weight (this such range includes intervening doses) or more per administration, and any particular dose derivable therein. In non-limiting examples of a range derivable from the numbers listed herein, a range of about 5 μg/kg/body weight to about 100 mg/kg/body weight, about 5 μg/kg/body weight to about 500 mg/kg/body weight, etc., can be administered. The practitioner responsible for administration will, in any event, determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject.

**[0093]** An "anti-cancer" agent is capable of negatively affecting a cancer cell/tumor in a subject, for example, by promoting killing of cancer cells, inducing apoptosis in cancer cells, reducing the growth rate of cancer cells, reducing the incidence or number of metastases,

reducing tumor size, inhibiting tumor growth, reducing the blood supply to a tumor or cancer cells, promoting an immune response against cancer cells or a tumor, preventing or inhibiting the progression of cancer, or increasing the lifespan of a subject with cancer.

**[0094]** The term "immune checkpoint" refers to a component of the immune system which provides inhibitory signals to its components in order to regulate immune reactions. Known immune checkpoint proteins comprise CTLA-4, PD-1 and its ligands PD-L1 and PD-L2 and in addition LAG-3, BTLA, B7H3, B7H4, TIM3, KIR. The pathways involving LAG3, BTLA, B7H3, B7H4, TIM3, and KIR are recognized in the art to constitute immune checkpoint pathways similar to the CTLA-4 and PD-1 dependent pathways (see *e.g.* Pardoll, 2012, *Nature Rev Cancer* 12:252-264; Mellman *et al.*, 201 1, *Nature* 480:480- 489).

**[0095]** The term "PD- 1 axis binding antagonist" refers to a molecule that inhibits the interaction of a PD-1 axis binding partner with either one or more of its binding partners, so as to remove T-cell dysfunction resulting from signaling on the PD- 1 signaling axis - with a result being to restore or enhance T-cell function *(e.g.,* proliferation, cytokine production, target cell killing). The term "PD-1" axis" refers to any component of the PD-1 immune checkpoint *(e.g.,* PD-1, PD-L1, and PD-L2). As used herein, a PD-1 axis binding antagonist includes a PD-1 binding antagonist, a PD-L1 binding antagonist and a PD-L2 binding antagonist.

**[0096]** The term "PD-1 binding antagonist" refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-1 with one or more of its binding partners, such as PD-L1 and/or PD-L2. The PD-1 binding antagonist may be a molecule that inhibits the binding of PD- 1 to one or more of its binding partners. In a specific aspect, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-Ll and/or PD-L2. For example, PD-1 binding antagonists include anti-PD-1 antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-1 with PD-L1 and/or PD-L2. An exemplary PD-1 binding antagonist is an anti-PD-1 antibody. For example the PD-1 binding antagonist is MDX-1106 (nivolumab), MK-3475 (pembrolizumab), CT-011 (pidilizumab), or AMP-224.

**[0097]** The term "PD-L1 binding antagonist" refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L1 with either one or more of its binding partners, such as PD-1 or B7-1. For example,

a PD-Ll binding antagonist is a molecule that inhibits the binding of PD-Ll to its binding partners. In a specific aspect, the PD-Ll binding antagonist inhibits binding of PD-Ll to PD-1 and/or B7-1. The PD-Ll binding antagonists may include anti-PD-Ll antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-Ll with one or more of its binding partners, such as PD-1 or B7-1. For example, a PD-Ll binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-Ll so as to render a dysfunctional T-cell less dysfunctional *(e.g.*, enhancing effector responses to antigen recognition). In one example, a PD-Ll binding antagonist is an anti-PD-Ll antibody. The anti-PD-Ll antibody may be YW243.55.S70, MDX-1105, MPDL3280A, or MEDI4736.

**[0098]** The term "PD-L2 binding antagonist" refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1. A PD-L2 binding antagonist may be a molecule that inhibits the binding of PD-L2 to one or more of its binding partners. For example, the PD-L2 binding antagonist inhibits binding of PD-L2 to PD-1, such as PD-L2 antagonists including anti-PD-L2 antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1.

**[0099]** An "immune checkpoint inhibitor" refers to any compound inhibiting the function of an immune checkpoint protein. Inhibition includes reduction of function and full blockade. In particular the immune checkpoint protein is a human immune checkpoint protein. Thus the immune checkpoint protein inhibitor in particular is an inhibitor of a human immune checkpoint protein.

**[00100]** "Subject" and "patient" refer to either a human or non-human, such as primates, mammals, and vertebrates. In particular embodiments, the subject is a human.

**[00101]** As used herein, the terms "treat," "treatment," "treating," or "amelioration" when used in reference to a disease, disorder or medical condition, refer to therapeutic treatments for a condition, wherein the object is to reverse, alleviate, ameliorate,

inhibit, slow down or stop the progression or severity of a symptom or condition. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a condition. Treatment is generally "effective" if one or more symptoms or clinical markers are reduced. Alternatively, treatment is "effective" if the progression of a condition is reduced or halted. That is, "treatment" includes not just the improvement of symptoms or markers, but also a cessation or at least slowing of progress or worsening of symptoms that would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of the deficit, stabilized *(i.e.,* not worsening) state of a tumor or malignancy, delay or slowing of tumor growth and/or metastasis, and an increased lifespan as compared to that expected in the absence of treatment.

**[00102]** The "gut microbiota" or "gut microbiome" designates the population of microorganisms living in the intestine of a subject.

**[00103]** The term "alpha diversity" is a measure of intra-sample diversity and refers to the distribution and assembly patterns of all microbiota within samples and is calculated as a scalar value for each sample. "Beta diversity" is a term for inter-sample diversity, and involves the comparison of samples to each which provides a measure of the distance or dissimilarity between each sample pair.

**[00104]** The term "relative amount", which can also be designated as the "relative abundance", is defined as the number of bacteria of a particular taxonomic level (from phylum to species) as a percentage of the total number of bacteria of that level in a biological sample. This relative abundance can be assessed, for example, by measuring the percentage of 16S rRNA gene sequences present in the sample which are assigned to these bacteria. It can be measured by any appropriate technique known by the skilled artisan, such as 454 pyrosequencing and quantitative PCR of these specific bacterial 16S rRNA gene markers or quantitative PCR of a specific gene.

**[00105]** In the present text, a "good responder to a treatment", also called a "responder" or "responsive" patient or in other words a patient who "benefits from" this treatment, refers to a patient who is affected with a cancer and who shows or will show a clinically significant relief in the cancer after receiving this treatment. Conversely, a "bad responder" or "non-responder" is one who does not or will not show a clinically significant

relief in the cancer after receiving this treatment. The decreased response to treatment may be assessed according to the standards recognized in the art, such as immune- related response criteria (irRC), WHO or RECIST criteria.

**[00106]** The term "isolated" encompasses a bacterium or other entity or substance that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature or in an experimental setting), and/or (2) produced, prepared, purified, and/or manufactured by the hand of man. Isolated bacteria may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated bacteria are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components.

**[00107]** The terms "purify," "purifying" and "purified" refer to a bacterium or other material that has been separated from at least some of the components with which it was associated either when initially produced or generated (e.g., whether in nature or in an experimental setting), or during any time after its initial production. A bacterium or a bacterial population may be considered purified if it is isolated at or after production, such as from a material or environment containing the bacterium or bacterial population, and a purified bacterium or bacterial population may contain other materials up to about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or above about 90% and still be considered "isolated." In some embodiments, purified bacteria and bacterial populations are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. In the instance of bacterial compositions provided herein, the one or more bacterial types present in the composition can be independently purified from one or more other bacteria produced and/or present in the material or environment containing the bacterial type. Bacterial compositions and the bacterial components thereof are generally purified from residual habitat products.

## II. Purified Bacterial Population

**[00108]** Embodiments of the present disclosure concern short-chain fatty acid-containing compositions, such as butyrate-containing compositions and purified bacterial populations *(e.g.,* short-chain fatty acid-containing bacterial populations, such as butyrate-producing bacterial populations) for the treatment of cancer, such as in a subject being or having been administered an immune checkpoint inhibitor. In some embodiments, the subject is administered a prebiotic and/or probiotic to enrich for butyrate-producing bacteria. In certain aspects, the subject undergoes dietary changes to enrich for butyrate-producing bacteria.

**[00109]** In certain embodiments, the present disclosure provides probiotic compositions and live bacterial products which comprise bacterial populations beneficial for immune checkpoint therapy response. The probiotic composition may comprise bacteria of the phylum Firmicutes. The bacterial population may belong to the class Clostridia, specifically to the order Clostridales, or one or more bacterial populations may belong to the family Clostridiaceae, Ruminococcaceae *(e.g.,* specifically to the genus *Ruminococcus* or the genus *Faecalibacterium),* Micrococcaceae *(e.g.,* specifically to the genus *Rothia),* Lachnospiraceae, and/or Veilonellaceae. In further aspects, the bacterial population may belong to the phylum Tenericutes, particularly to the class Mollicutes. The bacteria may belong to the genus *Peptoniphilus,* particularly to the species *P. asaccharolyticus, P. gorbachii, P. harei, P. ivorii, P. lacrimalis,* and/or *P. olsenii.* Further exemplary bacterial populations for the probiotic composition may include bacterial populations that belong to the genus *Porphyromonas,* particularly to the species *Porphyromonas pasteri,* the species *Clostridium hungatei,* the genus *Phascolarctobacterium* or the species *Phascolarctobacterium faecium.*

**[00110]** For example, bacterial populations of the genus *Ruminococcus* can include bacteria of the species *Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus flavefaciens, Ruminococcus champanellensis, Ruminococcus faecis, Ruminococcus gauvreauii, Ruminococcus gnavus, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus lactaris, Ruminococcus luti , Ruminococcus obeum, Ruminococcus palustris , Ruminococcus pasteurii, Ruminococcus productus, Ruminococcus schinkii,* and/or *Ruminococcus torques.* Bacterial populations of the genus *Faecalibacterium* can include bacteria of the species *Faecalibacterium prausnitzii.*

[00111] Exemplary bacterial populations of the genus *Rothia* can include bacteria of the species *R. aeria, R. amarae, R. dentocariosa, R. endophytica, R mucilaginosa, R. nasimurium,* and/or *R. terrae.*

[00112] Exemplary bacterial populations for inclusion in the probiotic composition include bacterial populations that belong to the phylum Firmicutes, class Clostridia, family Ruminococcaceae, species *Faecalibacterium prausnitzii,* genus *Ruminococcus,* species *Porphyromonas pasteri,* family Veilonellaceae, species *Colostridium hungatei,* genus *Phascolarctobacterium,* species *Phascolarctobacterium faecium,* genus *Peptoniphilus,* family Micrococcaceae, class Mollicutes, and/or genus *Rothia.*

[00113] In particular aspects, the probiotic composition or live bacterial product does not comprise bacterial populations of the order *Bacteroidales,* such as of the genus *Bacteroides,* particularly of the species *B. thetaiotaomicron, B. fragilis, B. vulgatus, B. distasonis, B. ovatus, B. stercoris, B. merda, B. uniformis, B. eggerithii,* or *B. caccae.* In particular, the probiotic composition does not comprise bacterial populations of the genus *Gardnerella* or of the species *Collinsella stercoris, Desuljovibrio alaskensis, Bacteroides mediterraneensis, Prevotella histicola* or *Gardnerella vaginalis.*

Table 1: Operational taxonomic units of Sets 1-3

| OTUs | Sei | TAX_id | Phylum | Class | Order | Famiiy | Genius | Species | ei |
|---|---|---|---|---|---|---|---|---|---|
| OTU_219 | SEQ ID NO: 3 | 28113 | Bacteroidetes | Bacteroidia | Bacieroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides heparmolyticus* | -1.00 |
| OTU_140 | SEQ ID NO: 3 | 1852370 | Bacteroidetes | Bacteroidia | Bacieroidales | Prevotel!aceae | *Prevotellamassilia* | *PrevoteUamassiiia tirnonensis* | -1.00 |
| OTU_320 | SEQ ID NO: 3 | 1122135 | Proteobacteria | Aiphaproteobacieria | Kiionieilales | Kilonieilaceae | *Kilonieiia* | *Kilonieiia iaminariae DSM 19542* | -1.00 |
| OTU_166 | SEQ ID NO: 3 | 1796646 | Bacteroidetes | Bacteroidia | Bacieroidales | Poϕ hyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | -1.00 |
| OTU_1381 | SEQ ID NO: 3 | 1348613 | Firmicutes | Clostridia | Clostridia!es | Defiuviite!eaceae | *Valliialea* | *Valliialea pronyensis* | -0.64 |
| OTU_2558 | SEQ ID NO: 3 | 1841856 | Bacteroidetes | Bacteroidia | Bacieroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides mediterrcmeensis* | -1.00 |
| OTU_788 | SEQ ID NO: 3 | 1002367 | Bacteroidetes | Bacteroidia | Bacieroidales | Prevotellaceae | *Prevoieiia* | *Prevotella stercorea DSM 18206* | -1.00 |
| OTU_1772 | SEQ ID NO: 3 | 1841856 | Bacteroidetes | Bacteroidia | Bacieroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides mediterraneensis* | -1.00 |
| OTU_2085 | SEQ ID NO: 3 | 58134 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Laciinoclosiridiiim* | *[Desulfotomaculum] guttoideum* | -1.00 |
| OTU_648 | SEQ ID NO: 3 | 1527 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerocoiumna* | *Anaerocoiumna ammovalerica* | -1.00 |
| OTU_623 | SEQ ID NO: 3 | 187979 | Firmicutes | Negaiivicutes | Seienomonadales | Seienomonadaceae | *Mitsuokeila* | *Mitsuokeila jalaludmii* | -1.00 |
| OTU_671 | SEQ ID NO: 3 | 1841857 | Bacteroidetes | Bacteroidia | Bacieroidales | Odoribacteraceae | *Cultiiromica* | *Culturomica massiliensis* | -1.00 |
| OTU_600 | SEQ ID NO: 3 | 387661 | Bacteroidetes | Bacteroidia | Bacieroidales | Poϕ hyromonadaceae | *Parabacteroides* | *Parabacteroides johnsonii* | -1.00 |
| OTU_1038 | SEQ ID NO: 3 | 1841857 | Bacteroidetes | Bacteroidia | Bacieroidales | Odoribacteraceae | *Cultiiromica* | *Culturomica massiliensis* | -1.00 |
| OTU_2899 | SEQ ID NO: 3 | 357276 | Bacteroidetes | Bacteroidia | Bacieroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides dorei* | -0.64 |
| OTU_1079 | SEQ ID NO: 3 | 45254 | Bacteroidetes | Bacteroidia | Bacieroidales | PorplryromQnadaceae | *Dysgonomonas* | *Dysgonomonas capnocytophagoides* | -1.00 |
| OTU_546 | SEQ ID NO: 3 | 762984 | Bacteroidetes | Bacteroidia | Bacieroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides clarus YIT 12056* | -1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1213 | SEQ ID NO: 3 | 544645 | Bacteroidetes | Bacteroidia | Bacteroidales | Odoribacteraceae | *Butyricimonas* | *Butyricimonas virosa* | -0.55 |
| OTU_823 | SEQ ID NO: 3 | 204516 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides massiliensis* | -0.55 |
| OTU_954 | SEQ ID NO: 3 | 1796646 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | -1.00 |
| OTU_886 | SEQ ID NO: 3 | 537011 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella copri DSM 18205* | -0.55 |
| OTU_2805 | SEQ ID NO: 3 | 52226 | Firmicutes | Negativicutes | Selenomonadales | Selenomonadaceae | *Mitsuokella* | *Mitsuokella multiacida.* | -1.00 |
| OTU_611 | SEQ ID NO: 3 | 742742 | Actinobacteria | Coriobacteriia | Coriobacteriales | Coriobacteriaceae | *Collinsella* | *Collinsella tanakaei YIT 12063* | -1.00 |
| OTU_1853 | SEQ ID NO: 3 | 291644 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides salyersiae* | -1.00 |
| OTU_1691 | SEQ ID NO: 3 | 484018 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides pleheius DSM 17135* | -1.00 |
| OTU_2206 | SEQ ID NO: 3 | 484018 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides plebeius DSM 17135* | -1.00 |
| OTU_749 | SEQ ID NO: 3 | 204516 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides massiliensis* | -0.64 |
| OTU_2557 | SEQ ID NO: 3 | 1841856 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides mediterraneensis* | -1.00 |
| OTU_2249 | SEQ ID NO: 3 | 820 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides uniformis* | -1.00 |
| OTU_418 | SEQ ID NO: 3 | 1796620 | Firmicutes | Clostridia | Clostridials | Ruminococcaceae | *Acutalibacter* | *Acutalibacter muris* | -0.51 |
| OTU_2640 | SEQ ID NO: 3 | 342942 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] glycyrrhizinilyticum* | -1.00 |
| OTU_2555 | SEQ ID NO: 3 | 1841856 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides mediterraneensis* | -1.00 |
| OTU_1263 | SEQ ID NO: 3 | 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerotruncus* | *Anaeroiruncus colihommis* | -1.00 |
| OTU_1641 | SEQ ID NO: 3 | 1298596 | Firmicutes | Clostridia | Clostiidiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus faecis JCM 15917* | -1.00 |
| OTU_884 | SEQ ID NO: 3 | 147206 | Actinobacteria | Coriobacteriia | Coriobacteriales | Coriobacteriaceae | *Collinsella* | *Collinsella stercoris* | -1.00 |
| OTU_2384 | SEQ ID NO: 3 | 290054 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium coprostanoligenes* | -1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_620 | SEi T 3 | 253257 | Firmicutes | Clostridia | Clostridiaies | Lachiiospiraceae | *Lachnoclostridium* | *[Clostridium] amygdalinum* | -0.64 |
| OTIJ_1559 | SEi T 3 | 817 | Bacteroideies | Bacteroidia | Bacteroidaies | Bacteroidaceae | *Bacteroides* | *Bacteroides fragi!is* | -0.80 |
| OTU_3115 | SE T 3 | 47678 | f3actero ideies | Bacteroidia | Bacteroidaies | Bacteroidaceae | *Bacteroides* | *Bacteroides cac.cae* | -0.64 |
| OTU_935 | SE T 3 | 40545 | Proteobacteria | Betaproieobacieria | Burkhoideriales | Sutterellaceae | *Sutterella* | *Sutterella wadsworthensis* | -1.00 |
| OTU_2415 | i SEi T 3 | 645466 | Firmicuies | Clostridia | Clostridiaies | Lachnospiraceae | *Anaerostipes* | *Anaerostipes buiyraticus* | -1.00 |
| OTU_876 | SEi T 3 | 1776382 | Firmicutes | Clostridia | Ciostiidiaies | Ruminococcaceae | *Neglecta* | *Neglecta timonensis* | -1.00 |
| OTU_1027 | SEi T 3 | 1852367 | Firmicutes | Clostridia | Clostridiaies | Clostridiaies Family XIII. Inceitae Sedis | *Ihubacter* | *Ihubacter massiliensis* | -0.64 |
| OTU_2412 | SE T 3 | 1532 | Firmicutes | Clostridia | Clostridiaies | Lachnospiraceae | *Biauiia* | *Biautia coccoides* | -1.00 |
| OTU_1305 | SE T 3 | 1841857 | Bacteroideies | Bacteroidia | Bacteroidaies | Odoribacteraceae | *Cuituromica* | *Cuituromica massiliensis* | -1.00 |
| OTU_1554 | SEi T 3 | 1535 | Firmicutes | Clostridia | i Clostridiaies | Ruminococcaceae | *Ruminic!ostridium* | *[Clostridium] leptum* | -1.00 |
| OTU_567 | i SEi T 3 | 333367 | Firmicutes | Clostridia | Ciostiidiaies | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] asparagiforme* | -0.55 |
| OTU_815 | SEi T 3 | 544645 | Bacteroideies | Bacteroidia | Bacteroidaies | Odoribactemceae | *Butyricimonas* | *Butyricimonas virosa* | -1.00 |
| OTU_1898 | SE T 3 | 454154 | Bacteroideies | Bacteroidia | Bacteroidaies | Prevotellaceae | *ParaprevoteUa* | *ParaprevoteUa ciara* | -0.64 |
| OTU_1143 | SEi T 3 | 46503 | Bacteroideies | Bacteroidia | Bacteroidaies | Poipliyronionadaceae | *Parabacteroides* | *Parabacteroides merdae* | -1.00 |
| OTU_3106 | SEi T 3 | 454154 | Bacteroidetes | Bacteroidia | i Bacteroidaies | Prevotellaceae | *ParaprevoteUa* | *ParaprevoteUa clara* | -1.00 |
| OTU_576 | i SEi T 3 | 1535 | Firmicutes | Clostridia | Ciostiidiaies | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] leptum* | -0.59 |
| OTU_740 | SEi T 3 | 156456 | Firmicutes | Negaiivicutes | Veillonellales | Veilionellaceae | *Anaeroglobus* | *Anaeroglobus geminatus* | -1.00 |
| OTU_1827 | SE T 3 | 470145 | Bacteroideies | Bacteroidia | Bacteroidaies | Bacteroidaceae | *Bacteroides* | *Bacteroides coprocola DSM i l 136* | -1.00 |
| OTU_3025 | SEi T 3 | 169435 | Firmicutes | Clostridia | Clostridiaies | Ruminococcaceae | *Anaerotruncus* | *Anaerotruncus colihominis* | -1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1709 | SE T3 | 46206 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Pseudobutyrivibrio* | *Pseudobutyrivibrio ruminis* | -1.00 |
| OTU_3158 | SE T3 | 820 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides uniformis* | -1.00 |
| OTU_2145 | SE T3 | 544645 | Bacteroidetes | Bacteroidia | Bacteroidales | Odoribacteraceae | *Butyricimonas* | *Butyricimonas virosa* | -0.64 |
| OTU_3211 | SE T3 | 449673 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides stercoris ATCC 43183* | -0.64 |
| OTU_2912 | SE T3 | 180164 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia schinkii* | -1.00 |
| OTU_3210 | SE T3 | 123242 8 | Firmicutes | Negativicutes | Veillonellales | Veillonellaceae | *Megasphaera* | *Megasphaera massiliensis* | -0.75 |
| OTU_2843 | SE T3 | 449673 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides stercoris ATCC 43183* | -0.75 |
| OTU_1531 | SE T3 | 123242 8 | Firmicutes | Negativicutes | Veillonellales | Veillonellaceae | *Megasphaera* | *Megasphaera massiliensis* | -1.00 |
| OTU_750 | SE T3 | 239935 | Verrucomicrobia | Verrucomicrobiae | Verrucomicrobiales | Akkermansiaceae | *Akkermansia* | *Akkermansia muciniphila* | -0.55 |
| OTU_1801 | SE T3 | 204516 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides massiliensis* | -0.80 |
| OTU_1621 | SE T3 | 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] methylpentosum* | -1.00 |
| OTU_2179 | SE T3 | 449673 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides stercoris ATCC 43183* | -1.00 |
| OTU_2121 | SE T3 | 1544 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] oroticum* | -0.64 |
| OTU_2070 | SE T3 | 204516 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides massiliensis* | -1.00 |
| OTU_1071 | SE T3 | 585528 | Actinobacteria | Actinobacteria | Bifidobacteriales | Bifidobacteriaceae | *Gardnerella* | *Gardnerella vaginalis ATCC 14018 = JCM 11026* | -1.00 |
| OTU_767 | SE T3 | 33039 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *[Ruminococcus] torques* | -0.55 |
| OTU_2257 | SE T3 | 821 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides vulgatus* | -0.55 |
| OTU_2072 | SE T3 | 339860 | Euryarchaeota | Methanobacteria | Methanobacteriales | Methanobacteriaceae | *Methanosphaera* | *Methanosphaera stadtmanae DSM 3091* | -1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1321 | SET 3 | 1535 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumimclostridm* | *[Clostridium] leptum* | -1.00 |
| OTU_2533 | SET 3 | 308994 | Firmieutes | Negaiivicutes | Veilloneliales | Veillonellaceae | *Dialisier* | *Dialister propionicifaciens* | -1.00 |
| OTU_{105 | SET 3 | 1796618 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Cuneatibacter* | *Cuneatibacter caecimuris* | -0.64 |
| OTU_2403 | SET 3 | 824 | Proteobacteria | Epsiionproteobacteria | Campylobacterales | Campylobacteraceae | *Campylobacter* | *Campylobacter gracilis* | -1.00 |
| OTU_1914 | SET 3 | 204516 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides massiUensis* | -0.55 |
| OTU_2553 | SET 3 | 1841856 | Bacteroidetes | Bactero idia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides mediterraneensis* | -1.00 |
| OTU_2977 | SET 3 | 40519 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus cattidus* | -1.00 |
| OTU_2988 | SET 3 | 301302 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Roseburia* | *Roseburia faecis* | -1.00 |
| OTU_3116 | SET 3 | 33025 | Firmieutes | Negaiivicutes | Acidaminococcales | Acidaminococcaceae | *Phascoiarctobacterium* | *; Phascolarctobacterium faecium* | -1.00 |
| OTU_3019 | SET 3 | 487175 | Proteobacteria | Betaproteobacteria | Burkholde dales | Sutterellaceae | *Parasuiterella* | *Parasuiterella excrementihominis* | -0.75 |
| OTU_2198 | SET 3 | 39496 | Firmieutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium ventnosum* | -1.00 |
| OTU_46 | SET 3 | 199 | Proteobacteria | Epsiionproteobacteria | Campylobacterales | Campylobacteraceae | *Campylobacter* | *Campylobacter concisus* | -0.55 |
| OTU_2942 | SET 3 | 871665 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia faecis* | -0.75 |
| OTU_1361 | SET 3 | 626937 | Firmieutes | Clostridia | Clostridiales | Christensenellaceae | *Christenseneila* | *Christenseneila minuta* | -0.64 |
| OTU_2636 | SET 3 | 1265 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *; Ruminococcus flavejaciens* | -1.00 |
| OTU_2285 | SET 3 | 1232428 | Firmieutes | Negaiivicutes | Veilloneliales | Veillonellaceae | *Megasphaera* | *Megasphaera massiUensis* | -1.00 |
| OTU_3094 | SET 3 | 84026 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumimclostridm* | *[Clostridium] meihylpeniosum* | -0.75 |
| OTU_{358 | SET 3 | 40519 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus calliclus* | -0.64 |
| OTU_2259 | SET 3 | 46867 | Firmieutes | Clostridia | Clostridiales | Ciostndiaceae | *Clostridium* | *Clostridium chauvoei* | -0.64 |

| OTU_3181 | SE | 218538 | Frrmicutes | Negativicutes | Veillonellales | Veilioneliaceae | *Diaiister* | *Diaiister invisus* | -0.64 |
|---|---|---|---|---|---|---|---|---|---|
| OTU_2642 | SE | 253257 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] amygdalinum* | -1.00 |
| OTU_2552 | SE | 12365 1 5 | Bacteroidetes | Bacteroidia | Bacieroidaies | Bacteroidaceae | *Bacteroides* | *Bacteroides sartorii JCM 17136 = DSM 21941* | -1.00 |
| OTU_2556 | SE | 153 1 | Firmieutes | Clostridia | Clostridiales | Lachno spiraceae | *Lachnoclostridium* | *[Clostridium] clostridioforme* | -1.00 |
| OTU_2616 | SE | 1 16085 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Coprococcus* | *Coprococcus caius* | -1.00 |
| OTU_2943 | SE | 292800 | Firmieutes | Clostridia | Clostridiales | unclassified.NA | *Flavonifractor* | *Flavonifractor plautii* | -1.00 |
| OTU_2989 | SE | 112111 5 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Biautia* | *Biautia wexlerae DSM 19850* | -1.00 |
| OTU_2624 | SE | 357276 | Bacteroidetes | Bacteroidia | Bacieroidaies | Bacteroidaceae | *Bacteroides* | *Bacteroides dorei* | -0.64 |
| OTU_2243 | SE | 109624 6 | Firmieutes | Clostridia | Clostridiales | Ciostridiaceae | *Htmgatella* | *; Hungatella effhivii* | -0.64 |
| OTU_22 14 | SE | 123242 8 | Firmieutes | Negativicutes | Veillonellales | Veilioneliaceae | *Megasphaera* | *; Megasphaera massiliensis* | -0.55 |
| OTU_2199 | SE | 454154 | Bacteroidetes | Bacteroidia | Bacieroidaies | Prevotellaceae | *Paraprevotella* | *Paraprevotella clara* | -0.64 |
| OTU_1990 | SE | 53701 1 | Bacteroidetes | Bacteroidia | Bacieroidaies | Prevotellaceae | *Prevotella* | *Prevotella copri DSM 18205* | -1.00 |
| OTU_3002 | SE | 4585 1 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Butyrivibrio* | *Butyrivibrio crossotus* | -1.00 |
| OTU_1596 | SE | 172901 | Lentispliaerae | Lentispliaeria | Viciivallaies | Victivallaceae | *Victivallis* | *\ Victivallis vadensis* | -1.00 |
| OTU_115 1 | SE | 765 17 | Proteobacteria | Epsiionproteobacteria | Campviobacteraies | Campylobacteraceae | *Campylobacter* | *Campylobacter hominis* | -1.00 |
| OTU_1322 | SE | 168384 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Marvinbryantia* | *j Marvinbryantia formatexigens* | -1.00 |
| OTU_2692 | SE | 166486 | Firmieutes | Clostridia | Clostridiales | Lachno spiraceae | *Fioseburia* | *Roseburia intestinalis* | -1.00 |
| OTU_3054 | SE | 147 176 1 | Firmieutes | Bacilli | Bacillales | Thermoactinomyceiaceae | *Novibacillus* | *Novibacillus ihermophilus* | - 1.00 |
| OTU_3137 | SE | 2045 16 | Bacteroidetes | Bacteroidia | Bacieroidaies | Bacteroidaceae | *Bacteroides* | *Bacteroides massiliensis* | -1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_2905 | SET 3 | 204516 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides massiliensis* | -1.00 |
| OTU_1783 | SET 3 | 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] meihylpeniosum* | -1.00 |
| OTU_1498 | SET 3 | 824 | Proteobacteria | Epsilonproteobacteria | Campj'iobacterales | Campylobacteraceae | *Campylobacter* | *Campylobacter gracilis* | -1.00 |
| OTU_2450 | SET 3 | 154046 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Hungatella* | *Hungatella hathewayi* | -1.00 |
| OTU_3004 | SET 3 | 69825 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridhtm* | *[Clostridium] indolis* | -1.00 |
| OTU_95 | SET 3 | 28135 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella oris* | -0.75 |
| OTU_1368 | SET 3 | 1776382 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Neglecta* | *Neglecta timonensis* | -1.00 |
| OTU_S460 | SET 3 | 381308 | Proteobacteria | Gammaproteobacteria | Chromatiales | Thioalkalispiraceae | *Thiohalophilus* | *Thiohalophilus thiocyanatoxydans* | -1.00 |
| OTU_1488 | SET 3 | 28446 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Tyzzereila* | *[Clostridium] propionicum* | -1.00 |
| OTU_1601 | SET 3 | 181487 | Actinobacteria | Actinobacteria | Actinomycetales | Actinomycetaceae | *Actinomyces* | *Actinomyces cardiffensis* | -1.00 |
| OTU_69 | SET 3 | 505 | Proteobacteria | Betaproteobacteria | Neisseriales | Neisseriaceae | *Kingella* | *Kingella oralis* | -1.00 |
| OTU_2301 | SET 3 | 515620 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *[Eubacterium] eligens ATCC 27750* | -0.64 |
| OTU_5310 | SET 3 | 113107 | Firmicutes | Bacilli | Lactobacillales | Streptococcaceae | *Streptococcus* | *Streptococcus australis* | -0.75 |
| OTU_2258 | SET 3 | 871665 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia faecis* | -0.64 |
| OTU_2473 | SET 3 | 213810 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus champanellensis ISP13 = JCM 17042* | -1.00 |
| OTU_1671 | SET 3 | 40545 | Proteobacteria | Betaproteobacteria | Burkholderiales | Sutterellaceae | *Sutterella* | *Sutterella wadsivorthensis* | -1.00 |
| OTU_2545 | SET 3 | 1002367 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella stercorea DSM 18206* | -1.00 |
| OTU_2620 | SET 3 | 1796636 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Frisingicoccus* | *; Frisingicoccus caecimuris* | -1.00 |
| OTU_2956 | SET 3 | 470145 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides coprocola DSM 17136* | -1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1598 | SET 3 | 1264 | Frrmicutes | Clostridia | Clostridiaies | Ruminococcaceae | *Ruminococcus* | *Ruminococcus a!bus* | -1.00 |
| OTU_2537 | SET 3 | 745368 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Gemmiger* | *GemmigerJbrmicilis* | -1.00 |
| OTU_684 | SET 3 | 644 | Proteobacteria | Gammaproteobacteria | Aeromona dales | Aeromonadaceae | *Aeromonas* | *Aeromonas hydrophila* | -1.00 |
| OTU_951 | SET 3 | 47847 | Actinobacteria | Aciinobacieiia | Micrococcales | Dermabacteraceae | *Brachybacten urn* | *Brachybacterium nesterenkovh* | -1.00 |
| OTU_286 | SET 3 | 888828 | Proteobacteria | Gammar>roteobacteria | Pasteurel!ales | Pasteutellaceae | *Haemophilus* | *Haemophilus parainfluenzae ATCC 33392* | -0.64 |
| OTU_1238 | SET 3 | 553973 | Firmieutes | Clostridia | Clostridiaies | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] hylemonae ¡)SM 15053* | -0.75 |
| OTU_1135 | SET 3 | 638849 | Synergistates | Synergi stia | Synergistales | Synergistaceae | *Pyramidobacter* | *Pyramidobacter piscolens* | -1.00 |
| OTU_1789 | SET 3 | 454 154 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Paraprevotella* | *Paraprevotella clara* | - 1.00 |
| OTU_526 | SET 3 | 470565 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella histicoia* | -0.80 |
| OTU_1166 | SET 3 | 28137 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella veroraiis* | -0.64 |
| OTU_1281 | SET 3 | 1417852 | Firmieutes | Clostridia | Clostridiaies | unclassified.NA | *Flintibacter* | *Flintibacter butyricus* | -0.64 |
| OTU_883 | SET 3 | 1348613 | Firmieutes | Clostridia | Clostridiaies | Defluvntaleaceae | *Vallitalea* | *Vallitalea pronyensis* | -1.00 |
| OTU_1445 | SET 3 | 29364 | Firmieutes | Clostridia | Clostridiaies | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] polysaccharolyticum* | - 1.00 |
| OTU_1582 | SET 3 | 169435 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Anaerotruncus* | *Anaerotruncus colihominis* | -1.00 |
| OTU_1958 | SET 3 | 58134 | Firmieutes | Clostridia | Clostridiaies | Lachnospiraceae | *Lachnoclostridium* | *[Desulfotomaculum] guttoideiim* | -1.00 |
| OTU_352 | SET 3 | 52693 | Firmieutes | Clostridia | Clostridiaies | Eubacteriaceae | *Acetobacierium* | *Acetobacierium paludosum* | -1.00 |
| OTU_941 | SET 3 | 425941 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella nanceiensis* | -1.00 |
| OTU_1495 | SET 3 | 43675 | Actinobacteria | Actmob acteria | Micrococcales | Micrococcaceae | *Roihia* | *Rothia mucilaginosa* | - 1.00 |
| OTU_2172 | SET 3 | 187326 | Firmieutes | Negativicutes | Veilloneliales | Veillonellaceae | *Megasphaera* | *Megasphaera micronuciformis* | -1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_511 | SET 3 | 228603 | Bacteroideies | Bacteroidia | Bacieroidales | Prevotellaceae | *PrevoteUa* | *PrevoteUa shahii* | -1.00 |
| OTU_601 | SET 3 | 1236516 | Bacteroideies | Bacteroidia | Bacteroidales | Prevotellaceae | *PrevoteUa* | *PrevoteUa saccharolyiica JCM 17484* | -1.00 |
| OTU_1074 | SET 3 | 264463 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerosporobacter* | *Anaerosporobacter mobilis* | -1.00 |
| OTU_48 | SET 1 | 717959 | Bacteroideies | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes shahii WAL 8301* | 1.00 |
| OTU_242 | SET 1 | 587 | Proteobacteria | Gammar>roteobacteria | Enterobacterales | Morganellaceae | *Providencia* | *Providencia retigeri* | 1.00 |
| OTU_194 | SET 1 | 758823 | unclassified.NA | unciassified.NA | unclassified.NA | unclassified.NA | *Vampirovibrio* | *Vampirovibrio chlorellavorus* | 1.00 |
| OTU_262 | SET 1 | 649756 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerostipes* | *Anaerostipes hadriis* | 1.00 |
| OTU_1226 | SET 1 | 44749 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacier* | *Sporobaeter termitidis* | 1.00 |
| OTU_213 | SET 1 | 671218 | Bacteroideies | Bacteroidia | Bacteroidales | Prevotellaceae | *Alloprevotella* | *; Alloprevotella rava* | 1.00 |
| OTU_350 | SET I | 1264 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *; Ruminococcus albus* | 1.00 |
| OTU_249 | SET 1 | 1122135 | Proteobacteria | Alphaproteobacteria | Kiioniellales | Kilonieiiaceae | *Kilonielia* | *Kilonielia laminariae DS.U 19542* | 1.00 |
| OTU_477 | SET 1 | 853 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Faeca!ibacterium* | *Faecalibacterhim prausnitzii* | 1.00 |
| OTU_356 | SET 1 | 484018 | Bacteroideies | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *\ Bacieroides plebeius DSM 17135* | 1.00 |
| OTU_426 | SET 1 | 46503 | Bacteroideies | Bacteroidia | Bacteroidales | Poipliyronionadaceae | *Parabacteroides* | *; Parabacteroides merdae* | 1.00 |
| OTU_143 | SET I | 54565 | Proteobacteria | Deltaproteobacteria | Desillfovibrionales | Desulfovibrionaceae | *Desulfovibrio* | *\ Desulfovfbrio simplex* | 1.00 |
| OTU_386 | SET 1 | 290052 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Acetivibrio* | *j Acetivibrio etkanolgignens* | 1.00 |
| OTU_387 | SET 1 | 21693 | Tenericutes | Mollicuies | Entomoplasniatales | Spiroplasmaiaceae | *Spirop!asma* | *Spiroplasma allegheiiense* | 1.00 |
| OTU_1618 | SET 1 | 575978 | Proteobacteria | Deltaproteobacteria | Desulfovibriona!es | Desulfovib rionaceae | *Desulfovibrio* | *Desulfovibrio idahonensis* | 1.00 |
| OTU_380 | SET 1 | 433321 | Firmicutes | Negativicutes | Selenomonadales | Seienomonadaceae | *Propionispira* | *Propionispira arcuata* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_359 | SEQ ID NO: 1 | 1796646 | Bacteroideies | Bacteroidia | Bacieroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | 1.00 |
| OTU_28 | SEQ ID NO: 1 | 112213 5 | Proteobacteria | Alphaproteobacteria | Kilonieilales | Kilonellaceae | *Kilonieila* | *Kilonieila larninariae DSM 19542* | 1.00 |
| OTU_536 | SEQ ID NO: 1 | 213810 | Firmicutes | Clostridia | Closiridiales | Ruminococcaceae | *Rurninococcus* | *Rurninococcus champanellensis J8PI3 JCM 17042* | 1.00 |
| OTU_392 | SEQ ID NO: 1 | 112213 5 | Proteobacteria | Alphaproteobacieria | Kilonieilales | Kiionieilaceae | *Kilonieila* | *Kilonieila larninariae DSM 19542* | 1.00 |
| OTU_499 | SEQ ID NO: 1 | 228924 | Firmicutes | Clostridia | Clostridiales | Closiridiales Family XII. Incertae Sedis | *Chiggenheimella* | *Chiggenheimella bovis* | 1.00 |
| OTU_264 | SEQ ID NO: 1 | 717959 | Bacteroideies | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes shahii WAL 8301* | 1.00 |
| OTU_110 | SEQ ID NO: 1 | 1796646 | Bacteroideies | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | 1.00 |
| OTU_215 | SEQ ID NO: 1 | 290054 | Firmicutes | Clostridia | Closiridiales | Eubacteriaceae | *Eiibaclerium* | *Eubacteriuin coprostanoligenes* | 1.00 |
| OTU_484 | SEQ ID NO: 1 | 1509 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Clostridium* | *Clostridium sporogenes* | 1.00 |
| OTU_86 | SEQ ID NO: 1 | 146291 9 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Mobilitalea* | *Mobilitalea sibirica* | 1.00 |
| OTU_275 | SEQ ID NO: 1 | 29375 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[ClostridiumJ xylanolyticum* | 1.00 |
| OTU_178 | SEQ ID NO: 1 | 337097 | Firmicutes | Bacilli | Bacillales | Baciliaceae | *Vulcanibaciilus* | *Vulcanibaciilus rnodesiicaldus* | 1.00 |
| OTU_2653 | SEQ ID NO: 1 | 129859 6 | Firmicutes | Clostridia | Closiridiales | Ruminococcaceae | *Rurninococcus* | *Rurninococcus faecis JCM 15917* | 1.00 |
| OTU_337 | SEQ ID NO: 1 | 487174 | Bacteroideies | Bacteroidia | Bacteroidales | Poipliy romonadaceae | *Bamesiella* | *Bamesiella mtestimhominis* | 1.00 |
| OTU_530 | SEQ ID NO: 1 | 642492 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Cellulosilyticum* | *Clostridium lentocellum DSM 5427* | 1.00 |
| OTU_123 | SEQ ID NO: 1 | 1735 | Firmicutes | Erysipelotrichia | Erysipeloirichales | Erysipelotrichaceae | *Holdemanella* | *Holdemanella biformis* | 1.00 |
| OTU_1846 | SEQ ID NO: 1 | 129742 4 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerobacterium* | *Anaerobacterium chariisolvens* | 1.00 |
| OTU_134 | SEQ ID NO: 1 | 742766 | Bacteroideies | Bacieroidia | Bacteroidales | Poip hy romonadaceae | *Dysgonotnonas* | *Dysgonomonas gadei ATCC BAA-286* | 1.00 |
| OTU_654 | SEQ ID NO: 1 | 146291 9 | Firmicutes | Clostridia | Closiridiales | Lachnospiraceae | *Mobilitalea* | *Mobilitalea sibirica* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_621 | SEQ | 46680 | Proteobacteria | Gammaproteobacteria | Pseudonionadaies | Pseudomonadaceae | *Methylobacillus* | *Pseudomonas niProreducens* | 1.00 |
| OTU_233 | SEQ | 132925 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium bowmanii* | **1.00** |
| OTU_271 | SEQ | 758823 | **unclassified.NA** | unclassified.NA | unclassified.NA | **unclassified.NA** | *Vampirovibrio* | *Vampirovibrio chioreliavorus* | 1.00 |
| OTU_561 | SEQ | 41467 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Pseudoflavonifractor* | *Pseudoflavonifractor capillosus ATCC 29799* | **1.00** |
| OTU_687 | SEQ | 1122135 | **Proteobacteria** | **Alphaproteobacteria** | Kiloniellales | **Kiloniellaceae** | *Kilonieiia* | *Kilonieiia laminariae DSM 19542* | **1.00** |
| OTU_707 | SEQ | 13184655 | Tenericutes | Mollicutes | **Acholeplasmatales** | **Acholeplasmataceae** | *Acholeplasma* | *Acholeplasma brassicae 0502* | **1.00** |
| OTU_1950 | SEQ | 1852367 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *Ihubacter* | *Ihubacter massiliensis* | **1.00** |
| OTU_1113 | SEQ | 1841857 | Bacteroidetes | **Bacteroidia** | **Bacteroidales** | Odoribacteraceae | *Cultwomica* | *Culturomica massiliensis* | **1.00** |
| OTU_344 | SEQ | 169679 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium saccharobutylicum* | **1.00** |
| **OTU_529** | SEQ | 175296 | **Euryarchaeota** | **Thermoplasmata** | **Methanomassiliicoccales** | **Methanoinassiliicoccaceae** | *Meihanomassiliiccoccus* | *Methanomassiliicoccus lumiriyensis B10* | 1.00 |
| OTU_58 | SEQ | 1122135 | Proteobacteria | Alphaproteobacteria | Kiionieilales | Kiloniellaceae | *Kiionieiia* | *Kilonieiia laminariae DSM 19542* | **1.00** |
| OTU_2607 | SEQ | 259063 | Firmicutes | Clostridia | Clostridiales | **Lachnospiraceae** | *Anaerocolumna* | *Anaerocolumna jejuensis* | 1.00 |
| OTU_542 | SEQ | 172901 | Lentisphaerae | **Lenusphaeria** | Victrvalialaies | **Victivallaceae** | *Victivallis* | *Victivallis vadensis* | **1.00** |
| OTU_724 | SEQ | 39488 | Firmicutes | Clostridia | Clostridiales | **Eubacteriaceae** | *Eubacterium* | *[Eubacterium j hallii* | **1.00** |
| **OTU_473** | SEQ | 57172 | Firmicutes | Clostridia | **Clostridiales** | Peptococcaceae | *Desulfotomaculum* | *Desuljotornaculurn halophilum* | 1.00 |
| OTU_2146 | SEQ | 28118 | Bacteroideies | **Bacteroidia** | Bacteroidales | Odoribacteraceae | *Odoribacter* | *Odoribacter splanchnicus* | **1.00** |
| OTU_793 | SEQ | 166486 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Roseburia* | *Roseburia iniestinalis* | 1.00 |
| OTU_90 | SEQ | 28133 | Bacteroidetes | Bacteroidia | Bacteroidales | **Prevotellaceae** | *Prevotella* | *Prevotella nigrescens* | **1.00** |
| OTU_593 | SEQ | 758823 | unclassified.NA | unclassified.NA | unclassified.NA | unclassified.NA | *Vampirovibrio* | *Vampirovibrio chioreliavorus* | **1.00** |

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| οτυ_504 | SET 1 | 1529 | Firmieutes | Clostridia | Clostridiaies | Ciostridiaceae | *Clostridium* | *Clostridium cadaveris* | 1.00 |
| OTU_322 | SET 1 | 44749 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacter* | *Sporobacter terrnitidis* | 1.00 |
| OTU_524 | SET 1 | 694434 | Firmieutes | Clostridia | Clostridiaies | Gracilibacteraceae | *Gracilibacter* | *Gracilibacter thermoiolerans JW/YJL-Si* | 1.00 |
| OTU_805 | SET 1 | 1007096 | Firmieutes | Clostridia | Clostridiaies | Osciilospiraceae | *Oscillibacier* | *Oscillibacier ruminantium GH1* | 1.00 |
| OTU_798 | SET 1 | 84030 | Firmieutes | Clostridia | Clostridiaies | Lachnospiraceae | *Lachnoclostridium* | *['Clostridium] sacckarolyticum* | 1.00 |
| OTU_300 | SET 1 | 56774 | Firmieutes | Clostridia | Clostridiaies | Clostridiales Family XIII. Incertae Sedis | *unclassified.NA* | *[Eubacterium] infirmum* | 1.00 |
| OTU_617 | SET 1 | 102148 | Firmieutes | Erysipelotrichia | Erysipelotrichales | Ery sipelotrichaceae | *Solobacterium* | *Solobacterium moorei* | 1.00 |
| OTU_156 | SET 1 | 626947 | Proteobacteria | Betaproteobacteria | Burkholderiales | Sutterellaceae | *Parasutterella* | *Parasutterella secunda.* | 1.00 |
| OTU_1449 | SET 1 | 1297424 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Anaerobacterium* | *; Anaerobacterium chartisolvens* | 1.00 |
| OTU_109 | SET I | 290054 | Firmieutes | Clostridia | Clostridiaies | Eubacteriaceae | *Eubacterium* | *; Eubacterium coprostanoligenes* | 1.00 |
| OTU_1622 | SET 1 | 216933 | Tenericutes | Mollicutes | Entomoplasmatales | Spiroplasmataceae | *Spiroplasma* | *Spiroplasma ciirysopicola* | 1.00 |
| OTU_205 | SET 1 | 626947 | Proteobacteria | Betaproteobacteria | Burkholderiales | Sutterellaceae | *Parasutlerella* | *Parasutterella secunda* | 1.00 |
| OTU_306 | SET 1 | 758823 | unclassified.NA | unclassified.NA | unclassified.NA | unclassified.NA | *Vampirovibrio* | *Vampirovibrio ciilorellavorus* | 1.00 |
| OTU_206 | SET 1 | 1348613 | Firmieutes | Clostridia | Clostridiaies | Defluviitaleaceae | *Val!italea* | *\ Vallita!eapronyensis* | 1.00 |
| OTU_2657 | SET I | 44749 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Sporobacter* | *\ Sporobacter terminals* | 1.00 |
| OTU_2102 | SET 1 | 1472417 | Bacteroidetes | Bactero idia | Bacteroidales | Odoribacteraceae | *Butyricimonas* | *Butyricimonas paravirosa* | 1.00 |
| OTU_329 | SET 1 | 100176 | Firmieutes | Clostridia | Clostiidiaies | Ruminococcaceae | *Papiilibacter* | *Papiilibacter cinnamivorans* | 1.00 |
| OTU_1499 | SET 1 | 824 | Proteobacteria | Epsilonproteobacteria | Campylobacterales | Campvlobacteraceae | *'Campylobacter* | *Campylobacter gracilis* | 1.00 |
| OTU_756 | SET 1 | 1471761 | Firmieutes | Bacilli | Bacillales | Thermoactinomy cetaceae | *Novibacillus* | *\ Novibacillus thermophilus* | 1.00 |

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| OTU_634 | SE T1 | 129761 7 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Intestinimonas* | *Intestinimonas butyriciproducens* | 1.00 |
| OTU_374 | SE T1 | 288966 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Lutispora* | *Lutispora thermophila* | 1.00 |
| OTU_527 | SE T1 | 131712 5 | Bacteroidetes | Cytophagia | Cytophagales | Hymenobacteraceae | *Pontibacter* | *Pontibacter indicus* | 1.00 |
| OTU_772 | SE T1 | 28197 | Proteobacteria | Epsilonproteobacteria | Campylobacterales | Campylobacteraceae | *Arcobacter* | *Arcobacter butzleri* | 1.00 |
| OTU_2652 | SE T1 | 358743 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] citroniae* | 1.00 |
| OTU_1352 | SE T1 | 642492 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Cellulosilyticum* | *Clostridium lentocellum DSM 5427* | 1.00 |
| OTU_678 | SE T1 | 264639 | Tenericutes | Mollicutes | Acholeplasmatales | Acholeplasmataceae | *Acholeplasma* | *Acholeplasma parvum* | 1.00 |
| OTU_468 | SE T1 | 1265 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus flavefaciens* | 1.00 |
| OTU_775 | SE T1 | 112213 5 | Proteobacteria | Alphaproteobacteria | Kiloniellales | Kiloniellaceae | *Kiloniella* | *Kiloniella laminariae DSM 19542* | 1.00 |
| OTU_1526 | SE T1 | 1335 | Firmicutes | Bacilli | Lactobacillales | Streptococcaceae | *Streptococcus* | *Streptococcus equinus* | 1.00 |
| OTU_2951 | SE T1 | 66219 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *Lachnoclostridium phytofermentans* | 1.00 |
| OTU_953 | SE T1 | 69473 | Tenericutes | Mollicutes | Acholeplasmatales | Acholeplasmataceae | *Acholeplasma* | *Acholeplasma vituli* | 1.00 |
| OTU_431 | SE T1 | 115117 | Proteobacteria | Deltaproteobacteria | Desulfovibrionales | Desulfovibrionaceae | *Desulfovibrio* | *Desulfovibrio desulfuricans subsp. desulfuricans* | 1.00 |
| OTU_1952 | SE T1 | 341220 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Lactonifactor* | *Lactonifactor longoviformis* | 1.00 |
| OTU_599 | SE T1 | 758823 | unclassified.NA | unclassified.NA | unclassified.NA | unclassified.NA | *Vampirovibrio* | *Vampirovibrio chlorellavorus* | 1.00 |
| OTU_362 | SE T1 | 1732 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium oxidoreducens* | 1.00 |
| OTU_340 | SE T1 | 873513 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella buccae ATCC 33574* | 1.00 |
| OTU_1032 | SE T1 | 179664 6 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | 1.00 |
| OTU_2116 | SE T1 | 411467 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Pseudoflavonifractor* | *Pseudoflavonifractor capillosus ATCC 29799* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1480 | SEQ ID | 742766 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Dysgonomonas* | *Dysgonomonas gadei ATCC BAA-286* | 1.00 |
| OTU_103 | SEQ ID | 487174 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Barnesiella* | *Barnesiella intestinihominis* | 0.55 |
| OTU_2458 | SEQ ID | 396504 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] sufflavum* | 1.00 |
| OTU_1020 | SEQ ID | 179661 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Irregularibacter* | *Irregularibacter maris* | 1.00 |
| OTU_967 | SEQ ID | 184185 | Bacteroidetes | Bacteroidia | Bacteroidales | Odoribacteraceae | *Cultwomica* | *Culturomica massiliensis* | 1.00 |
| OTU_2801 | SEQ ID | 45851 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Butyrivibrio* | *Butyrivibrio crossotus* | 1.00 |
| OTU_942 | SEQ ID | 1509 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium sporogenes* | 1.00 |
| OTU_2995 | SEQ ID | 259063 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerocolumna* | *Anaerocolumna jejuensis* | 1.00 |
| OTU_865 | SEQ ID | 2741 | Firmicutes | Clostridia | Clostridiales | Peptococcaceae | *Peptococcus* | *[Peptococcus] niger* | 1.00 |
| OTU_1158 | SEQ ID | 105841 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerostipes* | *[Anaerostipes] caccae* | 1.00 |
| OTU_1693 | SEQ ID | 86332 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *Mogibacterium* | *[Mogibacterium] pumilum* | 1.00 |
| OTU_236 | SEQ ID | 134982 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Coprobacter* | *Coprobacter fastidiosus NSB1* | 1.00 |
| OTU_2554 | SEQ ID | 84037 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Syntrophococcus* | *Syntrophococcus sucromuians* | 1.00 |
| OTU_558 | SEQ ID | 180311 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Hespellia* | *[Hespellia] stercorisuis* | 1.00 |
| OTU_223 | SEQ ID | 44749 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacter* | *Sporobacter terminals* | 0.59 |
| OTU_925 | SEQ ID | 54291 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Enterobacteriaceae | *Raoultella* | *Raoultella ornithinolytica* | 1.00 |
| OTU_1965 | SEQ ID | 1509 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium sporogenes* | 1.00 |
| OTU_608 | SEQ ID | 29375 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] xylanolyticum* | 1.00 |
| OTU_836 | SEQ ID | 121728 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Parabacteroides* | *Parabacteroides faecis* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| οτυ_862 | SET 1 | 172901 | Lentisphaerae | Lentisphaeria | Victivallales | Victivallaceae | *VictivaUis* | *VictivaUis vadensis* | 1.00 |
| OTU_227 | SET 1 | 694434 | Firmieutes | Clostridia | Clostridiales | Gracilibacteraceae | *Gracilibacier* | *Gracilibacier tliermoiolerans JW/YJL-Sl* | 1.00 |
| OTU_185 | SET 1 | 762984 | Bacteroidetes | Bacteroidia | Bacteroidaies | Bacteroidaceae | *Bacteroides* | *Bacteroides clarus YIT 12056* | 1.00 |
| OTU_406 | SET 1 | 1185412 | Firmieutes | Clostridia | Clostridiales | Defluviitaleaceae | *Valhtaiea* | *Vallitalea guaymasensis* | 1.00 |
| OTU_479 | SET 1 | 154046 | Firmieutes | Clostridia | Clostridiales | Clostridiaceae | *r!ungatella* | *Hungatella hathewayi* | 1.00 |
| OTU_127 | SET 1 | 1122135 | Proteobacteria | Alphaproteobacteria | KiionieMes | Kiloniellaceae | *Kilonieila* | *Kilonieila laminariae DSM 19542* | 1.00 |
| OTU_1344 | SET 1 | 663278 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Eihanoligenens* | *Eihanoligenens harbinense YUAN-3* | 1.00 |
| OTU_136 | SET 1 | 1543 | Firmieutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium oceanlcum* | 0.65 |
| OTU_1050 | SET 1 | 626947 | Proteobacteria | Betaproteobacteria | Burkhoideriales | Sutterellaceae | *Parasuitereila* | *; Parasuiierella secunda* | 1.00 |
| OTU_995 | SET I | 3985 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Pseudobacteroides* | *; Pseudobacteroides cellulosolvens \ ATCC 35603 = DSM 2933* | 1.00 |
| OTU_2543 | SET 1 | 1297424 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerobacterium* | *Anaerobacterium chartisolvens* | 1.00 |
| OTU_2983 | SET 1 | 1335 | Firmieutes | Bacilli | Lactobacillales | Streptococcaeeae | *Streptococcus* | *Streptococcus equinus* | 1.00 |
| OTU_1869 | SET 1 | 587 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Morganellaceae | *Providencia* | *Providencia rettgeri* | 1.00 |
| OTU_190 | SET 1 | 66219 | Firmieutes | Clostridia | Clostridiales | Lachno spiraceae | *Lachnoclostridium* | *; Lachnoclostridium phytofermentans* | 1.00 |
| OTU_1714 | SET I | 69825 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachrioclostridium* | *[Clostridium] indolis* | 1.00 |
| OTU_657 | SET 1 | 1175296 | Eur}'archaeota | Thermoplasmata | Methanomassiliicoccales | Methanomassiliicoccaceae | *Meihanomassllilcoccus* | *Methanomassiliicoccus luminyensis \ B10* | 1.00 |
| OTU_957 | SET 1 | 1841867 | Firmieutes | Clostridia | Clostiidiaies | Ruminococcaceae | *Phocea* | *Phocea massiliensis* | 1.00 |
| OTU_346 | SET 1 | 1535 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *(Clostridium] leptum* | 1.00 |
| OTU_1979 | SET 1 | 1265 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus flavefaciens* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_2606 | SE T 1 | 15 10 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] sircorarium* | 1.00 |
| OTU_989 | SE T 1 | 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] methylpeniosum* | 1.00 |
| OTU_2820 | SE T 1 | 1502 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium perfringens* | 1.00 |
| OTU_1434 | SE T 1 | 129742 4 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerobacterium* | *Anaerobacterium chartisolvens* | 1.00 |
| OTU_596 | SE T 1 | 161923 4 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerobium* | *Anaerobium aceteihylicum* | 1.00 |
| OTU_1447 | SE T 1 | 3985 12 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Pseudobacteroi.des* | *Pseudobacteroid.es cellulosolvens ATCC 35603 = DSM 2933* | 1.00 |
| OTU_2980 | SE T 1 | 1335 | Firmicutes | Bacilli | Lactobacillales | Streptoeoccaeeae | *Streptococcus* | *Streptococcus equinus* | 1.00 |
| OTU_1848 | SE T 1 | 39497 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium xylanophilum* | 1.00 |
| OTU_1802 | SE T 1 | 1544 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | */Clostridiumj oroticum* | 1.00 |
| OTU_2171 | SE T 1 | 8735 13 | Bacteroidetes | Baeteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella buccaeATCC 33574* | 1.00 |
| OTU_1141 | SE T 1 | 29343 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] celhilosi* | 1.00 |
| OTU_83 | SE T 1 | 4585 1 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Buiyrivibrio* | *Buiyrivibrio crossotus* | 1.00 |
| OTU_627 | SE T 1 | 694434 | Firmicutes | Clostridia | Clostridiales | Gracilibacteraceae | *Gracilibacter* | *Gracilibacter thermoiolerans JWYYJL-S!* | 1.00 |
| OTU_3010 | SE T 1 | 56774 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *unclassified.NA* | *[Eubacterium] infinitum* | 1.00 |
| OTU_1055 | SE T 1 | 1732 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium oxidoreducens* | 1.00 |
| OTU_2647 | SE T 1 | 649762 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia kiti DSM 14534* | 1.00 |
| OTU_1230 | SE T 1 | 154046 | Firmicutes | Clostridia | Clostiidiaies | Clostridiaceae | *Hungaiella* | *Hungaiella hathewayi* | 1.00 |
| OTU_1549 | SE T 1 | 290054 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium coprostanoligenes* | 1.00 |
| OTU_1985 | SE T 1 | 332095 | Firmicutes | Tissierellia | unclassified.NA | unclassified.NA | *Dethiosulfatibacter* | *Deihiosulfiatibacter aminovorans* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|---|
| OTU_1040 | SE T1 | 536633 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia glucerasea* | 1.00 |
| OTU_404 | SE T1 | 103373 1 | Bacteroidetes | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes timonensis JC136* | 1.00 |
| OTU_722 | SE T1 | 129761 7 | Firmicutes | Clostridia | Clostridiales | unclassified NA | *Intestinimonas* | *Intestinimonas butyriciproducens* | 1.00 |
| OTU_173 | SE T1 | 574930 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Parabacteroides* | *Parabacteroides gordonii* | 0.55 |
| OTU_932 | SE T1 | 742818 | Actinobacteria | Coriobacteriia | Eggerthellales | Eggerthellaceae | *Slackia* | *Slackia piriformis YIT 12062* | 1.00 |
| OTU_1296 | SE T1 | 1264 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus albus* | 1.00 |
| OTU_801 | SE T1 | 177412 | Verrucomicrobia | Verrucomicrobiae | Verrucomicrobiales | Verrucomicrobiaceae | *Fucophilus* | *Fucophilus fucoidanolyticus* | 1.00 |
| OTU_1320 | SE T1 | 112130 8 | Firmicutes | Clostridia | Clostridiales | Peptostreptococcaceae | *Clostridioides* | *Clostridioides difficile ATCC 9689 = DSM 1296* | 0.50 |
| OTU_2930 | SE T1 | 419208 | Firmicutes | Negativicutes | Veillonellales | Veillonellaceae | *Veillonella* | *Veillonella denticariosi* | 1.00 |
| OTU_503 | SE T1 | 167371 7 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaeromassilibacillus* | *Anaeromassilibacillus senegalensis* | 1.00 |
| OTU_708 | SE T1 | 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] methylpentosum* | 1.00 |
| OTU_129 | SE T1 | 180311 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Hespellia* | *Hespellia stercorisuis* | 0.59 |
| OTU_385 | SE T1 | 55779 | Firmicutes | Clostridia | Thermoanaerobacterales | Thermoanaerobacteraceae | *Moorella* | *Moorella glycerini* | 0.55 |
| OTU_279 | SE T1 | 28117 | Bacteroidetes | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes putredinis* | 1.00 |
| OTU_1489 | SE T1 | 626937 | Firmicutes | Clostridia | Clostridiales | Christensenellaceae | *Christensenella* | *Christensenella minuta* | 1.00 |
| OTU_1237 | SE T1 | 180332 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Robinsoniella* | *Robinsoniella peoriensis* | 1.00 |
| OTU_1951 | SE T1 | 213810 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus champanellensis 18P13 = JCM 17042* | 1.00 |
| OTU_2662 | SE T1 | 177638 2 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Neglecta* | *Neglecta timonensis* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_3108 | SEQ ID NO: 405 | 19 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus callidus* | 1.00 |
| OTU_12011 | SEQ ID NO: 34062 | 1 | Proteobacteria | Gammaproteobacteria | Pseudomonadales | Moraxellaceae | *Moraxella* | *Moraxella osloensis* | 1.00 |
| OTU_551 | SEQ ID NO: 405 | 18 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus bromii* | 1.00 |
| OTU_1077 | SEQ ID NO: 74426 | 1 | Actinobacteria | Coriobacteriia | Coriobacteriales | Coriobacteriaceae | *CoiimseUa* | *Coltmsella aerofaciens* | 1.00 |
| OTU_11261 | SEQ ID NO: 121606 | 2 | Firmicutes | Clostridia | Clostridiales | Peptococcaceae | *Desulfotornaculum* | *Desuljotornaslum tongense* | 1.00 |
| OTU_1138 | SEQ ID NO: 293826 | 1 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Alkaliphilus* | *Alkaliphilus metalliredigens QYMF* | 1.00 |
| OTU_952 | SEQ ID NO: 161923 | 4 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerobhim* | *Anaerobium aceiethylicum* | 1.00 |
| OTU_2954 | SEQ ID NO: 4585 | 1 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Btiiyrivibrio* | *Buiyrivibrio crossotus* | 1.00 |
| OTU_1721 | SEQ ID NO: 84026 | 1 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rummiclostridium* | *[Clostridium] methylpentosum* | 1.00 |
| OTU_1084 | SEQ ID NO: 850 | 1 | Fusobacteria | Fusobacteriia | Fusobaeteriales | Fusobacteriaceae | *Fusobacierium* | *Fusobacierium mortiferum* | 1.00 |
| OTU_106 | SEQ ID NO: 44749 | 1 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacter* | *Sporobacter termitidis* | 0.50 |
| OTU_1013 | SEQ ID NO: 645466 | 1 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerostipes* | *Anaerostipes butyraticus* | 1.00 |
| OTU_1345 | SEQ ID NO: 474960 | 1 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Hydrogenoanaerobacterium* | *Hydrogenoanaerobacterium saccharovorans* | 1.00 |
| OTU_1775 | SEQ ID NO: 84030 | 1 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium! saccharofyticum* | 1.00 |
| OTU_666 | SEQ ID NO: 36835 | 1 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Tyzzereila* | *[Clostridium] colinum* | 1.00 |
| OTU_1602 | SEQ ID NO: 115544 | 1 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Parasporobacteri.um* | *Parasporobacterium paucivorans* | 1.00 |
| OTU_550 | SEQ ID NO: 1515 | 1 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rmnimclostridim* | *Rwmni Clostridium thermocellum* | 1.00 |
| OTU_851 | SEQ ID NO: 1515 | 1 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *Ruminiclostridium thermocellum* | 1.00 |
| OTU_1982 | SEQ ID NO: 8843 | 1 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Dorea* | *Dorea longicatena* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_486 | SET1 | 1515 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumimclostridium* | *Rwmni Clostridium thermocettum* | 1.00 |
| OTU_1024 | SET1 | 216932 | Tenericutes | Mollicutes | Entomoplasmatales | Spiropiasmataceae | *Spiroplasma* | *Spiroplasma ciiinense* | 1.00 |
| OTU_1262 | SET1 | 853 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Faecalibacterium* | *Faecalibacterium prausnitzU* | 1.00 |
| OTU_382 | SET1 | 141785 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Flintibacter* | *Flmtibacter butyricus* | 0.73 |
| OTU_472 | SET1 | 694434 | Firmicutes | Clostridia | Clostridiales | Gracilibacteraceae | *Gracilibacter* | *Gracilibacter ihermotolerans JW/YJL-Sl* | 1.00 |
| OTU_1076 | SET1 | 39492 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumimclostridium* | *[Eubacterium] siraeum* | 1.00 |
| OTU_686 | SET1 | 290054 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium coprostanoligenes* | 1.00 |
| OTU_458 | SET1 | 1583 | Firmicutes | Bacilli | Lactobacillales | Leiiconostocaceae | *WeisseUa* | *\ Weissella confuse:.* | 1.00 |
| OTU_449 | SET1 | 663278 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ethcmoligenens* | *Ethanoligenens harbinense YTJAN-3* | 1.00 |
| OTU_555 | SET1 | 154046 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Hungateiia* | *Hungateiia hathɛwayi* | 1.00 |
| OTU_1623 | iSETi | 129761 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *!ntestinimonas* | *Iniestinimonas buiyriciproducens* | 1.00 |
| OTU_703 | SET1 | 1515 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumimclostridium* | *Ruminiclostridium thermocelliim* | 1.00 |
| OTU_347 | SET1 | 420247 | Euryarchaeota | Methanobacteria | Meihanobacteriai es | Methanobacleriaceae | *Meihanobrevibacter* | *Methanobrevibacter smithii ATCC \ 35061* | 0.55 |
| OTU_1139 | SET1 | 118967 | Bacteroidetes | Bacteroidia | Bacieroidales | Bacteroidaceae | *Anaerorhabdus* | *Anaerorhabdus furcosa* | 1.00 |
| OTU_1407 | SET1 | 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerotruncus* | *j Anaeroiruncus colihominis* | 1.00 |
| OTU_1414 | SET1 | 37658 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lacimoclostridium* | *[Clostridium J populeti* | 1.00 |
| OTU_791 | SET1 | 138595 | Actinobacteria | Coriobacteriia | Coriobacteriales | Atopobiaceae | *Olsenella* | *Olsenella profusa* | 1.00 |
| OTU_1246 | SET1 | 31971 | Firmicutes | Erysipelotrichia | Erysipelotrichales | Erysipeloirichaceae | *unclassified.NA* | *[Eubacterium] dolichum* | 1.00 |
| OTU_216 | SET1 | 100886 | Firmicutes | Erysipelotrichia | Erysipelotrichales | Erysipeloirichaceae | *Catenibacterium* | *Caienibacierium mitsuokai* | 1.00 |

| OTU_1147 | SE T 1 | 119771 7 | Synergistetes | Synergistia | Synergistales | Synergistaceae | *Cloacibacillus* | *Cloacibacillus porcorum* | 1.00 |
|---|---|---|---|---|---|---|---|---|---|
| OTU_733 | SE T 1 | 234908 | Proteobacteria | Betaproteobacteria | Burkholderiales | Sutterellaceae | *Sutterella* | *Sutterella siercoricanis* | 1.00 |
| OTU_2095 | SE T 1 | 44749 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacier* | *Sporobacter termitidis* | 1.00 |
| OTU_659 | SE T 1 | 2741 | Firmicutes | Clostridia | Clostridiales | Peptococcaceae | *Peptococcus* | *Peptococcus niger* | 1.00 |
| OTU_757 | SE T 1 | 185236 7 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *ihubacter* | *Ihubacter massiliensis* | 1.00 |
| OTU_2678 | SE T 1 | 141785 2 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Flmtihacter* | *Flmtihacter butyricus* | 1.00 |
| OTU_1477 | SE T 1 | 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] meihylpeniosum* | 0.68 |
| OTU_1402 | SE T 1 | 762984 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacleroidaceae | *Bacteroides* | *Bacteroides clams YIT 12056* | 1.00 |
| OTU_2277 | SE T 1 | 537007 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia hansenii DSM 20583* | 1.00 |
| OTU_2566 | SE T 1 | 487174 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Barnesiella* | *Barnesiella inlestinihominis* | 1.00 |
| OTU_2119 | SE T 1 | 1732 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium oxidoreducens* | 1.00 |
| OTU_1039 | SE T 1 | 1535 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] leptum* | 1.00 |
| OTU_1603 | SE T 1 | 228924 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XII. Incertae Sedis | *Gv.ggenheimella* | *(ittiggenheimella bovis* | 1.00 |
| OTU_2669 | SE T 1 | 319644 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Saccharofermentans* $a_{HS}$ | *Saccharofermentans acetigenes* | 1.00 |
| OTU_2044 | SE T 1 | 168384 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *M* $\bar{a}_{FVIII}$*bryantia* | *Marvinbryantiajormaiexigens* | 1.00 |
| OTU_411 | SE T 1 | 915173 | Firmicutes | Erysipelotrichia | Erysipelotrichales | Erysipelotrichaceae | *Faecalicoccus* | *Faecalicoccus acidiformans* | 1.00 |
| OTU_357 | SE T 1 | 95159 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Caloramaior* | *Caloramaior coolhaasii* | 0.68 |
| OTU_1616 | SE T 1 | 31971 | Firmicutes | Erysipelotrichia | Erysipelotrichales | Erysipelotrichaceae | *unclassified.NA* | *[Eubacterium] dolichum* | 1.00 |
| OTU_541 | SE T 1 | 1515 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *Ruminiclostridium thermocellum* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1737 | SEQ_TAX | 1816678 | Firmicutes | Clostridia | Clostridiales | Christensenellaceae | *Christensenella* | *Christensenella timonensis* | 1.00 |
| OTU_2707 | SEQ_TAX | 1417852 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Fhniibacter* | *Fiintibacter butyricus* | 1.00 |
| OTU_255 | SEQ_TAX | 626940 | Firmicutes | Negativicutes | Acidaminococcales | Acidaminococcaceae | *Phascolarctobacterium* | *Phascolarctobacterium succinatutens* | 1.00 |
| OTU_1901 | SEQ_TAX | 501571 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Butyricicoccus* | *Butyricicoccus pulicaecorum* | 0.50 |
| OTU_3081 | SEQ_TAX | 179662 | Firmicutes | Clostridia | Clostridiales | Ruiniiiococcaceae | *Acutalibacter* | *Acutalibacter muris* | 1.00 |
| OTU_2902 | SEQ_TAX | 888727 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Inceriae Sedis | *unclassified.NA* | *Eubacterium sulci A TCC 35585* | 1.00 |
| OTU_2418 | SEQ_TAX | 114713 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Caloramator* | *Caloramator quimbayensis* | 1.00 |
| OTU_2936 | SEQ_TAX | 129859 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus faecis JCM 15917* | 1.00 |
| OTU_1244 | SEQ_TAX | 376806 | Bacteroidetes | Bacteroidia | Bacieroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides gallinarum* | 0.55 |
| OTU_1333 | SEQ_TAX | 151 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiciosiridiii m* | *Ruminiciostridium thermoceUum* | 1.00 |
| OTU_1340 | SEQ_TAX | 127435 | Firmicutes | Bacilli | BaciUales | Thermoactinomycetaceae | *Kroppenstedtia* | *Kroppenstedtia guangzhouensis* | 1.00 |
| OTU_900 | SEQ_TAX | 1267 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Clostridium* | *Clostridium veniriculi* | 1.00 |
| OTU_1684 | SEQ_TAX | 1335 | Firmicutes | Bacilli | Lactobacillales | Stteptococcaceae | *Streptococcus* | *Streptococcus equinus* | 1.00 |
| OTU_3012 | SEQ_TAX | 39495 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium uniforme* | 1.00 |
| OTU_3013 | SEQ_TAX | 21381 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus champanellensis 18P13 = JCM 17042* | 1.00 |
| OTU_1300 | SEQ_TAX | 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerotruncus* | *Anaerotruncus colihommis* | 1.00 |
| OTU_912 | SEQ_TAX | 185236 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Inceriae Sedis | *Ihubacter* | *Ihubacter massi'ieiisis* | 1.00 |
| OTU_786 | SEQ_TAX | 404403 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Hovi'ardelta* | *Howardella ureilytica* | 1.00 |
| OTU_1277 | SEQ_TAX | 1348 | Firmicutes | Bacilli | Lactobacillales | Streptococcaceae | *Streptococcus* | *Streptococcus parauberis* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1617 | SEQ_1 | 172901 | Lentisphaerae | Lentisphaeria | Victivallales | Victivallaceae | *VictivaUis* | *Victivallis vadensis* | 1.00 |
| OTU_1994 | SEQ_1 | 458451 | Firmicutes | Clostridia | Clostridiales | Lachnospiraeeae | *Butyrivibrio* | *Butyrivibrio crossotus* | 1.00 |
| OTU_1850 | SEQ_1 | 253314 | Firmicutes | Clostridia | Clostiidiales | Ruminococcaceae | *Ruminiclostridium* | *j Clostridium J straminisolvens* | 1.00 |
| OTU_2802 | SEQ_1 | 458451 | Firmicutes | Clostridia | Clostridiales | Lachnospiraeeae | *Butyrivibrio* | *Butyrivibrio crossotus* | 1.00 |
| OTU_581 | SEQ_1 | 1796619 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Irregiiiaribacter* | *Irregiiiaribacter ₘuris* | 1.00 |
| OTU_1747 | SEQ_1 | 258515 | Firmicutes | Clostridia | Clostiidiales | Ruminococcaceae | *Acetanaerobacterₘm* | *Acetanaerobacterium elongatum* | 0.50 |
| OTU_2428 | SEQ_1 | 1297617 | Firmicutes | Clostridia | Clostridiales | unelassified.NA | *Intestinimonas* | *Intestinimonas butyriciproducens* | 1.00 |
| OTU_157 | SEQ_1 | 33033 | Firmicutes | Tissierellia | Tissierellales | Peptoniphilaceae | *Parvimonas* | *Parvimonas micro.* | 1.00 |
| OTU_630 | SEQ_1 | 1007096 | Firmicutes | Clostridia | Clostridiales | Osciilospiraceae | *OsciUibacier* | *Osciilibacter rumiₙaᵢitium GH!* | 0.55 |
| OTU_1366 | SEQ_I | 1297617 | Firmicutes | Clostridia | Clostridiales | unelassified.NA | *Intestinimonas* | *Ɉatesᵢinimonas buiyriciproducens* | 1.00 |
| OTU_1247 | SEQ_1 | 649762 | Firmicutes | Clostridia | Clostiidiales | Lachnospiraeeae | *Blautia* | *Blautia iuti DSM 14534* | 1.00 |
| OTU_1590 | SEQ_1 | 111806 1 | Bacteroideies | Bacteroidia | Bacteroidales | Rikenellaceae | *Aiistipes* | *Aiistipes obesi* | 1.00 |
| OTU_3014 | SEQ_1 | 357276 | Bacteroideies | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacieroides dorᵢ̈i* | 1.00 |
| OTU_489 | SEQ_1 | 214851 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Subdoligranuium* | *Subdoligranulum variabile* | 0.50 |
| OTU_1311 | SEQ_I | 320502 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] alkaiice!lu!osi* | 1.00 |
| OTU_1389 | SEQ_1 | 217731 | Tenericutes | Mollicutes | Entomoplasmatales | Entomoplasmataceae | *Mesoplasma* | *Mesoplasma photuris* | 1.00 |
| OTU_1086 | SEQ_1 | 246787 | Bacteroideies | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacieroides* | *Bacteroides cellulosilyiicus* | 0.59 |
| OTU_1131 | SEQ_1 | 626937 | Firmicutes | Clostridia | Clostridiales | Ciirislensenellaceae | *Christensenella* | *Christensenella miₙutₐ* | 1.00 |
| OTU_704 | SEQ_1 | 1841867 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Phocea* | *Phocea massiliensis* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| οτυ_710 | SET 1 | 29371 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Rumimclostridium* | *[Clostridium] termitidis* | 1.00 |
| OTU_2810 | SET 1 | 84030 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Laciinoclosiridium* | *[Clostridium] saccharolyticum* | 1.00 |
| OTU_921 | SET 1 | 649764 | Actinobacteria | Coriobacteriia | Eggerthellales | Eggerthellaceae | *Slackia* | *Slackia exigua ATCC 700122* | 1.00 |
| OTU_1159 | SET 1 | 290054 | Firmieutes | Clostridia | Clostridiaies | Eubacteriaceae | ***Eubacterium*** | *Eubacterium coprosianoligenes* | 1.00 |
| OTU_2583 | SET 1 | 901 | Proteobacteria | Deltaproteobacteria | Desiilfovibrionales | Desu!fovibrionaeeae | *Desnlfovibrio* | *Desulfovibrio piger* | 1.00 |
| OTU_1767 | SET 1 | 1776382 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Neglecta* | *Neglecta timonensis* | 1.00 |
| OTU_984 | SET 1 | 29374 | Firmieutes | Clostridia | Clostridiaies | Peptostreptococcaceae | *Filifactor* | *FiUfactor villosus* | 1.00 |
| OTU_1065 | SET 1 | 1776382 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Neglecta* | *Neglecta timonensis* | 1.00 |
| OTU_1763 | SET 1 | 29343 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Ruminiclostridium* | *\ [Clostridium] cellulosi* | 1.00 |
| OTU_1768 | SET I | 33043 | Firmieutes | Clostridia | Clostridiaies | Lachnospiraceae | *Coprococcus* | *; Coprococcus euiactus* | 1.00 |
| OTU_1525 | SET 1 | 39778 | Firmieutes | Negativicutes | Veilionellaies | Veilionellaceae | *Veillonella* | *\ Veillonella dispar* | 1.00 |
| OTU_2860 | SET 1 | 39778 | Firmieutes | Negativicutes | Veilloneliales | Veillonellaceae | *Veillonella* | *Veillonella dispar* | 1.00 |
| OTU_2297 | SET 1 | 86332 | Firmieutes | Clostridia | Clostridiaies | Clostridiaies Family XIII. ¡ncerţae Sedis | *Mogjbacierium* | *Mogibacterium pumiium* | 1.00 |
| OTU_842 | SET 1 | 682400 | Firmieutes | Clostridia | Clostridiaies | unclassified.NA | *Natranaerovirga* | *\ Natranaerovirga pectiinvora* | 0.55 |
| OTU_1567 | SET I | 871665 | Firmieutes | Clostridia | Clostridiaies | Lachnospiraceae | *Blautia* | *\ Blautia jaecis* | 1.00 |
| OTU_1774 | SET 1 | 160404 | Firmieutes | Clostridia | Clostridiaies | Lachnospiraceae | *Tyzzerella* | *[Clostridium] lactatifermenians* | 1.00 |
| OTU_974 | SET 1 | 626937 | Firmieutes | Clostridia | Clostridiaies | Christensenellaceae | *Christensenel!a* | *Christensenella minuta* | 1.00 |
| OTU_1578 | SET 1 | 396504 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Ruminiclostridium* | *\ [Clostridium] suffiavum* | 1.00 |
| OTU_1196 | SET 1 | 214851 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *S.ubdoligranulum* | *Subdoligranulum variabile* | 0.50 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1680 | SEQ ID NO: 1502 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium perfringens* | 1.00 |
| OTU_562 | SEQ ID NO: 40519 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus callidus* | 1.00 |
| OTU_1455 | SEQ ID NO: 745368 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Gemmiger* | *Gemmiger formicilis* | 1.00 |
| OTU_2413 | SEQ ID NO: 408 | Proteobacteria | Alphaproteobacteria | Rhizobiales | Meihylobacteriaceae | *Methylobacterium* | *Methylobacterium extorquens* | 1.00 |
| OTU_575 | SEQ ID NO: 1535 | **Firmicutes** | Clostridia | Clostridiales | Ruiniuococcaceae | *Ruminiclostridium* | *[Clostridium] leptum* | 1.00 |
| OTU_294 | SEQ ID NO: 1584 | Firmicutes | **Bacilli** | **Lactobacillales** | Lactobacillaceae | *Lactobacillus* | *Lactobacillus delbrueckii* | 1.00 |
| OTU_1362 | SEQ ID NO: 288966 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Luiispora* | *Lutispora fnermophi!a* | 1.00 |
| OTU_1931 | SEQ ID NO: 100176 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *PapiHibacter* | *PapiHibacter cinnamivorans* | 1.00 |
| OTU_1619 | SEQ ID NO: 1510 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium/ stercorarium* | 1.00 |
| **OTU_779** | SEQ ID NO: 333367 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] asparagiforme* | 1.00 |
| OTU_1119 | SEQ ID NO: 47246 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] viride* | 1.00 |
| OTU_731 | SEQ ID NO: 694434 | Firmicutes | Clostridia | Clostridiales | Gracilibacteraceae | *Gracilibacter* | *Gracilibacter tliermoiolerans JW/YJL-S1* | 0.59 |
| OTU_403 | SEQ ID NO: 1007096 | Firmicutes | Clostridia | Clostridiales | **Oscillospiraceae** | *Oscillibacter* | *Oscillibacter rummanium GH1* | 0.55 |
| OTU_1279 | SEQ ID NO: 47246 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium/ viride* | 1.00 |
| **OTU_1514** | SEQ ID NO: 1096246 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Hungateila* | *Hungateila effluvii* | 1.00 |
| OTU_1992 | SEQ ID NO: 154046 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Hungateila* | *Hungatella hathewayi* | 1.00 |
| OTU_2248 | SEQ ID NO: 290052 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Acetivibno* | *Acetivibrio eihano!gignens* | 1.00 |
| OTU_2668 | SEQ ID NO: 642492 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Celiulosilyticurn* | *Clostridium lentocellum DSM 5427* | 1.00 |
| OTU_631 | SEQ ID NO: 53342 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Caloramotor* | *Caloramotor proteoclosticus* | 0.63 |

