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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 March 2021 (11.03.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/044415 A1

(51) International Patent Classification:
C12Q 1/6888 (2018.01) *A61P 3/10* (2006.01)
C12N 1/20 (2006.01) *C12R 1/01* (2006.01)
C12Q 1/689 (2018.01)

(21) International Application Number:
PCT/IL2020/050955

(22) International Filing Date:
02 September 2020 (02.09.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/894,895 02 September 2019 (02.09.2019) US

(71) Applicant: **MY-OR DIAGNOSTICS LTD.** [IL/IL]; 29 Bareket Street, 3093674 Zikhron Yaakov (IL).

(72) Inventors: **KOHN, Ron**; 246 Hachivayai Street, 9973500 Kefar Uriya (IL). **BRANDWEIN, Michael**; 26 Gofna Street, 9094200 Elazar (IL). **KATZ, Ariel**; 29 Bareket Street, 3093674 Zichron Yaakov (IL).

(74) Agent: **KESTEN, Dov** et al.; 100 Hahashmonaim Street, P.O. Box 52630, 6713317 Tel Aviv (IL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: SKIN MICROBIOME MONITORING FOR IMPROVING SYSTEMIC HEALTH

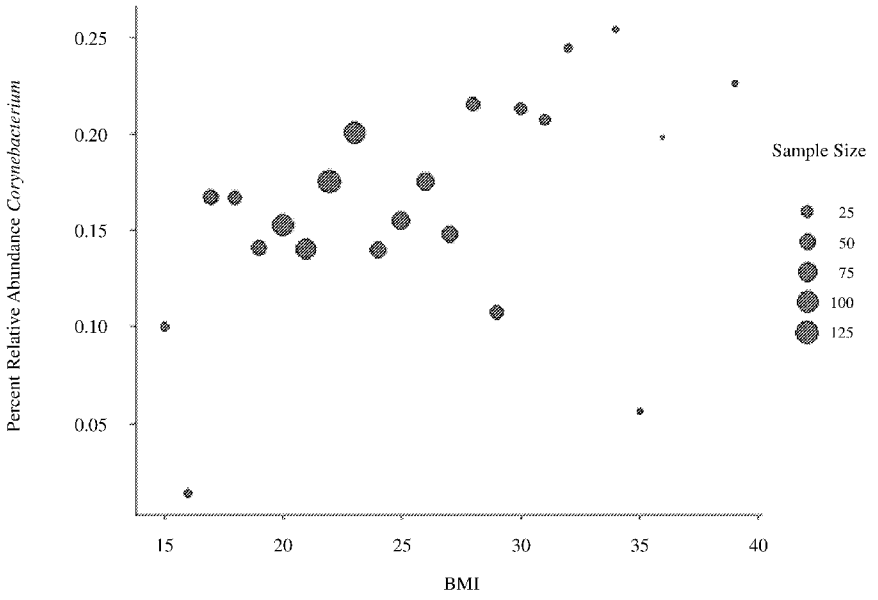

FIGURE 5B

(57) Abstract: The present invention is directed to a method for determining predisposition to developing a metabolic syndrome or a condition associated therewith in a subject including determining the bacterial diversity in a facial skin of the subject. Further provided is a method for treating or preventing a metabolic syndrome or a condition associated therewith in a subject in need thereof.

WO 2021/044415 A1

[Continued on next page]

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

SKIN MICROBIOME MONITORING FOR IMPROVING SYSTEMIC HEALTH

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 62/894,895 titled "SKIN MICROBIOME MONITORING FOR IMPROVING SYSTEMIC HEALTH", filed September 2, 2019, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The invention relates generally to the field of microbiome and diseases associated therewith.

BACKGROUND

[0003] The global obesity pandemic has far-reaching social, economic and health-related ramifications. Its incidence has risen at an alarming rate, with nearly one-fifth of children and over one-third of adults in the US are obese, and national initiatives and/or programs to curb obesity have so far been unsuccessful. Obesity is the result of higher energy intake than expenditure and is the central factor leading to the development of the metabolic syndrome. Several important mediators have been identified in obesity, including the Western diet, oxidative stress, the microbiome, and chronic inflammation.

[0004] Early microbiome studies established the link between obesity and the human gut microbiome. These studies have shown that the ratio of Firmicutes to Bacteroidetes is elevated in both obese mice and humans. Furthermore, weight loss induces a compositional shift whereby Bacteroidetes increase and Firmicutes decrease. Further studies documented the lack of microbial diversity of the Western gut microbiome compared to populations which consume a more traditional plant-based diet.

[0005] For the most part, microbiome studies on obesity have been limited to the gut microbiome.

[0006] The American Gut Project (AGP), launched in 2012, aims to establish a comprehensive reference set for microbiome research by engaging the general public globally. It allows members of the general public to submit oral, skin or fecal samples for microbiome profiling and the results are then made available to the donor and are deidentified and added to the larger, freely-available database. This paradigm-shifting endeavor has shown that the diversity of plants that are consumed are strongly correlated with gut microbiome composition.

[0007] A method for detecting or diagnosing metabolic syndrome or a condition associated therewith based on the subject's skin microbiome, is still greatly needed.

SUMMARY

[0008] The following embodiments and aspects thereof are described and illustrated in conjunction with systems, tools and methods which are meant to be exemplary and illustrative, not limiting in scope.

[0009] According to a first aspect, there is provided a method for determining predisposition to developing a metabolic syndrome or a condition associated therewith in a subject, the method comprising: determining the bacterial diversity in a facial skin of the subject; and comparing the determined bacterial diversity to a control, thereby determining predisposition to developing a metabolic syndrome in the subject.

[0010] According to another aspect, there is provided a method for treating or preventing a metabolic syndrome or a condition associated therewith in a subject in need thereof, the method comprising: (a) determining whether the subject is at increased risk of developing a metabolic syndrome or a condition associated therewith, according to the method disclosed herein; and administering to a subject determined as being at an increased risk, a therapeutically effective amount of a pharmaceutical or a nutraceutical composition comprising an agent selected from the group consisting of: an appetite suppressant, a probiotic agent, a prebiotic agent, an anti-inflammatory drug, a topical solution, and any combination thereof, thereby treating or preventing a metabolic syndrome or a condition associated therewith in a subject.

[0011] In some embodiments, determining comprises determining any one of: abundance of *Corynebacteriaceae* species, ratio of *Corynebacteriaceae* to *Staphylococcaceae*, and both, in a facial skin of the subject.

[0012] In some embodiments, a reduction of at least 5% in bacterial diversity in a facial skin of the subject compared to control is indicative of the subject being at increased risk of developing a metabolic syndrome or a condition associated therewith.

[0013] In some embodiments, an abundance of at least 15% of a *Corynebacteriaceae* species in a facial skin of the subject is indicative of the subject being at increased risk of developing a metabolic syndrome or a condition associated therewith.

[0014] In some embodiments, a *Corynebacteriaceae* to *Staphylococcaceae* abundance ratio ranging from 3.2:1 to 9:1 in a facial skin of the subject is indicative of the subject being at increased risk of developing a metabolic syndrome or a condition associated therewith.

[0015] In some embodiments, the subject has a body mass index (BMI) value ranging from 19 to 29.

[0016] In some embodiments, the subject has a BMI value ranging from 19 to 26.

[0017] In some embodiments, facial skin is the skin of any one of: the forehead, the glabella, or a combination thereof.

[0018] In some embodiments, the metabolic syndrome or the condition associated therewith is selected from the group consisting of: obesity, pre-diabetes, diabetes, hyperglycemia, diabetic dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, and insulin-resistance or insulin-resistance related.

[0019] In some embodiments, determining is determining in a sample derived from the subject.

[0020] In some embodiments, the method further comprises providing a sample from the subject and performing the determining in the sample.

[0021] In some embodiments, the method further comprises modifying the diet of the subject.

[0022] In some embodiments, modifying is providing any one of: a diet low on calories, a diet low on fat content, a diet low on carbohydrates content, and any combination thereof.

[0023] In some embodiments, modifying is providing a diet low on calories.

[0024] In some embodiments, modifying is alternating the timing of food consumption.

[0025] In some embodiments, preventing comprises any one of: reducing the severity, delaying the onset, reducing the cumulative incidence, and any combination thereof, of the metabolic syndrome or the condition associated therewith.

[0026] In some embodiments, the metabolic syndrome or the condition associated therewith is selected from the group consisting of: obesity, pre-diabetes, diabetes, hyperglycemia, diabetic dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, and insulin-resistance or insulin-resistance related.