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|---|---|---|---|---|---|---|---|---|---|
| οτυ_1998 | SEi T 1 | 54291 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Enterobacteriaceae | *Raoultella* | *Raoultella ormtlnnolyiica* | 1.00 |
| OTIJ_103 | SEi T 1 | 438033 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus gauvreauii* | 1.00 |
| OTU_299 | SET 1 | 35 1091 | Firmieutes | Clostridia | Clostridiales | Osciilospiraceae | *Oscillibacter* | *Oscillibacter valericigenes* | 0.55 |
| OTU_2032 | SEi T 1 | 1796622 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Extibacter* | *Extibacter muris* | 1.00 |
| OTU_2641 | i SEi T 1 | 169435 | Firmieutes | Clostridia | Clostridiales | Ruiniiiococcaceae | *Anaerotntncus* | *Anaerotruncus colihominis* | 1.00 |
| OTU_1657 | SEi T 1 | 44749 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacter* | *Sporobacter termitidis* | 0.55 |
| OTU_880 | SEi T 1 | 694434 | Firmieutes | Clostridia | Clostridiales | Gracilibacteraceae | *Gracilibacier* | *Gracilibacier fnermoiolerans JW/YJL-Sl* | 1.00 |
| OTU_405 | SET 1 | 1776384 | Firmieutes | Clostridia | Clostridiales | Clostridiales Family XIII. ¡ncer¡ae Sedis | *Emergencia* | *Emergencia timonensis* | 0.50 |
| OTU_809 | SEi T 1 | 39492 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Rummiclostridium* | *[Eubaciernimj siraeum* | 1.00 |
| OTU_2167 | SEi T I | 8¡7 | Baetero idetes | Baetero idia | i Bac!eroidales | Baeteroidaceae | *Bacieroides* | *Bacteroiaesfragilis* | 1.00 |
| OTU_2670 | i SEi T 1 | 84026 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Rummiclostridium* | *[Clostridium] methylpentosum* | 1.00 |
| OTU_2671 | SEi T 1 | ¡4 17852 | Firmieutes | Clostridia | Clostridiales | unelassified.NA | *Flintibacter* | *Flintibacter butyricus* | 1.00 |
| OTU_1056 | SET 1 | 4 11467 | Firmieutes | Clostridia | Clostridiales | imclassified.NA | *Pseudoflavonifractor* | *Pseudoflavonifractor capillosus A TCC 29799* | 1.00 |
| OTU_1597 | SEi T 1 | 1776384 | Firmieutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *Emergencia* | *Emergencia timonensis* | 1.00 |
| OTU_739 | SEi T I | 48256 | Firmieutes | Clostridia | i Clostridiales | Ruminococcaceae | *Rummiclostridium* | *[Clostridium] hungatei* | 1.00 |
| OTU_894 | i SEi T 1 | 853 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Faecalibacterium* | *Faecalibacterium prausnitzii* | 1.00 |
| OTU_961 | SEi T 1 | 853 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Faecalibacterium* | *Faecalibacterium prausnitzii* | 1.00 |
| OTU_820 | SET 1 | 15 15 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *Ruminiclostridium thermocellum* | 1.00 |
| OTU_1466 | SEi T 1 | 1796620 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Acutalibacter* | *Acutalibacter muris* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1741 | SEQ ID NO: | 720554 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] clariflavum DSM 19732* | 1.00 |
| OTU_1984 | SEQ ID NO: | 1007096 | Firmicutes | Clostridia | Clostridiales | Osciilospiraceae | *Oscillibacter* | *Oscillibacter rummantium GUI* | 1.00 |
| OTU_2004 | SEQ ID NO: | 47246 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] viride* | 1.00 |
| OTU_2005 | SEQ ID NO: | 500632 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Tyzzereila* | *Tyzzereila nexilis DSM 1787* | 1.00 |
| OTU_2655 | SEQ ID NO: | 44749 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacter* | *Sporobacter iermiiidis* | 1.00 |
| OTU_1548 | SEQ ID NO: | 626937 | Firmicutes | Clostridia | Clostridiales | Christenseneilaceae | *Christensenelia* | *Christensenelia minuta* | 1.00 |
| OTU_1307 | SEQ ID NO: | 1776382 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Neglecta* | *Neglecta timonensis* | 1.00 |
| OTU_1329 | SEQ ID NO: | 694434 | Firmicutes | Clostridia | Clostridiales | Gracilibacteraceae | *Gracilibacter* | *Gracilibacter thermoiolerans JW/YJL-S!* | 1.00 |
| OTU_1081 | SEQ ID NO: | 100176 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Papillibacter* | *Papillibacter cinnamivorans* | 1.00 |
| OTU_2028 | SEQ ID NO: | 15[5 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *; Ruminiclostridhim thermoce!!um* | 1.00 |
| OTU_1766 | SEQ ID NO: | 36849 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Qxobacter* | *Oxobacter pfennigii* | 1.00 |
| OTU_2219 | SEQ ID NO: | 301302 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Roseburia* | *Roseburia jaecis* | 1.00 |
| OTU_2117 | SEQ ID NO: | 879970 | Firmicutes | Clostridia | Clostridiales | Defluviilaleaceae | *Defluviitalea* | *\ Defhiviiiaka saccharophila* | 1.00 |
| OTU_410 | SEQ ID NO: | 655811 | Firmicutes | Tissierellia | Tissierellales | Peptomphilaceae | *Anaerococcus* | *Anaerococcus vaginalis ATCC 51170* | 1.00 |
| OTU_1411 | SEQ ID NO: | 1096246 | Firmicutes | Clostridia | Clostridiaies | Clostridiaceae | *HungateUa* | *Hungatella effluvii* | 1.00 |
| OTU_2567 | SEQ ID NO: | 264463 | Firmicutes | Clostridia | Clostridiaies | Lachnospiraceae | *Anaerosporobacier* | *\Anaerosporobacter mobilis* | 1.00 |
| OTU_864 | SEQ ID NO: | 1532 | Firmicutes | Clostridia | Clostridiaies | Lachnospiraceae | *Blauiia* | *Blautia coccoides* | 1.00 |
| OTU_2001 | SEQ ID NO: | 29375 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclosiridium* | *[Clostridium] xylanolytiairn* | 1.00 |
| OTU_1535 | SEQ ID NO: | 285 | Proteobacteria | Betaproteobacteria | Burkhoifleriales | Comamonadaceae | *Comamonas* | *Comamonas testosteroni* | 1.00 |

| OTU_2111 | SE T 1 | 995 | Bacteroideles | Sphingobacteriia | Sphingobacteriales | Sphingobacteriaceae | *Solitalea* | *Solitalea canadensis* | 1.00 |
|---|---|---|---|---|---|---|---|---|---|
| OTU_978 | SE T 1 | 242750 | Bacteroideles | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella bergensis* | 1.00 |
| OTU_765 | SE T 1 | 100709 6 | Firmicutes | Clostridia | Clostridiales | Oscillospiraceae | *Oscillibacter* | *Oscillibacter ruminantium GH1* | 1.00 |
| OTU_2419 | SE T 1 | 29539 | Actinobacteria | Thermoleophilia | Thermoleophilales | Thermoleophilaceae | *Thermoleophilum* | *Thermoleophilum album* | 1.00 |
| OTU_2853 | SE T 1 | 143205 2 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Eisenbergiella* | *Eisenbergiella. iayi* | 1.00 |
| OTU_1220 | SE T 1 | 167371 7 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaeromassilibacillus* | *Anaeromassilibacillus senegalensis* | 1.00 |
| OTU_850 | SE T 1 | 168384 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Marvinbryantia* | *Marvinbryantia formatexigens* | 1.00 |
| OTU_777 | SE T 1 | 39492 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Eubacterium / siraeum* | 0.50 |
| OTU_713 | SE T 1 | 1535 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] leptum* | 0.63 |
| OTU_2973 | SE T 1 | 6223 12 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Roseburia* | *Roseburia inulinivorans DSM 16841* | 1.00 |
| OTU_1324 | SE T 1 | 36849 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Oxobacter* | *Oxobacter pfennigii* | 1.00 |
| OTU_1061 | SE T 1 | 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rummiclostridium* | *[Clostridium] methylpeniosum* | 1.00 |
| OTU_3167 | SE T 1 | 6223 12 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Roseburia* | *Roseburia inulinivorans DSM 16841* | 0.72 |
| OTU_1337 | SE T 1 | 179663 6 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Frisingicoccus* | *Frisingicoccus caecrmuris* | 1.00 |
| OTU_2731 | SE T 1 | 21485 1 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Subdoligranulum* | *Subdoligranulum variabile* | 1.00 |
| OTU_2654 | SE T 1 | 100176 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Papillibacter* | *Papillibacter cinnamivorans* | 1.00 |
| OTU_2807 | SE T 1 | 133705 1 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Murimonas* | *Murimonas intestini* | 1.00 |
| OTU_3041 | SE T 1 | 328814 | Bacteroideles | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes shahii* | 0.65 |
| OTU_1861 | SE T 1 | 28446 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Tyzzerella* | */Clostridium/ propionicum* | 1.00 |

| OTU_1726 | SEQ_ID_NO_1776382 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Neglecia* | *Neglecia timonensis* | 1.00 |
|---|---|---|---|---|---|---|---|---|
| OTU_2618 | SEQ_ID_NO_1796620 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Acutalibacter* | *Acutalibacter muris* | 1.00 |
| OTU_2484 | SEQ_ID_NO_1491 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium butyricum* | 1.00 |
| OTU_1378 | SEQ_ID_NO_694434 | Firmicutes | Clostridia | Clostridiales | Gracilibacteraceae | *Gracilibacter* | *Gracilibacter thermotolerans JW/YJL-S1* | 1.00 |
| OTU_2645 | SEQ_ID_NO_820 | Bacteroidetes | Bacteroidia | Bacteioidales | Bacteroidaceae | *Bacteroides* | *Bacteroides unifarmis* | 1.00 |
| OTU_1258 | SEQ_ID_NO_213810 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus champanellensis 18P13 = JCM 17042* | 1.00 |
| OTU_1829 | SEQ_ID_NO_853 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Faecalibacterium* | *Faecalibacterium prausnitzii* | 1.00 |
| OTU_1999 | SEQ_ID_NO_44749 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacier* | *Sporobacier ierrniiidis* | 1.00 |
| OTU_2796 | SEQ_ID_NO_29375 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium! xylanofyticum* | 1.00 |
| OTU_2614 | SEQ_ID_NO_39496 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacieriurn* | *Eubacterium venirtosurn* | 1.00 |
| OTU_522 | SEQ_ID_NO_169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerotruncus* | *Anaerotruncus colihommis* | 0.55 |
| OTU_2071 | SEQ_ID_NO_52786 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerojiium* | *Anaerofiliim agile* | 1.00 |
| OTU_1859 | SEQ_ID_NO_1535 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *(Clostridium] lepium* | 1.00 |
| OTU_2913 | SEQ_ID_NO_39492 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Eubacieriurn] siraeum* | 1.00 |
| OTU_3126 | SEQ_ID_NO_39497 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacieriurn* | *Eubacterium xylanophilum* | 1.00 |
| OTU_2123 | SEQ_ID_NO_44749 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacter* | *Sporobacter termitidis* | 1.00 |
| OTU_2676 | SEQ_ID_NO_1549 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *jClostridium] sporosphaeroides* | 1.00 |
| OTU_2118 | SEQ_ID_NO_179661 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Cuneatibacier* | *Cuneatibacier caecimuris* | 1.00 |
| OTU_1091 | SEQ_ID_NO_582 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Morganellaceae | *Morganella* | *Morganella morganii* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1800 | SEQ ID | 160404 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Tyzzerella* | *[Clostridium] lactatifermentans* | 1.00 |
| OTU_1190 | SEQ ID | 213810 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus champanellensis 18P13 = JCM 17042* | 1.00 |
| OTU_2220 | SEQ ID | 40519 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rurninococcus* | *Ruminococcus callidus* | 1.00 |
| OTU_373 | SEQ ID | 46507 | Firmicutes | Tissierellia | unclassified.NA | unclassified.NA | *unclassified.NA* | *[Bacteroidesl coagulans* | 1.00 |
| OTU_1094 | SEQ ID | 694434 | Firmicutes | Clostridia | Clostridiales | Graciiibacieraceae | *Gracilibacter* | *Gracilibacter ihermotolerans JW/YJL-S1* | 1.00 |
| OTU_1473 | SEQ ID | 109327 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Inceriae Sedis | *Anaerovorax* | *Anaerovorax odorimutans* | 1.00 |
| OTU_2273 | SEQ ID | 1531 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] closiridioforme* | 1.00 |
| OTU_210 | SEQ ID | 1382 | Actinobacteria | Coriobacieriia | Coriobacteriales | Atopobiaceae | *Atopobium* | *Atopobium parvulum* | 1.00 |
| OTU_2632 | SEQ ID | 853 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Faecalibacterium* | *Faecalibacterium prausnitzii* | 0.75 |
| OTU_2850 | SEQ ID | 33039 | Firmicutes | Clostridia | i Clostridiales | Lachnospiraceae | *Blautia* | *[Ruminococcus] torques* | 1.00 |
| OTU_2808 | SEQ ID | 1432052 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Eisenbergiella* | *Eisenbergiella iayi.* | 1.00 |
| OTU_754 | SEQ ID | 311460 | Firmicutes | Bacilli | Bacillales | Baciiiaceae | *Anoxybaciilus* | *Anoxybaciilus rupiensis* | 1.00 |
| OTU_1278 | SEQ ID | 1264 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus albus* | 1.00 |
| OTU_972 | SEQ ID | 582 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Morganeilaceae | *Morganella* | *Morganella morganii* | 0.50 |
| OTU_3152 | SEQ ID | 301302 | Firmicutes | Clostridia | i Clostridiales | Lachnospiraceae | *Roseburia* | *Roseburia faecis* | 1.00 |
| OTU_177 | SEQ ID | 230143 | Actinobacteria | Actinobacteria | Bifidobacteriales | Bifidobacteriaceae | *Scardovia* | *Scardovia vviggsiae* | 1.00 |
| OTU_802 | SEQ ID | 216935 | Tenericutes | Mollicuies | Entomoplasmiatales | Spiroplasmaiaceae | *Spiroplasma* | *Spiroplasma culicicola* | 1.00 |
| OTU_445 | SEQ ID | 853 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Faecalibacterium* | *Faecalibacterium prausnitzii* | 1.00 |
| OTU_1973 | SEQ ID | 133705 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Murimonas* | *Murimonas intestini* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1650 | SEi T i | 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rmnimelostridm* | *ʃClostridium] methylpentosum* | 1.00 |
| OTU_1782 | SEi T 1 | 539 | Proteobacteria | Betaproteobac!eria | Neisseriales | Neisseriaceae | *Eikeneila* | *Eikeneila corrodens* | 1.00 |
| OTU_310 | SET 1 | 355ł9 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Inceitae Sedis | *Mogibacterium* | *Mogibacterium timidum* | 1.00 |
| OTU_2045 | SET 1 | 1681 | Actinobacteria | Aciinobacieiia | Bifidobacteriales | Bifidobacteriaceae | *Bifidobacterium* | *Bifidobacterium bifidum* | 1.00 |
| OTU_3178 | i SEi T 1 | 3288ł3 | Bacteroidetes | Bacteroidia | Bacteioidales | Rikeŋelȷaceae | *Alistipes* | *Alistipes onderdonkii* | 1.00 |
| OTU_1468 | SEi T i | 214853 | Firmicutes | Clostridia | Ciostiidiales | Eubacteriaceae | *Anaerofiistis* | *Anaerofiustis siercorihominis* | 1.00 |
| OTU_2798 | SEi T 1 | 154046 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Hungatella* | *Hungatella ɦathₑwɑyi* | 1.00 |
| OTU_799 | SET 1 | 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerotruncus* | *Anaerotruncus colihominis* | 1.00 |
| OTU_1365 | SEi T 1 | 39495 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium uniforme* | 1.00 |
| OTU_1773 | SEi T I | 129761 | Firmicutes | Clostridia | i Clostridiales | unclassified.NA | *Intestinimonas* | *Intestinimonas buiyriciproducens* | 1.00 |
| OTU_3011 | i SEi T i | 290054 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium coprostanoligenes* | 1.00 |
| OTU_1433 | SEi T 1 | 109327 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Inceitae Sedis | *Anaerovorax* | *Anaerovorax odorimutans* | 1.00 |
| OTU_1863 | SET 1 | 89014 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Biauiia.* | *Blautia luti* | 1.00 |
| OTU_2270 | SEi T 1 | 33043 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Coprococcus* | *Coprococcus euiactus* | 1.00 |
| OTU_2596 | SEi T I | 216933 | Tenericutes | Mɑ̨liɕuɪes | Entomoplasmatales | Spiroplasmataceae | *Spiroplasrna* | *Spiroplasrna chrysopicola* | 1.00 |
| OTU_826 | i SEi T i | 537007 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia hansenii DSM 20583* | 1.00 |
| OTU_2844 | SEi T 1 | 1121115 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Biauiia* | *Blautia wexlerae DSM 19850* | 0.55 |
| OTU_2120 | SET 1 | ł58597 4 | Firmicutes | Clostridia | Clostridiales | Ciostndiaceae | *Beduini* | *Beduini massiliensis* | 1.00 |
| OTU_2927 | SEi T 1 | 29466 | Firmicutes | Negativicutes | Veillonellales | Veilioneliaceae | *Veillonella* | *Veillonella parvula* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_2750 | SET 1 | 290052 | Firmicutes | Clostridia | Clostiidiaies | Rummococcaceae | *Acetivibno* | *Acetivibrio ethanolgignens* | 1.00 |
| OTU_262 | SET 1 | 1796646 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | 1.00 |
| OTU_996 | SET 1 | 1363 | Firmicutes | Bacilli | Lactobacillales | Streptococcaceae | *Lactococcus* | *Lactococcus garvieae* | 1.00 |
| OTU_1877 | SET 1 | 54291 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Enterobacteriaceae | *Raoultella* | *Raoultella omithinolytica* | 1.00 |
| OTU_3051 | SET 1 | 411467 | Firmicutes | Clostridia | Ciostridiales | unclassified.NA | *Pseudoflavonifractor* | *Pseudoflavonifractor capillosus ATCC 29799* | 1.00 |
| OTU_2033 | SET 1 | 292800 | Firmicutes | Clostridia | Clostiidiaies | unclassified. NA | *Flavonifractor* | *Flavonifractor plautii* | 1.00 |
| OTU_2000 | SET 1 | 270498 | Firmicutes | Clostridia | Ciostridiales | Catabacteriaceae | *Catabacter* | *Catabacter hongkongensis* | 1.00 |
| OTU_945 | SET 1 | 214856 | Bacteroidetes | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes finegoldii* | 0.70 |
| OTU_1636 | SET 1 | 142877 | Firmicutes | Clostridia | Ciostridiales | Peptococcaceae | *Desulfitobacterium* | *Desulfitobacterium metallireducens* | 1.00 |
| OTU_2027 | SET I | 341220 | Firmicutes | Clostridia | Ciostridiales | Clostridiaceae | *Lactonifactor* | *Lactonifactor longoviformis* | 1.00 |
| OTU_3205 | SET 1 | 820 | Bacteroideies | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides uniformis* | 1.00 |
| OTU_1174 | SET 1 | 109327 | Firmicutes | Clostridia | Ciostridiales | Ciostridiales Family XIII. Incertae Sedis | *Anaerovorax* | *Anaerovorax odorimutans* | 1.00 |
| OTU_1866 | SET 1 | 133926 | Actinobacteria | Coriobacteriia | Coriobacteria!es | Atopobiaceae | *Olsenella* | *Olsenella uli* | 1.00 |
| OTU_2265 | SET 1 | 1583 | Firmicutes | Bacilli | Lactobacillales | Leuconostocaceae | *Weissei!a* | *Weissella confusa* | 1.00 |
| OTU_2518 | SET I | 84026 | Firmicutes | Clostridia | Ciostridiales | Ruminococcaceae | *Ruminiclosfridium* | *[Clostridium] methyipentosum* | 1.00 |
| OTU_2874 | SET 1 | 209880 | Firmicutes | Negativicutes | Veilionellaies | Veilionellaceae | *Allisonella* | *Allisonella histaminiformans* | 1.00 |
| OTU_2877 | SET 1 | 179628 | Firmicutes | Clostridia | Clostiidiaies | Clostridiaceae | *Clostridium* | *Clostridium co!icanis* | 1.00 |
| OTU_3077 | SET 1 | 100176 | Firmicutes | Clostridia | Ciostridiales | Ruminococcaceae | *F'apiliibacter* | *Papillibacter cinnamivorans* | 1.00 |
| OTU_980 | SET 1 | 1776382 | Firmicutes | Clostridia | Ciostridiales | Ruminococcaceae | *Neglecta* | *Neglecta timonensis* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| οτυ_ł101 | SET i | 15 10 | Firmieutes | Clostridia | Clostiidiaies | Ruminococcaceae | *Rumimclostridium* | *[Clostridium] siercorarium* | 1.00 |
| OTŲJ_1962 | SET 1 | 84030 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] saccharolyticum* | 1.00 |
| OTU_2309 | SET 1 | 166486 | Firmieutes | Clostridia | Clostiidiaies | Lachnospiraceae | *Roseburia* | *Roseburia iniestinalis* | 0.50 |
| OTU_2282 | SET 1 | 153 1 | Firmieutes | Clostridia | Clostridiales | Lachno spiraceae | *Lachnoclostridium* | *[Clostridium] clostridioforme* | 1.00 |
| OTŲJ_215 1 | SET 1 | 1544 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] oroticum* | 1.00 |
| OTU_1068 | SET i | 2741 | Firmieutes | Clostridia | Clostridiales | Peptococcaceae | *Peptococcus* | *Peptococcus niger* | 1.00 |
| OTU_2427 | SET 1 | 213810 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus champanellensis 18P13 = JCM 17042* | 1.00 |
| OTU_ł148 | SET 1 | 169435 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaeroiruncus* | *Anaeroiruncus colihominis* | 0.55 |
| OTU_919 | SET 1 | 1297424 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerobacterium* | *Anaerobacterium chartisolvens* | 1.00 |
| OTU_1222 | SET I | 871665 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia faecis* | 0.63 |
| OTU_2569 | SET i | 84026 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] methylpentosum* | 1.00 |
| OTU_1049 | SET 1 | 1673717 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaeromassilibacillus* | *Anaernassilibacillus senegalensis* | 1.00 |
| OTU_1496 | SET 1 | 54291 | Proteobacteria | Gammaproteobacteria | Ente robacte rales | Enterobacteriaceae | *Raoulteila* | *Raoulteila ornithinolyiica* | 1.00 |
| OTU_948 | SET 1 | 28446 | Firmieutes | Clostridia | Clostridiales | Lachno spiraceae | *Tyzzereila* | *[Clostridium/ propionicum* | 1.00 |
| OTU_914 | SET I | ł12ł102 | Proteobacteria | Epsiionproteobacteria | Campy lobacterales | Campylobacteraceae | *Campylobacter* | *Campylobacter ureolyiicus DSM 20703* | 1.00 |
| OTU_1342 | SET i | 69473 | Tenericutes | Mollicutes | Acholeplasmatales | Acholeplasmataceae | *Acholeplasma* | *Acholeplasma vituli* | 1.00 |
| OTU_2210 | SET 1 | 1298596 | Firmieutes | Clostridia | Clostiidiaies | Ruminococcaceae | *Ruminococcus* | *Ruminococcus faecis JCM 15917* | 1.00 |
| OTU_1706 | SET 1 | 1007096 | Firmieutes | Clostridia | Clostridiales | Oscillospiraceae | *Oscillibacter* | *\ Oscillibacter ruminantium GH1* | 1.00 |
| OTU_2656 | SET 1 | 105612 | Firmieutes | Bacilli | Lactobacillales | Lactobacillaceae | *Lactobacillus* | *: Lactobacillus algidus* | 1.00 |

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|---|---|---|---|---|---|---|---|---|
| OTU_909 | SE T i | 185236 7 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *Ihubacier massiliensis* | 1.00 |
| OTU_1964 | SE T 1 | 179661 5 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia caecimuris* | 1.00 |
| OTU_{234 | SE T 1 | 39492 | Firmicutes | Clostridia | Clostridiales | Rummococcaceae | *Ruminiclostridium* | *[Eubactenum j siraeum* | 1.00 |
| OTU_501 | SE T 1 | 682400 | Firmicutes | Clostridia | Clostridiales | unclassif$_{1e}$d.NA | *Ñatranaerovirga* | *Ñatranaerovirgapectinivora* | 1.00 |
| OTU_2939 | SE T 1 | 820 | Bacteroidetes | Bacteroidia | Bacteioidales | Bacteroidaceae | *Bacteroides* | *Bacteroides unijormis* | 1.00 |
| OTU_556 | SE T i | 39777 | Firmicutes | Negativicutes | Veilionellaies | Veilionellaceae | *VeiiloneHa* | *VeiiloneHa atypica* | 0.63 |
| OTU_1023 | SE T 1 | 177638 2 | Firmicutes | Clostridia | Clostridiales | Rummococcaceae | *Neglecta* | *Neglecta iimonensis* | 0.50 |
| OTU_{198 | SE T 1 | 141785 2 | Firmicutes | Clostridia | Clostridiales | unclassifled.NA | *Flintibacter* | *\ Fiintibacter b$_{it}$f i· c$_{it}$s* | 1.00 |
| OTU_2650 | SE T 1 | 56774 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. incertae Sedis | *unclassified.NA* | *[Eubactenum] infirmum* | 1.00 |
| OTU_1338 | SE T I | 84026 | Firmicutes | Clostridia | Clostridiales | Rummococcaceae | *Ruminiclostridium* | *; [Clostridium] methylpentosum* | 1.00 |
| OTU_2434 | SE T i | 129859 6 | Firmicutes | Clostridia | Clostridiales | Rummococcaceae | *Ruminococcus* | *Ruminococcus faecis JCM 15917* | 1.00 |
| OTU_1197 | SE T 1 | 29353 | Firmicutes | Clostridia | Clostridiales | Rummococcaceae | *Ruminiclostridium* | *[Clostridium] aldrichii* | 1.00 |
| OTU_433 | SE T 1 | 1579 | Firmicutes | Bacilli | Lactobacillales | Lactobacillaceae | *Lactobacillus* | *Lactobacillus acidophilus* | 1.00 |
| OTU_394 | SE T 1 | 163665 | Bacteroidetes | Bacteroidia | Bacieroidales | Poipliyronionadaceae | *Dysgonomonas* | *; Dysgonomonas mossii* | 1.00 |
| OTU_2748 | SE T I | 47246 | Firmicutes | Clostridia | Clostridiales | Rummococcaceae | *Ruminiclostridium* | *\ [Clostridium] viride* | 1.00 |
| OTU_225 1 | SE T i | 53443 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia hydrogenotrophica* | 1.00 |
| OTU_1272 | SE T 1 | 261299 | Firmicutes | Clostridia | Clostridiales | Peptostreptococcaceae | *Iniestinibacter* | *Iniestinibacter bartleitii* | 0.59 |
| OTU_1388 | SE T 1 | 1302 | Firmicutes | Bacilli | Lactobacillales | Streptococcaceae | *Streptococcus* | *Streptococcus gordonii* | 1.00 |
| OTU_2677 | SE T 1 | i 15029 8 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Fusicatenibacter* | *Fusicatenibacter saccharivorans* | 1.00 |

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|---|---|---|---|---|---|---|---|---|
| OTU_464 | SEQ ID NO: 1 | 938289 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Levyella* | *Levyella massiliensis* | 1.00 |
| OTU_1462 | SEQ ID NO: 1 | 288966 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Luiispora* | *Lutispora thermophila* | 1.00 |
| OTU_1871 | SEQ ID NO: 1 | 292800 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Flavonifractor* | *Flavonifractor plautii* | 1.00 |
| OTU_1649 | SEQ ID NO: 1 | 288966 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Lutispora* | *Lutispora thermophila* | 1.00 |
| OTU_2063 | SEQ ID NO: 1 | 3288 | Bacteroidetes | Bacteroidia | Bacteioidales | Rikenellaceae | *Alistipes* | *Alistipes shahii* | 1.00 |
| OTU_2525 | SEQ ID NO: 1 | 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerotruncus* | *Anaeroiruncus colihommis* | 1.00 |
| OTU_2422 | SEQ ID NO: 1 | 185236 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incsat ae Sedis | *Ihubacter* | *Ihubacter massiliensis* | 1.00 |
| OTU_1697 | SEQ ID NO: 1 | 44749 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Sporobacier* | *Sporobacier terrnitidis* | 1.00 |
| OTU_3061 | SEQ ID NO: 1 | 53342 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Caloramator* | *Caloramator proteoclasticus* | 1.00 |
| OTU_2213 | SEQ ID NO: 1 | 358742 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] aldenense* | 1.00 |
| OTU_1302 | SEQ ID NO: 1 | 48256 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] hungatei* | 1.00 |
| OTU_811 | SEQ ID NO: 1 | 55779 | Firmicutes | Clostridia | Thermoanaerobacteraies | Thermoanaerobacteraceae | *Moorella* | *Moorella glycerini* | 0.55 |
| OTU_3114 | SEQ ID NO: 1 | 762984 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides clarus YIT 12056* | 1.00 |
| OTU_2828 | SEQ ID NO: 1 | 471875 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rummococcus* | *Rummococcus lactaris ATCC 29176* | 1.00 |
| OTU_2542 | SEQ ID NO: 1 | 2585 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Acetanaerobacter iurn* | *Acetanaerobacterhim elongatum* | 1.00 |
| OTU_3143 | SEQ ID NO: 1 | 53443 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia hydrogenotrophica* | 1.00 |
| OTU_2311 | SEQ ID NO: 1 | 817 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides fragilis* | 1.00 |
| OTU_1588 | SEQ ID NO: 1 | 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerotruncus* | *Anaerotruncus colikominis* | 1.00 |
| OTU_1881 | SEQ ID NO: 1 | 214853 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Anaerofustis* | *Anaerofustis stercorihominis* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| οτυ_1924 | SEQ ID NO: 1 | 1007096 | Firmicutes | Clostridia | Clostiidiaies | Osciilospiraceae | *Osciihbacter* | *Osciihbacter ruminantium Gill* | 1.00 |
| OTU_2816 | SEQ ID NO: 1 | 154046 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Hungatella* | *Hungatella hathewayi* | 1.00 |
| OTU_534 | SEQ ID NO: 1 | 938278 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *Casaltella* | *Casaltella massiliensis* | 1.00 |
| OTU_2825 | SEQ ID NO: 1 | 1796613 | Bacteroideies | Bacteroidia | Bacieroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides caecimuris* | 0.68 |
| OTU_2142 | SEQ ID NO: 1 | 341220 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Lactonifactor* | *Lactonifactor longoviformis* | 1.00 |
| OTU_1605 | SEQ ID NO: 1 | 184186 7 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Phocea* | *Phocea massiliensis* | 1.00 |
| OTU_377 | SEQ ID NO: 1 | 118057 | Firmicutes | Tissierellia | Tissierellales | Peptoniphilaceae | *Peptoniphilus* | *Peptoniphilus grossensis ph5* | 0.50 |
| OTU_315 | SEQ ID NO: 1 | 1077144 | Actinobacteria | Actinobacteria | Corynebacteriales | Dietziaceae | *Dietzia* | *Dietzia alimentaria 72* | 1.00 |
| OTU_2544 | SEQ ID NO: 1 | 1737 | Firmicutes | Clostridia | Clostridiales | Peptostreptococcaceae | *PaeniClostridium* | *[Eubacterium] tenue* | 1.00 |
| OTU_2858 | SEQ ID NO: 1 | 112 1308 | Firmicutes | Clostridia | Clostridiales | Peptostreptococcaceae | *Clostndioides* | *Clostridioides difficile ATCC 9689 = DSM 1296* | 1.00 |
| OTU_557 | SEQ ID NO: 1 | 1796646 | Bacteroideies | Bacteroidia | Bacieroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intesiinale* | 1.00 |
| OTU_1059 | SEQ ID NO: 1 | 411467 | Firmicutes | Clostridia | Clostridiales | unelassified.NA | *Pseudoflavonifractor* | *Pseudoflavonifractor capillosus ATCC 29799* | 1.00 |
| OTU_2020 | SEQ ID NO: 1 | 218205 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Garcielia* | *Garcielia. niiratireducens* | 1.00 |
| OTU_931 | SEQ ID NO: 1 | 1121298 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium amylolyiicum* | 1.00 |
| OTU_1695 | SEQ ID NO: 1 | 684066 | Firmicutes | Bacilli | Lactobaciliales | Streptococcaceae | *Streptococcus* | *Streptococcus laciarius* | 1.00 |
| OTU_1981 | SEQ ID NO: 1 | 2585 15 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Acetanaerobactermm* | *Acetanaerobacterium elongatum* | 1.00 |
| OTU_2600 | SEQ ID NO: 1 | 649756 | Firmicutes | Clostridia | Clostiidiaies | Lachnospiraceae | *Anaerostipes* | *Anaerostipes hadrus* | 1.00 |
| OTU_1887 | SEQ ID NO: 1 | 433659 | Actinobacteria | Actinobacteria | Propionibacteriales | Nocatdioidaceae | *Nocardioides* | *Nocardioides mesophihis* | 1.00 |
| OTU_2058 | SEQ ID NO: 1 | 52699 | Actinobacteria | Actinobacteria | Propionibacteriales | Nocardiokiaceae | *Aeromicrobium* | *Aeromicrobium fasti diosum* | 1.00 |

| OTU_2235 | SE T i | 2045 16 | Bactero ideies | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides massiliensis* | 1.00 |
|---|---|---|---|---|---|---|---|---|---|
| OTU_{005 | SE T 1 | 234908 | Proteob açteria | Betaproteobac! eria | Burkholderiales | Sutterellaceae | *Sutierella* | *Sutierella stercoricanis* | 1.00 |
| OTU_{910 | SE T 1 | 706562 | Firmicu tes | Bacilli | Lactobacillales | Lactobacillaceae | *Lactobacillus* | *Lactobacillus rogosae* | 0.55 |
| OTU_3085 | SE T 1 | 253257 | Firmicu tes | Clostridia | Clostridiales | Lachno spiraceae | *Lachnoclosiridiu m* | *[Clostridium! amygdalinum* | 0.50 |
| OTU_{583 | SE T 1 | 84026 | Firmicu tes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridiu m* | *[Clostridium] methyipentosum* | 1.00 |
| OTU_2308 | SE T i | 39496 | Firmicu tes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium ventriosum* | 1.00 |
| OTU_643 | SE T 1 | 84026 | Firmicu tes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridiu m* | *[Clostridium] methyipentosum* | 0.65 |
| OTU_{191 | SE T 1 | {15544 | Firmicu tes | Clostridia | Clostridiales | Lachno spiraceae | ] *Parasporobacteri um* | *Parasporobacierium paucivorans* | 1.00 |
| OTU_1997 | SE T 1 | 84030 | Firmicu tes | Clostridia | Clostridiales | Lachno spiraceae | *Lachnoclosiridiu m* | *[Clostridium! saccharolyticum* | 1.00 |
| OTU_3166 | SE T 1 | 706562 | Firmicu tes | Bacilli | Lactobacillales | Lactobacillaceae | *Lactobacillus* | *Lactobacillus rogosae* | 0.68 |
| OTU_1406 | SE T i | 501571 | Firmicu tes | Clostridia | Clostridiales | Clostridiaceae | *Butyricicoccus* | *Butyricicoccus pullicaecorum* | 1.00 |
| OTU_3047 | SE T 1 | 1509 | Firmicu tes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium sporogenes* | 1.00 |
| OTU_2916 | SE T 1 | 328812 | Bactero ideies | Bacteroidia | Bacteroidales | Po ϕ hy romonadaceae | *Parabacteroides* | *Parabacteroides goldsteinii* | 0.59 |
| OTU_276 | SE T 1 | 1280 | Firmicu tes | Bacilli | Baciilales | Staphyiococcaceae | *Staphylococcus* | *Staphylococcus aureus* | 0.50 |
| OTU_2864 | SE T 1 | 112 111 5 | Firmicu tes | Clostridia | Clostridiales | Lachno spiraceae | *Blaiitia* | *Blaulia wex!erae DSM 19850* | 1.00 |
| OTU_313 1 | SE T i | 762984 | Bactero ideies | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides cla$_{rus}$ YLT 12056* | 1.00 |
| OTU_414 | SE T 1 | 147802 | Firmicu tes | Bacilli | Lactobacillales | Lactobacillaceae | *Lactobacillus* | *Lactobacillus iners* | 1.00 |
| OTU_790 | SE T 1 | 58134 | Firmicu tes | Clostridia | Clostridiales | Lachno spiraceae | *Lachnoclosiridiu m* | *'Desulfotomaculum[ guttoideuni* | 1.00 |
| OTU_891 | SE T 1 | 133561 3 | Actinob aeteria | Coriobacteriia | Eggerthellales | Eggerthellaceae | *Gordonihacter* | *Gordonihacter urolithinfaciens* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| οτυ_2009 | SE T 1 | 153 1 | Firmieu tes | Clostridia | Clostiidiaies | Lachiio spiraceae | *Lacimoclostridiu m* | *[Clostridium] closiridiofiorme* | 0.63 |
| OTU_1870 | SE T 1 | 745368 | Firmieu tes | Clostridia | Clostridiales | Rummococcaceae | *Gemmiger* | *Gemmiger Jbrmicilis* | 0.50 |
| OTU_ł 175 | SE T 1 | 52786 | Firmieu tes | Clostridia | Clostridiales | Rummococcaceae | *Anaerofiium* | *Anaerofiium agile* | 1.00 |
| OTU_1395 | SE T 1 | 328814 | Bactero ideies | Bacteroidia | Bacieroidales | Rikenellaceae | *Alistipes* | *Alistipes shahii* | 0.63 |
| OTU_1236 | SE T 1 | 891 | Proteob acteria | Deltaproteobac teria | Desulfuromonadal es | Desu!furomonadaceae | *Desutfitromonas* | *Desulfiuromonas acetoxidans* | 1.00 |
| OTU_2197 | SE T 1 | 585394 | Firmieu tes | Clostridia | Clostridiales | Lachno spiraceae | *Roseburia* | *Roseburia hominis A2-183* | 1.00 |
| OTU_487 | SE T 1 | 1582 | Firmieu tes | Bacilli | Lactobaeillales | Lactobaciliaeeae | *Lactobacillus* | *Lactobacillus casei* | 1.00 |
| OTU_964 | SE T 1 | 23593 1 | Firmieu tes | Clostridia | Clostridiales | Eubacteriaceae | *Alkalibacier* | *Alkalibacter saccharofiermentans* | 1.00 |
| OTU_3184 | SE T 1 | 308994 | Firmieu tes | Negaiivicutes | Veillonellales | Veilioneliaceae | *Dialister* | *; Dialister propiomcifaciens* | 1.00 |
| OTU_226 | SE T I | 29466 | Firmieu tes | Negativicutes | Veilionellaies | Veillonellaeeae | *Veillonella* | *\ Veillonella parvula* | 1.00 |
| OTU_1037 | SE T 1 | 1589 | Firmieu tes | Bacilli | Lactobaeillales | Lactobaciliaeeae | *Lactobacillus* | *Lactobacillus peniosus* | 1.00 |
| OTU_1021 | SE T 1 | 626937 | Firmieu tes | Clostridia | Clostridiales | Christensenellaceae | *Ciirisiensenella* | *Ciirisiensenella minuta* | 1.00 |
| OTU_1288 | SE T 1 | 264463 | Firmieu tes | Clostridia | Clostridiales | Lachno spiraceae | *Anaerosporobact er* | *Anaerosporobacter mobilis* | 1.00 |
| OTU_2276 | SE T 1 | 1682 | Actinob acteria | Actinobacteria | Bifidobacteriaies | Bifidobacteriaceae | *Bifidobacterium* | *; Bifidobacterium longum subsp. infantis* | 1.00 |
| OTU_695 | SE T I | 1736 | Firmieu tes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacieriurn* | *; Eubacterium limosurn* | 1.00 |
| OTU_ł 11 | SE T 1 | 28129 | Bactero ideies | Bacteroidia | Bacieroidales | Prevotellaceae | *Prevotella* | *\ Prevotella denticola* | 1.00 |
| OTU_1899 | SE T 1 | 301302 | Firmieu tes | Clostridia | Clostiidiaies | Lachno spiraceae | *Lioseburia* | *Roseburia faecis* | 1.00 |
| OTU_2162 | SE T 1 | 160404 | Firmieu tes | Clostridia | Clostridiales | Lachno spiraceae | *Tyzzerella* | *[Clostridium] lactatifermentans* | 1.00 |
| OTU_1053 | SE T 1 | 178001 | Firmieu tes | Bacilli | Lactobaeillales | Leiico nostocaceae | *Leuconostoc* | *; Leuconostoc inhae* | 1.00 |

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| οτυ_2698 | SEST 1 | 29375 | Firmieutes | Clostridia | Clostridiaies | Lachno spiraceae | *Lachnoclostridium* | *[Clostridium] xylanolyticum* | 1.00 |
| OTU_934 | SEST 1 | 1509 | Firmieutes | Clostridia | Clostridiaies | Clostridiaeeae | *Clostridium* | *Clostridium sporogenes* | 1.00 |
| OTU_ł 194 | SEST 1 | 55 1788 | Firmieutes | Clostridia | Clostridiaies | Caldicoprobacteraceae | *Caidicoprobacter* | *Caidicoprobacter oshimai* | 1.00 |
| OTU_1580 | SEST 1 | 84026 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Ruminiclostridium* | *ıClostridiumȷ methylpentosum* | 1.00 |
| OTU_645 | SEST 1 | 205 1 | Actmobacteria | Actinobacteria | Aclinomycetales | Actinomycetaceae | *Mobiiuncus* | *Mobiluncus curiisii* | 1.00 |
| OTU_13 19 | SEST 1 | 856 | Fusobacteria | Fusobacteriia | Fusobacteriales | Fusobacteriaceae | *Fusobacterium* | *Fusobacterium varium* | 1.00 |
| OTU_1738 | SEST 1 | ł 18562 | Cyanobacteria | uneiassified.NA | Osciilatoriales | Microcoleaceae | *Arfnrospira* | *Arfnrospira platensis* | 1.00 |
| OTU_2168 | SEST 1 | 214856 | Bacteroideies | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes finegoldii* | 1.00 |
| OTU_1503 | SEST 1 | 1302 | Firmieutes | Bacilli | Lactobaciilales | Streptococcaceae | *Streptococcus* | *Streptococcus gordonii* | 1.00 |
| OTU_1185 | SEST I | 292800 | Firmieutes | Clostridia | Clostridiaies | unclassified.NA | *Flavonifracior* | *Flavoni/ractor plautii* | 1.00 |
| OTU_2365 | SEST 1 | 101070 | Firmieutes | Bacilli | Baciilales | Planococcaceae | *Rummeliibacillus* | *Rummeliibacillus pyenus* | 1.00 |
| OTU_1822 | SEST 1 | 515619 | Firmieutes | Clostridia | Clostridiaies | Lachno spiraceae | *Myxococcus* | *[Eubacterium rectale] ATCC 33656* | 0.55 |
| OTU_463 | SEST 1 | 40215 | Proteobacteria | Gammaproteobacteria | Pseudoinonadales | Moraxellaceae | *Acinetobacter* | *Acinetobacter junii* | 1.00 |
| OTU_3029 | SEST 1 | 745368 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Gemmiger* | *Gemmigerform ıcilis* | 1.00 |
| OTU_2649 | SEST I | 187979 | Firmieutes | Negativicutes | Selenomonadales | Selenomonadaceae | *Hitsuokella* | *Mitsuokella jalaludinii* | 1.00 |
| OTU_2666 | SEST 1 | 82979 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Budviciaceae | *Budvicia* | *Budvicia aquatica* | 1.00 |
| OTU_2895 | SEST 1 | 154046 | Firmieutes | Clostridia | Clostiidiaies | Clostridiaeeae | *Hungaiella* | *Hungaiella hathewayi* | 1.00 |
| OTU_3020 | SEST 1 | 29363 | Firmieutes | Clostridia | Clostridiaies | Clostridiaeeae | *Clostridium* | *Clostridium paraputrificum* | 1.00 |
| OTU_3163 | SEST 1 | 160404 | Firmieutes | Clostridia | Clostridiaies | Lachno spiraceae | *Tyzzerella* | \ *[Clostridium] lactatifermentans* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| **OTU_1357** | SE T 1 | **177639** | **Firmicutes** | Clostridia | Clostridiales | Peptostreptococcaceae | *Fiomboutsia* | *Rombouisia iimonensis* | **1.00** |
| **OTU_1550** | SE T 1 | **128519** | Firmicutes | Clostridia | Clostridiales | Peptococcaceae | *Desulfotomaculum* | *Desulfotomaculum intricatum* | **1.00** |
| **OTU_2275** | SE T 1 | **841** | **Actinobacteria** | **Coriobacteriia** | **Eggerthellales** | **Eggerthellaceae** | *EggertheUa* | *EggertheUa tenia* | **1.00** |
| **OTU_1828** | SE T 1 | **46503** | **Bacteroidetes** | Bacteroidia | Bacieroidales | Poipliyronionadaceae | *Parabacteroides* | *Parabacteroides merdae* | **1.00** |
| **OTU_1647** | SE T 1 | **157688** | Fusobacteria | **Fusobacteriia** | **Fusobacteriales** | **Leptotrichiaceae** | *Leptotrichia* | *Leptotrichia ho/stadii* | **1.00** |
| **OTU_425** | SE T 1 | **38304** | Actinobacteria | **Actinobacteria** | Corynebacteriales | Cory**nebactenaceae** | *Coryneb'acterium* | *Coryneb'acterium tuberculostearicum* | **1.00** |
| **OTU_3121** | SE T 1 | **109624** | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Hungatella* | *Hungatella effluvii* | **1.00** |
| **OTU_2982** | SE T 1 | **105841** | **Firmicutes** | Clostridia | Clostridiales | **Lachnospiraceae** | *Anaerosiipes* | *Anaerosiipes caccae* | **1.00** |
| **OTU_2929** | SE T 1 | **292800** | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Flavonifractor* | *Flavonifractor plautii* | **1.00** |
| **OTU_2019** | SE T 1 | **15** | Firmicutes | Clostridia | Clostridiales | **Ruminococcaceae** | *Ruminiclostridium* | *Ruminiclostridium thermocellum* | **1.00** |
| **OTU_508** | SE T 1 | **141785** | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Flintibacter* | *\ Flintibacter bufyricus* | **1.00** |
| **OTU_1664** | SE T 1 | **185236** | Firmicutes | Clostridia | Clostridiales | Clostridiaies **Family** XIII. Incertae Sedis | *Ihubacter* | *Ihubacter massiliensis* | **1.00** |
| **OTU_1854** | SE T 1 | **259063** | **Firmicutes** | Clostridia | Clostridiales | Lachnospiraceae | *Anaerocolumna* | *Anaerocolumna jejuensis* | **1.00** |
| **OTU_2847** | SE T 1 | **36850** | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *; Clostridium quinii* | **1.00** |
| **OTU_3191** | SE T 1 | **341694** | Firmicutes | Clostridia | Clostridiales | Peptostreptococcaceae | *Peptostreplococcus* | **j** *Peptosireptococcus stomatis* | **1.00** |
| **OTU_3208** | SE T 1 | **287** | Proteobacteria | **Gammaproteobacteria** | **Pseudomonadales** | **Pseudomonadaceae** | *Pseudomonas* | *Pseudomonas aeruginosa* | **1.00** |
| **OTU_2253** | SE T 1 | **75612** | Proteobacteria | **Gammaproteobacteria** | Pseudomonadales | **Pseudomonadaceae** | *Porphyromonas* | *Pseudomonas mandelii* | **1.00** |
| **OTU_2511** | SE T 1 | **90** | Proteobacteria | **Deltaproteobacteria** | **Desulfovibrionales** | **Desulfovib rionaceae** | *Desulfovibrio* | *Desulfovibrio piger* | **1.00** |
| **OTU_2002** | SE T 1 | **141785** | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Flintibacter* | *\ Flintibacter butyricus* | **1.00** |

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| otu_2524 | SE T i | 818 | Bactero idetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides thetaiotaomicron* | 1.00 |
| OTU_2530 | SE T 1 | 371674 | Firmieu tes | Clostridia | Clostridiales | Lachnospiraceae | *Moryella* | *Moryella indoligenes* | 1.00 |
| OTU_2536 | SE T 1 | 338188 | Bactero idetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides finegotdii* | 1.00 |
| OTU_2608 | SE T 1 | 69825 | Firmieu tes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] indolis* | 1.00 |
| OTU_568 | SE T 1 | 88164 | Firmieu tes | Bacilli | Lactobacillus | Lactobacillaceae | *Lactobacillus* | *Lactobacillusjornicalis* | 1.00 |
| OTU_2872 | SE T i | 1121115 | Firmieu tes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia wexlerae DSM 19850* | 1.00 |
| OTU_816 | SE T 1 | 588581 | Firmieu tes | Clostridia | Clostridiales | Rummococcaceae | *Ruminiclostridium* | *[Clostridium Jpapyrosolvens DSM 2782* | 1.00 |
| OTU_1060 | SE T 1 | 35 1091 | Firmieu tes | Clostridia | Clostridiales | Oscillospiraceae | *OsciUibacter* | *\ Osciilibacter vaiericigenes* | 1.00 |
| OTU_1193 | SE T 1 | 676965 | Firmieu tes | Clostridia | Thermoanaerobacteraceae | Tliermoanaerobacteraceae | *Moore!la* | *;Moorella humnferrea* | 1.00 |
| OTU_1639 | SE T 1 | 358742 | Firmieu tes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] aldenense* | 1.00 |
| OTU_1727 | SE T i | 84026 | Firmieu tes | Clostridia | Clostridiales | Rummococcaceae | *Ruminiclostridium* | *[Clostridium] methylpentosum* | 1.00 |
| OTU_221 | SE T 1 | 546271 | Firmieu tes | Negativicutes | Selenomonadales | Selenomonadaceae | *Selenornonas* | *Selenornonas sputigena ATCC 35185* | 1.00 |
| OTU_2468 | SE T 1 | 15 15 | Firmieu tes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *Ruminiclostridiurn thermocellum* | 1.00 |
| OTU_3057 | SE T 1 | 47246 | Firmieu tes | Clostridia | Clostridiales | Rummococcaceae | *Ruminiclostridium* | *\ [Clostridium] viride* | 1.00 |
| OTU_3093 | SE T 1 | 123651 2 | Bactero idetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *\ Bacteroides rodenlium JCM 16496* | 1.00 |
| OTU_3098 | SE T i | 405 18 | Firmieu tes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus bromii* | 1.00 |
| OTU_732 | SE T 1 | 13 1846 5 | Teneric utes | Mollicutes | Achoieplasmatales | Acliolepiasmataceae | *Acholeplasma* | *Acholeplasma brassicae 0502* | 1.00 |
| OTU_837 | SE T 1 | 178338 | Firmieu tes | Tissierellia | unclassified.NA | imlassified.NA | *Sedimentibacter* | *Sedimentibacter hongkongensis* | 1.00 |
| OTU_871 | SE T 1 | 154046 | Firmieu tes | Clostridia | Clostridiales | Clostridiaceae | *Hungatella* | *Hungatella hathewayi* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_923 | SEQ ID NO: 328813 | Bacteroidetes | Bacteroidia | Bacteroidales | Rikenellaceae | *AUstipes* | *AUstipes onderdonkii* | 1.00 |
| OTU_991 | SEQ ID NO: 264463 | Firmicutes | Clostridia | Clostridiales | Lachnospiraeeae | *Anaerosporobacter* | *Anaerosporobacter mobilis* | 1.00 |
| OTU_768 | SEQ ID NO: 862517 | FirmicUtes | Tissierellia | Tissierellales | Peptoniphilaceae | *Peptoniphilus* | *Peptoniphilus duerdenii ATCC BAA-1764* | 1.00 |
| OTU_1251 | SEQ ID NO: 157687 | Fusobacteria | Fusobacteriia | Fusobacteiiales | Leptotrichiaceae | *Leptotrichia* | *Leptotrichia wadei* | 1.00 |
| OTU_160 | SEQ ID NO: 158 | Spirochaetes | Spirocliaetia | Spirocliaetales | Spirochaetaceae | *Treponema* | *Treponema deniicola* | 1.00 |
| OTU_1633 | SEQ ID NO: 184186 7 | Firmicutes | Clostridia | Ciostiidiales | Ruminococcaceae | *Phocea* | *Phocea massiilensis* | 1.00 |
| OTU_2294 | SEQ ID NO: 29466 | Firmicutes | Negaiivicutes | Veilloneliales | Veillonellaceae | *Veillonella* | *Veillonella parvuia* | 1.00 |
| OTU_2993 | SEQ ID NO: 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] methylpentosum* | 1.00 |
| OTU_926 | SEQ ID NO: 51048 | Proteobacteria | Gammaproteobacteria | Pasteurellales | Pasteurellaceae | *Actinobacillus* | *Actinobacillus porcinus* | 1.00 |
| OTU_16 | SEQ ID NO: 158333 1 | Bacteroidetes | Bacteroidia | Bacieroidales | Porphyromonadaceae | *Porphyromonas* | *Porphyromonaspasteri* | 1.00 |
| OTU_1170 | SEQ ID NO: 411467 | Firmicutes | Clostridia | Clostridiales | unclassified. NA | *Pseudoflavonifractor* | *Pseudoflavonifractor capiUosus ATCC 29799* | 1.00 |
| OTU_1566 | SEQ ID NO: 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaeroirimciis* | *Anaerotruncus colihominis* | 1.00 |
| OTU_863 | SEQ ID NO: 529 | Proteobacteria | Alphaproteobacteria | Rhizobiales | Biucellaceae | *Ochrobactruni* | *Ochrobactrum anthropi* | 1.00 |
| OTU_3206 | SEQ ID NO: 134982 2 | Bacteroidetes | Bacteroidia | Bacieroidales | Poipliyronionadaceae | *Coprobacter* | *Coprobacterfastidiosus NSB1* | 1.00 |
| OTU_1518 | SEQ ID NO: 288966 | Firmicutes | Clostridia | i Clostridiales | Clostridiaceae | *Lutispora* | *Lutispora thermophila* | 1.00 |
| OTU_1678 | SEQ ID NO: 901 | Proteobacteria | Deltaproteobacteria | Desuifovibrionales | Desulfovibrionaceae | *Desulfovibrio* | *Desulfovibrio piger* | 1.00 |
| OTU_2086 | SEQ ID NO: 290052 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Acetivibrio* | *Acetivibrio ethanolgignens* | 1.00 |
| OTU_2560 | SEQ ID NO: 1535 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] leptum* | 1.00 |
| OTU_2976 | SEQ ID NO: 536633 | Firmicutes | Clostridia | Clostridiales | Lachnospiraeeae | *Blautia* | *Blautia glucerasea* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_3190 | SEQ ID NO: 706562 | Firmicutes | Bacilli | Lactobacillales | Lactobacillaceae | *Lactobacillus* | *Lactobacillus rogosae* | 1.00 |
| OTU_3195 | SEQ ID NO: 820 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides uniformis* | 1.00 |
| OTU_625 | SEQ ID NO: 888745 | Firmicutes | Bacilli | Lactobacillales | Streptococcaceae | *Streptococcus* | *Streptococcus agalactiae ATCC 13813* | 1.00 |
| OTU_1063 | SEQ ID NO: 21485 1 | Firmicutes | Clostridia | Clostridiales | Rummococcaceae | *Subdoligranulum* | *Subdoligranulum variabile* | 1.00 |
| OTU_1865 | SEQ ID NO: 626937 | Firmicutes | Clostridia | Clostridiales | Chnsienseneiiaceae | *Christensenella* | *Christensenella minuta* | 1.00 |
| OTU_1926 | SEQ ID NO: 1732 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium oxidoredncens* | 1.00 |
| OTU_3050 | SEQ ID NO: 100176 | Firmicutes | Clostridia | Clostridiales | Rummococcaceae | *Papillibacter* | *Papillibacter cinnamivorans* | 1.00 |
| OTU_993 | SEQ ID NO: 308994 | Firmicutes | Negativicutes | Veillonellales | VeiHonellaceae | *Dialister* | *Dialister propionicifaciens* | 1.00 |
| OTU_2923 | SEQ ID NO: 89014 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia luti* | 0.59 |
| OTU_3040 | SEQ ID NO: 357276 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides dorei* | 0.55 |
| OTU_2300 | SEQ ID NO: 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerotruncus* | *Anaerotruncus colihommis* | 1.00 |
| OTU_940 | SEQ ID NO: 394340 | Actiniobacteria | Coriobacteriia | Eggeithellales | Eggenheilaceae | *Asaccharobacier* | *Asaccharobacier celatus* | 0.55 |
| OTU_1116 | SEQ ID NO: 40545 | Proteobacteria | Betaproteobacteria | Burkholderiales | Sutterellaceae | *Sutterelia* | *Sutterelia wadsworthiensis* | 1.00 |
| OTU_1442 | SEQ ID NO: 184186 7 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Phocea* | *Phocea massiliensis* | 1.00 |
| OTU_1656 | SEQ ID NO: 855 | Fusobacteria | Fusobacteriia | Fusobacteiiales | Fusobacteriaceae | *Fusobacterium* | *Fusobacterium simiae* | 1.00 |
| OTU_2376 | SEQ ID NO: 357276 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides dorei* | 1.00 |
| OTU_2538 | SEQ ID NO: 515619 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Myxococcus* | *[Eubacterium rectale] ATCC 33656* | 1.00 |
| OTU_2602 | SEQ ID NO: 161923 4 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerobium* | *Anaerobium acetethyiicum* | 1.00 |
| OTU_2603 | SEQ ID NO: 553973 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | */Clostridium/ hylemonae DSM 15053* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| οτυ_2604 | SEST 1 | 213810 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Ruminococcus* | *Ruminococcus champanel!ensis 18P13 = JCM 17042* | 1.00 |
| OTU_1658 | SEST 1 | 253257 | Firmieutes | Clostridia | Clostridiales | Lachnospiraeeae | *Lachnoclostridium* | *[Clostridium] arnygdalinum* | 1.00 |
| OTU_1188 | SEST 1 | 938293 | Firmieutes | Tissiereilia | Tissierellales | Peptoniphilaceae | *Anaerococcus* | *Anaerococcus provenciensis* | 1.00 |
| OTU_1374 | SEST 1 | 93063 | Proteobacteria | Alphaproteobacieria | Sphingomonadales | Spliingomoiiadaceae | *Sphingomonas* | *Sphingomonas aquatilis* | 1.00 |
| OTU_1558 | SEST 1 | 1796646 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intesiinale* | 1.00 |
| OTU_2232 | SEST 1 | 708634 | Proteobacteria | Betaproteobacteria | Burkholderiales | unclassified.NA | *Aquabacterium* | *Aquabacterium limnoticum* | 1.00 |
| OTU_2563 | SEST 1 | 179995 | Proteobacteria | Gammaaroteobacteria | Aeromona dales | Succinivibrionaceae | *Anaerobiospirillum* | *Anaerobiospirillum ihomasii* | 1.00 |
| OTU_745 | SEST 1 | 35519 | Firmieutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *Mogibacterium* | *Mogibacterium timidum* | 1.00 |
| OTU_1506 | SEST 1 | 1351 | Firmieutes | Bacilli | Lactobaciilales | Enierococcaceae | *Enterococcus* | *; Enterococcus faecalis* | 1.00 |
| OTU_1114 | SEST I | 476652 | Firmieutes | Clostridia | Clostridiales | Peptococcaceae | *DesulfosDOFOsinus* | *Desulfosporosinus acididurans* | 1.00 |
| OTU_2029 | SEST 1 | 1417852 | Firmieutes | Clostridia | Clostridiaies | unclassified.NA | *Flintibacter* | *\ Flintibacter bufyricus* | 1.00 |
| OTU_439 | SEST 1 | 1464038 | Firmieutes | Tissiereilia | unclassified.NA | unclassified.NA | *Ezakielia* | *Ezakielia peruensis* | 1.00 |
| OTU_1638 | SEST 1 | 555088 | Firmieutes | Clostridia | Clostridiales | Syntrophorinonadaceae | *Dethiobacter* | *Dethiobacter alkaliphilus AHT 1* | 1.00 |
| OTU_1740 | SEST 1 | 44749 | Firmieutes | Clostridia | Clostridiaies | Ruminococcaceae | *Sporobacter* | *; Sporobacter termitidis* | 1.00 |
| OTU_1725 | SEST I | 1841867 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Phocea* | *j Phocea massiliensis* | 1.00 |
| OTU_2319 | SEST 1 | 166486 | Firmieutes | Clostridia | Clostridiaies | Lachnospiraeeae | *Roseburia* | *Roseburia mtestinalis* | 1.00 |
| OTU_2322 | SEST 1 | 237576 | Firmieutes | Clostridia | Clostridiaies | Lachno spiraceae | *Oribacterium* | *Oribacterium sinus* | 1.00 |
| OTU_1301 | SEST 1 | 1776382 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Neglecta* | *Neglecta iimonensis* | 1.00 |
| OTU_1328 | SEST 1 | 358742 | Firmieutes | Clostridia | Clostridiales | Lachnospiraeeae | *Lachnoclostridium* | *j Clostridium j aldenense* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1579 | SE T i | 15 15 | Frrmicutes | Clostridia | Clostiidiales | Rummococcaceae | *Rumimclostridium* | *RuimniClostridium thermocettum* | 1.00 |
| OTU_1889 | SE T 1 | 879566 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Aceiatifactor* | *Acetatifacior muris* | 1.00 |
| OTU_2460 | SE T 1 | 185237 1 | Actinobacteria | Coriobacteriia | Eggerthellales | Eggerthellaceae | *Raoultibacter* | *Raoultibacter massiliensis* | 1.00 |
| OTU_830 | SE T 1 | 404403 | Firmieutes | Clostridia | Clostridiales | unclassif$_{1e}$d.NA | *Hawardella* | *Hawardella ureilytica* | 1.00 |
| OTU_1173 | SE T 1 | 185236 7 | Firmieutes | Clostridia | Clostridiales | Clostridiales Family XIII .Incertae Sedis | *Ihubacter* | *Ihubacter massiliensis* | 1.00 |
| OTU_2007 | SE T i | 2533 14 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumimclostridium* | *[Clostridium] straminisolvens* | 1.00 |
| OTU_1836 | SE T 1 | 328814 | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes shahii* | 1.00 |
| OTU_2353 | SE T 1 | 742727 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *\Bacieroides oleiciplenus YjT 12058* | 0.50 |
| OTU_1178 | SE T 1 | 2533 14 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumimclostridium* | *[Clostridium/ stramimsolvens* | 1.00 |
| OTU_1463 | SE T 1 | 626937 | Firmieutes | Clostridia | Clostridiales | Christensenellaceae | *Christensenella* | *; Christensenella minuta* | 1.00 |
| OTU_1977 | SE T i | 1377 | Firmieutes | Bacilli | Lactobaciiiales | Aerococcaceae | *Aerococcus* | *Aerococcus viridans* | 1.00 |
| OTU_2610 | SE T 1 | 588581 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumimclostridium* | *[Clostridium]papwosolvens DSM 2782* | 1.00 |
| OTU_261 i | SE T 1 | 153 1 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclosiridium* | *\[Clostridium] clostridioforme* | 1.00 |
| OTU_2612 | SE T 1 | 35830 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Acetivibrio* | *Acetivibrio cellulolyticus* | 1.00 |
| OTU_26 15 | SE T 1 | 84026 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumimclostridium* | *[Clostridium] methylpentosum* | 1.00 |
| OTU_2619 | SE T i | 100176 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Papillibacter* | *Papillibacter cinnamivorans* | 1.00 |
| OTU_2799 | SE T 1 | 626947 | Proteobacteria | Betaproieobacteria | Burkhoideriales | Sutierellaceae | *Parasutterella* | *Parasutterella secunda* | 1.00 |
| OTU_300 1 | SE T 1 | 129859 6 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Rumi$_{1}$ococcus* | *Ruminococcus faecis JCM 1591 7* | 1.00 |
| OTU_3036 | SE T 1 | 438033 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus gauvreauii* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| otu_726 | SE_T 1 | 1732 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Eubacterium* | *Eubacterium oxidoreducens* | 1.00 |
| OTU_138 | SE_T 1 | 997353 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella pollens ATCC 700821* | 1.00 |
| OTU_1325 | SE_T 1 | 143205 2 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Liisenbergiella* | *Eisenbergie.Ua tayi* | 1.00 |
| OTU_1561 | SE_T 1 | 649756 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerostipes* | *Anaerostipes hadrus* | 1.00 |
| OTU_512 | SE_T 1 | 33043 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Coprococcus* | *Coprococcus eutacius* | 0.50 |
| OTU_2968 | SE_T 1 | 218538 | Firmicutes | Negativicutes | Veillonellales | Veillonellaceae | *Diaiister* | *Diaiister invisus* | 1.00 |
| OTU_1308 | SE_T 1 | 214856 | Bacteroidetes | Bacteroidia | Bacteroidales | Rikenellaceae | *Aiistipes* | *Aiistipes finegoldii* | 1.00 |
| OTU_1057 | SE_T 1 | 83771 | Proteobacteria | Gammaproteobacteria | Aeromonadales | Succinivibrionaceae | *Succinivibrio* | *Succinivibrio dextrinosotvens* | 1.00 |
| OTU_1547 | SE_T 1 | 671218 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Alloprevotella* | *Alloprevotella rava* | 1.00 |
| OTU_2298 | SE_T 1 | 1605 | Firmicutes | Bacilli | Lactobacillales | Lactobacillaceae | *Lactobacillus* | *; Lactobacillus animalis* | 1.00 |
| OTU_2915 | SE_T 1 | 281 11 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides eggerthii* | 1.00 |
| OTU_461 | SE_T 1 | 13 1109 | Actinobacteria | Actinobacteria | Actinomycetales | Actinomycetaceae | *Actinomyces* | *Actinomyces bowdenii* | 1.00 |
| OTU_959 | SE_T 1 | 1302 | Firmicutes | Bacilli | Lactobacillales | Streptococcaceae | *Streptococcus* | *Streptococcus gordonii* | 1.00 |
| OTU_2069 | SE_T 1 | 46609 | Firmicutes | Clostridia | Clostridiales | Ciostridiaceae | *Clostridium* | *; Clostridium pascui* | 1.00 |
| OTU_3092 | SE_T 1 | 129761 7 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Intestinimonas* | j *Intestinimonas butyriciproducens* | 1.00 |
| OTU_1371 | SE_T 1 | 690567 | Firmicutes | Clostridia | Clostridiales | Syntrophomonadaceae | *Syntrophomonas* | *Syntrophomonas zehnderi OL-4* | 1.00 |
| OTU_2008 | SE_T 1 | 46206 | Firmicutes | Clostridia | Clostridiales | Lachno spiraceae | *Pseudobutyrivibrio* | *Pseudobutyrivibrio ruminis* | 1.00 |
| OTU_874 | SE_T 1 | 155615 | Fusobacteria | Fusobacteriia | Fusobacteriales | Fusobacteriaceae | *Fusobacterium* | *Fusobacterium nucleatum subsp. vincentii* | 0.50 |
| OTU_1382 | SE_T 1 | 333367 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lacknoclostridium* | */Clostridium/ asparagiforme* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_2065 | SEQ ID NO: 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rmnimelostridm* | *[Clostridium] meihylpeniosum* | 1.00 |
| OTU_1569 | SEQ ID NO: 51616 | Firmicutes | Clostridia | Clostridiales | Peptococcaceae | *Desulfitobacteriu m* | *Desidfitobacterium chlororespirans* | 1.00 |
| OTU_2838 | SEQ ID NO: 129859 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Rurninococcus* | *Rurninococcus faecis JCM 15917* | 0.50 |
| OTU_1890 | SEQ ID NO: 179662 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Acutalibacter* | *Acutalibacter muris* | 1.00 |
| OTU_112 | SEQ ID NO: 40542 | Fusobacteria | Fusobacteriia | Fusobacteriales | Leptotrichiaceae | *Leptotrichia* | *Leptotrichia buccalis* | 1.00 |
| OTU_2136 | SEQ ID NO: 396504 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridiu m* | *[ClostridiumJ stifflavum* | 1.00 |
| OTU_1280 | SEQ ID NO: 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaeroirimciis* | *Anaerotruncus colihominis* | 1.00 |
| OTU_88 | SEQ ID NO: 203 | Proteobacteria | Epsilonproteobacteria | Campylobacterales | Campylobacteraceae | *Campylobacter* | *Campylobacter rectus* | 1.00 |
| OTU_3193 | SEQ ID NO: 328814 | Bacteroidetes | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes shahii* | 1.00 |
| OTU_810 | SEQ ID NO: 294 | Proteobacteria | Gammaproteobacteria | Pseudomonadales | Pseudomoiiadaceae | *Pseudomonas* | *Pseudomonas fluorescens* | 1.00 |
| OTU_2803 | SEQ ID NO: 411467 | Firmicutes | Clostridia | Clostridiales | unclassified. NA | *Pseudoflavonifractor* | *Pseudoflavonifi actor capiUosus ATCC 29799* | 1.00 |
| OTU_2813 | SEQ ID NO: 1605 | Firmicutes | Bacilli | Lactobacillales | Lactobacillaceae | *Lactobacillus* | *Lactobacillus animalis* | 1.00 |
| OTU_3096 | SEQ ID NO: 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaeroiruncus* | *Anaerotruncus colihominis* | 1.00 |
| OTU_2955 | SEQ ID NO: 103434 | Firmicutes | Erysipelotrichia | Erysipelotrichales | Erysipelotrichaceae | *Dielma* | *Die!mafasiidiosa* | 1.00 |
| OTU_395 | SEQ ID NO: 156456 | Firmicutes | Negativieutes | Veillonellales | Veillonellaceae | *Anaeroglobus* | *Anaeroglobus geminatus* | 1.00 |
| OTU_3097 | SEQ ID NO: 169435 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Anaeroiruncus* | *Anaeroiruncus colihominis* | 1.00 |
| OTU_819 | SEQ ID NO: 80866 | Proteobacteria | Betaproteobacteria | Burkhoideriales | Comamonadaceae | *Delfiia* | *Delfiia acidovorans* | 1.00 |
| OTU_1299 | SEQ ID NO: 358742 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclosiridiu m* | *i Clostridium] aldenense* | 0.59 |
| OTU_3058 | SEQ ID NO: 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridiu m* | */Clostridium/ methylpentosum* | 1.00 |

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| otu_915 | SE T 1 | 179664 6 | Bactero ideies | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | 1.00 |
| OTU_256¡ | SE T 1 | 44749 | Firmieu tes | Clostridia | Clostridiales | Rummococcaceae | *Sporobacter* | *Sporobacter termitidis* | 1.00 |
| OTU_1857 | SE T 1 | 84026 | Firmieu tes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridiu m* | *j'Clostridium/ methylpentosum* | 1.00 |
| OTU_887 | SE T 1 | 84030 | Firmieu tes | Clostridia | Clostridiales | Lachno spiraceae | *Lachnoclostridiu m* | *[Clostridium! saccharolyticum* | 1.00 |
| OTU_1593 | SE T 1 | 264463 | Firmieu tes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerosporobacl er* | *Anaerosporobacier mobilis* | 1.00 |
| OTU_2096 | SE T 1 | 820 | Bactero ideies | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides umformis* | 1.00 |
| OTU_1572 | SE T 1 | 169435 | Firmieu tes | Clostridia | Clostridiales | Ruminococcaceae | *Anaerotruncus* | *Anaerotruncus colihominis* | 1.00 |
| OTU_2402 | SE T 1 | 853 | Firmieu tes | Clostridia | Clostridiales | Ruminococcaceae | *Faecalibacterhtm* | i *Faecalibacterium prausnitzu* | 1.00 |
| OTU_64 | SE T 1 | 554406 | Fusoba cteria | Fusobacteriia | Fusobacieiiales | Leptotrichiaceae | *Leptotric!na* | *; Leptotrichia hongkongensis* | 1.00 |
| OTU_1306 | SE T 1 | 290054 | Firmieu tes | Clostridia | Clostridiales | Eubacteriaeeae | *Eubacteriurn* | *; Eubacteriurn coprostcmoUgenes* | 1.00 |
| OTU_197 | SE T 1 | 796942 | Firmieu tes | Clostridia | Clostridiales | Lachnospiraceae | *Stomatobaeulum* | *Stomatohaculum longum* | 1.00 |
| OTU_2572 | SE T 1 | 1605 | Firmieu tes | Bacilli | Lactobaeillales | Lactobacillaeeae | *Lactobacillus* | *Lactobacillus animalis* | 1.00 |
| OTU_296 | SE T 1 | 100236 7 | Bactero ideies | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevolella stercorea DSM 18206* | 0.55 |
| OTU_171 1 | SE T 1 | 29347 | Firmieu tes | Clostridia | Clostridiales | Lachno spiraceae | *Lachnoclostridiu m* | *; [Clostridium! scindens* | 1.00 |
| OTU_254 | SE T 1 | 796944 | Firmieu tes | Clostridia | Clostridiales | Lachnospiraceae | *Oribacierium* | *; Oribacteriurn asaccharolyticurn ACB7* | 1.00 |
| OTU_139 | SE T 1 | 61592 | Actinob acteria | Actinobacteria | Corynebacteriales | Corynebactenaceae | *Corynebacterium* | *Corynebacterium durum* | 1.00 |
| OTU_1332 | SE T 1 | 184185 7 | Bactero ideies | Bacteroidia | Bacteroidales | Odoribacteraceae | *Culturomica* | *Culturomica massiliensis* | 1.00 |
| OTU_565 | SE T 1 | 487175 | Proteob acteria | Betaproteobact eria | Burkholderiales | Sutterellaceae | *Parasutlerella* | *Parasutterella excrementihominis* | 1.00 |
| OTU_569 | SE T 1 | 45851 | Firmieu tes | Clostridia | Clostridiales | Lachnospiraceae | *Buiyrivibrio* | *Butyrivibrio crossotus* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1956 | SEQ ID NO: 69825 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] mdolis* | 1.00 |
| OTU_1733 | SEQ ID NO: 105020 | Firmicutes | Erysipelotrichia | Erysipelotrichales | Erysipelotrichaceae | *AUobaculum* | *AUobaculum stercoricanis DSAf 13633* | 1.00 |
| OTU_3144 | SEQ ID NO: 818 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides thetaiotaomicron* | 1.00 |
| OTU_8 | SEQ ID NO: 762948 | Actinobacteria | Actinobacteria | Micrococcales | Micrococcaceae | *Rothia* | *Rothia deniocariosa ATCC 17931* | 0.63 |
| OTU_325 | SEQ ID NO: 137732 | Firmicutes | Bacilli | Lactobacillales | Caino bacteriaceae | *Granuticatella* | *Granulicatella elegans* | 1.00 |
| OTU_165 1 | SEQ ID NO: 103434 6 | Firmicutes | Erysipelotrichia | Etysipelotrichales | Erv'sipelotrichaceae | *Dielma* | *Dielma fastidiosa* | 1.00 |
| OTU_3198 | SEQ ID NO: [2 1181 9 | Firmicutes | Erysipelotrichia | Eiysipelotrichales | Erysipelotrichaceae | *Holdemania* | *Holdemania massiliensis AP2* | 1.00 |
| OTU_2160 | SEQ ID NO: 153 1 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *¡Clostridiu#1] clostridioforme* | 1.00 |
| OTU_1093 | SEQ ID NO: 1019 | Bacteroidetes | Flavobacteriia | Flavobacteriales | Flavobacteriaceae | *Capnocytophaga* | *Capnocytophaga sputigena* | 1.00 |
| OTU_1655 | SEQ ID NO: 288966 | Firmicutes | Clostridia | i Clostridiales | Ciostridiaceae | *Lutispora* | *Lutispora thermophila* | 1.00 |
| OTU_1269 | SEQ ID NO: 74426 | Actinobacteria | Coriobacteriia | Coriobacteriales | Coriobacteriaceae | *Collinsella* | *Collinsella aerofaciens* | 1.00 |
| OTU_1781 | SEQ ID NO: 272548 | Actinobacteria | Actinobacteria | Actinomycetales | Actinomyceiaeeae | *Actinomyces* | *Actinomyces dentalis* | 1.00 |
| OTU_1825 | SEQ ID NO: 39777 | Firmicutes | Negativicutes | Veillonelialeş | Veillonellaceae | *Veillonella* | *Veillonella aiypica* | 1.00 |
| OTU_2240 | SEQ ID NO: 46503 | Bacteroidetes | Bacteroidia | Bacteroidales | Poipliyronionadaceae | *Parabacteroides* | *Parabacteroides merdae* | 1.00 |
| OTU_3124 | SEQ ID NO: 17[7 | Actinobacteria | Actinobacteiia | i Corynebacteriales | Cory nebacteriaceae | *Corynebacterium* | *Coryneb'acterium dip'hlheriae* | 1.00 |
| OTU_315 1 | SEQ ID NO: 841 12 | Actinobacteria | Coriobacterna | Eggertheilales | Eggeitheiiaceae | *Eggerthella* | *Eggerthella lenta* | 1.00 |
| OTU_728 | SEQ ID NO: 384636 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides xylanolyticus* | 1.00 |
| OTU_939 | SEQ ID NO: 216940 | Tenericutes | Mollicutes | Entomoplasmatales | Spiroplasmataceae | *Spiroplasma* | *Spiroplasma lampyridicola* | 1.00 |
| OTU_947 | SEQ ID NO: 2087 | Tenericutes | Mollicutes | Anaeroplasmatales | Anae roplasniataceae | *Anaeroplasma* | *Anaeroplasma abactoclasticum* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1036 | SET 1 | 1796646 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | 1.00 |
| OTU_2880 | SET 1 | 45634 | Firmicutes | Bacilli | Lactobacillales | Streptococcaceae | *Streptococcus* | *Streptococcus cristatus* | 1.00 |
| OTU_1594 | SET 1 | 89014 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia luti* | 1.00 |
| OTU_1852 | SET 1 | 253257 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] amygdalinum* | 1.00 |
| OTU_969 | SET 1 | 466107 | Proteobacteria | Deltaproteobacteria | Desulfovibrionales | Desulfovibrionaceae | *Desulfovibrio* | *Desulfovibrio litoralis* | 0.50 |
| OTU_2702 | SET 1 | 871665 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Blautia* | *Blautia faecis* | 1.00 |
| OTU_1134 | SET 1 | 938293 | Firmicutes | Tissierellia | Tissierellales | Peptoniphilaceae | *Anaerococcus* | *Anaerococcus provericiensis* | 1.00 |
| OTU_1264 | SET 1 | 29466 | Firmicutes | Negativicutes | Veillonellales | Veillonellaceae | *Veillonella* | *Veillonella parvula* | 1.00 |
| OTU_1355 | SET 1 | 1689 | Actinobacteria | Actinobacteria | Bifidobacteriales | Bifidobacteriaceae | *Bifidobacterium* | *Bifidobacterium dentium* | 1.00 |
| OTU_1422 | SET 1 | 47678 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides caccae* | 1.00 |
| OTU_1431 | SET 1 | 259063 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerocolumna* | *Anaerocolumna jejuensis* | 1.00 |
| OTU_1504 | SET 1 | 879566 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Acetatifactor* | *Acetatifactor muris* | 1.00 |
| OTU_1683 | SET 1 | 158333 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Porphyromonas* | *Porphyromonas pasteri* | 1.00 |
| OTU_2053 | SET 1 | 575 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Enterobacteriaceae | *Raoultella* | *Raoultella planticola* | 1.00 |
| OTU_235 | SET 1 | 979627 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoanaerobaculum* | *Lachnoanaerobaculum orale* | 1.00 |
| OTU_2479 | SET 1 | 33033 | Firmicutes | Tissierellia | Tissierellales | Peptoniphilaceae | *Parvimonas* | *Parvimonas micro* | 1.00 |
| OTU_2881 | SET 1 | 51048 | Proteobacteria | Gammaproteobacteria | Pasteurellales | Pasteurellaceae | *AcinobaciUus* | *Actinobacillus porcinus* | 1.00 |
| OTU_304 | SET 1 | 840 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *PrevoteUa* | *Prevoiella loescheii* | 1.00 |
| OTU_330 | SET 1 | 158333 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Porphyromonas* | *Porphyromonas pasteri* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_383 | SE T i | 1660 | Actinobacteria | Actinomycetales | Actinomycetaceae | *Actinomyces* | *Actinomyces odontolyiicus* | 1.00 |
| OTU_549 | SE T 1 | 29466 | Negaiivicutes | Veillonellales | Veillonellaceae | *Veillonella* | *Veillonella parvula* | 1.00 |
| OTU_572 | SE T 1 | 320502 | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | */Clostridium] alkalicellulosi* | 1.00 |
| OTU_622 | SE T 1 | 12365 17 | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella fusca JCM 17724* | 1.00 |
| OTU_743 | SE T 1 | 617123 | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoanaerobaculum* | *Lachnoanaerobaculum umeaense* | 1.00 |
| OTU_2250 | SE T i | 546 | Gammaproteobacteria | Enterobacteriales | Enterobacteriaceae | *Citrobacter* | *Citrobacterfreundii* | 1.00 |
| OTU_1367 | SE T 1 | 129859 6 | Clostridia | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus faecis JCM 1591 7* | 1.00 |
| OTU_1067 | SE T 1 | 179664 6 | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestincUe* | 1.00 |
| OTU_1072 | SE T 1 | 358743 | Firmieutes | Clostridiales | Lachnospiraceae | *Lacknoclostridium* | *; [Clostridium! citroniae* | 1.00 |
| OTU_1963 | SE T 1 | 105020 1 | Firmieutes | Erysipelotrichales | Eiysipelotnchaceae | *Allobaculum* | *Allobaculum stercoricanis DSM 13633* | 1.00 |
| OTU_1171 | SE T i | 1264 | Firmieutes | Clostridiales | Ruminococcaceae | *Ruminococcus* | *j Ruminococcus albus* | 1.00 |
| OTU_1895 | SE T 1 | 471875 | Firmieutes | Clostridiales | Ruminococcaceae | *Ruminococcus* | *Ruminococcus lactaris ATCC 29176* | 1.00 |
| OTU_211 | SE T 1 | 28135 | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotel!a* | *\ Prevotella oris* | 1.00 |
| OTU_2165 | SE T 1 | 82171 | Deltaproteobacteria | Desuifovibrionales | Desulfovibrionaceae | *Desulfovibrio* | *; Desulfovibrio zosterae* | 1.00 |
| OTU_2395 | SE T I | 37658 | Firmieutes | Clostridiales | Lachnospiraceae | *Lacknoclostridium* | *[Clostridium] populeti* | 1.00 |
| OTU_2682 | SE T i | 483 | Betaproteobacteria | Neisseriales | Neisseriaceae | *Chromobacterium* | *Neisseria cinerea* | 1.00 |
| OTU_2766 | SE T 1 | 333367 | Firmieutes | Clostiidiaies | Lachno spiraceae | *Lachnoclostridium* | *[Clostridium] asparagiforme* | 1.00 |
| OTU_309 | SE T 1 | 501496 | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Porphyromonas* | *Porphyromonas bennonis* | 1.00 |
| OTU_723 | SE T 1 | 99656 | Firmieutes | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | */Clostridium/ fimetarium* | 1.00 |

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|---|---|---|---|---|---|---|---|---|
| OTU_973 | SEQ ID NO: 1379 | Firmicutes | Bacilli | Bacillales | unclassified.NA | *Gemella* | *Gemella haemolysans* | 1.00 |
| OTU_1231 | SEQ ID NO: 84032 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] fnermosuccinogenes* | 1.00 |
| OTU_2687 | SEQ ID NO: 123651 2 | Bacteroidetes | Bacteroidia | Bacteroidaies | Bacteroidaceae | *Bacteroides* | *Bacteroides rodentium JCM 16496* | 1.00 |
| OTU_2840 | SEQ ID NO: 129761 n, | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Intestinimonas* | *Intestinimonas butyriciproducens* | 1.00 |
| OTU_3053 | SEQ ID NO: 41467 | Firmicutes | Clostridia | Clostridiales | unclassified.NA | *Pseudoflavonifractor* | *Pseudoflavonifractor capillosus ATCC 29799* | 1.00 |
| OTU_3199 | SEQ ID NO: 39483 | Firmicutes | Erysipelotrichia | Erysipelotrichales | Erysipelotrichaceae | *FaecaUtaiea* | *FaecaUtaiea cylmdroides* | 1.00 |
| OTU_3207 | SEQ ID NO: 46503 | Bacteroidetes | Bacteroidia | Bacteroidaies | Porphyromonadaceae | *Parabacteroides* | *Parabacteroides merdae* | 1.00 |
| OTU_1427 | SEQ ID NO: 879566 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Acetatifactor* | *Acetatifactor muris* | 1.00 |
| OTU_901 | SEQ ID NO: 110731 6 | Proteobacteria | Betaproteobacteria | Neisseriales | Neisseriaceae | *Neisseria* | *Neisseria oralis* | 1.00 |
| OTU_1223 | SEQ ID NO: 584 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Morganeliaceae | *Proteus* | *Proteus mirabilis* | 1.00 |
| OTU_1608 | SEQ ID NO: 28124 | Bacteroidetes | Bacteroidia | Bacteroidaies | Porphyromonadaceae | *Porphyromonas* | *Porphyromonas endodontalis* | 1.00 |
| OTU_1798 | SEQ ID NO: 166486 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Roseburia* | *Roseburia iniestinaiis* | 1.00 |
| OTU_2066 | SEQ ID NO: 109327 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *Anaerovorax* | *Anaerovorax odorimuians* | 1.00 |
| OTU_2280 | SEQ ID NO: 103374 4 | Firmicutes | Tissierellia | Tissierellales | Peptoniphiiaceae | *Peptoniphilus* | *Peptoniphilus senegalensis JC140* | 1.00 |
| OTU_2393 | SEQ ID NO: 320502 | Firmicutes | Clostridia | Clostridiaks | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] alkalicellulosi* | 1.00 |
| OTU_3125 | SEQ ID NO: 901 | Proteobacteria | Deltaproteobacteria | Desuifovibrionales | Desulfovibrionaceae | *Desulfovibrio* | *Desulfovibrio piger* | 1.00 |
| OTU_1762 | SEQ ID NO: 483 | Proteobacteria | Betaproteobacteria | Neisseriales | Neisseriaceae | *Chromobacterium* | *Neisseria cinerea* | 1.00 |
| OTU_2848 | SEQ ID NO: 657309 | Bacteroidetes | Bacteroidia | Bacteroidaies | Bacteroidaceae | *Bacteroides* | *Bacteroides xylanisolvens XB1A* | 1.00 |
| OTU_298 | SEQ ID NO: 671218 | Bacteroidetes | Bacteroidia | Bacteroidaies | Prevotellaceae | *AUoprevotelia* | *AUoprevotelia rava* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_376 | SE T 1 | 536441 | Bacteroideies | Flavobacteriia | Flavobacteriales | Flavobacteriaceae | *Chryseobacterium* | *Chryseobacterium taklimakanense* | 1.00 |
| OTU_571 | SE T 1 | 873513 | Bacteroideies | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella buccae ATCC 33574* | 1.00 |
| OTU_618 | SE T 1 | 76123 | Bacteroideies | Bacteroidia | Bacieroidaies | Prevotellaceae | *Prevotella* | *Prevotella enoeca* | 1.00 |
| OTU_2595 | SE T 1 | 111806 0 | Actinobacteria | Coriobacteriia | Coriobacieriales | Coriobacteriaceae | *Enorma* | *Enorma massiliensis phi* | 1.00 |
| OTU_266 | SE T 1 | 89152 | Firmicutes | Clostridia | Clostridiales | Peptostreptococcaceae | *Achromobacter* | *[Clostridium] hirononis* | 1.00 |
| OTU_514 | SE T 1 | 888727 | Firmicutes | Clostridia | Clostridiales | Clostridiales Family XIII. Incertae Sedis | *unclassified.NA* | *Eubacterium sulci ATCC 35585* | 1.00 |
| OTU_94 | SE T 1 | 76122 | Bacteroideies | Bacteroidia | Bacteroidales | Prevotellaceae | *AUoprevotetta* | *Alloprevotella tannerae* | 1.00 |
| OTU_2059 | SE T 1 | 303 | Proteobacteria | Gammaproteobacteria | Pseudomonadaies | Pseudomonadaceae | *Pseitdomonas* | *P,seudo,,onas putida* | 1.00 |
| OTU_3060 | SE T 1 | 1541 | Firmicutes | Clostridia | Clostridiales | Peptostreptococcaceae | *Terrisporobacier* | *; Terrisporobacter mayombei* | 1.00 |
| OTU_1475 | SE T 1 | 507751 | Firmicutes | Tissierellia | Tissiereilales | Peptoniphilaceae | *Pep'toniphihis* | ] *Peptoniphilus koenoeneniae* | 1.00 |
| OTU_1204 | SE T 1 | 179664 6 | Bacteroideies | Bacteroidia | Bacteroidales | Porpbyromonadaceae | *Muribaculum* | *; Muribaculum intestinale* | 1.00 |
| OTU_1626 | SE T 1 | 179664 6 | Bacteroideies | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | 1.00 |
| OTU_3028 | SE T 1 | 515620 | Firmicutes | Clostridia | Clostridiales | Eubacteriaceae | *Enbaclerium* | *[Eubacterium] eligens ATCC 27750* | 1.00 |
| OTU_1090 | SE T 1 | 38302 | Actinobacteria | Actinobacteria | Coryiiebacteriales | Corynebacteriaceae | *Corynebacterium* | *; Corynebacterium mycetoides* | 1.00 |
| OTU_186 | SE T 1 | 53419 | Spirochaetes | Spirochaetia | Spirochaetales | Spirochaetaceae | *Treponema* | *; Treponema socranskii* | 1.00 |
| OTU_2158 | SE T 1 | 179664 6 | Bacteroideies | Bacteroidia | Bacteroidales | Porpbyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | 1.00 |
| OTU_2205 | SE T 1 | 726 | Proteobacteria | Gammaaroteobacteria | Pasteurellales | Pasteurellaceae | *Haemophilus* | *Haemophilus haemolyticus* | 1.00 |
| OTU_2345 | SE T 1 | 328812 | Bacteroideies | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Parabacteroides* | *Parabacteroides goldsieinii* | 1.00 |
| OTU_1408 | SE T 1 | 40324 | Proteobacteria | Gammaproteobacteria | Xanthomonadales | Xantho monadaceae | *S.tenotrophomonas* | *Stenoirophomonas maltophilia* | 1.00 |

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|---|---|---|---|---|---|---|---|---|
| otu_1476 | SE T i | 129761 7 | Firmicutes | Clostridia | Clostiidiaies | unclassified.NA | *Intestinimonas* | *Intestinimonas butyriciproducens* | 1.00 |
| OTU_173 | SE T 1 | 555088 | Firmicutes | Clostridia | Clostridials | Syntrophomonadaceae | *Dethiobader* | *Dethiobader alkaliphiius AHT 1* | 1.00 |
| OTU_2082 | SE T 1 | 901 | Proteobacteria | Deltaproteobacteria | Desulfovibrional es | Desulfovibrionaceae | *Desulfovibrio* | *Desulfovibrio piger* | 1.00 |
| OTU_2114 | SE T 1 | 179664 6 | Bacteroidetes | Bacteroidia | Bacieroidales | Poipliyronionadaceae | *Muribaeuium* | *Muribaeuium miestinale* | 1.00 |
| OTU_2283 | SE T 1 | 308994 | Firmicutes | Negativicutes | Veillonellales | Veilloiiellaceae | *Dialister* | *Dialister propionicifaciens* | 1.00 |
| OTU_238 | SE T i | 179664 6 | Bacteroidetes | Bacteroidia | Bacieroidales | Porpby romonadaceae | *Muribaeuium* | *Muribaeuium intesiinale* | 1.00 |
| OTU_2517 | SE T 1 | 29375 | Firmicutes | Clostridia | Clostridiaies | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] xylanolyticum* | 1.00 |
| OTU_609 | SE T 1 | 179661 0 | Actinobacteria | Coriobacteriia | Eggerthellales | Eggerthellaceae | *Enierorhabdus* | *Enterorhabdus maris* | 1.00 |
| OTU_1208 | SE T 1 | 290052 | Firmicutes | Clostridia | Clostridiaies | Ruminococcaceae | *Acetivibrio* | *;Acetivibrio ethanolgignens* | 1.00 |
| OTU_1844 | SE T 1 | 546 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Ente robacteriaceae | *Citrobacter* | *Citrobacterfreundii* | 1.00 |
| OTU_1560 | SE T i | 988946 | Cyanobacteria | unciassified.NA | Nostocales | Symphyonemataceae | *Lorieilopsis* | *Lorieilopsis cavemicola* | 1.00 |
| OTU_1819 | SE T 1 | 1605 | Firmicutes | Bacilli | Lactobaciilales | Lactobacillaceae | *Lactobacillus* | *Lactobacillus animalis* | 1.00 |
| OTU_2423 | SE T 1 | 166486 | Firmicutes | Clostridia | Clostridiaies | Lachnospiraceae | *Roseburia* | *Roseburia iniestinalis* | 1.00 |
| OTU_1517 | SE T 1 | 160404 | Firmicutes | Clostridia | Clostridiaies | Lachno spiraceae | *Tyzzereila* | *; [Clostridium] lactatifermenians* | 1.00 |
| OTU_114 | SE T I | 185237 0 | Bacteroidetes | Bacteroidia | Bacieroidales | Prevotellaceae | *Prevotellamassili a* | *; Prevote!lamassilia tirnonensis* | 1.00 |
| OTU_1248 | SE T i | 474960 | Firmicutes | Clostridia | Clostridiaies | Ruminococcaceae | *Hydrogenoanaerobacterium* | *Hydrogenoanaerobacterium ; saccharovorans* | 1.00 |
| OTU_84 | SE T 1 | 1017 | Bacteroidetes | Flavobacteriia | Flavobacteriales | Flavobacteriaceae | *Capnocytophaga* | *Capnocytophaga gingivalis* | 1.00 |
| OTU_1624 | SE T 1 | 1;16828 9 | Bacteroidetes | Bacteroidia | Bacieroidales | Marinilabiliaceae | *Marinilabiiia* | *Marinilabilia salmonicolor JCM 21150* | 1.00 |
| OTU_2918 | SE T 1 | 246787 | Bacteroidetes | Bacteroidia | Bacieroidales | Bacteroidaceae | *Bacteroides* | *\ Bacteroid.es cellulosifyticus* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_1293 | SET 1 | 76936 | Proteobacteria | Epsilonproteobacteria | Campylobacterales | Helicobacteraceae | *Helicobacter* | *Helicobacter typhlonius* | 1.00 |
| OTU_2664 | SET 1 | 94869 | Firmicutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium gasigenes* | 1.00 |
| OTU_2728 | SET 1 | 204516 | Bacteroidetes | Bacteroidia | Bacteroidales | Bacteroidaceae | *Bacteroides* | *Bacteroides massiliensis* | 1.00 |
| OTU_911 | SET 1 | 1161098 | Firmicutes | Tissierellia | Tissierellales | Peptoniphilaceae | *Anaerococcus* | *Anaerococcus octavius NCTC 9810* | 1.00 |
| OTU_1930 | SET 1 | 28117 | Bacteroidetes | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes putredinis* | 1.00 |
| OTU_1625 | SET 1 | 1002367 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella stercorea DSM 18206* | 1.00 |
| OTU_3162 | SET 1 | 261299 | Firmicutes | Clostridia | Clostridiales | Peptostreptococcaceae | *Intestinibacter* | *Intestinibacter bartlettii* | 1.00 |
| OTU_1255 | SET 1 | 46206 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Pseudobutyrivibrio* | *Pseudobutyrivibrio ruminis* | 1.00 |
| OTU_2161 | SET 1 | 515619 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Myxococcus* | *[Eubacterium rectale] ATCC 33656* | 1.00 |
| OTU_2320 | SET 1 | 28118 | Bacteroidetes | Bacteroidia | Bacteroidales | Odoribacteraceae | *Odoribacter* | *Odoribacter splanchnicus* | 1.00 |
| OTU_2674 | SET 1 | 1531 | Firmicutes | Clostridia | Clostridiales | Lachnospiraceae | *Lachnoclostridium* | *[Clostridium] clostridioforme* | 1.00 |
| OTU_729 | SET 1 | 215580 | Proteobacteria | Betaproteobacteria | Burkholderiales | Comamonadaceae | *Schlegelella* | *Schlegelella thermodepolymerans* | 1.00 |
| OTU_730 | SET 1 | 1796646 | Bacteroidetes | Bacteroidia | Bacteroidales | Porphyromonadaceae | *Muribaculum* | *Muribaculum intestinale* | 1.00 |
| OTU_994 | SET 1 | 1125779 | Actinobacteria | Actinobacteria | Corynebacteriales | Corynebacteriaceae | *Corynebacterium* | *Corynebacterium pyruviciproducens ATCC BAA-1742* | 1.00 |
| OTU_1282 | SET 1 | 84026 | Firmicutes | Clostridia | Clostridiales | Ruminococcaceae | *Ruminiclostridium* | *[Clostridium] methylpentosum* | 1.00 |
| OTU_1717 | SET 1 | 327575 | Bacteroidetes | Flavobacteriia | Flavobacteriales | Flavobacteriaceae | *Capnocytophaga* | *Capnocytophaga leadbetteri* | 1.00 |
| OTU_2829 | SET 1 | 549 | Proteobacteria | Gammaproteobacteria | Enterobacterales | Erwiniaceae | *Pantoea* | *Pantoea agglomerans* | 1.00 |
| OTU_398 | SET 1 | 28129 | Bacteroidetes | Bacteroidia | Bacteroidales | Prevotellaceae | *Prevotella* | *Prevotella denticola* | 1.00 |

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|---|---|---|---|---|---|---|---|---|---|
| OTU_i 971 | SET 1 | 483 | Proteobacteria | Betaproteobacteria | Neisseriales | Neisseriaceae | *Chromobacterium* | *Neisseria cinerea* | 1.00 |
| OTU_i 1659 | SET 1 | 1450648 | Firmieutes | Clostridia | Clostridiales | Clostridiaceae | *Clostridium* | *Clostridium oryzae* | 1.00 |
| OTU_i 881 | SET 1 | 214856 | Bacteroidetes | Bacteroidia | Bacteroidales | Rikenellaceae | *Alistipes* | *Alistipes finegoldii* | 1.00 |
| OTU_i 1581 | SET 1 | 264463 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Anaerosporobacter* | *Anaerosporobacier mobilis* | 1.00 |
| OTU_i 2148 | SET 1 | 319644 | Firmieutes | Clostridia | Clostridiales | Ruminococcaceae | *Saccharofeintentarts* | *Saccharofermentans acetigenes* | 1.00 |
| OTU_i 2969 | SET 1 | 515619 | Firmieutes | Clostridia | Clostridiales | Lachnospiraceae | *Myxococcus* | *[Eubacterium rectale] ATCC 33656* | 1.00 |
| OTU_i 717 | SET 1 | 478 | Proteobacteria | Gammaproteobacteria | Pseudomonadales | Moraxellaceae | *Moraxella* | *Moraxella nonliquefaciens* | 1.00 |