[0027] Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

[0028] Further embodiments and the full scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and 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.

[0029] In addition to the exemplary aspects and embodiments described above, further aspects and embodiments will become apparent by reference to the figures and by study of the following detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0030] **Fig. 1** includes a graph showing clustering of microbial communities by body site. Gut, oral and skin sites cluster separately, thereby necessitating research hypothesis that look at these communities separately.

[0031] **Figs. 2A-2C** include donut charts and vertical bar graphs showing taxonomic composition of microbial communities by body site. Gut, oral and skin sites are all dominated by Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria **(2A)**, yet their percent community composition is significantly different between sites **(2B-2C)**. Gut, oral and skin body sites are inhabited by varying bacterial families, with Bacteroidaceae, Ruminococcaceae and Lachnospiraceae dominating gut samples, Streptococcaceae and Micrococcaceae dominating oral samples and Staphylococcaceae and Corynebacteriaceae dominating skin samples.

[0032] **Figs. 3A-3C** include graphs showing bacterial community diversity according to body site and BMI category. Gut **(3A)**, oral **(3B)**, and skin **(3C)** Shannon diversity measurements are presented according to BMI category. Gut microbial diversity is significantly different between all three categories, while no significance is observed between oral communities. There is a significant difference in microbial diversity between underweight and normal individuals and between underweight and obese individuals in skin communities.

[0033] **Fig. 4** includes a graph showing the clustering of skin microbial communities by BMI category. Skin microbial communities are partitioned by BMI, with underweight individuals' skin microbiome markedly different than those of overweight and obese individuals. Normal individuals are plotted, yet their points are smaller to allow visualization of the other groups.

[0034] **Figs. 5A-5B** include graphs showing differentially abundant bacteria by BMI category. LEfSe results indicating significantly enriched taxa by BMI category **(5A)**. Additionally, Corynebacterium relative abundance correlates significantly with BMI **(5B**, $p=0.0002$). Point size is reflective of sample size in BMI levels portrayed.

[0035] **Figs. 6A-6C** include donut charts showing microbiome taxonomy in the gut **(6A)**, oral **(6B)**, and skin **(6C)**. BMI categories (overweight/obese, normal, and underweight) are indicated.

[0036] **Figs. 7A-7E** include graphs and pie charts showing taxonomical composition of skin microbiome samples by skin site. **(7A and 7B)** are graphs showing phyla and families distribution, respectively. **(7A)** shows that Actinobacteria, in contrast to Proteobacteria, were more prominent in nares than in the palm and in the forehead. **(7C)** is a graph showing nare clustering separately from forehead and palm in PCoA (beta diversity). **(7D and 7E)** are graphs of Shannon diversity **(7D)** and Faith's phylogenetic diversity **(7E)** representing alpha diversity measures, showing statistically significant differences between skin sites.

[0037] **Figs. 8A-8D** include graphs showing forehead microbiome analyses. **(8A)** is a Shannon (alpha) diversity analysis of forehead samples by BMI category. Statistical significance is shown between groups. **(8B)** is a graph showing that bacterial populations derived from forehead skin of underweight subjects clustered separately from overweight and obese. **(8C)** is a graph showing statistically significant correlation between Corynebacterium relative abundance and BMI. **(8D)** is a LDA analysis with list of bacteria over-/under-represented in obese/overweight or underweight individuals.

[0038] **Figs. 9A-9C** include graphs showing nare microbiome analyses. **(9A)** is a Shannon (alpha) diversity analysis of nare samples by BMI category. Statistical significance is not shown between groups. **(9B)** is a graph showing that bacterial populations derived from nare skin of underweight subjects clustered separately from overweight and obese. **(9C)** is a graph showing statistically significant correlation between Corynebacterium relative abundance and BMI.

[0039] **Figs. 10A-10C** include graphs showing palm microbiome analyses. **(10A)** is a Shannon (alpha) diversity analysis of palm skin samples by BMI category. Statistical significance is not shown between groups. **(10B)** is a graph showing that bacterial populations derived from palm skin of underweight subjects did not cluster separately from overweight and obese. **(10C)** is a graph showing statistically significant correlation between Corynebacterium relative abundance and BMI.

DETAILED DESCRIPTION

[0040] According to some embodiments, there is provided a method for determining predisposition to developing a metabolic syndrome or a condition associated therewith in a subject, comprising determining the bacterial diversity in a facial skin of the subject; and comparing the determined bacterial diversity to a control, thereby determining predisposition to developing a metabolic syndrome in the subject.

[0041] According to some embodiments, there is provided a method for treating or preventing a metabolic syndrome or a condition associated therewith in a subject in need thereof, the method comprising: determining whether the subject is at increased risk of developing a metabolic syndrome or a condition associated therewith; and administering to a subject determined as being at an increased risk, a therapeutically effective amount of a composition comprising an agent selected from: an appetite suppressant, a probiotic agent, a prebiotic agent, an anti-inflammatory drug, a topical solution, or any combination thereof.

[0042] As used herein, the term "predisposition" refers to the susceptibility of a subject to a syndrome, a disease, or a condition associated therewith such as a metabolic syndrome. In some embodiments, determining a predisposition comprises determining the presence of the disease itself. In some embodiments, determining a predisposition comprises any one of: determining the risk of developing the disease, determining the susceptibility of the subject to developing the disease, having a poor prognosis for the disease, or any combination thereof. In some embodiments, a subject having a predisposition to a disease is at risk or at increased risk of developing the disease.

[0043] The terms "predisposition" and "likelihood" are used herein interchangeably.

[0044] In some embodiments, the method is directed to determining predisposition to developing a metabolic syndrome or a condition associated therewith, based on a skin microbiome analysis.

[0045] As used herein, the term "skin microbiome" refers to the microbiome of a facial skin. In some embodiments, facial skin comprises the skin of the forehead, the skin of the glabella, or any combination thereof.

[0046] In some embodiments, skin microbiome analysis comprises the analysis of facial skin microbiome. In some embodiments, facial skin comprises the skin of any part of a subject's face. In some embodiments, facial skin comprises the skin of the forehead skin, the skin of the glabella, or any combination thereof.

[0047] In some embodiments, skin microbiome analysis comprises determining any one of: abundance of a microorganism species or a strain thereof, the ratio of two or more species or strains of microorganisms, or both, in facial skin or any sample obtained or derived therefrom.

[0048] In one embodiment, a skin microbiome indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith comprises reduced bacterial community diversity, e.g., reduced number of different bacterial species, strains, or both. In one embodiment, determining that a skin microbiome is indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith comprises determining any one of: abundance of a species belonging to any family selected from: Streptococcaceae, Corynebacteriaceae, Staphylococcaceae, Micrococcaceae, Neisseriaceae, Pasteurellaceae, Prevotellaceae, and Moraxellaceae, ratio of two or more species belonging to any one of the aforementioned families, or both, in a facial skin of said subject. In another embodiment, a skin microbiome indicative of increased likelihood to develop the metabolic syndrome or a condition associated therewith comprises colonization of one or more bacteria belonging to any family selected from: Streptococcaceae, Corynebacteriaceae, Staphylococcaceae, Micrococcaceae, Neisseriaceae, Pasteurellaceae, Prevotellaceae, and Moraxellaceae. In another embodiment, a skin microbiome indicative of increased likelihood to develop the metabolic syndrome or a condition associated therewith comprises Corynebacterium colonization. In another embodiment, a skin microbiome indicative of increased likelihood to develop the metabolic syndrome or a condition associated therewith comprises Staphylococcus aureus colonization. In another embodiment, a skin microbiome indicative of increased likelihood to develop the metabolic syndrome or a condition associated therewith comprises high *Corynebacterium kroppenstedtii* colonization. In another embodiment, a skin microbiome indicative of increased likelihood to develop the metabolic syndrome or a condition associated therewith comprises high Staphylococcus aureus colonization. In another embodiment, a skin microbiome indicative of increased

likelihood to develop the metabolic syndrome or a condition associated therewith comprises increased Corynebacterium, e.g., C. *kroppenstedtii*, colonization, increased Staphylococcus, e.g., S. aureus, colonization, reduced S. epidermidis colonization, reduced S. hominis colonization, or any combination thereof.

[0049] Methods of determining bacterial diversity are common and would be apparent to one of ordinary skill in the art. Non-limiting examples of methods for determining bacterial diversity, such as exemplified hereinbelow, include but are not limited to, phylogenetic diversity (PD)-whole-tree, e.g., Shannon diversity, and Bray-Curtis dissimilarity. Alpha diversity and taxonomic relative abundance can be further compared with the Wilcoxon rank sum test in R, and multiple hypothesis correction can be carried out using a false discovery rate.

[0050] In some embodiments, the method comprises determining the bacterial diversity prior to the appearance of the metabolic syndrome or a condition associated therewith. In some embodiments, the method comprises determining cutaneous bacterial diversity in a normally appearing skin.

[0051] As used herein, the term "normally appearing" refers to the gross morphology of a skin tissue as observed by the naked eye, by microscopy, or both.

[0052] In some embodiments, the determining excludes determining bacterial diversity on a cutaneous lesion evident after the appearance of the metabolic syndrome or a condition associated therewith. In some embodiments, the determining excludes determining bacterial diversity on a cutaneous lesion known to be induced by the metabolic syndrome.

[0053] As used herein, the terms "high", "low", "increased", and "decreased" are compared to control. In some embodiments, the control is a skin microbiome of a healthy subject. In some embodiments, the control is a skin microbiome of a non-facial skin derived or obtained from either the subject or a healthy subject. In some embodiments, the control is a microbiome of a non-skin tissue derived or obtained from either the subject or a healthy subject. In some embodiments, the control is value threshold representing a healthy subject or a skin microbiome of same.

[0054] In some embodiments, the method of the invention is directed to a skin microbiome analysis comprising determining any one of: the abundance of a Corynebacteriaceae species or a strain thereof, the ratio of a Corynebacteriaceae species or a strain thereof to a Staphylococcaceae species or a strain thereof, or both.

[0055] In some embodiments, determining the abundance of any one of Corynebacteriaceae species, Staphylococcaceae species, or both, comprises DNA sequencing a skin microbiome for or using Corynebacteriaceae-specific sequence, Staphylococcaceae-specific sequences, or both.

[0056] In some embodiments, the method comprises a determining step in a sample derived from the subject. In some embodiments, the determining step is performed in vitro.

[0057] As used herein, in vitro is in a tube, a plate, or any equivalent thereof. In some embodiments, in vitro is outside a subject's body. In some embodiments, in vitro comprises ex vivo.

[0058] In some embodiments, the method further comprises providing a sample obtained, isolated, or derived from the subject, and performing the determining step in the sample.

[0059] In one embodiment, the step of detecting Staphylococcus colonization comprises detecting S. aureus, S. epidermidis, S. hominis, or a combination thereof. In one embodiment, the step of detecting Staphylococcus colonization on the skin of the subject comprises identification of a specific nucleotide sequence unique to cutaneous associated S. aureus species via PCR amplification of a gene fragment by gene-specific PCR primers.

[0060] In one embodiment, a step of analyzing the microbiome comprises culturing the sample derived from the skin of the subject on selective substrate, for example agar. In another embodiment, the step of analyzing the microbiome comprises nucleotide sequencing of bacterial nucleotide sequences present in the skin sample derived from the subject. In one embodiment, the nucleotide sequencing comprises sequencing of the gene encoding the 16S ribosomal RNA (16S rRNA).

[0061] In another embodiment, analyzing the skin microbiome in the sample comprises 16S rRNA gene sequencing or whole genome shotgun metagenomics. In one embodiment, the nucleotide sequencing comprises DNA sequencing.

[0062] In some embodiments, determining the abundance of any one of Corynebacteriaceae species, Staphylococcaceae species, or both, comprises detecting Corynebacteriaceae-specific region of the 16S ribosomal RNA gene, Staphylococcaceae-specific region of the 16S ribosomal RNA gene, or both.

[0063] In another embodiment, the step of analyzing the skin microbiome comprises identification of a specific nucleotide sequence via amplification, such as by PCR, of a gene fragment by gene-specific PCR primers.

[0064] In another embodiment, the step of analyzing the skin microbiome comprises an optical detection technique, an electrochemical detection technique, or a mass detection technique.

[0065] In embodiments, methods are provided which comprise, inter alia, collecting a biological sample from skin of a subject and analyzing the microbiome in the sample derived from the skin. Modern techniques for skin microbial analysis are known and within the understanding of the ordinarily skilled artisan and specific methods and techniques can be employed and adjusted to best suit the aims of the study.

[0066] In general, several procedural practices should be considered before the study begins, including avoiding contamination by environmental DNA, storage in warm conditions, and the exposure of the samples to researchers and clinicians. Further, precautions should be taken to ensure a sterile technique is utilized, and that bacterial DNA sequences (not only live bacterial organisms) are not introduced into the sample from sampling equipment, lab reagents, and clinicians.

[0067] To obtain samples, microorganisms from the skin can be collected by any suitable method known in the art, including, without limitation, swabbing, tape stripping, scraping or collecting biopsies using sterile techniques. Skin samples can be collected from any suitable location, including, without limitation, the nare, axillary vault, antecubital fossa, interdigital webspace, inguinal crease, gluteal crease, popliteal fossa, plantar heel, umbilicus, or a combination thereof. Appropriate and effective sample storage conditions should also be employed. If sterile sample collection is combined with effective storage conditions, an accurate representation of the skin microbiome should be maintained prior to DNA extraction and analysis. Once the samples are obtained and properly stored, DNA extractions

can then be performed. Several different methods have been developed for the extraction of skin microbiome samples, including the REPLI-g Midi kit (Qiagen, Limberg, The Netherlands), Qiagen DNA Extraction Kit (Qiagen), and DNeasy DNA Extraction kit (Qiagen). In an effort to obtain the most accurate representation of the microbial diversity, studies have also explored different kit and non-kit based extraction methods, such as disruption of bacterial cell walls (e.g., bead beating or enzymatic lysis).

[0068] After DNA extraction, the specific target species or classes of microorganisms need to be identified to determine the most appropriate sequencing strategy. For example, bacterial communities can be assessed by amplifying a variable region of the conserved 16S ribosomal RNA gene, while fungal species and/or other eukaryote species can be targeted by applying 18S ribosomal RNA gene or the internal transcribed spacer.

[0069] While culturing methods can be used in detecting bacterial strains in accordance with embodiments described herein, targeted sequencing approaches do not require any culturing methods and hundreds of samples can be analyzed on a single sequencing run, providing an efficient and cost-effective means to examining microbial communities. Alternatively, shotgun sequencing can be performed, which will identify a subset of random DNA sequences from the sample. In either approach, sequencing technologies should also be taken into account. While Roche 454 or Illumina MiSeq can provide adequate sequencing coverage or depth for targeted amplicon sequencing, deeper coverage attainable through Illumina HiSeq or Pacific Biosciences technologies may be better suited for shotgun sequencing.

[0070] 16S data processing - The 16S sequence data can be processed in accordance with any suitable techniques known to one of skill in the art, including as previously described (McDonald, et al., 2018). In one embodiment, processing can use a sequence variant method, such as Deblur v1.0.2, trimming to 125 nucleotides, to maximize the specificity of 16S data. Following processing by Deblur, previously recognized bloom sequences can be removed. The Deblur sOTUs can be inserted into the Greengenes 13_8 (19) 99% reference tree using SEPP. SEPP uses the simultaneous alignment and tree estimation strategy as previously described (Liu et al., 2009) to identify reasonable placements for sequence fragments within

an existing phylogeny and alignment. Taxonomy can be assigned using an implementation of the RDP classifier as implemented in QIIME2. (McDonald, et al.).

[0071] Principal coordinates analysis can be undertaken in accordance with any suitable techniques known to one of skill in the art. In one embodiment, a distance matrix can be constructed using, for example, without limitation, the Bray Curtis dissimilarity index. In an embodiment, principal coordinates analyses can be implemented using, for example, without limitation, EMPeror software.

[0072] In some embodiments, the bacterial diversity of a skin microbiome which is indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith, is reduced by at least 5%, at least 10%, at least 20%, at least 35%, at least 50%, at least 65%, at least 80%, at least 90%, at least 95%, or at least 99%, compared to control, or any value and range therebetween. Each possibility represents a separate embodiment of the invention. In some embodiments, the bacterial diversity of a skin microbiome which is indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith, is reduced by 1-25%, 5-45%, 10-75%, 15-85%, 5-35%, 40-95%, 25-100%, 30-65%, 45-85%, or 60-99%. Each possibility represents a separate embodiment of the invention.