**[00114]** Table 2: Differences in WGS-derived fecal bacteria species by treatment response status.

| CAG Number | Unadjusteel p-value | Response status | CAG Number | Taxonomy Level | species | Genus | Family |
|---|---|---|---|---|---|---|---|
| CAG00720 | 0.017 | NR | CAG00720 | Species | Anaeroinmcus coiihominis | Anaerotruncus | Ruminococcaceae |
| CAG00J 24 | O.OiS | NR | CAG00124 | Species | Klebsiella variicoia | Klebsiella | Enterobacteriaceae |
| CAGOOOl l | 0.035 | NR | CAGOOOll | Species | Escher chia coli | Esclericbia | Enterobacieriaceae |
| CAG00050 | 0.043 | NR | CAG00050 | Species | Bacteroides tbeiaiotaomicroii | Bacteroides | Bacteroidaceae |
| CAG00834 | 0.047 | NR | CAG00834 | Species | Oxalobacter formigenes | Oxalobacter | Oxalobacteraceae |
| CAG00426 | 0.06 | NR | CAG00426 | Species | Paraprevotella ciara | Paraprevoiella | Prevotellaceae |
| CAGO 1272 | 0.06 | NR | CAG01272 | Species | Adlercreuizia equoiifaciess | Adlercreutzia | Eggertliellaceae |
| CAGO1320 | 0.066 | NR | CAG013 20 | Species | Clostridium bolteae | Lachnoclostridium | Lachnospiraceae |
| CAG00012 | 0.069 | NR | CAG00012 | Species | Klebsiella pneumoniae | Klebsiella | Enterobacteriaceae |
| CAG00826 | 0.089 | NR | CAG00826 | Genus | unclassified Clostridium | Clostridium | Clostridiaceae |
| CAG00117 | 0.092 | NR | CAG001 17 | Species | Parabacteroides merdae | Parabacieroides | Porphyroinonadaceae |
| CAG00093 | 0.116 | NR | CAG00093 | Species | Klebsiella quasipneumoniae | Klebsiella | Enterobacteriaceae |

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|---|---|---|---|---|---|---|---|
| CAG00114 | 0.116 | NR | CAG00114 | Genus | unclassified Lachnoclostndmm | Lachnoelostridium | Lachnospiraceae |
| CAG00161 | 0.116 | NR | CAG00161 | Species | Bacteroides coprocola | Bacteroides | Bacteroidaceae |
| CAG00163 | 0.116 | NR | CAG00163 | Species | Prevotella sp. CAG:255 | Prevotella | Prevotellaceae |
| CAG00256 | 0.116 | NR | CAG00256 | Family | unclassified Lachnospiraceae | unclassified Lachnospiraceae | Lachnospiraceae |
| CAG00462 | 0.116 | NR | CAG00462 | Species | Strepiococcus pasieurianus | Streptococcus | Streptococcaceae |
| CAG00815 | 0.116 | NR | CAG00815 | Species | Laciococcus iactis | Lactococcus | Streptococcaceae |
| CAG00817 | 0.116 | NR | CAG00817 | Order | unclassified Ciosiridiales | unclassified Clostridiales | unclassified Clostridiales |
| CAGOOOiO_2 | 0.116 | NR | CAG00010_2 | NA | unclassified | unclassified | unclassified |
| CAG01203 | 0.116 | NR | CAG01203 | Species | Streptococcus mutans | Streptococcus | Streptococcaceae |
| CAG00949 | 0.12 | NR | CAG00949 | Species | Ruminococcaceae bacterium D16 | unclassified Ruminococcaceae | Ruminococcaceae |
| CAG00775 | 0.13 | NR | CAG00775 | Species | Firmicutes bacterium CAG:102 | unclassified Firmicutes | unclassified Firmicutes |
| CAG00931 | 0.131 | NR | CAG00931 | Genus | unclassified Oscillibacter | Oscillibacter | Oscillospiraceae |
| CAG01263 | 0.154 | NR | CAG01263 | Species | Clostridium clostridioforme | Lachnoclostridium | Lachnospiraceae |
| CAG00086 | 0.154 | NR | CAG00086 | Species | Bacteroides massiliensis | Bacteroides | Bacteroidaceae |
| CAG00113 | 0.157 | NR | CAG00113 | Species | Clostridium scindens | Lachnoclostridium | Lachnospiraceae |
| CAG01323 | 0.165 | NR | CAG01323 | Species | Parabacteroides merdae | Parabacteroides | Porphyromonadaceae |
| CAG00502 | 0.184 | NR | CAG00502 | Species | Eubacterium sp. CAG:161 | Eubacterium | Eubacteriaceae |
| CAG00254 | 0.193 | NR | CAG00254 | Species | Ruminococcus gnavus | Blautia | Lachnospiraceae |
| CAG01264 | 0.197 | NR | CAG01264 | Species | Clostridium clostridioforme | Lachnoclostridium | Lachnospiraceae |
| CAG00327 | 0.009 | R | CAG00327 | family | unclassified Ruminococcaceae | unclassified Ruminococcaceae | Ruminococcaceae |
| CAG00659 | 0.017 | R | CAG00659 | Order | unclassified Ciostridiales | unclassified Ciosiridiales | unclassified Clostridiales |
| CAG00492 | 0.034 | R | CAG00492 | Genus | unclassified Faecalibacterium | Faecalibacterium | Ruminococcaceae |
| CAG00518 | 0.034 | R | CAG00518 | Genus | unclassified Faecalibacterium | Faecalibacterium | Ruminococcaceae |
| CAG01146 | 0.034 | R | CAG01146 | Genus | unclassified Oscillibacter | Oscillibacter | Oscillospiraceae |
| CAG00079 | 0.038 | R | CAG00079 | Species | Clostridium sp. CAG:7 | unclassified Clostridiales | unclassified Clostridiales |
| CAG00393 | 0.048 | R | CAG00393 | Species | Eubacterium sp. CAG:S6 | Eubacterium | Eubacteriaceae |
| CAG00766 | 0.065 | R | CAG00766 | Species | Firmicutes bacterium CAG:176 | unclassified Firmicutes | unclassified Firmicutes |
| CAG00095 | 0.065 | R | CAG00095 | Species | Akkermansia sp. CAG:344 | Akkermansia | AJdcermansiaceae |
| CAGOOOIO_1 | 0.065 | R | CAGOOOIO_1 | Order | unclassified Ciosiridiales | unclassified Clostridiales | unclassified Clostridiales |

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|---|---|---|---|---|---|---|---|
| CAG00342 | 0.065 | R | CAG00342 | Species | Bifidobacterium pseudocatenulatum | Bifidobacterium | Bifidobacieriaceae |
| CAG00303 | 0.065 | R | CAG00303 | Genus | unclassified Ciostridiales | unclassified Ciostridiales | unclassified Ciostridiales |
| CAG00337 | 0.065 | R | CAG003 37 | Genus | unclassified Faecalibactenum | Faecalibacterium | Ruminococcaceae |
| CAG00381 | 0.065 | R | CAG00381 | Species | Clostridium sp. CAG:242 | unclassified Ciostridiales | unclassified Ciostridiales |
| CAG00559 | 0.065 | R | CAG00559 | Family | unclassified Ciostridiales | unclassified Ciostridiales | unclassified Ciostridiales |
| CAG00570 | 0.065 | R | CAG00570 | NA | unclassified | unclassified | unclassified |
| CAG00635 | 0.065 | R | CAG00635 | Species | Bifidobacterium bifidutn | Bifidobacterium | Bifidobacieriaceae |
| CAG00636 | 0.065 | R | CAG00636 | Genus | unclassiiied Roseburia | Roseburia | Lachnospiraceae |
| CAG00660 | 0.065 | R | CAG00660 | Species | Alistipes timonensis | Alistipes | Rikeneliaceae |
| CAG00669 | 0.065 | R | CAG00669 | Genus | unclassified Firmicutes | unclassified Firmicutes | unci assifi ed Firms eutes |
| CAG00708 | 0.065 | R | CAG00708 | Species | Alistipes senegalensis | Alistipes | Rikeneliaceae |
| CAG00773 | 0.065 | R | CAG00773 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00807 | 0.065 | R | CAG00807 | Genus | unclassified Ho!demane!!a | Holdemanella | Erysipelotnchaceae |
| CAG00880 | 0.065 | R | CAGOOSSO | Species | Subdo!igranulum sp. CAG:3 l4 | Subdoligranulum | Ruminococcaceae |
| CAG00907 | 0.065 | R | CAG00907 | Family | unclassified Ciostridiales | unclassiiied Ciostridiales | unclassified Ciostridiales |
| CAGO 1086 | 0.065 | R | CAG01086 | Genus | unclassiiied Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG01215 | 0.065 | R | CAG01215 | family | unclassified Ciostridiales | unclassified Ciostridiales | unclassified Ciostridiales |
| CAG01277 | 0.065 | R | CAG01277 | Genus | unclassified Ciostridiales | unclassified Ciostridiales | unclassified Ciostridiales |
| CAG01308 | 0.065 | R | CAG01308 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00577 | 0.073 | R | CAG00577 | Species | Faecalibactenum prausmtzii 3 (L2-6) | Faecalibacterium | Ruminococcaceae |
| CAG00506 | 0.083 | R | CAG00506 | Genus | unclassified Ruminococcaceae | unclassified Ruminococcaceae | Ruminococcaceae |
| CAG00852 | 0.087 | R | CAG00S52 | Species | Clostridium spiroforme | Erysipelatoclostridium | Erysipclotricliaceae |
| CAGO 1046 | 0.091 | R | CAG01046 | Genus | unclassiiied Intestinimonas | Intestinimonas | unclassified Ciostridiales |
| CAG00320 | 0.092 | R | CAGOO320 | Species | Phascolarctobacierium sp. CAG:207 | Phascoiarctobacterium | Acidaminococcaceae |
| CAG00619 | 0.097 | R | CAG00619 | Genus | unclassified Faecalibacterium | Faecalibacterium | Ruminococcaceae |
| CAGO1366 | 0.098 | R | CAG01366 | Species | Streptococcus parasanguinis | Streptococcus | Streptococcaceae |
| CAG00509 | 0.1 | R | CAG00509 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG0044! | 0.104 | R | CAG00441 | Genus | unclassified B!autia | Blautia | Lachnospraceae |
| CAG00249 | 0.106 | R | CAG00249 | Species | Clostridium ieptum | Ruminiclostridium | Ruminococcaceae |

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|---|---|---|---|---|---|---|---|
| CAGS0003 | 0.12 | R | CAG50003 | Genus | unclassified Ciostridia!es | unclassified Clostridiales | unclassified Clostridiales |
| CAG00039 | Q121 | R | CAG00039 | Genus | imciassified Firmicutes | unclassified Firmicutes | unci assifi ed Firms eutes |
| CAG00127 | 0.121 | R | CAGOOl 27 | Family | imciassified Laclmospiraceae | unclassified Laclmospiraceae | Lachnospiraceae |
| CAG00854 | 0.121 | R | CAG00854 | Family | unclassified Rumiuococcaceae | unclassified Ruiiiinococcaceae | Ruminococcaceae |
| CAG00166 | 0.121 | R | CAGOOl66 | Order | unclassified C!ostridiales | unclassified Clostridiales | unclassified Clostridiales |
| CAG00272 | 0.121 | R | CAG00272 | Species | FaecaJibacterium 5 (sp. CAG:74) | Faecalibacterium | Ruminococcaceae |
| CAG00294 | 0.121 | R | CAG00294 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00367 | 0.12 1 | R | CAG00367 | Species | Firmicutes bacterium CAG:170 | unclassified Firmicutes | unclassified Firmicutes |
| CAG00445 | 0.121 | R | CAG00445 | Order | unclassified Ciostridia!es | unclassified Clostridiales | unclassified Clostridiales |
| CAG00452 | 0.121 | R | CAG00452 | Species | Clostridium sp. CAG:167 | unclassified Clostridiales | unclassified Clostridiales |
| CAG00497 | 0.121 | R | CAG00497 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00505 | 0.121 | R | CAG00505 | Genus | imciassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00721 | 0.121 | R | CAG00721 | Species | Methanobrevibacter smithii ! | Methanobrevibacter | Methanobactenaceae |
| CAG00624 | 0.121 | R | CAG00624 | Phyl um | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicu tes |
| CAG00648 | 0.121 | R | CAG00648 | Genus | unclassified Eubacterium | Eubacterium | Eubacteriaccae |
| CAG00735 | 0.121 | R | CAG00735 | Genus | unclassified Eubacterium | Eubacterium | Eubacieriaceae |
| CAG00770 | 0.121 | R | CAG00770 | Family | unclassified Eggerthellaceae | unclassified Eggerthellaceae | Eggerthellaceae |
| CAG00S12 | 0.121 | R | CAG00812 | Species | Catembacterium sp. CAG:290 | Catenibacterium | ErysipeJotrichaceae |
| CAG00S61 | 0.121 | R | CAG00861 | Species | Oscillibacter sp. CAG:241 | Oscillibacter | Osciiiospiraceae |
| CAG00863 | 0.121 | R | CAG00863 | Genus | imciassified Firnsicuies | unclassified Firmicutes | unclassified Firmicutes |
| CAG00925 | 0.12! | R | CAG00925 | NA | unclassified | unclassified | unclassified |
| CAG00934 | 0.121 | R | CAG00934 | Order | unclassified Clostridiales | unclassified Clostridiales | unclassified Clostridiales |
| CAG01003 | 0.121 | R | CAG01003 | Family | unclassified Rumiuococcaceae | unclassified Rumiuococcaceae | Ruminococcaceae |
| CAG01325 | 0.121 | R | CAG01323 | Genus | unclassified Lacnnoclostridium | Lachnoclostridium | Lachnospiraceae |
| CAG02021 | 0.121 | R | CAG0202! | Genus | unclassified Ciostridia!es | unclassified Clostridiales | unclassified Clostridiales |
| CAG01349 | 0.121 | R | CAGO1349 | NA | imciassified | unclassified | unclassified |
| CAG01350 | 0.121 | R | CAG01350 | Order | unclassified Clostridiales | unclassified Clostridiales | unclassified Clostridiales |
| CAGO 1402 | 0.121 | R | CAG01402 | Species | Turicibacter sp. H121 | Turicibacter | Erysipelotrichaceae |
| CAG0I403 | 0.121 | R | CAG01403 | Species | Bacteroides stercorirosoris | Bacteroides | Bacteroidaceae |
| CAGOI551 | 0.121 | R | CAG01551 | Genus | unclassified Oscillibacter | Oscillibacter | Osciiiospiraceae |

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|---|---|---|---|---|---|---|---|
| CAGO 1028 | 0.13 | R | CAG01028 | Species | Ruminococcaceae bacterium LM158 | unclassified1Ruminococcacea e | Ruminococcaceae |
| CAG00121 | 0.Ï34 | R | CAG001 21 | Species | Bacteroides finegoldii | Bacteroides | Bacteroidaceae |
| CAG00670 | 0.134 | R | CAG00670 | Ge$_n$us | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00324 | 0.137 | R | CAG00324 | Species | Firmicutes bacterium CAG:94 | unclassified Firmicutes | unclassified Firmicutes |
| CAG00218 | 0.143 | R | CAG00218 | Species | Bamesiella intestimhominis | Bamesieila | Porphyromonadaceae |
| CAG00755 | 0. 143 | R | CAG00755 | Genus | unclassified Faecalibacterium | Faecalibacterium | Ruminococcaceae |
| CAG00560 | 0.175 | R | CAG00560 | Genus | unclassified Subdoligianulum | Subdoiigranulum | Ruminococcaceae |
| CAG00259 | 0.177 | R | CAG00259 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAGO 1039 | 0.177 | R | CAG01039 | Genus | unclassified Faecalibacterium | Faecalibacterium | Ruminococcaceae |
| CAG00239 | 0.183 | R | CAG00239 | Species | Flavonifractor piautii | Fiavonifractor | unclassified Clostridiales |
| CAG00112 | 0.184 | R | CAG001 12 | Species | Blautia sp. CAG:52 | Blautia | Lachnospiraceae |
| CAG00697 | 0.196 | R | CAG00697 | Genus | unclassified Hungaielia | Hungatella | Clostridiaceae |
| CAG00595 | 0.20! | R | CAG00595 | Order | unclassified CSostridiales | unclassified Clostridiales | unclassified Clostridiales |
| CAG00629 | 0.2 13 | R | CAG00629 | Species | Firmicutes bacterium CAG:1 24 | unclassified Firmicutes | unclassified Firmicutes |
| CAG00549 | 0.219 | R | CAG00549 | Species | Bifidobacterium longum | Bifidobacterium | Bifidobacteriaceae |
| CAG00328 | 0.22 1 | R | CAG00328 | Species | A!istipes indistmctus | Aiistipes | Rikenellaceae |
| CAG00760 | 0.222 | R | CAG00760 | Species | Ruminococcus sp. CAG:177 | Ruminococcus | Ruminococcaceae |
| CAG00031 | 0.222 | R | CAG0003! | NA | unclassified | unclassified | unclassified |
| CAG00102 | 0.222 | R | CA GOO 102 | Genus | unclassified Clostridiales | unclassified1Clostridiales | unclassified Clostridiales |
| CAG00130 | 0.222 | R | CAG00130 | Species | Weisse!!a confusa | Weissella | Leuconostocaceae |
| CAG00134 | 0.222 | R | CAG00134 | Species | Cloaci bacillus porcoram | Cloacibacillus | Synergistaceae |
| CAG00145 | 0.222 | R | CAG00145 | Genus | unclassified Clostridiales | unclassified Clostridiaies | unclassified Clostridiales |
| CAG00200 | 0.222 | R | CAG00200 | Genus | unclassified Fiavonifractor | Fiavonifractor | unclassified Clostridiales |
| CAG00179 | 0.222 | R | CAG00179 | Species | Blautia sp. CAG:237 | Blautia | Lachnospiraceae |
| CAG00183 | 0.222 | R | CAG001 83 | Species | Ruminococcus sp. CAG:60 | Ruminococcus | Ruminococcaceae |
| CAG00198 | 0.222 | R | CAG00198 | NA | unclassified | unclassified | unclassified |
| CAG00214 | 0.222 | R | CAG00214 | Species | Prevotella corporis | Prevotella | Prevotellaceae |
| CAG00261 | 0.222 | R | CAG00261 | Genus | unclassified Oscillibacter | Oscillibacter | Oscillospiraceae |
| CAG00241 | 0.222 | R | CAG00241 | Species | Anaerotruncus sp. CAG:390 | Anaerotruncus | Ruminococcaceae |
| CAG00363 | 0.222 | R | CAG00363 | Genus | unclassified Intestmimonas | Intestinimonas | unclassified Clostridiales |

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|---|---|---|---|---|---|---|---|
| CAG00373 | 0.222 | R | CAG00373 | Genus | unclassified Oscillibacter | Oscillibacter | Oscillospiraceae |
| CAG00436 | 0.222 | R | CAG00436 | Species | Clostridium sp. CAG:299 | unclassified Clostridiales | unclassified Clostridiales |
| CAG00470 | 0.222 | R | CAG00470 | Family | unclassified Ruminococcaceae | unclassified Ruminococcaceae | Ruminococcaceae |
| CAG00541 | 0.222 | R | CAG00541 | Species | Dorea sp. CAG:105 | Dorea | Lachnospiraceae |
| CAG00542 | 0.222 | R | CAG00542 | Species | Butyrivibrio crossotus | Butyrivibrio | Lachnospiraceae |
| CAG00644 | 0.222 | R | CAG00644 | Species | Clostridium sp. CAG:226 | unclassified Clostridiales | unclassified Clostridiales |
| CAG00658 | 0.222 | R | CAG00658 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00676 | 0.222 | R | CAG00676 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00698 | 0.222 | R | CAG00698 | Genus | unclassified Ruminococcus | Ruminococcus | Ruminococcaceae |
| CAG00703 | 0.222 | R | CAG00703 | Species | Candidatus Methanomassiliicoccus intestinalis | Methanomassiliicoccus | Methanomassiliicoccaceae |
| CAG00831 | 0.222 | R | CAG00831 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00841 | 0.222 | R | CAG00841 | Species | Firmicutes bacterium CAG:345 | unclassified Firmicutes | unclassified Firmicutes |
| CAG00850 | 0.222 | R | CAG00850 | Genus | unclassified Blautia | Blautia | Lachnospiraceae |
| CAG00851 | 0.222 | R | CAG00851 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00048_1 | 0.222 | R | CAG00048_1 | Order | unclassified Clostridiales | unclassified Clostridiales | unclassified Clostridiales |
| CAG00866 | 0.222 | R | CAG00866 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00892 | 0.222 | R | CAG00892 | Phylum | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00959 | 0.222 | R | CAG00959 | Genus | unclassified Alistipes | Alistipes | Rikenellaceae |
| CAG00965 | 0.222 | R | CAG00965 | Genus | unclassified Firmicutes | unclassified Firmicutes | unclassified Firmicutes |
| CAG00988 | 0.222 | R | CAG00988 | Species | Clostridium sp. CAG:349 | unclassified Clostridiales | unclassified Clostridiales |
| CAG01047 | 0.222 | R | CAG01047 | Family | unclassified Clostridiales Family XIII. Incertae Sedis | unclassified Clostridiales Family XIII. Incertae Sedis | Clostridiales Family XIII. Incertae Sedis |
| CAG01075 | 0.222 | R | CAG01075 | Order | unclassified Clostridiales | unclassified Clostridiales | unclassified Clostridiales |
| CAG01099 | 0.222 | R | CAG01099 | Species | Raoultella ornithinolytica | Raoultella | Enterobacteriaceae |
| CAG01108 | 0.222 | R | CAG01108 | Species | Clostridium sp. CAG:798 | unclassified Clostridiales | unclassified Clostridiales |
| CAG01145 | 0.222 | R | CAG01145 | Genus | unclassified Bacteroides | Bacteroides | Bacteroidaceae |
| CAG01156 | 0.222 | R | CAG01156 | Genus | unclassified Eubacterium | Eubacterium | Eubacteriaceae |
| CAG01169 | 0.222 | R | CAG01169 | Family | unclassified Ruminococcaceae | unclassified Ruminococcaceae | Ruminococcaceae |
| CAG01240 | 0.222 | R | CAG01240 | Species | Parabacteroides gordonii | Parabacteroides | Porphyromonadaceae |
| CAG00068_2 | 0.222 | R | CAG00068_2 | Genus | unclassified Porphyromonas | Porphyromonas | Porphyromonadaceae |

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|---|---|---|---|---|---|---|---|
| CAG01372 | 0.222 | R | CAG01372 | Genus | unclassified Oscillibacter | Oscillibacter | Oscillospiraceae |
| CAG01394 | 0.222 | R | CAG01394 | Genus | unclassified Blautia | Blautia | Lachnospiraceae |
| CAG00052 | 0.225 | R | CAG00052 | Species | Parabacteroides goldsteinii | Parabacteroides | Porphyromonadaceae |
| CAG00116 | 0.225 | R | CAG00116 | Species | Bacteroides nordii | Bacteroides | Bacteroidaceae |
| CAG00429 | 0.225 | R | CAG00429 | Species | Eubacterium sp. CAG:248 | Eubacterium | Eubacteriaceae |
| CAG00702 | 0.24 | R | CAG00702 | Species | Bifidobacterium adolescentis | Bifidobacterium | Bifidobacteriaceae |
| CAG00309 | 0.243 | R | CAG00309 | Species | Alistipes onderdonkii | Alistipes | Rikenellaceae |
| CAG01637 | 0.259 | R | CAG01637 | Species | Firmicutes bacterium CAG:65 | unclassified Firmicutes | unclassified Firmicutes |
| CAG01051 | 0.265 | R | CAG01051 | Genus | unclassified Oscillibacter | Oscillibacter | Oscillospiraceae |
| CAG00792 | 0.265 | R | CAG00792 | Species | Firmicutes bacterium CAG:65 | unclassified Firmicutes | unclassified Firmicutes |
| CAG00208 | 0.266 | R | CAG00208 | Species | Faecalibacterium sp | Faecalibacterium | Ruminococcaceae |
| CAG01700 | 0.279 | R | CAG01700 | Family | unclassified Ruminococcaceae | unclassified Ruminococcaceae | Ruminococcaceae |
| CAG01371 | 0.279 | R | CAG01371 | Species | Escherichia coli | Escherichia | Enterobacteriaceae |
| CAG00653 | 0.29 | R | CAG00653 | Species | Eubacterium siraeum | Ruminiclostridium | Ruminococcaceae |
| CAG00520 | 0.29 | R | CAG00520 | Species | Firmicutes bacterium CAG:56 | unclassified Firmicutes | unclassified Firmicutes |
| CAG00273 | 0.311 | R | CAG00273 | Species | Blautia sp. CAG:37 | Blautia | Lachnospiraceae |

**[00115]** Table 2A - Shows the bacterial genes used for characterizing bacteria co-abundance gene groups (CAG) and the corresponding SEQ ID NO for each gene in the bacteria of interest. Each of the listed CAG group and gene is available on the world wide web at meta.genomics.cn/meta/dataTools, and is incorporated herein by reference.

| CAG ID | gene_name | SEQ ID |
|---|---|---|
| CAG00327 | V1.FI20_GL0119476 | SEQ ID NO: 877 |
| CAG00327 | V1.UC26-4_GL0088915 | SEQ ID NO: 878 |
| CAG00327 | V1.FI17_GL0037272 | SEQ ID NO: 879 |
| CAG00327 | V1.FI17_GL0078727 | SEQ ID NO: 880 |
| CAG00327 | O2.UC24-2_GL0094271 | SEQ ID NO: 881 |
| CAG00327 | V1.FI17_GL0207542 | SEQ ID NO: 882 |
| CAG00327 | MH0348_GL0074623 | SEQ ID NO: 883 |
| CAG00327 | MH0348_GL0010939 | SEQ ID NO: 884 |
| CAG00327 | MH0373_GL0012294 | SEQ ID NO: 885 |
| CAG00327 | MH0448_GL0074435 | SEQ ID NO: 886 |
| CAG00327 | V1.UC26-4_GL0005764 | SEQ ID NO: 887 |
| CAG00327 | O2.UC52-0_GL0057691 | SEQ ID NO: 888 |
| CAG00327 | V1.UC26-4_GL0145819 | SEQ ID NO: 889 |
| CAG00327 | V1.FI17_GL0032281 | SEQ ID NO: 890 |
| CAG00327 | V1.UC26-4_GL0185580 | SEQ ID NO: 891 |
| CAG00327 | V1.FI17_GL0175729 | SEQ ID NO: 892 |
| CAG00327 | V1.UC26-4_GL0030591 | SEQ ID NO: 893 |
| CAG00327 | MH0343_GL0081662 | SEQ ID NO: 894 |
| CAG00327 | MH0348_GL0118307 | SEQ ID NO: 895 |
| CAG00327 | V1.UC26-4_GL0004865 | SEQ ID NO: 896 |
| CAG00327 | V1.UC26-4_GL0083941 | SEQ ID NO: 897 |
| CAG00327 | V1.UC26-4_GL0101656 | SEQ ID NO: 898 |
| CAG00327 | MH0348_GL0087364 | SEQ ID NO: 899 |
| CAG00327 | V1.FI17_GL0122971 | SEQ ID NO: 900 |
| CAG00327 | MH0372_GL0069396 | SEQ ID NO: 901 |
| CAG00327 | MH0366_GL0119156 | SEQ ID NO: 902 |
| CAG00327 | MH0372_GL0071516 | SEQ ID NO: 903 |
| CAG00327 | MH0348_GL0064411 | SEQ ID NO: 904 |
| CAG00327 | MH0343_GL0166170 | SEQ ID NO: 905 |
| CAG00327 | V1.UC26-4_GL0076251 | SEQ ID NO: 906 |
| CAG00327 | MH0343_GL0092435 | SEQ ID NO: 907 |
| CAG00327 | V1.FI17_GL0016953 | SEQ ID NO: 908 |
| CAG00327 | V1.UC26-4_GL0143205 | SEQ ID NO: 909 |
| CAG00327 | MH0372_GL0055320 | SEQ ID NO: 910 |

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|---|---|---|
| CAG00327 | V1.UC26-4_GL0055452 | SEQ ID NO: 911 |
| CAG00327 | M H0348_G L0106302 | SEQ ID NO: 912 |
| CAG00327 | M H0372_G L0097771 | SEQ ID NO: 913 |
| CAG00327 | 764062976-stooll_revised_scaffold l2924_l_genel47101 | SEQ ID NO: 914 |
| CAG00327 | O2. UC48-l_G L0017424 | SEQ ID NO: 915 |
| CAG00327 | O2. UC48-l_G L0207849 | SEQ ID NO: 916 |
| CAG00327 | V1.FI 17_G L0115 124 | SEQ ID NO: 917 |
| CAG00327 | M H0203_G L0130549 | SEQ ID NO: 918 |
| CAG00327 | V1.UC26-4_GL0093892 | SEQ ID NO: 919 |
| CAG00327 | M H0348_G L0072323 | SEQ ID NO: 920 |
| CAG00327 | M H0348_G L0058041 | SEQ ID NO: 921 |
| CAG00327 | 764062976-stooll_revised_scaffold30750_l_genel62103 | SEQ ID NO: 922 |
| CAG00327 | 764062976-stooll_revised_scaffold4128_l_gene64730 | SEQ ID NO: 923 |
| CAG00327 | M H0343_G L0169255 | SEQ ID NO: 924 |
| CAG00327 | M H0343_G L00933 10 | SEQ ID NO: 925 |
| CAG00327 | V1.UC26-4_GL0016002 | SEQ ID NO: 926 |
| CAG00659 | O2. UC48-0_G L0168719 | SEQ ID NO: 927 |
| CAG00659 | V1.UC55-0_GL0148491 | SEQ ID NO: 928 |
| CAG00659 | V1.UC55-0_GL0157646 | SEQ ID NO: 929 |
| CAG00659 | O2. UC48-0_G L0022850 | SEQ ID NO: 930 |
| CAG00659 | V1.UC55-0_GL0065136 | SEQ ID NO: 931 |
| CAG00659 | V1.UC55-0_GL0003249 | SEQ ID NO: 932 |
| CAG00659 | O2. UC48-0_G L0232704 | SEQ ID NO: 933 |
| CAG00659 | V1.UC55-0_GL0081417 | SEQ ID NO: 934 |
| CAG00659 | V1.UC55-0_GL0120641 | SEQ ID NO: 935 |
| CAG00659 | V1.UC55-0_GL0068968 | SEQ ID NO: 936 |
| CAG00659 | V1.UC55-0_GL0134495 | SEQ ID NO: 937 |
| CAG00659 | O2. UC48-0_G L0312586 | SEQ ID NO: 938 |
| CAG00659 | V1.UC55-0_GL0136172 | SEQ ID NO: 939 |
| CAG00659 | V1.UC55-0_GL0132419 | SEQ ID NO: 940 |
| CAG00659 | V1.UC55-0_GL0141266 | SEQ ID NO: 941 |
| CAG00659 | V1.UC55-0_GL0038453 | SEQ ID NO: 942 |
| CAG00659 | O2. UC48-0_G L0001916 | SEQ ID NO: 943 |
| CAG00659 | V1.UC55-0_GL0168942 | SEQ ID NO: 944 |
| CAG00659 | V1.UC55-0_GL0011960 | SEQ ID NO: 945 |
| CAG00659 | O2. UC48-0_G L0003471 | SEQ ID NO: 946 |
| CAG00659 | V1.UC55-0_GL0028121 | SEQ ID NO: 947 |
| CAG00659 | O2. UC48-0_G L0286932 | SEQ ID NO: 948 |
| CAG00659 | V1.UC55-0_GL0085245 | SEQ ID NO: 949 |

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|---|---|---|
| CAG00659 | V1.UC55-0_GL0230349 | SEQ ID NO: 950 |
| CAG00659 | V1.UC55-0_GL0020063 | SEQ ID NO: 951 |
| CAG00659 | V1.UC55-0_GL0185502 | SEQ ID NO: 952 |
| CAG00659 | O2. UC48-0_G L0167135 | SEQ ID NO: 953 |
| CAG00659 | V1.UC55-0_GL0188691 | SEQ ID NO: 954 |
| CAG00659 | V1.UC55-0_GL0039924 | SEQ ID NO: 955 |
| CAG00659 | O2. UC48-0_G L0301463 | SEQ ID NO: 956 |
| CAG00659 | V1.UC55-0_GL0135343 | SEQ ID NO: 957 |
| CAG00659 | O2. UC48-0_G L0045674 | SEQ ID NO: 958 |
| CAG00659 | V1.UC55-0_GL0250090 | SEQ ID NO: 959 |
| CAG00659 | V1.UC55-0_GL0100024 | SEQ ID NO: 960 |
| CAG00659 | V1.UC55-0_GL0027986 | SEQ ID NO: 961 |
| CAG00659 | V1.UC55-0_GL0144487 | SEQ ID NO: 962 |
| CAG00659 | O2. UC48-0_G L0091878 | SEQ ID NO: 963 |
| CAG00659 | V1.UC55-0_GL0027028 | SEQ ID NO: 964 |
| CAG00659 | O2. UC48-0_G L0166121 | SEQ ID NO: 965 |
| CAG00659 | V1.UC55-0_GL0002100 | SEQ ID NO: 966 |
| CAG00659 | V1.UC55-0_GL0248648 | SEQ ID NO: 967 |
| CAG00659 | V1.UC55-0_GL0200340 | SEQ ID NO: 968 |
| CAG00659 | V1.UC55-0_GL0184665 | SEQ ID NO: 969 |
| CAG00659 | V1.UC55-0_GL0206589 | SEQ ID NO: 970 |
| CAG00659 | V1.UC55-0_GL0195608 | SEQ ID NO: 971 |
| CAG00659 | V1.UC55-0_GL0195112 | SEQ ID NO: 972 |
| CAG00659 | O2. UC48-0_G L0293274 | SEQ ID NO: 973 |
| CAG00659 | V1.UC55-0_GL0148492 | SEQ ID NO: 974 |
| CAG00659 | V1.UC55-0_GL0095333 | SEQ ID NO: 975 |
| CAG00659 | O2. UC48-0_G L0215527 | SEQ ID NO: 976 |
| CAG00492 | V1.FI 17_G L0043088 | SEQ ID NO: 977 |
| CAG00492 | M H0348_G L0110975 | SEQ ID NO: 978 |
| CAG00492 | M H0348_G L0058897 | SEQ ID NO: 979 |
| CAG00492 | M H0348_G L01295 12 | SEQ ID NO: 980 |
| CAG00492 | V1.CD46-0_GL0039934 | SEQ ID NO: 981 |
| CAG00492 | V1.CD46-0_GL0064253 | SEQ ID NO: 982 |
| CAG00492 | V1.CD46-0_GL0117608 | SEQ ID NO: 983 |
| CAG00492 | V1.FI08_G L0017847 | SEQ ID NO: 984 |
| CAG00492 | M H0373_G L0129260 | SEQ ID NO: 985 |
| CAG00492 | V1.CD46-0_GL0075229 | SEQ ID NO: 986 |
| CAG00492 | V1.CD46-0_GL0136740 | SEQ ID NO: 987 |
| CAG00492 | M H0348_G L0008929 | SEQ ID NO: 988 |
| CAG00492 | V1.CD46-0_GL0135816 | SEQ ID NO: 989 |
| CAG00492 | V1.CD46-0_GL0068552 | SEQ ID NO: 990 |

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|---|---|---|
| CAG00492 | V1.CD46-0_GL0077963 | SEQ ID NO: 991 |
| CAG00492 | M H0348_G L0074142 | SEQ ID NO: 992 |
| CAG00492 | V1.FI08_G L0104771 | SEQ ID NO: 993 |
| CAG00492 | V1.FI 17_G L0153 167 | SEQ ID NO: 994 |
| CAG00492 | M H0348_G L0055971 | SEQ ID NO: 995 |
| CAG00492 | V1.FI08_G L0146851 | SEQ ID NO: 996 |
| CAG00492 | V1.FI08_G L0053807 | SEQ ID NO: 997 |
| CAG00492 | V1.CD46-0_GL0112049 | SEQ ID NO: 998 |
| CAG00492 | V1.CD46-0_GL0089014 | SEQ ID NO: 999 |
| CAG00492 | M H0348_G L0053234 | SEQ ID NO: 1000 |
| CAG00492 | V1.FI08_G L0145379 | SEQ ID NO: 1001 |
| CAG00492 | V1.FI08_G L0165033 | SEQ ID NO: 1002 |
| CAG00492 | V1.FI08_G L0008571 | SEQ ID NO: 1003 |
| CAG00492 | V1.FI08_G L0166887 | SEQ ID NO: 1004 |
| CAG00492 | V1.FI 17_G L0066347 | SEQ ID NO: 1005 |
| CAG00492 | M H0348_G L0136454 | SEQ ID NO: 1006 |
| CAG00492 | V1.FI08_G L0087488 | SEQ ID NO: 1007 |
| CAG00492 | M H0348_G L0023440 | SEQ ID NO: 1008 |
| CAG00492 | V1.FI08_G L0138599 | SEQ ID NO: 1009 |
| CAG00492 | V1.FI08_G L0073 194 | SEQ ID NO: 1010 |
| CAG00492 | V1.FI08_G L0127100 | SEQ ID NO: 1011 |
| CAG00492 | M H0348_G L0136728 | SEQ ID NO: 1012 |
| CAG00492 | V1.FI08_G L0073404 | SEQ ID NO: 1013 |
| CAG00492 | M H0348_G L0118964 | SEQ ID NO: 1014 |
| CAG00492 | V1.FI08_G L013 1066 | SEQ ID NO: 1015 |
| CAG00492 | V1.FI08_G L0136903 | SEQ ID NO: 1016 |
| CAG00492 | V1.CD46-0_GL014103 1 | SEQ ID NO: 1017 |
| CAG00492 | M H0348_G L0074552 | SEQ ID NO: 1018 |
| CAG00492 | M H0373_G L0093766 | SEQ ID NO: 1019 |
| CAG00492 | V1.FI 17_G L0041765 | SEQ ID NO: 1020 |
| CAG00492 | V1.FI08_G L0036958 | SEQ ID NO: 1021 |
| CAG00492 | V1.FI08_G L0034796 | SEQ ID NO: 1022 |
| CAG00492 | V1.FI08_G L0141490 | SEQ ID NO: 1023 |
| CAG00492 | M H0348_G L0038049 | SEQ ID NO: 1024 |
| CAG00492 | V1.CD46-0_GL0006897 | SEQ ID NO: 1025 |
| CAG00492 | M H0348_G L0128273 | SEQ ID NO: 1026 |
| CAG00518 | V1.FI 17_G L0223 127 | SEQ ID NO: 1027 |
| CAG00518 | V1.FI 17_G L0056536 | SEQ ID NO: 1028 |
| CAG00518 | V1.FI 17_G L015 1283 | SEQ ID NO: 1029 |
| CAG00518 | V1.FI 17_G L0105002 | SEQ ID NO: 1030 |
| CAG00518 | V1.FI 17_G L0034777 | SEQ ID NO: 1031 |

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|---|---|---|
| CAG00518 | V1.FI 17_G L0056308 | SEQ ID NO: 1032 |
| CAG00518 | V1.FI 17_G L0174918 | SEQ ID NO: 1033 |
| CAG00518 | V1.FI 17_G L0222796 | SEQ ID NO: 1034 |
| CAG00518 | V1.FI 17_G L0067073 | SEQ ID NO: 1035 |
| CAG00518 | V1.FI 17_G L0178176 | SEQ ID NO: 1036 |
| CAG00518 | V1.FI 17_G L0179703 | SEQ ID NO: 1037 |
| CAG00518 | V1.FI 17_G L0189443 | SEQ ID NO: 1038 |
| CAG00518 | V1.FI 17_G L0084116 | SEQ ID NO: 1039 |
| CAG00518 | V1.FI 17_G L0170320 | SEQ ID NO: 1040 |
| CAG00518 | V1.FI 17_G L0172798 | SEQ ID NO: 1041 |
| CAG00518 | V1.FI 17_G L0080116 | SEQ ID NO: 1042 |
| CAG00518 | V1.FI 17_G L0064860 | SEQ ID NO: 1043 |
| CAG00518 | V1.FI 17_G L0005908 | SEQ ID NO: 1044 |
| CAG00518 | V1.FI 17_G L0081029 | SEQ ID NO: 1045 |
| CAG00518 | V1.FI 17_G L0123216 | SEQ ID NO: 1046 |
| CAG00518 | V1.FI 17_G L0049498 | SEQ ID NO: 1047 |
| CAG00518 | V1.FI 17_G L0096107 | SEQ ID NO: 1048 |
| CAG00518 | V1.FI 17_G L0145670 | SEQ ID NO: 1049 |
| CAG00518 | V1.FI 17_G L0095433 | SEQ ID NO: 1050 |
| CAG00518 | V1.FI 17_G L0098541 | SEQ ID NO: 1051 |
| CAG00518 | V1.FI 17_G L0213327 | SEQ ID NO: 1052 |
| CAG00518 | V1.FI 17_G L0026647 | SEQ ID NO: 1053 |
| CAG00518 | V1.FI 17_G L0130881 | SEQ ID NO: 1054 |
| CAG00518 | V1.FI 17_G L0119514 | SEQ ID NO: 1055 |
| CAG00518 | V1.FI 17_G L0152624 | SEQ ID NO: 1056 |
| CAG00518 | V1.FI 17_G L0230043 | SEQ ID NO: 1057 |
| CAG00518 | V1.FI 17_G L0084105 | SEQ ID NO: 1058 |
| CAG00518 | V1.FI 17_G L0054899 | SEQ ID NO: 1059 |
| CAG00518 | V1.FI 17_G L0090574 | SEQ ID NO: 1060 |
| CAG00518 | V1.FI 17_G L0214395 | SEQ ID NO: 1061 |
| CAG00518 | V1.FI 17_G L0220845 | SEQ ID NO: 1062 |
| CAG00518 | V1.FI 17_G L0050024 | SEQ ID NO: 1063 |
| CAG00518 | V1.FI 17_G L0207008 | SEQ ID NO: 1064 |
| CAG00518 | V1.FI 17_G L0147404 | SEQ ID NO: 1065 |
| CAG00518 | V1.FI 17_G L0175 176 | SEQ ID NO: 1066 |
| CAG00518 | V1.FI 17_G L0023 173 | SEQ ID NO: 1067 |
| CAG00518 | V1.FI 17_G L0177478 | SEQ ID NO: 1068 |
| CAG00518 | V1.FI 17_G L0061078 | SEQ ID NO: 1069 |
| CAG00518 | V1.FI 17_G L0039499 | SEQ ID NO: 1070 |
| CAG00518 | V1.FI 17_G L0091846 | SEQ ID NO: 1071 |
| CAG00518 | V1.FI 17_G L0224471 | SEQ ID NO: 1072 |

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|---|---|---|
| CAG00518 | V1.FI 17_G L0118783 | SEQ ID NO: 1073 |
| CAG00518 | V1.FI 17_G L0056307 | SEQ ID NO: 1074 |
| CAG00518 | V1.FI 17_G L0088351 | SEQ ID NO: 1075 |
| CAG00518 | V1.FI 17_G L0073252 | SEQ ID NO: 1076 |
| CAG01146 | V1.FI28_G L0195377 | SEQ ID NO: 1077 |
| CAG01146 | O2. UC49-0_G L0025609 | SEQ ID NO: 1078 |
| CAG01146 | V1.UC38-4_GL0044141 | SEQ ID NO: 1079 |
| CAG01146 | V1.UC38-4_GL0021935 | SEQ ID NO: 1080 |
| CAG01146 | O2. UC35-l_G L0026285 | SEQ ID NO: 1081 |
| CAG01146 | V1.FI06_G L0004599 | SEQ ID NO: 1082 |
| CAG01146 | V1.UC38-4_GL0034407 | SEQ ID NO: 1083 |
| CAG01146 | V1.UC38-4_GL0057326 | SEQ ID NO: 1084 |
| CAG01146 | O2. UC36-l_G L0134634 | SEQ ID NO: 1085 |
| CAG01146 | V1.UC38-4_GL0088839 | SEQ ID NO: 1086 |
| CAG01146 | V1.FI34_G L0143 132 | SEQ ID NO: 1087 |
| CAG01146 | V1.UC38-0_GL0106709 | SEQ ID NO: 1088 |
| CAG01146 | V1.UC38-4_GL0027899 | SEQ ID NO: 1089 |
| CAG01146 | V1.FI06_G L0061656 | SEQ ID NO: 1090 |
| CAG01146 | O2. UC35-l_G L0054016 | SEQ ID NO: 1091 |
| CAG01146 | V1.UC38-0_GL0104749 | SEQ ID NO: 1092 |
| CAG01146 | V1.UC38-4_GL0045647 | SEQ ID NO: 1093 |
| CAG01146 | V1.UC38-4_GL0072341 | SEQ ID NO: 1094 |
| CAG01146 | V1.UC38-0_GL0057730 | SEQ ID NO: 1095 |
| CAG01146 | V1.FI28_G L0124663 | SEQ ID NO: 1096 |
| CAG01146 | V1.UC38-0_GL0040549 | SEQ ID NO: 1097 |
| CAG01146 | V1.FI06_G L0139057 | SEQ ID NO: 1098 |
| CAG01146 | O2. UC35-l_G L0063806 | SEQ ID NO: 1099 |
| CAG01146 | V1.UC38-0_GL0149389 | SEQ ID NO: 1100 |
| CAG01146 | V1.UC38-4_GL0071470 | SEQ ID NO: 1101 |
| CAG01146 | V1.FI06_G L005 1314 | SEQ ID NO: 1102 |
| CAG01146 | O2. UC35-l_G L0076721 | SEQ ID NO: 1103 |
| CAG01146 | V1.UC38-4_GL0050715 | SEQ ID NO: 1104 |
| CAG01146 | V1.FI28_G L0211259 | SEQ ID NO: 1105 |
| CAG01146 | V1.UC11-0_GL0036916 | SEQ ID NO: 1106 |
| CAG01146 | V1.UC38-0_GL0052356 | SEQ ID NO: 1107 |
| CAG01146 | V1.UC38-4_GL0065035 | SEQ ID NO: 1108 |
| CAG01146 | O2. UC49-0_G L0018610 | SEQ ID NO: 1109 |
| CAG01146 | V1.UC38-4_GL00563 19 | SEQ ID NO: 1110 |
| CAG01146 | O2. UC49-0_G L0158507 | SEQ ID NO: 1111 |
| CAG01146 | V1.UC38-0_GL0073167 | SEQ ID NO: 1112 |
| CAG01146 | O2. UC35-l_G L0026564 | SEQ ID NO: 1113 |

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|---|---|---|
| CAG01146 | V1.UC38-4_GL0006756 | SEQ ID NO: 1114 |
| CAG01146 | V1.FI28_G L005 1866 | SEQ ID NO: 1115 |
| CAG01146 | V1.UC38-0_GL0081759 | SEQ ID NO: 1116 |
| CAG01146 | V1.UC11-0_GL0026546 | SEQ ID NO: 1117 |
| CAG01146 | V1.UC38-4_GL0091721 | SEQ ID NO: 1118 |
| CAG01146 | V1.FI28_G L0206130 | SEQ ID NO: 1119 |
| CAG01146 | V1.UC38-0_GL0013101 | SEQ ID NO: 1120 |
| CAG01146 | V1.UC38-4_GL0061996 | SEQ ID NO: 1121 |
| CAG01146 | V1.UC38-4_GL0142563 | SEQ ID NO: 1122 |
| CAG01146 | V1.UC38-4_GL0156200 | SEQ ID NO: 1123 |
| CAG01146 | V1.FI06_G L0070368 | SEQ ID NO: 1124 |
| CAG01146 | V1.UC38-4_GL0162695 | SEQ ID NO: 1125 |
| CAG01146 | O2. UCll-l_G L0117762 | SEQ ID NO: 1126 |
| CAG00079 | N017A_G L0059153 | SEQ ID NO: 1127 |
| CAG00079 | SZEY-104A_GL0060090 | SEQ ID NO: 1128 |
| CAG00079 | M H0020_G L0000529 | SEQ ID NO: 1129 |
| CAG00079 | M H0301_G L0097161 | SEQ ID NO: 1130 |
| CAG00079 | M H0006_G L0148832 | SEQ ID NO: 1131 |
| CAG00079 | M H0006_G L0157059 | SEQ ID NO: 1132 |
| CAG00079 | M H0087_G L0033669 | SEQ ID NO: 1133 |
| CAG00079 | M H0087_G L0001927 | SEQ ID NO: 1134 |
| CAG00079 | M H0006_G L0200708 | SEQ ID NO: 1135 |
| CAG00079 | M H0006_G L0085266 | SEQ ID NO: 1136 |
| CAG00079 | V1.CD11-0_GL0023861 | SEQ ID NO: 1137 |
| CAG00079 | M H0087_G L0026189 | SEQ ID NO: 1138 |
| CAG00079 | M H0020_G L0009728 | SEQ ID NO: 1139 |
| CAG00079 | M H0305_G L0021042 | SEQ ID NO: 1140 |
| CAG00079 | M H0087_G LOO 14945 | SEQ ID NO: 1141 |
| CAG00079 | M H0087_G L0048780 | SEQ ID NO: 1142 |
| CAG00079 | M H0087_G L0025847 | SEQ ID NO: 1143 |
| CAG00079 | M H0109_G L0086398 | SEQ ID NO: 1144 |
| CAG00079 | SZEY-64A_GL0001256 | SEQ ID NO: 1145 |
| CAG00079 | M H0006_G L0111726 | SEQ ID NO: 1146 |
| CAG00079 | M H0420_G L0006194 | SEQ ID NO: 1147 |
| CAG00079 | M H0074_G L0014285 | SEQ ID NO: 1148 |
| CAG00079 | M H0006_G L0100867 | SEQ ID NO: 1149 |
| CAG00079 | SZEY-78A_GL0051586 | SEQ ID NO: 1150 |
| CAG00079 | M H0087_G L0041527 | SEQ ID NO: 1151 |
| CAG00079 | M H0274_G L0125787 | SEQ ID NO: 1152 |
| CAG00079 | M H0087_G L0010722 | SEQ ID NO: 1153 |
| CAG00079 | M H0006_G L0161952 | SEQ ID NO: 1154 |

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| CAG00766 | O2. UC40-l_G L0192463 | SEQ ID NO: 1269 |
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| CAG01366 | M H0003_G L0070887 | SEQ ID NO: 2644 |
| CAG01366 | M H0003_G L0097555 | SEQ ID NO: 2645 |
| CAG01366 | M H0003_G L0075033 | SEQ ID NO: 2646 |
| CAG01366 | 760570. HM PREF0833_10311 | SEQ ID NO: 2647 |
| CAG01366 | M H0003_G L0050527 | SEQ ID NO: 2648 |
| CAG01366 | M H0003_G L0070890 | SEQ ID NO: 2649 |
| CAG01366 | M H0003_G L0075034 | SEQ ID NO: 2650 |
| CAG01366 | M H0003_G L0114233 | SEQ ID NO: 2651 |
| CAG01366 | NLM027_G L0005333 | SEQ ID NO: 2652 |
| CAG01366 | M H0003_G L0002987 | SEQ ID NO: 2653 |
| CAG01366 | M H0003_G L0088953 | SEQ ID NO: 2654 |
| CAG01366 | M H0003_G L0042367 | SEQ ID NO: 2655 |
| CAG01366 | M H0287_G L0136304 | SEQ ID NO: 2656 |
| CAG01366 | M H0003_G L0039649 | SEQ ID NO: 2657 |

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|---|---|---|
| **CAG01366** | **MH0003_GL0046477** | SEQ ID NO: 2658 |
| **CAG01366** | **MH0003_GL0001128** | SEQ ID NO: 2659 |
| **CAG01366** | **MH0003_GL0029627** | SEQ ID NO: 2660 |
| **CAG01366** | **MH0003_GL0036396** | SEQ ID NO: 2661 |
| **CAG01366** | **MH0003_GL0037301** | SEQ ID NO: 2662 |
| **CAG01366** | **MH0287_GL0182172** | SEQ ID NO: 2663 |
| **CAG01366** | **MH0003_GL0024528** | SEQ ID NO: 2664 |
| **CAG01366** | **MH0003_GL0046587** | SEQ ID NO: 2665 |
| **CAG01366** | **760570.HMPREF0833_11647** | SEQ ID NO: 2666 |
| **CAG01366** | **MH0003_GL0009545** | SEQ ID NO: 2667 |
| **CAG01366** | **MH0003_GL0087011** | SEQ ID NO: 2668 |
| **CAG01366** | **760570.HMPREF0833_10973** | SEQ ID NO: 2669 |
| **CAG01366** | **MH0003_GL0103117** | SEQ ID NO: 2670 |
| **CAG01366** | **MH0003_GL0114020** | SEQ ID NO: 2671 |
| **CAG01366** | **MH0003_GL0088954** | SEQ ID NO: 2672 |
| **CAG01366** | **MH0003_GL0079951** | SEQ ID NO: 2673 |
| **CAG01366** | **MH0003_GL0034625** | SEQ ID NO: 2674 |
| **CAG01366** | **ED9A_GL0070789** | SEQ ID NO: 2675 |
| **CAG01366** | **MH0003_GL0078182** | SEQ ID NO: 2676 |

**[00116]** The present disclosure also provides a pharmaceutical composition comprising one or more microbial cultures as described above. The bacterial species therefore are present in the dose form as live bacteria, whether in dried, lyophilized, or sporolated form. This may be preferably adapted for suitable administration; for example, in tablet or powder form, potentially with an enteric coating, for oral treatment.

**[00117]** In particular aspects, the composition is formulated for oral administration. Oral administration may be achieved using a chewable formulation, a dissolving formulation, an encapsulated/coated formulation, a multi-layered lozenge (to separate active ingredients and/or active ingredients and excipients), a slow release/timed release formulation, or other suitable formulations known to persons skilled in the art. Although the word "tablet" is used herein, the formulation may take a variety of physical forms that may commonly be referred to by other terms, such as lozenge, pill, capsule, or the like.

**[00118]** While the compositions of the present disclosure are preferably formulated for oral administration, other routes of administration can be employed, however, including, but

not limited to, subcutaneous, intramuscular, intradermal, transdermal, intraocular, intraperitoneal, mucosal, vaginal, rectal, and intravenous.

**[00119]** The desired dose of the composition of the present disclosure may be presented in multiple *(e.g.,* two, three, four, five, six, or more) sub-doses administered at appropriate intervals throughout the day.

**[00120]** In one aspect, the disclosed composition may be prepared as a capsule. The capsule *(i.e.,* the carrier) may be a hollow, generally cylindrical capsule formed from various substances, such as gelatin, cellulose, carbohydrate or the like.

**[00121]** In another aspect, the disclosed composition may be prepared as a suppository. The suppository may include but is not limited to the bacteria and one or more carriers, such as polyethylene glycol, acacia, acetylated monoglycerides, carnuba wax, cellulose acetate phthalate, corn starch, dibutyl phthalate, docusate sodium, gelatin, glycerin, iron oxides, kaolin, lactose, magnesium stearate, methyl paraben, pharmaceutical glaze, povidone, propyl paraben, sodium benzoate, sorbitan monoleate, sucrose talc, titanium dioxide, white wax and coloring agents.

**[00122]** In some aspects, the disclosed probiotic may be prepared as a tablet. The tablet may include the bacteria and one or more tableting agents *(i.e.,* carriers), such as dibasic calcium phosphate, stearic acid, croscarmellose, silica, cellulose and cellulose coating. The tablets may be formed using a direct compression process, though those skilled in the art will appreciate that various techniques may be used to form the tablets.

**[00123]** In other aspects, the disclosed probiotic may be formed as food or drink or, alternatively, as an additive to food or drink, wherein an appropriate quantity of bacteria is added to the food or drink to render the food or drink the carrier.

**[00124]** The probiotic compositions of the present disclosure may further comprise one or more prebiotics known in the art, such as lactitol, inulin, or a combination thereof.

**[00125]** In some embodiments, the compositions of the embodiments comprise one or more of the species of bacteria that produce short chain fatty acids. In particular aspects, the

species of bacteria produce butyrate. For example, the bacterial population can comprise one or more bacterial species of the order Clostridiales. The Clostridiales bacteria may be substantially in spore form. In particular aspects, the bacterial species is from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriacease. In some embodiments, the Clostridiales bacteria comprise a first family and a second family. In some embodiments, the first family is selected from the group consisting of Ruminococcaceae, Christensenellaceae, Clostridiaceae and Coriobacteriacease, and the second family is not identical to the first family. Examples of bacterial species include, but are not limited to, *Faecalibacterium prausnitzii, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus flavefaciens, Ruminococcus champanellensis, Ruminococcus faecis, Ruminococcus gauvreauii, Ruminococcus gnavus, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus lactaris, Ruminococcus luti , Ruminococcus obeum, Ruminococcus palustris , Ruminococcus pasteurii, Ruminococcus productus, Ruminococcus schinkii, Ruminococcus torques, Subdoligranulum variabile, Butyrivibrio fibrisolvens, Roseburia intestinalis, Anaerostipes caccae, Blautia obeum, Eubacterium nodatum,* and *Eubacterium oxidoreducens.* In particular aspects, the bacterial species is *Faecalibacterium prausnitzii.* In certain embodiments, the bacterial population does not comprise bacterial species of the class Bacteroidia or family Prevotellaceae.

**[00126]** In some embodiments, the bacterial population comprises bacteria of the order Clostridiales in an amount effective or sufficient to produce one or more metabolites capable of enhancing immune checkpoint therapy in the subject. In some embodiments, the one or more metabolites comprise a short chain fatty acid. In particular aspects, the short chain fatty acid is butyrate. In some embodiments, the order Clostridiales produce one or more short chain fatty acids *{e.g.,* butyrate) in an effective amount to increase the local short chain fatty acid concentration by 2-fold, 4-fold, 5-fold, 10-fold, 50-fold, 100-fold, 1000-fold, or over 1000-fold.

**[00127]** In some embodiments, the probiotic composition may further comprise a food or a nutritional supplement effective to stimulate the growth of bacteria of the order Clostridiales present in the gastrointestinal tract of the subject. In some embodiments, the nutritional supplement is produced by a bacterium associated with a healthy human gut microbiome. In certain embodiments, the nutritional supplement is produced by bacteria of the

order Clostridiales. In certain embodiments, the nutritional supplement comprises a short chain fatty acid. In certain embodiments, the short chain fatty acid is selected from butyrate, propionate, or a combination thereof. In particular embodiments, the short chain fatty acid is butyrate.

**[00128]** Accordingly, certain embodiments of the present disclosure concern administering butyrate prodrugs or salts to a subject who has been or is currently being administered an immune checkpoint inhibitor. For example, the butyrate may be sodium butyrate, arginine butyrate, ethylbutyryl lactate, tributyrin, 4-phenyl butyrate, AN-9 or AN-10. Prodrugs and salts of butyrate have been described in WO 96/15660 and in U.S. Patent No. 5,763,488, the disclosures of which are herein incorporated by reference. Other orally available prodrugs and salts of butyrate that may be admnistered include, but are not limited to, isobutyramide, 1-octyl butyrate, orthonitrobenzyl butyrate, monobutyrate-3- monoacetone glucose, monobutyrate-l-monoacetone mannose, monobutyrate xylitol, isobutyramide, 4- phenylbutyrate, and 4-phenyl acetate. Each of these compounds releases butyrate or a butyrate analog into the blood stream upon administration. One or more isoforms of butyrate can include butyl butyrate, amyl butyrate, isobutyl butyrate, benzyl butyrate, a-methylbenzyl butyrate, hexyl butyrate, heptyl butyrate, pennetyl butyrate, methyl butyrate, and 2-hydroxy-3-methylbutanoic acid.

**[00129]** In further embodiments, the present disclosure concerns methods of obtaining a microbiome profile, comprising the steps of: i) obtaining a sample obtained from a subject *(e.g.,* a human subject), ii) isolating one or more bacterial species from the sample, iii) isolating one or more nucleic acids from at least one bacterial species, iv) sequencing the isolated nucleic acids, and v) comparing the sequenced nucleic acids to a reference nucleic acid sequence. When performing the methods necessitating genotyping, any genotyping assay can be used. For example, this can be done by sequencing the 16S or the 23S ribosomal subunit or by metagenomics shotgun DNA sequencing associated with metatranscriptomics. The biological sample may be selected from the group comprising: whole blood, blood plasma, urine, tears, semen, saliva, buccal mucosa, interstitial fluid, lymph fluid, meningeal fluid, amniotic fluid, glandular fluid, sputum, feces, perspiration, mucous, vaginal secretion, cerebrospinal fluid, hair, skin, fecal material, wound exudate, wound homogenate, and wound fluid. In particular aspects, the sample is fecal material or a buccal sample.

**[00130]** In some embodiments, the microbiome profile is identified to be favorable for immune checkpoint therapy. A favorable microbial profile would have a high relative abundance of one or more bacterial species from the phylum Firmicutes, class Clostridia, order Clostridiales, family Ruminococcaceae, genus *Ruminococcus*, genus *Hydrogenoanaerobacterium*, genus *Faecalibacterium*, phylum Actinobacteria, class Coriobacteriia, order Coriaobacteriales, family Coriobacteriaceae, domain Archaea, phylum Cyanobacteria, phylum Euryarchaeota or famly Christensenellaceae. A favorable microbial profile would have a low relative abundance of bacteria from the genus *Dialister*, family Veillonellaceae, phylum Bacteroidetes, class Bacteroida, order Bacteroidales or family Prevotellaceae. Accordingly, a favorable microbial profile would have a higher relative abundance of one or more bacterial species from the phylum Firmicutes, class Clostridia, order Clostridiales, famiy Ruminococcaceae, genus *Ruminococcus*, genus *Hydrogenoanaerobacterium*, phylum Actinobacteria, class Coriobacteria, order Coriaobacteriales, family Coriobacteriaceae, domain Archaea, phylum Cyanobacteria, phylum Euryarchaeota or family Christensenellaceae, and would have a decreased abundance of one or more bacterial species from genus *Dialister*, family Veillonellaceae, phylum Bacteroidetes, class Bacteroida, order Bacteroidales and/or family Prevotellaceae.

## III. Immune Checkpoint Blockade

**[00131]** The present disclosure provides methods of enhancing the efficacy of immune checkpoint blockade by modulating the microbiome of a subject, such as by administering a short-chain fatty acid, such as butyrate, and/or a composition comprising one or more populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria. Immune checkpoints either turn up a signal *(e.g.,* co-stimulatory molecules) or turn down a signal. Inhibitory immune checkpoint molecules that may be targeted by immune checkpoint blockade include adenosine A2A receptor (A2AR), B7-H3 (also known as CD276), B and T lymphocyte attenuator (BTLA), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, also known as CD152), indoleamine 2,3-dioxygenase (IDO), killer-cell immunoglobulin (KIR), lymphocyte activation gene-3 (LAG3), programmed death 1 (PD-1), T-cell immunoglobulin domain and mucin domain 3 (TIM-3) and V-domain Ig suppressor of T cell activation (VISTA). In particular, the immune checkpoint inhibitors target the PD-1 axis and/or CTLA-4.

**[00132]** The immune checkpoint inhibitors may be drugs such as small molecules, recombinant forms of ligand or receptors, or, antibodies, such as human antibodies *(e.g.,* International Patent Publication No. WO2015016718; Pardoll, *Nat Rev Cancer,* 12(4): 252-64, 2012; both incorporated herein by reference). Known inhibitors of the immune checkpoint proteins or analogs thereof may be used, in particular chimerized, humanized or human forms of antibodies may be used. As the skilled person will know, alternative and/or equivalent names may be in use for certain antibodies mentioned in the present disclosure. Such alternative and/or equivalent names are interchangeable in the context of the present invention. For example it is known that lambrolizumab is also known under the alternative and equivalent names MK-3475 and pembrolizumab.

**[00133]** It is contemplated that any of the immune checkpoint inhibitors that are known in the art to stimulate immune responses may be used. This includes inhibitors that directly or indirectly stimulate or enhance antigen-specific T-lymphocytes. These immune checkpoint inhibitors include, without limitation, agents targeting immune checkpoint proteins and pathways involving PD-L2, LAG3, BTLA, B7H4 and TIM3. For example, LAG3 inhibitors known in the art include soluble LAG3 (IMP321, or LAG3-Ig disclosed in WO2009044273) as well as mouse or humanized antibodies blocking human LAG3 *(e.g.,* IMP701 disclosed in WO2008 132601), or fully human antibodies blocking human LAG3 (such as disclosed in EP 2320940). Another example is provided by the use of blocking agents towards BTLA, including without limitation antibodies blocking human BTLA interaction with its ligand (such as 4C7 disclosed in WO201 1014438). Yet another example is provided by the use of agents neutralizing B7H4 including without limitation antibodies to human B7H4 (disclosed in WO 2013025779, and in WO2013067492) or soluble recombinant forms of B7H4 (such as disclosed in US20120177645). Yet another example is provided by agents neutralizing B7-H3, including without limitation antibodies neutralizing human B7-H3 *(e.g.* MGA271 disclosed as BRCA84D and derivatives in US 20120294796). Yet another example is provided by agents targeting TIM3, including without limitation antibodies targeting human TIM3 *(e.g.* as disclosed in WO 2013006490 A2 or the anti-human TIM3, blocking antibody F38-2E2 disclosed by Jones *et al.,* J Exp Med. 2008; 205(12):2763-79).

### A. PD-1 Axis Antagonists

**[00134]** T cell dysfunction or anergy occurs concurrently with an induced and sustained expression of the inhibitory receptor, programmed death 1 polypeptide (PD-1). Thus, therapeutic targeting of PD-1 and other molecules which signal through interactions with PD-1, such as programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) is provided herein. PD-L1 is overexpressed in many cancers and is often associated with poor prognosis (Okazaki T *et al.,* Intern. Immun. 2007 19(7):8 13). Thus, improved methods of treating cancer by inhibiting the PD-L1/PD- 1 interaction in combination with modulating the microbiome is provided herein.

**[00135]** For example, PD-1 axis binding antagonists include a PD-1 binding antagonist, a PDLl binding antagonist and a PDL2 binding antagonist. Alternative names for "PD-1" include CD279 and SLEB2. Alternative names for "PDLl" include B7-H1, B7-4, CD274, and B7-H. Alternative names for "PDL2" include B7-DC, Btdc, and CD273. In some embodiments, PD-1, PDLl, and PDL2 are human PD-1, PDLl and PDL2.

**[00136]** In some embodiments, the PD-1 binding antagonist is a molecule that inhibits the binding of PD-1 to its ligand binding partners. In a specific aspect, the PD-1 ligand binding partners are PDLl and/or PDL2. In another embodiment, a PDLl binding antagonist is a molecule that inhibits the binding of PDLl to its binding partners. In a specific aspect, PDLl binding partners are PD-1 and/or B7-1. In another embodiment, the PDL2 binding antagonist is a molecule that inhibits the binding of PDL2 to its binding partners. In a specific aspect, a PDL2 binding partner is PD- 1. The antagonist may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or oligopeptide. Exemplary antibodies are described in U.S. Patent Nos. US8735553, US8354509, and US8008449, all incorporated herein by reference. Other PD-1 axis antagonists for use in the methods provided herein are known in the art such as described in U.S. Patent Application No. US20140294898, US2014022021, and US201 10008369, all incorporated herein by reference.

**[00137]** In some embodiments, the PD-1 binding antagonist is an anti-PD-1 antibody *{e.g.,* a human antibody, a humanized antibody, or a chimeric antibody). In some embodiments, the anti-PD-1 antibody is selected from the group consisting of nivolumab,

pembrolizumab, and CT-011. In some embodiments, the PD-1 binding antagonist is an immunoadhesin *(e.g.,* an immunoadhesin comprising an extracellular or PD-1 binding portion of PDL1 or PDL2 fused to a constant region *(e.g.,* an Fc region of an immunoglobulin sequence). In some embodiments, the PD-1 binding antagonist is AMP- 224. Nivolumab, also known as MDX-1106-04, MDX-1106, ONO-4538, BMS-936558, and OPDIVO®, is an anti-PD-1 antibody described in WO2006/121168. Pembrolizumab, also known as MK-3475, Merck 3475, lambrolizumab, KEYTRUDA®, and SCH-900475, is an anti-PD-1 antibody described in WO2009/1 14335. CT-011, also known as hBAT or hBAT-1, is an anti-PD-1 antibody described in WO2009/101611. AMP-224, also known as B7-DCIg, is a PDL2-Fc fusion soluble receptor described in WO2010/027827 and WO201 1/066342. Additional PD- 1 binding antagonists include Pidilizumab, also known as CT-011, MEDI0680, also known as AMP-514, and REGN2810.

**[00138]** In some embodiments, the immune checkpoint inhibitor is a PD-L1 antagonist such as Durvalumab, also known as MEDI4736, atezolizumab, also known as MPDL3280A, or avelumab, also known as MSB00010118C. In certain aspects, the immune checkpoint inhibitor is a PD-L2 antagonist such as rHIgM12B7. In some aspects, the immune checkpoint inhibitor is a LAG-3 antagonist such as, but not limited to, IMP321, and BMS-986016. The immune checkpoint inhibitor may be an adenosine A2a receptor (A2aR) antagonist such as PBF-509.

**[00139]** In some embodiments, the antibody described herein (such as an anti-PD-1 antibody, an anti-PDLl antibody, or an anti-PDL2 antibody) further comprises a human or murine constant region. In a still further aspect, the human constant region is selected from the group consisting of IgGl, IgG2, IgG2, IgG3, and IgG4. In a still further specific aspect, the human constant region is IgGl. In a still further aspect, the murine constant region is selected from the group consisting of IgGl, IgG2A, IgG2B, and IgG3. In a still further specific aspect, the antibody has reduced or minimal effector function. In a still further specific aspect, the minimal effector function results from production in prokaryotic cells. In a still further specific aspect the minimal effector function results from an "effector-less Fc mutation" or aglycosylation.

**[00140]** Accordingly, an antibody used herein can be aglycosylated. Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the

carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine- X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxy amino acid, most commonly serine or threonine, although 5- hydroxyproline or 5 -hydroxy lysine may also be used. Removal of glycosylation sites form an antibody is conveniently accomplished by altering the amino acid sequence such that one of the above-described tripeptide sequences (for N-linked glycosylation sites) is removed. The alteration may be made by substitution of an asparagine, serine or threonine residue within the glycosylation site another amino acid residue *(e.g.,* glycine, alanine or a conservative substitution).

**[00141]** The antibody or antigen binding fragment thereof, may be made using methods known in the art, for example, by a process comprising culturing a host cell containing nucleic acid encoding any of the previously described anti-PDLl, anti-PD-1, or anti-PDL2 antibodies or antigen-binding fragment in a form suitable for expression, under conditions suitable to produce such antibody or fragment, and recovering the antibody or fragment.

**B. CTLA-4**

**[00142]** Another immune checkpoint that can be targeted in the methods provided herein is the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), also known as CD152. The complete cDNA sequence of human CTLA-4 has the Genbank accession number L15006. CTLA-4 is found on the surface of T cells and acts as an "off switch when bound to CD80 or CD86 on the surface of antigen-presenting cells. CTLA4 is a member of the immunoglobulin superfamily that is expressed on the surface of Helper T cells and transmits an inhibitory signal to T cells. CTLA4 is similar to the T-cell co-stimulatory protein, CD28, and both molecules bind to CD80 and CD86, also called B7-1 and B7-2 respectively, on antigen-presenting cells. CTLA4 transmits an inhibitory signal to T cells, whereas CD28 transmits a stimulatory signal. Intracellular CTLA4 is also found in regulatory T cells and may be important to their function. T cell activation through the T cell receptor and CD28 leads to increased expression of CTLA-4, an inhibitory receptor for B7 molecules.

**[00143]** In some embodiments, the immune checkpoint inhibitor is an anti-CTLA-4 antibody *(e.g.,* a human antibody, a humanized antibody, or a chimeric antibody), an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or oligopeptide.

**[00144]** Anti-human-CTLA-4 antibodies (or VH and/or VL domains derived therefrom) suitable for use in the present methods can be generated using methods well known in the art. Alternatively, art recognized anti-CTLA-4 antibodies can be used. For example, the anti-CTLA-4 antibodies disclosed in: US 8,119,129, WO 01/14424, WO 98/42752; WO 00/37504 (CP675,206, also known as tremelimumab; formerly ticilimumab), U.S. Patent No. 6,207,156; Hurwitz *et al.,* 1998; can be used in the methods disclosed herein. The teachings of each of the aforementioned publications are hereby incorporated by reference. Antibodies that compete with any of these art-recognized antibodies for binding to CTLA-4 also can be used. For example, a humanized CTLA-4 antibody is described in International Patent Application No. WO2001014424, WO2000037504, and U.S. Patent No. US8017114; all incorporated herein by reference.

**[00145]** An exemplary anti-CTLA-4 antibody is ipilimumab (also known as 10D1, MDX- 010, MDX- 101, and Yervoy®) or antigen binding fragments and variants thereof (see, *e.g.,* WOO 1/14424). In other embodiments, the antibody comprises the heavy and light chain CDRs or VRs of ipilimumab. Accordingly, in one embodiment, the antibody comprises the CDR1, CDR2, and CDR3 domains of the VH region of ipilimumab, and the CDR1, CDR2 and CDR3 domains of the VL region of ipilimumab. In another embodiment, the antibody competes for binding with and/or binds to the same epitope on CTLA-4 as the above- mentioned antibodies. In another embodiment, the antibody has at least about 90% variable region amino acid sequence identity with the above-mentioned antibodies *(e.g.,* at least about 90%, 95%, or 99% variable region identity with ipilimumab).

**[00146]** Other molecules for modulating CTLA-4 include soluble CTLA-4 ligands and receptors such as described in U.S. Patent Nos. US5844905, US5885796 and International Patent Application Nos. WO1995001994 and WO1998042752; all incorporated herein by reference, and immunoadhesins such as described in U.S. Patent No. US8329867, incorporated herein by reference.

### C. Killer Immunoglobulin-like Receptor (KIR)

**[00147]** Another immune checkpoint inhibitor for use in the present disclosure is an anti-KIR antibody. Anti-human- KIR antibodies (or VH/VL domains derived therefrom) suitable for use in the present methods can be generated using methods well known in the art.

**[00148]** Alternatively, art recognized anti-KIR antibodies can be used. The anti-KIR antibody can be cross-reactive with multiple inhibitory KIR receptors and potentiates the cytotoxicity of NK cells bearing one or more of these receptors. For example, the anti-KIR antibody may bind to each of KIR2D2DL1, KIR2DL2, and KIR2DL3, and potentiate NK cell activity by reducing, neutralizing and/or reversing inhibition of NK cell cytotoxicity mediated by any or all of these KIRs. In some aspects, the anti-KIR antibody does not bind KIR2DS4 and/or KIR2DS3. For example, monoclonal antibodies 1-7F9 (also known as IPH2101), 14F1, 1-6F1 and 1-6F5, described in WO 2006/003179, the teachings of which are hereby incorporated by reference, can be used. Antibodies that compete with any of these art-recognized antibodies for binding to KIR also can be used. Additional art-recognized anti-KIR antibodies which can be used include, for example, those disclosed in WO 2005/003 168, WO 2005/009465, WO 2006/072625, WO 2006/072626, WO 2007/042573, WO 2008/084106, WO 2010/065939, WO 2012/071411 and WO 2012/160448.

**[00149]** An exemplary anti-KIR antibody is lirilumab (also referred to as BMS-986015 or IPH2102). In other embodiments, the anti-KIR antibody comprises the heavy and light chain complementarity determining regions (CDRs) or variable regions (VRs) of lirilumab. Accordingly, in one embodiment, the antibody comprises the CDR1, CDR2, and CDR3 domains of the heavy chain variable (VH) region of lirilumab, and the CDR1, CDR2 and CDR3 domains of the light chain variable (VL) region of lirilumab. In another embodiment, the antibody has at least about 90% variable region amino acid sequence identity with lirilumab.

## IV. Methods of Treatment

**[00150]** Provided herein are methods for treating or delaying progression of cancer in an individual comprising administering to the individual an effective or suffcicient amount of a short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate -producing bacteria, to a subject who has been or is currently being

administered immune checkpoint therapy. Also provided herein are methods of selecting subjects who will respond favorably to immune checkpoint therapy by assessing the microbial profile of the subject and administering immune checkpoint inhibitor to a subject identified to have a favorable microbial profile.

**[00151]** In some embodiments, the treatment results in a sustained response in the individual after cessation of the treatment. The methods described herein may find use in treating conditions where enhanced immunogenicity is desired such as increasing tumor immunogenicity for the treatment of cancer. Also provided herein are methods of enhancing immune function such as in an individual having cancer comprising administering to the individual an effective amount of an immune checkpoint inhibitor *(e.g.,* PD-1 axis binding antagonist and/or CTLA-4 antibody) and a short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria. In some embodiments, the individual is a human.

**[00152]** Examples of cancers contemplated for treatment include lung cancer, head and neck cancer, breast cancer, pancreatic cancer, prostate cancer, renal cancer, bone cancer, testicular cancer, cervical cancer, gastrointestinal cancer, lymphomas, pre-neoplastic lesions in the lung, colon cancer, melanoma, metastatic melanoma, basal-cell skin cancer, squamous-cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, and angiosarcoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma, Desmoplastic Melanoma, and bladder cancer.

**[00153]** In some embodiments, the individual has cancer that is resistant (has been demonstrated to be resistant) to one or more anti-cancer therapies. In some embodiments, resistance to anti-cancer therapy includes recurrence of cancer or refractory cancer. Recurrence may refer to the reappearance of cancer, in the original site or a new site, after treatment. In some embodiments, resistance to anti-cancer therapy includes progression of the cancer during treatment with the anti-cancer therapy. In some embodiments, the cancer is at early stage or at late stage.

**[00154]** The individual may have a cancer that expresses (has been shown to express *e.g.,* in a diagnostic test) PD-Ll biomarker. In some embodiments, the patient's cancer expresses low PD-Ll biomarker. In some embodiments, the patient's cancer expresses high PD-Ll biomarker. The PD-Ll biomarker can be detected in the sample using a method selected from the group consisting of FACS, Western blot, ELISA, immunoprecipitation, immunohistochemistry, immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, HPLC, surface plasmon resonance, optical spectroscopy, mass spectrometery, HPLC, qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, and FISH, and combinations thereof.

**[00155]** In some embodiments of the methods of the present disclosure, the cancer has low levels of T cell infiltration. In some embodiments, the cancer has no detectable T cell infiltrate. In some embodiments, the cancer is a non-immunogenic cancer *(e.g.,* non-immunogenic colorectal cancer and/or ovarian cancer). Without being bound by theory, the combination treatment may increase T cell *(e.g.,* $CD4^+$ T cell, $CD8^+$ T cell, memory T cell) priming, activation, proliferation, and/or infiltration relative to prior to the administration of the combination.

### A. Administration

**[00156]** The therapy provided herein comprises administration of an immune checkpoint inhibitor, a prebiotic or probiotic composition comprising a short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria. The therapy may be administered in any suitable manner known in the art. For example, of an immune checkpoint inhibitor *(e.g.,* PD-1 axis binding antagonist and/or CTLA-4 antibody), and a short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, may be administered sequentially (at different times) or concurrently (at the same time). In some embodiments, the one or more immune checkpoint inhibitors are in a separate composition as the probiotic therapy. In some embodiments, the immune checkpoint inhibitor is in the same composition as the probiotic composition.

**[00157]** According to a preferred embodiment, the probiotic bacterial composition is formulated for oral administration. The skilled artisan knows a variety of formulas which can

encompass living or killed microorganisms and which can present as food supplements *(e.g.,* pills, tablets and the like) or as functional food such as drinks or fermented yogurts.

**[00158]** The one or more immune checkpoint inhibitors and the short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, may be administered by the same route of administration or by different routes of administration. In some embodiments, the immune checkpoint inhibitor is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the short-chain fatty acid, such as butyrate, and/or population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In particular aspects, the immune checkpoint inhibitor is administered intravenously and the short-chain fatty acid, such as butyrate, and/or population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, is administered orally. An effective amount of the immune checkpoint inhibitor and the short-chain fatty acid, such as butyrate, and/or population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, may be administered for prevention or treatment of disease. The appropriate dosage of immune checkpoint inhibitor and/or the short-chain fatty acid, such as butyrate, and/or population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria may be determined based on the type of disease to be treated, severity and course of the disease, the clinical condition of the individual, the individual's clinical history and response to the treatment, and the discretion of the attending physician.

**[00159]** For example, the therapeutically effective or sufficient amount of the immune checkpoint inhibitor, such as an antibody and/or short-chain fatty acid, such as butyrate, that is administered to a human will be in the range of about 0.01 to about 50 mg/kg of patient body weight whether by one or more administrations. In some embodiments, the antibody used is about 0.01 to about 45 mg/kg, about 0.01 to about 40 mg/kg, about 0.01 to about 35 mg/kg, about 0.01 to about 30 mg/kg, about 0.01 to about 25 mg/kg, about 0.01 to about 20 mg/kg, about 0.01 to about 15 mg/kg, about 0.01 to about 10 mg/kg, about 0.01 to about 5 mg/kg, or about 0.01 to

about 1 mg/kg administered daily, for example. In some embodiments, the antibody is administered at 15 mg/kg. However, other dosage regimens may be useful. In one embodiment, an anti-PDLl antibody described herein is administered to a human at a dose of about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg or about 1400 mg on day 1 of 21-day cycles. The dose may be administered as a single dose or as multiple doses *(e.g.,* 2 or 3 doses), such as infusions. The progress of this therapy is easily monitored by conventional techniques.

**[00160]** For example, the therapeutically effective or sufficient amount of each of the at least one isolated or purified population of bacteria or each of the at least two isolated or purified populations of bacteria of the probiotic or live bacterial product compositions of the embodiments that is administered to a human will be at least about $1x10^3$ colony forming units (CFU) of bacteria or at least about $1x10^4$ (CFU). In some embodiments, a single dose will contain about $1x10^4$, $1x10^5$, $1x10^6$, $1x10^7$, $1x10^8$, $1x10^9$, $1x10^{10}$, $1x10^{11}$, $1x10^{12}$, $1x10^{13}$, $1x10^{14}$, $1x10^{15}$ or greater than $1x10^{15}$ CFU of bacteria. In specific embodiments, the bacteria are provided in spore form or as sporulated bacteria. In particular embodiments, the concentration of spores of each isolated or purified population of bacteria, for example of each species, subspecies or strain, is $1x10^4$, $1x10^5$, $1x10^6$, $1x10^7$, $1x10^8$, $1x10^9$, $1x10^{10}$, $1x10^{11}$, $1x10^{12}$, $1x10^{13}$, $1x10^{14}$, $1x10^{15}$ or greater than $1x10^{15}$ viable bacterial spores per gram of composition or per administered dose.

**[00161]** Intratumoral injection, or injection into the tumor vasculature is specifically contemplated for discrete, solid, accessible tumors. Local, regional or systemic administration also may be appropriate. For tumors of >4 cm, the volume to be administered will be about 4-10 ml (in particular 10 ml), while for tumors of <4 cm, a volume of about 1-3 ml will be used (in particular 3 ml). Multiple injections delivered as single dose comprise about 0.1 to about 0.5 ml volumes. For example, adenoviral particles may advantageously be contacted by administering multiple injections to the tumor.

**[00162]** Treatment regimens may vary as well, and often depend on tumor type, tumor location, disease progression, and health and age of the patient. Obviously, certain types of tumors will require more aggressive treatment, while at the same time, certain patients cannot

tolerate more taxing protocols. The clinician will be best suited to make such decisions based on the known efficacy and toxicity (if any) of the therapeutic formulations.

**[00163]** In certain embodiments, the tumor being treated may not, at least initially, be resectable. Treatments with therapeutic viral constructs may increase the resectability of the tumor due to shrinkage at the margins or by elimination of certain particularly invasive portions. Following treatments, resection may be possible. Additional treatments subsequent to resection will serve to eliminate microscopic residual disease at the tumor site.

**[00164]** The treatments may include various "unit doses." Unit dose is defined as containing a predetermined-quantity of the therapeutic composition. The quantity to be administered, and the particular route and formulation, is within the skill of determination of those in the clinical arts. A unit dose need not be administered as a single injection but may comprise continuous infusion over a set period of time.

### B. Additional Anti-Cancer Therapies

**[00165]** In some embodiments, the immune checkpoint inhibitor, composition comprising a short-chain fatty acid, such as butyrate, and/or composition comprising a population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, provided herein may be administered in combination with at least one additional therapeutic. The additional therapy may be a cancer therapy such as radiation therapy, surgery, chemotherapy, gene therapy, DNA therapy, viral therapy, RNA therapy, immunotherapy, bone marrow transplantation, nanotherapy, monoclonal antibody therapy, or a combination of the foregoing. The additional therapy may be in the form of adjuvant or neoadjuvant therapy.

**[00166]** In some embodiments, the additional cancer therapy is the administration of a small molecule enzymatic inhibitor or anti-metastatic agent. In some embodiments, the additional therapy is the administration of side- effect limiting agents *(e.g.,* agents intended to lessen the occurrence and/or severity of side effects of treatment, such as anti-nausea agents, *etc.).* In some embodiments, the additional cancer therapy is radiation therapy. In some embodiments, the additional cancer therapy is surgery. In some embodiments, the additional cancer therapy is a combination of radiation therapy and surgery. In some embodiments, the additional cancer therapy is gamma irradiation. In some embodiments, the additional cancer therapy is therapy targeting

PBK/AKT/mTOR pathway, HSP90 inhibitor, tubulin inhibitor, apoptosis inhibitor, and/or chemopreventative agent. The additional cancer therapy may be one or more of the chemotherapeutic agents known in the art.

**[00167]** Various combinations may also be employed. For the example below the immune checkpoint inhibitor, butyrate, and/or butyrate-producing bacterial population is "A" and an additional cancer therapy is "B":

A/B/A B/A/B B/B/A A/A/B A/B/B B/A/A A/B/B/B B/A/B/B
B/B/B/A B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A
B/A/B/A B/A/A/B A/A/A/B B/A/A/A A/B/A/A A/A/B/A

**[00168]** Administration of any compound or therapy of the present embodiments to a patient will follow general protocols for the administration of such compounds, taking into account the toxicity, if any, of the agents. Therefore, in some embodiments there is a step of monitoring toxicity that is attributable to combination therapy.

### 1. Chemotherapy

**[00169]** A wide variety of chemotherapeutic agents may be used in accordance with the present embodiments. The term "chemotherapy" refers to the use of drugs to treat cancer. A "chemotherapeutic agent" is used to connote a compound or composition that is administered in the treatment of cancer. These agents or drugs are categorized by their mode of activity within a cell, for example, whether and at what stage they affect the cell cycle. Alternatively, an agent may be characterized based on its ability to directly cross-link DNA, to intercalate into DNA, or to induce chromosomal and mitotic aberrations by affecting nucleic acid synthesis.

**[00170]** Examples of chemotherapeutic agents include alkylating agents, such as thiotepa and cyclosphosphamide; alkyl sulfonates, such as busulfan, improsulfan, and piposulfan; aziridines, such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines, including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide, and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues);

cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards, such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, and uracil mustard; nitrosureas, such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics, such as the enediyne antibiotics *(e.g.,* calicheamicin, especially calicheamicin gammall and calicheamicin omegall); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authrarnycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, such as mitomycin C, mycophenolic acid, nogalarnycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin; anti-metabolites, such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues, such as denopterin, pteropterin, and trimetrexate; purine analogs, such as fludarabine, 6-mercaptopurine, thiamiprine, and thioguanine; pyrimidine analogs, such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine; androgens, such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, and testolactone; anti-adrenals, such as mitotane and trilostane; folic acid replenisher, such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids, such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSKpolysaccharide complex; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol;

pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; taxoids, *e.g.,* paclitaxel and docetaxel gemcitabine; 6-thioguanine; mercaptopurine; platinum coordination complexes, such as cisplatin, oxaliplatin, and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan *(e.g.,* CPT-11); topoisomerase inhibitor RFS 2000; difluorometlhylornithine (DMFO); retinoids, such as retinoic acid; capecitabine; carboplatin, procarbazine,plicomycin, gemcitabien, navelbine, farnesyl-protein tansferase inhibitors, transplatinum, and pharmaceutically acceptable salts, acids, or derivatives of any of the above^

**2. Radiotherapy**

**[00171]** Other factors that cause DNA damage and have been used extensively include what are commonly known as γ-rays, X-rays, and/or the directed delivery of radioisotopes to tumor cells. Other forms of DNA damaging factors are also contemplated, such as microwaves, proton beam irradiation (U.S. Patents 5,760,395 and 4,870,287), and UV-irradiation. It is most likely that all of these factors affect a broad range of damage on DNA, on the precursors of DNA, on the replication and repair of DNA, and on the assembly and maintenance of chromosomes. Dosage ranges for X-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 wk), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

**3. Immunotherapy**

**[00172]** The skilled artisan will understand that immunotherapies may be used in combination or in conjunction with the methods described herein. In the context of cancer treatment, immunotherapeutics generally rely on the use of immune effector cells and molecules to target and destroy cancer cells. Rituximab (RITUXAN®) is an example of an immunotherapy. The immune effector may be, for example, an antibody specific for a marker on the surface of a tumor cell. The antibody alone may serve as an effector of therapy or it may recruit other cells to actually effect cell killing. The antibody also may be conjugated to a drug or toxin (chemotherapeutic, radionuclide, ricin A chain, cholera toxin, pertussis toxin, etc.) and serve as a targeting agent. Alternatively, the effector may be a lymphocyte carrying a surface molecule that

interacts, either directly or indirectly, with a tumor cell target. Various effector cells include cytotoxic T cells and NK cells

**[00173]** Antibody-drug conjugates have emerged as a breakthrough approach to the development of cancer therapeutics. Antibody-drug conjugates (ADCs) comprise monoclonal antibodies (MAbs) that are covalently linked to cell-killing drugs. This approach combines the high specificity of MAbs against their antigen targets with highly potent cytotoxic drugs, resulting in "armed" MAbs that deliver the payload (drug) to tumor cells with enriched levels of the antigen. Targeted delivery of the drug also minimizes its exposure in normal tissues, resulting in decreased toxicity and improved therapeutic index. The approval of two ADC drugs, ADCETRIS® (brentuximab vedotin) in 201 1 and KADCYLA® (trastuzumab emtansine or T-DM1) in 2013 by FDA validated the approach. There are currently more than 30 ADC drug candidates in various stages of clinical trials for cancer treatment. As antibody engineering and linker-payload optimization are becoming more and more mature, the discovery and development of new ADCs are increasingly dependent on the identification and validation of new targets that are suitable to this approach and the generation of targeting MAbs. Two criteria for ADC targets are upregulated/high levels of expression in tumor cells and robust internalization.

**[00174]** In one aspect of immunotherapy, the tumor cell must bear some marker that is amenable to targeting, *i.e.,* is not present on the majority of other cells. Many tumor markers exist and any of these may be suitable for targeting in the context of the present embodiments. Common tumor markers include CD20, carcinoembryonic antigen, tyrosinase (p97), gp68, TAG-72, HMFG, Sialyl Lewis Antigen, MucA, MucB, PLAP, laminin receptor, erb B, and p i 55. An alternative aspect of immunotherapy is to combine anticancer effects with immune stimulatory effects. Immune stimulating molecules also exist including: cytokines, such as IL-2, IL-4, IL-12, GM-CSF, gamma-IFN, chemokines, such as MIP-1, MCP-1, IL-8, and growth factors, such as FLT3 ligand.

### 4. Surgery

**[00175]** Approximately 60% of persons with cancer will undergo surgery of some type, which includes preventative, diagnostic or staging, curative, and palliative surgery. Curative surgery includes resection in which all or part of cancerous tissue is physically removed, excised,

and/or destroyed and may be used in conjunction with other therapies, such as the treatment of the present embodiments, chemotherapy, radiotherapy, hormonal therapy, gene therapy, immunotherapy, and/or alternative therapies. Tumor resection refers to physical removal of at least part of a tumor. In addition to tumor resection, treatment by surgery includes laser surgery, cryosurgery, electrosurgery, and microscopically-controlled surgery (Mohs' surgery).