[0073] In some embodiments, a skin microbiome indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith comprises a Corynebacteriaceae species having an abundance of at least 5%, at least 10%, at least 15%, at least 25%, at least 30%, at least 45%, at least 55%, at least 75%, at least 85%, at least 95%, or at least 99%, within the skin microbiome, or any value and range therebetween. Each possibility represents a separate embodiment of the invention. In some embodiments, a skin microbiome indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith comprises a Corynebacteriaceae species having an abundance of 1-25%, 5-35%, 15-55%, 10-85%, 20-99%, 1-50%, 20-75%, 30-65%, 75-95%, 60-100%, within the skin microbiome. Each possibility represents a separate embodiment of the invention.

[0074] In some embodiments, a skin microbiome indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith comprises a

Corynebacteriaceae species and a Staphylococcaceae species in an abundance ratio ranging from 3:1 to 9:1. In some embodiments, a skin microbiome indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith comprises a Corynebacteriaceae species and a Staphylococcaceae species in an abundance ratio ranging from 3.2:1 to 9:1. In some embodiments, ratio ranging from 3.2:1 to 9:1 comprises: 3.2:1 to 8:1, 3.2:1 to 7:1, 3.2:1 to 6:1, 3.2:1 to 5:1, 3.2:1 to 4:1, 4:1 to 9:1, 5:1 to 8:1, 6:1 to 9:1, or 7:1 to 12:1. Each possibility represents a separate embodiment of the invention.

[0075] In some embodiments, the subject has a body mass index (BMI) value ranging from 19 to 29. In some embodiments, the subject has a BMI value ranging from 19 to 26. In some embodiments, a BMI value ranging from 19 to 29 comprises a BMI value of 19 to 28, 19 to 27, 20 to 26, 19 to 25, 25 to 29, 26 to 29, 27 to 29, 28 to 30. Each possibility represents a separate embodiment of the invention.

[0076] BMI calculation would be apparent to one of ordinary skill in the art.

[0077] In some embodiments, a skin microbiome indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith comprises a Corynebacteriaceae species having an abundance of at least 5%, at least 10%, at least 15%, at least 25%, at least 30%, at least 45%, at least 55%, at least 75%, at least 85%, at least 95%, or at least 99%, within the skin microbiome of a subject having a BMI value ranging from 19 to 29, 19 to 27, 20 to 26, 19 to 25, 25 to 29, 26 to 29, 27 to 29, 28 to 30.

[0078] In some embodiments, a subject having a skin microbiome indicative of increased likelihood to develop a metabolic syndrome or a condition associated therewith comprises a Corynebacteriaceae species having an abundance of at least 15% within the skin microbiome and has a BMI value of 19 to 26.

[0079] As used herein the term "metabolic syndrome" refers to any disease, disorder, or condition characterized by any one of the following: excess abdominal fat, hypertension, abnormal fasting plasma glucose level or insulin resistance, high triglyceride levels, and low high-density lipoprotein (HDL) cholesterol level. The metabolic syndrome which can be predicted or treated according to the present invention include, but is not limited to, fatty liver, obesity, pre-diabetes, diabetes, hyperglycemia, diabetic dyslipidemia, hyperlipidemia,

hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, insulin-resistance or insulin-resistance related.

[0080] In one embodiment, the metabolic syndrome is a fatty liver disease. The term "fatty liver disease" (FLD) refers to a disease or a pathological condition caused by, at least in part, abnormal hepatic lipid deposits. Fatty liver disease includes, e.g., alcoholic fatty liver disease, nonalcoholic fatty liver disease, and acute fatty liver of pregnancy. Fatty liver disease may be, e.g., macrovesicular steatosis or microvesicular steatosis. In one embodiment, the metabolic syndrome is nonalcoholic steatohepatitis (i.e., fatty liver). In one embodiment, the metabolic syndrome comprises hepatotoxicity, nephrotoxicity or both, wherein the hepatotoxicity, nephrotoxicity, or both are fat-induced. As used herein, fat induced-hepatotoxicity, and fat-induced nephrotoxicity, refer to any disease or condition encompassing increased toxicity to cells of the liver, kidney, or both which is attributed to the accumulation of fat, triglycerides, free fatty acid, lipid droplet, or any equivalent thereof, which negatively impacts the intoxicated cell. Intoxicated cells, for example, undergo necrosis, lose membrane integrity, undergo cell lysis, cease growing or cell division, actively induce apoptosis.

[0081] In one embodiment, the metabolic syndrome is a fatty kidney disease (FKD). The term "fatty kidney disease" encompasses any disease or a pathological condition comprising ectopic lipid deposits in the kidney.

[0082] In some embodiments, the metabolic syndrome is diabetes. In some embodiments, diabetes is type 2 diabetes (T2DM). In some embodiments, the metabolic syndrome is an insulin resistance-related disease. In some embodiments, the metabolic syndrome is an insulin resistance-related-T2DM. In some embodiments, the metabolic syndrome is an insulin resistance-dependent-T2DM. In some embodiments, the metabolic syndrome is a muscular disease. In some embodiments, the metabolic syndrome is a metabolic muscular disease. In some embodiments, the metabolic syndrome is a cardiac muscle metabolic disease (i.e., cardiometabolic disease). In some embodiments, the metabolic syndrome is a skeletal muscle metabolic disease.

[0083] In some embodiments, a subject having increased likelihood to develop a metabolic syndrome or a condition associated therewith, is characterized by having or by being

afflicted with: abnormal fat metabolism, alcoholism, advanced age (e.g., greater than 40, 50, 60, or 70 years of age), celiac disease, diabetes mellitus (e.g., type II diabetes mellitus), dyslipidemia, exposure to industrial solvents, galactosemia, glycogen storage diseases, homocystinuria, hyperferritinemia, hyperinsulinemia, hyperlipidemia, hypertension, hypertriglyceridemia, hyperuricemia, hypoxia, impaired fasting glycemia, inborn metabolic disorders (e.g., related to galactose, glycogen, homocysteine, or tyrosine metabolism), insulin resistance, iron overload, jejunal bypass surgery, low levels of high-density lipoprotein, Madelung's lipomatosis, malnutrition, Mauriac syndrome, metabolic syndrome, mitochondrial dysfunction, mitochondrial injury, mitochondrialopathies, niacin deficiency, Niemann-Pick disease, obesity (especially visceral adiposity or central obesity), overnutrition, pantothenic acid deficiency, peroxisomal diseases, polycystic ovarian syndrome, pregnancy, rapid weight loss, riboflavin deficiency, sleep apnea, starvation, tyrosemia, Weber-Christian disease, or Wilson's disease may have, or be at increased risk of developing, a disorder associated with hepatic lipid deposits. In some embodiments, a subject having increased likelihood to develop a metabolic syndrome, or a condition associated therewith, is treated with certain medications, such as, e.g., amiodarone, corticosteroids, estrogens (e.g., synthetic estrogens), maleate, methotrexate, perhexyline, salicylate, tamoxifen, tetracycline, and valproic acid.

[0084] In some embodiments, the metabolic syndrome or a condition associated therewith is selected from: obesity, pre-diabetes, diabetes, hyperglycemia, diabetic dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, and insulin-resistance or insulin-resistance related.

[0085] In some embodiments, the agent or composition comprising thereof is modifying the skin microbiome.

[0086] As used herein, the term "appetite suppressant agent" refers to any compound capable of reducing appetite, and thereby reduces food consumption and/or promotes weight loss. Types of appetite suppressants are common and would be apparent to a skilled artisan. In some embodiments, an appetite suppressant comprises any one of: conjugated linoleic acid (CLA), synephrine, Garcinia cambogia, glucomannan, Hoodia gordonii, green coffee bean extract, Guarana, Acacia fiber, Saffron extract, Guar gum, Forskolin (or Coleus

forskohii extract), Chromium picolinate, Fenugreek, Gymnema sylvestre, 5-hydroxytryptophan (or Griffonia simlicifolia extract), Caralluma fimbriata, and Yerba mate.