**[00176]** Upon excision of part or all of cancerous cells, tissue, or tumor, a cavity may be formed in the body. Treatment may be accomplished by perfusion, direct injection, or local application of the area with an additional anti-cancer therapy. Such treatment may be repeated, for example, every 1, 2, 3, 4, 5, 6, or 7 days, or every 1, 2, 3, 4, and 5 weeks or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months. These treatments may be of varying dosages as well.

### 5. Other Agents

**[00177]** It is contemplated that other agents may be used in combination with certain aspects of the present embodiments to improve the therapeutic efficacy of treatment. These additional agents include agents that affect the upregulation of cell surface receptors and GAP junctions, cytostatic and differentiation agents, inhibitors of cell adhesion, agents that increase the sensitivity of the hyperproliferative cells to apoptotic inducers, or other biological agents. Increases in intercellular signaling by elevating the number of GAP junctions would increase the anti-hyperproliferative effects on the neighboring hyperproliferative cell population. In other embodiments, cytostatic or differentiation agents can be used in combination with certain aspects of the present embodiments to improve the anti-hyperproliferative efficacy of the treatments. Inhibitors of cell adhesion are contemplated to improve the efficacy of the present embodiments. Examples of cell adhesion inhibitors are focal adhesion kinase (FAKs) inhibitors and Lovastatin. It is further contemplated that other agents that increase the sensitivity of a hyperproliferative cell to apoptosis, such as the antibody c225, could be used in combination with certain aspects of the present embodiments to improve the treatment efficacy.

## V. Examples

**[00178]** The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the

practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

## Example 1 - Characterization of Microbiome of Melanoma Patients

**[00179]** To better understand the role of the microbiome in response to immune checkpoint blockade in cancer patients, microbiome samples were prospectively collected from patients with metastatic melanoma going onto treatment with PD-1 blockade (n=112 patients). Oral (buccal) and gut (fecal) microbiome samples were collected at treatment initiation, and tumor biopsies and blood samples were collected when feasible to assess for genomic alterations as well as the density and phenotype of tumor-infiltrating and circulating immune cell subsets (FIG. 1A). Taxonomic profiling via 16S rRNA gene sequencing was performed on all available oral and gut samples, with metagenomic whole genome shotgun sequencing (WGS) on a subset. Patients were classified as responders (R) or non-responders (NR) based on imaging analysis via RECIST 1.1 criteria (Schwartz *et al.,* 2016). Of note, patients in R versus NR groups were relatively similar with respect to age, gender, primary type, prior therapy, concurrent therapy and serum LDH (Table 3). The frequency of specific melanoma driver mutations and total mutational load were also similar between the groups (FIG. 5) *(17).*

**[00180]** Table 3: Patient characteristics table by microbiome sample type.

| **Oral Microbiome Samples** | | | | **Fecal Microbiome Samples** | | | |
|---|---|---|---|---|---|---|---|
| | **R** | **NR** | **p*** | | **R** | **NR** | **p*** |
| | n=52 (%) | n=34 (%) | | | \ n=30 (%) | n=13 (%) | |
| **Age** | | | 0.57 | \ | | | 0.60 |
| Median | 66.5 | 64.5 | | Median | 64 | 70 | |
| Range | 21-88 | 32-87 | | Range | 21-88 | 42-80 | |
| **Gender** | | | 0.14 | | | | 0.74 |
| Male | 41 (79) | 22 (65) | | Male | 20 (67) | 8 (62) | i |
| Female | 11 (21) | 12 (35) | | Female | \ 10 (33) | 5 (38) | |
| **Ethnicity** | | | 0.47 | \ | | | 0.57 |
| White | 48 (92) | 29 (85) | | White | \ 28 (94) | 11 (85) | |
| Other | 4 (6) | 5 (6) | | Other | I 2 (6) | 2 (15) | j |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Primary Type** | | | 0.032 | | | | 0.68 |
| Cutaneous | 44 (85) | 22 (65) | | Cutaneous | 25 (83) | 10 (77) | |
| Other** | 8 (15) | 12 (35) | | Other** | 5 (17) | 3 (23) | |
| **Prior Targeted Therapy** | | | 0.76 | | | | 0.76 |
| Yes | 8 (15) | 4 (12) | | Yes | 5 (17) | 6 (46) | |
| No | 44 (85) | 30 (88) | | No | | | |
| **Prior Checkpoint Therapy** | | | 0.81 | | | | 0.46 |
| Yes | 17 (33) | 12 (35) | | Yes | 9 (30) | 2 (15) | |
| No | 35 (67) | 22 (65) | | No | 21 (70) | 11 (85) | |
| **Disease Stage** | | | 0.053 | | | | 0.0006 |
| III | 14 (27) | 3 (9) | | III | 20 (67) | 1 (8) | |
| IV | 38 (73) | 31 (91) | | IV | 10 (33) | 12 (92) | |
| **Lactate Dehydrogenase****** | | | | | | | 0.21 |
| < 618 IU | 44 (85) | 23 (68) | 0.11 | < 618 IU | 26 (87) | 9 (69) | |
| ≥ 618 IU | 8 (15) | 10 (30) | | ≥ 618 IU | 3 (10) | 4 (31) | |
| **Treatment Type** | | | 0.053 | | | | 0.22 |
| PD1 Monotherapy | 50 (96) | 28 (82) | | PD1 Monotherapy | 29 (97) | 11 (85) | |
| PD1 Combination*** | 2 (4) | 6 (18) | | PD1 Combination*** | 1 (3) | 2 (15) | |

*p values calculated by Wilcoxon rank sum (age),chi-squared (gender, prior checkpoint) and Fisher's exact (all others)

**other includes acral, mucosal, unknown primaries

***combos include: Abraxane, Urelumanb, Aldera cream

**** 1 missing value from 1 R who didn't have a baseline LDH read

**[00181]** The landscape of the oral and fecal microbiota in patients was first assessed with metastatic melanoma via 16S sequencing (V4 region), noting that both communities were relatively diverse, with a high abundance of Lactobacillales in the oral microbiome and Bacteroidales in the fecal microbiome (FIG. IB). Bipartite network analysis (Muegge *et al.,* 201 1) demonstrated a clear separation of community structure between the oral and fecal microbiomes in terms of both matched and aggregate samples (FIGS. 1C and 6), suggesting that these communities are distinct.

**[00182]** Loss of diversity (dysbiosis) is associated with chronic health conditions (Turnbaugh *et al.,* 2008; Qin *et al.,* 2010) and cancer (Garrett *et al.,* 2015; Segre *et al.,* 2015; Drewes *et al.,* 2016)), and is also associated with poor outcomes to certain forms of cancer therapy including allogeneic stem cell transplant (Taur *et al.,* 2014). Based on these data diversity of the oral and gut microbiomes was tested in patients on PD-1 blockade, and found that diversity of the

gut microbiome was significantly higher in R compared to NR using several indices (p=0.009, FIGS. ID and 7). No significant differences were observed in the oral microbiome (p=0.11, FIG. 8). The relationship of diversity with progression-free survival (PFS) was tested in the cohort, demonstrating that patients with a high diversity in the fecal microbiome had significantly prolonged PFS compared to those with intermediate or low diversity (p=0.021 and 0.041, respectively; FIGS. 1E-F and 9). No differences in PFS were noted when comparing diversity of the oral microbiome (FIG. 10A-D).

**[00183]** Compositional differences in the microbiome may also influence cancer development and response to therapy (Sivan *et al.,* 2015; Iida *et al,* 2013; Viaud *et al,* 2013; Vetizou *et al,* 2015), thus it was also sought to determine if differences existed in component microbiota in the oral or gut microbiomes of R and NR to PD-1 blockade. To test this, enrichment index *(ei)* of operational taxonomic units (OTUs) was calculated and compared R versus NR, demonstrating that distinct sets of bacteria were associated with response to anti-PD-1 therapy, with enrichment of Clostridiales in R and Bacteroidales in NR in the gut microbiome (p<0.001, FIG. 2A-B and 11). No significant differences in enrichment were noted in the oral microbiome of R versus NR (FIG. 12A-B). To further explore these findings, high dimensional class comparisons were performed via linear discriminant analysis of effect size (LEfSe) (Segata *et al.,* 2011), which again demonstrated differentially abundant bacteria in the fecal microbiome of R versus NR to PD-1 blockade, with Clostridiales/Ruminococcaceae enriched in R and Bacteroidales enriched in NR (FIG. 2C-D). No significant differences were observed in the oral microbiome between R and NR, with the exception of higher Bacteroidales in NR to PD-1 blockade (FIG. 13A-B). Pairwise comparisons were then performed for bacterial taxa at all levels by response. In addition to confirming the previous taxonomic differences, these analyses identified *Faecalibacterium prausnitzii* species as significantly enriched in R (FIG. 2E, Table 4). Metagenomic WGS further revealed enrichment of *Faecalibacterium* species in addition to others including *Akkermansia* in R, whilst *Bacteroides thetaiotaomicron, Escherichia coli,* and *Anaerotruncus colihominis* were enriched in NR (FIG. 2F, Table 4). Of note, the gut microbiome was shown to be relatively stable over time in a limited number of longitudinal samples tested (FIG. 14A-C).

**[00184]** Based on these insights, it was next asked whether bacterial composition and abundances within the gut and/or oral microbiomes could predict response to PD-1 blockade in the inventors' cohort. To do this, all identified OTUs were grouped into clusters of related OTUs (crOTUs) via construction of a phylogenetic tree from sequence alignment data (Peled *et al.,* 2017). This technique involves comparison of abundances of different potential groupings of bacteria based on 16S sequence similarity and helps address the sparse distribution of OTU abundances observed in the absence of this approach (FIG. 15A-B). Unsupervised hierarchical clustering of crOTU abundances within the gut and oral microbiomes was then performed without input of response data. Results demonstrated that patients segregated into 2 distinct clusters, with one cluster (cluster 1) comprised entirely of R and the other (cluster 2) comprised of a mixture of R and NR (p=0.02) with enrichment of Clostridiales in cluster 1 and Bacteroidales in cluster 2 (FIG. 3A-B). PFS was then assessed in each of these clusters, demonstrating a significantly shorter time to progression on PD-1 blockade among patients in cluster 1 compared to those in cluster 2 (p=0.02) (FIG. 3C). To better understand compositional differences in these clusters, pairwise comparisons of the gut microbiota were performed, and identified a pattern very similar to that seen when clustering by response, with Clostridiales/Ruminococcaceae enriched in cluster 1, and Bacteroidales enriched in cluster 2 (FIG. 3D, Table 5). Analysis of crOTUs in the oral microbiome revealed no apparent relationship to treatment response (FIG. 16A-B).

**[00185]** To explore the association of specific bacterial taxa and treatment response, the inventors compared PFS to anti-PD-1 therapy as it related to the "top hits" consistently observed across analyses (*F. prausnitzii* in R and Bacteroidales in NR), dichotomizing patients into high versus low categories based on the median relative abundance of these taxa in the gut microbiome. Patients with high *F. prausnitzii* abundance had a significantly prolonged PFS versus those with a low abundance (p=0.03). Conversely, patients with a high abundance of Bacteroidales had a shortened PFS compared to those with a low abundance (p=0.05) (FIG. 3E). This is in line with recently published data in a small cohort of patients on CTLA-4 blockade, where patients with a higher abundance of *Faecalibacterium* had a prolonged PFS compared to those with a higher abundance of Bacteroides in the gut microbiome (Chaput *et al.,* 2017)). In addition, Cox proportional hazards analyses were performed in the inventors' cohort, demonstrating that the strongest predictors of response to PD-1 blockade were alpha-diversity (HR= 3.94; 95% C.I. =1.02-12.52), abundance of *F.prausnitzii* (HR= 2.92; 95% C.I. =1.08-7.89) and crOTU clusters

(HR=3.80; 95% C.I. =1.09-13.21) in the fecal microbiome. These effects remained significant in multivariate analyses after adjusting for prior treatment with immunotherapy (Table 6).

**[00186]** Table 4: Pairwise comparisons of bacterial taxa between R and NR by 2-sided MW test within each level of taxonomy.

| **Taxon** | **\ p-value** | **Effect Size** | **FDR-Adjusted p-Value** | **Taxonomy Level** |
|---|---|---|---|---|
| *Bacteroidetes* | 0.000939 | 19.06232 | 0.002664 | Phylum |
| *Firmicutes* | 0.001776 | -16.9273 | 0.002664 | Phylum |
| *Proteobacteria* | 0.927224 | 0 | 0.927224 | Phylum |
| *Bacteroidia* | 0.000939 | 21.3498 | 0.002165 | Class |
| *Clostridia* | 0.001443 | -14.9449 | 0.002165 | Class |
| *Gammaproteobacteria* | 0.628911 | 0 | 0.628911 | Class |
| *Bacteroidales* | 0.000939 | 19.67232 | 0.002165 | Order |
| *Clostridiales* | 0.001443 | -16.6223 | 0.002165 | Order |
| *Enterobacterales* | 0.842779 | 0 | 0.842779 | Order |
| *Bacteroidaceae* | 0.159028 | 9.721784 | 0.307087 | Family |
| *Clostridiaceae* | 0.175479 | -6.44306 | 0.307087 | Family |
| *Enterobacteriaceae* | 0.863521 | 0.419371 | 0.863521 | Family |
| *Lachnospiraceae* | 0.48832 | -2.6306 | 0.683647 | Family |
| *Porphyromonadaceae* | 0.061699 | -9.34054 | 0.215948 | Family |
| *Rikenellaceae* | 0.750983 | -0.41937 | 0.863521 | Family |
| *Ruminococcaceae* | 0.000118 | -19.5579 | 0.000827 | Family |
| *Alistipes* | 0.750983 | -3.43122 | 0.844806 | Genus |
| *Bacteroides* | 0.159028 | 6.709937 | 0.424075 | Genus |
| *Blautia* | 0.844806 | -0.305 | 0.844806 | Genus |
| *Escherichia* | 0.551319 | 1.982481 | 0.844806 | Genus |
| *Faecalibacterium* | 0.005128 | -17.3848 | 0.041026 | Genus |
| *Lachnoclostridium* | 0.539046 | 2.13498 | 0.844806 | Genus |
| *Parabacteroides* | 0.098795 | -11.1324 | 0.395182 | Genus |
| *Roseburia* | 0.804154 | 0 | 0.844806 | Genus |
| *Alistipes onderdonkii* | 0.577459 | 0.038125 | 0.577459 | Species |
| *Bacteroides caccae* | 0.569645 | -0.03812 | 0.577459 | Species |
| *Bacteroides ovatus* | 0.397414 | -1.63936 | 0.577459 | Species |
| *Bacteroides thetaiotaomicron* | 0.412328 | 8.120549 | 0.577459 | Species |
| *Bacteroides uniformis* | 0.475213 | 7.510555 | 0.577459 | Species |
| *Bacteroides vulgatus* | 0.300376 | -2.7831 | 0.577459 | Species |
| *Escherichia coli* | 0.551319 | 6.824311 | 0.577459 | Species |

| | | | | |
|---|---|---|---|---|
| *Faecalibacterium prausnitzii* | 0.005128 | i -12.543 | 0.046155 | Species |
| *Parabacteroides merdae* | 0.440288 | j -1.18186 | 0.577459 | Species |

**[00187]** Table 5: Pairwise comparisons of 16S-derived bacterial taxa between crOTU community type 1 and crOTU community type 2 by 2 sided Mann-Whitney test within each level of taxonomy.

| **Taxon** | **p-value** | **Effect Size** | **FDR-adjusted p-value[a]** | **Taxonomic Level** |
|---|---|---|---|---|
| Bacteroidetes | 6.95e-10 | -25.62 | 2.09e-09 | Phylum |
| Firmicutes | 3.37e-08 | 26.53 | 5.06e-08 | Phylum |
| Proteobacteria | 0.86 | 0.00 | 0.86 | Phylum |
| Bacteroidia | 6.95e-10 | -37.97 | 2.09e-09 | Class |
| Clostridia | 9.42e-08 | 13.72 | 1.41e-07 | Class |
| Gammaproteobacteria | 0.04 | 0.00 | 0.04 | Class |
| Bacteroidales | 6.95e-10 | -38.12 | 2.09e-09 | Order |
| Clostridiales | 9.42e-08 | 13.57 | 1.41e-07 | Order |
| Enterobacterales | 0.04 | 0.00 | 0.04 | Order |
| Bacteroidaceae | 4.83e-08 | -27.75 | 3.38e-07 | Family |
| Ruminococcaceae | 0.00 | 15.55 | 0.00 | Family |
| Clostridiaceae | 0.0011 | 14.79 | 0.00 | Family |
| Lachnospiraceae | 0.01 | 11.59 | 0.02 | Family |
| Enterobacteriaceae | 0.04 | 8.84 | 0.06 | Family |
| Rikenellaceae | 0.36 | -7.55 | 0.42 | Family |
| Porphyromonadaceae | 0.67 | 0.00 | 0.67 | Family |
| Bacteroides | 4.83e-08 | -28.52 | 3.87e-07 | Genus |
| Blautia | 0.07 | 6.86 | 0.19 | Genus |
| Faecalibacterium | 0.07 | 6.71 | 0.19 | Genus |
| Roseburia | 0.18 | 4.27 | 0.36 | Genus |
| Alistipes | 0.36 | -8.31 | 0.57 | Genus |
| Lachnoclostridium | 0.57 | 0.00 | 0.76 | Genus |
| Escherichia | 0.71 | -1.07 | 0.79 | Genus |
| Parabacteroides | 0.79 | -4.73 | 0.79 | Genus |
| Bacteroides .vulgatus | 0.00 | -20.47 | 0.00 | Species |
| Bacteroides .uniformis | 0.00 | -18.72 | 0.01 | Species |
| Bacteroides .thetaiotaomicron | 0.00 | -17.80 | 0.01 | Species |
| Bacteroides.ovatus | 0.07 | -11.86 | 0.13 | Species |
| Faecalibacterium.prausnitzii | 0.07 | 8.20 | 0.13 | Species |
| Bacteroides.caccae | 0.21 | -8.73 | 0.31 | Species |
| Alistipes.onderdonkii | 0.36 | -6.82 | 0.46 | Species |

| | | | | |
|---|---|---|---|---|
| Escherichia.coli | 0.71 | 0.42 | 0.80 | Species |
| Parabacteroides.merdae | 0.82 | -0.42 | 0.82 | Species |

**[a]FDR *p*-values are adjusted within each level of taxonomy level**

**[00188]** Next, it was sought to gain insight into the mechanism through which the gut microbiome may influence response to anti-PD-1 therapy, and first conducted functional genomic profiling of gut microbiome samples via metagenomic WGS in R vs NR to therapy. Organism- specific gene hits were assigned to the Kyoto Encyclopedia of Genes and Genomes (KEGG) orthology (KO), and based on these annotations, metagenomes for each sample were reconstructed into metabolic pathways using the MetaCyc hierarchy of pathway classifications (Caspi *et al,* 2008; Kanehisa *et al.,* 2000). Unsupervised hierarchical clustering on relative abundances of both KOs and predicted pathways identified three groups of patient samples, with response rates of 72.7%, 57.1%, and 42.9%. Comparisons of gene function abundances across these groups showed changes in metabolic functions, with anabolic functions predominating in R including amino acid biosynthesis (FIG. 3F), which may promote host immunity (Blacher *et al.,* 2017), whereas catabolic functions predominated in NR (FIG. 3F, 17, Table 7).

**[00189]** There is clear evidence in pre-clinical models that differential composition of the gut microbiome may influence therapeutic responses to PD-1 blockade at the level of the tumor microenvironment (Sivan *et al,* 2015), thus the relationship between the gut microbiota and systemic and anti-tumor immune responses was interrogated in the cohort of patients on PD-1 blockade. To do this the tumor associated immune infiltrates were compared via multi-parameter IHC, and observed a higher density of $CD8^+$ T lymphocytes in baseline samples of R versus NR ($p=0.04$), consistent with prior reports (FIG. 4A and 18A-F) (Tumeh *et al.,* 2014; Chen *et al.,* 2016). Pairwise comparisons using Spearman rank correlation were then performed between specific bacterial taxa enriched in the gut microbiome of R and NR and immune markers in the tumor microenvironment, demonstrating a strong positive correlation between the abundance of *RuminococcaceadFaecalibacterium* in the gut and cytotoxic T-cell infiltrate in the tumor, and a strong negative correlation with Bacteroidales (FIG. 4B-C and 19-20). Analysis of systemic immune responses via flow cytometry and cytokine assays revealed that patients with a high abundance of Ruminococcaceae in the gut had higher levels of effector $CD4^+$ and $CD8^+$ T cells in the systemic circulation with a preserved cytokine response to PD-1 blockade, whereas patients

with a higher abundance of Bacteroidales in the gut microbiome had higher levels of regulatory T cells (Treg) and myeloid derived suppressor cells (MDSC) in the systemic circulation, with a blunted cytokine response (FIG. 4D and 21-22). To better understand the influence of compositional differences in the gut microbiome on antigen processing and presentation within the tumor microenvironment, multiplex IHC targeting the myeloid compartment was performed (Tsujikawa *et al.,* 2017). In these studies, patients with a high abundance of *Faecalibacterium* in the gut microbiome had a higher density of immune cells and markers of antigen processing and presentation compared to those with a high abundance of Bacteroidales (FIG. 4E-F and 23-24), suggesting a possible mechanism through which the gut microbiome may modulate anti-tumor immune responses (Sivan *et al.,* 2015).

**[00190]** Placing these insights in the context of published literature, it was proposed that the gut microbiome modulates responses to treatment with anti-PD-1 therapy (FIG. 4G). Specifically, it was proposed that patients with a "favorable" gut microbiome (with high diversity and abundance of *RuminococcaceadFaecalibacterium)* have enhanced systemic and anti-tumor immune responses mediated by enhanced antigen presentation at the level of the lymph node and tumor, as well as preserved effector T cell function in the periphery and the tumor microenvironment. In contrast, patients with an "unfavorable" gut microbiome (with low diversity and high relative abundance of Bacteroidales) have impaired systemic and anti-tumor immune responses mediated by limited intratumoral infiltration of both lymphoid and myeloid elements, weakened antigen presentation capacity, and skewing towards immunoregulatory cellular and humoral elements in the periphery, including Treg and MDSC. These findings highlight the potential for parallel modulation of the gut microbiome to significantly enhance checkpoint blockade efficacy.

**[00191]** Table 6: Univariate and multivariate Cox proportional hazards models for progression-free survival in the fecal analysis cohort.

| Variable | Univariate HRa (95% C.I.) | *p*-value | HRa- Final modelb (95% C.I.)a | *p*-value |
|---|---|---|---|---|
| **alpha-diversity (Inverse Simpson)c** | | | | |
| High (ref) | | | | |
| Intermediate | 3.57 (1.01-12.74) | **0.05** | | |
| Low | 3.94 (1.02-12.52) | **0.05** | | |

| | | | | |
|---|---|---|---|---|
| ***Faecalibacterium* abundanced** | | | | |
| High (ref) | | | | |
| Low | 2.92 (1.08-7.89) | **0.03** | 3.64 (1.28-10.40) | **0.02** |
| **Bacteroidales abundanced** | | | | |
| High (ref) | | | | |
| Low | 0.39 (0.15-1.03) | 0.06 | | |
| **crOTU Cluster** | | | | |
| Cluster 1 (ref) | | | | |
| Cluster 2 | 3.80 (1.09-13.21) | **0.04** | | |
| **Sex** | | | | |
| Male (ref) | | | | |
| Female | 0.84 (0.30-2.35) | 0.1 1 | | |
| **Ethnicity** | | | | |
| White (ref) | | | | |
| Other | 3.23 (0.86-12.09) | 0.08 | | |
| **Age** | 1.01 (0.98-1.03) | 0.10 | | |
| **Primary Site** | | | | |
| Cutaneous (ref) | | | | |
| Other | 1.02 (0.23-4.52) | 0.98 | | |
| **Stage** | | | | |
| III (ref) | | | | |
| IV | 1.18 (0.34-4.16) | 0.08 | | |
| **Baseline LDH** | | | | |
| Normal (ref) | | | | |
| Elevatedc | 2.24 (0.79-6.32) | 0.13 | | |
| **Prior Immunotherapy** | | | | |
| No (ref) | | | | |
| Yes | 2.28 (1.11-7.18) | **0.03** | | |
| **Prior Targeted therapy** | | | | |
| No (ref) | | | | |
| Yes | 1.88 (0.66-5.31) | 0.24 | | |
| **Aiiti-PD-1 combination vs monotherapy** | | | | |
| Monotherapy (ref) | | | | |
| Combinations | 1.40 (0.23-6.13) | 0.20 | | |
| **CD8+ density in baseline tumord** | 0.99 (0.99-1.00) | 0.07 | | |

a HRs represent 4 patients excluded from analysis due to insufficient follow up data
b Final model determine by forwards selection and best subsets approach. Alpha Diversity was included as a binary variable based on the median cut point.
c elevated LDH: exceeding the upper limit of normal (618 IU/niL), all samples assayed in a common laboratory
d CD8+ density based on samples from 15 patients with baseline tumor available

**[00192]** Table 7: Pairwise comparison of MetaCyc pathway class by response.

| Pathway | Estimate[a] | p-value | Enrichment Index | Enriched In |
|---|---|---|---|---|
| glycolate and glyoxylate degradation I | 0.05 | 0.00 | -0.52 | NR |
| oxalate degradation II | 0.08 | 0.03 | -0.36 | NR |
| formate to trimethylamine N-oxide electron transfer | 0.1 1 | 0.04 | -0.29 | NR |
| D-sorbitol degradation II | 0.00 | 0.05 | -0.22 | NR |
| ketogluconate metabolism | 0.00 | 0.05 | -0.22 | NR |
| phenylacetate degradation I (aerobic) | 0.14 | 0.09 | -0.23 | NR |
| pyridoxal 5'-phosphate biosynthesis I | 0.18 | 0.10 | -0.31 | NR |
| superpathway of pyridoxal 5'-phosphate biosynthesis and salvage | 0.18 | 0.10 | -0.31 | NR |
| 4-aminobutanoate degradation III | 0.00 | 0.1 1 | -0.17 | NR |
| hydrogen to trimethylamine N-oxide electron transfer | 0.00 | 0.1 1 | -0.17 | NR |
| 4-hydroxybenzoate biosynthesis II (microbes) | 0.22 | 0.1 1 | -0.34 | NR |
| glycocholate metabolism (bacteria) | 0.24 | 0.12 | -0.38 | NR |
| malonate decarboxylase activation | 0.21 | 0.18 | -0.52 | NR |
| 4-aminobutanoate degradation II | 0.19 | 0.18 | -0.17 | NR |
| aspartate superpathway | 0.19 | 0.18 | -0.17 | NR |
| D-malate degradation | 0.19 | 0.18 | -0.17 | NR |
| formate to dimethyl sulfoxide electron transfer | 0.19 | 0.18 | -0.17 | NR |
| L-lysine degradation I | 0.19 | 0.18 | -0.17 | NR |
| NAD biosynthesis I (from aspartate) | 0.19 | 0.18 | -0.17 | NR |
| nitrate reduction III (dissimilatory) | 0.19 | 0.18 | -0.17 | NR |
| 2-methylcitrate cycle I | 0.24 | 0.21 | -0.24 | NR |
| GDP-D-glycero-alpha-D-manno-heptose biosynthesis | 0.24 | 0.21 | -0.24 | NR |
| sulfoquinovose degradation I | 0.24 | 0.21 | -0.24 | NR |
| superpathway of 4-aminobutanoate degradation | 0.24 | 0.21 | -0.24 | NR |
| tetrahydromonapterin biosynthesis | 0.24 | 0.21 | -0.24 | NR |
| mevalonate pathway I | 0.30 | 0.23 | -0.26 | NR |
| superpathway of geranylgeranyldiphosphate biosynthesis I (via mevalonate) | 0.30 | 0.23 | -0.26 | NR |
| D-galactonate degradation | 0.00 | 0.23 | -0.12 | NR |
| trehalose degradation I (low osmolarity) | 0.00 | 0.23 | -0.12 | NR |
| 4-aminobutanoate degradation I | 0.31 | 0.23 | -0.18 | NR |
| adenine and adenosine salvage V | 0.31 | 0.23 | -0.18 | NR |
| guanine and guanosine salvage III | 0.31 | 0.23 | -0.18 | NR |
| superpathway of guanine and guanosine salvage | 0.31 | 0.23 | -0.18 | NR |
| L-ascorbate degradation II (bacterial, aerobic) | 0.33 | 0.24 | -0.28 | NR |
| fatty acid beta-oxidation I | 0.26 | 0.34 | -0.12 | NR |
| glucose and glucose-1-phosphate degradation | 0.26 | 0.34 | -0.12 | NR |
| glyoxylate cycle | 0.26 | 0.34 | -0.12 | NR |

| | | | | |
|---|---|---|---|---|
| L-gulonate degradation | 0.26 | 0.34 | -0.12 | NR |
| superpathway of glyoxylate bypass and TCA | 0.26 | 0.34 | -0.12 | NR |
| 3-phenylpropanoate and 3-(3-hydroxyphenyl)propanoate degradation to 2-oxopent-4-enoate | 0.34 | 0.39 | -0.36 | NR |
| L-phenylalanine biosynthesis II | 0.34 | 0.39 | -0.36 | NR |
| tetrathionate reduction I (to thiosulfate) | 0.34 | 0.39 | -0.36 | NR |
| urate degradation to allantoin II | 0.34 | 0.39 | -0.36 | NR |
| cob(II)yrinate a,c-diamide biosynthesis I (early cobalt insertion) | 0.41 | 0.41 | -0.12 | NR |
| glycerol-3-phosphate to cytochrome bo oxidase electron transfer | 0.41 | 0.41 | -0.12 | NR |
| NADH to cytochrome bo oxidase electron transfer I | 0.41 | 0.41 | -0.12 | NR |
| proline to cytochrome bo oxidase electron transfer | 0.41 | 0.41 | -0.12 | NR |
| pyruvate to cytochrome bo oxidase electron transfer | 0.41 | 0.41 | -0.12 | NR |
| succinate to cytochrome bo oxidase electron transfer | 0.41 | 0.41 | -0.12 | NR |
| cinnamate and 3-hydroxycinnamate degradation to 2-oxopent-4-enoate | 0.39 | 0.41 | -0.19 | NR |
| Entner-Doudoroff pathway I | 0.39 | 0.41 | -0.19 | NR |
| superpathway of glycolysis and Entner-Doudoroff | 0.39 | 0.41 | -0.19 | NR |
| glycerol degradation II | 0.44 | 0.43 | -0.20 | NR |
| L-threonine degradation III (to methylglyoxal) | 0.44 | 0.43 | -0.20 | NR |
| neurosporene biosynthesis | 0.44 | 0.43 | -0.20 | NR |
| phenylethylamine degradation I | 0.44 | 0.43 | -0.20 | NR |
| trans-lycopene biosynthesis I (bacteria) | 0.44 | 0.43 | -0.20 | NR |
| acetate formation from acetyl-CoA II | 0.49 | 0.43 | -0.23 | NR |
| crotonate fermentation (to acetate and cyclohexane carboxylate) | 0.49 | 0.43 | -0.23 | NR |
| D-allose degradation | 0.49 | 0.43 | -0.23 | NR |
| 2-O-alpha-mannosyl-D-glycerate degradation | 0.48 | 0.43 | -0.21 | NR |
| galactitol degradation | 0.48 | 0.43 | -0.21 | NR |
| malonate degradation I (biotin-independent) | 0.48 | 0.43 | -0.21 | NR |
| (R)-acetoin biosynthesis I | 0.48 | 0.43 | -0.21 | NR |
| (R,R)-butanediol biosynthesis | 0.48 | 0.43 | -0.21 | NR |
| (R,R)-butanediol degradation | 0.48 | 0.43 | -0.21 | NR |
| aerobactin biosynthesis | 0.00 | 0.44 | -1.00 | NR |
| benzoyl-CoA degradation I (aerobic) | 0.00 | 0.44 | -1.00 | NR |
| glutaryl-CoA degradation | 0.00 | 0.44 | -1.00 | NR |
| nitrate reduction I (denitrification) | 0.00 | 0.44 | -1.00 | NR |
| pectin degradation II | 0.00 | 0.44 | -1.00 | NR |
| fluoroacetate and fluorothreonine biosynthesis | 0.00 | 0.49 | -0.08 | NR |
| catechol degradation to beta-ketoadipate | 0.36 | 0.56 | -0.44 | NR |
| chondroitin sulfate degradation I (bacterial) | 0.36 | 0.56 | -0.44 | NR |
| dermatan sulfate degradation I (bacterial) | 0.36 | 0.56 | -0.44 | NR |
| L-methionine salvage cycle III | 0.36 | 0.56 | -0.44 | NR |
| phenylmercury acetate degradation | 0.36 | 0.56 | -0.44 | NR |

| | | | | |
|---|---|---|---|---|
| urea degradation I | 0.36 | 0.56 | -0.44 | NR |
| 4-hydroxyphenylpyruvate biosynthesis | 0.38 | 0.60 | -0.07 | NR |
| glutathionylspermidine biosynthesis | 0.38 | 0.60 | -0.07 | NR |
| L-phenylalanine biosynthesis I | 0.38 | 0.60 | -0.07 | NR |
| methylerythritol phosphate pathway II | 0.38 | 0.60 | -0.07 | NR |
| nitrate reduction IX (dissimilatory) | 0.38 | 0.60 | -0.07 | NR |
| nitrate reduction X (periplasmic, dissimilatory) | 0.38 | 0.60 | -0.07 | NR |
| paraoxon degradation | 0.38 | 0.60 | -0.07 | NR |
| parathion degradation | 0.38 | 0.60 | -0.07 | NR |
| superpathway of aromatic amino acid biosynthesis | 0.38 | 0.60 | -0.07 | NR |
| 3-methylthiopropanoate biosynthesis | 0.49 | 0.66 | -0.26 | NR |
| allantoin degradation to glyoxylate III | 0.49 | 0.66 | -0.26 | NR |
| gallate degradation I | 0.49 | 0.66 | -0.26 | NR |
| sulfoacetaldehyde degradation III | 0.49 | 0.66 | -0.26 | NR |
| syringate degradation | 0.49 | 0.66 | -0.26 | NR |
| (5Z)-dodec-5-enoate biosynthesis | 0.57 | 0.66 | -0.07 | NR |
| fatty acid beta-oxidation III (unsaturated, odd number) | 0.57 | 0.66 | -0.07 | NR |
| formaldehyde oxidation II (glutathione-dependent) | 0.57 | 0.66 | -0.07 | NR |
| oleate biosynthesis IV (anaerobic) | 0.57 | 0.66 | -0.07 | NR |
| superpathway of fatty acids biosynthesis (E. coli) | 0.57 | 0.66 | -0.07 | NR |
| superpathway of unsaturated fatty acids biosynthesis (E. coli) | 0.57 | 0.66 | -0.07 | NR |
| NAD salvage pathway III | 0.51 | 0.68 | -0.12 | NR |
| NAD salvage pathway IV | 0.51 | 0.68 | -0.12 | NR |
| superpathway of ubiquinol-8 biosynthesis (prokaryotic) | 0.51 | 0.68 | -0.12 | NR |
| ubiquinol-7 biosynthesis (prokaryotic) | 0.51 | 0.68 | -0.12 | NR |
| ubiquinol-8 biosynthesis (prokaryotic) | 0.51 | 0.68 | -0.12 | NR |
| ubiquinol-9 biosynthesis (prokaryotic) | 0.51 | 0.68 | -0.12 | NR |
| dTDP-N-acetylthomosamine biosynthesis | 0.58 | 0.69 | -0.12 | NR |
| putrescine degradation II | 0.58 | 0.69 | -0.12 | NR |
| taurine degradation IV | 0.58 | 0.69 | -0.12 | NR |
| bile acids degradation | 0.64 | 0.70 | -0.12 | NR |
| guanine and guanosine salvage II | 0.64 | 0.70 | -0.12 | NR |
| guanosine nucleotides degradation II | 0.64 | 0.70 | -0.12 | NR |
| superpathway of phenylethylamine degradation | 0.64 | 0.70 | -0.12 | NR |
| formaldehyde assimilation I (serine pathway) | 0.68 | 0.70 | -0.12 | NR |
| L-arginine degradation II (AST pathway) | 0.68 | 0.70 | -0.12 | NR |
| S-methyl-5'-thioadenosine degradation II | 0.68 | 0.70 | -0.12 | NR |
| superpathway of (R,R)-butanediol biosynthesis | 0.68 | 0.70 | -0.12 | NR |
| 2,3-dihydroxybenzoate biosynthesis | 0.94 | 1.00 | -0.01 | NR |
| 2-oxoisovalerate decarboxylation to isobutanoyl-CoA | 0.00 | 1.00 | -0.04 | NR |
| acyl carrier protein metabolism | 0.77 | 1.00 | -0.05 | NR |

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|---|---|---|---|---|
| allantoin degradation IV (anaerobic) | 0.61 | 1.00 | -0.03 | NR |
| allantoin degradation to ureidoglycolate II (ammonia producing) | 0.61 | 1.00 | -0.03 | NR |
| allantoin degradation to ureidoglycolate I (urea producing) | 0.78 | 1.00 | -0.12 | NR |
| anthranilate degradation I (aerobic) | 0.78 | 1.00 | -0.12 | NR |
| Bifidobacterium shunt | 0.69 | 1.00 | -0.06 | NR |
| cyanate degradation | 0.71 | 1.00 | -0.12 | NR |
| D-glucarate degradation II | 0.00 | 1.00 | -0.04 | NR |
| D-gluconate degradation | 0.00 | 1.00 | -0.04 | NR |
| D-glucosaminate degradation | 0.76 | 1.00 | -0.12 | NR |
| D-serine degradation | 0.00 | 1.00 | -0.04 | NR |
| glucose degradation (oxidative) | 0.84 | 1.00 | -0.04 | NR |
| glutathione-glutaredoxin redox reactions | 0.00 | 1.00 | -0.04 | NR |
| heme biosynthesis I (aerobic) | 0.94 | 1.00 | -0.01 | NR |
| heptadecane biosynthesis | 0.61 | 1.00 | -0.03 | NR |
| lactose and galactose degradation I | 0.71 | 1.00 | -0.12 | NR |
| L-methionine degradation I (to L-homocysteine) | 0.74 | 1.00 | -0.12 | NR |
| L-methionine salvage cycle I (bacteria and plants) | 0.76 | 1.00 | -0.12 | NR |
| maltose degradation | 0.00 | 1.00 | -0.04 | NR |
| mannitol degradation I | 0.00 | 1.00 | -0.04 | NR |
| mannosylglycerate biosynthesis I | 0.90 | 1.00 | -0.03 | NR |
| PRPP biosynthesis II | 0.77 | 1.00 | -0.05 | NR |
| pseudouridine degradation | 0.69 | 1.00 | -0.06 | NR |
| purine nucleotides degradation II (aerobic) | 0.00 | 1.00 | -0.04 | NR |
| pyrimidine deoxyribonucleotides de novo biosynthesis III | 0.94 | 1.00 | -0.01 | NR |
| pyrimidine deoxyribonucleotides dephosphorylation | 0.90 | 1.00 | -0.03 | NR |
| pyrimidine nucleobases salvage II | 0.00 | 1.00 | -0.04 | NR |
| pyrroloquinoline quinone biosynthesis | 0.76 | 1.00 | -0.12 | NR |
| pyruvate decarboxylation to acetyl CoA | 0.00 | 1.00 | -0.04 | NR |
| quinate degradation I | 0.90 | 1.00 | -0.03 | NR |
| (R)-acetoin biosynthesis II | 0.82 | 1.00 | -0.02 | NR |
| (S)-acetoin biosynthesis | 0.77 | 1.00 | -0.05 | NR |
| salicylate biosynthesis I | 0.90 | 1.00 | -0.03 | NR |
| shikimate degradation I | 0.90 | 1.00 | -0.03 | NR |
| S-methyl-5'-thioadenosine degradation I | 0.90 | 1.00 | -0.03 | NR |
| S-methyl-5-thio-alpha-D-ribose 1-phosphate degradation | 0.76 | 1.00 | -0.12 | NR |
| (S,S)-butanediol biosynthesis | 0.77 | 1.00 | -0.05 | NR |
| (S.S)-butanediol degradation | 0.77 | 1.00 | -0.05 | NR |
| sulfate reduction I (assimilatory) | 0.00 | 1.00 | -0.04 | NR |
| sulfate reduction III (assimilatory) | 0.00 | 1.00 | -0.04 | NR |
| sulfite oxidation III | 0.00 | 1.00 | -0.04 | NR |
| sulfur reduction II (via polysulfide) | 0.78 | 1.00 | -0.12 | NR |

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|---|---|---|---|---|
| superpathway of L-arginine, putrescine, and 4-aminobutanoate degradation | 0.90 | 1.00 | -0.03 | NR |
| superpathway of ornithine degradation | 0.90 | 1.00 | -0.03 | NR |
| TCA cycle I (prokaryotic) | 0.00 | 1.00 | -0.04 | NR |
| trehalose biosynthesis IV | 0.00 | 1.00 | -0.04 | NR |
| trehalose biosynthesis V | 0.78 | 1.00 | -0.12 | NR |
| trehalose degradation II (trehalase) | 0.61 | 1.00 | -0.03 | NR |
| trehalose degradation VI (periplasmic) | 0.61 | 1.00 | -0.03 | NR |
| two-component alkanesulfonate monooxygenase | 0.94 | 1.00 | -0.01 | NR |
| UDP-2,3-diacetamido-2,3-dideoxy-alpha-D-mannuronate biosynthesis | 0.61 | 1.00 | -0.03 | NR |
| urate biosynthesis/inosine 5'-phosphate degradation | 0.00 | 1.00 | -0.04 | NR |
| vanillin and vanillate degradation II | 0.90 | 1.00 | -0.03 | NR |
| vancomycin resistance II | Inf | 0.02 | 1.00 | R |
| inosine-5'-phosphate biosynthesis III | Inf | 0.11 | 1.00 | R |
| fructan biosynthesis | 4.48 | 0.11 | 0.40 | R |
| putrescine degradation I | 6.84 | 0.13 | 0.19 | R |
| L-cysteine degradation II | 4.66 | 0.18 | 0.22 | R |
| D-serine metabolism | 5.21 | 0.18 | 0.59 | R |
| bis(guanylyl molybdenum cofactor) biosynthesis | Inf | 0.18 | 0.10 | R |
| gentisate degradation I | Inf | 0.23 | 1.00 | R |
| kojibiose degradation | Inf | 0.23 | 1.00 | R |
| methanogenesis from H2 and C02 | Inf | 0.23 | 1.00 | R |
| phosphopantothenate biosynthesis III | Inf | 0.23 | 1.00 | R |
| reductive acetyl coenzyme A pathway II (autotrophic methanogens) | Inf | 0.23 | 1.00 | R |
| (R)-cysteate degradation | 3.00 | 0.24 | 0.28 | R |
| L-cysteine biosynthesis III (from L-homocysteine) | 2.86 | 0.24 | 0.22 | R |
| glycolysis IV (plant cytosol) | 3.26 | 0.35 | 0.15 | R |
| UDP-N-acetyl-D-galactosamine biosynthesis I | 2.91 | 0.39 | 0.18 | R |
| formaldehyde oxidation I | 2.41 | 0.41 | 0.33 | R |
| trehalose degradation IV | 2.41 | 0.41 | 0.33 | R |
| heme biosynthesis II (anaerobic) | 2.56 | 0.41 | 0.29 | R |
| superpathway of heme biosynthesis from uroporphyrinogen-III | 2.56 | 0.41 | 0.29 | R |
| 8-amino-7-oxononanoate biosynthesis III | 2.25 | 0.43 | 0.22 | R |
| 2-oxoglutarate decarboxylation to succinyl-CoA | Inf | 0.44 | 0.05 | R |
| CMP-N-acetylneuraminate biosynthesis II (bacteria) | Inf | 0.44 | 0.05 | R |
| cob(II)yrinate a,c-diamide biosynthesis II (late cobalt incorporation) | Inf | 0.44 | 0.05 | R |
| cyclopropane fatty acid (CFA) biosynthesis | Inf | 0.44 | 0.05 | R |
| guanylyl molybdenum cofactor biosynthesis | Inf | 0.44 | 0.05 | R |
| hydrogen production III | Inf | 0.44 | 0.05 | R |
| hydrogen production VI | Inf | 0.44 | 0.05 | R |
| L-arginine degradation I (arginase pathway) | Inf | 0.44 | 0.05 | R |
| L-arginine degradation VI (arginase 2 pathway) | Inf | 0.44 | 0.05 | R |

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|---|---|---|---|---|
| L-citrulline biosynthesis | Inf | 0.44 | 0.05 | R |
| L-ornithine biosynthesis II | Inf | 0.44 | 0.05 | R |
| L-proline biosynthesis III | Inf | 0.44 | 0.05 | R |
| pectin degradation III | Inf | 0.44 | 0.05 | R |
| putrescine biosynthesis IV | Inf | 0.44 | 0.05 | R |
| adenine and adenosine salvage VI | Inf | 0.49 | 1.00 | R |
| alginate degradation | Inf | 0.49 | 1.00 | R |
| glycine biosynthesis III | Inf | 0.49 | 1.00 | R |
| sulfolactate degradation I | Inf | 0.49 | 1.00 | R |
| superpathway of L-cysteine biosynthesis (mammalian) | Inf | 0.49 | 1.00 | R |
| L-histidine degradation III | 2.77 | 0.56 | 0.06 | R |
| nitrogen fixation I (ferredoxin) | 2.77 | 0.56 | 0.06 | R |
| chlorosalicylate degradation | 2.63 | 0.60 | 0.40 | R |
| methylsalicylate degradation | 2.63 | 0.60 | 0.40 | R |
| salicylate degradation I | 2.63 | 0.60 | 0.40 | R |
| acrylate degradation | 2.18 | 0.62 | 0.08 | R |
| L-methionine degradation II | 2.18 | 0.62 | 0.08 | R |
| cyanophycin metabolism | 1.76 | 0.66 | 0.22 | R |
| TCA cycle VII (acetate-producers) | 1.76 | 0.66 | 0.22 | R |
| Kdo transfer to lipid IVA II | 1.95 | 0.68 | 0.22 | R |
| aminopropanol phosphate biosynthesis I | 1.71 | 0.69 | 0.16 | R |
| hopanoid biosynthesis (bacteria) | 1.57 | 0.70 | 0.1 1 | R |
| D-galactarate degradation I | 1.48 | 0.70 | 0.08 | R |
| D-glucarate degradation I | 1.48 | 0.70 | 0.08 | R |
| formaldehyde assimilation II (RuMP Cycle) | 1.48 | 0.70 | 0.08 | R |
| ribose degradation | 1.48 | 0.70 | 0.08 | R |
| superpathway of D-glucarate and D-galactarate degradation | 1.48 | 0.70 | 0.08 | R |
| 1,2-dichloroethane degradation | Inf | 1.00 | 1.00 | R |
| 1,4-dihydroxy-2-naphthoate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| 2-aminoethylphosphonate degradation I | 0.00 | 1.00 | 0.00 | R |
| 2'-deoxy-alpha-D-ribose 1-phosphate degradation | 0.00 | 1.00 | 0.00 | R |
| [2Fe-2S] iron-sulfur cluster biosynthesis | 0.00 | 1.00 | 0.00 | R |
| 2-heptyl-3-hydroxy-4( 1H)-quinolone biosynthesis | Inf | 1.00 | 1.00 | R |
| 3-dehydroquinate biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| 4-amino-2-methyl-5-diphosphomethylpyrimidine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| 4-aminobenzoate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| 4-deoxy-L-threo-hex^l-enopyranuronate degradation | 0.00 | 1.00 | 0.00 | R |
| 5-aminoimidazole ribonucleotide biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| 6-hydroxymethyl-dihydropterin diphosphate biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| 8-amino-7-oxononanoate biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| acetate conversion to acetyl-CoA | 0.00 | 1.00 | 0.00 | R |

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|---|---|---|---|---|
| acetate formation from acetyl-CoA I | 0.00 | 1.00 | 0.00 | R |
| adenine and adenosine salvage I | 0.00 | 1.00 | 0.00 | R |
| adenine and adenosine salvage III | 0.00 | 1.00 | 0.00 | R |
| adenine salvage | 0.00 | 1.00 | 0.00 | R |
| adenosine deoxyribonucleotides de novo biosynthesis | 0.00 | 1.00 | 0.00 | R |
| adenosine deoxyribonucleotides de novo biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| adenosine nucleotides degradation II | 0.00 | 1.00 | 0.00 | R |
| adenosine nucleotides degradation III | 0.00 | 1.00 | 0.00 | R |
| adenosine ribonucleotides de novo biosynthesis | 0.00 | 1.00 | 0.00 | R |
| adenosylcobalamin biosynthesis from cobyrinate a,c-diamide I | 0.00 | 1.00 | 0.00 | R |
| adenosylcobalamin biosynthesis from cobyrinate a,c-diamide II | 0.00 | 1.00 | 0.00 | R |
| adenosylcobalamin salvage from cobalamin | 0.00 | 1.00 | 0.00 | R |
| adenosylcobalamin salvage from cobinamide I | 0.00 | 1.00 | 0.00 | R |
| ADP-L-glycero-beta-D-manno-heptose biosynthesis | 1.32 | 1.00 | 0.02 | R |
| aerobic respiration I (cytochrome c) | 1.63 | 1.00 | 0.22 | R |
| allantoin degradation to glyoxylate I | Inf | 1.00 | 1.00 | R |
| ammonia assimilation cycle III | 0.00 | 1.00 | 0.00 | R |
| androstenedione degradation | Inf | 1.00 | 1.00 | R |
| anhydromuropeptides recycling | 0.00 | 1.00 | 0.00 | R |
| arginine dependent acid resistance | 0.00 | 1.00 | 0.00 | R |
| arsenate detoxification II (glutaredoxin) | 0.00 | 1.00 | 0.00 | R |
| autoinducer AI-2 biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| autoinducer AI-2 degradation | 0.00 | 1.00 | 0.00 | R |
| base-degraded thiamine salvage | 0.00 | 1.00 | 0.00 | R |
| beta-alanine biosynthesis II | Inf | 1.00 | 1.00 | R |
| beta-alanine biosynthesis III | 0.00 | 1.00 | 0.00 | R |
| beta-D-glucuronide and D-glucuronate degradation | 0.00 | 1.00 | 0.00 | R |
| biotin biosynthesis from 8-amino-7-oxononanoate I | 0.00 | 1.00 | 0.00 | R |
| biotin biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| biotin-carboxyl carrier protein assembly | 0.00 | 1.00 | 0.00 | R |
| C4 photosynthetic carbon assimilation cycle, NAD-ME type | 0.00 | 1.00 | 0.00 | R |
| Calvin-Benson-Bassham cycle | Inf | 1.00 | 1.00 | R |
| CDP-diacylglycerol biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| CDP-diacylglycerol biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| cellulose and hemicellulose degradation (cellulolosome) | 1.29 | 1.00 | 0.01 | R |
| cellulose biosynthesis | 1.32 | 1.00 | 0.02 | R |
| chitin degradation II | 0.00 | 1.00 | 0.00 | R |
| chitobiose degradation | 0.00 | 1.00 | 0.00 | R |
| chorismate biosynthesis from 3-dehydroquinate | 0.00 | 1.00 | 0.00 | R |
| chorismate biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| cis-genanyl-CoA degradation | 1.63 | 1.00 | 0.22 | R |

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|---|---|---|---|---|
| cis-vaccenate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| citrate degradation | 0.00 | 1.00 | 0.00 | R |
| citrate lyase activation | 0.00 | 1.00 | 0.00 | R |
| CMP-3-deoxy-D-manno-octulosonate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| CMP phosphorylation | 0.00 | 1.00 | 0.00 | R |
| coenzyme A biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| creatinine degradation I | 0.00 | 1.00 | 0.00 | R |
| cytidylyl molybdenum cofactor biosynthesis | 0.00 | 1.00 | 0.00 | R |
| D-arabinose degradation I | 0.00 | 1.00 | 0.00 | R |
| demethylmenaquinol-6 biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| demethylmenaquinol-8 biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| demethylmenaquinol-9 biosynthesis | 0.00 | 1.00 | 0.00 | R |
| D-fructuronate degradation | 0.00 | 1.00 | 0.00 | R |
| D-galactarate degradation II | 0.00 | 1.00 | 0.00 | R |
| D-galactose degradation I (Leloir pathway) | 0.00 | 1.00 | 0.00 | R |
| D-galactose degradation V (Leloir pathway) | 0.00 | 1.00 | 0.00 | R |
| D-galacturonate degradation I | 0.00 | 1.00 | 0.00 | R |
| di-trans,poly-cis-undecaprenyl phosphate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| D-mannose degradation | 0.00 | 1.00 | 0.00 | R |
| D-sorbitol degradation I | 0.00 | 1.00 | 0.00 | R |
| dTDP-L-rhamnose biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| ethanolamine utilization | 0.00 | 1.00 | 0.00 | R |
| ethanol degradation I | 0.00 | 1.00 | 0.00 | R |
| ethanol degradation II | 0.00 | 1.00 | 0.00 | R |
| fatty acid biosynthesis initiation I | 0.00 | 1.00 | 0.00 | R |
| fatty acid biosynthesis initiation III | Inf | 1.00 | 1.00 | R |
| fatty acid elongation —saturated | 0.00 | 1.00 | 0.00 | R |
| fatty acid salvage | Inf | 1.00 | 1.00 | R |
| flavin biosynthesis I (bacteria and plants) | 0.00 | 1.00 | 0.00 | R |
| fluoroacetate degradation | Inf | 1.00 | 1.00 | R |
| folate polyglutamylation | 0.00 | 1.00 | 0.00 | R |
| folate transformations I | 0.00 | 1.00 | 0.00 | R |
| formate assimilation into 5,10-methylenetetrahydrofolate | 0.00 | 1.00 | 0.00 | R |
| formate oxidation to C02 | 0.00 | 1.00 | 0.00 | R |
| fructose degradation | 0.00 | 1.00 | 0.00 | R |
| fucose degradation | 0.00 | 1.00 | 0.00 | R |
| GABA shunt | Inf | 1.00 | 1.00 | R |
| GDP-L-fucose biosynthesis I (from GDP-D-mannose) | 0.00 | 1.00 | 0.00 | R |
| GDP-mannose biosynthesis | 0.00 | 1.00 | 0.00 | R |
| geranyl diphosphate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| geranylgeranyl diphosphate biosynthesis | 0.00 | 1.00 | 0.00 | R |

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|---|---|---|---|---|
| gluconeogenesis I | 0.00 | 1.00 | 0.00 | R |
| glutaminyl-tRNAgln biosynthesis via transamidation | 0.00 | 1.00 | 0.00 | R |
| glutathione biosynthesis | 0.00 | 1.00 | 0.00 | R |
| glutathione-peroxide redox reactions | 0.00 | 1.00 | 0.00 | R |
| glycerol-3-phosphate to fumarate electron transfer | 0.00 | 1.00 | 0.00 | R |
| glycerol and glycerophosphodiester degradation | 0.00 | 1.00 | 0.00 | R |
| glycerol degradation I | 0.00 | 1.00 | 0.00 | R |
| glycerophosphodiester degradation | 0.00 | 1.00 | 0.00 | R |
| glycine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| glycine cleavage | 0.00 | 1.00 | 0.00 | R |
| glycogen biosynthesis I (from ADP-D-Glucose) | 0.00 | 1.00 | 0.00 | R |
| glycolysis I (from glucose 6-phosphate) | 0.00 | 1.00 | 0.00 | R |
| glycolysis III (from glucose) | 0.00 | 1.00 | 0.00 | R |
| gondoate biosynthesis (anaerobic) | 0.00 | 1.00 | 0.00 | R |
| guanine and guanosine salvage | 0.00 | 1.00 | 0.00 | R |
| guanosine deoxyribonucleotides de novo biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| guanosine deoxyribonucleotides de novo biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| guanosine nucleotides degradation III | 0.00 | 1.00 | 0.00 | R |
| guanosine ribonucleotides de novo biosynthesis | 0.00 | 1.00 | 0.00 | R |
| heptaprenyl diphosphate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| histamine biosynthesis | 1.36 | 1.00 | 0.04 | R |
| homolactic fermentation | 0.00 | 1.00 | 0.00 | R |
| hyaluronan degradation | 0.00 | 1.00 | 0.00 | R |
| hydrogen oxidation I (aerobic) | 0.00 | 1.00 | 0.00 | R |
| hydrogen oxidation III (anaerobic, NADP) | 0.00 | 1.00 | 0.00 | R |
| hydrogen to dimethyl sulfoxide electron transfer | 0.00 | 1.00 | 0.00 | R |
| hydrogen to fumarate electron transfer | 0.00 | 1.00 | 0.00 | R |
| hydroxymethylpyrimidine salvage | 0.00 | 1.00 | 0.00 | R |
| hypotaurine degradation | Inf | 1.00 | 1.00 | R |
| incomplete reductive TCA cycle | 0.00 | 1.00 | 0.00 | R |
| inosine-5'-phosphate biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-l,2-propanediol degradation | 1.03 | 1.00 | 0.01 | R |
| lactose degradation III | 0.00 | 1.00 | 0.00 | R |
| L-alanine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-alanine biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| L-alanine biosynthesis III | 0.00 | 1.00 | 0.00 | R |
| L-alanine degradation IV | 0.00 | 1.00 | 0.00 | R |
| L-arabinose degradation I | 0.00 | 1.00 | 0.00 | R |
| L-arginine biosynthesis II (acetyl cycle) | 0.00 | 1.00 | 0.00 | R |
| L-arginine biosynthesis I (via L-ornithine) | 0.00 | 1.00 | 0.00 | R |
| L-arginine degradation III (arginine decarboxylase/agmatinase pathway) | 0.00 | 1.00 | 0.00 | R |

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|---|---|---|---|---|
| L-arginine degradation V (arginine deiminase pathway) | 0.00 | 1.00 | 0.00 | R |
| L-asparagine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-asparagine biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| L-asparagine biosynthesis III (tRNA-dependent) | 0.00 | 1.00 | 0.00 | R |
| L-asparagine degradation I | 0.00 | 1.00 | 0.00 | R |
| L-aspartate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| L-aspartate degradation I | 0.00 | 1.00 | 0.00 | R |
| L-citrulline degradation | 0.00 | 1.00 | 0.00 | R |
| L-cysteine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| leucine degradation IV | Inf | 1.00 | 1.00 | R |
| L-glutamate biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-glutamate biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| L-glutamate biosynthesis III | 0.00 | 1.00 | 0.00 | R |
| L-glutamate degradation I | 0.00 | 1.00 | 0.00 | R |
| L-glutamate degradation II | 0.00 | 1.00 | 0.00 | R |
| L-glutamate degradation IX (via 4-aminobutanoate) | 0.00 | 1.00 | 0.00 | R |
| L-glutamate degradation X | 0.00 | 1.00 | 0.00 | R |
| L-glutamine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-glutamine biosynthesis III | 0.00 | 1.00 | 0.00 | R |
| L-glutamine degradation I | 0.00 | 1.00 | 0.00 | R |
| L-glutamine degradation II | 0.00 | 1.00 | 0.00 | R |
| L-histidine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| L-histidine degradation I | 0.00 | 1.00 | 0.00 | R |
| L-homocysteine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| L-homoserine and L-methionine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| L-homoserine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| L-idonate degradation | 0.00 | 1.00 | 0.00 | R |
| lipid IVA biosynthesis | 0.00 | 1.00 | 0.00 | R |
| lipoate biosynthesis and incorporation I | 0.00 | 1.00 | 0.00 | R |
| lipoate biosynthesis and incorporation II | 0.00 | 1.00 | 0.00 | R |
| lipoate salvage I | 0.00 | 1.00 | 0.00 | R |
| L-isoleucine biosynthesis I (from threonine) | 0.00 | 1.00 | 0.00 | R |
| L-isoleucine degradation I | 0.00 | 1.00 | 0.00 | R |
| L-lactaldehyde degradation (anaerobic) | 0.00 | 1.00 | 0.00 | R |
| L-leucine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| L-leucine degradation I | 1.63 | 1.00 | 0.22 | R |
| L-lysine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-lysine biosynthesis III | 0.00 | 1.00 | 0.00 | R |
| L-lysine biosynthesis VI | 0.00 | 1.00 | 0.00 | R |
| L-lysine fermentation to acetate and butanoate | 0.00 | 1.00 | 0.00 | R |
| L-malate degradation II | 0.00 | 1.00 | 0.00 | R |

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|---|---|---|---|---|
| L-methionine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-methionine biosynthesis III | 0.00 | 1.00 | 0.00 | R |
| long-chain fatty acid activation | 0.00 | 1.00 | 0.00 | R |
| L-ornithine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-phenylalanine degradation I (aerobic) | Inf | 1.00 | 1.00 | R |
| L-proline biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-proline degradation | 0.00 | 1.00 | 0.00 | R |
| L-rhamnose degradation I | 0.00 | 1.00 | 0.00 | R |
| L-selenocysteine biosynthesis I (bacteria) | 0.00 | 1.00 | 0.00 | R |
| L-serine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| L-serine degradation | 0.00 | 1.00 | 0.00 | R |
| L-threonine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| L-threonine degradation II | 0.00 | 1.00 | 0.00 | R |
| L-threonine degradation IV | 0.00 | 1.00 | 0.00 | R |
| L-tryptophan biosynthesis | 0.00 | 1.00 | 0.00 | R |
| L-tryptophan degradation II (via pyruvate) | 0.00 | 1.00 | 0.00 | R |
| L-tryptophan degradation I (via anthranilate) | Inf | 1.00 | 1.00 | R |
| L-tryptophan degradation to 2-amino-3-carboxymuconate semialdehyde | Inf | 1.00 | 1.00 | R |
| L-tyrosine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| L-valine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| mannan degradation | 0.00 | 1.00 | 0.00 | R |
| melibiose degradation | 0.00 | 1.00 | 0.00 | R |
| menaquinol-6 biosynthesis | 0.00 | 1.00 | 0.00 | R |
| menaquinol-7 biosynthesis | 0.00 | 1.00 | 0.00 | R |
| menaquinol-8 biosynthesis | 0.00 | 1.00 | 0.00 | R |
| menaquinol-9 biosynthesis | 0.00 | 1.00 | 0.00 | R |
| methylerythritol phosphate pathway I | 0.00 | 1.00 | 0.00 | R |
| methylglyoxal degradation I | 0.00 | 1.00 | 0.00 | R |
| methylphosphonate degradation I | 0.00 | 1.00 | 0.00 | R |
| mevalonate degradation | 1.32 | 1.00 | 0.02 | R |
| mixed acid fermentation | 0.00 | 1.00 | 0.00 | R |
| molybdenum cofactor biosynthesis | 0.00 | 1.00 | 0.00 | R |
| myo-, chiro- and scillo-inositol degradation | 0.00 | 1.00 | 0.00 | R |
| myo-inositol biosynthesis | 0.00 | 1.00 | 0.00 | R |
| myo-inositol degradation I | 0.00 | 1.00 | 0.00 | R |
| N10-formyl-tetrahydrofolate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| N6-L-threonylcarbamoyladenosine37-modified tRNA biosynthesis | 0.00 | 1.00 | 0.00 | R |
| N-acetylglucosamine degradation I | 0.00 | 1.00 | 0.00 | R |
| N-acetylglucosamine degradation II | 1.03 | 1.00 | 0.01 | R |
| N-acetylneuraminate and N-acetylmannosamine degradation I | 0.00 | 1.00 | 0.00 | R |
| NAD biosynthesis from 2-amino-3-carboxymuconate semialdehyde | 0.00 | 1.00 | 0.00 | R |

| | | | | |
|---|---|---|---|---|
| NAD biosynthesis II (from tryptophan) | Inf | 1.00 | 1.00 | R |
| NAD biosynthesis III | 1.22 | 1.00 | 0.08 | R |
| NADH repair | 0.00 | 1.00 | 0.00 | R |
| NADH to cytochrome bd oxidase electron transfer I | 0.00 | 1.00 | 0.00 | R |
| NAD phosphorylation and dephosphorylation | 0.00 | 1.00 | 0.00 | R |
| NAD salvage pathway II | 0.00 | 1.00 | 0.00 | R |
| octane oxidation | Inf | 1.00 | 1.00 | R |
| octaprenyl diphosphate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| oleate beta-oxidation | 0.00 | 1.00 | 0.00 | R |
| oxidized GTP and dGTP detoxification | 0.00 | 1.00 | 0.00 | R |
| palmitate biosynthesis II (bacteria and plants) | 0.00 | 1.00 | 0.00 | R |
| palmitoleate biosynthesis I (from (5Z)-dodec-5-enoate) | 0.00 | 1.00 | 0.00 | R |
| pantothenate and coenzyme A biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| partial TCA cycle (obligate autotrophs) | 0.00 | 1.00 | 0.00 | R |
| pentose phosphate pathway | 0.00 | 1.00 | 0.00 | R |
| pentose phosphate pathway (non-oxidative branch) | 0.00 | 1.00 | 0.00 | R |
| pentose phosphate pathway (oxidative branch) | 0.00 | 1.00 | 0.00 | R |
| peptidoglycan biosynthesis I (meso-diaminopimelate containing) | 0.00 | 1.00 | 0.00 | R |
| peptidoglycan maturation (meso-diaminopimelate containing) | 0.00 | 1.00 | 0.00 | R |
| phosphate acquisition | 0.00 | 1.00 | 0.00 | R |
| phosphatidylethanolamine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| phosphatidylglycerol biosynthesis II (non-plastidic) | 0.00 | 1.00 | 0.00 | R |
| phosphatidylglycerol biosynthesis I (plastidic) | 0.00 | 1.00 | 0.00 | R |
| phospholipases | 0.00 | 1.00 | 0.00 | R |
| phosphopantothenate biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| polyisoprenoid biosynthesis (E. coli) | 0.00 | 1.00 | 0.00 | R |
| ppGpp biosynthesis | 0.00 | 1.00 | 0.00 | R |
| preQO biosynthesis | 0.00 | 1.00 | 0.00 | R |
| propanoyl CoA degradation I | 0.00 | 1.00 | 0.00 | R |
| protocatechuate degradation II (ortho-cleavage pathway) | 0.00 | 1.00 | 0.00 | R |
| PRPP biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| purine deoxyribonucleosides degradation I | 0.00 | 1.00 | 0.00 | R |
| purine ribonucleosides degradation | 0.00 | 1.00 | 0.00 | R |
| putrescine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| putrescine biosynthesis III | 0.00 | 1.00 | 0.00 | R |
| pyridoxal 5'-phosphate biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| pyridoxal 5'-phosphate salvage I | 0.00 | 1.00 | 0.00 | R |
| pyrimidine deoxyribonucleosides degradation | 0.00 | 1.00 | 0.00 | R |
| pyrimidine deoxyribonucleosides salvage | 0.00 | 1.00 | 0.00 | R |
| pyrimidine deoxyribonucleotide phosphorylation | 0.00 | 1.00 | 0.00 | R |
| pyrimidine deoxyribonucleotides de novo biosynthesis I | 0.00 | 1.00 | 0.00 | R |

| | | | | |
|---|---|---|---|---|
| pyrimidine deoxyribonucleotides de novo biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| pyrimidine nucleobases salvage I | 0.00 | 1.00 | 0.00 | R |
| pyrimidine ribonucleosides degradation | 0.00 | 1.00 | 0.00 | R |
| pyrimidine ribonucleosides salvage I | 0.00 | 1.00 | 0.00 | R |
| pyruvate fermentation to acetate and lactate II | 0.00 | 1.00 | 0.00 | R |
| pyruvate fermentation to acetate I | 0.00 | 1.00 | 0.00 | R |
| pyruvate fermentation to acetate IV | 0.00 | 1.00 | 0.00 | R |
| pyruvate fermentation to ethanol I | 0.00 | 1.00 | 0.00 | R |
| pyruvate fermentation to ethanol III | 0.00 | 1.00 | 0.00 | R |
| pyruvate fermentation to lactate | 0.00 | 1.00 | 0.00 | R |
| pyruvate to cytochrome bd terminal oxidase electron transfer | 0.00 | 1.00 | 0.00 | R |
| queuosine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| reactive oxygen species degradation | 0.00 | 1.00 | 0.00 | R |
| reductive acetyl coenzyme A pathway I (homoacetogenic bacteria) | 0.00 | 1.00 | 0.00 | R |
| reductive monocarboxylic acid cycle | 0.00 | 1.00 | 0.00 | R |
| rhamnogalacturonan type I degradation II (bacteria) | 0.00 | 1.00 | 0.00 | R |
| Rubisco shunt | Inf | 1.00 | 1.00 | R |
| S-adenosyl-L-methionine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| S-adenosyl-L-methionine cycle I | 0.00 | 1.00 | 0.00 | R |
| S-adenosyl-L-methionine cycle II | 0.00 | 1.00 | 0.00 | R |
| salicylate degradation II | Inf | 1.00 | 1.00 | R |
| selenate reduction | 0.00 | 1.00 | 0.00 | R |
| siroheme biosynthesis | 0.00 | 1.00 | 0.00 | R |
| S-methyl-5'-thioadenosine degradation III | 1.06 | 1.00 | 0.02 | R |
| spermidine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| stearate biosynthesis II (bacteria and plants) | 0.00 | 1.00 | 0.00 | R |
| succinate to cytochrome bd oxidase electron transfer | 0.00 | 1.00 | 0.00 | R |
| sucrose degradation III (sucrose invertase) | 0.00 | 1.00 | 0.00 | R |
| sucrose degradation IV (sucrose phosphorylase) | 0.00 | 1.00 | 0.00 | R |
| sulfate activation for sulfonation | 0.00 | 1.00 | 0.00 | R |
| sulfate reduction IV (dissimilatory) | Inf | 1.00 | 1.00 | R |
| sulfoacetaldehyde degradation I | Inf | 1.00 | 1.00 | R |
| sulfolactate degradation III | Inf | 1.00 | 1.00 | R |
| superoxide radicals degradation | 0.00 | 1.00 | 0.00 | R |
| superpathway of acetate utilization and formation | 0.00 | 1.00 | 0.00 | R |
| superpathway of adenosine nucleotides de novo biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| superpathway of adenosine nucleotides de novo biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| superpathway of beta-D-glucuronide and D-glucuronate degradation | 0.00 | 1.00 | 0.00 | R |
| superpathway of branched chain amino acid biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of demethylmenaquinol-8 biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of geranylgeranyl diphosphate biosynthesis II (via MEP) | 0.00 | 1.00 | 0.00 | R |

| | | | | |
|---|---|---|---|---|
| superpathway of glucose and xylose degradation | 0.00 | 1.00 | 0.00 | R |
| superpathway of guanosine nucleotides de novo biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| superpathway of guanosine nucleotides de novo biosynthesis II | 0.00 | 1.00 | 0.00 | R |
| superpathway of L-alanine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of L-asparagine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of L-aspartate and L-asparagine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of L-isoleucine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| superpathway of L-lysine, L-threonine and L-methionine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| superpathway of L-methionine biosynthesis (by sulfhydrylation) | 0.00 | 1.00 | 0.00 | R |
| superpathway of L-methionine biosynthesis (transsulfuration) | 0.00 | 1.00 | 0.00 | R |
| superpathway of L-serine and glycine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| superpathway of L-threonine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of menaquinol-7 biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of menaquinol-8 biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| superpathway of N-acetylglucosamine, N-acetylmannosamine and N-acetylneuraminate degradation | 0.00 | 1.00 | 0.00 | R |
| superpathway of purine deoxyribonucleosides degradation | 0.00 | 1.00 | 0.00 | R |
| superpathway of pyrimidine deoxyribonucleoside salvage | 0.00 | 1.00 | 0.00 | R |
| superpathway of pyrimidine deoxyribonucleosides degradation | 0.00 | 1.00 | 0.00 | R |
| superpathway of pyrimidine deoxyribonucleotides de novo biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of pyrimidine deoxyribonucleotides de novo biosynthesis (E. coli) | 0.00 | 1.00 | 0.00 | R |
| superpathway of pyrimidine nucleobases salvage | 0.00 | 1.00 | 0.00 | R |
| superpathway of pyrimidine ribonucleotides de novo biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of sulfate assimilation and cysteine biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of tetrahydrofolate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| superpathway of thiamine diphosphate biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| superpathway of UDP-glucose-derived O-antigen building blocks biosynthesis | 0.00 | 1.00 | 0.00 | R |
| taurine degradation I | Inf | 1.00 | 1.00 | R |
| taurine degradation III | 1.32 | 1.00 | 0.02 | R |
| TCA cycle VIII (helicobacter) | 1.36 | 1.00 | 0.04 | R |
| tetrahydrofolate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| tetrahydrofolate salvage from 5,10-methenyltetrahydrofolate | 0.00 | 1.00 | 0.00 | R |
| tetrapyrrole biosynthesis I (from glutamate) | 0.00 | 1.00 | 0.00 | R |
| thiamine diphosphate biosynthesis I (E. coli) | 0.00 | 1.00 | 0.00 | R |
| thiamine diphosphate biosynthesis II (Bacillus) | 0.00 | 1.00 | 0.00 | R |
| thiamine salvage II | 0.00 | 1.00 | 0.00 | R |
| thiamine salvage III | 0.00 | 1.00 | 0.00 | R |
| thiamine salvage IV (yeast) | 0.00 | 1.00 | 0.00 | R |
| thiazole biosynthesis I (facultative anaerobic bacteria) | 0.00 | 1.00 | 0.00 | R |
| thioredoxin pathway | 0.00 | 1.00 | 0.00 | R |
| thiosulfate disproportionation III (rhodanese) | 1.29 | 1.00 | 0.01 | R |

| | | | | |
|---|---|---|---|---|
| thymine degradation | 0.00 | 1.00 | 0.00 | R |
| trans, trans-farnesyl diphosphate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| trehalose biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| triacylglycerol degradation | 1.22 | 1.00 | 0.08 | R |
| tRNA charging | 0.00 | 1.00 | 0.00 | R |
| tRNA processing | 0.00 | 1.00 | 0.00 | R |
| UDP-alpha-D-glucuronate biosynthesis (from UDP-glucose) | 0.00 | 1.00 | 0.00 | R |
| UDP-D-galactose biosynthesis | 0.00 | 1.00 | 0.00 | R |
| UDP-D-galacturonate biosynthesis I (from UDP-D-glucuronate) | 0.00 | 1.00 | 0.00 | R |
| UDP-galactofuranose biosynthesis | 0.00 | 1.00 | 0.00 | R |
| UDP-glucose biosynthesis | 0.00 | 1.00 | 0.00 | R |
| UDP-N-acetyl-alpha-D-galactosaminuronate biosynthesis | Inf | 1.00 | 1.00 | R |
| UDP-N-acetyl-alpha-D-mannosaminouronate biosynthesis | 0.00 | 1.00 | 0.00 | R |
| UDP-N-acetyl-D-glucosamine biosynthesis I | 0.00 | 1.00 | 0.00 | R |
| UDP-N-acetylmuramoyl-pentapeptide biosynthesis II (lysine-containing) | 1.32 | 1.00 | 0.02 | R |
| UDP-N-acetylmuramoyl-pentapeptide biosynthesis I (meso-diaminopimelate containing) | 0.00 | 1.00 | 0.00 | R |
| UMP biosynthesis | 0.00 | 1.00 | 0.00 | R |
| uracil degradation III | 1.63 | 1.00 | 0.22 | R |
| urea cycle | 0.00 | 1.00 | 0.00 | R |
| urea degradation II | 0.00 | 1.00 | 0.00 | R |
| UTP and CTP de novo biosynthesis | 0.00 | 1.00 | 0.00 | R |
| UTP and CTP dephosphorylation I | 0.00 | 1.00 | 0.00 | R |
| xanthine and xanthosine salvage | 0.00 | 1.00 | 0.00 | R |
| xylose degradation I | 0.00 | 1.00 | 0.00 | R |

"Estimates apply to a subset of 25 patients who had Metagenomic WGS data available

**[00193]** Table 8: Individual values and summary statistics of metabolic reconstructions.

| Sample | Genes | Genes of known or predicted molecular function | Pathways | Metabolic Reactions | Transport Reactions | Compounds |
|---|---|---|---|---|---|---|
| 1 | 36475 | 23417 | 451 | 2016 | 276 | 1669 |
| 2 | 36914 | 23811 | 459 | 2089 | 281 | 1751 |
| 3 | 44948 | 28820 | 498 | 2312 | 323 | 1895 |
| 4 | 31710 | 20446 | 397 | 1861 | 234 | 1583 |
| 5 | 25541 | 15702 | 500 | 2272 | 339 | 1877 |
| 6 | 41761 | 26459 | 507 | 2372 | 324 | 1943 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | 27071 | 17620 | 404 | 1851 | 245 | 1559 |
| 8 | 29091 | 18566 | 481 | 2163 | 328 | 1793 |
| 9 | 27740 | 17946 | 486 | 2255 | 328 | 1854 |
| 10 | 44204 | 27899 | 523 | 2471 | 344 | 2009 |
| 11 | 26897 | 17433 | 400 | 1814 | 240 | 1547 |
| 12 | 22879 | 14385 | 490 | 2248 | 334 | 1857 |
| 13 | 37311 | 24090 | 435 | 2017 | 274 | 1708 |
| 14 | 35781 | 22589 | 444 | 2094 | 287 | 1770 |
| 15 | 23732 | 15066 | 491 | 2253 | 331 | 1886 |
| 16 | 19793 | 12789 | 395 | 1899 | 240 | 1619 |
| 17 | 23184 | 14702 | 436 | 2020 | 276 | 1695 |
| 18 | 31203 | 19760 | 517 | 2329 | 354 | 1919 |
| 19 | 24237 | 15593 | 458 | 2117 | 311 | 1785 |
| 20 | 35021 | 22007 | 498 | 2251 | 336 | 1853 |
| 21 | 32373 | 21032 | 492 | 2218 | 314 | 1825 |
| 22 | 30518 | 19678 | 463 | 2114 | 277 | 1792 |
| 23 | 29535 | 19148 | 467 | 2165 | 316 | 1793 |
| 24 | 24410 | 15301 | 506 | 2305 | 349 | 1894 |
| 25 | 38701 | 24639 | 515 | 2325 | 358 | 1928 |
| 26 | 28840 | 18767 | 399 | 1879 | 245 | 1601 |
| 27 | 26919 | 17486 | 439 | 2012 | 306 | 1684 |
| 28 | 28250 | 18066 | 449 | 2004 | 282 | 1715 |
| Mean | 30894 | 19758 | 464 | 2133 | 302 | 1779 |

## Example 2 - Materials and Methods

**[00194]** **Patient cohort:** An initial cohort of 112 patients with metastatic melanoma were included in this study. These patients were treated with anti-PDl immune checkpoint blockade therapy at The University of Texas (UT) MD Anderson Cancer Center between April 2015 and March 2016 and signed voluntary informed consent for collection and analysis of tumor, blood and microbiome samples under Institutional Review Board (IRB)-approved protocols. Patients who were diagnosed with uveal melanoma (n=10), or who got anti-PDl in combination with targeted agents or with adoptive T-cell transfer therapy (n=8), or in whom response could not be determined (n=6) were excluded from this analysis. Electronic medical charts were reviewed independently by three investigators to assign clinical response group and document other clinical parameters (Table 3). The primary outcome of clinical response (responder) (R) was defined by radiographic evidence of complete response (CR), partial response (PR) or stable disease (SD) per RECIST 1.1 criteria for at least 6 months. Lack of a clinical response (non responder) (NR) was

defined by disease progression (PD) on serial CT scans or a clinical benefit lasting less than 6 months (minimal benefit).

**[00195]** **Microbiome sample collection:** Bucccal samples were collected during routine pre-treatment clinic visits using the Catch-Ail Sample Collection Swab (Epicentre, Madison, WI). All patients were also given outpatient OMNIgene GUT kit (OMR-200) (DNA Genotek fecal sample collection kits and asked to return). Importantly, this kit helps maintain microbiome profile stability at room temperature for up to 60 days. All samples were frozen at -80 degree C before DNA extraction and analysis.

**[00196]** The final cohort consisted of buccal samples collected from 87 patients, of whom 52 were R and 34 were NR, and fecal samples collected from 43 patients (of whom 30 were R and 13 were NR. All but 2 buccal and 2 fecal samples were collected at baseline. These were included as a baseline surrogate as a subset analysis on longitudinal samples which showed no change after treatment intervention in this cohort.

**[00197]** **Tumor and blood sample collection:** Available tumor samples (n=23) at matched pre-treatment time points were obtained from the MD Anderson Cancer Center Department of Pathology archive and Institutional Tissue Bank. After samples underwent quality control checks for percent tumor viability by an MD Anderson pathologist, the inventors included 17 samples from R and 6 from NR. Blood samples collected and stored for research (protocols previously listed) at baseline (n=ll) were also queried for study inclusion yielding samples from 8R and 3 NR.

**[00198]** **DNA extraction and bacterial 16S sequencing:** Preparation and sequencing was done in collaboration with the Center for Metagenomics and Microbiome Research (CMMR) at The Baylor College of Medicine. 16S rRNA gene sequencing methods were adapted from the methods developed for the NIH-Human Microbiome Project (A framework for human microbiome research, 2012).

**[00199]** Briefly, bacterial genomic DNA was extracted using MO BIO PowerSoil DNA Isolation Kit (MO BIO Laboratories, USA). The 16S rDNA V4 region was amplified by PCR and sequenced in the MiSeq platform (Illumina, Inc, San Diego, CA) using the 2x250 bp

paired-end protocol yielding pair-end reads that overlap almost completely. The primers used for amplification contain adapters for MiSeq sequencing and single-end barcodes allowing pooling and direct sequencing of PCR products (Caporaso *et al,* 2012).

**[00200]** Quality filtered sequences with >97% identity were clustered into bins known as *Operational Taxonomic Units (OTUs),* using open-reference OTU picking (Edgar, 2010; Rognes *et al.,* 2016; Caporaso *et al.,* 2010), and classified at the species level against the NCBI 16S ribosomal RNA 16S sequence database using ncbi-blast+ package 2.5.0. Phylogenetic classification was obtained from the NCBI taxonomy database. The relative abundance of each OTU was determined for all samples. Taxonomic classification was validated using the Greengenes, SILVA and RDP databases.

**[00201]** A phylogenetic tree was empirically constructed using the FastTree algorithm (Price *et al.,* 2010) in the QIIME software package, as described previously (Peled *et al.,* 2016). Briefly, all nodes of the tree were considered as *clusters of related OTU (crOTU),* where the abundance of each crOTU was the sum of abundances of its member OTUs. The trees were constructed from a sequence alignment of all observed OTU's within both oral 1152 (97.5%% of 1182 OTUs) and gut 1434 (98.6% of 1455 OTUs) microbiomes. The resultant oral and gut microbiome crOTU trees contained 1152 and 1434 nodes respectively.

**[00202]** Taxonomical alpha-diversity was estimated using the Inverse Simpson Index. Rarefaction limits were set based on the least number of reads in all oral (13000) and fecal samples (8000) that were analyzed, where D=l/ $\sum_{k=1}^{S} pi^2$, where pi is the proportion of the total species S that is comprised by the species i. Since, it captures variance of the taxonomical abundance distribution, it is often considered to be among the most meaningful and robust diversity metrics (Shannon *et al,* 2013).

**[00203]** **Bipartite network to compare and contrast the oral and gut microbiota:** The biparitie network was constructed using *make_biparitite_network.py* script in QIIME using default parameters (Caporaso *et al.,* 2010) and then visualized in Cytoscape using edge-weighted spring-embedded layout. 2 networks were generated, using all buccal and fecal samples (FIG. 6) and using only paired samples (FIG. 1A), when both samples were obtained from the same patients.

**[00204] Enrichment Index to visualize differences in oral and gut microbiome between R and NR:** *OTU representation index (ri):* is used to quantify the representation of each species in R; (*ri*R), and NR (*ri*NR), as the proportion of samples within each group that had non-zero abundance for a particular species. The values of ri ranged from 0 (OTU not found in any sample within a group) to 1 (OTU found in all samples within a group).

**[00205]** *OTU enrichment index (ei):* was used to quantify and compare the enrichment of each OTU in R vs NR, where $ei=(riR - riNR) / (riR + riNR)$. This index has values ranging from -1 and +1. When a species is identified in all R samples but not in any NR samples, $ei = +l$. The contrary is true for $ei = -1$.

**[00206]** The distribution *ei* scores was used to classify all species into 3 sets, Set 1- differentially enriched in R, Set 2 - found in both groups, and Set 3- differentially enriched in NR. Within each set, all OTU's were sorted by abundance and then visualized as a heatmap of log(10)-transformed OTU abundances in all sample given as columns. Thresholds for the OTU abundances (low, medium and high) were derived from the distribution of the abundances for all OTUs.

**[00207] Statistical assessment of biomarkers using LEfSe:** The LEfSe method of analysis first compares abundances of all bacterial clades between R and NR in the oral and gut microbiomes, using the Kruskal-Wallis test at a pre-defined **a** of 0.05, Significantly different vectors resulting from the comparison of abundances *(e.g., Faecalibacterium* relative abundance) between groups are used as input to linear discriminant analysis (LDA), which produces an effect size (FIG. 2B). The primary advantage of LEfSe over traditional statistical tests is that an effect size is produced in addition to a p-value. This allows sorting of results of multiple tests by the magnitude of the difference between groups. In the case of hierarchically organized bacterial clades, there may be a lack of correlation between p values and effect sizes due to differences in the number of hypotheses considered at different levels since a greater number of comparisons would need to be made at the genus and species levels when compared to the phylum and class levels.

**[00208] Metagenomic whole genome shotgun (WGS) sequencing:** This was also done in collaboration with CMMR and Metagenopolis (MGP). Briefly, metagenomic sequencing

data provides species-level resolution of the bacteria, and the near-complete genomic content of the collection of microbes in a particular sample, also referred to as the pangenome (depth of sequencing directly relates to the amount of the pangenome that is covered in a particular dataset).

**[00209]** Whole Genome Shotgun (WGS) sequencing utilizes the same extracted bacterial genomic DNA used for 16S rRNA gene compositional analysis. However, WGS sequencing achieves a higher depth of sequencing by employing a more powerful sequencing platform. Individual libraries were constructed from each sample and loaded into the HiSeq platform (Illumina) and sequenced using the 2x100 bp pair-end read protocol. The process of quality filtering, trimming, and demultiplexing was carried out by in-house pipeline developed by assembling publicly available tools such as Casava vl.8.3 (Illumina) for the generation of fastqs, Trim Galore and cutadapt for adapter and quality trimming, and PRINSEQ for sample demultiplexing.

**[00210]** Gut microbiota analysis was performed using the quantitative metagenomics pipeline developed at MGP. This approach allow the analysis of the microbiota at the gene and species level. High quality reads were selected and cleaned to eliminate possible contaminants as human reads. These were mapped and counted using the MetaHIT hs_9.9M genes catalogue (Li *etal.*, 2014) using the METEOR Studio in house pipeline using a two steps procedure : first using uniquely mapping reads, then attributing shared reads (mapping different genes from the catalogue) according to their mapping ratio using unique reads. Mapping was performed using a > 95% identity threshold to account gene variability and the no redundant nature of the catalogue.

**[00211]** After a downsizing step at 14M reads (to correct for the different sequencing depth) and normalization (RPKM), a gene frequency profile matrix was obtained which was used as the reference to perform the analyses using MetaOMineR, a suite of R packages developed at MGP and dedicated to the analysis of large quantitative metagenomics datasets.

**[00212]** The hs_9-9M gene catalogue has been clustered into 1438 MGS (MetaGenomic Species, groups of >500 genes that co-vary in abundance among hundreds samples and thus belong to the same microbial species (Nielson *et al.,* 2014). The taxonomical annotation of the MGS was performed using the homology of its genes with previously sequenced organisms (using blastN against nt and wgs databanks). MGS signal among samples was calculated as the

mean or median signal of 50 marker genes. A MGS frequency profile matrix was constructed using the MGS mean signals and after normalization (sum of the MGS frequency of a sample = 1).

**[00213]** Reads whose genomic coordinates overlap with known KEGG orthologs were tabulated, and KEGG modules were calculated step-wise and determined to be complete if 65% of the reaction steps were present per detected species and for the metagenome. Pathways were constructed for each taxa and metagenome by calculating the minimum set through MinPath resulting from the gene orthologs present.

**[00214]** **Pathway Metagenome Databases (PGDB):** Databases were generated for each WGS sample using the PathoLogic program from the Pathway Tools software [PMID:26454094] . Inputs for the program were produced using predicted gene functions based on KEGG orthology and their taxonomy assignment in the metagenomes Thus, if the same function (KO group) had several taxonomic annotations, each of the annotations was considered as a separate gene. The definition of the KO group in KEGG was used as the gene function and the first name of the KO group, if available, was used as the gene name. EC numbers were assigned to the gene according to annotations of the KO group by the numbers in KEGG. The metabolic reconstructions were made in the automatic mode as described in the Pathway Tools manual with the option -tip to automatically predict transport reactions. The DOMAIN value 'TAX-2 (Bacteria)' was used as the organism class for the PGDB and the CODON-TABLE value to be equal 1. The generated PGDB were summarized and compared using Pathway Tools. The generated PGDBs are available upon request.

**[00215]** **Statistical Analyses:** Alpha-diversity was compared between R and NR using the Wilcoxon rank-sum or Mann-Whitney (MW) test. All patients were classified into high, intermediate or low diversity groups based on tertiles of the distribution. Pairwise comparisons of taxonomic abundances by both response and cluster were conducted using the MW test. Within each level (phylum, class, order, family, genus and species), the low abundance (<0.1%) and low variance taxa (<0.001) were excluded. Adjustments for multiple comparisons were done using the false-discovery rate method at an alpha level of 0.05. An effect size was estimated for each taxon as U/Vn, where U is test statistic for the MW test, and n is the total sample size (n=43) (Fritz *et al.*, 2012), and volcano plots were generated for loglO(FDR-adjusted p values) on the y-axis and

median-adjusted effect sizes on the x-axis. In addition, patients were also classified as having high or low abundance of *Faecalibacterium prausnitzii* or *Bacteroidales* based on the median abundance of these taxa in the gut microbiome. Kaplan-Meier estimates were estimated for each group and compared using the log-rank test. Hazard ratios were estimated using the Cox-proportional hazard model.

**[00216]** In general the MW test was used for comparisons between binary outcome variables (R vs NR), and the Spearman correlation test was used to compare continuous variables. Additionally, the Fishers exact test was used when proportions were compared between binary variables. Hypothesis testing was done using both one-sided and two-sided tests as appropriate at a 95% significance level. All analyses were conducted in R and GraphPad Prism (La Jolla, CA).

**[00217]** **Immunohistochemistry:** Briefly, sections (4μιη thickness) were prepared from formalin fixed paraffin embedded (FFPE) tissues. The presence of tumor was confirmed by a pathologist on hematoxylin & eosin-stained slides (H&E). Slides were then stained using a Leica Bond RX automated slide stainer (Leica Biosystems, Buffalo Grove, IL) for CD3 (n=17)(DAKO, Santa Clara, CA, 1:100), CD8 (n=21)(Thermo Scientific, Waltham, MA, 1:100), PD-1 (n=16)(Abcam, Cambridge, UK, 1:250), PD-Ll(n=15)(l:100, Cell Signaling, Danvers, MA), GzmB (n=17), RORyT (n=14)(l:800, EMD Millipore, Billerica, MA), FoxP3 (n=16)(l:50, BioLegend, San Diego, CA) and counter-stained with hematoxylin. Stained slides were then scanned using an automated Aperio Slide Scanner (Leica), and the density of the immune infiltrate was quantified in tumor regions using a modified version of the default "Nuclear v9" algorithm and expressed as positive counts/mm2 for CD3, CD8, PD-1, FoxP3, and RORyT and as an H-score for PD-L1 which takes into account a percentage of positive cells multiplied by their intensity on a scale of 1 to 3 for a score between 1-300.

**[00218]** Flow cytometry was performed on peripheral blood mononuclear cells (PBMC). PBMCs were stained with CD3 (UCHT1, BioLegend), CD4 (SK3, eBioscience, Thermo Scientific), CD8 (RPAT8, BD Biosciences, Mississauga, Canada), FoxP3 (PCH101, eBioscience), CD127 (HIL-7R-M21, BD Biosciences), CD19 (HIB-19, BioLegend), CD14 (61D3, eBioscience), HLA-DR (L243, BD Biosciences), CD33 (WM53, BD Biosciences), CD56 (NCAM1, BD Biosciences), and CDl lb (ICRF44, BD Biosciences) and acquisition was carried out on a Fortessa

Flow Cytometer (BD Biosciences). Analysis was performed with FlowJo version 10 (Tree Star Inc., Ashland, OR).version 10 (Tree Star Inc., Ashland, OR).

**[00219]** **Multiplex Immunohistochemistry:** Sequential 12-marker myeloid multiplex immunohistochemistry was performed as described previously (Tsujikawa, *Cell Reports*, 2017). Briefly, FFPE sections underwent sequential staining, scanning and destaining cycles using AEC as chromagen and scanned with an Aperio Slide Scanner (Leica). Following staining and scanning with hematoxylin for nuclei, CD68, Tryptase, CSF1R, DC-SIGN, CD66b, CD83, CD163, HLA-DR, PD-L1, CD3/CD20/CD56, and CD45. CD45-positive regions of all images were then extracted using ImageScope, aligned, overlayed and segmented using CellProfiler and layers pseudocolored for analysis and quantification using FCS Express.

**[00220]** **Cytokine Multiplexing:** 41 plasma cytokine levels were assessed using multiplex bead assay (Bio-Rad, Hercules, CA). Cytokines, chemokines and soluble mediators quantified included IL-lb, IL-lra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, Eotaxin, FGF basic, G-CSF, GM-CSF, IFN-g, IP-10, MIP-la, PDGF-bb, MIP-lb, RANTES, TNF-a, VEGF, IL-2ra, HGF, TRAIL, IL-17A, IL-17F, IL-23, SDF1/CXCL12, CCL22, MCP-1/CCL2, Gro-a/CXCLl, ENA78/CXCL5, EGF, TGF-bl, TGF-b2, and TGF-b3.

## Example 3 - Modulation of the Gut Microbiome Enhances Anti-Tumor Responses in a Murine Melanoma Model

**[00221]** Next, it was sought to use insights gained from human studies to test the hypothesis that modulating the gut microbiome could enhance anti-tumor responses in a murine model of melanoma. Studies were performed to determine if modulation of the gut microbiome to enrich for short-chain fatty acid producing bacteria would enhance anti-tumor responses.

**[00222]** In these studies, a murine tumor model with a common driver mutation that is found in melanoma (BRAF) was used. The cells were implanted into genetically identical mice (C57BL6) purchased from 2 different vendors (Taconic farms versus Jackson laboratories) that differ significantly in their microbiome (with enriched short chain fatty acid producing bacteria in Taconic mice). The BRAF(V600E)/Pten $^{-/-}$ tumor cells were implanted into Taconic and Jackson mice, and substantial differences were observed in tumor growth (FIG. 33A) and survival (FIG. 33B) in these genetically identical mice with differing microbiomes. Interestingly, modulation of

the gut microbiome by co-housing Taconic and Jackson (FIG. 33C) (as mice are normally copropahgic) or by fecal transplant abrogated these differences, suggesting that modulation of the gut microbiome can alter tumor growth in the BRAF-mutant tumor model. As mice are copraphagic, cohousing leads the emrgence of a merged microbiome that draws from both individual microbiomes. 16S sequencing was performed on single-housed versus co-housed Taconic and Jackson mice, demonstrating distinct microbiomes in the single-housed mice and co-housed mice (FIGs. 33D & E), confirming modulation of the gut microbiome in these mice.

**[00223]** Based on the data in human patients, it was tested whether oral administration of butyrate (a short chain fatty acid) would enhance anti-tumor responses by providing adequate substrate to facilitate a favorable gut microbiome. In these studies, butyrate was administered orally to Taconic and Jackson mice. Treatment with butyrate was associated with an enhanced anti-tumor response in these studies (FIG. 33F), further suggesting that modulation of the gut microbiome may enhance anti-tumor responses.

**[00224]** Thus, these studies provide novel data regarding the diversity and composition of the oral and gut microbiome in patients with metastatic melanoma on systemic therapy, and importantly demonstrate that differential bacterial "signatures" exist in responders versus non-responders to immune checkpoint blockade (specifically PD-1 based therapy).

**Example 4 - Fecal Microbiota Transplantation**

**[00225]** **Fecal Microbiota Transplantation (FMT) of a favorable gut microbiome in germ-free (GF) mice reduces tumor growth (FMTl):** To investigate a causal link between a "favorable" gut microbiome and response to immune checkpoint blockade, Fecal Microbiome Transplantation (FMT) experiments were performed in germ-free (GF) recipient mice. A well-established syngeneic model of injectable murine melanoma driven by oncogenic $BRAF^{V600E}$ expression and PTEN deletion (BP cells) was used. In the first experiment (FMTl), it was sought to determine if FMT could have any impact on tumor growth. GF mice (n=3 per group) were transplanted by oral gavage with stool from a responder (R-FMT group) or from a non-responder (NR-FMT group) to anti-PD-1 therapy. Control group mice were transplanted with PBS alone. Two weeks after FMT, each mouse was injected subcutaneously with $8xl0^5$ BP cells, and

tumor growth was checked twice a week (FIG. 25A). Blood and fecal pellets were collected at different time points during the experiment.

**[00226]** Results from FMT1 demonstrated significantly delayed tumor growth by day 14 in R-FMT group compared to mice in those transplanted with stool from NR to anti-PD-1 (p=0.04, Figure IB).

**[00227]** Next, the systemic impact of FMT on the immune system was investigated using multicolor fluorescence activated cell sorting (FACS) analysis. Notably, mice receiving R-FMT had a higher percentage of innate effector cells (expressing $CD45^+CD11b^+Ly6G^+$) and lower frequency of suppressive myeloid cells (expressing $CDllb^+CDllc^+$) in the spleen compared to mice in the NR-FMT group (FIG. 26). These data suggested that specific subpopulations in the innate immune compartment play a role in the anti-tumoral response elicited by transplantation of a favorable gut microbiota in GF recipient mice.

**[00228]** This conclusion was further confirmed by quantitative confocal imaging on gut and tumor sections from mice that received FMT. Indeed, tumors of mice receiving R-FMT had a higher density of $CD45^+$ and $CD8^+$ T cells than mice receiving NR-FMT (FIG. 27A, and 27C upper panel). Moreover, FMT from R locally increased the number of $CD45^+$ immune and $CD8^+$ T cells in the gut compared to NR-FMT (FIG. 27B and 27C lower panel).

**[00229]** Additionally, taxonomic characterization using 16S sequencing revealed stark differences in the gut microbiome of germ-free mice before and after fecal microbiota transplantation (FMT), with major increases in Bacteroidales and Clostridiales taxa. As expected, control mice that received PBS, harbored markedly different taxa in their gut microbiome when compared to mice that received stool from responders (R-FMT) or non-responders (NR-FMT) to anti-PDl therapy. Furthermore, the gut microbiomes of mice receiving R-FMT and NR-FMT remained fairly stable over time post transplantation.

**[00230]** **FMT of a favorable gut microbiome in GF mice reduces tumor growth and enhances response to a-PD-Ll therapy (FMT2):** In the second FMT experiment (FMT2), it was asked if the microbiome from an R patient could enhance response to immune therapy when transplanted in mouse model of melanoma. To address this question, GF mice were transplanted

by oral gavage with stool from a responder (n=2, R-FMT group) or from a non-responder (n=3, NR-FMT group) to anti-PD-1 therapy. Control group mice (n=2) were transplanted with PBS alone. Two weeks after FMT, each mouse was injected with 8xl0$^5$ BP cells and tumor growth was checked twice a week. When tumor volume reached 250-500 mm$^3$, mice were treated with anti-PD-L1 antibody, administered by intra-peritoneal injection (FIG. 28A).

**[00231]** Results from FMT2 demonstrated significantly delayed tumor growth by day 14 in R-FMT group compared to mice in those transplanted with stool from NR to anti-PD-1 (p=0.04, FIG. 28B). Importantly, mice transplanted with R-FMT also exhibited improved responses to anti-PD-Ll therapy (FIG. 28C) compared to mice that were transplanted with stool from NR (NR-FMT).

**[00232]** Next, the mechanism through which the gut microbiome may influence systemic and anti-tumor immune responses was determined. FACS analysis of tumors and spleen immune infiltrates demonstrated that mice receiving R-FMT had higher percentage of CD45$^+$ myeloid cells infiltrating the tumor compared to mice in the NR-FMT group (FIG. 29A). In particular, a higher percentage of innate effector cells (expressing CD45$^+$CDllb $^+$Ly6G$^+$) and lower frequency of suppressive myeloid cells (expressing CDllb $^+$CDllc $^+$) were found in tumor immune infiltrates from R-FMT compared to NR-FMT (FIG. 29B-E). These data correlated specific subpopulations of the innate immune compartment to the anti-tumoral response induced by FMT from an R patient, both at peripheral (as showed in FMT1) and tumor level.

**[00233]** An increase in the frequency of RORγT$^+$ Thl7 cells in the tumor was also detected in NR-FMT mice (FIG. 30A and B), in line with observations made in tumors from patients who failed to respond to PD-1 blockade. Moreover, mice receiving NR-FMT also demonstrated higher levels of regulatory CD4$^+$ FOXP3$^+$ T cells (FIG. 30C) and CD4$^+$ IL-17$^+$ (FIG. 3ID) cells in the spleen, suggesting impaired host immune responses.

**[00234]** Mass cytometry (CyTOF) analysis using t-SNE dimension reduction was performed on tumors from mice, and demonstrated up-regulation of PD-L1 in the tumor microenvironment of mice receiving R-FMT versus NR-FMT (FIG. 31A), suggesting the development of a "hot" tumor microenvironment. CyTOF analysis also confirmed that distinct

myeloid subpopulation preferentially infiltrate tumors in R-FMT or non-responders NR-FMT (FIG. 3IB)

**[00235]** Longitudinal sampling and microbiome characterization of fecal pellets from FMT2 experiment showed results similar to FMT1, with relative stability in the gut microbiome over time.

**[00236]** **Stability of the microbiome in germ-free mice post engraftment with FMT.** 16S sequencing was performed on longitudinal fecal pellets collected from germ-free mice that received stool from a patient who responded to PD-1 blockade to versus a patient who did not. Examination of phylogenetic taxa at the order level and comparison of baseline pellets with those collected two weeks after FMT completion revealed successful engraftment. Moreover, persistence of the most abundant orders over time suggested that the engrafted microbiome was stable during the whole experiment.

**[00237]** Based on the hypotheses that certain bacteria within the R-FMT mice flora help slow tumor growth, and that certain bacteria in NR-FMT mice flora help stimulate tumor growth, we compared OTUs that were either present in R-FMT mice or NR-FMT mice only (or also missing from control mice). These were done in representative mice from each group from the 2 FMT experiments. The inventors also looked at the OTUs that showed consistent transfer results in both FMT experiments. This analysis revealed that OTUs classified as *Acetanaerobacterium elongatum, Alistipes timonensis, Anaerocolumna jejuensis, Anaerocolumna xylanovorans, Bacteroides fragilis, Bacteroides nordii, Bacteroides stercoris, Blautia faecis, Blautia glucerasea, Blautia hansenii, Blautia obeum, Blautia schinkii, Caproiciproducens galactitolivorans, Christensenella minuta, Clostridium aldenense, Clostridium alkalicellulosi, Clostridium amygdalinum, Clostridium oroticum, Clostridium polysaccharolyticum, Clostridium xylanolyticum, Coprobacillus cateniformis, Emergencia timonensis, Eubacterium hallii, Extibacter muris, Faecalibacterium prausnitzii, Ihubacter massiliensis, Neglecta timonensis, Novibacillus thermophilus, Oscillibacter ruminantium, Papillibacter cinnamivorans, Parabacteroides johnsonii, Parasporobacterium paucivorans, Peptococcus niger, Pseudoflavonifractor capillosus, Robinsoniella peoriensis, Ruminococcus gauvreauii,*

*Ruminococcus gnavus, Ruminococcus torques,* and *Slackia piriformis* were found only in R-FMT mice in both experiments.

**[00238] FMT from different R and NR donors in germ-free GF mice confirms the link between R microbiota and reduced tumor growth (FMT3).** To validate the finding that a "favorable" gut microbiome restrains tumor growth when transplanted in GF mice, an experiment was performed similar to FMT1 using stools from different R and NR patients. In this third experiment (FMT3), GF mice were transplanted by oral gavage with stool from one responder ((n=l, R-FMT group) or from one non-responder ((n=l, NR-FMT group) to anti-PD-1 therapy. Control group mice were transplanted with PBS alone (n=3, Control group). Two weeks after FMT, each mouse was injected subcutaneously with $2.5xl0^{5}$ BP cells, and tumor growth was checked twice a week (Figure 32A). Blood and fecal pellets were collected at different time points during the experiment.

**[00239]** Results from FMT3 confirmed significantly delayed tumor growth by day 14 in R-FMT group compared to mice in those transplanted with stool from NR to anti-PD-1 (Figure 32B). Importantly, this difference was maintained over time until the end point (FIG. 32C).

## Example 5 - Fecal Microbiota Transplantation Methods

**[00240] Fecal microbiota transplantation (FMT):** All animal studies were approved by the Animal Care and Use Committee, The UT at MD Anderson Cancer Center, in compliance with the Guide for the Care and Use of Laboratory Animals. B6 germ-free mice for murine studies were bought from the gnotobiotic facility of Baylor College of Medicine (Houston). All mice were transported in specialized autoclaved shipping cages, and were housed at MD Anderson Cancer Center mouse facility. All cages, bottles with stoppers and animal drinking water were autoclaved before being used. Food and bedding were double irradiated and tested to ensure sterility prior to being used in the experiment. Within each treatment category, a control group of mice received only pre-reduced PBS. All other mice from experimental groups received FMT from either an R donor or a NR donor, with each donor sample delivered to one, two or three mice. 200µ1 cleared supernatant from 0.1 g/µï human fecal suspension was obtained using a 100 µιη strainer and gavaged into mice for 3 doses over 1 week, followed by a break of 1-week to allow

microbiome establishment. Mice were then injected with BP syngeneic tumor cell line (Day 14), and animals were treated with anti-PD-Ll monoclonal antibody (purified low endotoxin, functional formulation, B7-H1, CD274, Leinco Technologies Inc.) once tumors reached -250-500 $mm^3$. Tumor growth/survival was assessed. Fecal specimens, blood, spleens and tumors were harvested and processed for further analysis.

**[00241] Flow cytometry of mouse tumor and spleen:** Tumors were isolated and minced into small pieces and digested for 1 hour in RPMI containing collagenase A (2 mg/mL; Roche, Cat.No. 11 088 793 001) and DNase I (40 units/mL; Sigma-Aldrich, Cat.No. D5025) with agitation at 37°C. Cell suspensions were passed through a cell strainer, washed in 2% RPMI supplemented with 2 mmol/L EDTA and resuspended in FACS buffer (PBS containing 2% heat-inactivated FBS with 2 mM EDTA supplementation). Spleens were smashed in FACS buffer and red blood cells lysed by incubation in ACK buffer (Gibco) for 2 minutes at room temperature. The pellet was then washed and resuspended in FACS buffer. For analysis of cell surface markers, the following antibodies were used: CD45 (30-F11, BD Biosciences), CDllb (Ml/70, eBioscience), CDllc (HL3, BD Pharmigen), Ly6G (RB6-8C5, eBioscience), Ly6C (AL-21, BD Bioscience), F4/80 (BM8, eBioscience). Cells were labeled with LIVE/DEAD viability stain (Life Technologies) and samples were acquired on a LSR Fortessa X20 flow cytometry (BD). Doublets were distinguished and excluded by plotting FSC area versus FSC height and data analyzed using FlowJo software (Tree Star).

**[00242] Immunofluorescence on FFPE samples:** Xenograft tumors, mouse gut and spleens were harvested, fixed in buffered 10% formalin first (4 hours at room temperature), then switched to 70% ethanol and stored at 4°C. Tissues were embedded in paraffin and 5 μιη sections were mounted on positively charged slides. Tissues were deparaffinized and antigen retrieval was performed in pH 6.0 Citrate buffer (Dako) using a microwave. Sections were blocked in blocking buffer (5% Goat Serum/0.3% BSA/0.0 l%Triton in PBS) followed by primary antibody incubation overnight at 4°C. Sections were washed and then incubated with Alexa-conjugated secondary antibody (1:500, Molecular Probes) for 1 hour at room temperature. Coverslips were washed 3 times in PBS/0.01% Triton and then incubated for 15 minutes at room temperature in Hoechst stain (1:5000, Invitrogen). After 3 washes in PBS, the samples were mounted in ProLog

Diamond mounting media (Molecular Probe). Images where captured using a Nikon A1R+ confocal microscope equipped with a four solid state laser system and a 20x objective.

**[00243]** **CyTOF:** Tumors were manually dissociated, digested using liberase TL (Roche) and DNase I for 30 minutes at 37°C, and passed through a 70 μιη mesh filter. Samples were then centrifuged using a discontinuous gradient of Histopaque 1119 (Sigma-Aldrich) and RMPI media. Single cell suspensions of up to 2.5 x $10^6$ cells per sample were Fc-receptor blocked and stained with a surface antibody mixture for 30 minutes at 4°C. Metal-conjugated antibodies were purchased from Fluidigm or conjugated using X8 polymer antibody labeling kits according to the manufacturer's protocol (Fluidigm). Samples were stained using 2.5 μM $^{194}$Pt-cisplatin (Fluidigm) for 1 minute and washed twice with 2% FCS PBS. Cells were barcoded using a palladium mass tag barcoding approach according to the manufacturer's protocol (Fluidigm) and combined after two washes with 2% FCS PBS. Cells were then fixed and permeabilized using FoxP3 transcription factor staining kit according to the manufacturer's protocol (eBioscience). Samples were then stained using a mixture of antibodies against intracellular targets for 30 minutes at room temperature. Samples were washed twice with 2% FCS PBS and then incubated overnight in a 1.6% PFA/100 nM iridium/PBS solution prior to acquisition using a Helios mass cytometer (Fluidigm).

**[00244]** Mass cytometry data were bead normalized and debarcoded using Fluidigm software. Total live and CD45+ cells were manually gated using FlowJo. t-SNE analyses were performed on total live and CD45+ cells using the Cyt package in Matlab. Data were arcsinh transformed using a co-efficient of 4 and randomly down-sampled to 50,000 events per sample prior to t-SNE analysis. t-SNE plots for each experimental group were then generated by merging samples from each group and displaying an equal number of randomly down-sampled events (50,000) from each treatment group.

**[00245]** Table 9: CyTOF panel.

| Target | Clone | Metal Tag | Stain | Source |
|---|---|---|---|---|
| CD45 | 30-F11 | 89Y | Surface | Fluidigm |
| c-MYC | 9E10 | 115In | Intracellular | eBioscience |

| | | | | |
|---|---|---|---|---|
| MHC-II | M5/114.15.2 | 139La | Surface | Biolegend |
| NK1.1 | PK136 | 141Pr | Surface | Biolegend |
| CDllc | N418 | 142Nd | Surface | Biolegend |
| CD80 | 16-10A1 | 143Nd | Surface | Biolegend |
| MHC-I | 28-14-8 | 144Nd | Surface | Fluidigm |
| CD4 | RM4-5 | 145Nd | Surface | Fluidigm |
| CD8a | 53-6.7 | 146Nd | Surface | Fluidigm |
| CD86 | GL-1 | 147Sm | Surface | Biolegend |
| CD27 | LG.3A10 | 148Nd | Surface | Biolegend |
| OX40 | OX-86 | 149Sm | Surface | eBio science |
| CD25 | 3C7 | 150Nd | Surface | Fluidigm |
| TIGIT | 1G9 | 151Eu | Surface | Biolegend |
| CD3e | 145-2C11 | 152Sm | Intracellular | Fluidigm |
| PD-L1 | 10F.9G2 | 153Eu | Surface | Fluidigm |
| BATF | D7C5 | 154Sm | Intracellular | Fluidigm |
| ICOS | 7E.17G9 | 155Gd | Surface | eBio science |
| CD69 | H1.2F3 | 156Gd | Surface | Biolegend |
| CXCR5 | 2G8 | 158Gd | Surface | BD |
| PD-1 | 29F.1A12 | 159Tb | Surface | Fluidigm |
| CD62L | MEL-14 | 160Gd | Surface | Fluidigm |
| CXCR3 | CXCR3-173 | 161Dy | Surface | Biolegend |
| TIM3 | RMT3-23 | 162Dy | Surface | Fluidigm |
| LAG3 | C9B7W | 163Dy | Surface | Biolegend |
| LAP-TGFp | TW7-16B4 | 164Dy | Surface | Fluidigm |
| FoxP3 | FJK-16s | 165Ho | Intracellular | Fluidigm |
| BCL2 | BCL/10C4 | 166Er | Intracellular | Biolegend |
| GATA3 | L50-823 | 167Er | Intracellular | BD |
| BCL6 | Kl 12-91 | 168Er | Intracellular | BD |
| CD117 | 2B8 | 169Tm | Surface | Biolegend |
| CD 127 | A7R34 | 170Er | Surface | Biolegend |

| | | | | |
|---|---|---|---|---|
| CTLA-4 | UC10-4B9 | 171Yb | Intracellular | Biolegend |
| CD lib | Ml/70 | 172Yb | Surface | Fluidigm |
| TBET | 4B10 | 173Yb | Intracellular | Biolegend |
| RORyT | Q3 1-378 | 174Yb | Intracellular | BD |
| CD28 | 37.51 | 175Lu | Surface | Biolegend |
| EOMES | Dan 1 1mag | 176Yb | Intracellular | eBio science |
| Live/Dead | N/A | 194Pt | Surface | Fluidigm |
| CD19 | 6D5 | 195Pt | Surface | Biolegend |
| TCRγδ | GL3 | 196Pt | Surface | Biolegend |
| KLRG1 | 2F1 | 198Pt | Surface | BD |
| CD44 | IM7 | 209BÏ | Surface | Fluidigm |

* * *

**[00246]** All of the methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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## CLAIMS

**WHAT IS CLAIMED IS:**

1. A composition comprising at least one isolated or purified population of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae.

2. A composition comprising at least two isolated or purified populations of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae.

3. The composition of claim 1 or claim 2, wherein each of the populations of bacteria is present in the composition at a concentration of at least 10^3 CFU.

4. The compositon of claim 1 or claim 2, wherein the composition is a live bacterial product or a live biotherapeutic product.

5. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria are provided as bacterial spores.

6. The compositon of claim 1 or claim 2, wherein the at least one population of bacteria or the at least two isolated or purified populations of bacteria belong to Clostridiales Family XII and/or Clostridiales Family XIII.

7. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the the family Ruminococcaceae and/or of the family Clostridiaceae.

8. The composition of claim 1 or claim 2, wherein the population of bacteria belonging to the family Ruminococcaceae is further defined as a population of bacteria belonging to the genus *Ruminococcus.*

9. The composition of claim 8, wherein the population of bacteria belonging to the genus *Ruminococcus* is further defined as a population of bacteria belonging to the species *Ruminococcus bromii.*

10. The composition of claim 1 or claim 2, wherein the population of bacteria belonging to the family Ruminococcaceae is further defined as a population of bacteria belonging to the genus *Faecalibacterium.*

11. The composition of claim 10, wherein the population of bacteria belonging to the genus *Faecalibacterium* is further defined as a population of bacteria belonging to the species *Faecalibacterium prausnitzii.*

12. The composition of claim 1 or claim 2, wherein the population of bacteria belonging to the family Micrococcaceae is further defined as a population of bacteria belonging to the genus *Rothia.*

13. The composition of claim 1 or claim 2, wherein the composition further comprises a population of bacteria belonging to the species *Porphyromonas pasteri,* the species *Clostridium hungatei,* the species *Phascolarctobacterium faecium,* the genus *Peptoniphilus,* and/or the class Mollicutes.

14. The composition of claim 1 or claim 2, wherein the composition is essentially free of populations of bacteria belonging to the order Bacteroidales.

15. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belongs to one or more of the species, subspecies or bacterial strains selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5.

16. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria are selected from the group consisting of the species in Table 1 with an "ei" equal to 1.

17. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria comprise a 16S ribosomal RNA (rRNA) nucleotide sequence that is at least 90% identical to the 16S rRNA nucleotide sequence of bacteria identified by NCBI Taxonomy IDs selected from the group consisting of NCBI Taxonomy ID: 717959, 587, 758823, 649756, 44749, 671218, 1264, 1122135, 853, 484018, 46503, 54565, 290052, 216931, 575978, 433321, 1796646, 213810, 228924, 290054, 1509, 1462919, 29375, 337097, 1298596, 487174, 642492, 1735, 1297424, 742766, 46680, 132925, 411467, 1318465, 1852367, 1841857, 169679, 1175296, 259063, 172901, 39488, 57172, 28118, 166486, 28133, 1529, 694434, 1007096, 84030, 56774, 102148, 626947, 216933, 1348613, 1472417, 100176, 824, 1471761, 1297617, 288966, 1317125, 28197, 358743, 264639, 1265, 1335, 66219, 69473, 115117, 341220, 1732, 873513, 396504, 1796619, 45851, 2741, 105841, 86332, 1349822, 84037, 180311, 54291, 1217282, 762984, 1185412, 154046, 663278, 1543, 398512, 69825, 1841867, 1535, 1510, 84026, 1502, 1619234, 39497, 1544, 29343, 649762, 332095, 536633, 1033731, 574930, 742818, 177412, 1121308, 419208, 1673717, 55779, 28117, 626937, 180332, 1776382, 40519, 34062, 40518, 74426, 1216062, 293826, 850, 645466, 474960, 36835, 115544, 1515, 88431, 216932, 1417852, 39492, 1583, 420247, 118967, 169435, 37658, 138595, 31971, 100886, 1197717, 234908, 537007, 319644, 168384, 915173, 95159, 1816678, 626940, 501571, 1796620, 888727, 1147123, 376806, 1274356, 1267, 39495, 404403, 1348, 253314, 258515, 33033, 1118061, 357276, 214851, 320502, 217731, 246787, 29371, 649764, 901, 29374, 33043, 39778, 682400, 871665, 160404, 745368, 408, 1584, 333367, 47246, 1096246, 53342, 438033, 351091, 1796622, 1776384, 817, 48256, 720554, 500632, 36849, 301302, 879970, 655811, 264463, 1532, 285, 995, 242750, 29539, 1432052, 622312, 1796636, 1337051, 328814, 28446, 1492, 820, 39496, 52786, 1549, 1796618, 582, 46507, 109327, 1531, 1382, 33039, 311460, 230143, 216935, 539, 35519, 1681, 328813, 214853, 89014, 1121115, 1585974, 29466, 1363, 292800, 270498, 214856, 142877, 133926, 209880, 179628, 1121102, 105612, 1796615, 39777, 29353, 1579, 163665, 53443, 261299, 1302, 1150298, 938289, 358742, 471875, 938278, 1796613, 1118057, 1077144, 1737, 218205, 1121298, 684066, 433659, 52699, 204516, 706562, 253257, 328812, 1280, 147802, 58134, 1335613, 891, 585394, 1582, 235931, 308994, 1589, 1682,

1736, 28129, 178001, 551788, 2051, 856, 118562, 101070, 515619, 40215, 187979, 82979, 29363, 1776391, 1285191, 84112, 157688, 38304, 36850, 341694, 287, 75612, 818, 371674, 338188, 88164, 588581, 676965, 546271, 1236512, 178338, 862517, 157687, 158, 51048, 1583331, 529, 888745, 394340, 40545, 855, 553973, 938293, 93063, 708634, 179995, 1351, 476652, 1464038, 555088, 237576, 879566, 1852371, 742727, 1377, 35830, 997353, 218538, 83771, 1605, 28111, 131109, 46609, 690567, 46206, 155615, 51616, 40542, 203, 294, 1034346, 156456, 80866, 554406, 796942, 1002367, 29347, 796944, 61592, 487175, 1050201, 762948, 137732, 1211819, 1019, 272548, 1717, 384636, 216940, 2087, 45634, 466107, 1689, 47678, 575, 979627, 840, 1660, 1236517, 617123, 546, 28135, 82171, 483, 501496, 99656, 1379, 84032, 39483, 1107316, 584, 28124, 1033744, 657309, 536441, 76123, 1118060, 89152, 76122, 303, 1541, 507751, 515620, 38302, 53419, 726, 40324, 1796610, 988946, 1852370, 1017, 1168289, 76936, 94869, 1161098, 215580, 1125779, 327575, 549, 1450648 and 478.

18. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria are a species, subspecies or bacterial strains comprising a 16S rRNA gene sequence at least 80% identical to the sequence of SEQ ID NO: 1-876.

19. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the species, subspecies or bacterial strains selected from the group consisting of *Bacteroides coagulans, Clostridium aldenense, Clostridium aldrichii, Clostridium alkalicellulosi, Clostridium amygdalinum, Clostridium asparagiforme, Clostridium cellulosi, Clostridium citroniae, Clostridium clariflavum DSM 19732, Clostridium clostridioforme, Clostridium colinum, Clostridium fimetarium, Clostridium hiranonis, Clostridium hungatei, Clostridium hylemonae DSM 15053, Clostridium indolis, Clostridium lactatifermentans, Clostridium leptum, Clostridium methylpentosum, Clostridium oroticum, Clostridium papyrosolvens DSM 2782, Clostridium populeti, Clostridium propionicum, Clostridium saccharolyticum, Clostridium scindens, Clostridium sporosphaeroides, Clostridium stercorarium, Clostridium straminisolvens, Clostridium sufflavum, Clostridium termitidis, Clostridium thermosuccinogenes, Clostridium viride, Clostridium xylanolyticum, Desulfotomaculum guttoideum, Eubacterium rectale ATCC 33656, Eubacterium dolichum, Eubacterium eligens ATCC 27750, Eubacterium hallii,*

*Eubacterium infirmum, Eubacterium siraeum, Eubacterium tenue, Ruminococcus torques, Acetanaerobacterium elongatum, Acetatifactor muris, Acetivibrio cellulolyticus, Acetivibrio ethanolgignens, Acholeplasma brassicae 0502, Acholeplasma parvum, Acholeplasma vituli, Acinetobacter junii, Actinobacillus porcinus, Actinomyces bowdenii, Actinomyces dentalis, Actinomyces odontolyticus, Acutalibacter muris, Aerococcus viridans, Aeromicrobium fastidiosum, Alistipes finegoldii, Alistipes obesi, Alistipes onderdonkii, Alistipes putredinis, Alistipes shahii, Alistipes shahii WAL 8301, Alistipes timonensis JC136, Alkalibacter saccharofermentans, Alkaliphilus metalliredigens QYMF, Allisonella histaminiformans, Allobaculum stercoricanis DSM 13633, Alloprevotella rava, Alloprevotella tannerae, Anaerobacterium chartisolvens, Anaerobiospirillum thomasii, Anaerobium acetethylicum, Anaerococcus octavius NCTC 9810, Anaerococcus provenciensis, Anaerococcus vaginalis ATCC 51170, Anaerocolumna jejuensis, Anaerofilum agile, Anaerofustis stercorihominis, Anaeroglobus geminatus, Anaeromassilibacillus senegalensis, Anaeroplasma abactoclasticum, Anaerorhabdus furcosa, Anaerosporobacter mobilis, Anaerostipes butyraticus, Anaerostipes caccae, Anaerostipes hadrus, Anaerotruncus colihominis, Anaerovorax odorimutans, Anoxybacillus rupiensis, Aquabacterium limnoticum, Arcobacter butzleri, Arthrospira platensis, Asaccharobacter celatus, Atopobium parvulum, Bacteroides caccae, Bacteroides caecimuris, Bacteroides cellulosilyticus, Bacteroides clarus YIT 12056, Bacteroides dorei, Bacteroides eggerthii, Bacteroides finegoldii, Bacteroides fragilis, Bacteroides gallinarum, Bacteroides massiliensis, Bacteroides oleiciplenus YIT 12058, Bacteroides plebeius DSM 17135, Bacteroides rodentium JCM 16496, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides xylanisolvens XB1A, Bacteroides xylanolyticus, Barnesiella intestinihominis, Beduini massiliensis, Bifidobacterium bifidum, Bifidobacterium dentium, Bifidobacterium longum subsp. infantis, Blautia caecimuris, Blautia coccoides, Blautia faecis, Blautia glucerasea, Blautia hansenii DSM 20583, Blautia hydrogenotrophica, Blautia luti, Blautia luti DSM 14534, Blautia wexlerae DSM 19850, Budvicia aquatica, Butyricicoccus pullicaecorum, Butyricimonas paravirosa, Butyrivibrio crossotus, Caldicoprobacter oshimai, Caloramator coolhaasii, Caloramator proteoclasticus, Caloramator quimbayensis, Campylobacter gracilis, Campylobacter rectus, Campylobacter ureolyticus DSM 20703, Capnocytophaga gingivalis, Capnocytophaga leadbetteri, Capnocytophaga sputigena, Casaltella massiliensis, Catabacter hongkongensis, Catenibacterium mitsuokai, Christensenella minuta, Christensenella timonensis, Chryseobacterium taklimakanense, Citrobacter freundii,*

*Cloacibacillus porcorum, Clostridioides difficile ATCC 9689 = DSM 1296, Clostridium amylolyticum, Clostridium bowmanii, Clostridium butyricum, Clostridium cadaveris, Clostridium colicanis, Clostridium gasigenes, Clostridium lentocellum DSM 5427, Clostridium oceanicum, Clostridium oryzae, Clostridium paraputrificum, Clostridium pascui, Clostridium perfringens, Clostridium quinii, Clostridium saccharobutylicum, Clostridium sporogenes, Clostridium ventriculi, Collinsella aerofaciens, Comamonas testosteroni, Coprobacter fastidiosus NSB1, Coprococcus eutactus, Corynebacterium diphtheriae, Corynebacterium durum, Corynebacterium mycetoides, Corynebacterium pyruviciproducens ATCC BAA-1742, Corynebacterium tuberculostearicum, Culturomica massiliensis, Cuneatibacter caecimuris, Defluviitalea saccharophila, Delftia acidovorans, Desulfitobacterium chlororespirans, Desulfitobacterium metallireducens, Desulfosporosinus acididurans, Desulfotomaculum halophilum, Desulfotomaculum intricatum, Desulfotomaculum tongense, Desulfovibrio desulfuricans subsp. desulfuricans, Desulfovibrio idahonensis, Desulfovibrio litoralis, Desulfovibrio piger, Desulfovibrio simplex, Desulfovibrio zosterae, Desulfuromonas acetoxidans, Dethiobacter alkaliphilus AHT 1, Dethiosulfatibacter aminovorans, Dialister invisus, Dialister propionicifaciens, Dielma fastidiosa, Dietzia alimentaria 72, Dorea longicatena, Dysgonomonas gadei ATCC BAA-286, Dysgonomonas mossii, Eggerthella lenta, Eikenella corrodens, Eisenbergiella tayi, Emergencia timonensis, Enorma massiliensis phi, Enterococcus faecalis, Enterorhabdus muris, Ethanoligenens harbinense YUAN-3, Eubacterium coprostanoligenes, Eubacterium limosum, Eubacterium oxidoreducens, Eubacterium sulci ATCC 35585, Eubacterium uniforme, Eubacterium ventriosum, Eubacterium xylanophilum, Extibacter muris, Ezakiella peruensis, Faecalibacterium prausnitzii, Faecalicoccus acidiformans, Faecalitalea cylindroides, Filifactor villosus, Flavonifractor plautii, Flintibacter butyricus, Frisingicoccus caecimuris, Fucophilus fucoidanolyticus, Fusicatenibacter saccharivorans, Fusobacterium mortiferum, Fusobacterium nucleatum subsp. vincentii, Fusobacterium simiae, Fusobacterium varium, Garciella nitratireducens, Gemella haemolysans, Gemmiger formicilis, Gordonibacter urolithinfaciens, Gracilibacter thermotolerans JW/YJL-S1, Granulicatella elegans, Guggenheimella bovis, Haemophilus haemolyticus, Helicobacter typhlonius, Hespellia stercorisuis, Holdemanella biformis, Holdemania massiliensis AP2, Howardella ureilytica, Hungatella effluvii, Hungatella hathewayi, Hydrogenoanaerobacterium saccharovorans, Ihubacter massiliensis, Intestinibacter bartlettii, Intestinimonas butyriciproducens,*

*Irregularibacter muris, Kiloniella laminariae DSM 19542, Kroppenstedtia guangzhouensis, Lachnoanaerobaculum orale, Lachnoanaerobaculum umeaense, Lachnoclostridium phytofermentans, Lactobacillus acidophilus, Lactobacillus algidus, Lactobacillus animalis, Lactobacillus casei, Lactobacillus delbrueckii, Lactobacillus fornicalis, Lactobacillus iners, Lactobacillus pentosus, Lactobacillus rogosae, Lactococcus garvieae, Lactonifactor longoviformis, Leptotrichia buccalis, Leptotrichia hofstadii, Leptotrichia hongkongensis, Leptotrichia wadei, Leuconostoc inhae, Levyella massiliensis, Loriellopsis cavernicola, Lutispora thermophila, Marinilabilia salmonicolor JCM 21150, Marvinbryantia formatexigens, Mesoplasma photuris, Methanobrevibacter smithii ATCC 35061, Methanomassiliicoccus luminyensis BIO, Methylobacterium extorquens, Mitsuokella jalaludinii, Mobilitalea sibirica, Mobiluncus curtisii, Mogibacterium pumilum, Mogibacterium timidum, Moorella glycerini, Moorella humiferrea, Moraxella nonliquefaciens, Moraxella osloensis, Morganella morganii, Moryella indoligenes, Muribaculum intestinale, Murimonas intestini, Natranaerovirga pectinivora, Neglecta timonensis, Neisseria cinerea, Neisseria oralis, Nocardioides mesophilus, Novibacillus thermophilus, Ochrobactrum anthropi, Odoribacter splanchnicus, Olsenella profusa, Olsenella uli, Oribacterium asaccharolyticum ACB7, Oribacterium sinus, Oscillibacter ruminantium GH1, Oscillibacter valericigenes, Oxobacter pfennigii, Pantoea agglomerans, Papillibacter cinnamivorans, Parabacteroides faecis, Parabacteroides goldsteinii, Parabacteroides gordonii, Parabacteroides merdae, Parasporobacterium paucivorans, Parasutterella excrementihominis, Parasutterella secunda, Parvimonas micra, Peptococcus niger, Peptoniphilus duerdenii ATCC BAA-1640, Peptoniphilus grossensis ph5, Peptoniphilus koenoeneniae, Peptoniphilus senegalensis JC140, Peptostreptococcus stomatis, Phascolarctobacterium succinatutens, Phocea massiliensis, Pontibacter indicus, Porphyromonas bennonis, Porphyromonas endodontalis, Porphyromonas pasteri, Prevotella bergensis, Prevotella buccae ATCC 33574, Prevotella denticola, Prevotella enoeca, Prevotella fusca JCM 17724, Prevotella loescheii, Prevotella nigrescens, Prevotella oris, Prevotella pollens ATCC 700821, Prevotella stercorea DSM 18206, Prevotellamassilia timonensis, Propionispira arcuata, Proteus mirabilis, Providencia rettgeri, Pseudobacteroides cellulosolvens ATCC 35603 = DSM 2933, Pseudobutyrivibrio ruminis, Pseudoflavonifractor capillosus ATCC 29799, Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas mandelii, Pseudomonas nitroreducens, Pseudomonas putida, Raoultella ornithinolytica, Raoultella planticola, Raoultibacter*

*massiliensis, Robinsoniella peoriensis, Romboutsia timonensis, Roseburia faecis, Roseburia hominis A2-183, Roseburia intestinalis, Roseburia inulinivorans DSM 16841 ,Rothia dentocariosa ATCC 17931, Ruminiclostridium thermocellum, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus champanellensis 18P13 = JCM 17042, Ruminococcus faecis JCM 1591 7, Ruminococcus flavefaciens, Ruminococcus gauvreauii, Ruminococcus lactaris ATCC 29176, Rummeliibacillus pycnus, Saccharofermentans acetigenes, Scardovia wiggsiae, Schlegelella thermodepolymerans, Sedimentibacter hongkongensis, Selenomonas sputigena ATCC 35185, Slackia exigua ATCC 700122, Slackia piriformis YIT 12062, Solitalea canadensis, Solobacterium moorei, Sphingomonas aquatilis, Spiroplasma alleghenense, Spiroplasma chinense, Spiroplasma chrysopicola, Spiroplasma culicicola, Spiroplasma lampyridicola, Sporobacter termitidis, Staphylococcus aureus, Stenotrophomonas maltophilia, Stomatobaculum longum, Streptococcus agalactiae ATCC 13813, Streptococcus cristatus, Streptococcus equinus, Streptococcus gordonii, Streptococcus lactarius, Streptococcus parauberis, Subdoligranulum variabile, Succinivibrio dextrinosolvens, Sutterella stercoricanis, Sutterella wadsworthensis, Syntrophococcus sucromutans, Syntrophomonas zehnderi OL-4, Terrisporobacter mayombei, Thermoleophilum album, Treponema denticola, Treponema socranskii, Tyzzerella nexilis DSM 1787, Vallitalea guaymasensis, Vallitalea pronyensis, Vampirovibrio chlorellavorus, Veillonella atypica, Veillonella denticariosi, Veillonella dispar, Veillonella parvula, Victivallis vadensis, Vulcanibacillus modesticaldus and Weissella confusa.*

20. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations belong to species of bacteria are selected from the species in Table 2 designated with a response status of responder (R).

21. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to species of bacteria are selected from the group consisting of the species in Table 2 designated with a response status of responder (R) and having an unadjusted p-value less than 0.1.

22. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria belong to

species, subspecies or strains comprising nucleotide sequences with at least 80 percent identity to the co-abundance gene group (CAG) sequences selected from the group consisting of SEQ ID NO: 877-926, SEQ ID NO: 927-976, SEQ ID NO: 977-1026, SEQ ID NO: 1027-1076, SEQ ID NO: 1077-1126, SEQ ID NO: 1127-1176, SEQ ID NO: 1177-1226, SEQ ID NO: 1227-1276, SEQ ID NO: 1277-1326, SEQ ID NO: 1327-1376, SEQ ID NO: 1377-1426, SEQ ID NO: 1427-1476, SEQ ID NO: 1477-1526, SEQ ID NO: 1527-1576, SEQ ID NO: 1577-1626, SEQ ID NO: 1627-1676, SEQ ID NO: 1677-1726, SEQ ID NO: 1727-1776, SEQ ID NO: 1777-1826, SEQ ID NO: 1827-1876, SEQ ID NO: 1877-1926, SEQ ID NO: 1927-1976, SEQ ID NO: 1977-2026, SEQ ID NO: 2027-2076, SEQ ID NO: 2077-2126, SEQ ID NO: 2127-2176, SEQ ID NO: 2177-2226, SEQ ID NO: 2227-2276, SEQ ID NO: 2277-2326, SEQ ID NO: 2327-2376, SEQ ID NO: 2377-2426, SEQ ID NO: 2427-2476, SEQ ID NO: 2477-2526, SEQ ID NO: 2527-2576, SEQ ID NO: 2577-2626 and SEQ ID NO: 2627-2676.

23. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria are selected from the group consisting of species comprising nucleotide sequences with at least 29% identity to SEQ ID NO: 877-926, at least 16.5% identity to SEQ ID NO: 927-976, at least 48.5% identity to SEQ ID NO: 977-1026, at least 28% identity to SEQ ID NO: 1027-1076, at least 93.5% identity to SEQ ID NO: 1077-1126, at least 99.5% identity to SEQ ID NO: 1127-1176, at least 99.5% identity to SEQ ID NO: 1177-1226, at least 99% identity to SEQ ID NO: 1227-1276, 100% identity to SEQ ID NO: 1277-1326, at least 21.5% identity to SEQ ID NO: 1327-1376, 100% identity to SEQ ID NO: 1377-1426, at least 97% identity to SEQ ID NO: 1427-1476, at least 55.5% identity to SEQ ID NO: 1477-1526, 100% identity to SEQ ID NO: 1527-1576, at least 34% identity to SEQ ID NO: 1577-1626, at least 14% identity to SEQ ID NO: 1627-1676, 100% identity to SEQ ID NO: 1677-1726, at least 93% identity to SEQ ID NO: 1727-1776, 100% identity to SEQ ID NO: 1777-1826, at least 45% identity to SEQ ID NO: 1827-1876, at least 99% identity to SEQ ID NO: 1877-1926, at least 74% identity to SEQ ID NO: 1927-1976, 100% identity to SEQ ID NO: 1977-2026, 100% identity to SEQ ID NO: 2027-2076, at least 20% identity to SEQ ID NO: 2077-2126, at least 84% identity to SEQ ID NO: 2127-2176, at least 35.5% identity to SEQ ID NO: 2177-2226, at least 32.5% identity to SEQ ID NO: 2227-2276, at least 70% identity to SEQ ID NO: 2277-2326, 100% identity to SEQ ID NO: 2327-2376, at least 70.5% identity to SEQ ID NO: 2377-2426, at least 99.5% identity to SEQ ID NO: 2427-2476, at least 68.5% identity to SEQ ID

NO: 2477-2526, 100% identity to SEQ ID NO: 2527-2576, at least 97.5% identity to SEQ ID NO: 2577-2626 or 100% identity to SEQ ID NO: 2627-2676.

24. The composition of claim 1 or claim 2, wherein the bacteria are lyophilized or freeze dried.

25. The composition of claim 1 or claim 2, wherein the composition is formulated for oral delivery.

26. The composition of claim 1 or claim 2, wherein the composition formulated for oral delivery is a tablet or capsule.

27. The composition of claim 1 or claim 2, wherein the tablet or capsule comprises an acid-resistant enteric coating.

28. The composition of claim 1 or claim 2, wherein the composition comprising the at least one isolated or purified population of bacteria or the at least two isolated or purified populationss of bacteria is formulated for administration rectally, via colonoscopy, sigmoidoscopy by nasogastric tube, or enema.

29. The composition of claim 1 or claim 2, wherein the composition is lyophilized or is frozen.

30. The composition of claim 1 or claim 2, wherein the composition is capable of being re-formulated for final delivery as comprising a liquid, a suspension, a gel, a geltab, a semisolid, a tablet, a sachet, a lozenge, a capsule, or as an enteral formulation.

31. The composition of claim 1 or claim 2, wherein the composition is formulated for multiple administrations.

32. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria comprise an antibiotic resistance gene.

33. The composition of claim 1 or claim 2, wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria are butyrate-producing populations of bacteria.

34. The composition of claim 1 or claim 2, further comprising butyrate.

35. A method of treating or preventing cancer in a subject comprising administering to the subject a composition in accordance with any one of claims 1-34.

36. The method of claim 35, wherein the cancer is a skin cancer.

37. The method of claim 35, wherein the cancer is basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

38. The method of claim 35, wherein the cancer is melanoma.

39. The method of claim 38, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

40. The method of claim 35, wherein the method further comprises administering at least one additional anticancer treatment.

41. The method of claim 40, wherein the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy.

42. The method of claim 41, wherein the biological therapy is a monoclonal antibody, siRNA, miPvNA, antisense oligonucleotide, ribozyme or gene therapy.

43. The method of claim 40, wherein the at least one immune checkpoint inhibitor and/or at least one additional anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion.

44. A method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium.*

45. The method of claim 44, wherein the cancer is a skin cancer.

46. The method of claim 44, wherein the cancer is basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

47. The method of claim 44, wherein the cancer is melanoma.

48. The method of claim 47, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

49. The method of claim 44, wherein the method further comprises administering at least one additional anticancer treatment.

50. The method of claim 49, wherein the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy.

51. The method of claim 50, wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

52. The method of claim 49, wherein the at least one immune checkpoint inhibitor and/or at least one additional anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion.

53. The method of claim 44, defined as method of treating a cancer wherein the subject has a tumor.

54. The method of claim 44, defined as method of preventing cancer wherein the subject is identified as at risk of developing a cancer.

55. The method of claim 44, wherein administration of the composition results in an increase of $CD8^+$ T lymphocytes in the tumor.

56. The method of claim 55, wherein the T lymphocytes are cytotoxic T lymphocytes.

57. The method of claim 44, wherein administration of the composition results in an increase of effector $CD4^+$, $CD8^+$ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject.

58. The method of claim 44, wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject.

59. The method of claim 44, wherein administration of the composition to the subject results in an increase in CD3, CD8, PDl, FoxP3, Granzyme B and/or PD-Ll expression in a tumor immune infiltrate.

60. The method of claim 44, wherein administration of the composition to the subject results in an decrease in RORyT expression in a tumor immune infiltrate.

61. The method of claim 44, wherein administration of the composition to the subject results in an increase in $CD45^+$, $CD3^+/CD20^+/CD56^+$, $CD68^+$ and/or HLA-$DR^+$ cells in the tumor.

62. The method of claim 44, wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject.

63. The method of claim 62, wherein the innate effector cells are $CD45^+CD1\,1b^+Ly6G^+$ cells.

64. The method of claim 44, wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject.

65. The method of claim 64, wherein suppressive myeloid cells are $CD45^{+}CDllb^{+}CDllc^{+}$ cells.

66. The method of claim 44, wherein the composition comprises the bacteria *Faecalibacterium prausnitzii.*

67. A method of treating cancer in a subject comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject, wherein the subject has been determined to have a favorable microbial profile in the gut microbiome having one or more of the bacterial populations of the composition of claim 1 or claim 2.

68. The method of claim 67, wherein the cancer is a skin cancer.

69. The method of claim 67, wherein the cancer is basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

70. The method of claim 67, wherein the cancer is melanoma.

71. The method of claim 70, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

72. The method of claim 67, wherein the method further comprises administering at least one additional anticancer treatment.

73. A method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises one or more of the bacterial populations of the composition of claim 1 or claim 2, the response to the immune checkpoint inhibitor is favorable.

74. The method of claim 73, wherein the cancer is a skin cancer.

75. The method of claim 73, wherein the cancer is basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

76. The method of claim 73, wherein the cancer is melanoma.

77. The method of claim 76, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

78. The method of claim 73, wherein the patient is administered an immune checkpoint inhibitor if the patient is predicted to have a favorable response to the immune checkpoint inhibitor.

79. The method of claim 73, wherein the microbial profile is a gut microbial profile.

80. A method of treating cancer in a subject comprising administering a therapeutically effective amount of butyrate, an isolated or purified butyrate-producing bacterial population, and/or a composition of claim 1 or 2 to said subject, wherein the subject has been administered an immune checkpoint inhibitor.

81. The method of claim 80, further comprising administering at least one immune checkpoint inhibitor.

82. The method of claim 81, wherein more than one checkpoint inhibitor is administered.

83. The method of claim 81, further comprising administering a prebiotic or probiotic.

84. The method of claim 80, wherein the isolated or purified butyrate-producing bacterial population comprises bacteria comprising an antibiotic resistance gene.

85. The method of claim 84, further comprising administering the butyrate-producing bacterial population comprising an antibiotic resistance gene.

86. The method of claim 85, further comprising administering the antibiotic to which the antibiotic resistance gene confers resistance.

87. The method of claim 80, wherein the butyrate-producing bacterial population comprises one or more bacterial species of the order Clostridiales.

88. The method of claim 87, wherein the one or more bacterial species are from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriaceae.

89. The method of claim 87, the one or more bacterial species are selected from the group consisting of *Faecalibacterium prausnitzii, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus flavefaciens, Ruminococcus champanellensis, Ruminococcus faecis, Ruminococcus gauvreauii, Ruminococcus gnavus, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus lactaris, Ruminococcus luti, Ruminococcus obeum, Ruminococcus palustris, Ruminococcus pasteurii, Ruminococcus productus, Ruminococcus schinkii, Ruminococcus torques, Subdoligranulum variabile, Butyrivibrio fibrisolvens, Roseburia intestinalis, Anaerostipes caccae, Blautia obeum, Eubacterium nodatum,* and *Eubacterium oxidoreducens.*

90. The method of claim 87, wherein the one or more bacterial species is *Faecalibacterium prausnitzii.*

91. The method of claim 80, the butyrate-producing bacterial population does not comprise bacterial species of the family Prevotellaceae.

92. The method of claim 80, wherein administering the butyrate comprises administering a butyrate prodrug or salt.

93. The method of claim 80, wherein administering butyrate comprises administering sodium butyrate, arginine butyrate, ethylbutyryl lactate, tributyrin, 4-phenyl butyrate, pivaloyloxymethyl butyrate (AN-9) or butylidenedi-butyrate (AN-10).

94. The method of claim 80, wherein the butyrate or butyrate-producing bacterial population, are administered orally, rectally, via colonoscopy, sigmoidoscopy, enema or by direct injection.

95. The method of claim 81, wherein the at least one immune checkpoint inhibitor is administered intravenously, and the butyrate and/or the butyrate-producing bacterial population is administered orally.

96. The method of claim 81, wherein the at least one checkpoint inhibitor is selected from an inhibitor of CTLA-4, PD-1, PD-Ll, PD-L2, LAG-3, BTLA, B7H3, B7H4, TIM3, KIR, or A2aR.

97. The method of claim 81, wherein the at least one immune checkpoint inhibitor is a human programmed cell death 1 (PD-1) axis-binding antagonist.

98. The method of claim 97, wherein the PD-1 axis-binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PDLl -binding antagonist and a PDL2-binding antagonist.

99. The method of claim 98, wherein the PD-1 axis-binding antagonist is a PD-l-binding antagonist.

100. The method of claim 99, wherein the PD-l-binding antagonist inhibits the binding of PD-1 to PDLl and/or PDL2.

101. The method of claim 99, wherein the PD-l-binding antagonist is a monoclonal antibody or antigen binding fragment thereof.

102. The method of claim 99, wherein the PD-l-binding antagonist is nivolumab, pembrolizumab, pidillizumab, KEYTRUDA®, AMP-514, REGN2810, CT-011, BMS 936559, MPDL3280A or AMP-224.

103. The method of claim 81, wherein the at least one immune checkpoint inhibitor is an anti-CTLA-4 antibody.

104. The method of claim 103, wherein the anti-CTLA-4 antibody is tremelimumab, YERVOY®, or ipilimumab.

105. The method of claim 81, wherein the at least one immune checkpoint inhibitor is an anti-killer-cell immunoglobulin-like receptor (KIR) antibody.

106. The method of claim 105, wherein the anti-KIR antibody is lirilumab.

107. The method of claim 80, wherein the cancer is a skin cancer.

108. The method of claim 80, wherein the cancer is basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

109. The method of claim 80, wherein the cancer is melanoma.

110. The method of claim 108, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

111. The method of claim 80, wherein the method further comprises administering at least one additional anticancer treatment.

112. The method of claim 111, wherein the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy.

113. The method of claim 112, wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

114. The method of claim 111, wherein the at least one immune checkpoint inhibitor and/or at least one additional anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion.

115. A method of treating cancer in a subject comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject, wherein the subject has been determined to have a favorable microbial profile in the gut microbiome.

116. The method of claim 115, wherein the cancer is a skin cancer.

117. The method of claim 115, wherein the cancer is basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

118. The method of claim 115, wherein the cancer is melanoma.

119. The method of claim 118, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

120. The method of claim 115, wherein the method further comprises administering at least one additional anticancer treatment.

121. The method of claim 115, wherein the favorable microbial profile is further defined as having (a) high alpha-diversity of the gut microbiome; (b) a high abundance of butyrate-producing bacteria in the gut microbiome; (c) one or more bacteria selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5 in the gut microbiome; or (d) one or more of the bacteria species in Table 2 designated with a response status of responder (R) in the gut microbiome.

122. The method of claim 115, wherein the favorable microbial profile is further defined as the presence or high abundance of bacteria of the phylum Firmicutes, class Clostridia, order Clostridiales, family Ruminococcaceae, genus *Ruminococcus*, genus *Faecalibacterium*, genus *Hydrogenoanaerobacterium*, phylum Actinobacteria, class Coriobacteriia, order Coriobacteriales, family Coriobacteriaceae, domain Archaea, phylum Cyanobacteria, phylum Euryarchaeota, or family Christensenellaceae.

123. The method of claim 115, wherein the favorable microbial profile is further defined as the absence or low abundance of bacteria of the species *Escherichia coli*, species *Anerotruncus colihominis*, genus *Dialister*, family Veillonellaceae, phylum Bacteroidetes, class Bacteroidia, order Bacteroidales or family Prevotellaceae.

124. The method of claim 115, wherein the favorable microbial profiles is defined as the presence or high abundance of bacteria of the class Clostridiales and the absence or low abundance of bacteria of the order Bacteroidales.

125. The method of claim 115, wherein the favorable microbial profile is further defined as a high abundance of butyrate-producing bacteria. the butyrate-producing bacteria comprises one or more species is from the genus *Ruminococcus* or *Faecalibacterium.*

126. The method of claim 115, wherein the subject is determined to comprise a favorable microbial profile or favorable gut microbiome by analyzing the microbiome in a patient sample.

127. The method of claim 115, wherein the patient sample is a fecal sample or buccal sample.

128. The method of claim 115, wherein analyzing comprises performing 16S ribosomal sequencing and/or metagenomics whole genome sequencing.

129. A method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises: (a) high alpha-diversity; (b) a high abundance of butyrate-producing bacteria; (c) one or more bacteria selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5; or (d) one or more of the bacteria species in Table 2 designated with a response status of responder (R), then the patient is predicted to have a favorable response to the immune checkpoint inhibitor.

130. The method of claim 129, wherein the cancer is a skin cancer.

131. The method of claim 129, wherein the cancer is basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

132. The method of claim 129, wherein the cancer is melanoma.

133. The method of claim 132, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

134. The method of claim 129, wherein the patient is administered an immune checkpoint inhibitor if the patient is predicted to have a favorable response to the immune checkpoint inhibitor.

135. The method of claim 134, wherein the patient is administered a second immune checkpoint inhibitor.

136. The method of claim 129, wherein the favorable microbial profile is a favorable gut microbial profile.

137. The method of claim 129, wherein the cancer is skin cancer.

138. The method of claim 137, wherein the skin cancer is melanoma or metastatic melanoma.

139. The method of claim 129, wherein the immune checkpoint inhibitor is an anti-PDl monoclonal antibody or an anti-CTLA4 monoclonal antibody.

140. The method of claim 129, wherein the butyrate-producing bacterial population comprises one or more bacterial species of the order Clostridiales.

141. The method of claim 140, wherein the one or more species is from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriacease.

142. The method of claim 140, wherein the one or more species are selected from the group consisting of *Faecalibacterium prausnitzii, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus flavefaciens, Ruminococcus champanellensis, Ruminococcus faecis, Ruminococcus gauvreauii, Ruminococcus gnavus, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus lactaris, Ruminococcus luti, Ruminococcus obeum, Ruminococcus palustris, Ruminococcus pasteurii, Ruminococcus productus, Ruminococcus schinkii, Ruminococcus torques, Subdoligranulum variabile, Butyrivibrio fibrisolvens, Roseburia intestinalis, Anaerostipes caccae, Blautia obeum, Eubacterium nodatum, and Eubacterium oxidoreducens.*

143. The method of claim 140, wherein the one or more species is *Faecalibacterium prausnitzii.*

144. The method of claim 140, wherein the immune checkpoint inhibitor is an anti-PDl monoclonal antibody or an anti-CTLA4 monoclonal antibody.

145. The method of claim 140, further comprising administering at least one additional anticancer treatment.

146. The method of claim 145, wherein the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy.

147. The method of claim 145, wherein the at least one additional anticancer treatment is butyrate and/or a butyrate-producing bacterial population.

148. The method of claim 145, further comprising administering a prebiotic or probiotic composition.

149. The method of claim 148, wherein probiotic composition is the composition of claim 1 or claim 2.

150. A method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises: (a) a low abundance of butyrate-producing bacteria; or (b) one or more of the bacteria species in Table 2 designated with a response status of non responder (NR), then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor.

151. The method of claim 150, further comprising administering to the patient a probiotic composition of claim 1 or claim 2 if the patient is predicted to not have a favorable response to the immune checkpoint inhibitor.

152. The method of claim 151, wherein a patient predicted to not have a favorable response to an immune checkpoint inhibitor is administered an immune checkpoint inhibitor after administration of the composition of claim 1 or claim 2.

153. The method of claim 150, further comprising administering at least one non-immune checkpoint inhibitor additional anticancer treatment to the subject predicted to not have a favorable response to the immune checkpoint inhibitor.

154. The method of claim 153, wherein the at least one anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy, an immune checkpoint inhibitor, a second immune checkpoint inhibitor or a biological therapy.

155. The method of claim 153, wherein the at least one additional anticancer treatment is butyrate and/or a butyrate-producing bacterial population.

156. The method of claim 153, wherein the anti-cancer therapy is a prebiotic or probiotic.

157. The method of claim 156, wherein the probiotic is a composition of claim 1 or claim 2.

158. The method of claim 150, wherein the cancer is skin cancer.

159. The method of claim 158, wherein the skin cancer is melanoma.

160. The method of claim 150, wherein the cancer is basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinoma, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

161. The method of claim 159, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

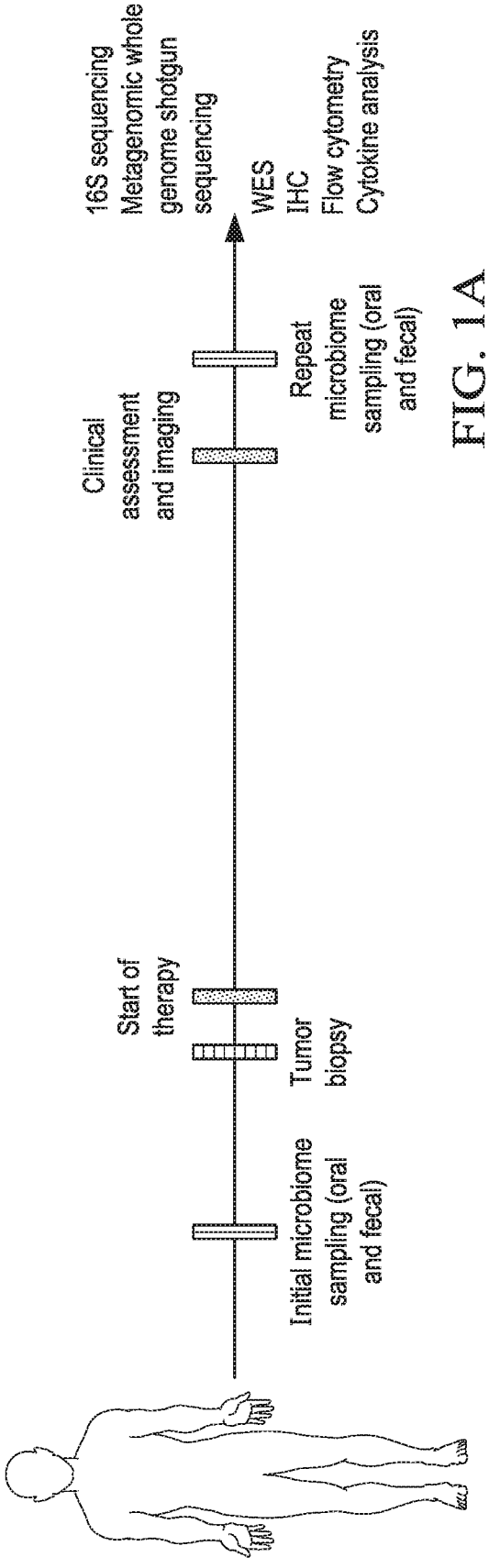

Initial microbiome sampling (oral and fecal)
Tumor biopsy
Start of therapy
Clinical assessment and imaging
Repeat microbiome sampling (oral and fecal)
WES
IHC
Flow cytometry
Cytokine analysis
16S sequencing
Metagenomic whole genome shotgun sequencing

FIG. 1A

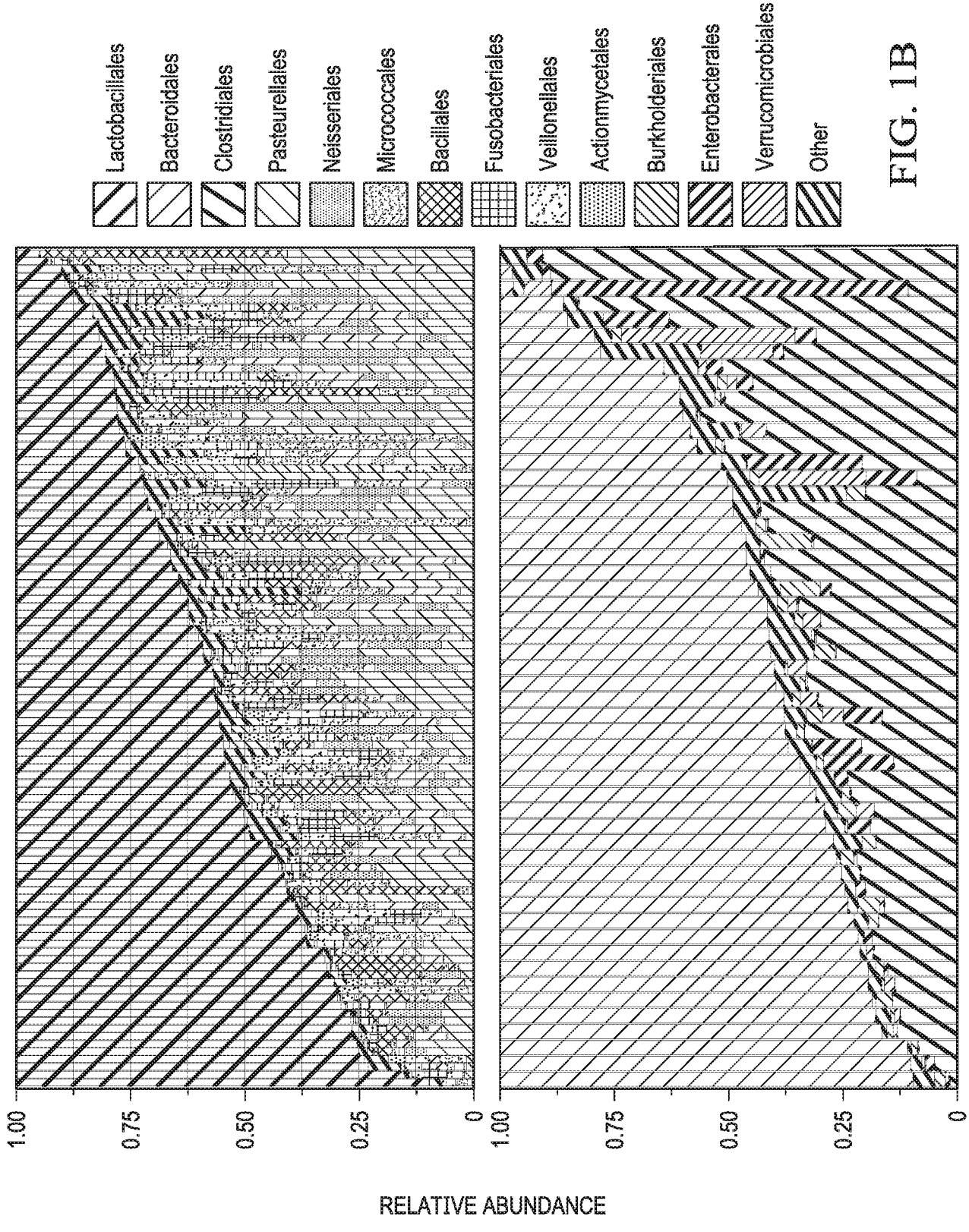

Lactobacillales
Bacteroidales
Clostridiales
Pasteurellales
Neisseriales
Micrococcales
Bacillales
Fusobacteriales
Veillonellales
Actinomycetales
Burkholderiales
Enterobacterales
Verrucomicrobiales
Other
1.00
0.75
0.50
0.25
0
RELATIVE ABUNDANCE

FIG. 1B

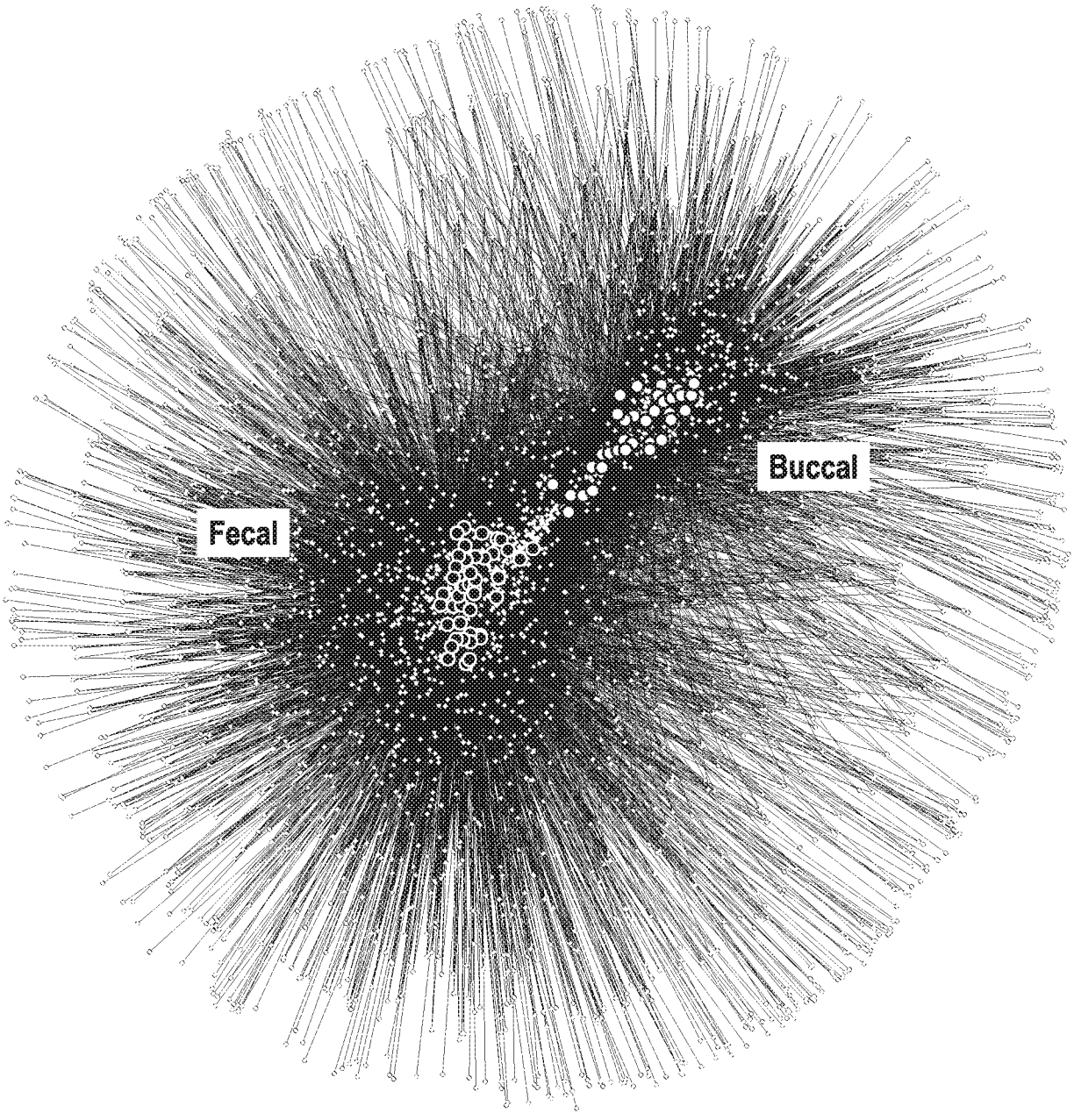
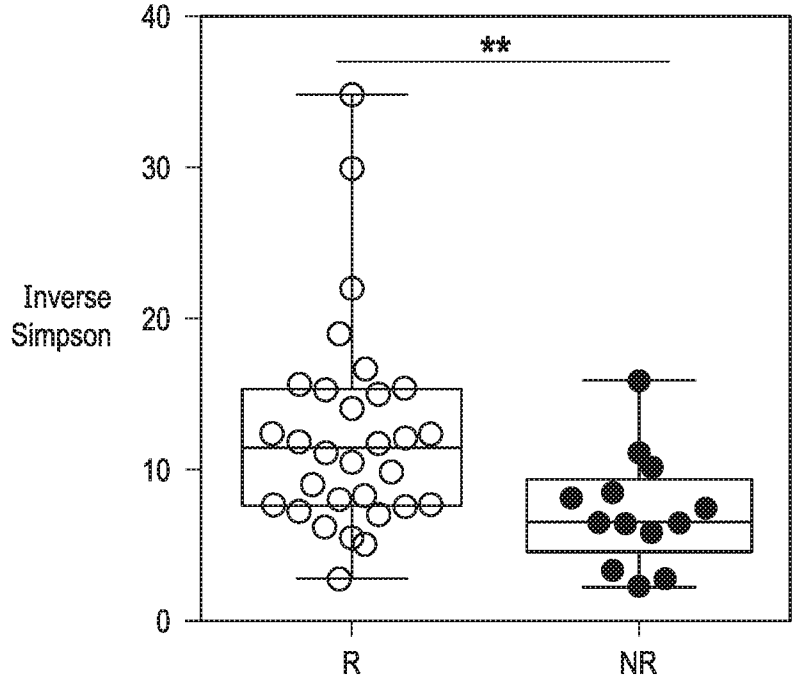



FIG. 1C

FIG. 1D



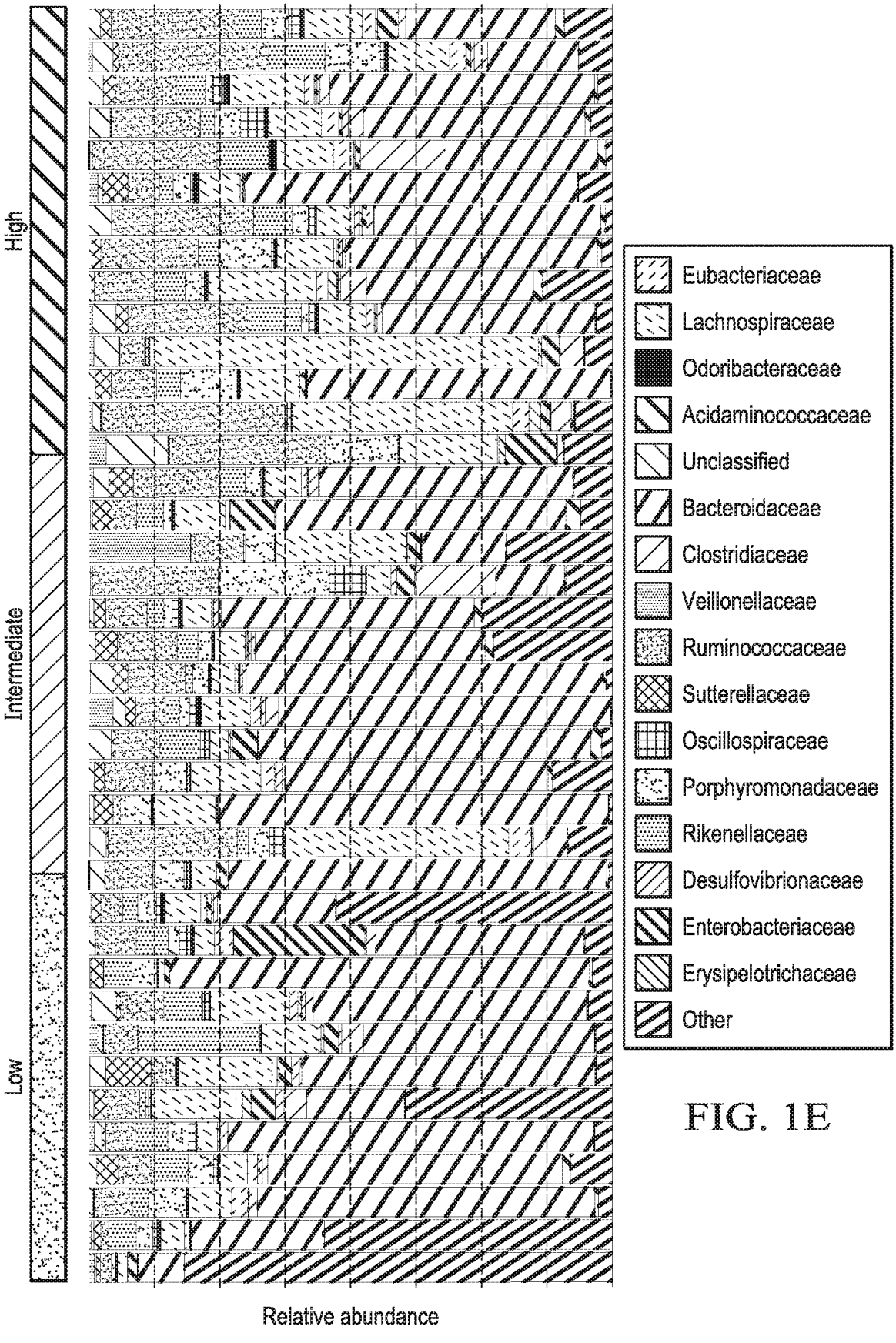

High
Intermediate
Low
Relative abundance
Eubacteriaceae
Lachnospiraceae
Odoribacteraceae
Acidaminococcaceae
Unclassified
Bacteroidaceae
Clostridiaceae
Veillonellaceae
Ruminococcaceae
Sutterellaceae
Oscillospiraceae
Porphyromonadaceae
Rikenellaceae
Desulfovibrionaceae
Enterobacteriaceae
Erysipelotrichaceae
Other

FIG. 1E

FIG. 1F

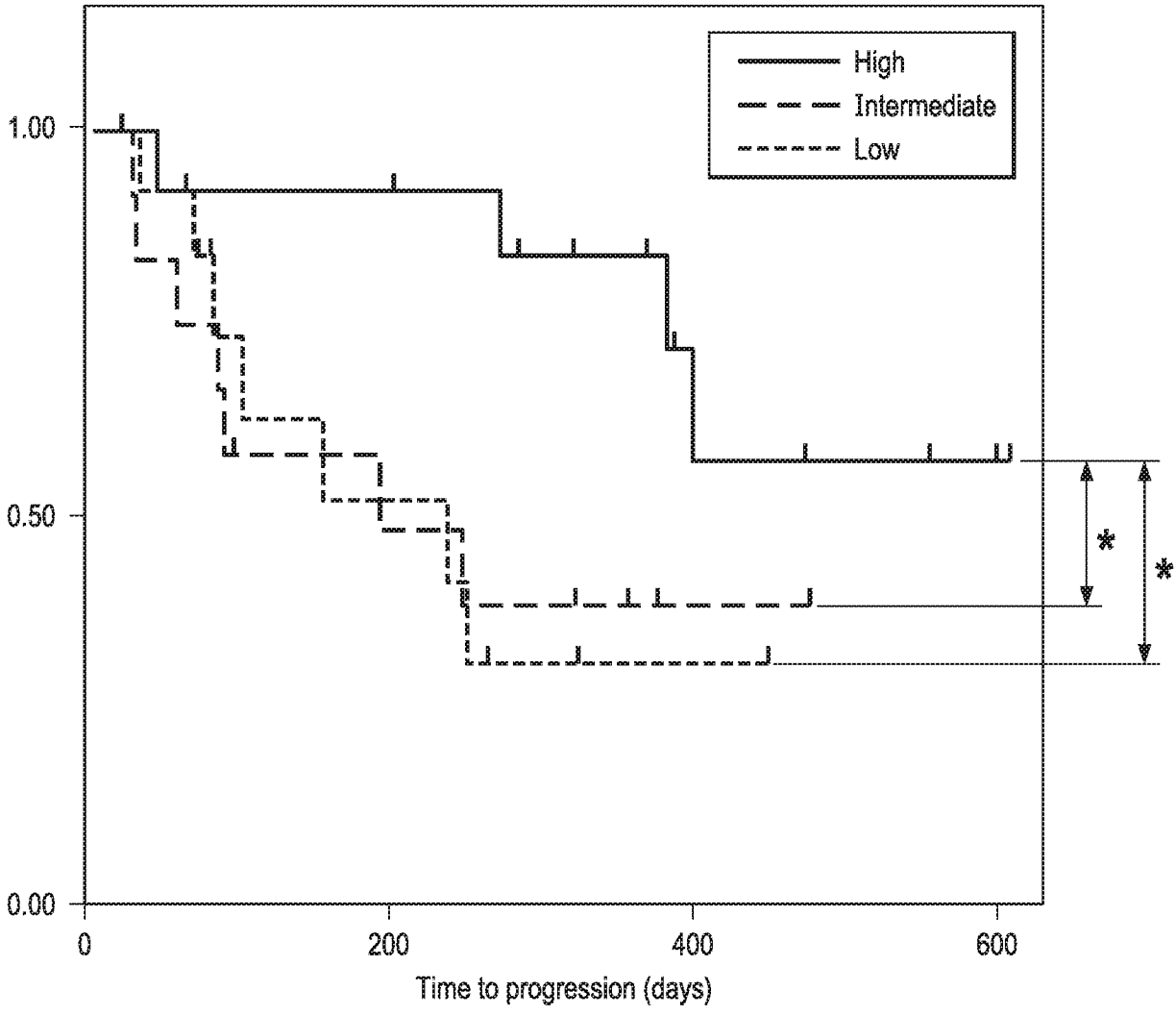
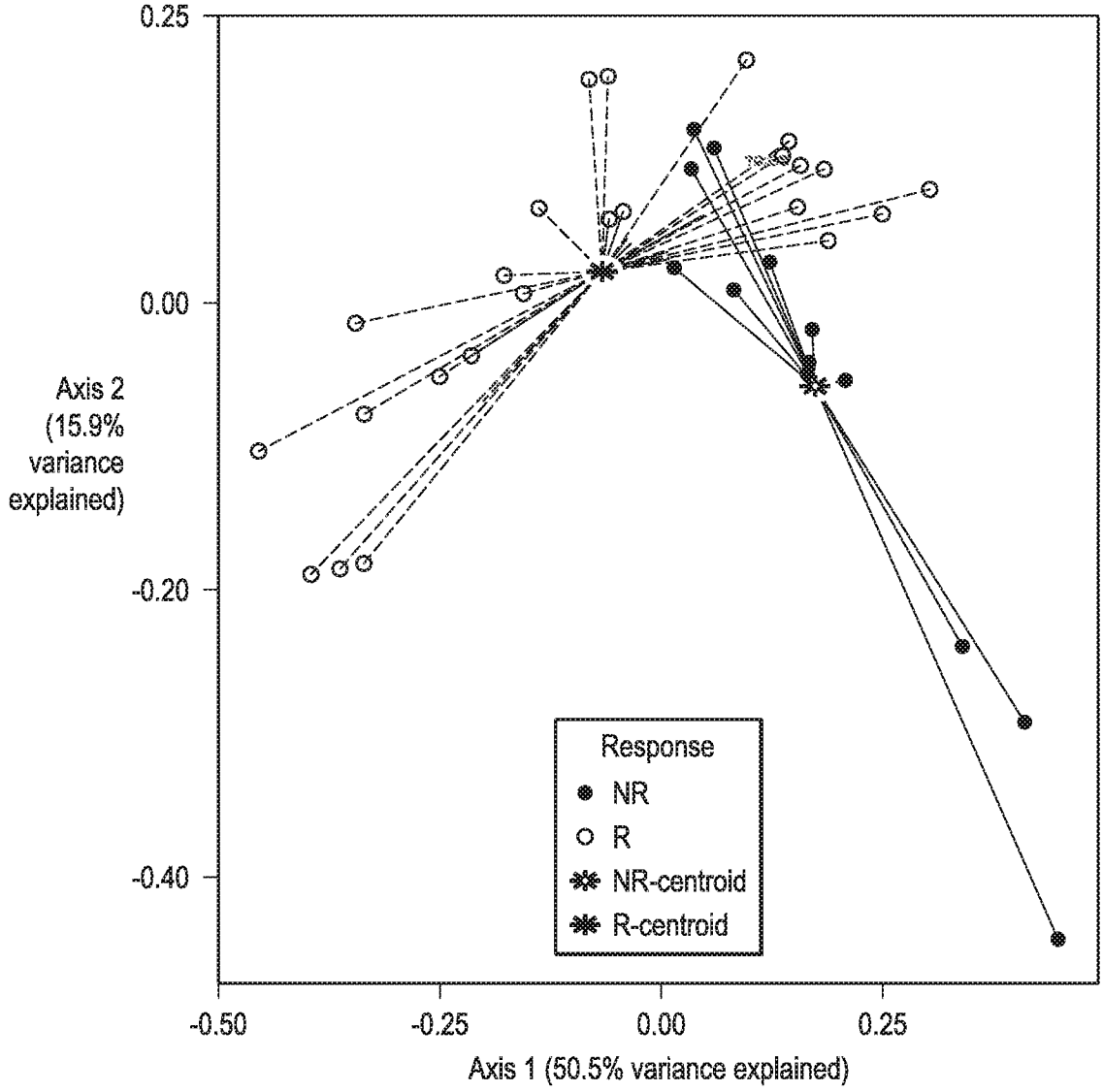

High
Intermediate
Low
1.00
0.50
0.00
0
200
400
600
Time to progression (days)
*
*

FIG. 1G


0.25
0.00
-0.20
-0.40
Axis 2
(15.9%
variance
explained)
-0.50
-0.25
0.00
0.25
Axis 1 (50.5% variance explained)
Response
NR
R
NR-centroid
R-centroid

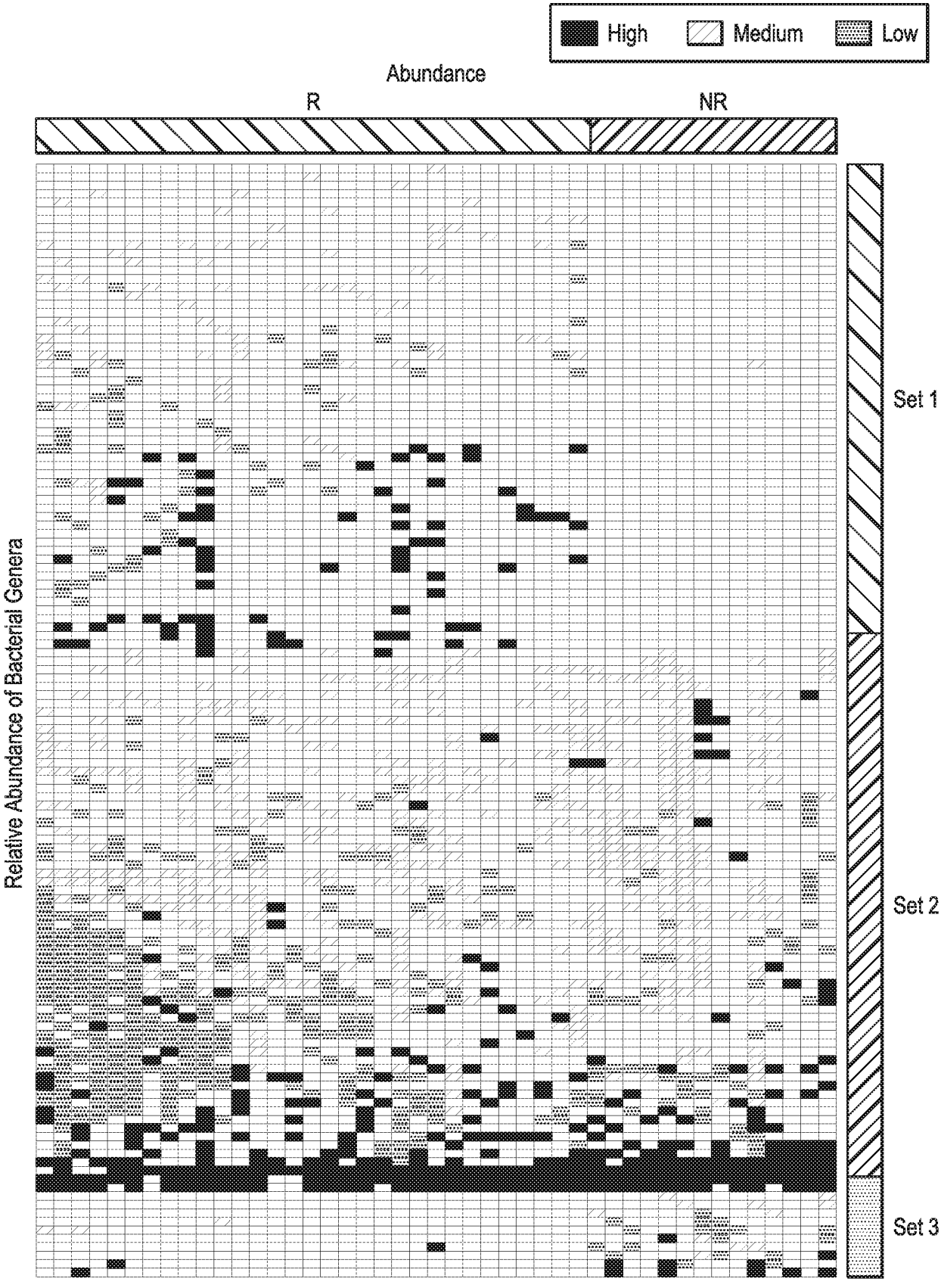

High
Medium
Low
Abundance
R
NR
Relative Abundance of Bacterial Genera
Set 1
Set 2
Set 3