[0087] As used herein, the term "probiotic agent" refers to any microorganism improving health benefits on a subject consuming the same. In some embodiments, a probiotic is defined as a living microorganism that, when administered in adequate amounts, confers a health benefit on the host. In some embodiments, the probiotic agent improves the subject's natural flora, or microbiome. In some embodiments, the probiotic agent restores the subject's natural flora or microbiome. Types of probiotics are common and would be apparent to a skilled artisan. In some embodiments, a probiotic is selected from: *Lactobacillus* (e.g., *L. rhamnosus*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. bulgaricus*), *Saccharomyces boulardii*, *Bifidobacterium* (e.g., *B. breve*, *B. longum*, *B. infantis*), and *Streptococcus thermophilus*.

[0088] As used herein, the term "prebiotic agent" refers to any dietary compound which induces or sustains activity, growth, or both, of beneficiary bacteria or fungi. Types of prebiotics are common and would be apparent to a skilled artisan. In some embodiments, a prebiotic is selected from raw, dry, or both, of any one of: chicory root, Jerusalem artichoke, dandelion greens, garlic, leek, onion, asparagus, wheat bran, whole wheat flour, banana, walnuts, oats, unrefined barely, yacon (also known as 'vegetarian bacon'), whole grain cereal. In some embodiments, a prebiotic comprises a prebiotic fiber. In some embodiments, the prebiotic fiber is selected from: beta glucan, pectin, gum, inulin, oligofructose, starch (e.g., a resistant-starch).

[0089] As used herein, the term "anti-inflammatory drug" refers to any compound capable of reducing or inhibiting an inflammatory response.

[0090] In some embodiments, an anti-inflammatory drug is any one of: an antibiotic, a tumor necrosis factor α (TNFα) inhibitor/blocker, a non-steroidal anti-inflammatory drug (NSAID), and any combination thereof.

[0091] In some embodiments, a TNFα inhibitor/blocker is selected from: infliximab, adalimumab, certolizumab pegol, golimumab, and etanercept. In some embodiments, a TNFα inhibitor/blocker is selected from: thalidomide, xanthine, dexamethasone, or tacrolimus.

[0092] In some embodiments, a NSAID is selected from: aspirin, celecoxib, diclofenac, diflunisal, etodolac, ibuprofen, indomethacin, or acetaminophen.

[0093] In another embodiment, the composition comprises a topical solution. In some embodiments, a composition comprising a topical solution is administered topically to body surfaces and is thus formulated in a form suitable for topical administration. Suitable topical formulations include gels, ointments, creams, lotions, drops and the like. For topical administration, the therapeutic agent is prepared and applied as a solution, suspension, or emulsion in a physiologically acceptable diluent with or without a pharmaceutical carrier.

[0094] In one embodiment, the treatment for modifying the skin microbiome comprises administering an emollient to the subject. In another embodiment, the treatment for modifying the skin microbiome comprises administering a food product to the subject. In one embodiment, the treatment for modifying the skin microbiome comprises administering an emollient and a food product to the subject. In one embodiment, the treatment for modifying the skin microbiome comprises a dietary supplement. In one embodiment, the food product is any one of: snack bar, cookie, muffin, cake, bread, cereal, juice, yogurt, milk, dairy product, infant formula, and the like. In one embodiment, the food product for modifying the skin microbiome or the dietary supplement comprises one or more probiotics, one or more prebiotics, or any combination thereof.

[0095] In another embodiment, the present invention provides a method of altering or modifying the skin microbiome in a subject having or prone to developing a metabolic syndrome or a condition associated therewith, comprising the step of administering to the subject a therapeutically effective amount of a composition comprising an agent capable of modifying the skin microbiome.

[0096] In some embodiments, the composition is a pharmaceutical composition, a nutraceutical composition, or a combination thereof.

[0097] In one embodiment, the composition modifies or alters the bacterial diversity of the skin microbiome. As used herein, the terms "modify" or "modifying" comprise increasing or decreasing. The terms “modify” and “alter” are used herein interchangeably.

[0098] In some embodiments the composition decreases *Corynebacteriaceae* abundance, colonization, or both. In some embodiments the composition decreases *Corynebacterium* abundance, colonization, or both. In some embodiments the composition decreases *S. aureus* abundance, colonization, or both. In some embodiments the composition increases the abundance, colonization, or both, of *S. epidermidis*, *S. homonis*, or both. In some embodiments the composition decreases the abundance, colonization, or both, of *Corynebacteriaceae* and S. aureus, and increases the abundance, colonization, or both, of *S. epidermidis*, *S. homonis*, or both.

[0099] In another embodiment, a composition as provided herein can be a controlled-release composition, i.e. composition in which the therapeutic agent is released over a period of time after administration. Controlled- or sustained-release compositions include formulation in lipophilic depots (e.g. fatty acids, waxes, oils). In another embodiment, the composition is an immediate-release composition, i.e. a composition in which all of the therapeutic agent is released immediately after administration.

[00100] In one embodiment, the composition is formulated in a unit dosage form. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[00101] It may be desirable to locally administer a composition in the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material. According to some embodiments, administration can be by direct injection e.g., via a syringe.

[00102] Effective dose of the composition for treatment of a condition or a disease vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Usually, the patient is a human, but non-human mammals including transgenic mammals can also be

treated. Treatment dosages may be titrated using routine methods known to those of skill in the art to optimize safety and efficacy. The composition thus may include a "therapeutically effective amount." A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of a molecule may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the molecule to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the molecule are outweighed by the therapeutically beneficial effects.

[00103] Furthermore, a skilled artisan would appreciate that the term "therapeutically effective amount" may encompass total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

[00104] The amount of a compound that will be effective in the treatment of a particular disorder or condition as disclosed herein, including a metabolic syndrome or a condition associated therewith, also will depend on the nature of the syndrome or condition, and can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. In one embodiment, the dosage will be within the range of 0.01-1,000 mg/kg of body weight per day. In another embodiment, the dosage will be within the range of 0.1 mg/kg per day to 100 mg/kg per day. In another embodiment, the dosage will be within the range of 1 mg/kg per day to 10 mg/kg per day. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test bioassays or systems.

[00105] For therapeutic purposes, the active compound is ordinarily combined with one or more adjuvants appropriate to the indicated route of administration.

[00106] A pharmaceutical composition as disclosed herein optionally comprises an additional agent selected from any pharmaceutically acceptable carrier, adjuvant, and vehicle.

[00107] In some embodiments, a method for treating a metabolic syndrome or a condition associated therewith further comprises modifying the diet of said subject, wherein modifying is changing in a personalized manner. The term "personalized" refers to the that the diet is changed in a manner so as to provide specific needs of the subject, based on, for example, the subject's lipid profile, gut microbiome, sugar levels, blood pressure, physical activity levels, any combination thereof, and others.

[00108] In some embodiments, the modified diet comprises any diet selected from: a diet low on calories, a diet low on fat content, a diet low on carbohydrates content, and any combination thereof.

[00109] In some embodiments, the modified diet comprises providing a diet low on calories.

[00110] In some embodiments, modifying is alternating the timing of food consumption. In some embodiments, alternating the timing of food consumption comprises: modifying the hours wherein food is consumed (e.g., earlier or later throughout a determined period of time, for example a day), modifying the gap or interval between meals or food consumption events, modifying the number of meals or food consumption events per a determined period of time, e.g., 24 hours or a day, and any combination thereof.

[00111] Types of diet, and personalization of same so as to meet the subject's specific physical needs, would be apparent to one of ordinary skill in the art of dietetics.

[00112] In some embodiments, the method is for preventing a metabolic syndrome or a condition associated therewith. In some embodiments, preventing comprises any one of: reducing the severity, delaying the onset, reducing the cumulative incidence, and any combination thereof, of a metabolic syndrome or a condition associated therewith.

[00113] As used herein, the terms "subject" or "individual" or "animal" or "patient" or "mammal," refers to any subject, particularly a mammalian subject, for whom therapy is desired, for example, a human.

[00114] In the discussion unless otherwise stated, adjectives such as "substantially" and "about" modifying a condition or relationship characteristic of a feature or features of an embodiment of the invention, are understood to mean that the condition or characteristic is defined to within tolerances that are acceptable for operation of the embodiment for an application for which it is intended. Unless otherwise indicated, the word "or" in the specification and claims is considered to be the inclusive "or" rather than the exclusive or, and indicates at least one of, or any combination of items it conjoins.

[00115] It should be understood that the terms "a" and "an" as used above and elsewhere herein refer to "one or more" of the enumerated components. It will be clear to one of ordinary skill in the art that the use of the singular includes the plural unless specifically stated otherwise. Therefore, the terms "a", "an" and "at least one" are used interchangeably in this application.

[00116] For purposes of better understanding the present teachings and in no way limiting the scope of the teachings, unless otherwise indicated, all numbers expressing quantities, percentages or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[00117] In the description and claims of the present application, each of the verbs, "comprise", "include" and "have" and conjugates thereof, are used to indicate that the object or objects of the verb are not necessarily a complete listing of components, elements or parts of the subject or subjects of the verb.

[00118] Other terms as used herein are meant to be defined by their well-known meanings in the art.

[00119] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive.

[00120] Throughout this specification and claims, the word “comprise” or variations such as “comprises” or “comprising,” indicate the inclusion of any recited integer or group of integers but not the exclusion of any other integer or group of integers.

[00121] As used herein, the term “consists essentially of”, or variations such as “consist essentially of” or “consisting essentially of” as used throughout the specification and claims, indicate the inclusion of any recited integer or group of integers, and the optional inclusion of any recited integer or group of integers that do not materially change the basic or novel properties of the specified method, structure or composition.

[00122] As used herein, the terms "comprises", "comprising", "containing", "having" and the like can mean "includes", "including", and the like; "consisting essentially of or "consists essentially" likewise has the meaning ascribed in U.S. patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments. In one embodiment, the terms "comprises", "comprising", "having" are/is interchangeable with "consisting".

[00123] Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

EXAMPLES

Material and Methods

The American Gut Project (AGP)

[00124] Sample processing, sequencing, and core amplicon data analysis were performed by the American Gut Project (www.americangut.org) and all amplicon sequence data and metadata have been made public through the AGP data portal (qiita.ucsd.edu; study ID

10317). Briefly, AGP sample collection and analyses was approved by the Institutional Review Boards of the University of Colorado Boulder and of the University of California, San Diego. Participants signed up online and self-reported metadata. Samples were shipped to the Knight lab and processed using the Earth Microbiome Project protocols. 16S rRNA data was processed using Deblur v1.0.2 and bloom sequences were removed. Greengenes 13_8, SEPP, RDP classifier and QIIME2 were used for alignment, tree building, and taxonomy assignment.

Data Accession & Sample selection

[00125] Data for these analyses were obtained from the American Gut ftp site (ftp://ftp.microbio.me/AmericanGut/). The inventors included all samples where Body mass index (BMI) data was made available, height and weight were provided. The inventors subsequently filtered the data to include individuals whose BMI was between 15 and 45.

Alpha Diversity, Beta-Diversity & Taxonomic Relative Abundance

[00126] Phylogenetic diversity (PD)-whole-tree, Shannon, Chao-1 and observed OTU diversity metrics were calculated with QIIME1 (alpha_diversity.py). Beta-diversity metrics were calculated and plotted using Bray-Curtis dissimilarity in QIIME1 (beta_diversity_through_plots.py) and significance between sample categories was tested with PERMANOVA in QIIME1 (compare_categories.py). Taxonomic relative abundance tables were generated at all taxonomic levels in QIIME1 (summarize_taxa.py). Alpha diversity plots and taxonomic relative abundance plots were plotted using GraphPad Prism 7.02. Alpha diversity and taxonomic relative abundance were compared with the Wilcoxon rank sum test in R (pairwise.wilcox.test). Multiple hypothesis correction was carried out using the false discovery rate.

Linear Discriminant Analysis Effect Size Analysis (LEfSe)

[00127] The inventors used the online Galaxy interface (https://huttenhower.sph.harvard.edu/galaxy/root) to identify differentially abundant genera by BMI category with LEfSe. BMI category was assigned as the comparison class, and overweight and obese individuals were clustered into the same category (Overweight/Obese). Default LEfSe settings were used, including 0.05 alpha value for

factorial Kruskal-Wallis test, 2.0 logarithmic linear discriminant analysis (LDA) score for discriminative features, and an all-against-all strategy for multi-class analysis.

EXAMPLE 1

Distinct Microbiomes by Body Site

[00128] The inventors analyzed 16,353 samples with BMI data, of which 14,287 samples were fecal (87.4%), 1,071 were oral (6.5%) and 995 were from skin sites (6.1%). The inventors observed significant partitioning using PERMANOVA between fecal, oral and skin microbiomes (**Fig. 1**), consistent with previous reports of the human microbiome. All body sites were dominated by the bacterial phyla *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*. *Cyanobacteria* were also represented on skin samples (**Fig. 2A**). While all body sites were dominated by *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*, their percent relative abundance on body sites were significantly different, with the exception of *Firmicutes* when comparing oral and skin sites (**Fig. 2C**). Dominant bacterial families in gut communities comprised of *Bacteroidaceae* and *Ruminococcaceae*, dominant bacterial families in oral communities comprised of *Streptococcaceae*, *Micrococcaceae*, *Veillonellaceae* and *Pasteurellaceae*, and dominant bacterial families in skin communities comprised of *Enterobacteriaceae*, *Corynebacteriaceae*, and *Staphylococcaceae*. These findings support previously established characterizations of the gut, oral and skin microbiomes.

EXAMPLE 2

Gut and Skin Bacterial Community Diversity is Shaped by BMI

[00129] The inventors clustered samples into four BMI categories; underweight (BMI 15-18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI 30-45). Sample distribution by site and BMI is illustrated in Table 1.

Table 1: AGP Sample Distribution by Body Site and BMI

	Fecal	Oral	Skin
Underweight	1,359	88	80

(BMI 15-18.5)	(9.5%)	(8.2%)	(8.1%)
Normal weight	8,092	621	580
(BMI 18.5-25)	(56.7%)	(58.1%)	(58.5%)
Overweight	3,425	124	81
(BMI 25-30)	(24.0%)	(22.0%)	(25.2%)
Obese	1,408	124	81
(BMI 30-45)	(9.9%)	(11.6%)	(8.2%)

[00130] A large majority of AGP samples were from the gut (14,284/16,063), yet oral and skin datasets were much larger than in most previously published microbiome research endeavors. Additionally, over half of samples in all body sites represented individuals with normal BMI, roughly one quarter were overweight and underweight and obese individuals accounted for about one tenth of samples respectively. BMI distribution is similar between fecal, oral and skin samples.

[00131] The inventors compared community diversity between BMI categories using the Shannon diversity index, which accounts for both species richness and evenness. Shannon diversity of gut microbial communities was significantly different between overweight/obese, normal and underweight individuals, consistent with previous reports of the gut microbiome and BMI (**Fig. 3A**). There were no significant differences in bacterial community diversity in the oral microbiome samples. Interestingly, skin microbiome communities were significantly different between overweight/obese individuals and underweights individuals ($p=0.02$, **Fig. 3B**), as well as between normal weight individuals and underweight individuals ($p=0.02$, **Fig. 3C**). There was no significance observed between normal and overweight/obese individuals on skin communities.

EXAMPLE 3

BMI Shapes the Skin Microbiome

[00132] Following the above-mentioned indication that community diversity is significantly altered based on BMI category, the inventors further explored the skin microbiome and its relationship to BMI. Significant partitioning was observed between BMI categories using PERMANOVA ($p=0.001$, **Fig. 4**). The inventors compared Bray-Curtis distances between all Obese vs. Normal and Normal vs. Underweight samples, which was highly significant ($p>0.0001$). The inventors then used the LEfSe algorithm to identify taxonomic differences of skin microbial communities associated with BMI categories (**Fig. 5A**). The inventors set the logarithmic LDA score cutoff to 2.0 to identify differentially abundant bacteria by BMI category. LEfSe results indicated ten different microbial genera enriched in underweight individuals, including *Gordonia*, Lupinus, and *Prevotella*. An additional seven genera were enriched in overweight/obese individuals, including *Anaerococcus*, *Finegoldia* and *Peptoniphilus*. Two genera were enriched in normal weight skin; *Alicyclobacilus* and *Gyrocarpus*.

[00133] Given the recently uncovered association between obesity in mice and cutaneous *Corynebacterium* colonization, the inventors plotted taxonomic relative abundance of *Corynbacterium* versus BMI levels (**Fig. 5B**). Corynebacterium taxonomic relative abundance was significantly correlated with BMI ($p=0.0002$), further expanding the connection between this microorganism and obesity.

[00134] While the present invention has been particularly described, persons skilled in the art will appreciate that many variations and modifications can be made. Therefore, the invention is not to be construed as restricted to the particularly described embodiments, and the scope and concept of the invention will be more readily understood by reference to the claims, which follow.