FIG. 2A

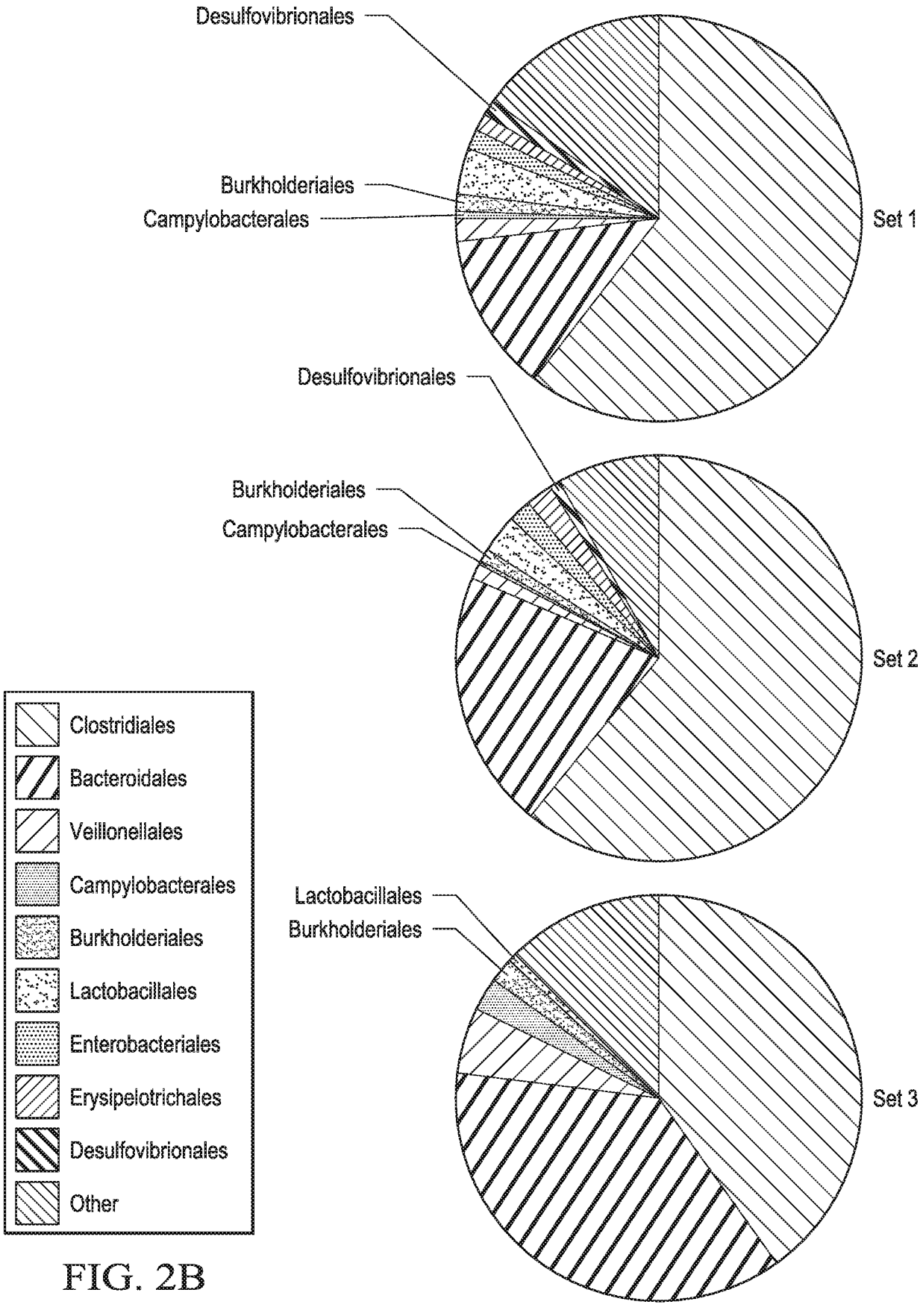

Desulfovibrionales
Burkholderiales
Campylobacterales
Set 1
Desulfovibrionales
Burkholderiales
Campylobacterales
Set 2
Lactobacillales
Burkholderiales
Set 3
Clostridiales
Bacteroidales
Veillonellales
Campylobacterales
Burkholderiales
Lactobacillales
Enterobacteriales
Erysipelotrichales
Desulfovibrionales
Other

FIG. 2B

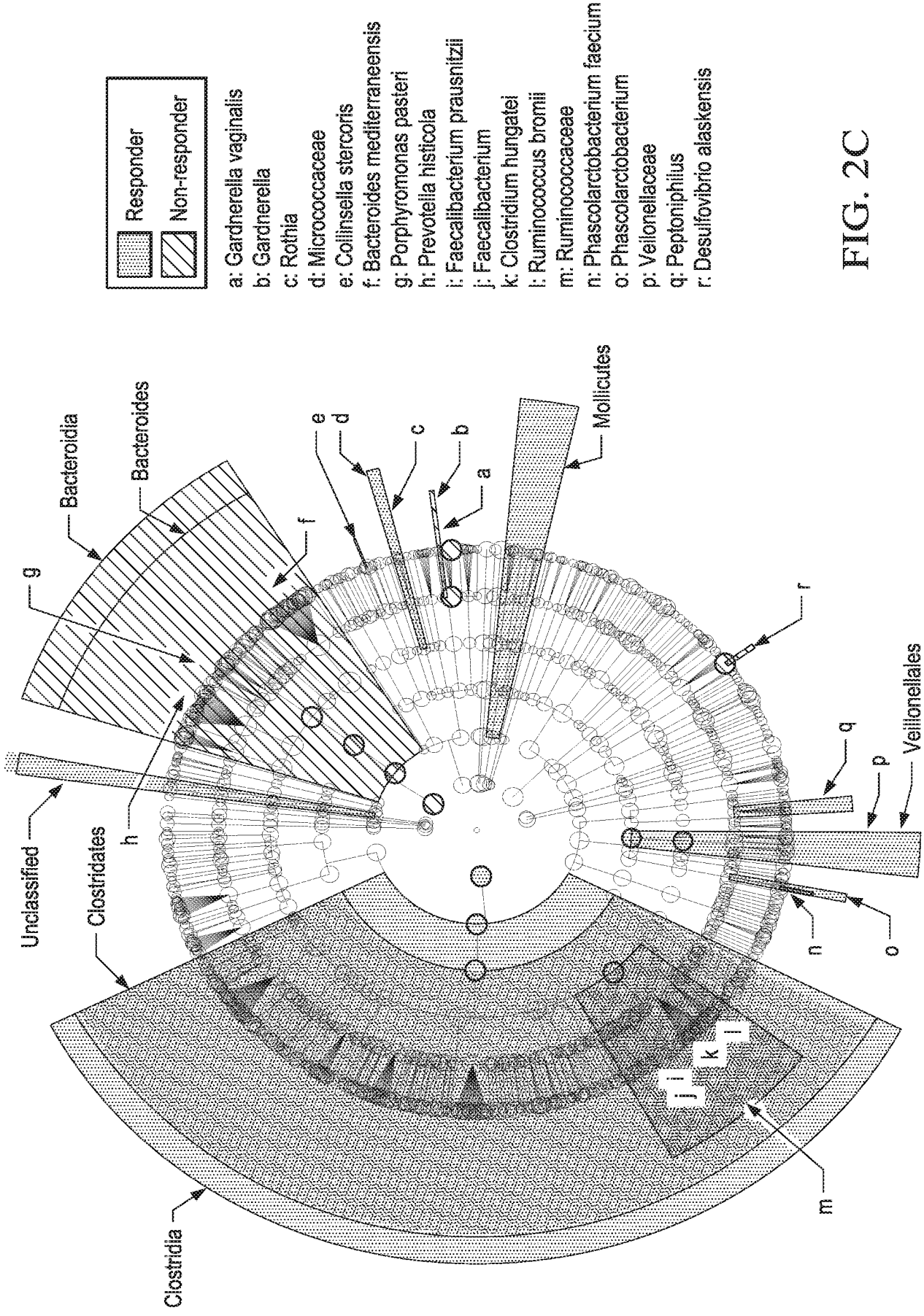

Responder
Non-responder
a: Gardnerella vaginalis
b: Gardnerella
c: Rothia
d: Micrococcaceae
e: Collinsella stercoris
f: Bacteroides mediterraneensis
g: Porphyromonas pasteri
h: Prevotella histicola
i: Faecalibacterium prausnitzii
j: Faecalibacterium
k: Clostridium hungatei
l: Ruminococcus bromii
m: Ruminococcaceae
n: Phascolarctobacterium faecium
o: Phascolarctobacterium
p: Veillonellaceae
q: Peptoniphilus
r: Desulfovibrio alaskensis
Bacteroidia
Bacteroides
Mollicutes
Unclassified
Clostridates
Clostridia
Veillonellales

FIG. 2C

FIG. 2D

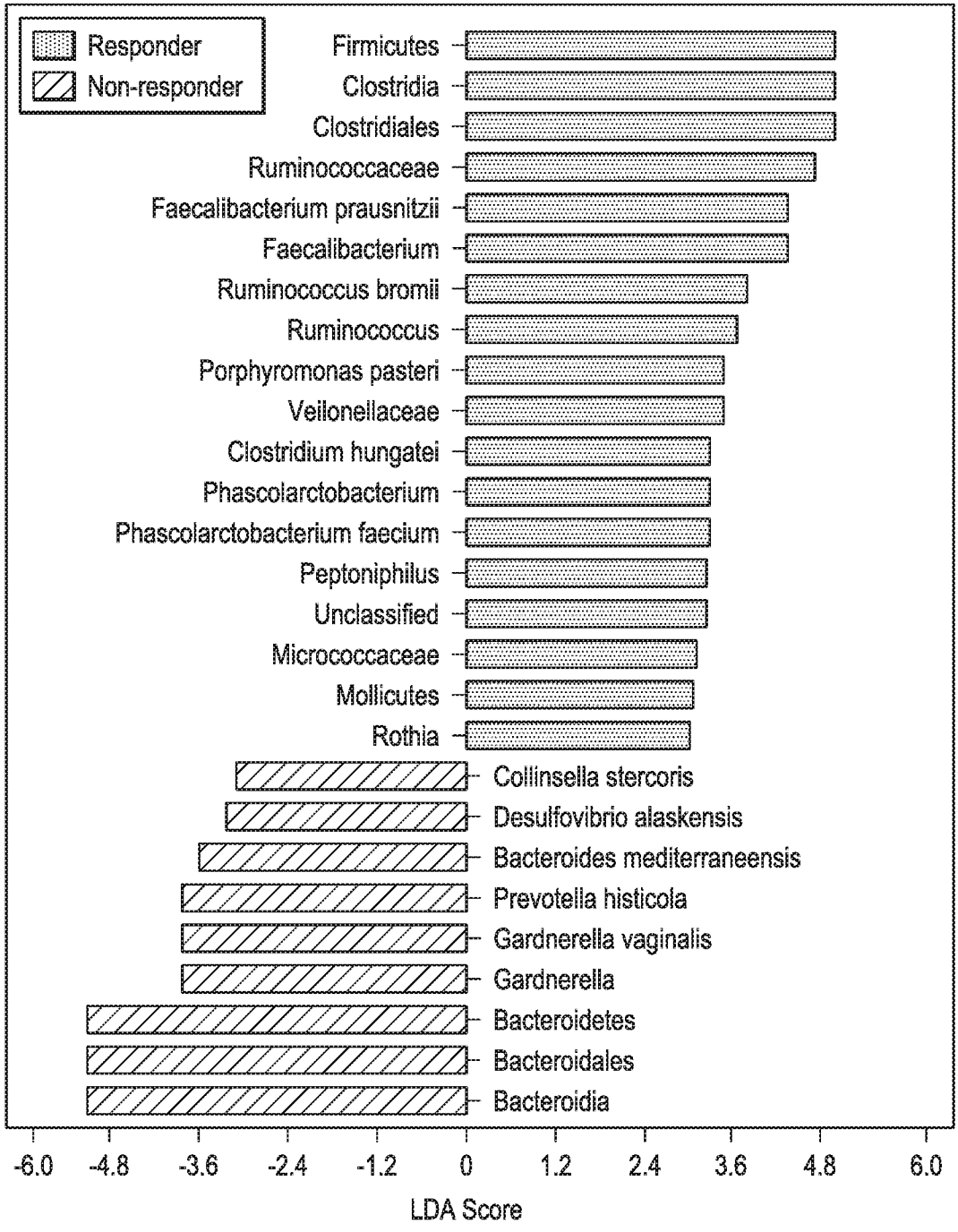
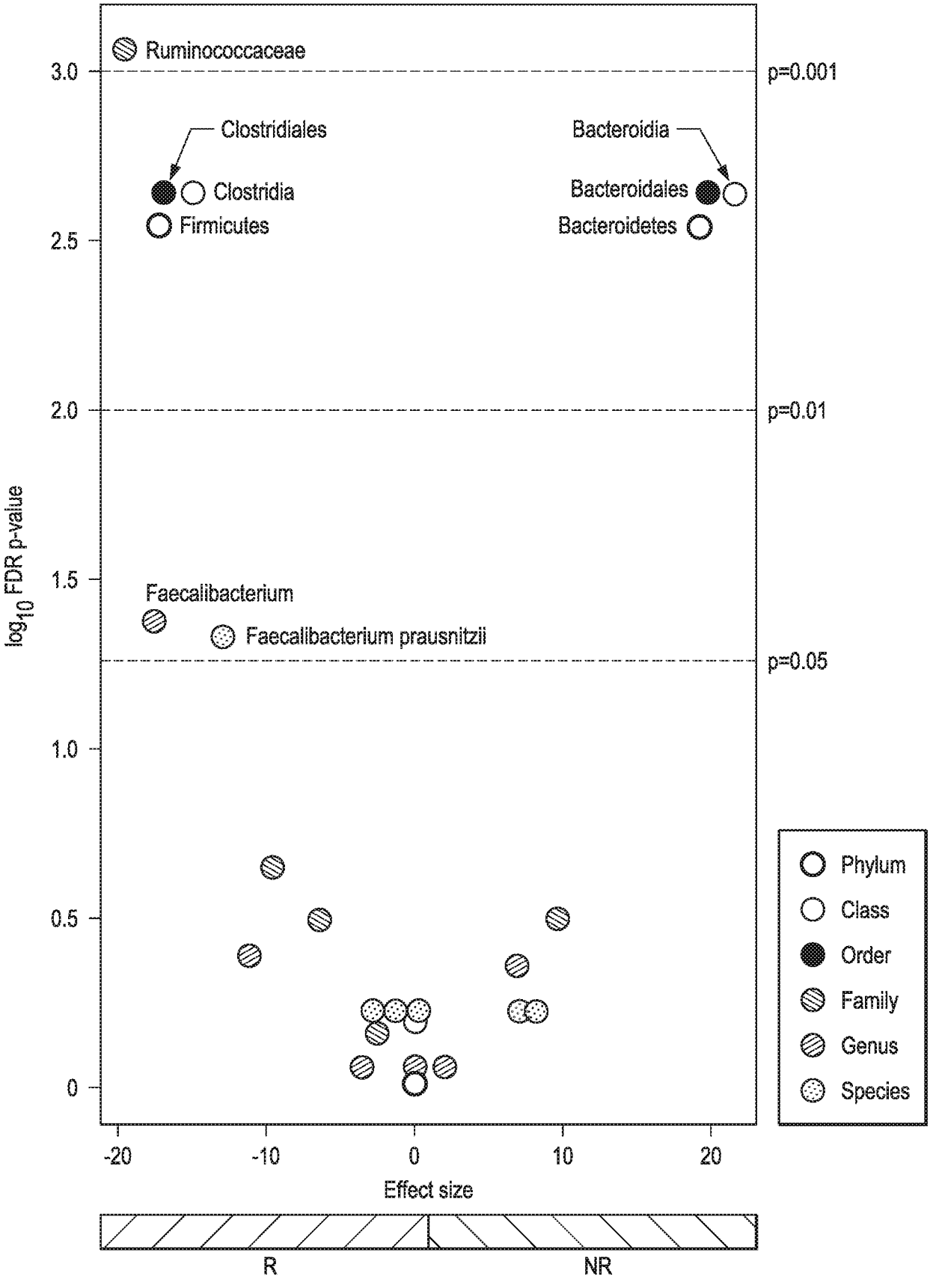

Responder
Non-responder
Firmicutes
Clostridia
Clostridiales
Ruminococcaceae
Faecalibacterium prausnitzii
Faecalibacterium
Ruminococcus bromii
Ruminococcus
Porphyromonas pasteri
Veillonellaceae
Clostridium hungatei
Phascolarctobacterium
Phascolarctobacterium faecium
Peptoniphilus
Unclassified
Micrococcaceae
Mollicutes
Rothia
Collinsella stercoris
Desulfovibrio alaskensis
Bacteroides mediterraneensis
Prevotella histicola
Gardnerella vaginalis
Gardnerella
Bacteroidetes
Bacteroidales
Bacteroidia
-6.0
-4.8
-3.6
-2.4
-1.2
0
1.2
2.4
3.6
4.8
6.0
LDA Score

FIG. 2E


Ruminococcaceae
p=0.001
Clostridiales
Bacteroidia
Clostridia
Bacteroidales
Firmicutes
Bacteroidetes
p=0.01
Faecalibacterium
Faecalibacterium prausnitzii
p=0.05
log10 FDR p-value
3.0
2.5
2.0
1.5
1.0
0.5
0
-20
-10
0
10
20
Effect size
R
NR
Phylum
Class
Order
Family
Genus
Species

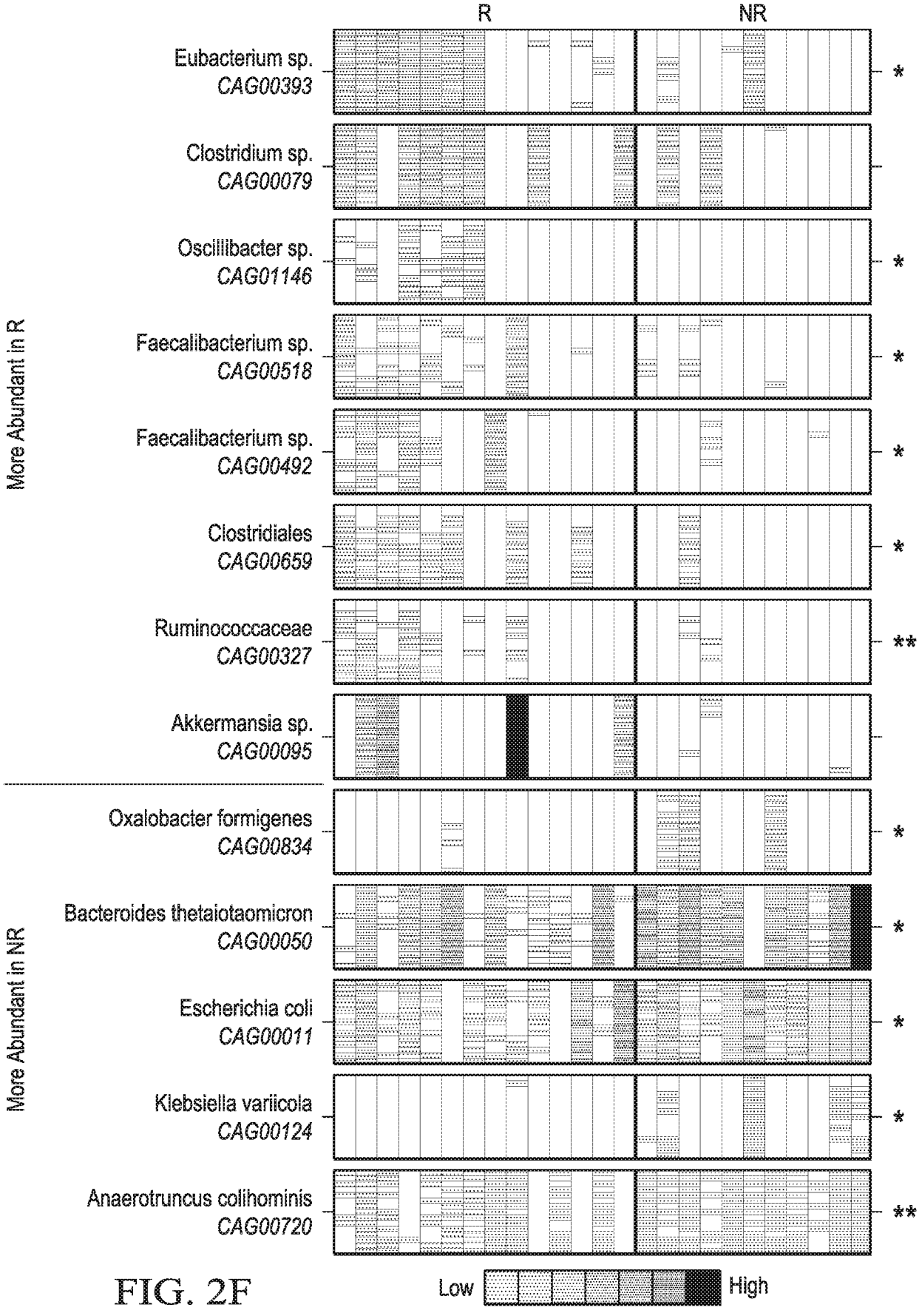

R
NR
More Abundant in R
More Abundant in NR
Eubacterium sp. CAG00393
Clostridium sp. CAG00079
Oscillibacter sp. CAG01146
Faecalibacterium sp. CAG00518
Faecalibacterium sp. CAG00492
Clostridiales CAG00659
Ruminococcaceae CAG00327
Akkermansia sp. CAG00095
Oxalobacter formigenes CAG00834
Bacteroides thetaiotaomicron CAG00050
Escherichia coli CAG00011
Klebsiella variicola CAG00124
Anaerotruncus colihominis CAG00720
*
*
*
*
*
*
**
*
*
*
*
**
Low
High

FIG. 2F

FIG. 3A

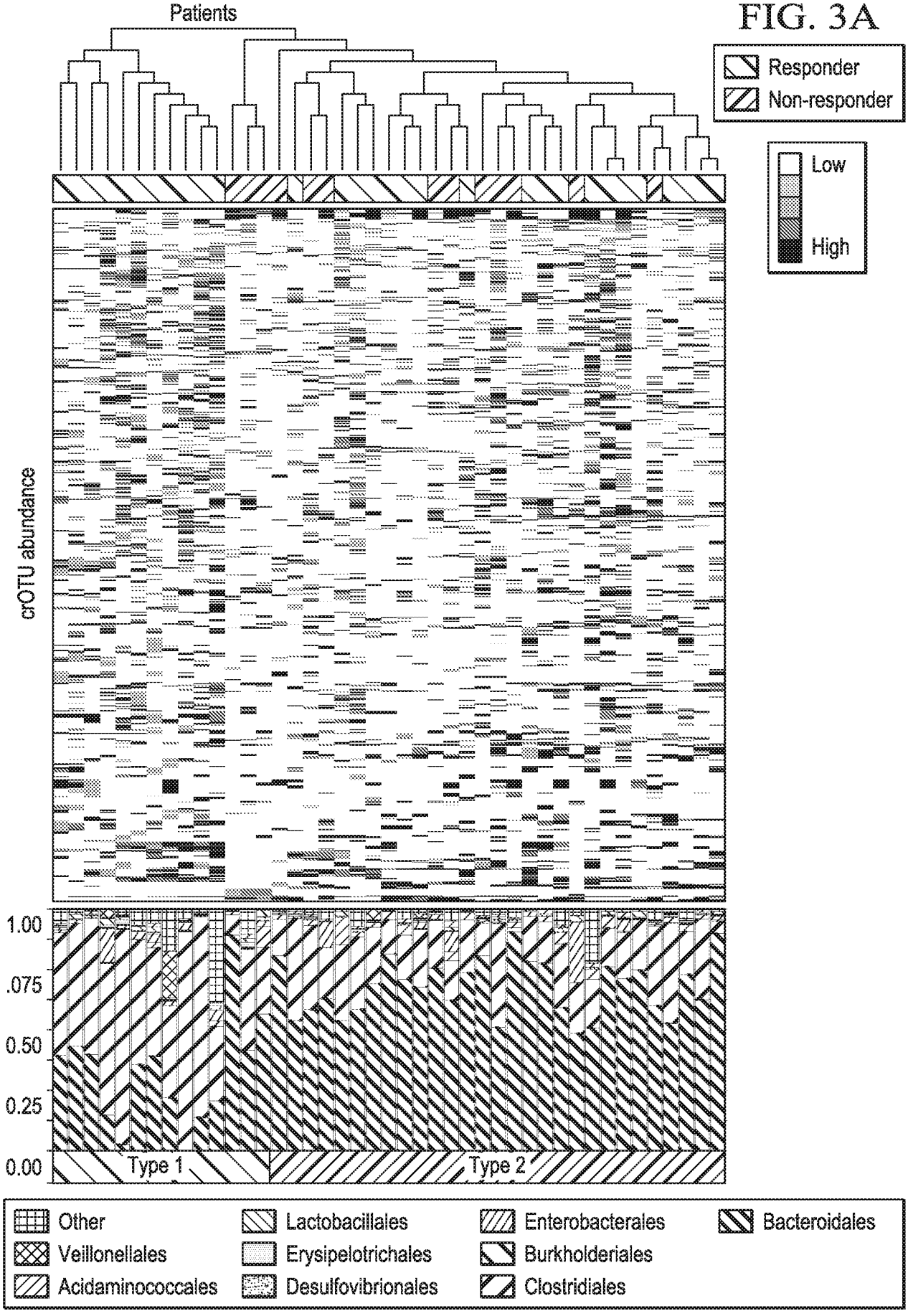

Patients
Responder
Non-responder
Low
High
crOTU abundance
1.00
.075
0.50
0.25
0.00
Type 1
Type 2
Other
Veillonellales
Acidaminococcales
Lactobacillales
Erysipelotrichales
Desulfovibrionales
Enterobacterales
Burkholderiales
Clostridiales
Bacteroidales

FIG. 3B

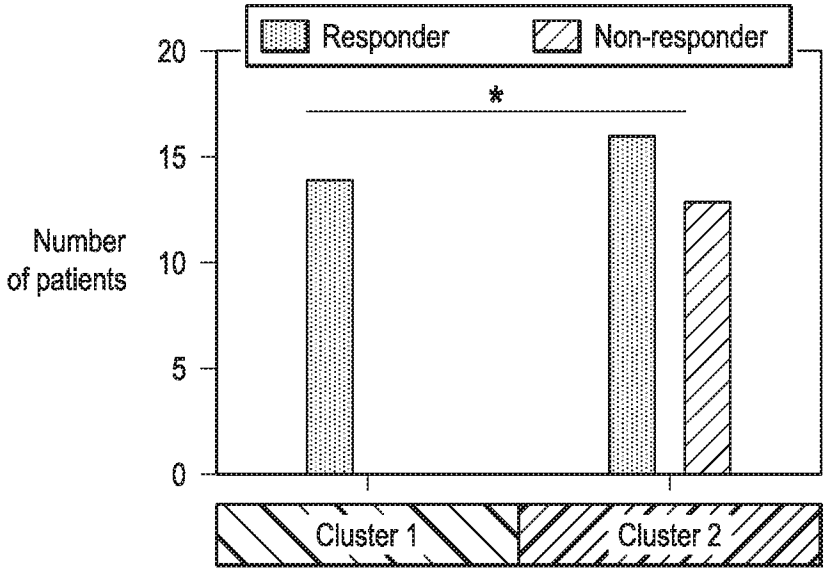

Responder
Non-responder
*
20
15
10
5
0
Number of patients
Cluster 1
Cluster 2

FIG. 3C

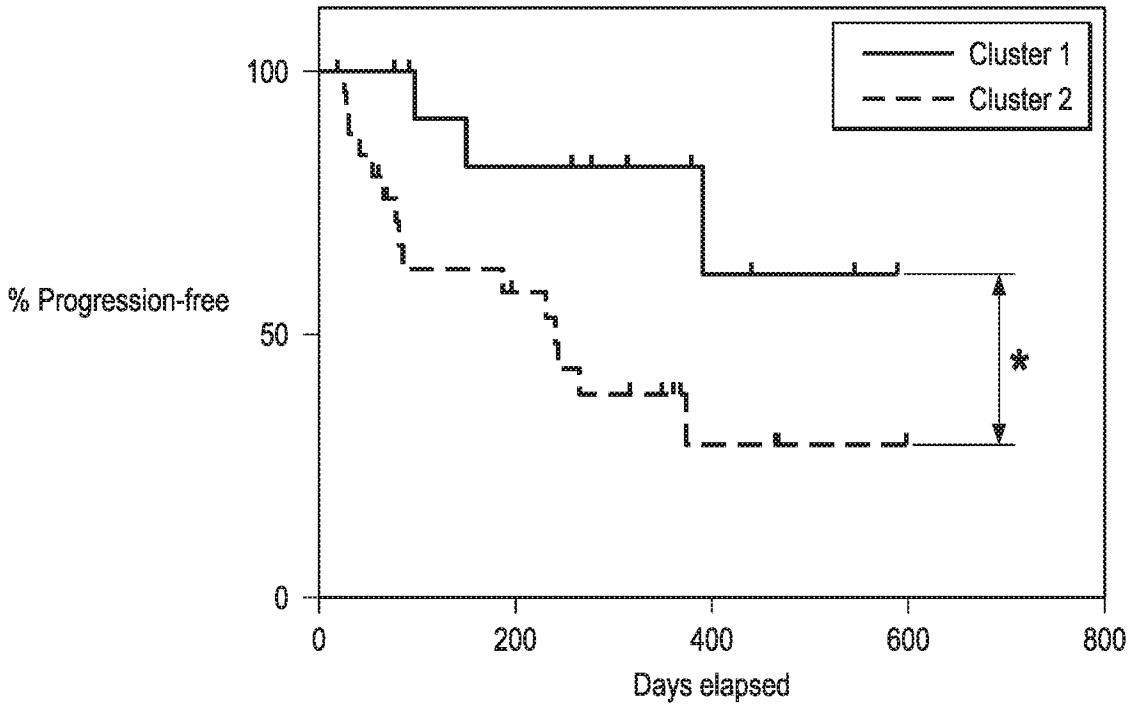

Cluster 1
Cluster 2
100
50
0
% Progression-free
*
0
200
400
600
800
Days elapsed

FIG. 3D

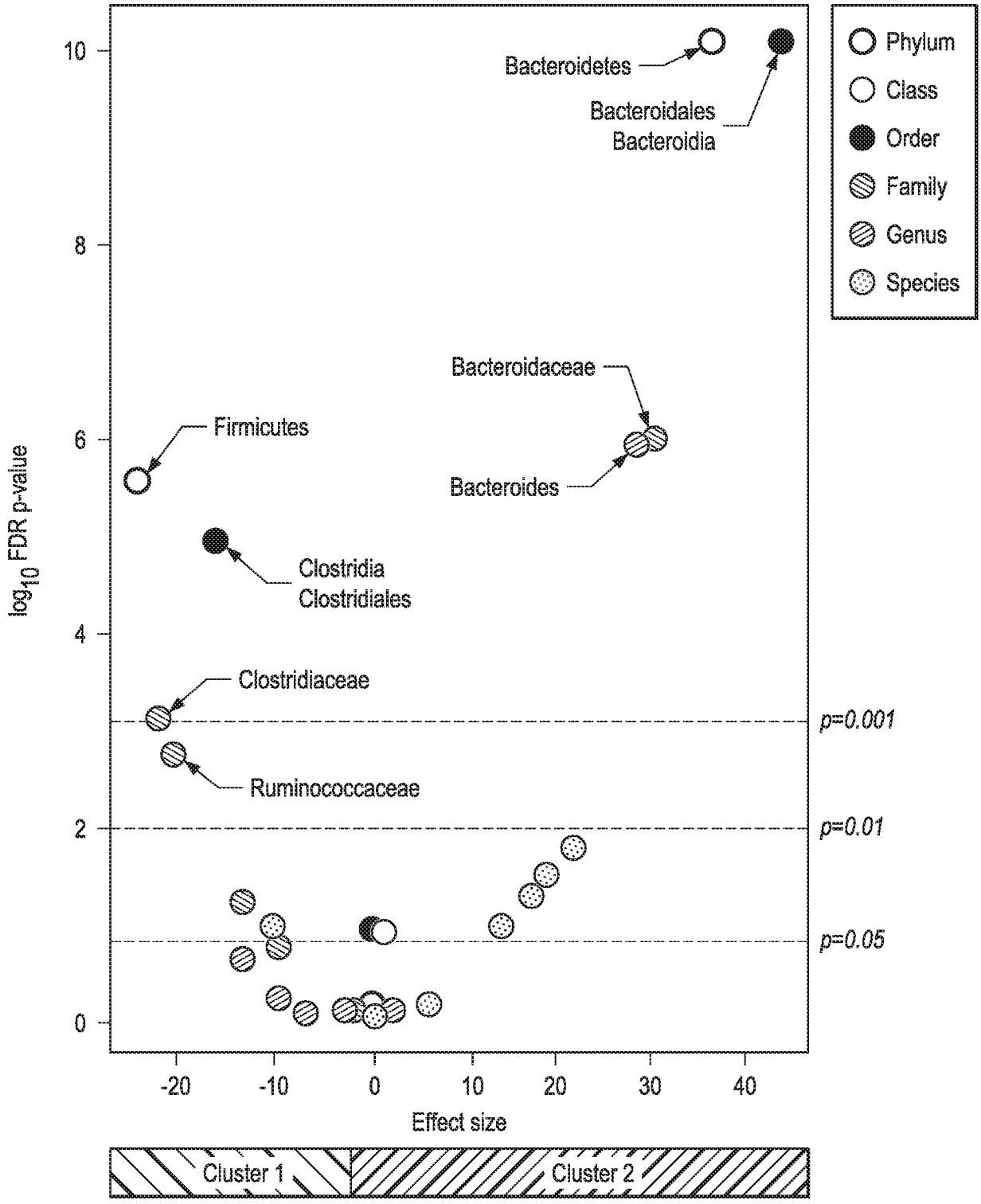
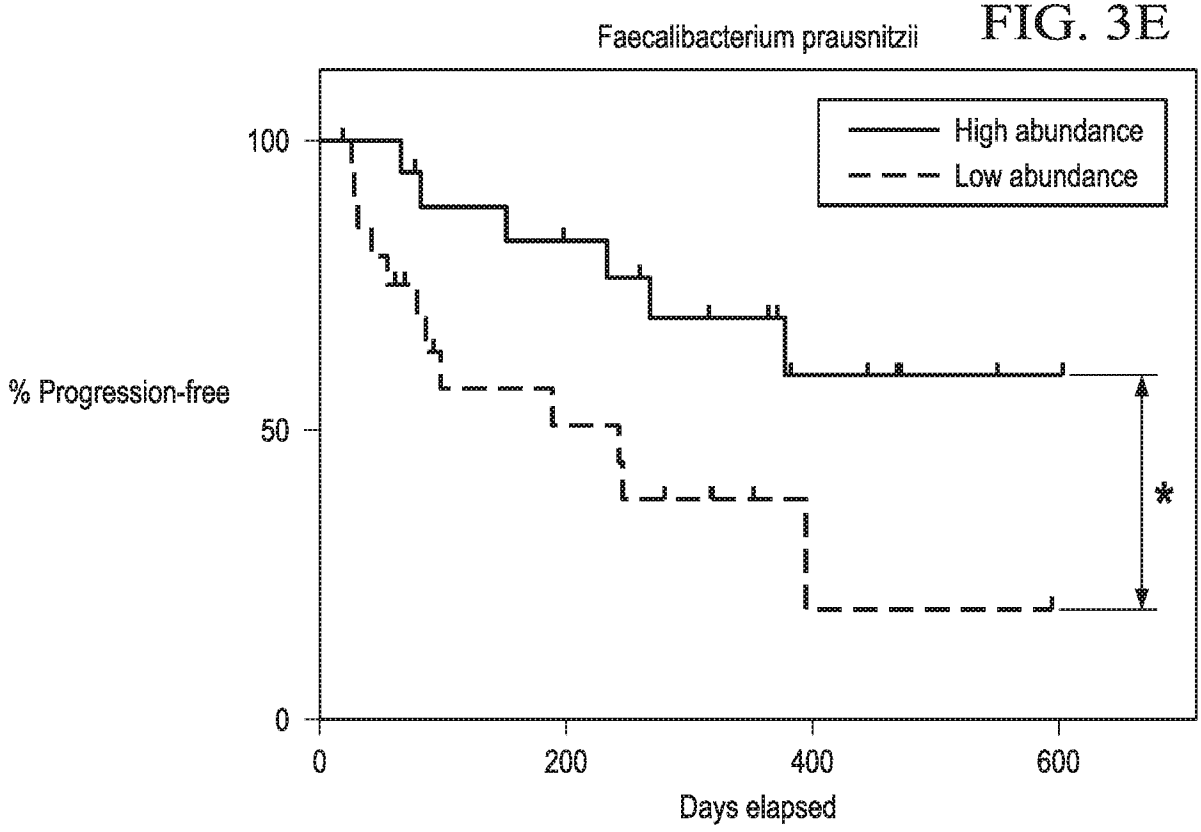
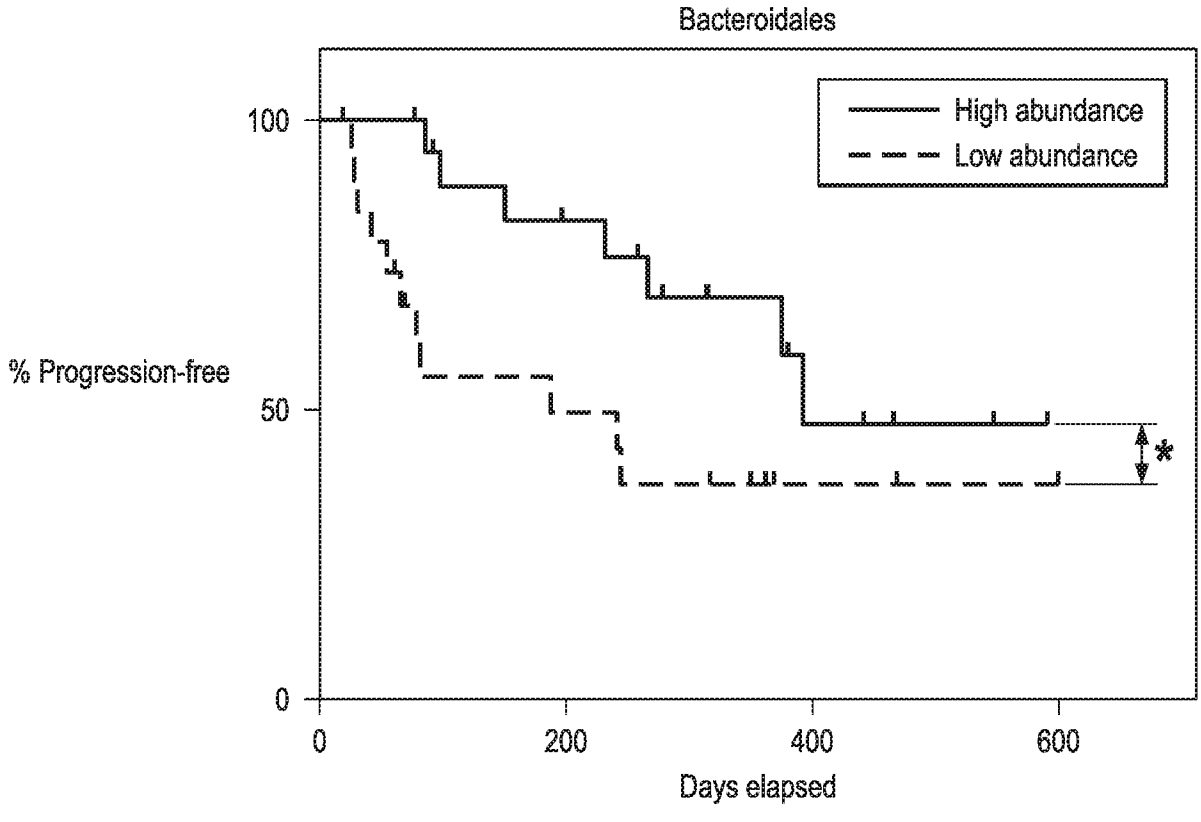

Phylum
Class
Order
Family
Genus
Species
Bacteroidetes
Bacteroidales
Bacteroidia
Bacteroidaceae
Bacteroides
Firmicutes
Clostridia
Clostridiales
Clostridiaceae
Ruminococcaceae
p=0.001
p=0.01
p=0.05
log10 FDR p-value
10
8
6
4
2
0
-20
-10
0
10
20
30
40
Effect size
Cluster 1
Cluster 2

FIG. 3E


Faecalibacterium prausnitzii
High abundance
Low abundance
% Progression-free
100
50
0
0
200
400
600
Days elapsed
*


Bacteroidales
High abundance
Low abundance
% Progression-free
100
50
0
0
200
400
600
Days elapsed
*

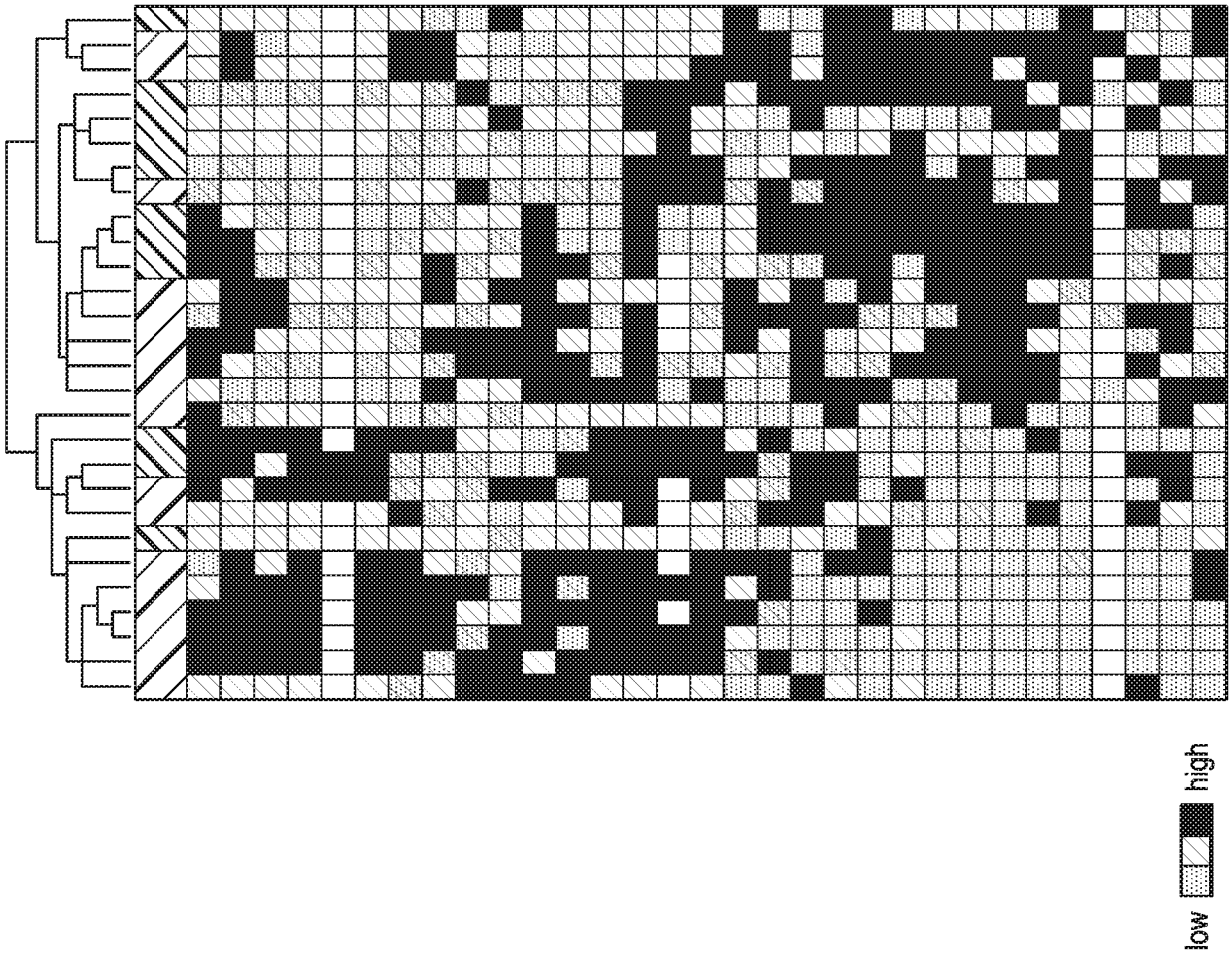

Biosynthesis
Degradation
Amines and polyamines biosynthesis
Biosynthesis
Amino acid biosynthesis
Aminoacyl-tRNA charging
Storage compound biosynthesis
Aldehyde degradation
Nucleosides and nucleotides biosynthesis
Amino acids degradation
Fatty acids and lipid biosynthesis
Carbohydrate biosynthesis
Cell structure biosynthesis
C1 compounds utilization and assimilation
Degradation/Utilization/Assimilation-other
Metabolic regulators biosynthesis
Bile acids degradation
Polymeric compounds degradation
Cofactors, prosthetic groups biosynthesis
Nucleosides and nucleotides degradation
Alcohols degradation
Secondary metabolites biosynthesis
Aromatic compounds biosynthesis
Carbohydrates degradation
Amines and polyamines degradation
Degradation/Utilization/Assimilation -Other
Aromatic compounds degradation
Secondary metabolites degradation
Carboxylates degradation
Chlorinated compounds degradation
Generation of precursor metabolites
Inorganic nutrients metabolism
Fatty acids and lipids degradation
low
high

FIG. 3F

FIG. 4A

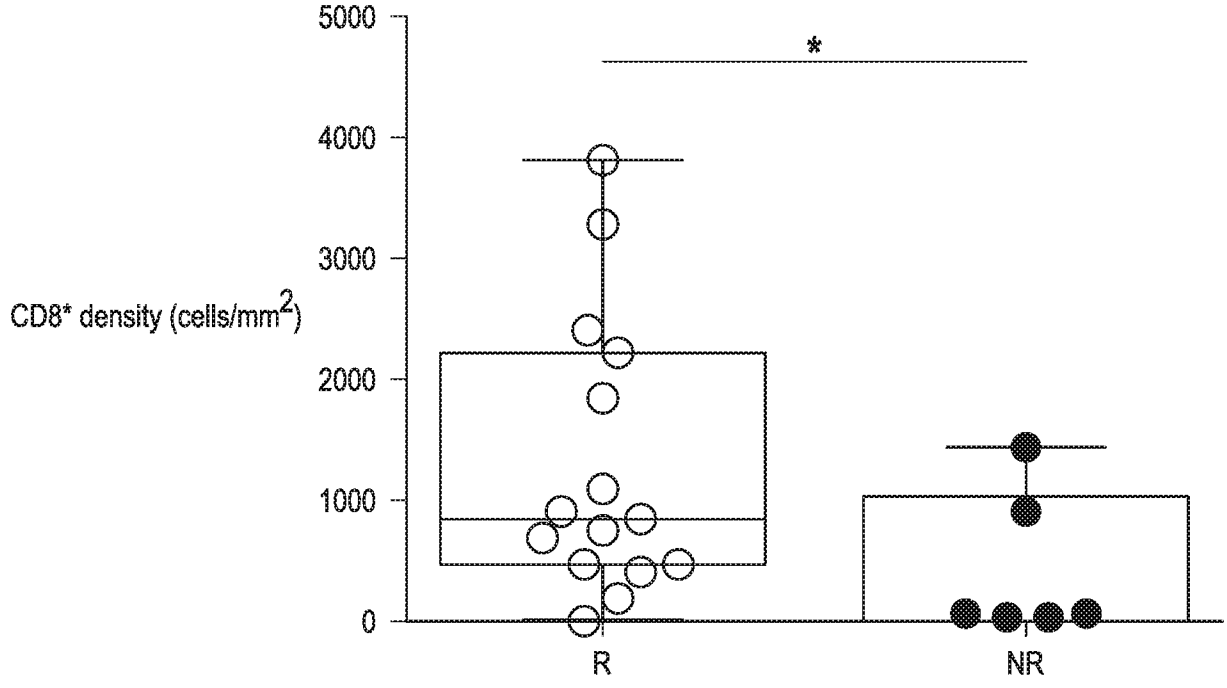

5000
4000
3000
2000
1000
0
CD8* density (cells/mm2)
*
R
NR

FIG. 4B

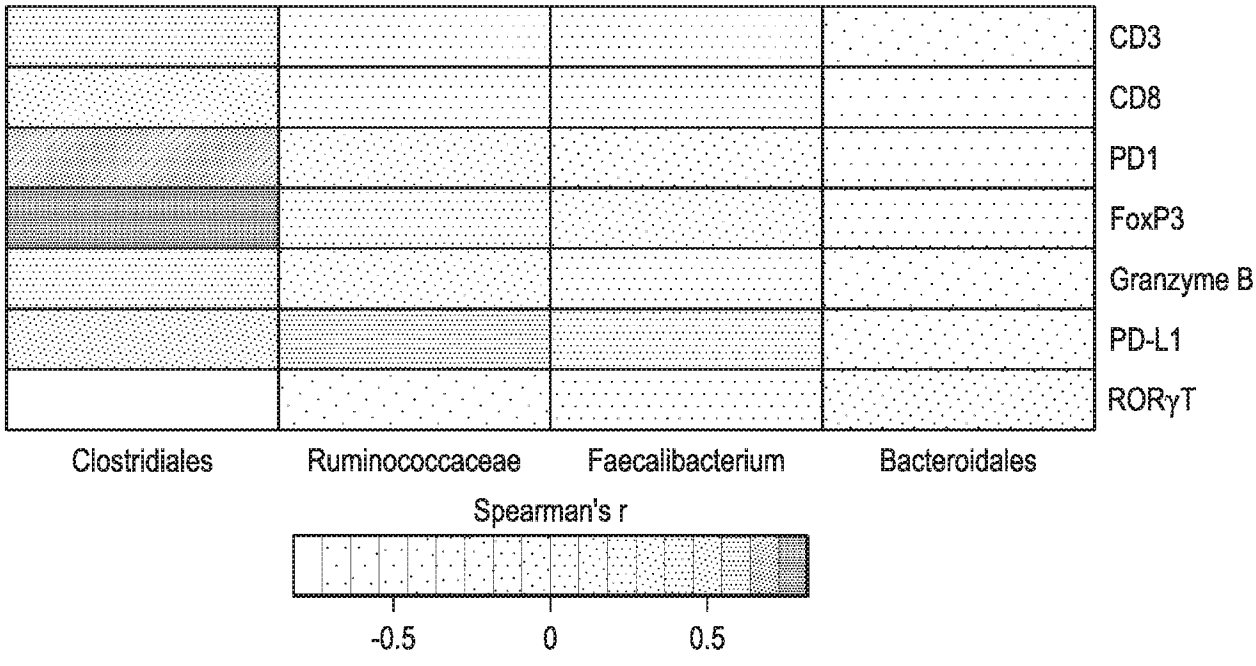

CD3
CD8
PD1
FoxP3
Granzyme B
PD-L1
RORγT
Clostridiales
Ruminococcaceae
Faecalibacterium
Bacteroidales
Spearman's r
-0.5
0
0.5

FIG. 4C

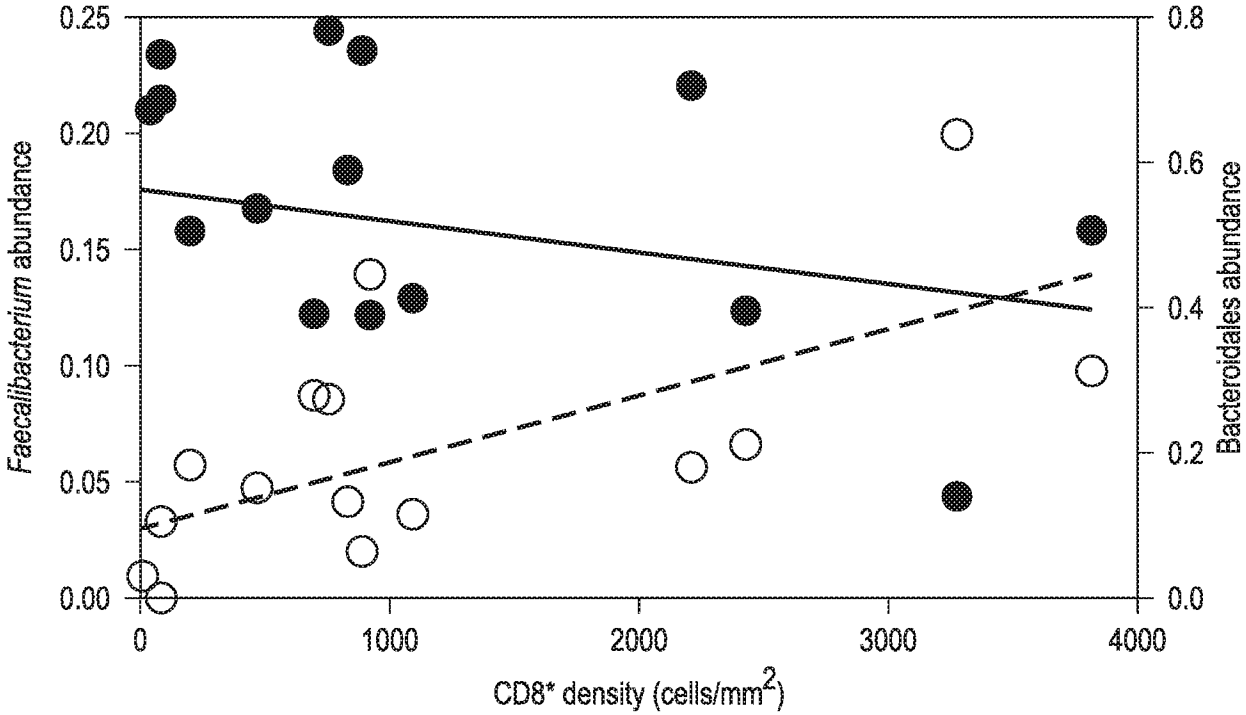

0.25
0.20
0.15
0.10
0.05
0.00
Faecalibacterium abundance
0.8
0.6
0.4
0.2
0.0
Bacteroidales abundance
0
1000
2000
3000
4000
CD8* density (cells/mm2)

FIG. 4D

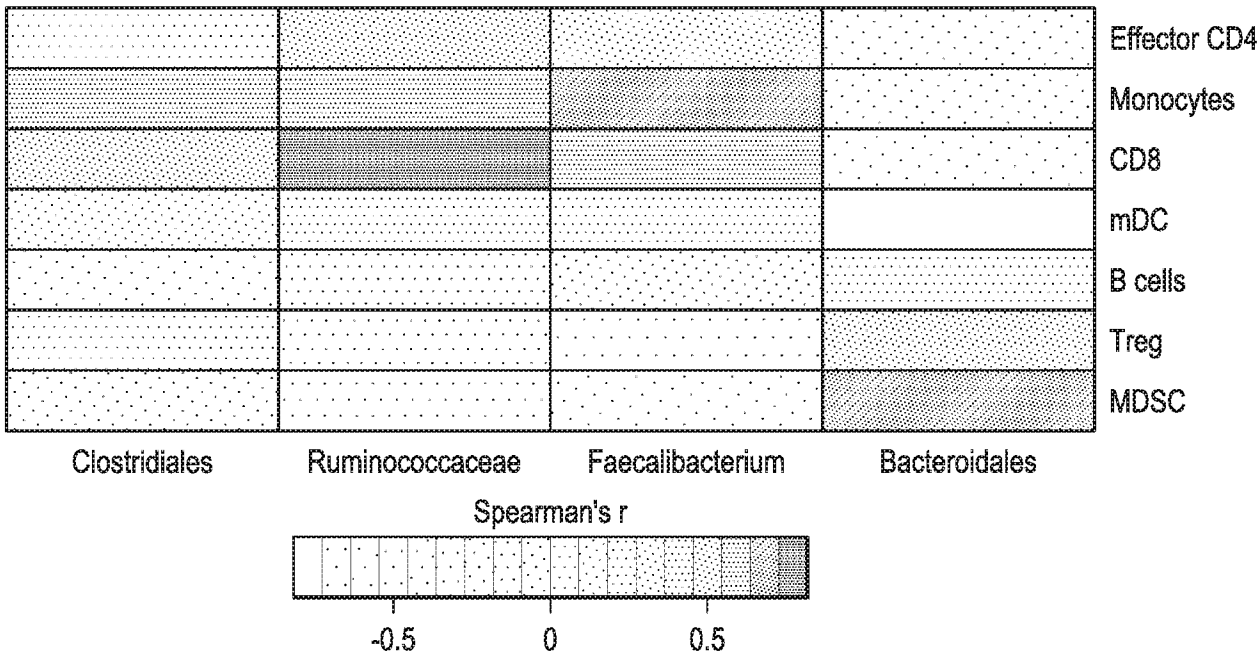

Effector CD4
Monocytes
CD8
mDC
B cells
Treg
MDSC
Clostridiales
Ruminococcaceae
Faecalibacterium
Bacteroidales
Spearman's r
-0.5
0
0.5

FIG. 4E

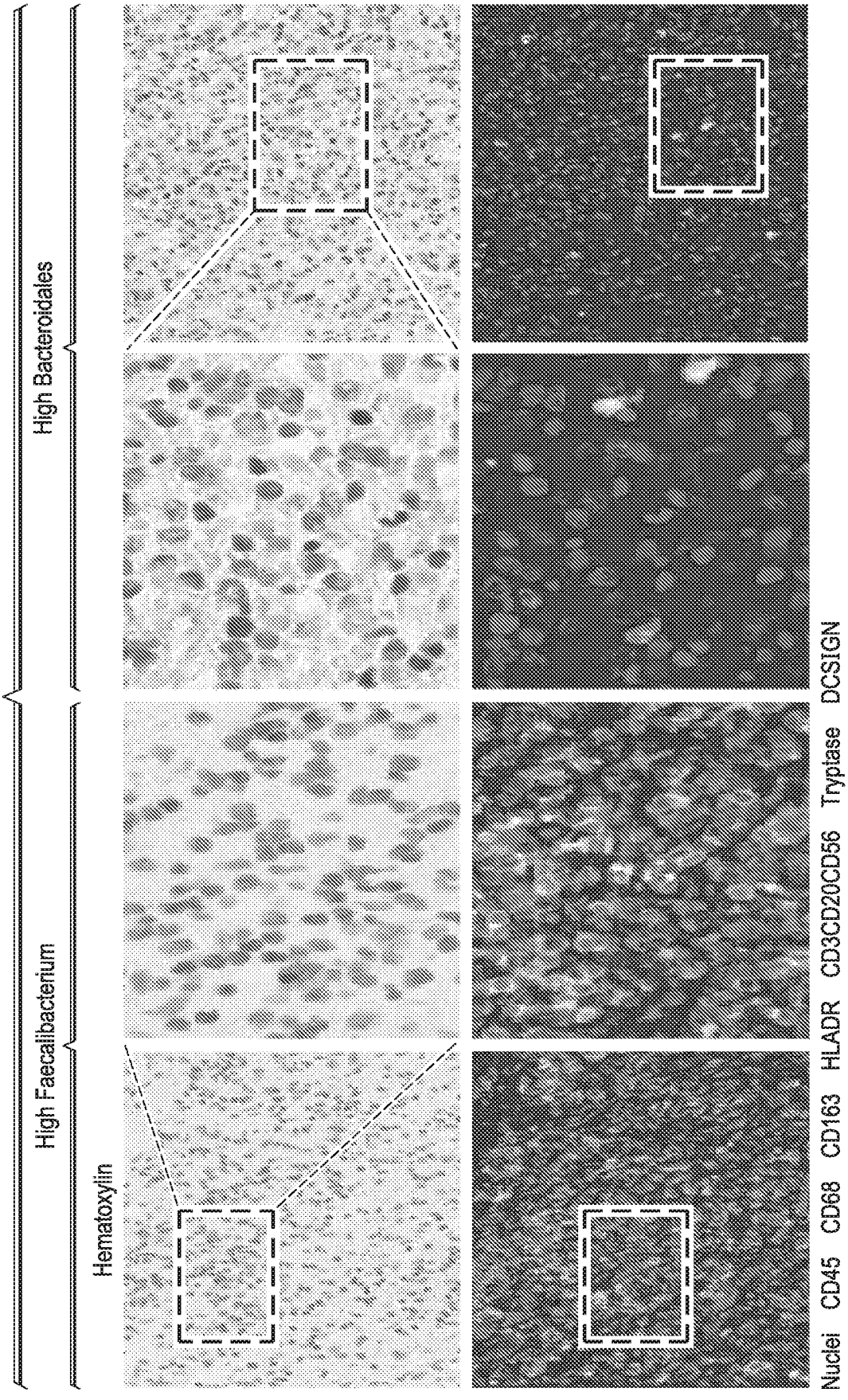
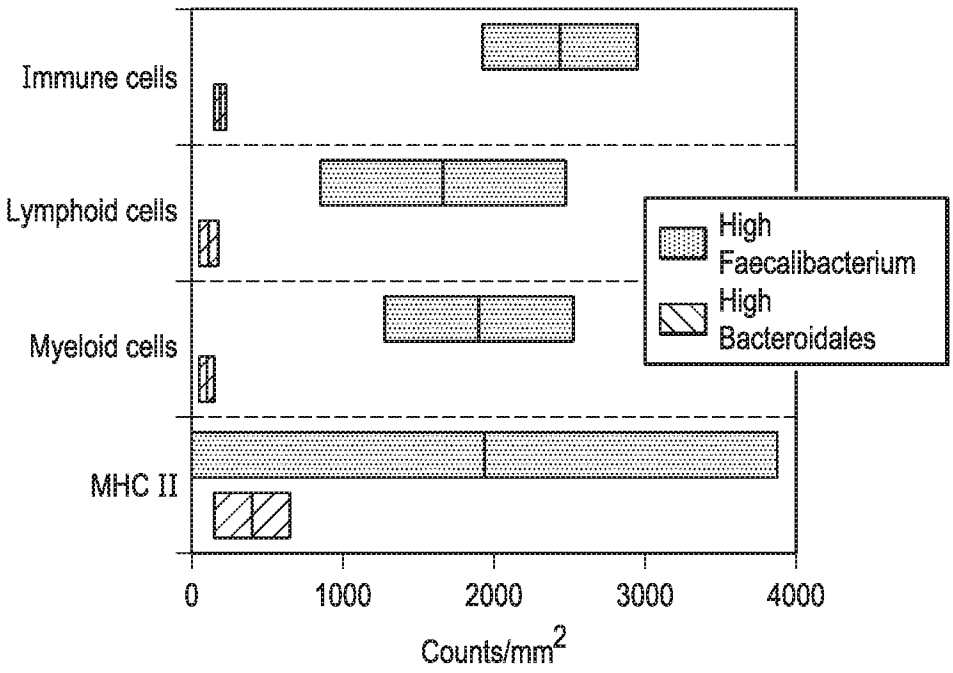

High Faecalibacterium
High Bacteroidales
Hematoxylin
Nuclei
CD45
CD68
CD163
HLADR
CD3CD20CD56
Tryptase
DCSIGN

FIG. 4F


Immune cells
Lymphoid cells
Myeloid cells
MHC II
High Faecalibacterium
High Bacteroidales
0
1000
2000
3000
4000
Counts/mm2

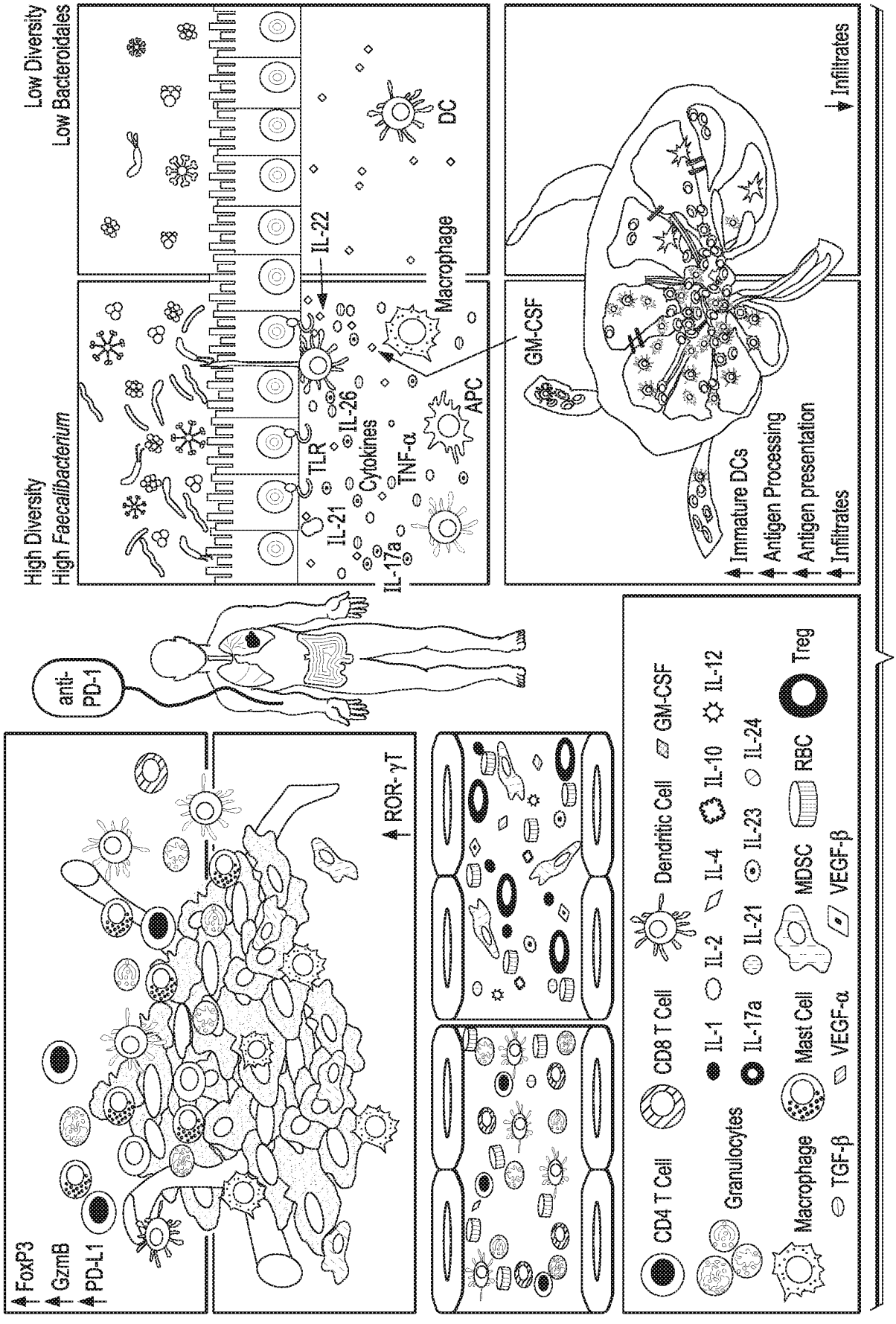

FoxP3
GzmB
PD-L1
ROR-γT
anti-PD-1
High Diversity
High Faecalibacterium
Low Diversity
Low Bacteroidales
TLR
IL-21
IL-26
Cytokines
IL-17a
TNF-α
APC
IL-22
Macrophage
DC
GM-CSF
Immature DCs
Antigen Processing
Antigen presentation
Infiltrates
Infiltrates
CD4 T Cell
CD8 T Cell
Dendritic Cell
GM-CSF
Granulocytes
IL-1
IL-2
IL-4
IL-10
IL-12
IL-17a
IL-21
IL-23
IL-24
Macrophage
Mast Cell
MDSC
RBC
Treg
TGF-β
VEGF-α
VEGF-β

FIG. 4G

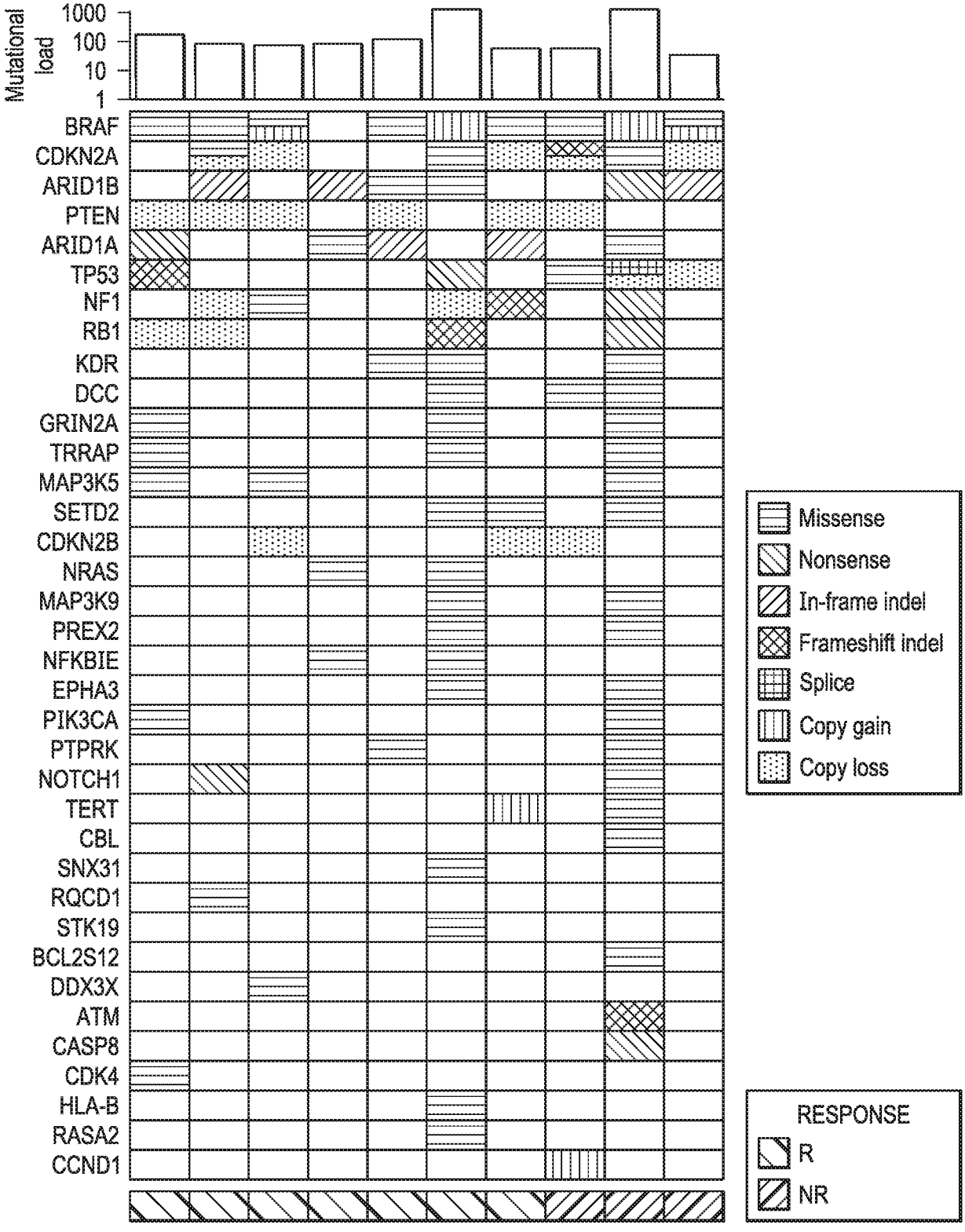
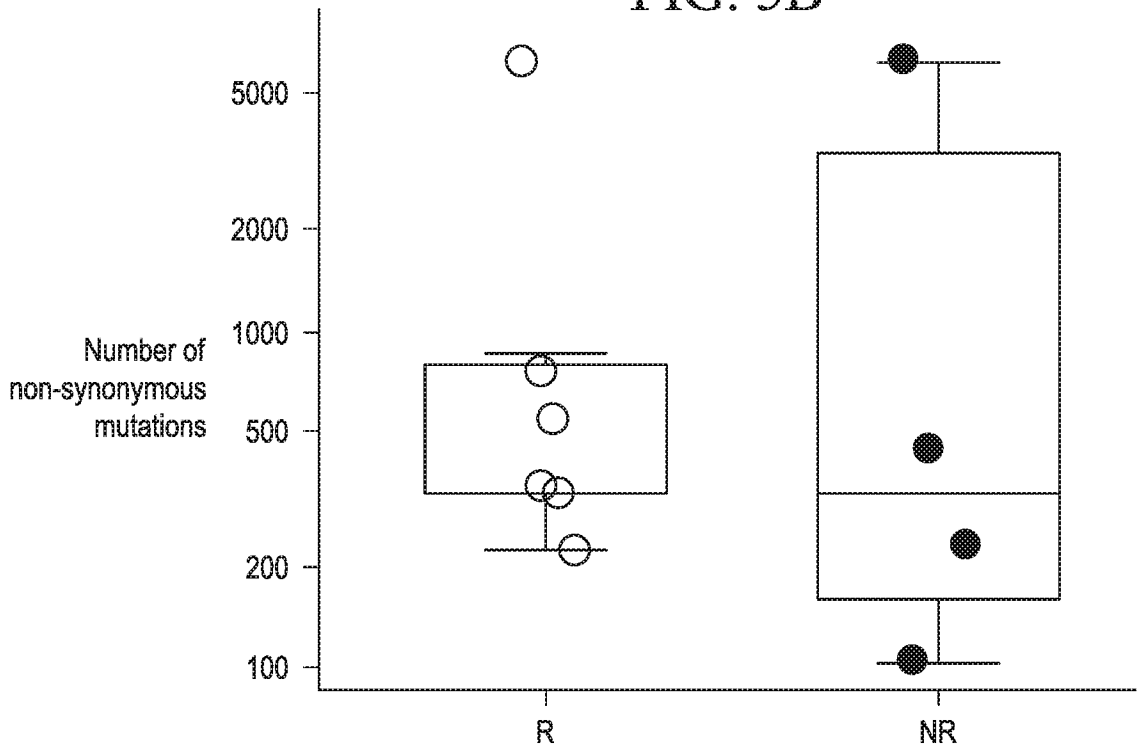

Mutational load
1000
100
10
1
BRAF
CDKN2A
ARID1B
PTEN
ARID1A
TP53
NF1
RB1
KDR
DCC
GRIN2A
TRRAP
MAP3K5
SETD2
CDKN2B
NRAS
MAP3K9
PREX2
NFKBIE
EPHA3
PIK3CA
PTPRK
NOTCH1
TERT
CBL
SNX31
RQCD1
STK19
BCL2S12
DDX3X
ATM
CASP8
CDK4
HLA-B
RASA2
CCND1
Missense
Nonsense
In-frame indel
Frameshift indel
Splice
Copy gain
Copy loss
RESPONSE
R
NR

FIG. 5A

FIG. 5B


Number of non-synonymous mutations
5000
2000
1000
500
200
100
R
NR

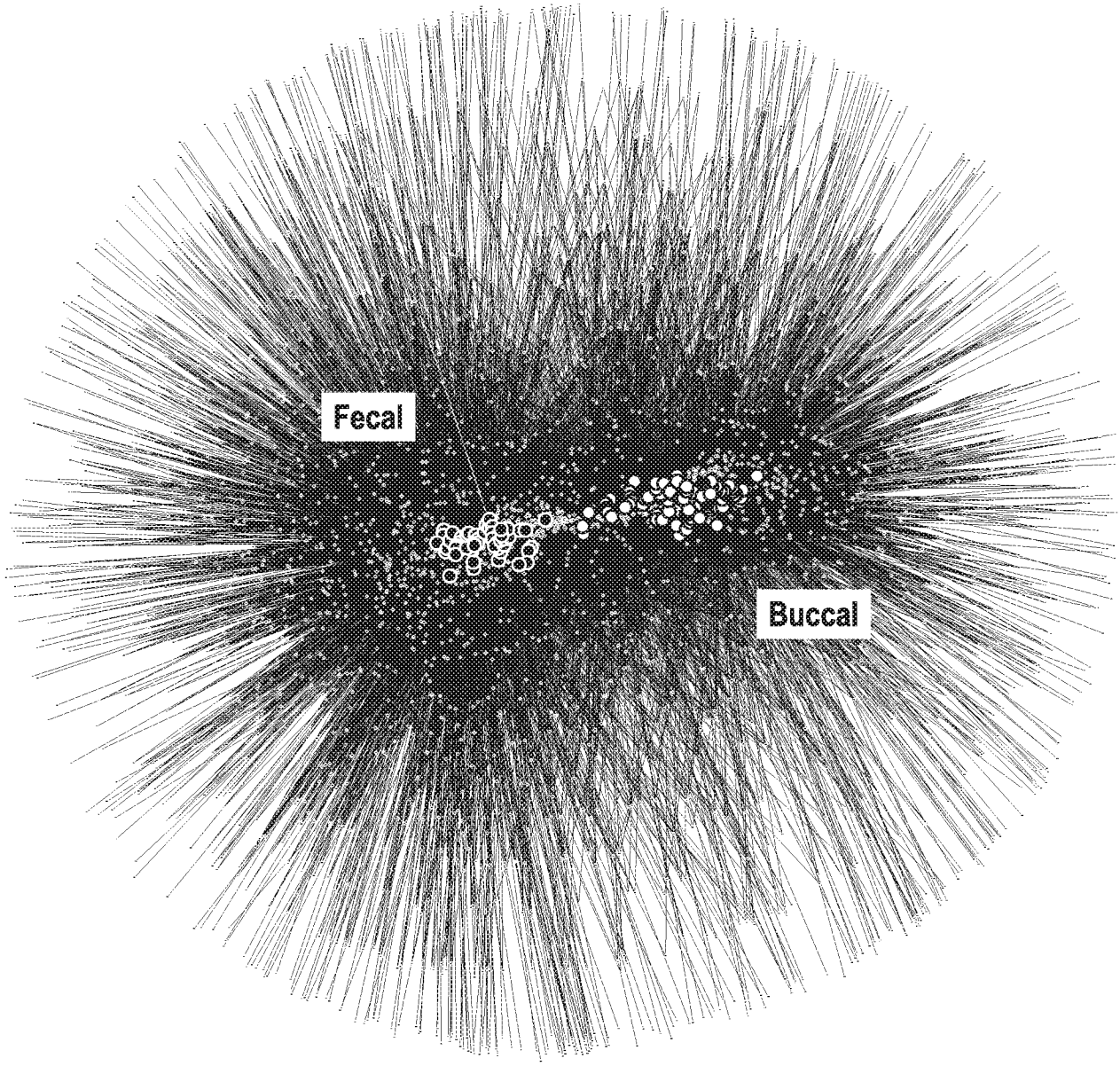



FIG. 6

FIG. 7A

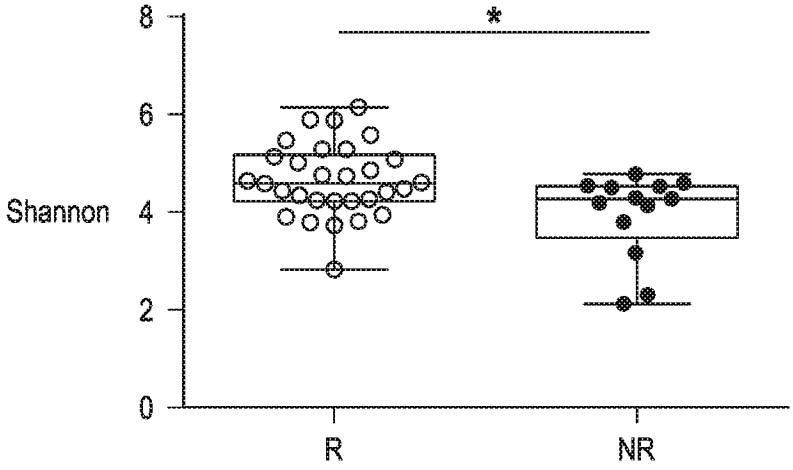



FIG. 7B

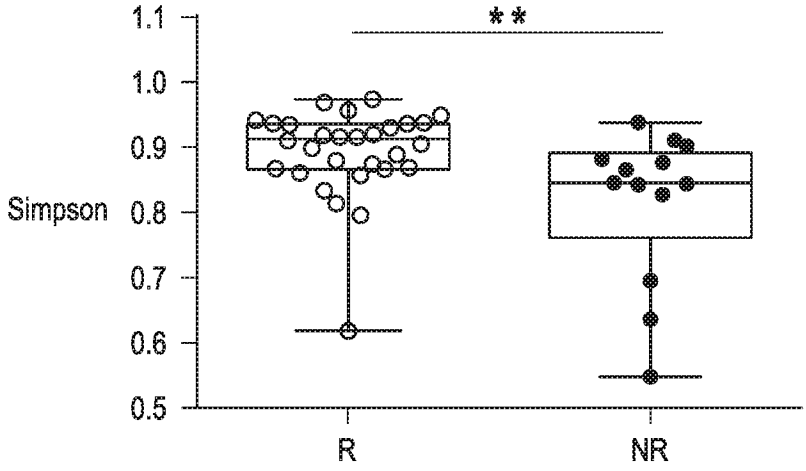



FIG. 7C

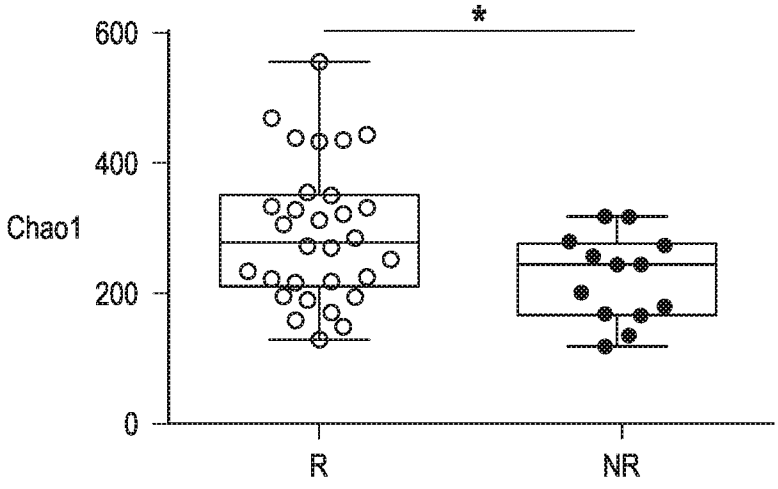


FIG. 8A

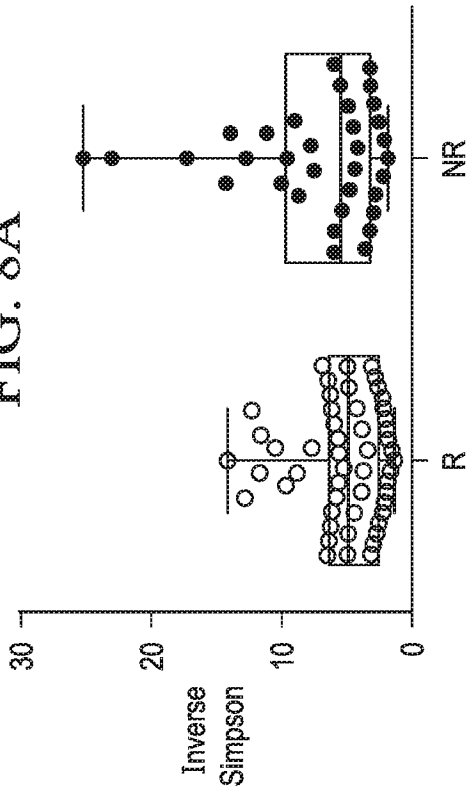



FIG. 8B

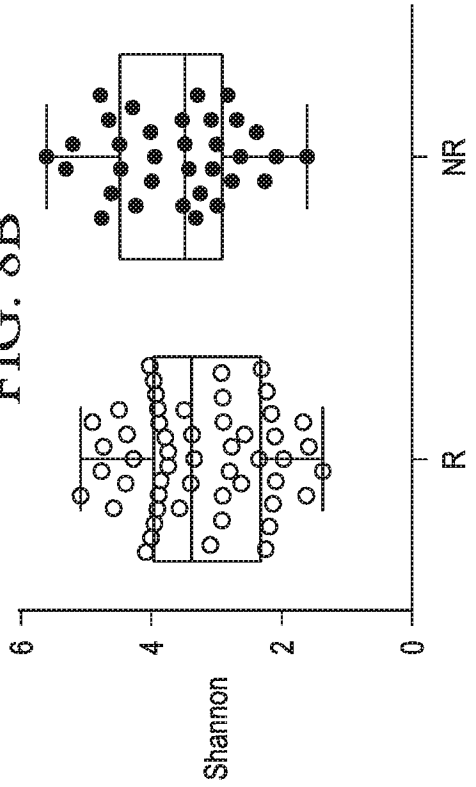



FIG. 8C

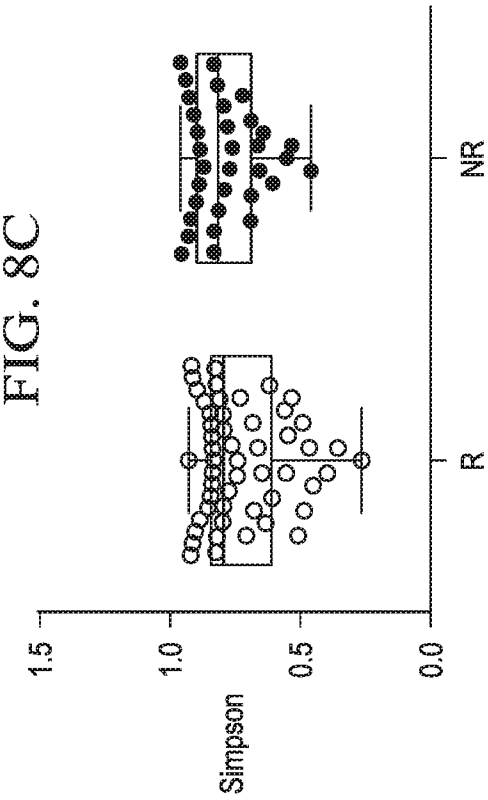



FIG. 8D

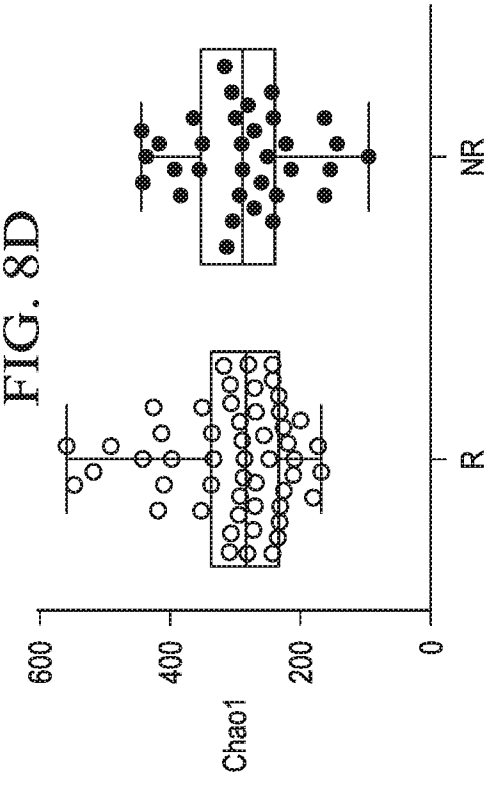


FIG. 9A

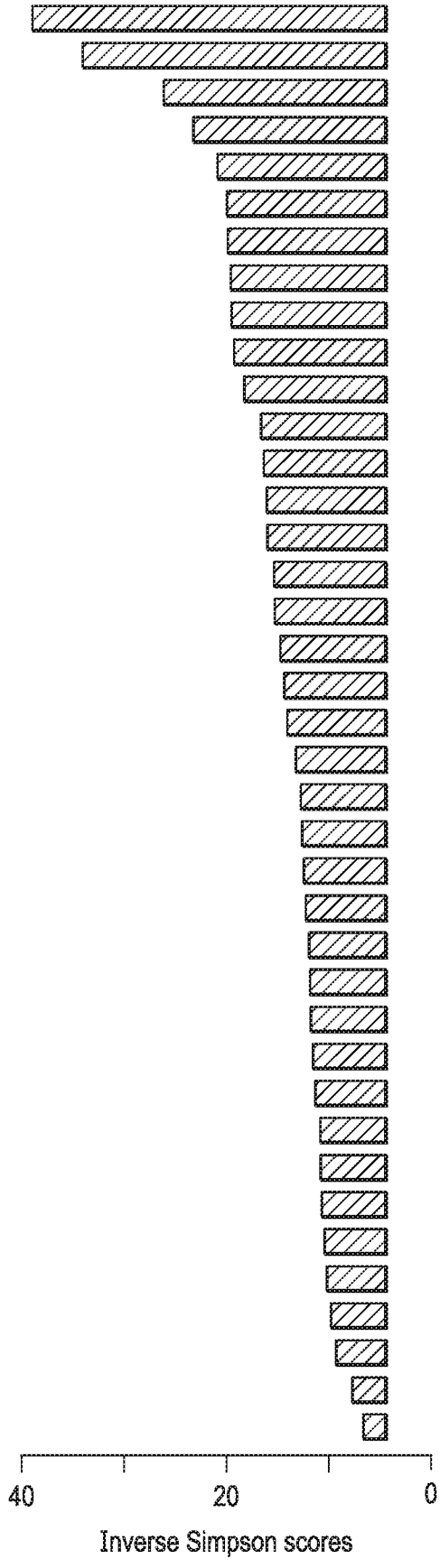
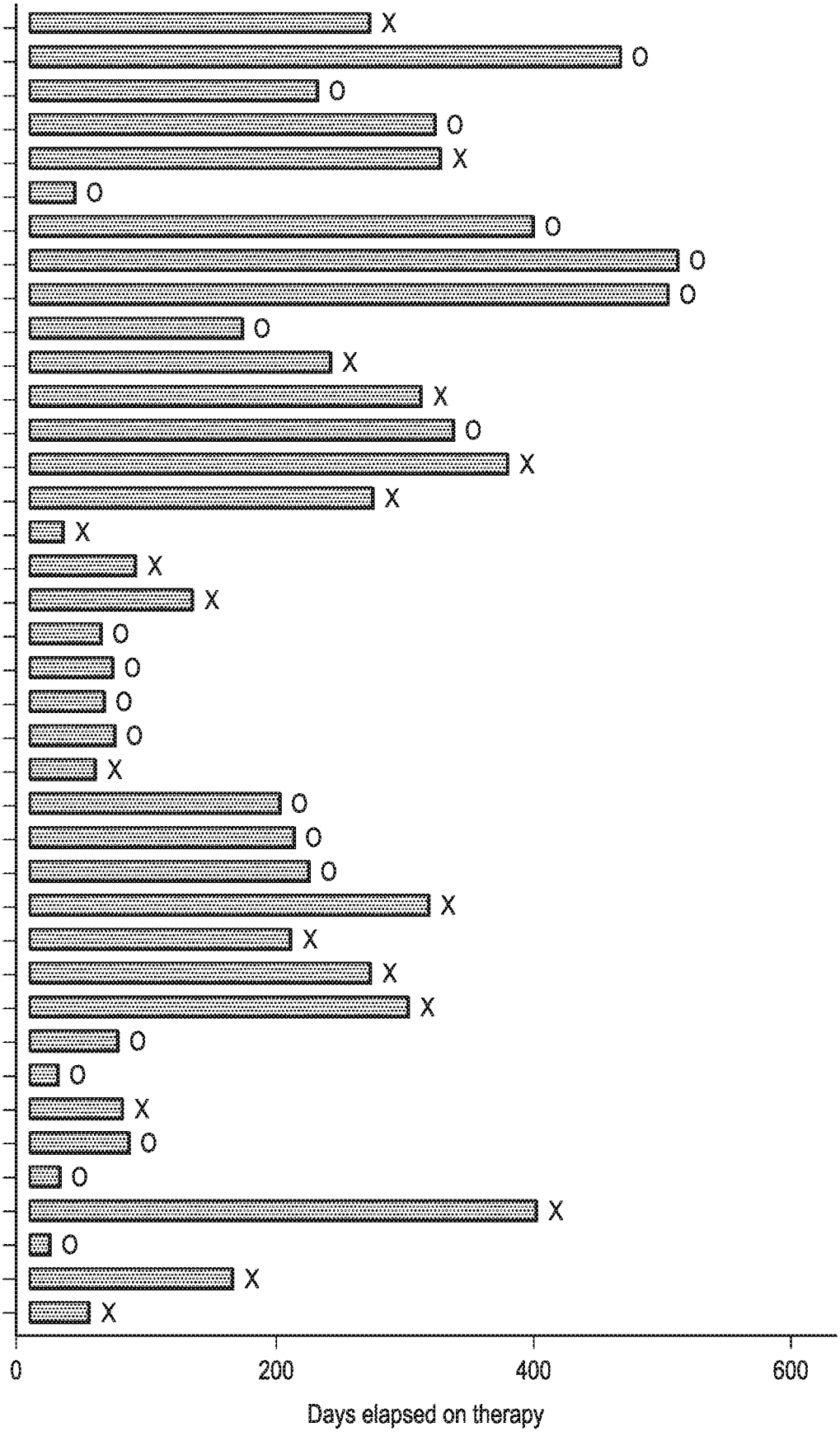