CLAIMS

What is claimed is:

1. A method for determining predisposition to developing a metabolic syndrome or a condition associated therewith in a subject, the method comprising: determining a bacterial diversity in a facial skin of said subject; and comparing said determined bacterial diversity to a control, thereby determining predisposition to developing a metabolic syndrome in the subject.

2. The method of claim 1, wherein said determining comprises determining any one of: abundance of *Corynebacteriaceae* species, ratio of *Corynebacteriaceae* to *Staphylococcaceae*, and both, in a facial skin of said subject.

3. The method of claim 1 or 2, wherein a reduction of at least 5% in bacterial diversity in a facial skin of said subject compared to control is indicative of said subject being at increased risk of developing a metabolic syndrome or a condition associated therewith.

4. The method of claim 2, wherein an abundance of at least 15% of a *Corynebacteriaceae* species in a facial skin of said subject is indicative of said subject being at increased risk of developing a metabolic syndrome or a condition associated therewith.

5. The method of claim 2, wherein a *Corynebacteriaceae* to *Staphylococcaceae* abundance ratio ranging from 3.2:1 to 9:1 in a facial skin of said subject is indicative of said subject being at increased risk of developing a metabolic syndrome or a condition associated therewith.

6. The method of any one of claims 1 to 5, wherein said subject has a body mass index (BMI) value ranging from 19 to 29.

7. The method of any one of claims 1 to 6, wherein said subject has a BMI value ranging from 19 to 26.

8. The method of any one of claims 1 to 7, wherein said facial skin is the skin of any one of: the forehead, the glabella, or a combination thereof.

9. The method of any one of claims 1 to 8, wherein said metabolic syndrome or said condition associated therewith is selected from the group consisting of: obesity, pre-diabetes, diabetes, hyperglycemia, diabetic dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, and insulin-resistance or insulin-resistance related.

10. The method of any one of claims 1 to 9, wherein said determining is determining in a sample derived from said subject.

11. The method of any one of claims 1 to 10, further comprising providing a sample from said subject and performing said determining in said sample.

12. A method for treating or preventing a metabolic syndrome or a condition associated therewith in a subject in need thereof, the method comprising:

a. determining whether said subject is at increased risk of developing a metabolic syndrome or a condition associated therewith, according to the method of any one of claims 1 to 11; and

b. administering to a subject determined as being at an increased risk, a therapeutically effective amount of a pharmaceutical or a nutraceutical composition comprising an agent selected from the group consisting of: an appetite suppressant, a probiotic agent, a prebiotic agent, an anti-inflammatory drug, a topical solution, and any combination thereof,

thereby treating or preventing a metabolic syndrome or a condition associated therewith in a subject.

13. The method of claim 12, further comprising modifying the diet of said subject.

14. The method of claim 13, wherein said modifying is providing any one of: a diet low on calories, a diet low on fat content, a diet low on carbohydrates content, and any combination thereof.

15. The method of claim 13 or 14, wherein said modifying is providing a diet low on calories.

16. The method of any one of claims 13 to 15, wherein said modifying is alternating the timing of food consumption.

17. The method of any one of claims 12 to 16, wherein said preventing comprises any one of: reducing the severity, delaying the onset, reducing the cumulative incidence, and any combination thereof, of said metabolic syndrome or said condition associated therewith.

18. The method of any one of claims 12 to 17, wherein said metabolic syndrome or said condition associated therewith is selected from the group consisting of: obesity, pre-diabetes, diabetes, hyperglycemia, diabetic dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, and insulin-resistance or insulin-resistance related.