FIG. 9B


X
O
O
O
X
O
O
O
O
O
X
X
O
X
X
O
X
X
X
O
O
O
O
X
O
O
O
X
X
X
X
O
O
X
O
O
X
O
X
0
200
400
600
Days elapsed on therapy

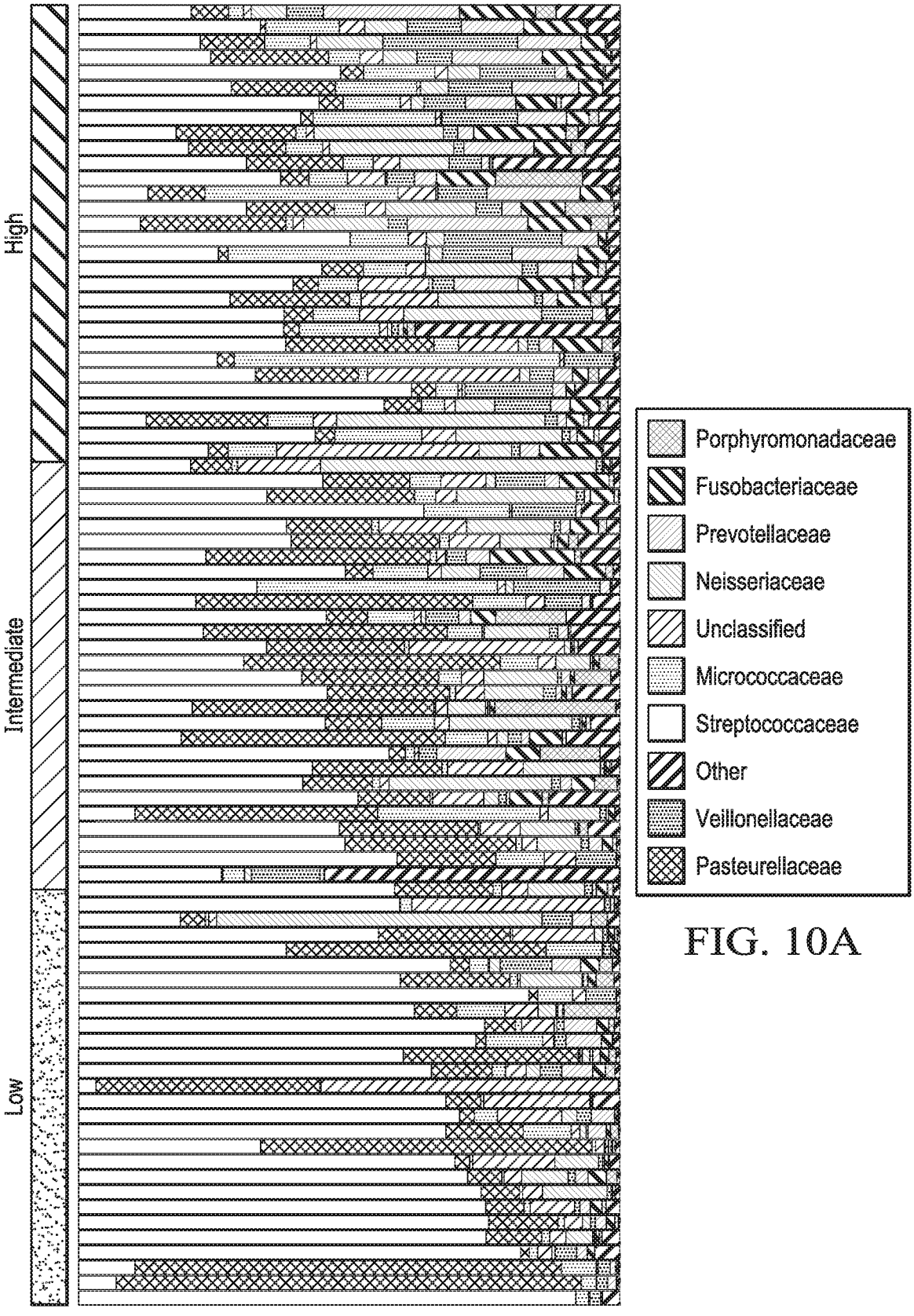

High
Intermediate
Low
Porphyromonadaceae
Fusobacteriaceae
Prevotellaceae
Neisseriaceae
Unclassified
Micrococcaceae
Streptococcaceae
Other
Veillonellaceae
Pasteurellaceae

FIG. 10A

FIG. 10B

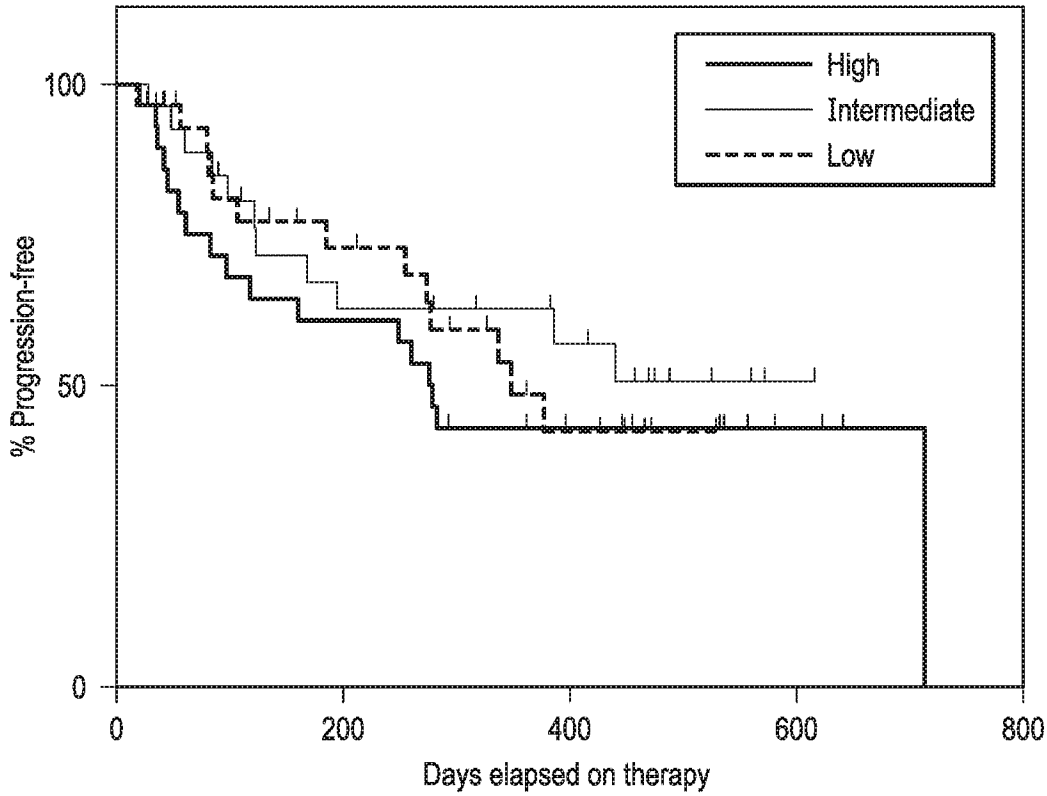

High
Intermediate
Low
100
50
0
% Progression-free
0
200
400
600
800
Days elapsed on therapy

FIG. 10C

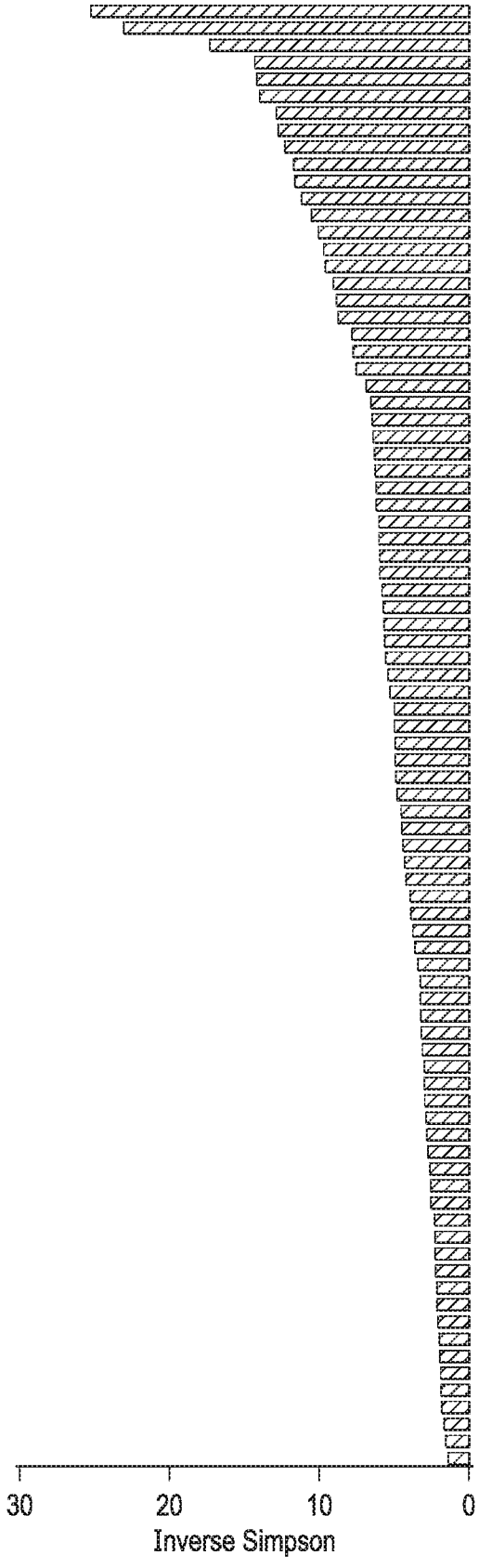


FIG. 10D

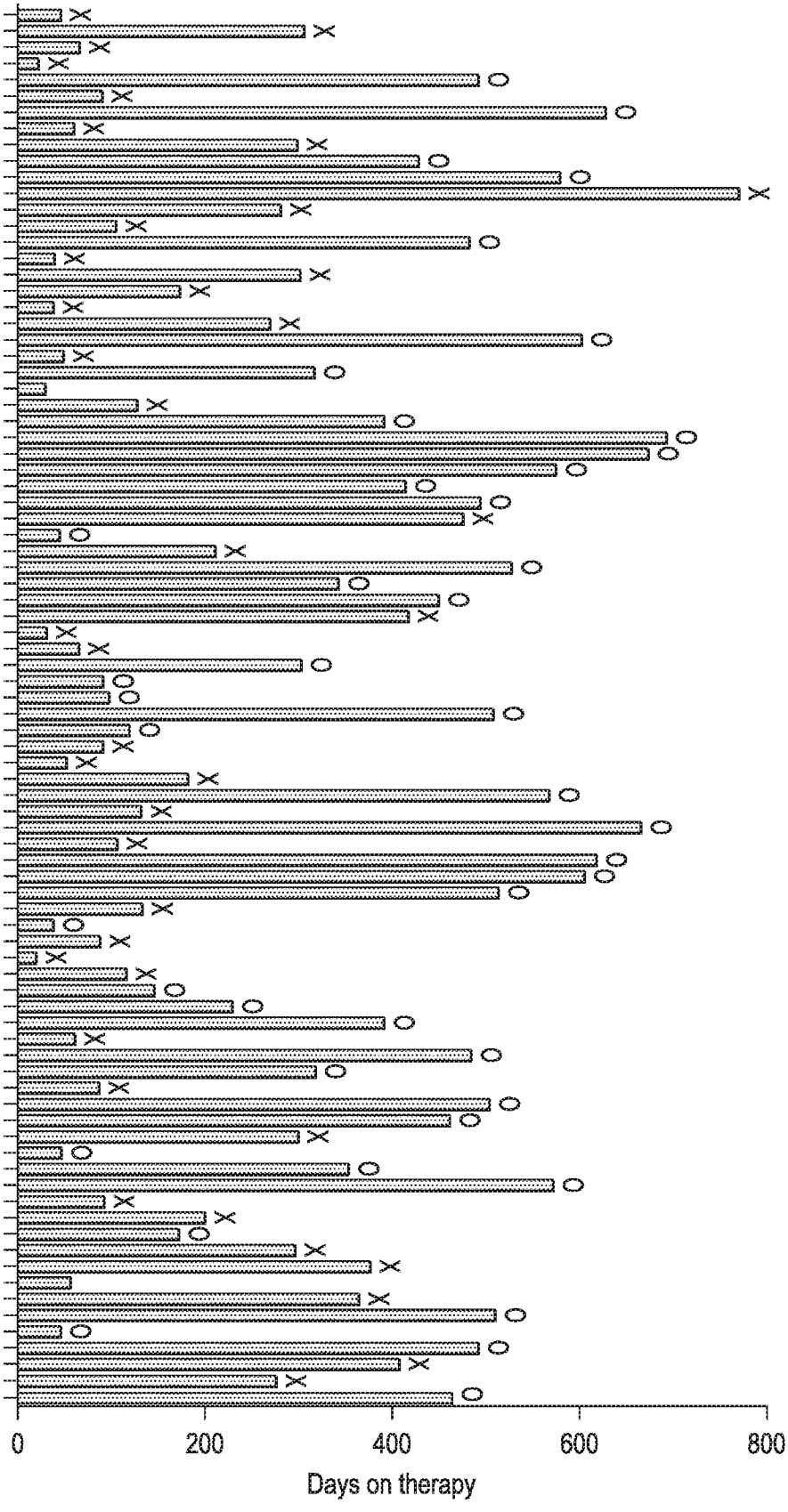


FIG. 11A

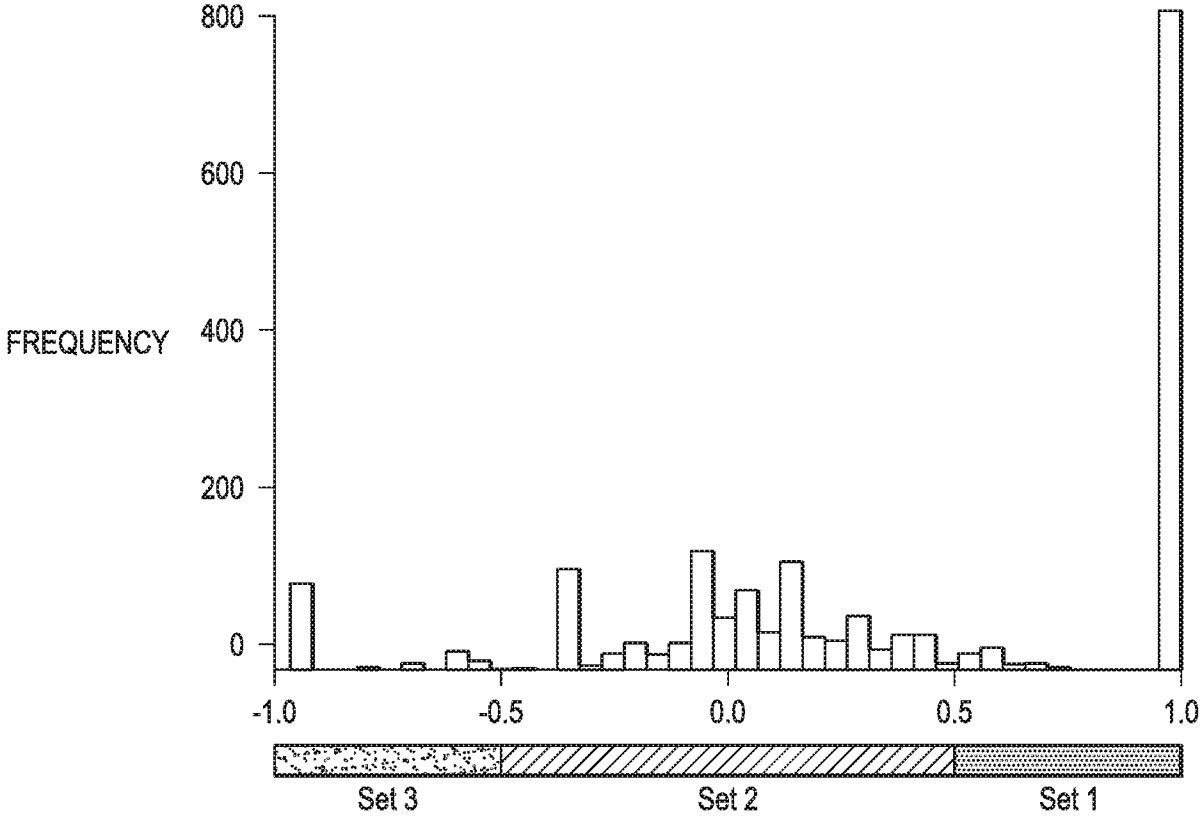



FIG. 11B

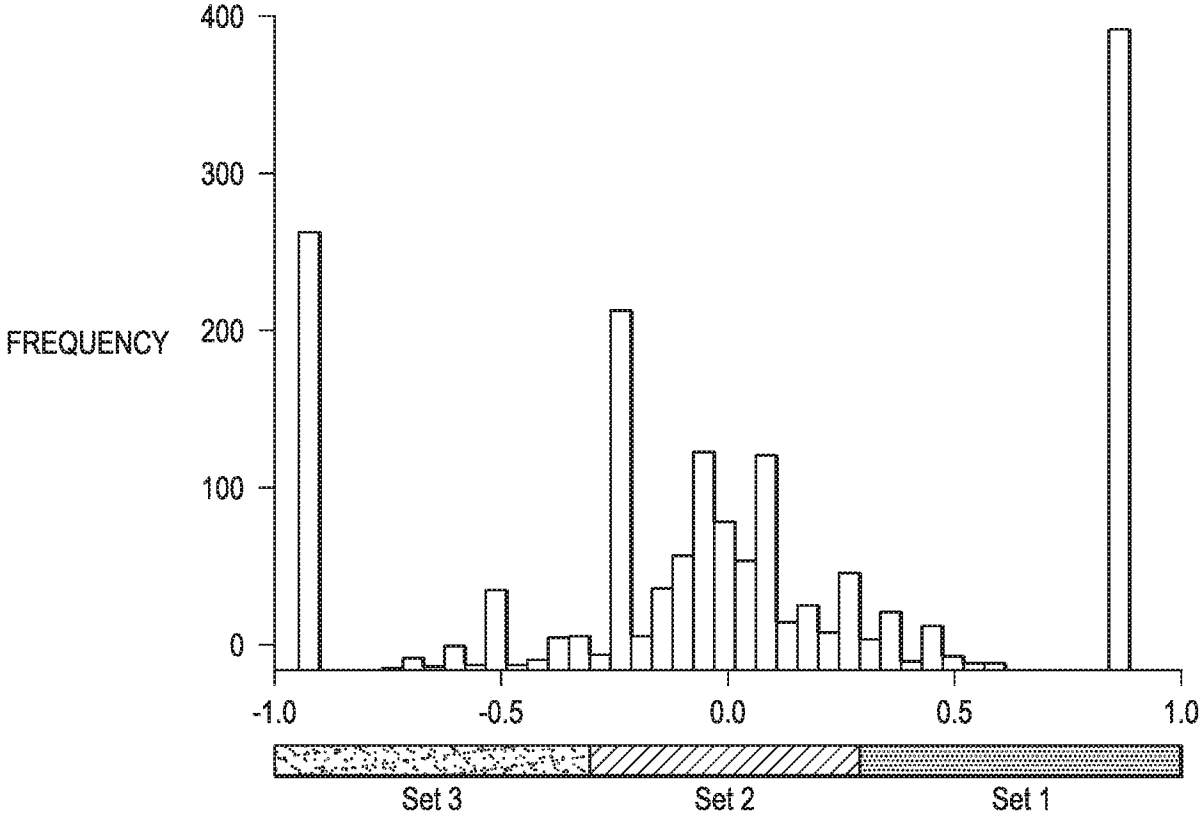


FIG. 11C

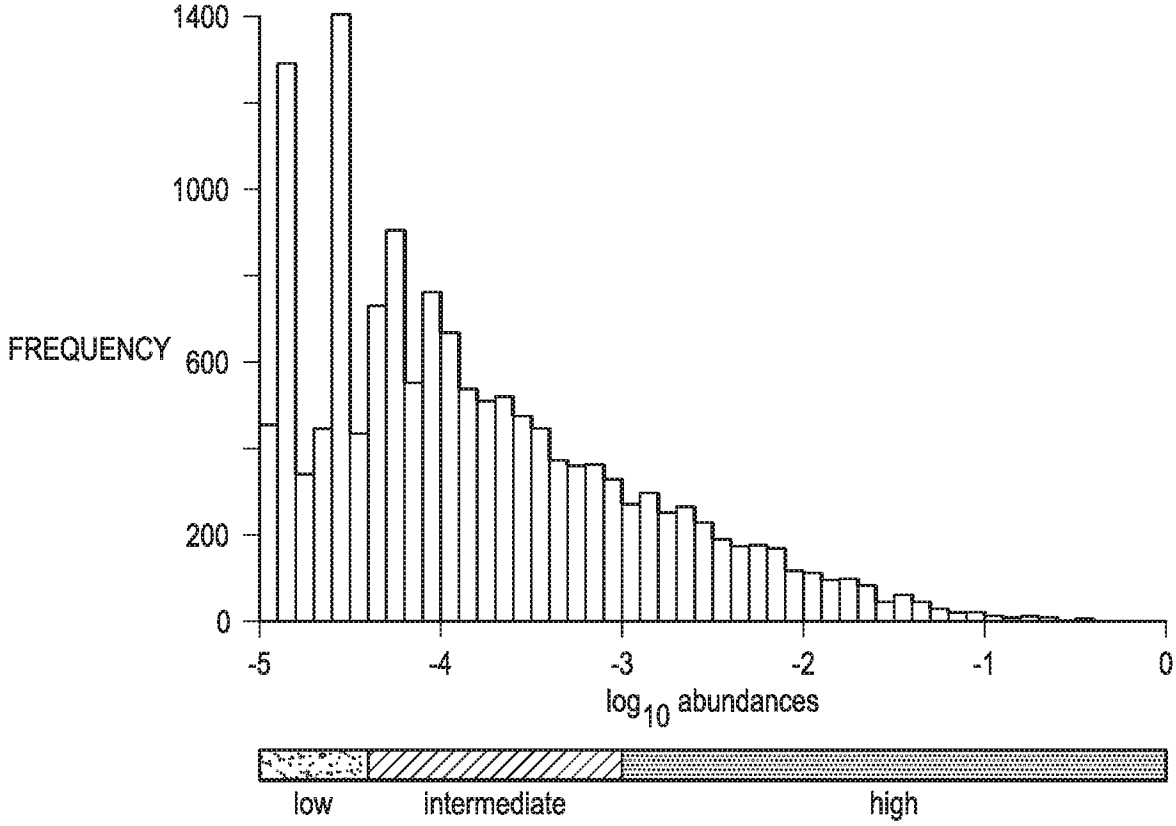
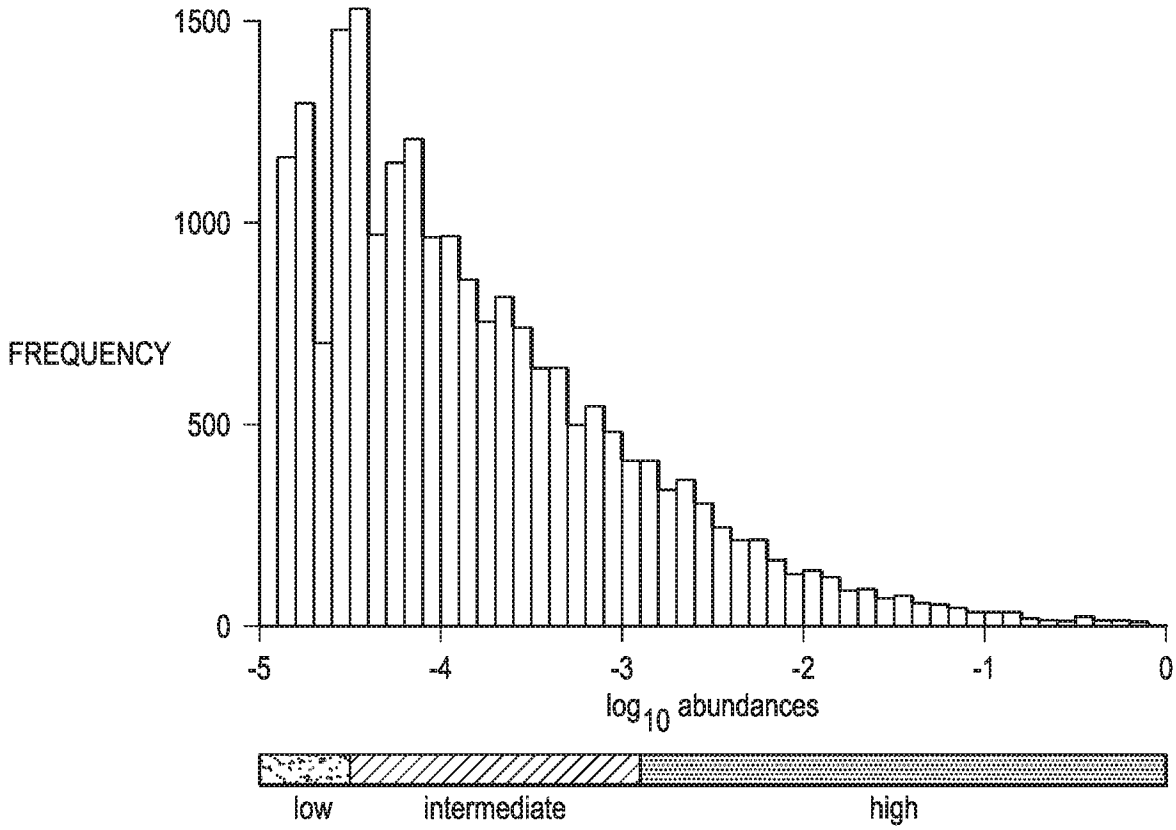



FIG. 11D



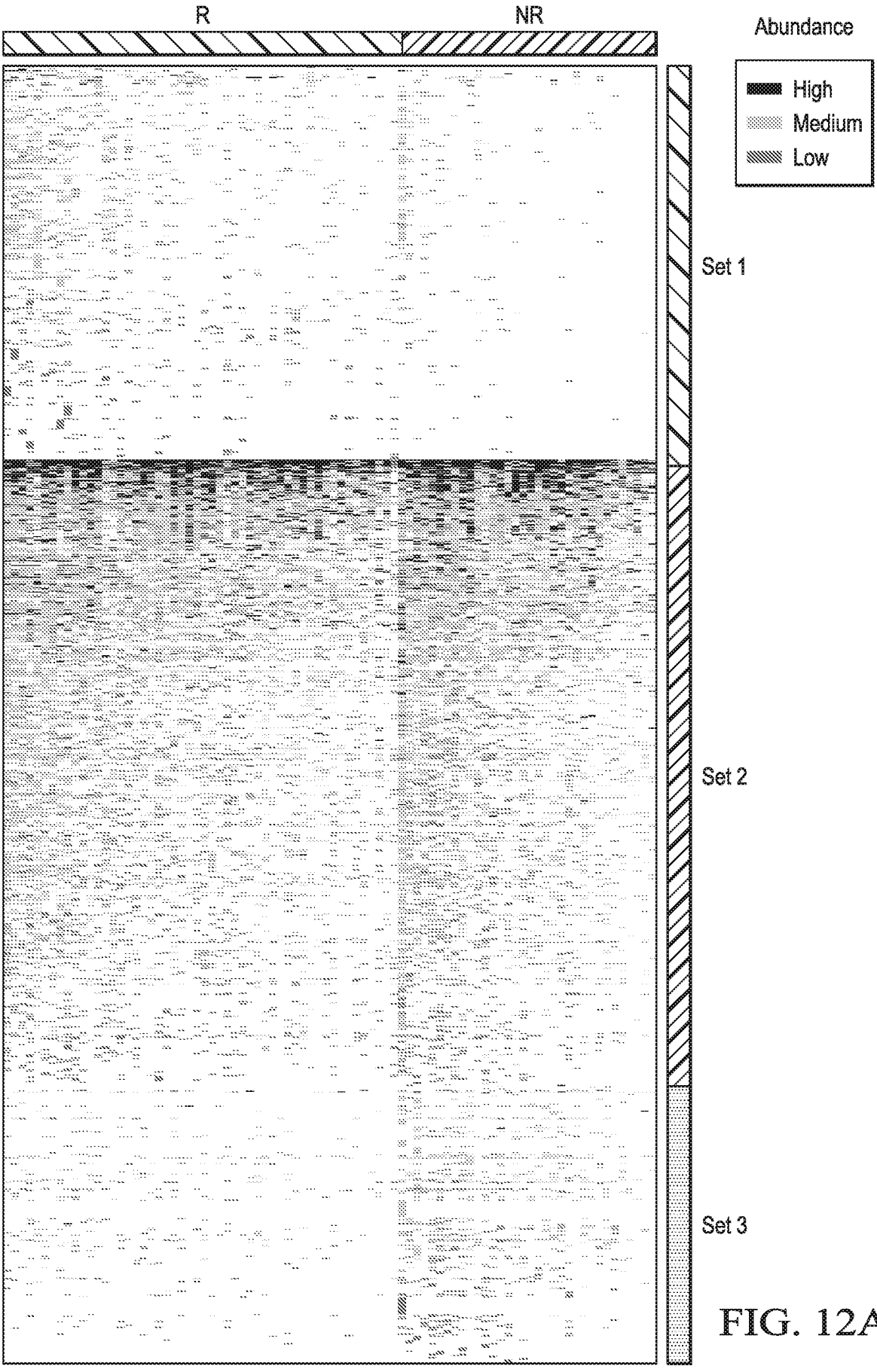



FIG. 12A

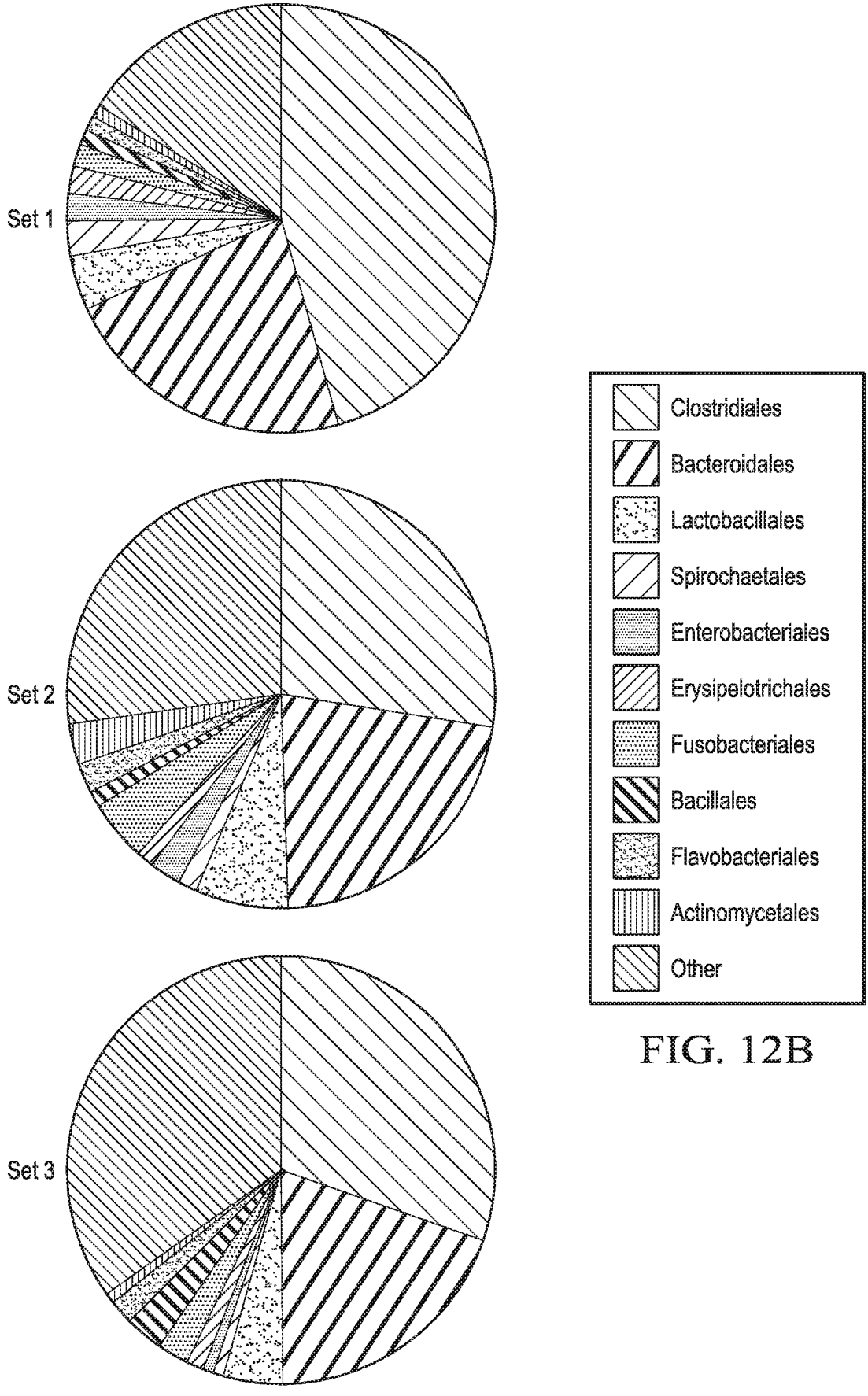

Set 1
Set 2
Set 3
Clostridiales
Bacteroidales
Lactobacillales
Spirochaetales
Enterobacteriales
Erysipelotrichales
Fusobacteriales
Bacillales
Flavobacteriales
Actinomycetales
Other

FIG. 12B

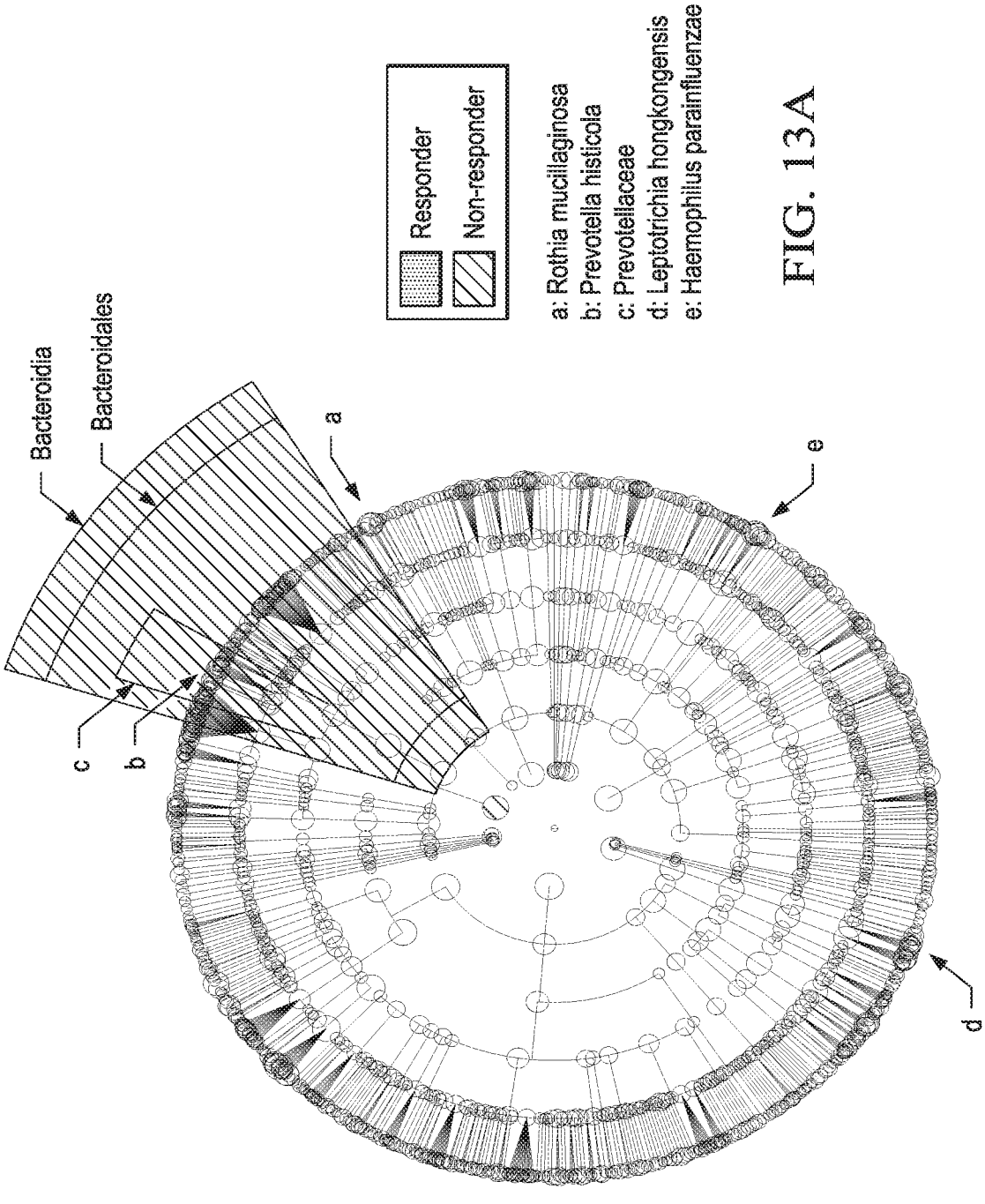

Bacteroidia
Bacteroidales
a
b
c
d
e
Responder
Non-responder
a: Rothia mucillaginosa
b: Prevotella histicola
c: Prevotellaceae
d: Leptotrichia hongkongensis
e: Haemophilus parainfluenzae

FIG. 13A

FIG. 13B

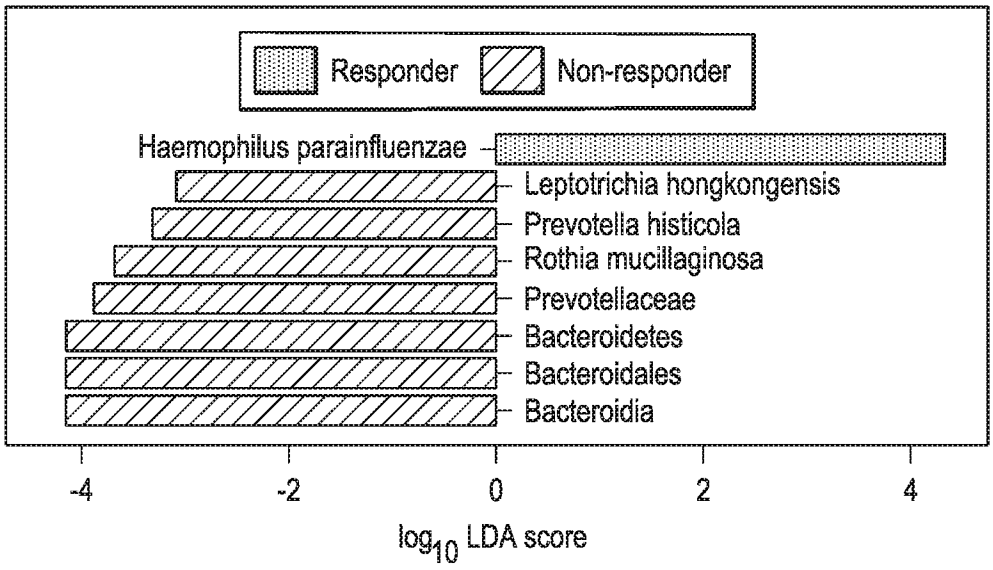



FIG. 14A

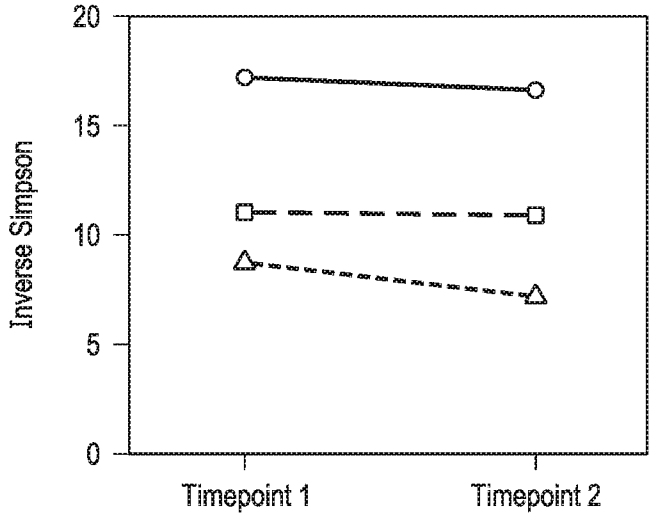
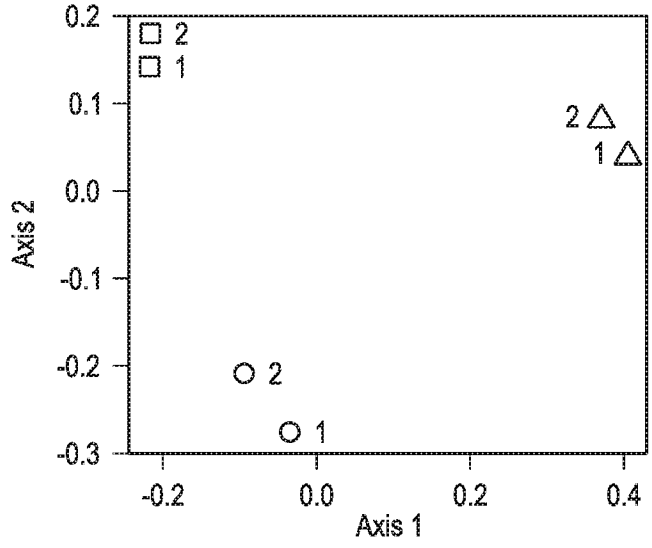



FIG. 14B



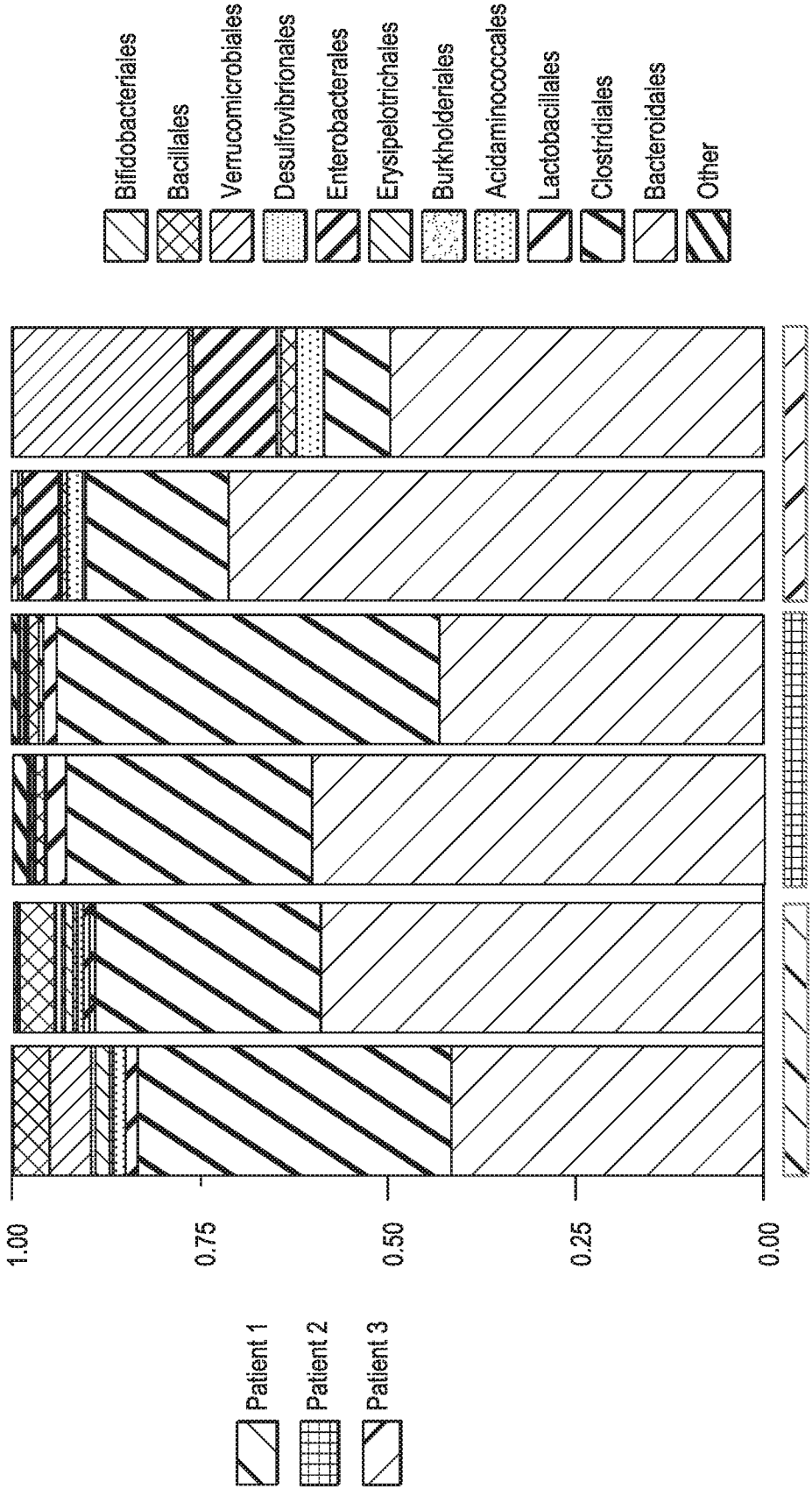

Bifidobacteriales
Bacillales
Verrucomicrobiales
Desulfovibrionales
Enterobacterales
Erysipelotrichales
Burkholderiales
Acidaminococcales
Lactobacillales
Clostridiales
Bacteroidales
Other
1.00
0.75
0.50
0.25
0.00
Patient 1
Patient 2
Patient 3

FIG. 14C

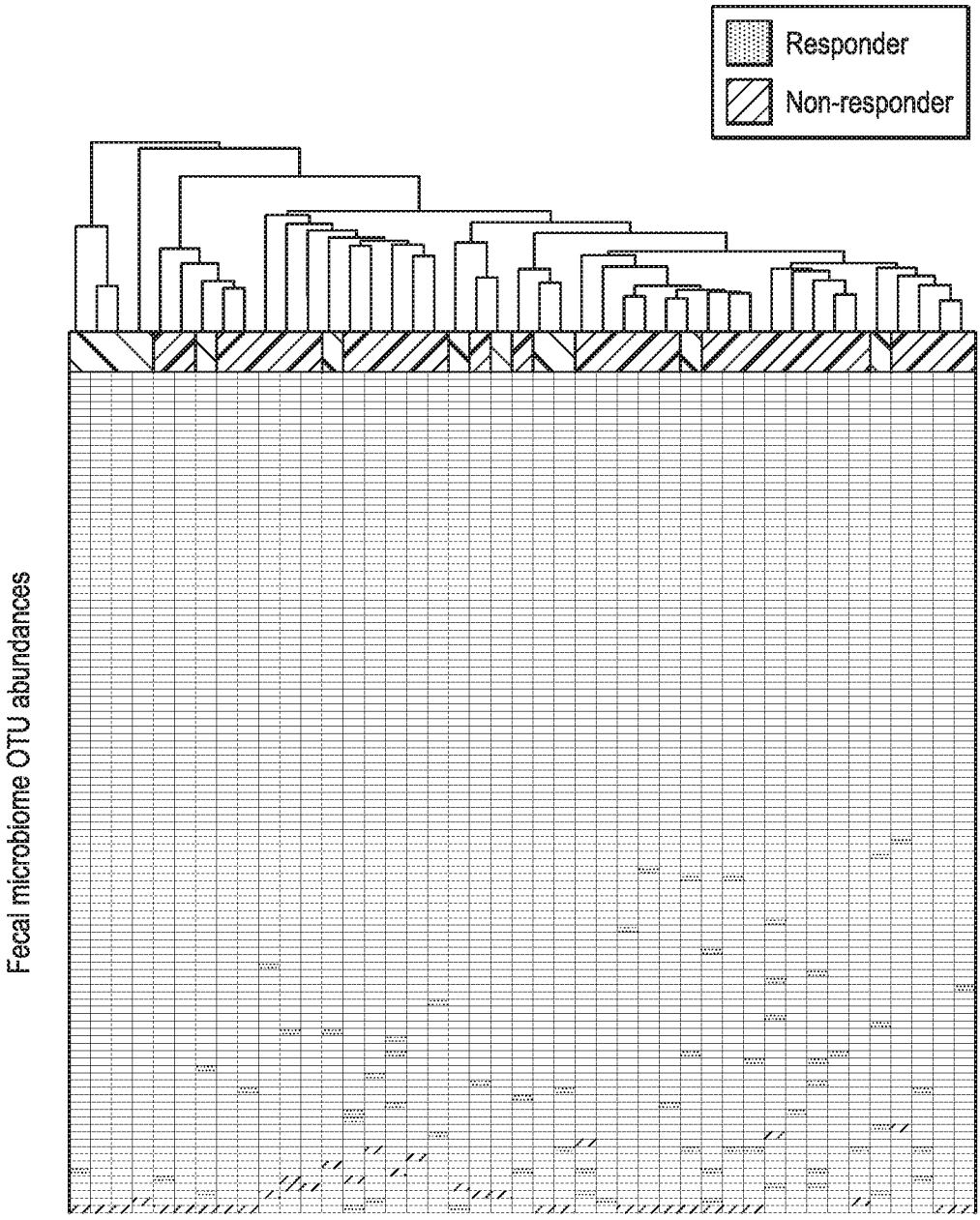



FIG. 15A

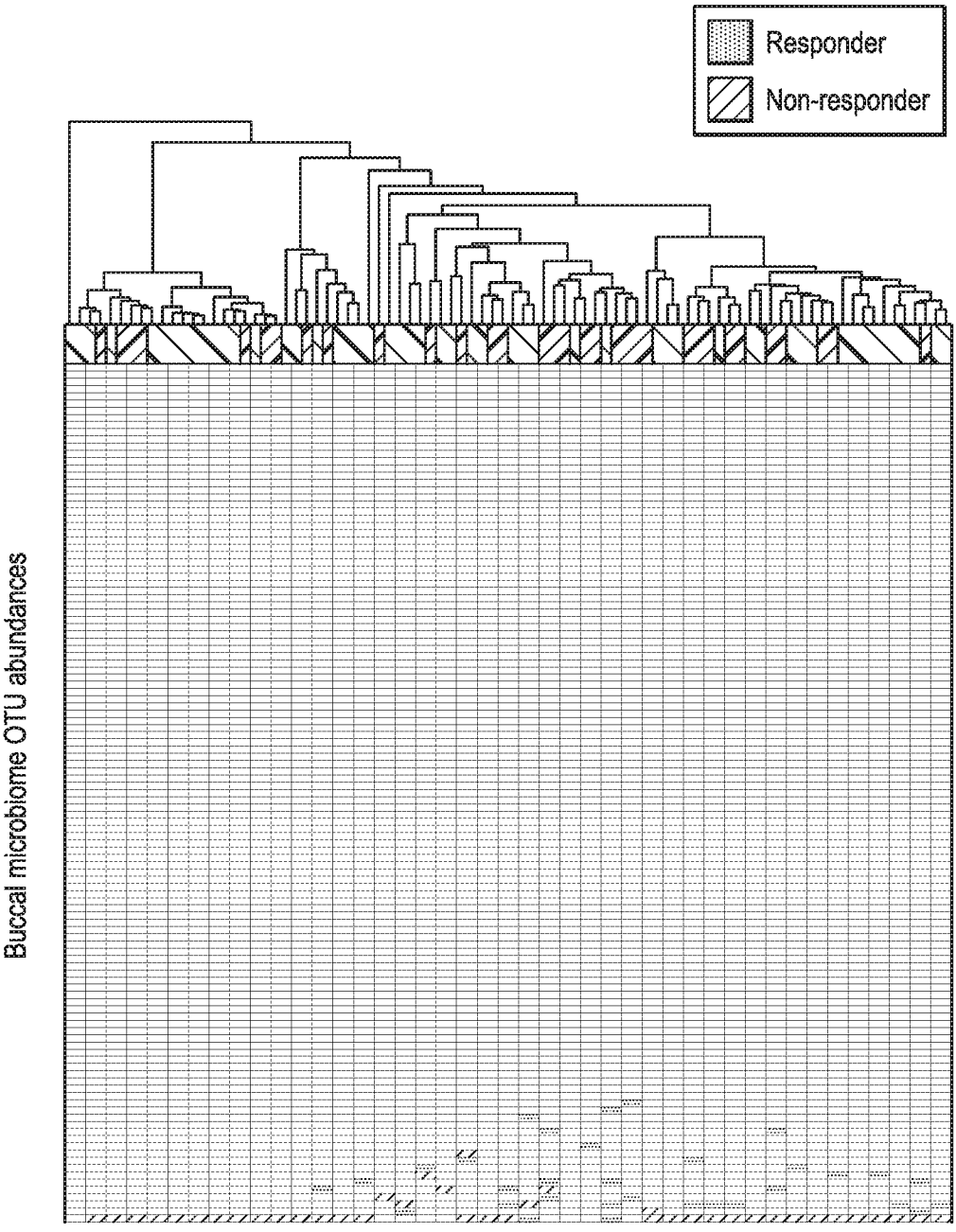

Responder
Non-responder
Buccal microbiome OTU abundances

FIG. 15B

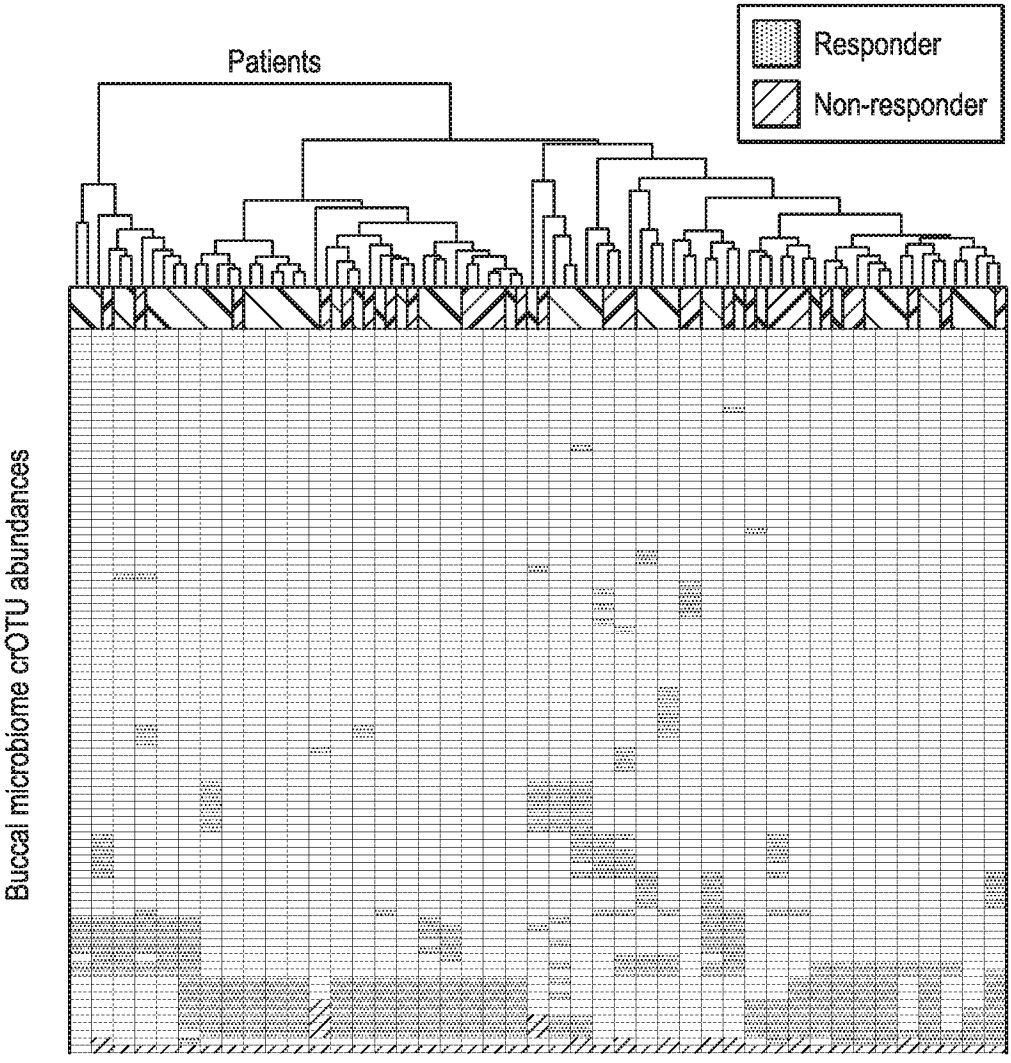



FIG. 16A

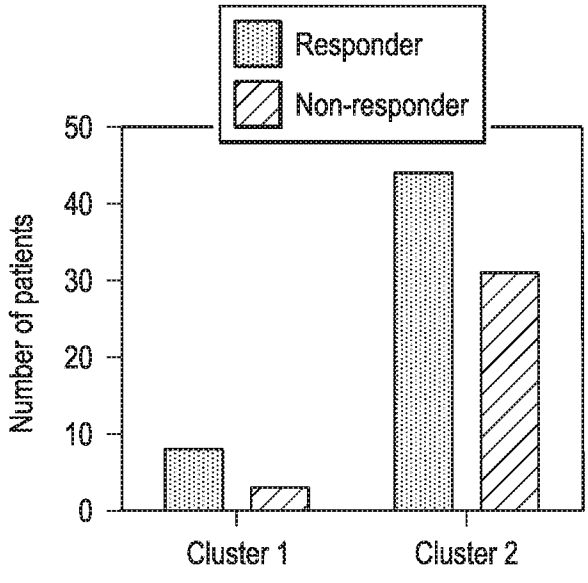
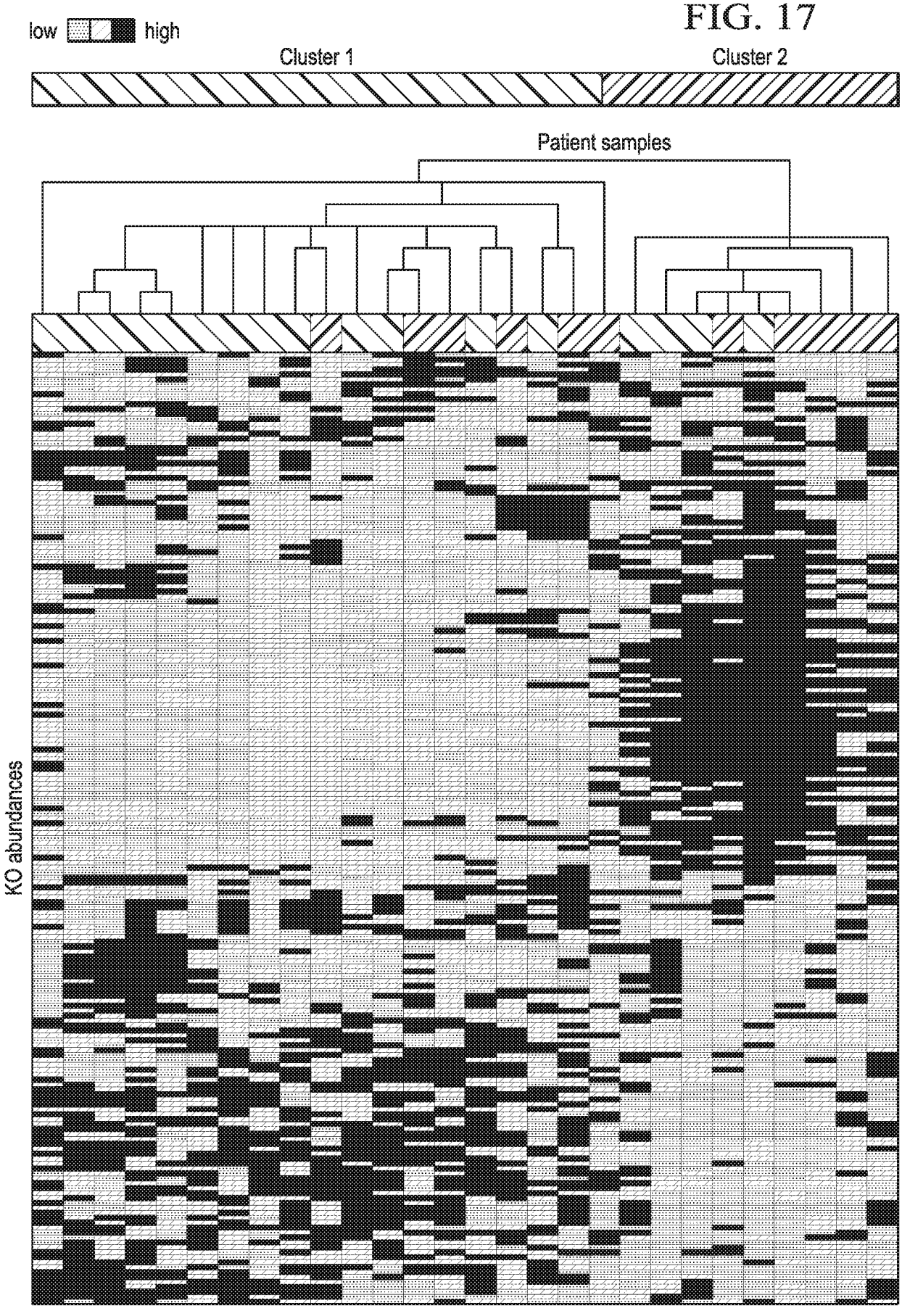



FIG. 16B

FIG. 17



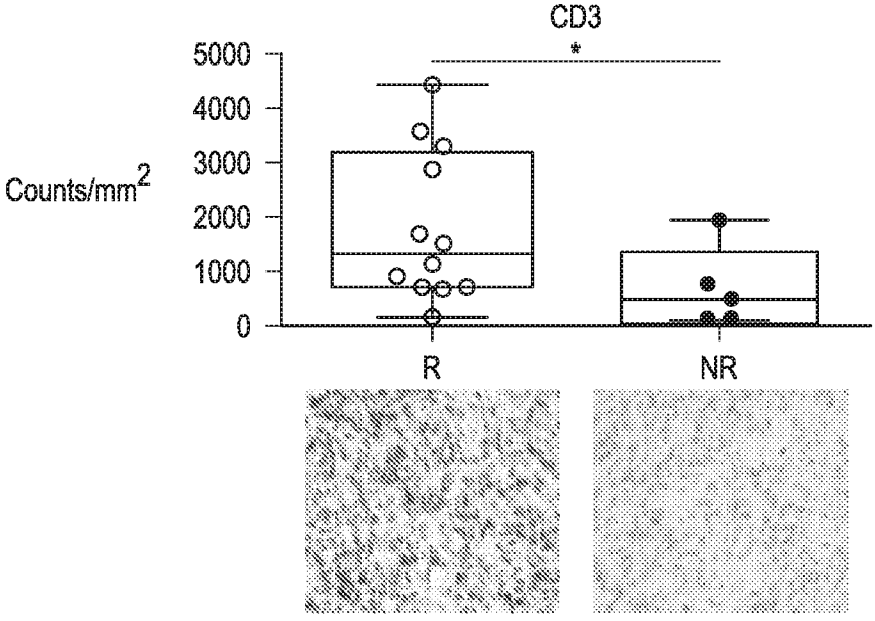



FIG. 18A

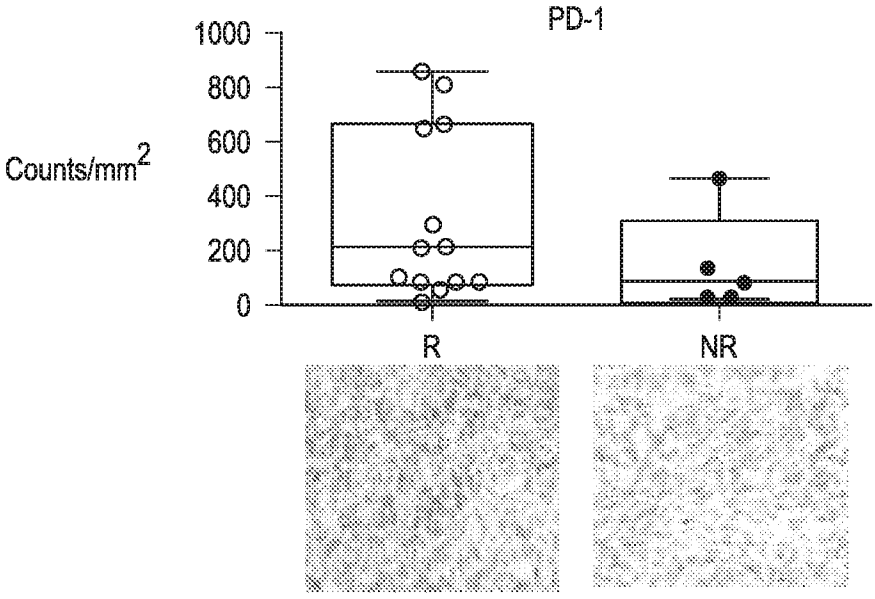



FIG. 18B

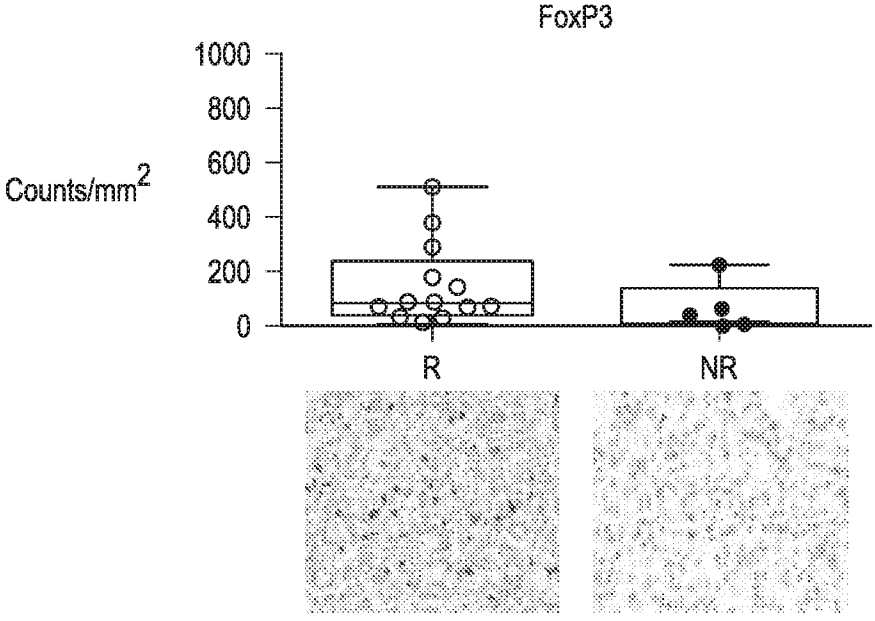



FIG. 18C

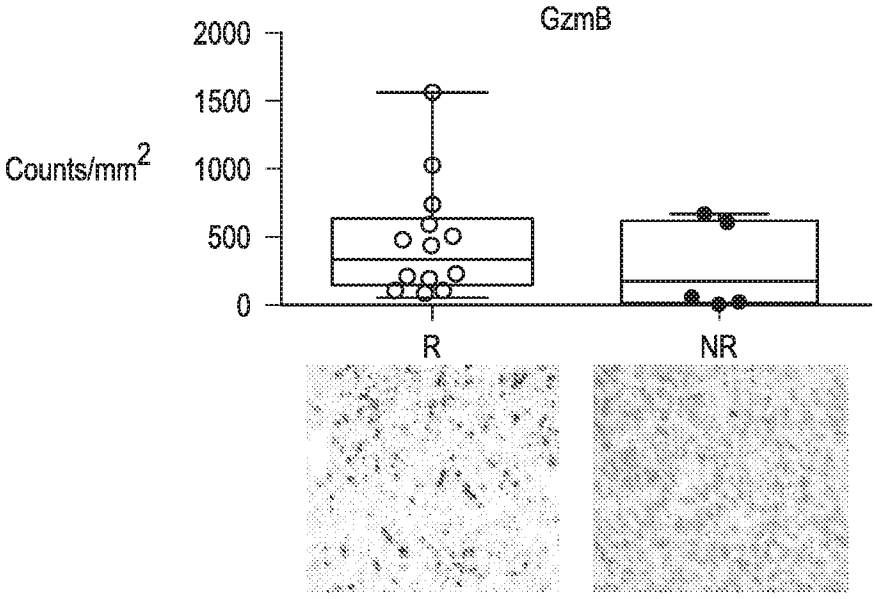



FIG. 18D

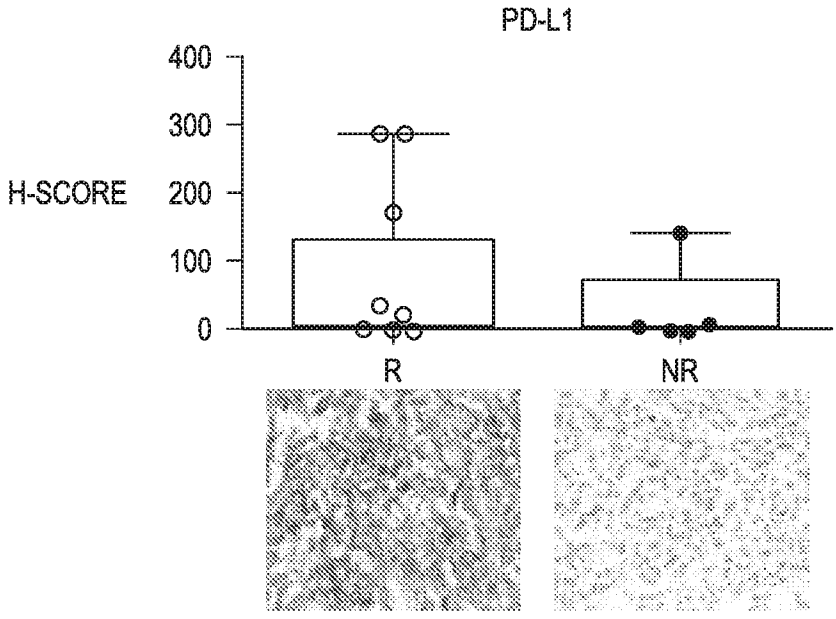



FIG. 18E

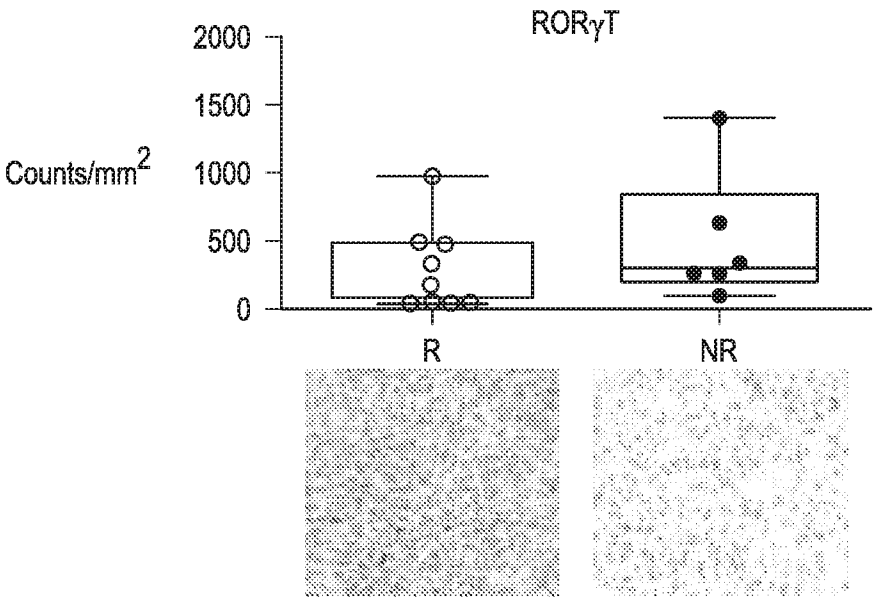
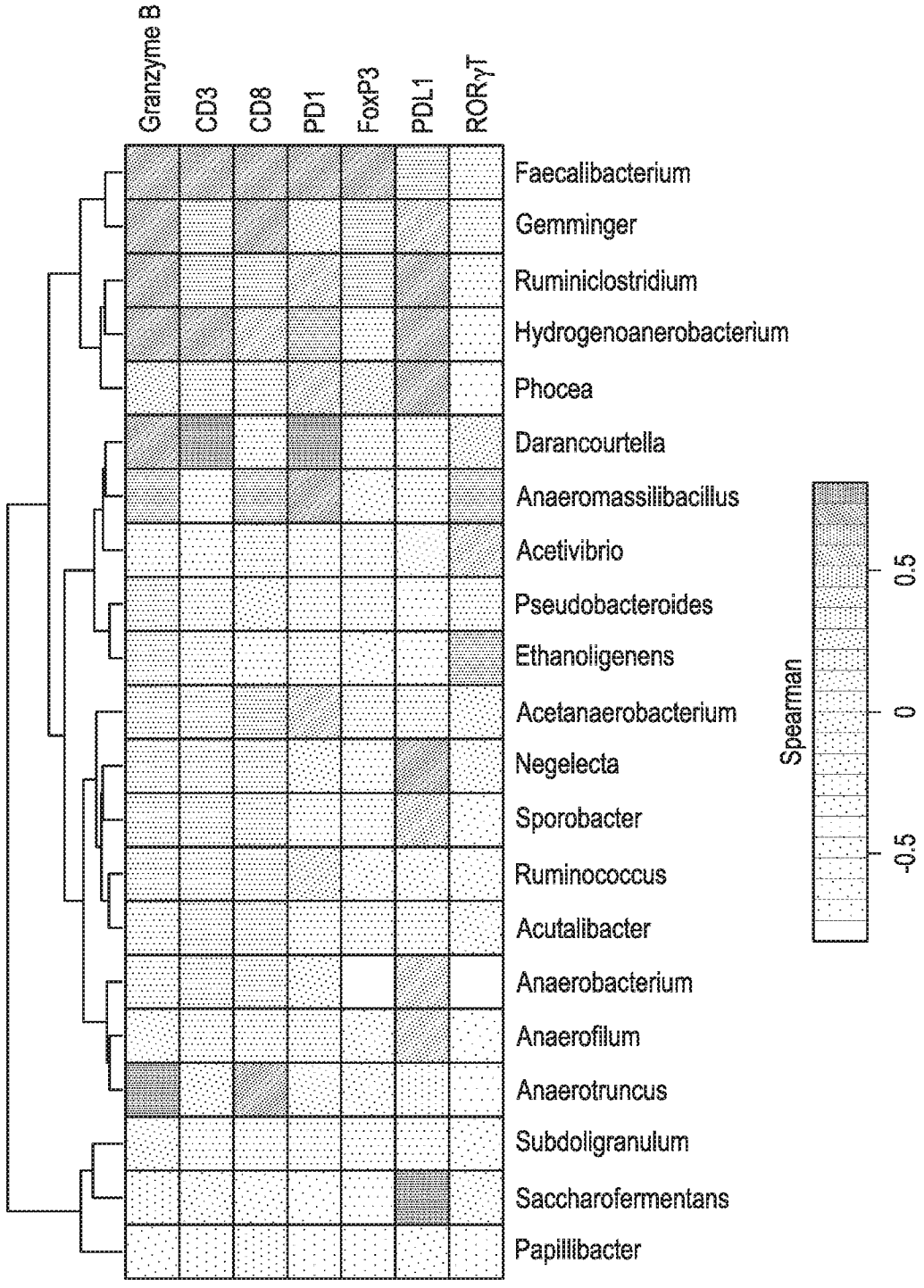



FIG. 18F

FIG. 19


Granzyme B
CD3
CD8
PD1
FoxP3
PDL1
RORγT
Faecalibacterium
Gemminger
Ruminiclostridium
Hydrogenoanerobacterium
Phocea
Darancourtella
Anaeromassilibacillus
Acetivibrio
Pseudobacteroides
Ethanoligenens
Acetanaerobacterium
Negelecta
Sporobacter
Ruminococcus
Acutalibacter
Anaerobacterium
Anaerofilum
Anaerotruncus
Subdoligranulum
Saccharofermentans
Papillibacter
Spearman
0.5
0
-0.5

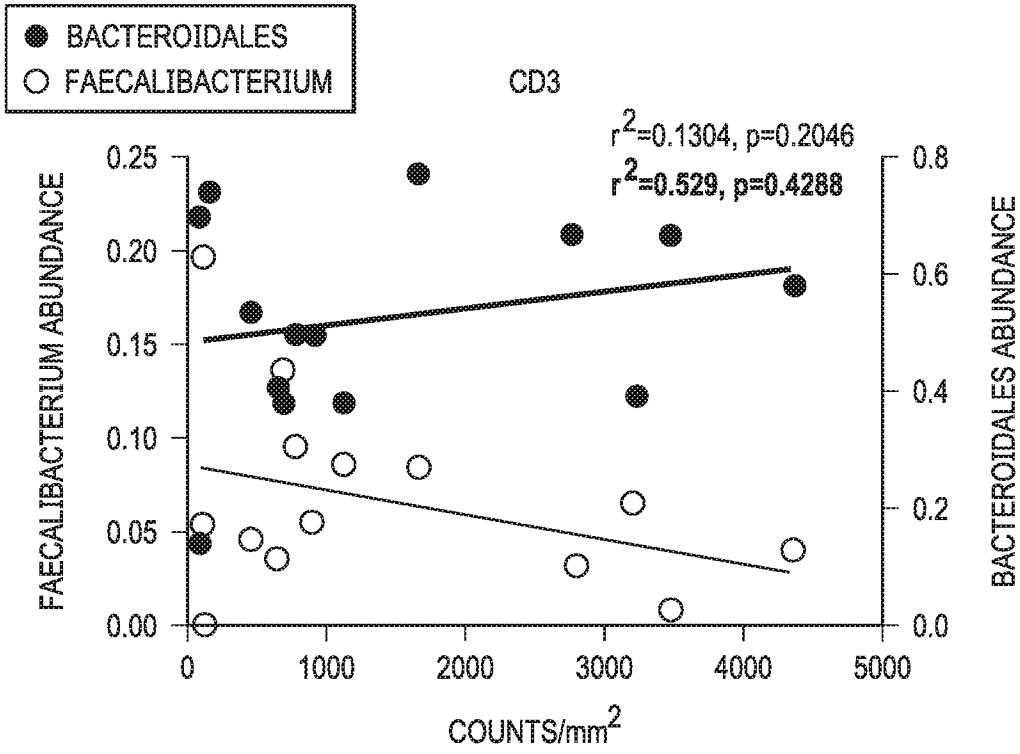



FIG. 20A

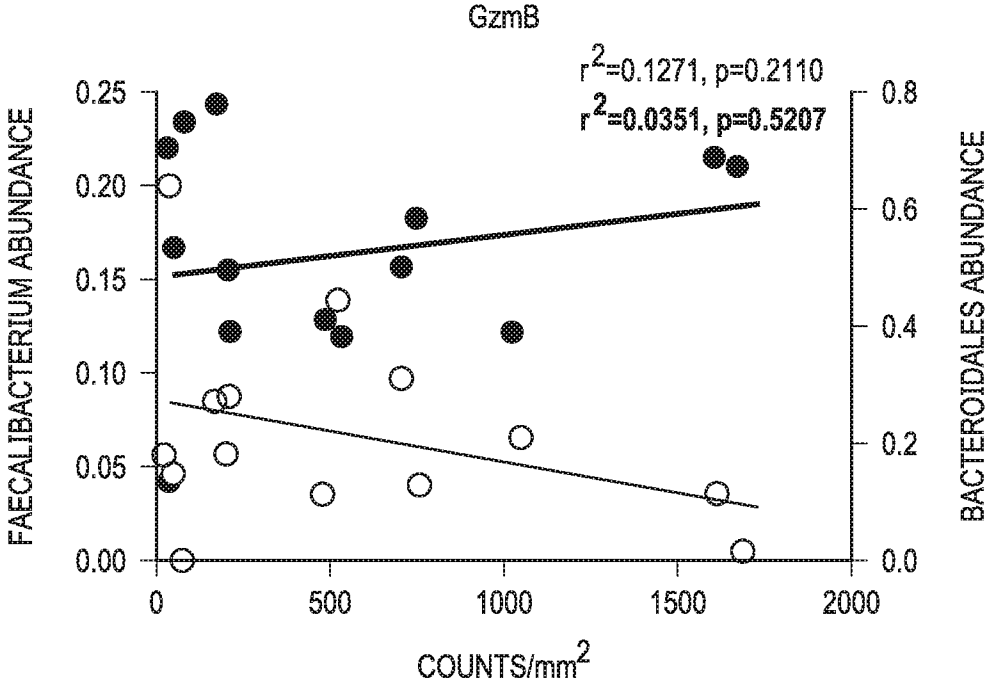



FIG. 20B

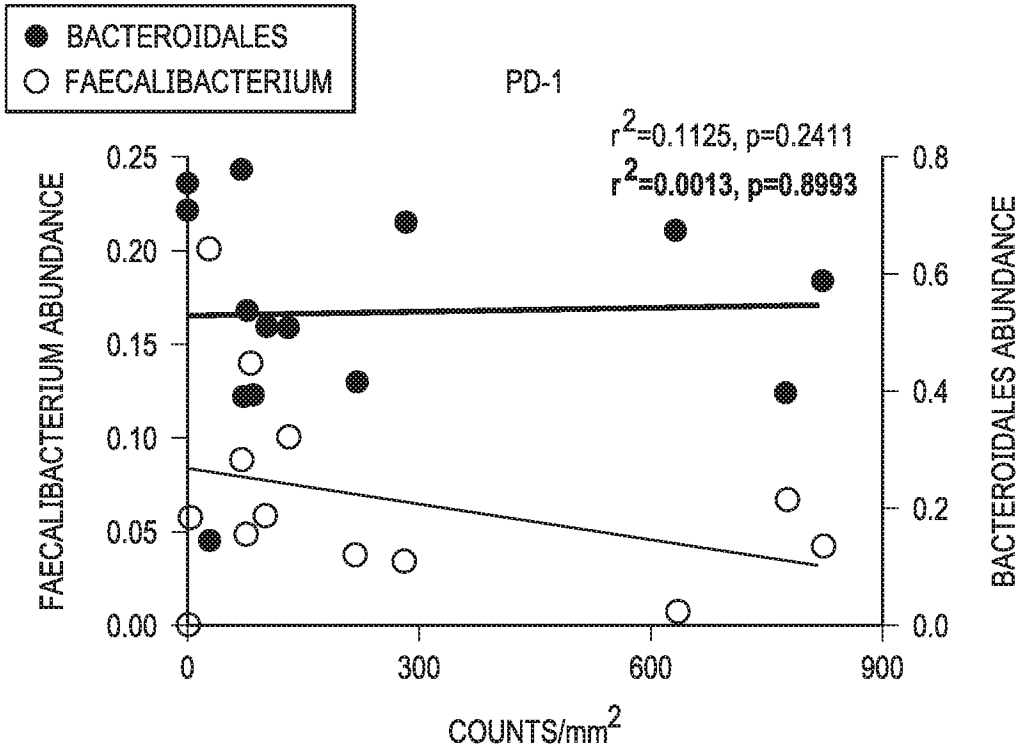



FIG. 20C

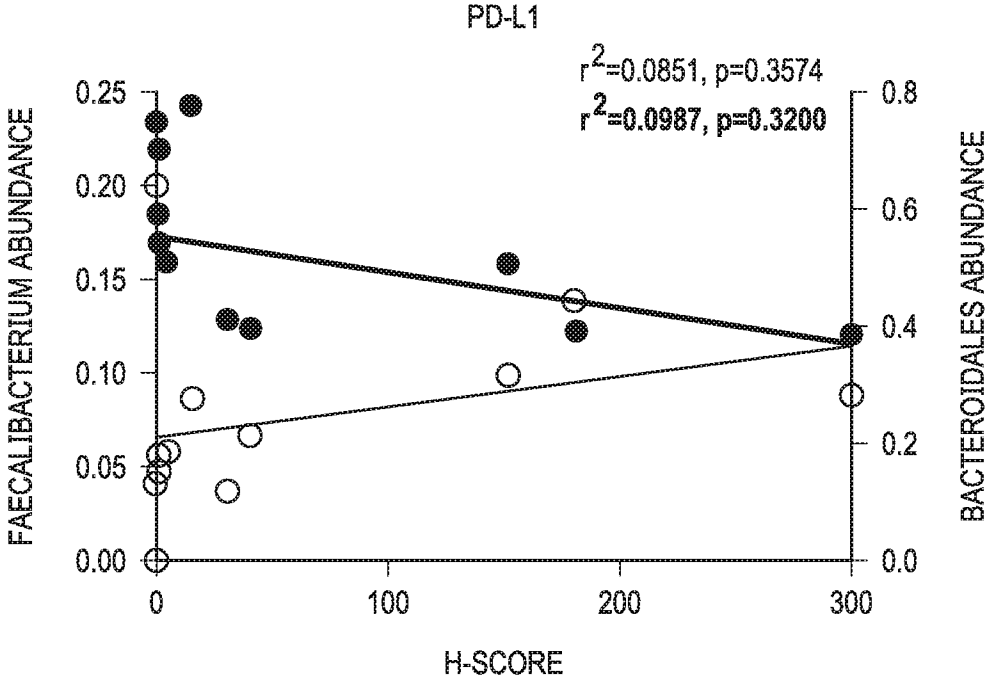



FIG. 20D

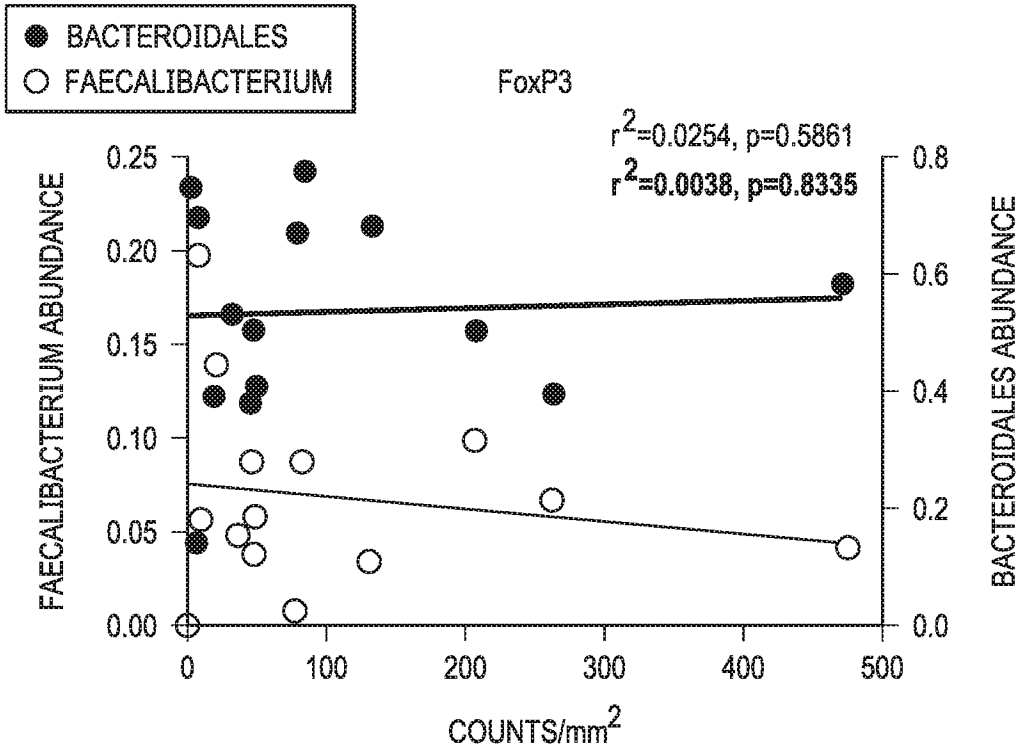



FIG. 20E

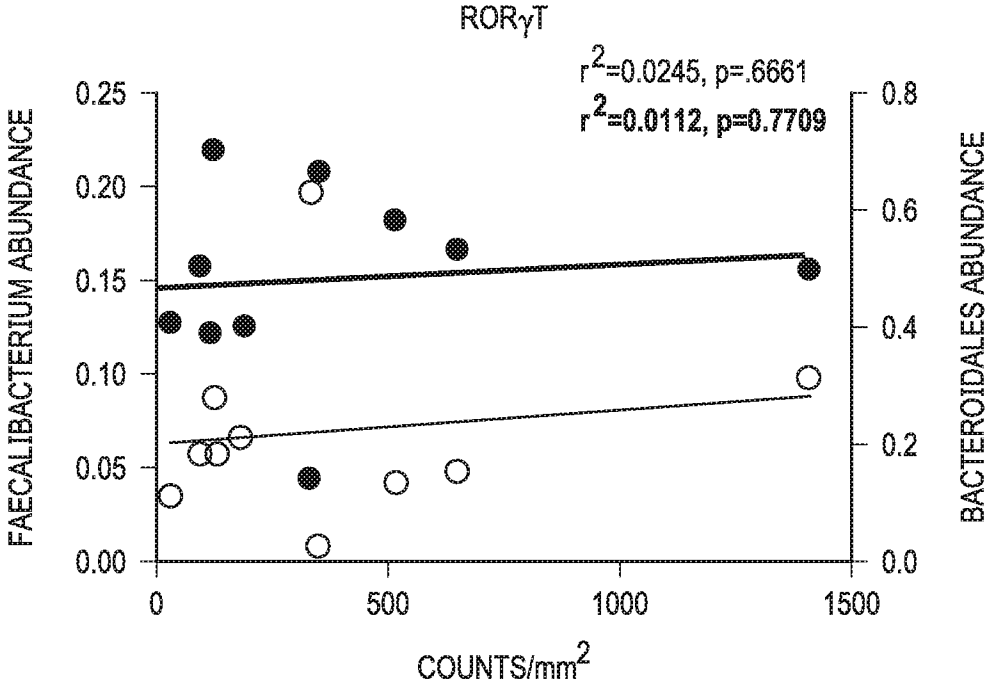



FIG. 20F

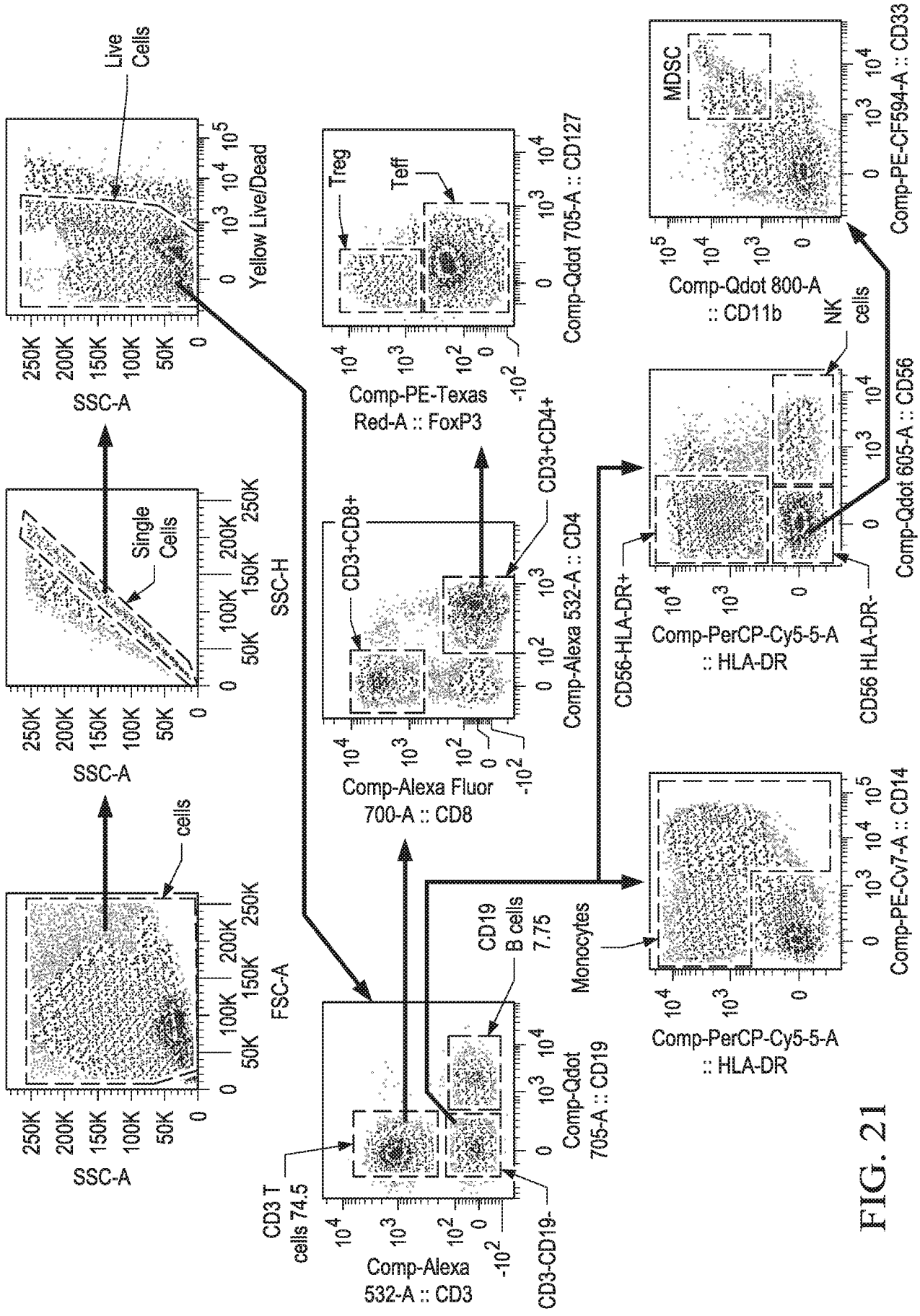

Live Cells
Yellow Live/Dead
SSC-A
Single Cells
SSC-H
cells
FSC-A
CD3 T cells 74.5
CD3-CD19-
Comp-Alexa 532-A :: CD3
CD19 B cells 7.75
Comp-Qdot 705-A :: CD19
Monocytes
Treg
Teff
Comp-PE-Texas Red-A :: FoxP3
Comp-Qdot 705-A :: CD127
CD3+CD8+
CD3+CD4+
Comp-Alexa Fluor 700-A :: CD8
Comp-Alexa 532-A :: CD4
CD56-HLA-DR+
CD56 HLA-DR-
Comp-PerCP-Cy5-5-A :: HLA-DR
NK cells
Comp-Qdot 605-A :: CD56
MDSC
Comp-Qdot 800-A :: CD11b
Comp-PE-CF594-A :: CD33
Comp-PE-Cy7-A :: CD14

FIG. 21

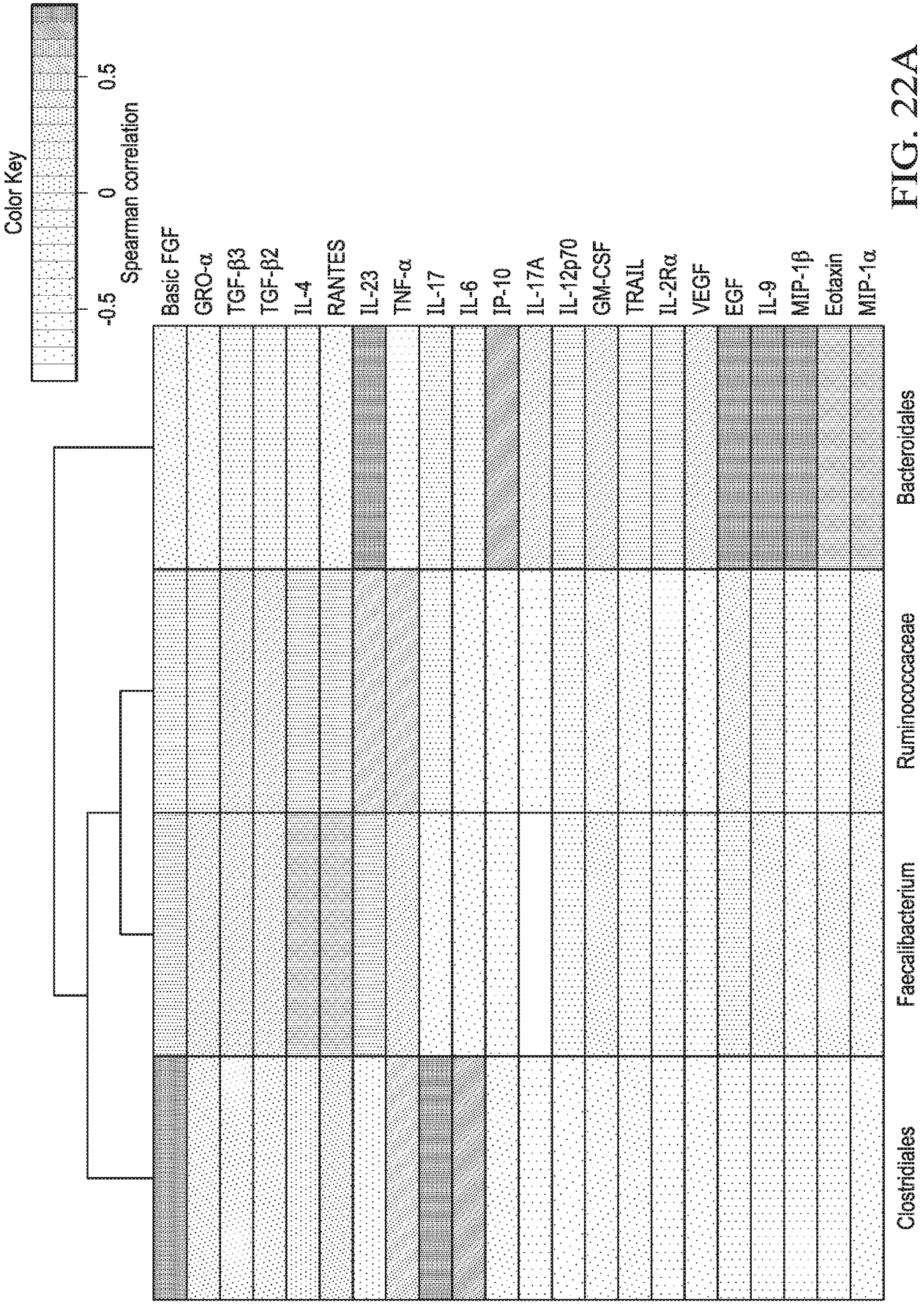

Color Key
-0.5
0
0.5
Spearman correlation
Basic FGF
GRO-α
TGF-β3
TGF-β2
IL-4
RANTES
IL-23
TNF-α
IL-17
IL-6
IP-10
IL-17A
IL-12p70
GM-CSF
TRAIL
IL-2Rα
VEGF
EGF
IL-9
MIP-1β
Eotaxin
MIP-1α
Clostridiales
Faecalibacterium
Ruminococcaceae
Bacteroidales

FIG. 22A

FIG. 22B

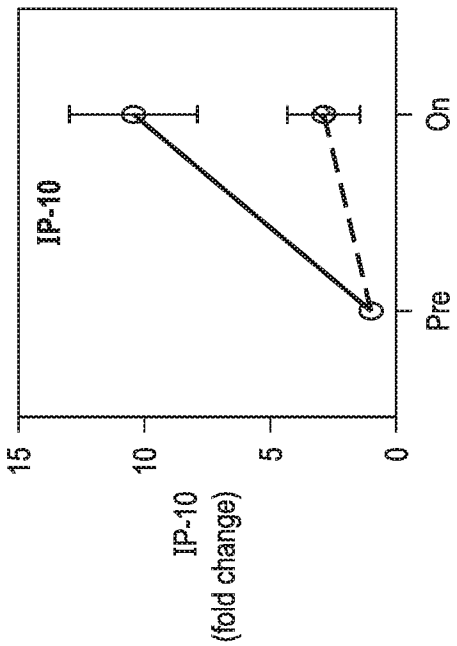



FIG. 22C

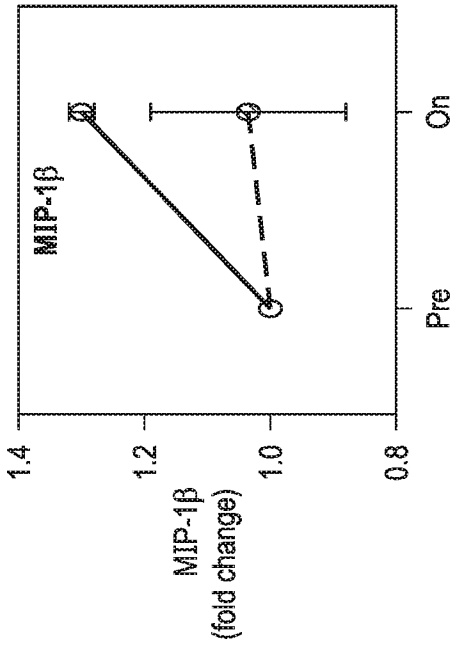
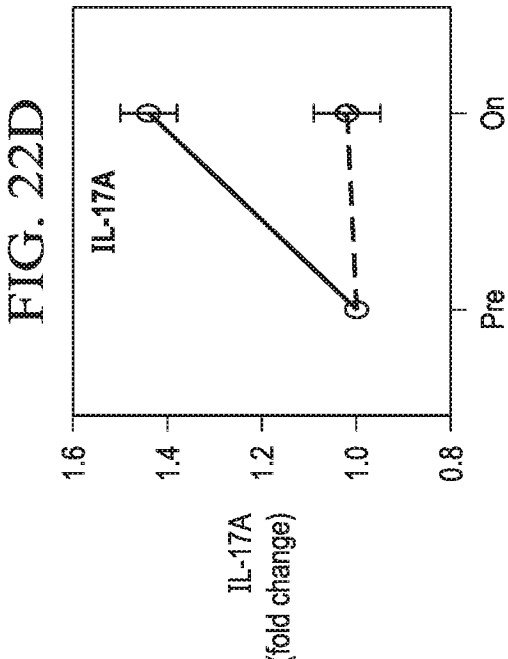



FIG. 22D



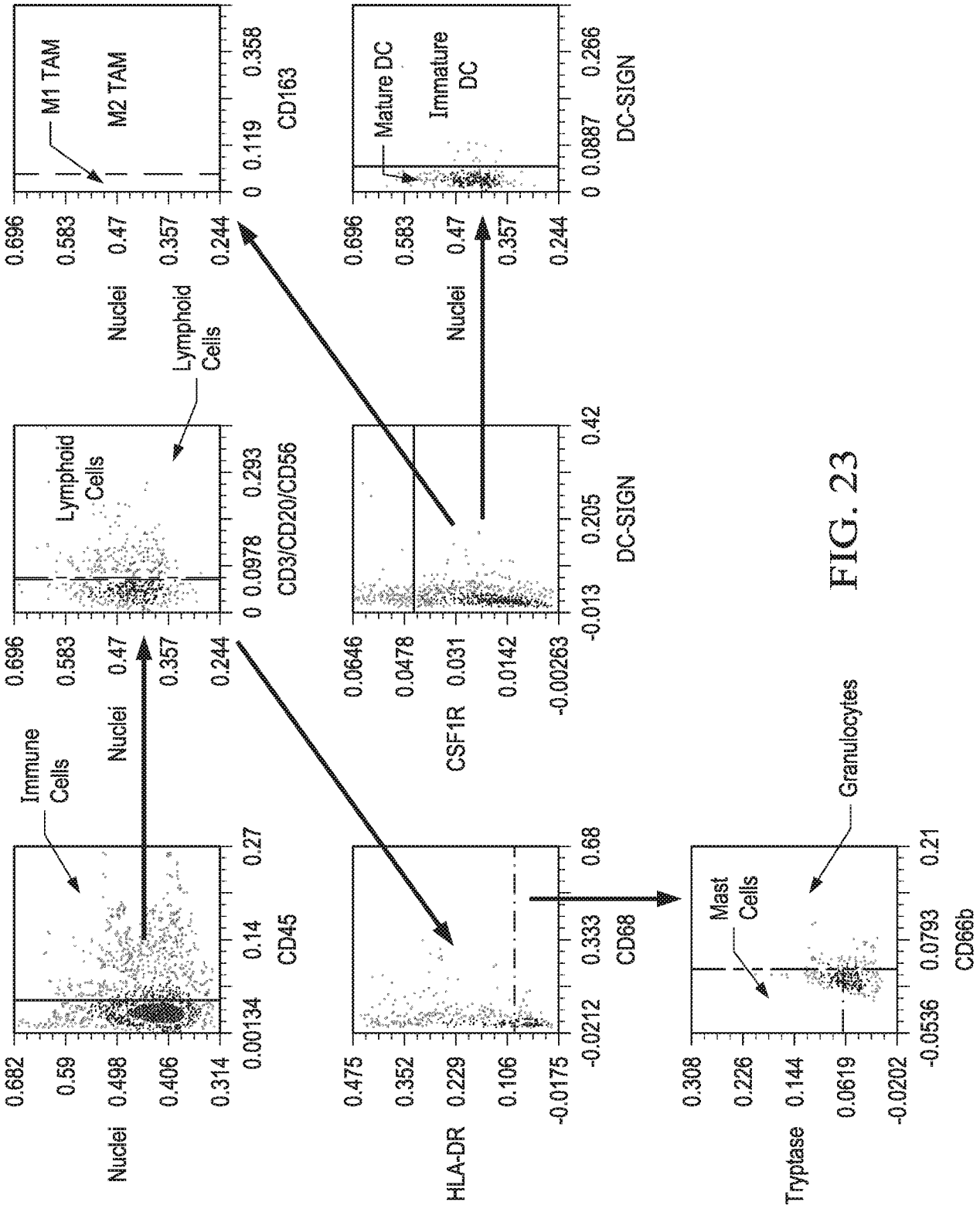

Immune Cells
Nuclei
CD45
Lymphoid Cells
CD3/CD20/CD56
M1 TAM
M2 TAM
CD163
HLA-DR
CD68
CSF1R
DC-SIGN
Mature DC
Immature DC
DC-SIGN
Tryptase
Mast Cells
Granulocytes
CD66b

FIG. 23

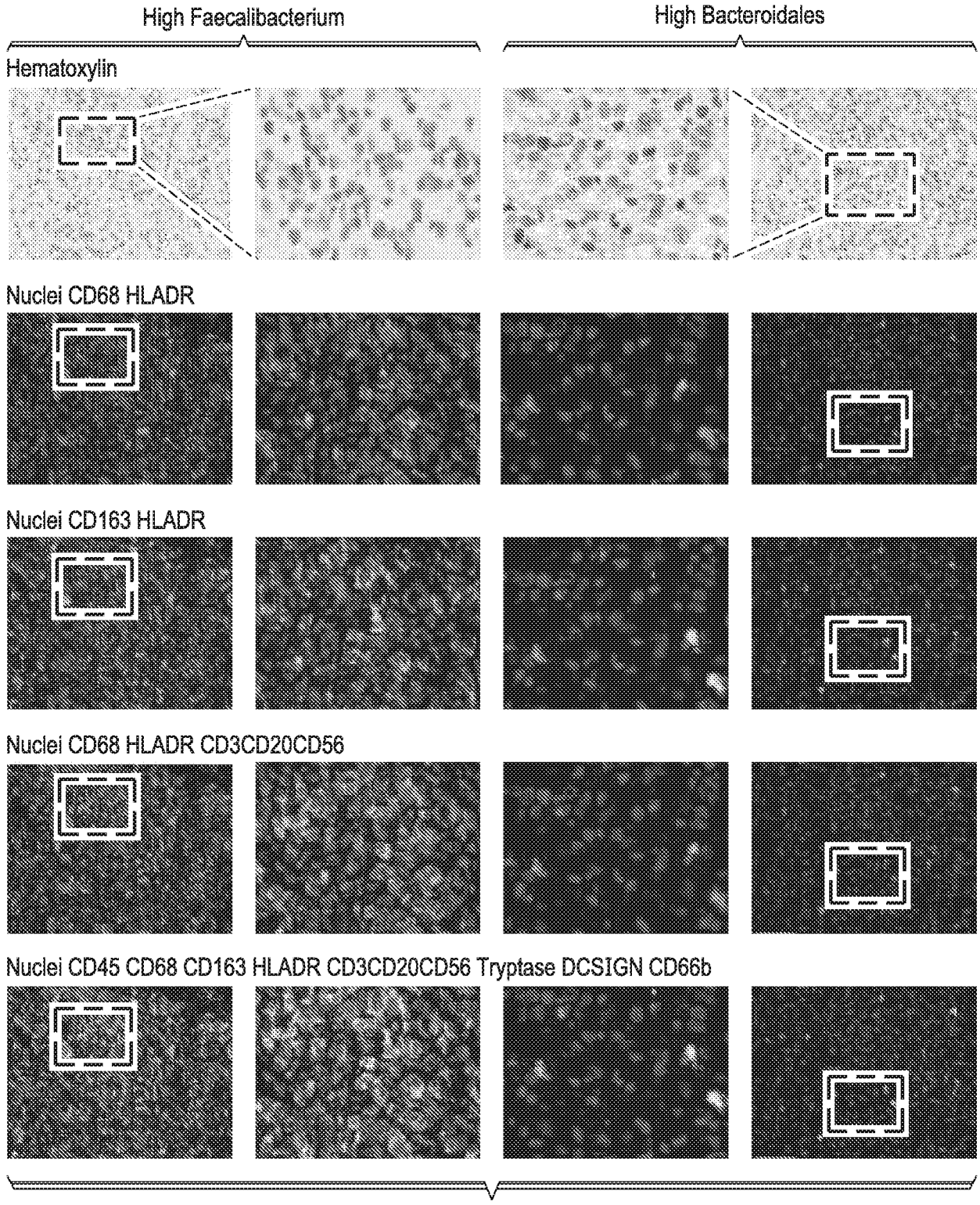

High Faecalibacterium
High Bacteroidales
Hematoxylin
Nuclei CD68 HLADR
Nuclei CD163 HLADR
Nuclei CD68 HLADR CD3CD20CD56
Nuclei CD45 CD68 CD163 HLADR CD3CD20CD56 Tryptase DCSIGN CD66b

FIG. 24A

FIG. 24C

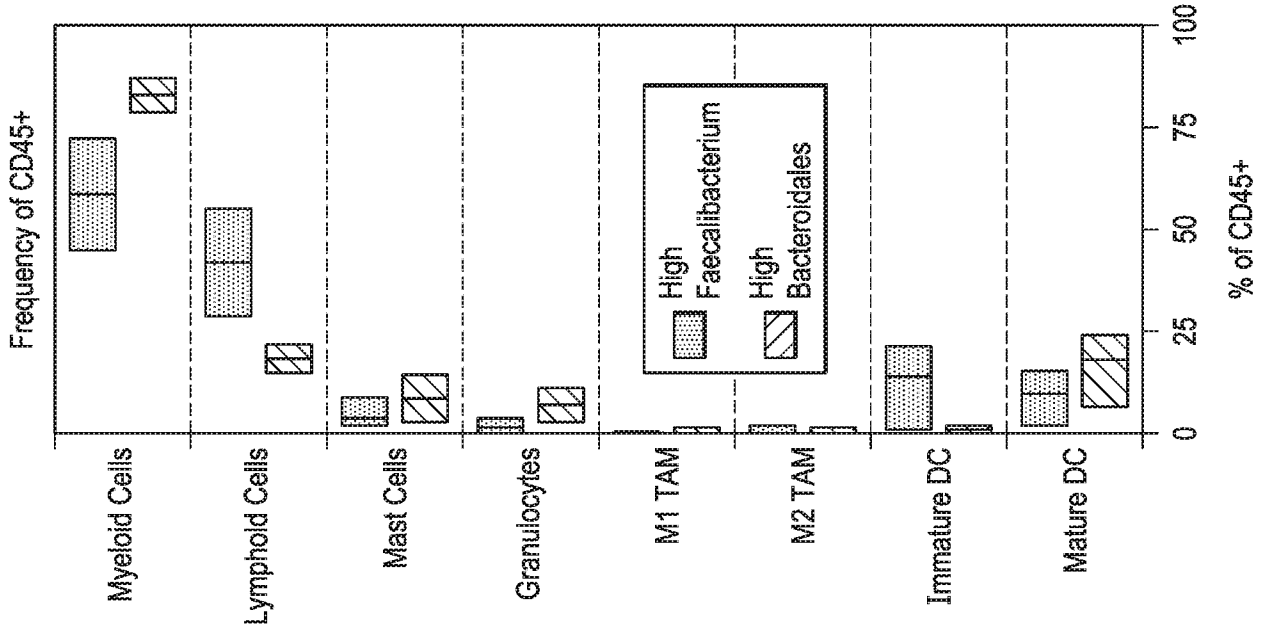
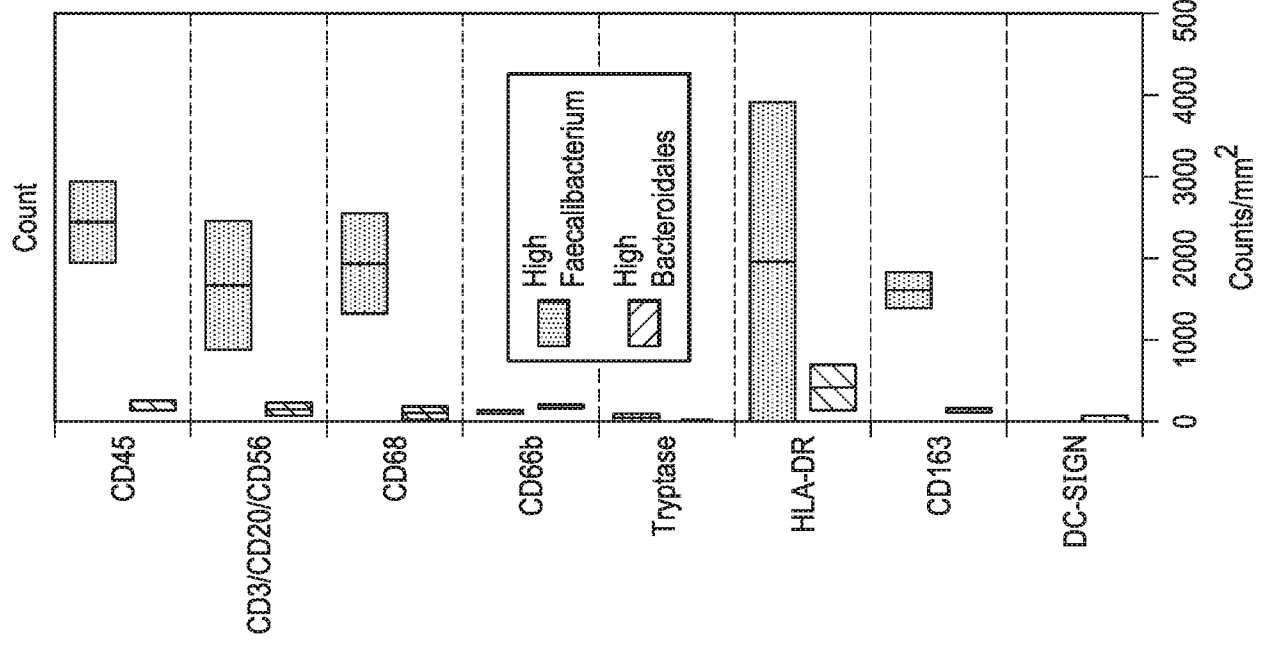



FIG. 24B



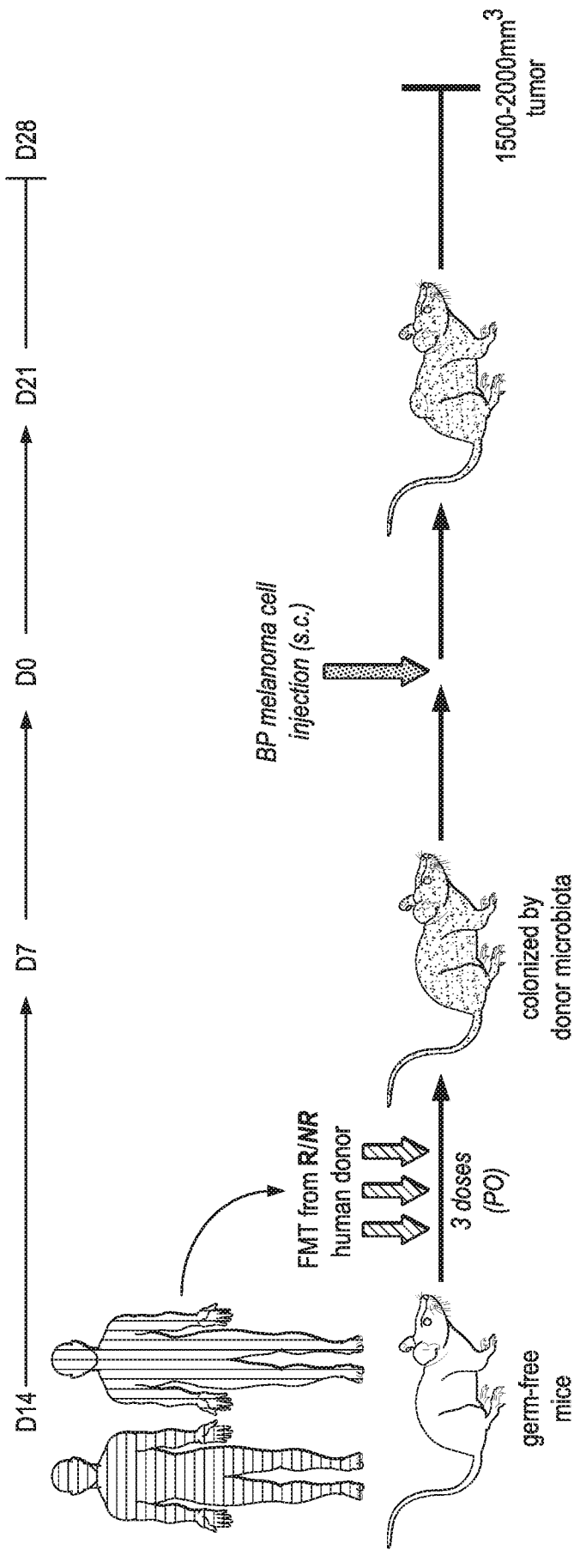

D14
D7
D0
D21
D28
germ-free mice
FMT from R/NR human donor
3 doses (PO)
colonized by donor microbiota
BP melanoma cell injection (s.c.)
1500-2000mm3 tumor

FIG. 25A

FIG. 25B

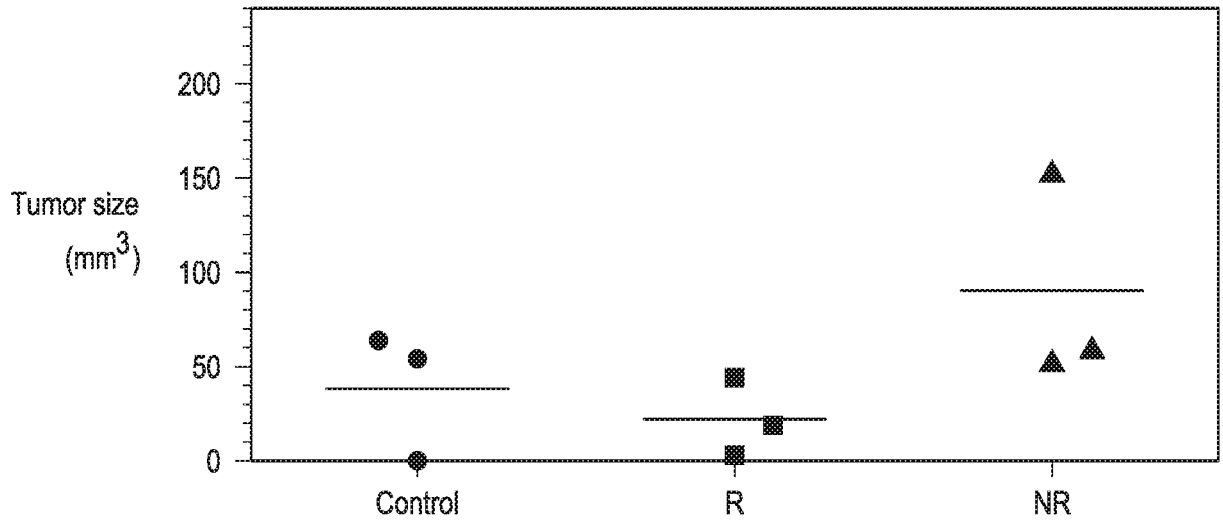


FIG. 26A

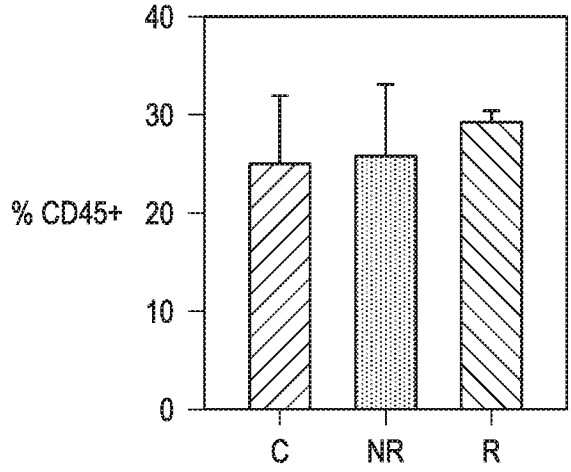



FIG. 26B

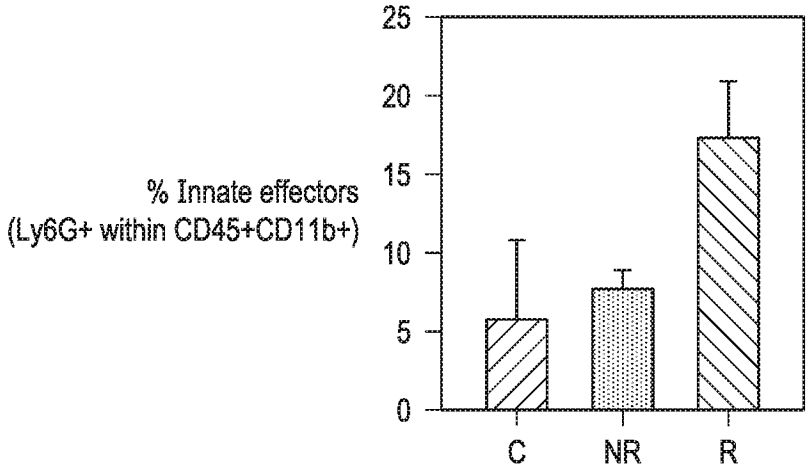
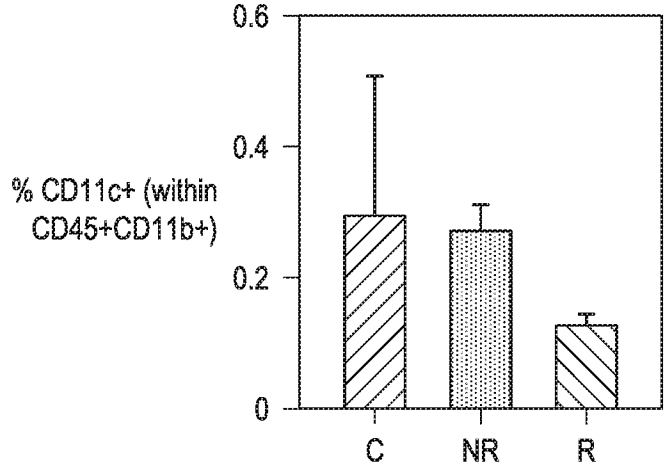



FIG. 26C



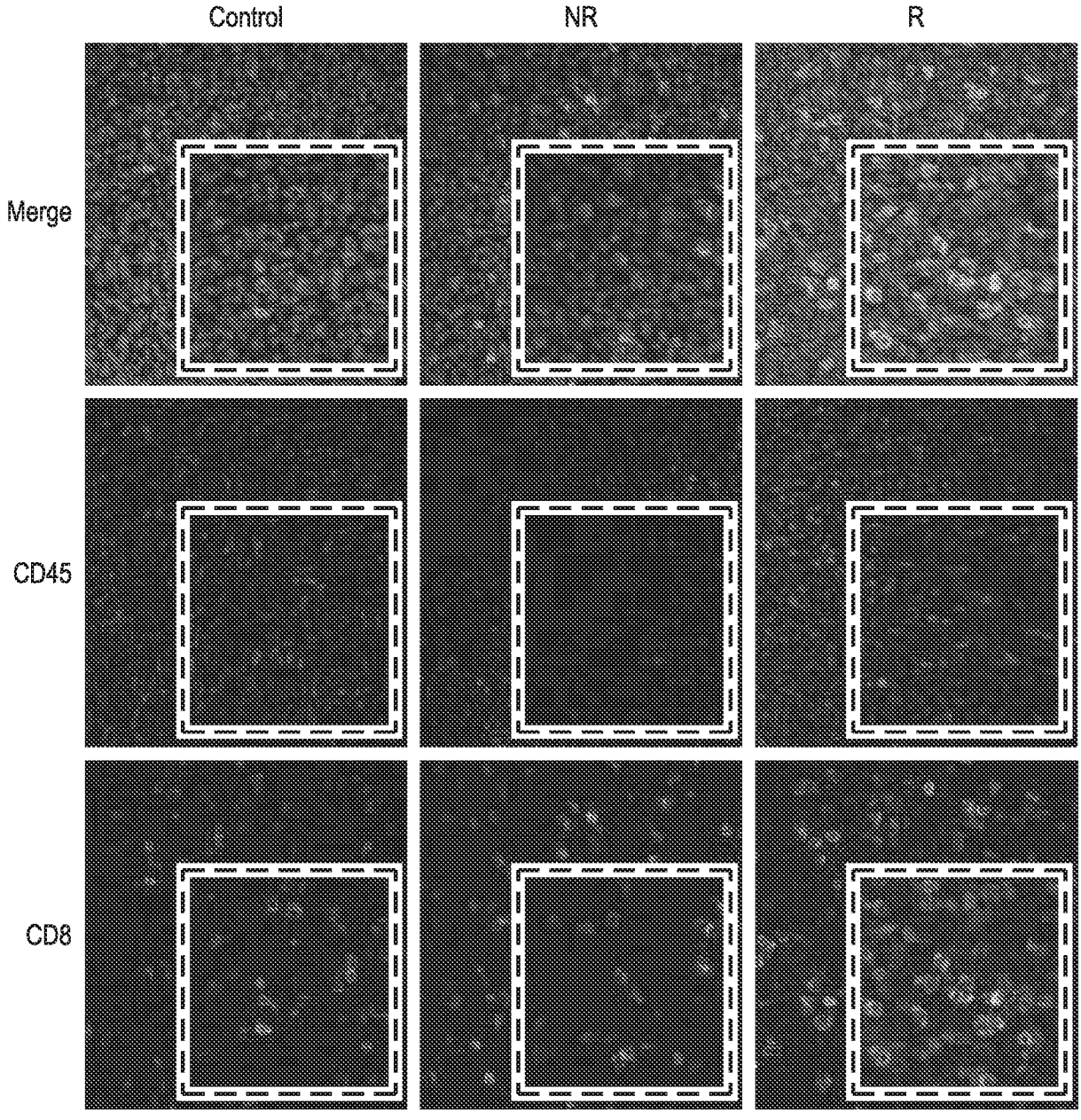



FIG. 27A

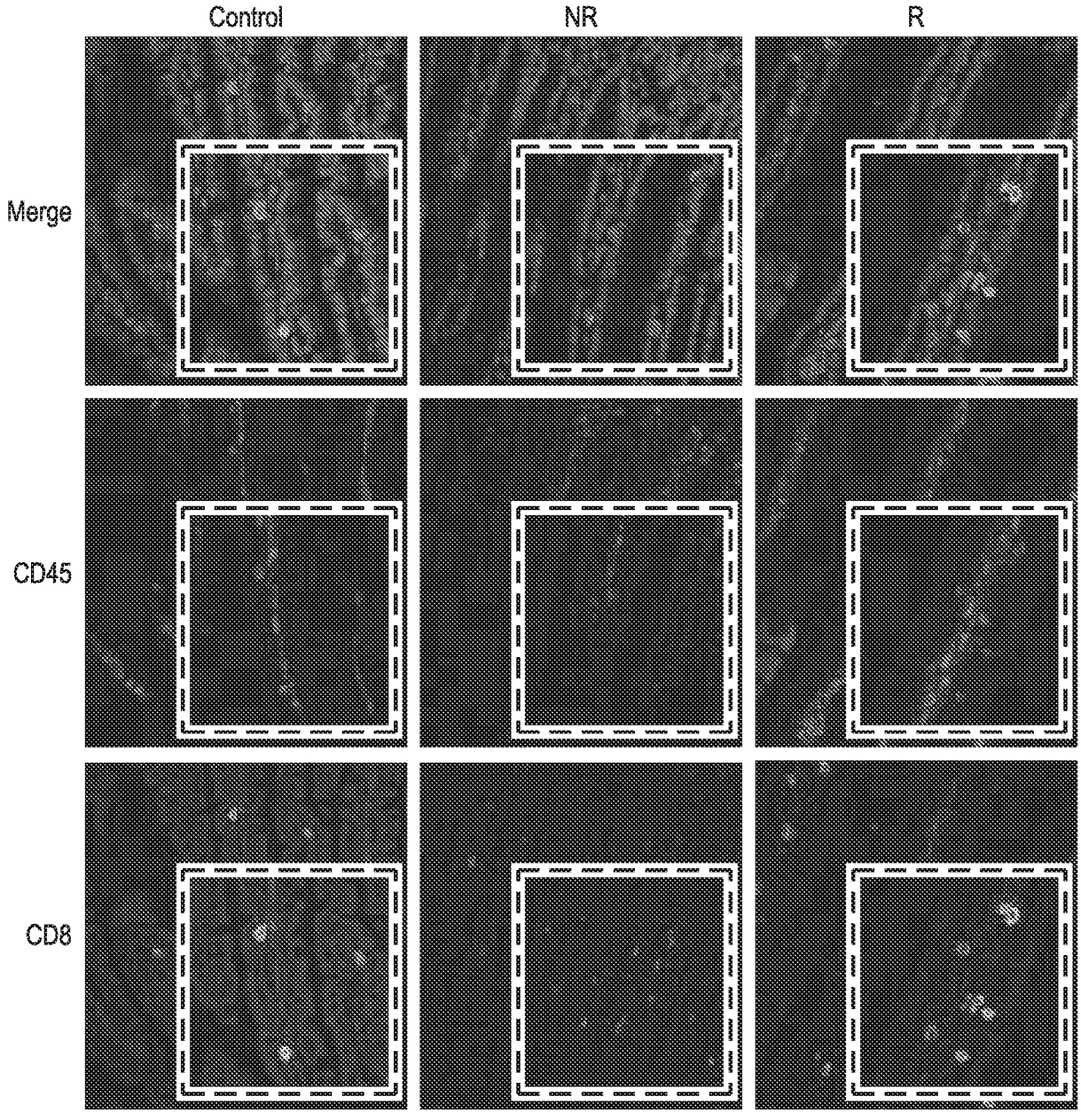



FIG. 27B

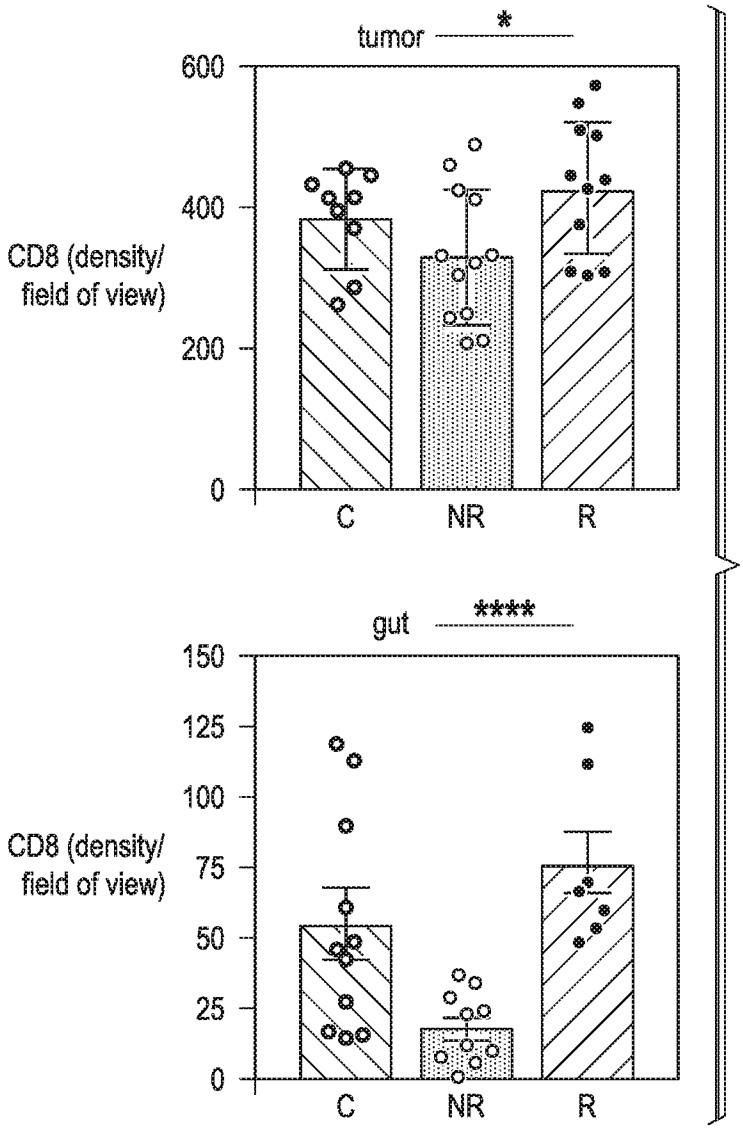

tumor
*
600
400
200
0
CD8 (density/ field of view)
C
NR
R
gut
****
150
125
100
75
50
25
0
CD8 (density/ field of view)
C
NR
R

FIG. 27C

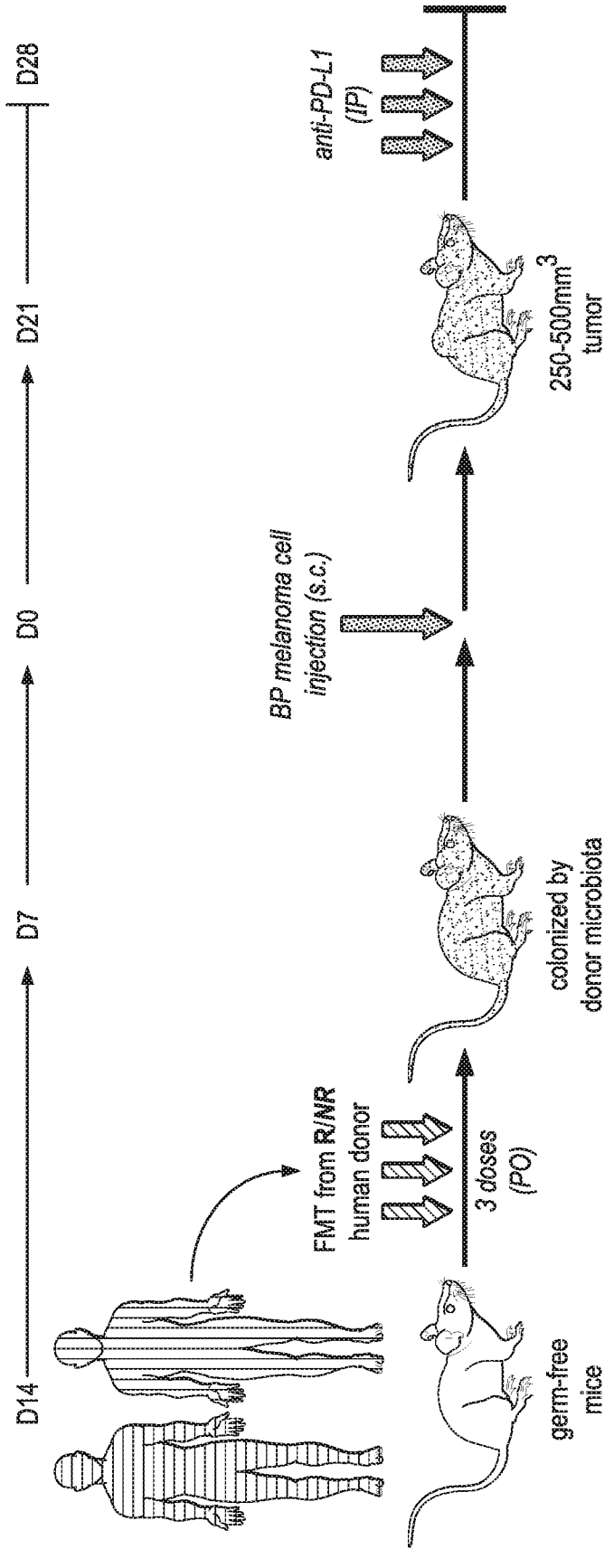

D14
D7
D0
D21
D28
germ-free mice
FMT from R/NR human donor
3 doses (PO)
colonized by donor microbiota
BP melanoma cell injection (s.c.)
250-500mm3 tumor
anti-PD-L1 (IP)

FIG. 28A

FIG. 28B

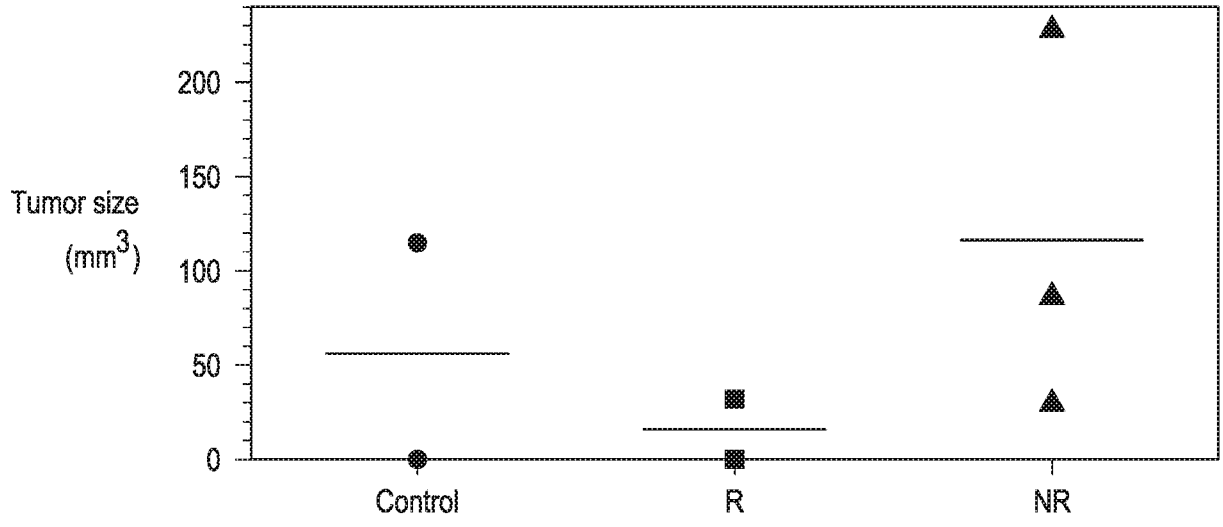



FIG. 28C

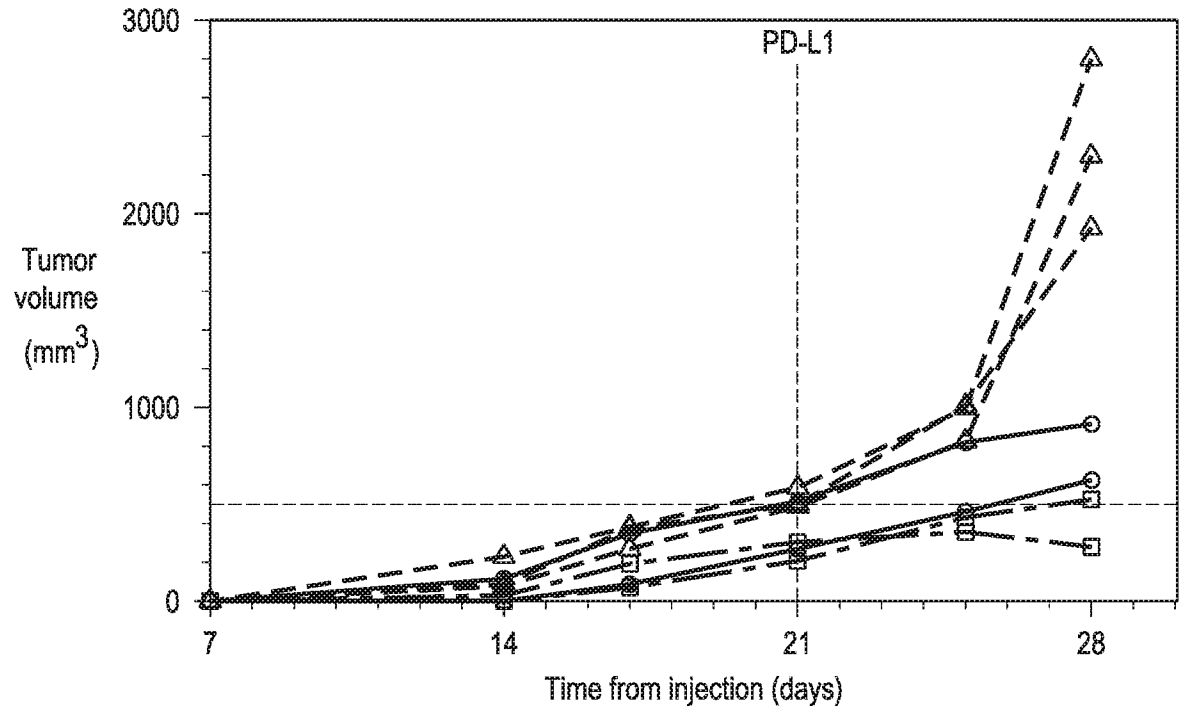


FIG. 29A

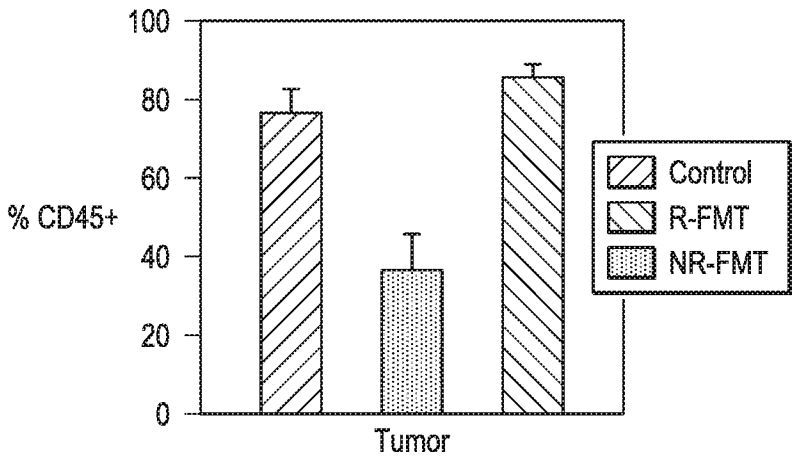


FIG. 29B

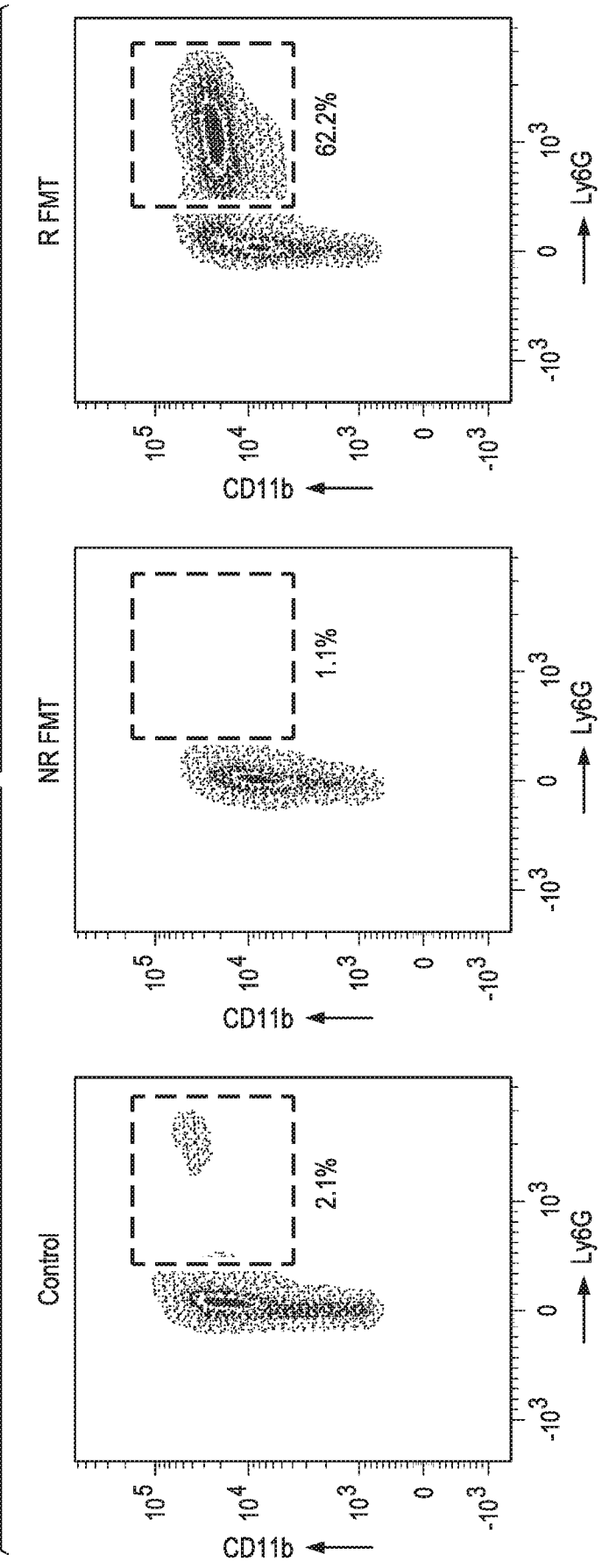



FIG. 29C

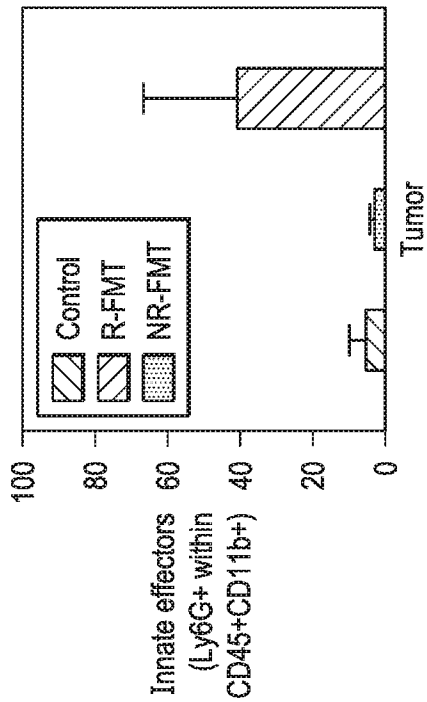


FIG. 29D

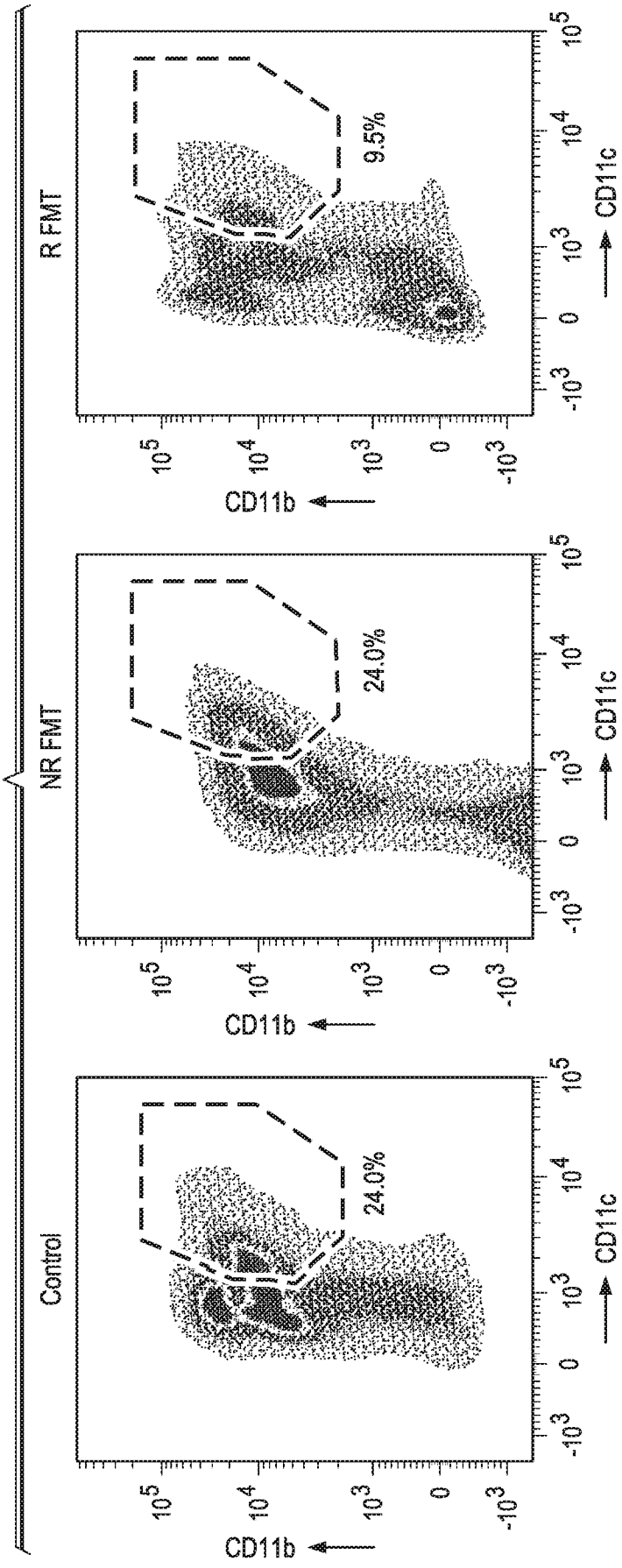



FIG. 29E

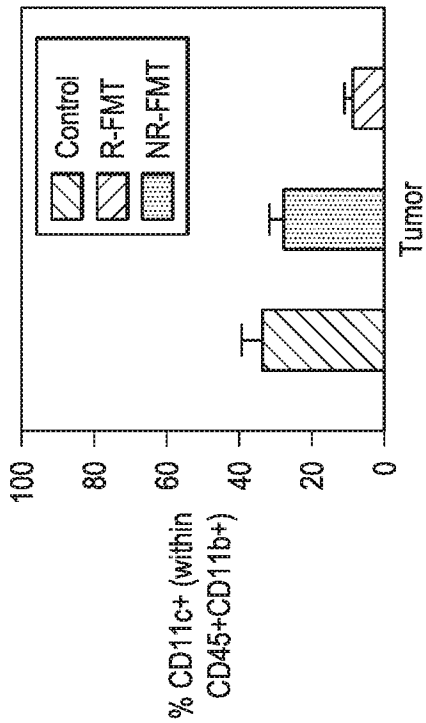


FIG. 30A

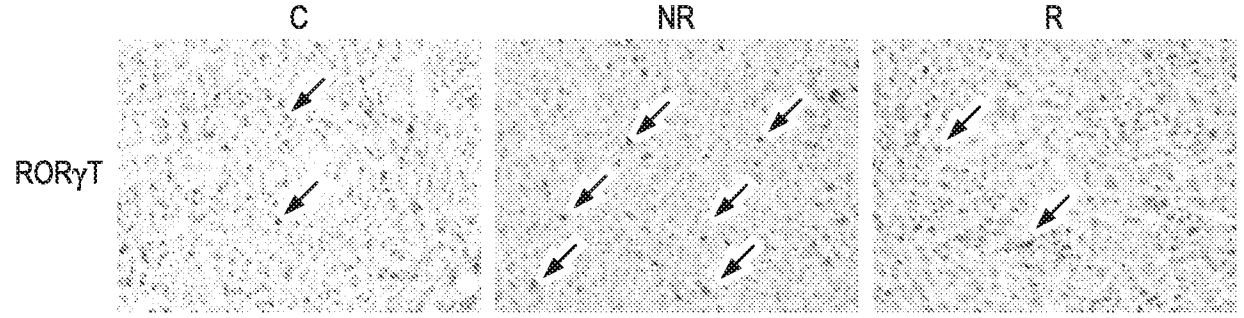



FIG. 30B

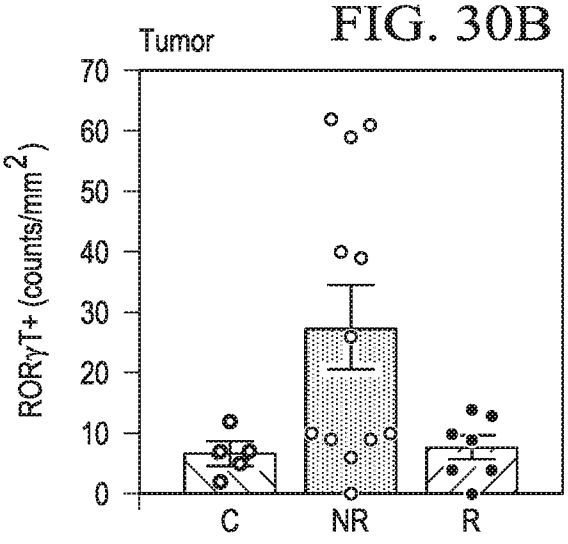



FIG. 30C

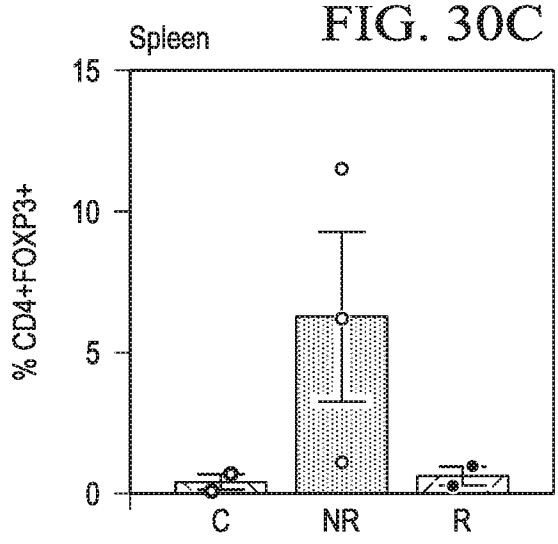
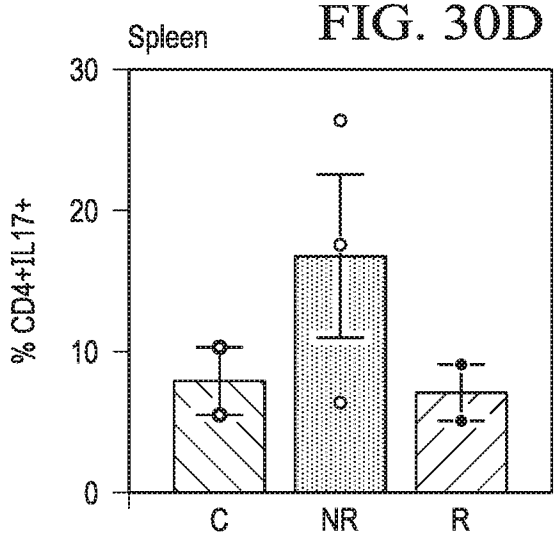



FIG. 30D



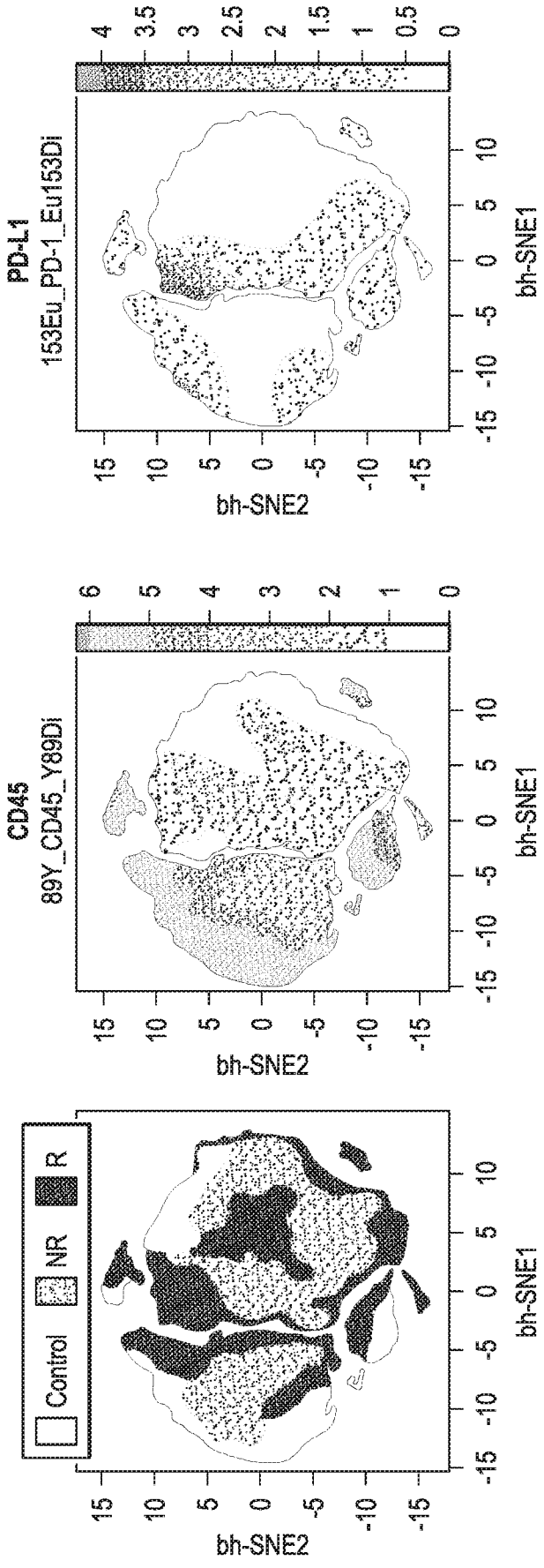

PD-L1
153Eu_PD-1_Eu153Di
CD45
89Y_CD45_Y89Di
Control
NR
R
bh-SNE1
bh-SNE2

FIG. 31A

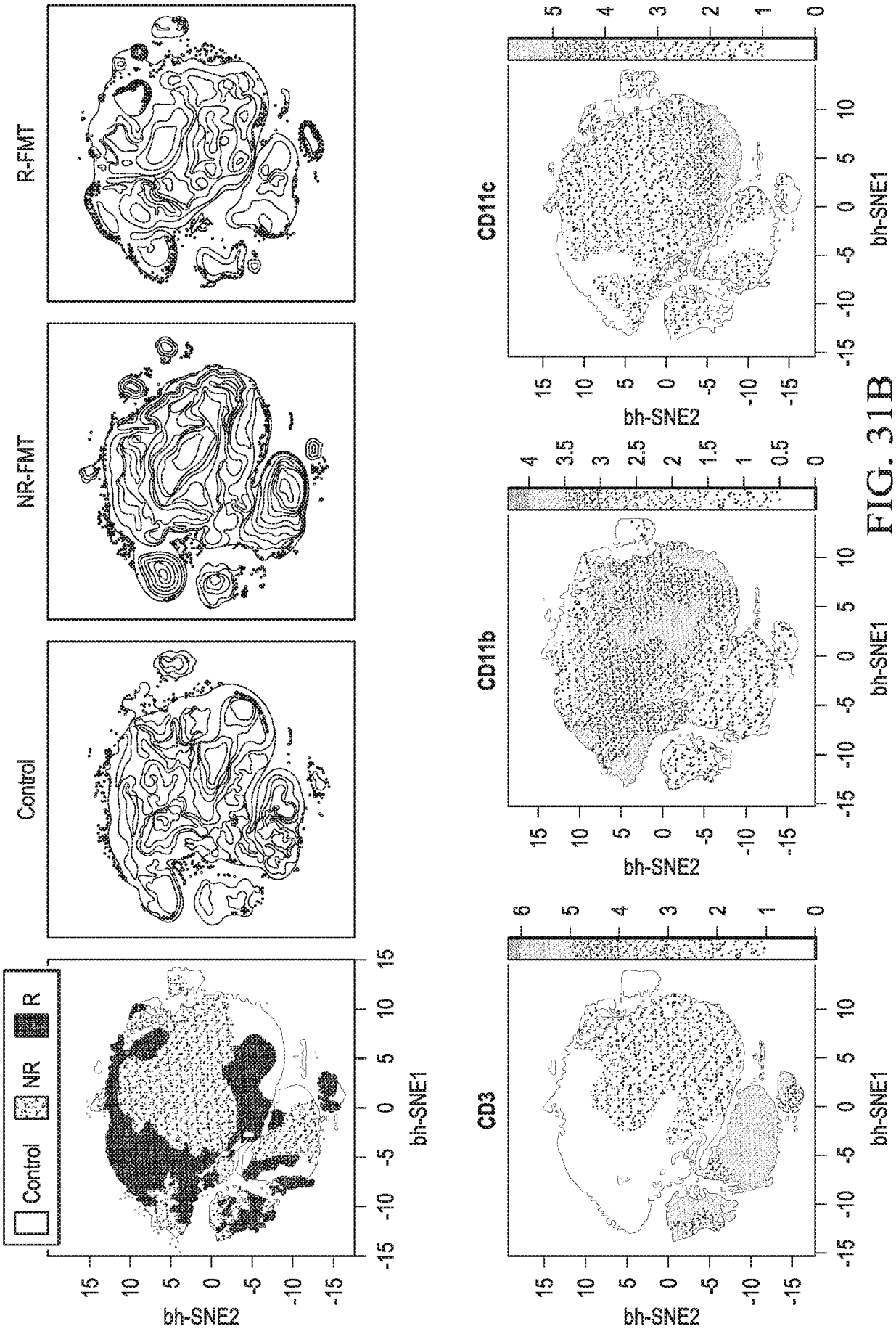

Control
NR
R
Control
NR-FMT
R-FMT
bh-SNE1
bh-SNE2
CD3
CD11b
CD11c

FIG. 31B

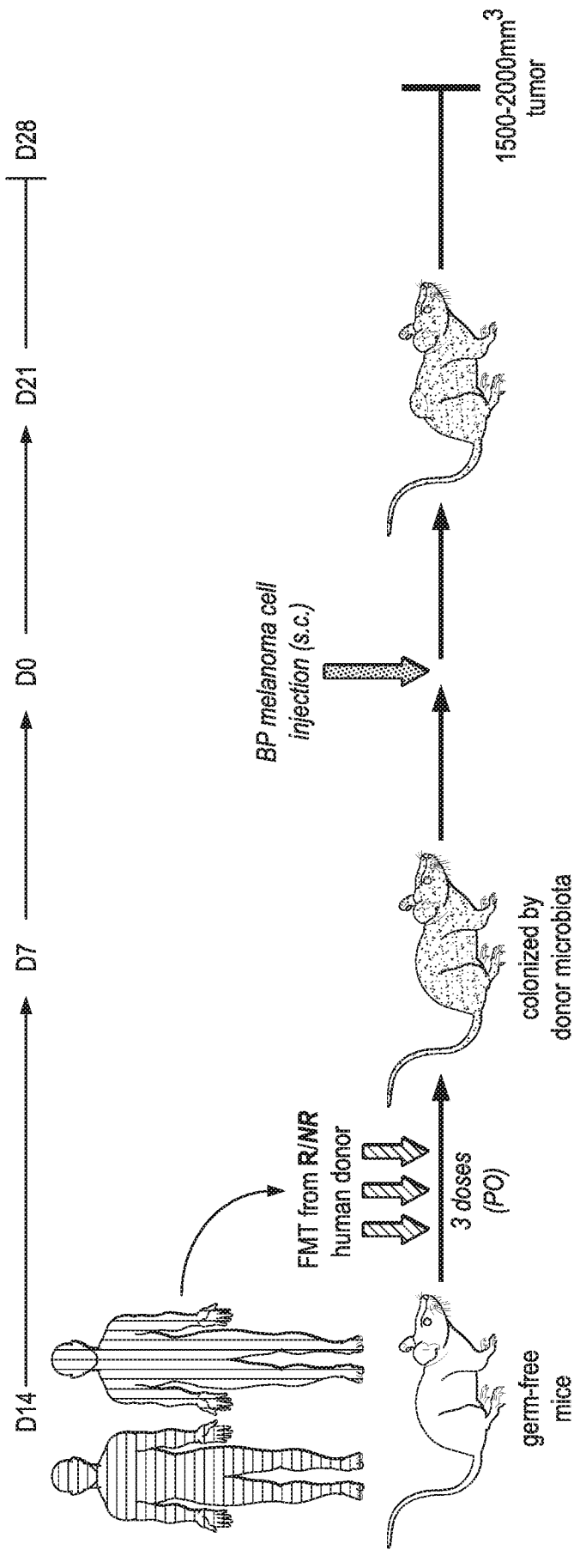

D14
D7
D0
D21
D28
germ-free mice
FMT from R/NR human donor
3 doses (PO)
colonized by donor microbiota
BP melanoma cell injection (s.c.)
1500-2000mm3 tumor

FIG. 32A

FIG. 32B

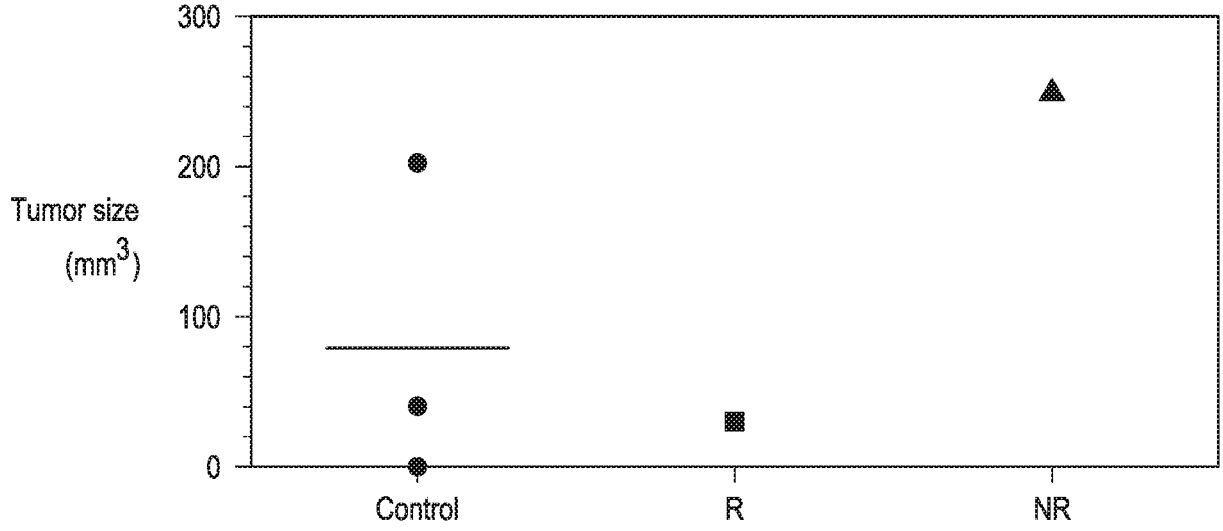



FIG. 32C

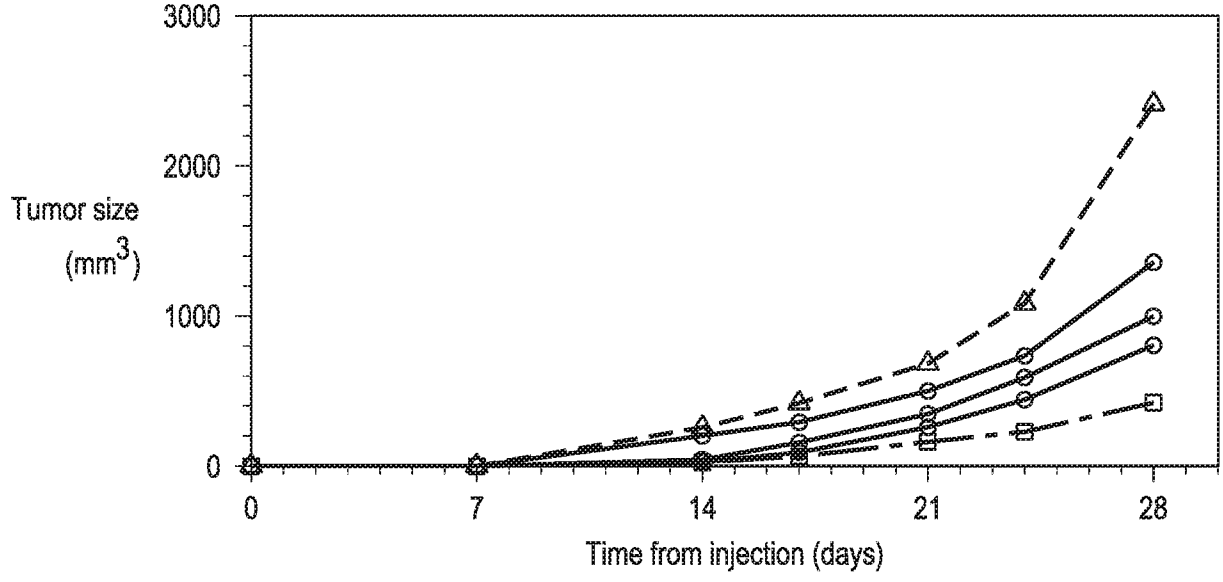


FIG. 33A

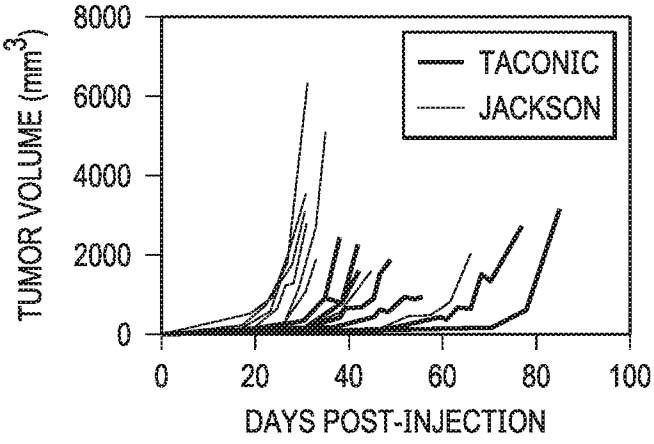



FIG. 33B

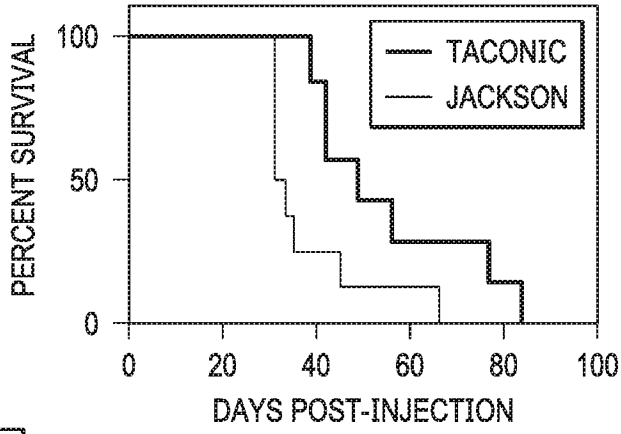



FIG. 33C

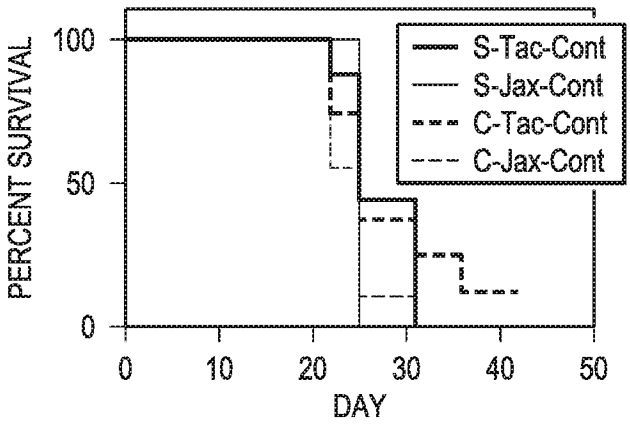



FIG. 33F

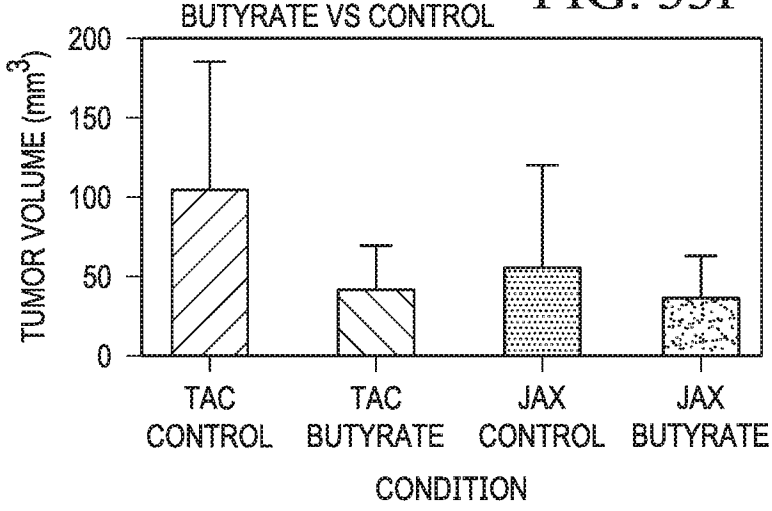
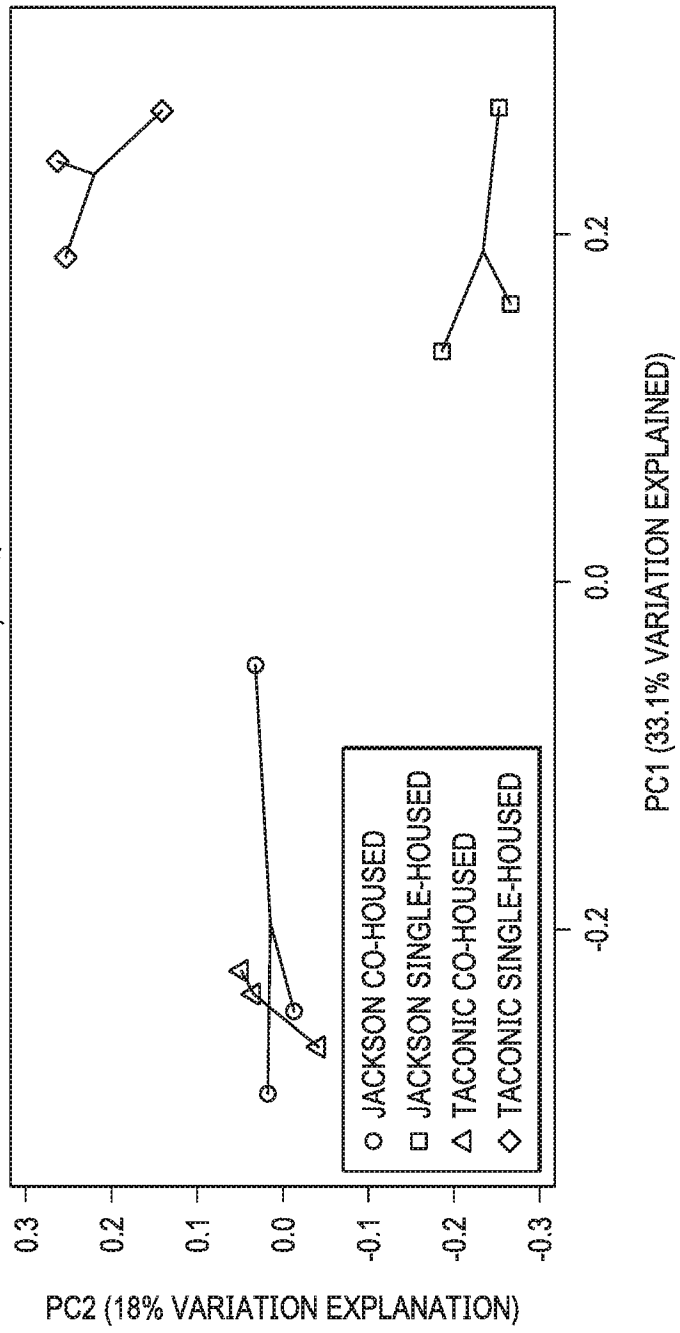


FIG. 33D


P-VALUE: 0.001; R-SQUARED: 0.702
JACKSON CO-HOUSED
JACKSON SINGLE-HOUSED
TACONIC CO-HOUSED
TACONIC SINGLE-HOUSED
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
PC2 (18% VARIATION EXPLANATION)
-0.2
0.0
0.2
PC1 (33.1% VARIATION EXPLAINED)

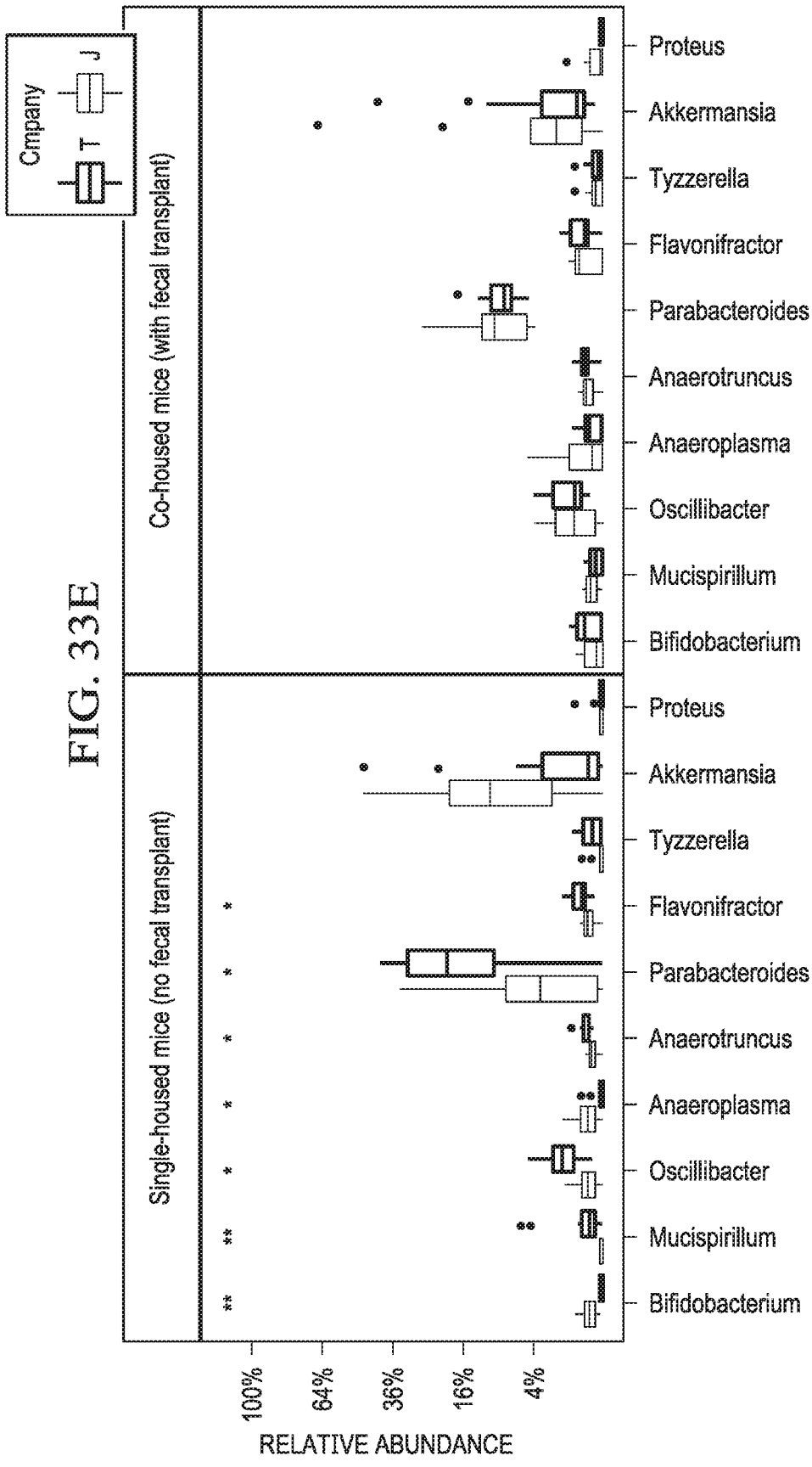

Cmpany
T
J
Co-housed mice (with fecal transplant)
Single-housed mice (no fecal transplant)
Proteus
Akkermansia
Tyzzerella
Flavonifractor
Parabacteroides
Anaerotruncus
Anaeroplasma
Oscillibacter
Mucispirillum
Bifidobacterium
100%
64%
36%
16%
4%
RELATIVE ABUNDANCE

FIG. 33E

FIG. 34A

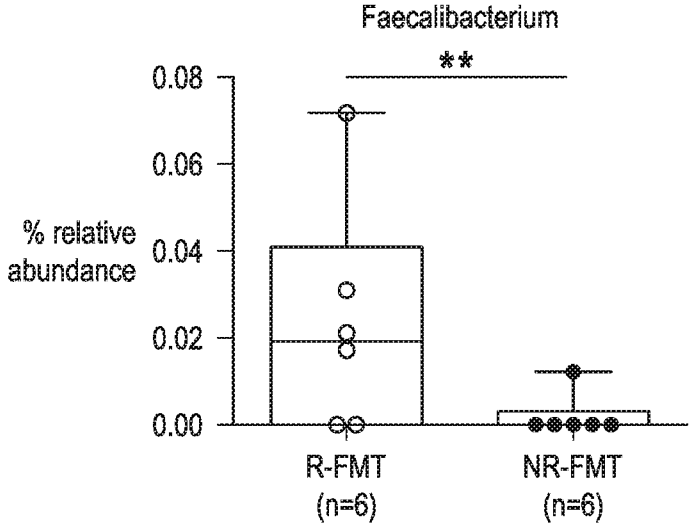



FIG. 34B

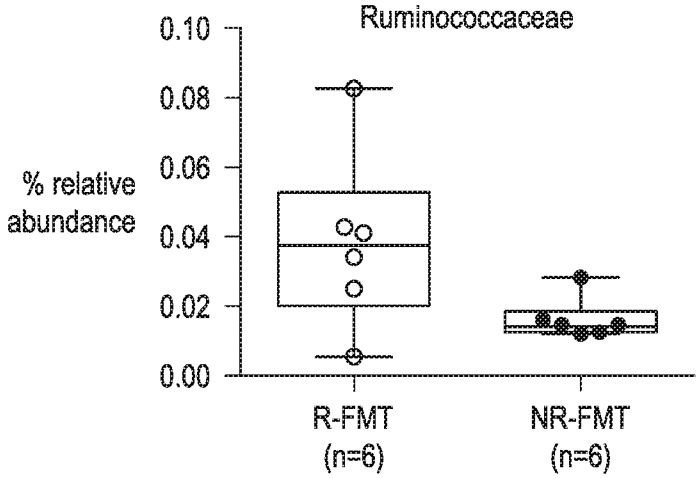



FIG. 34C