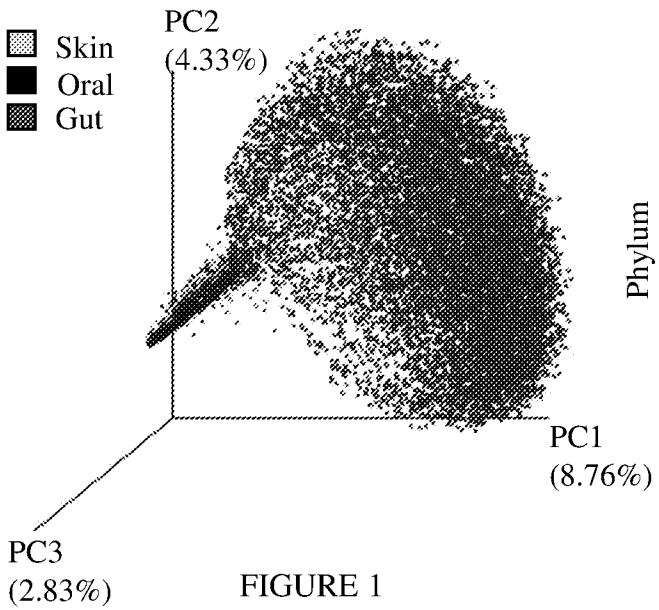

FIGURE 1

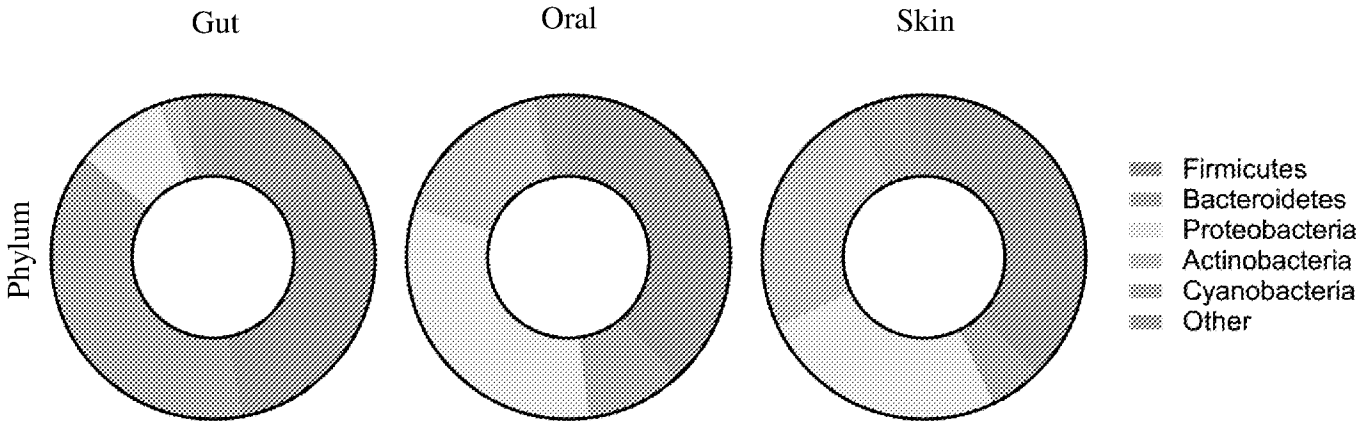

FIGURE 2A

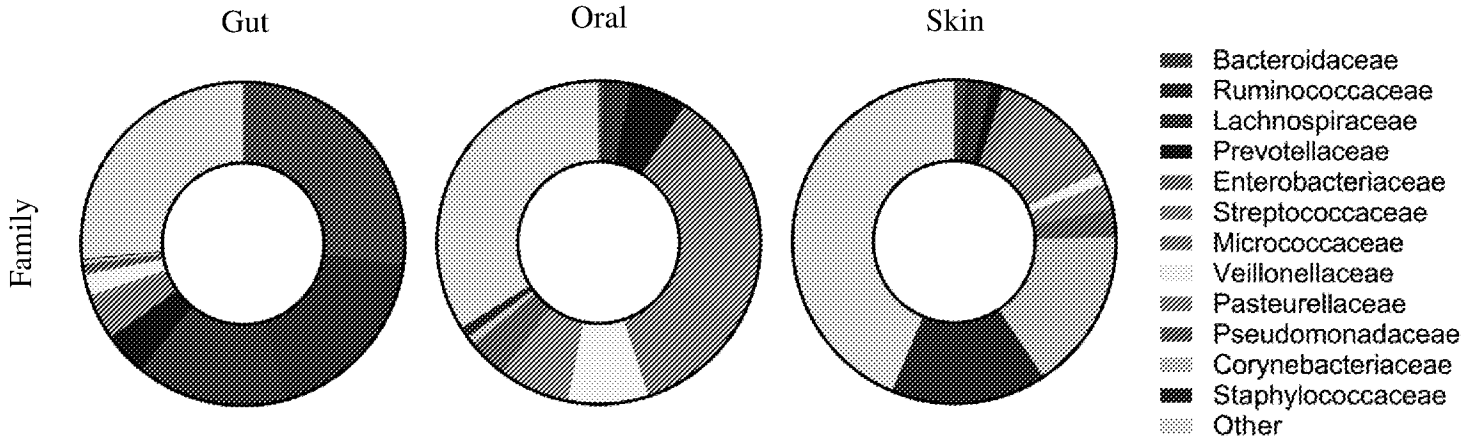

FIGURE 2B

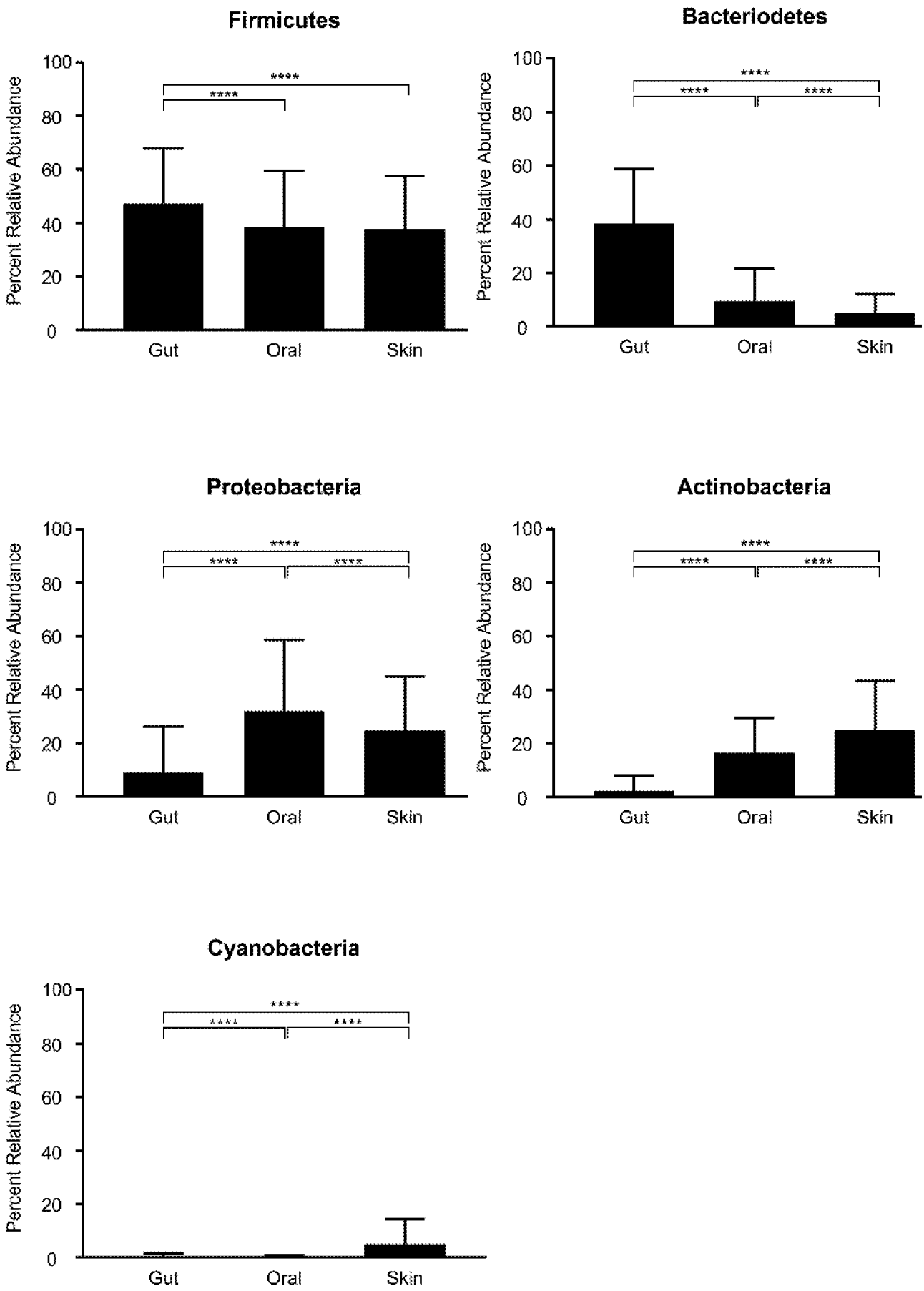
Firmicutes
Bacteriodetes
Proteobacteria
Actinobacteria
Cyanobacteria
Percent Relative Abundance
0
20
40
60
80
100
****
Gut
Oral
Skin

FIGURE 2C

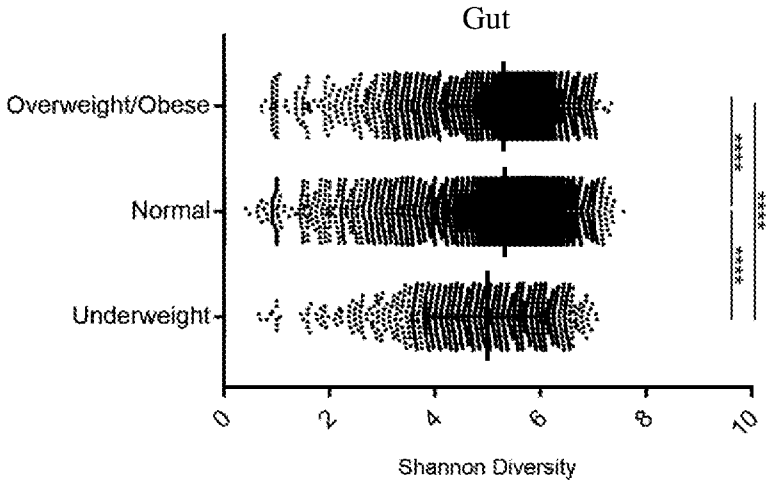

FIGURE 3A

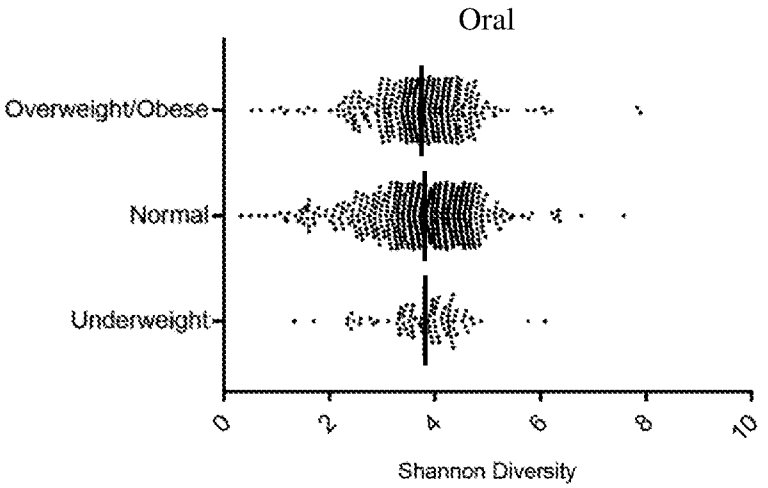

FIGURE 3B

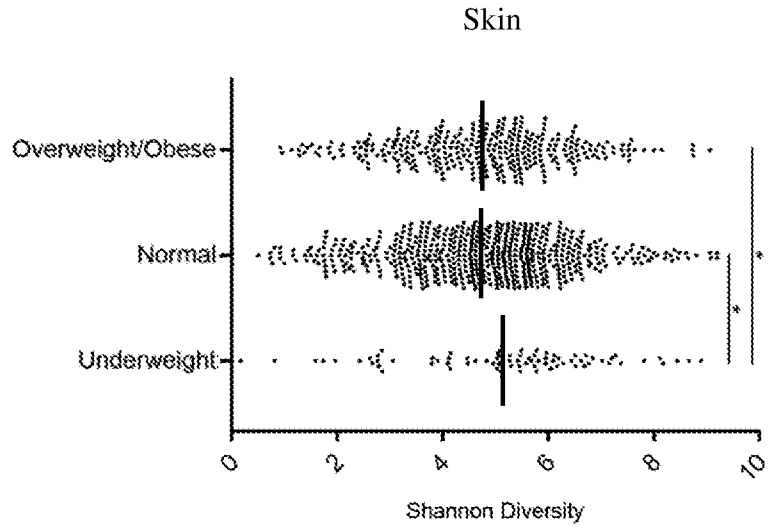

FIGURE 3C

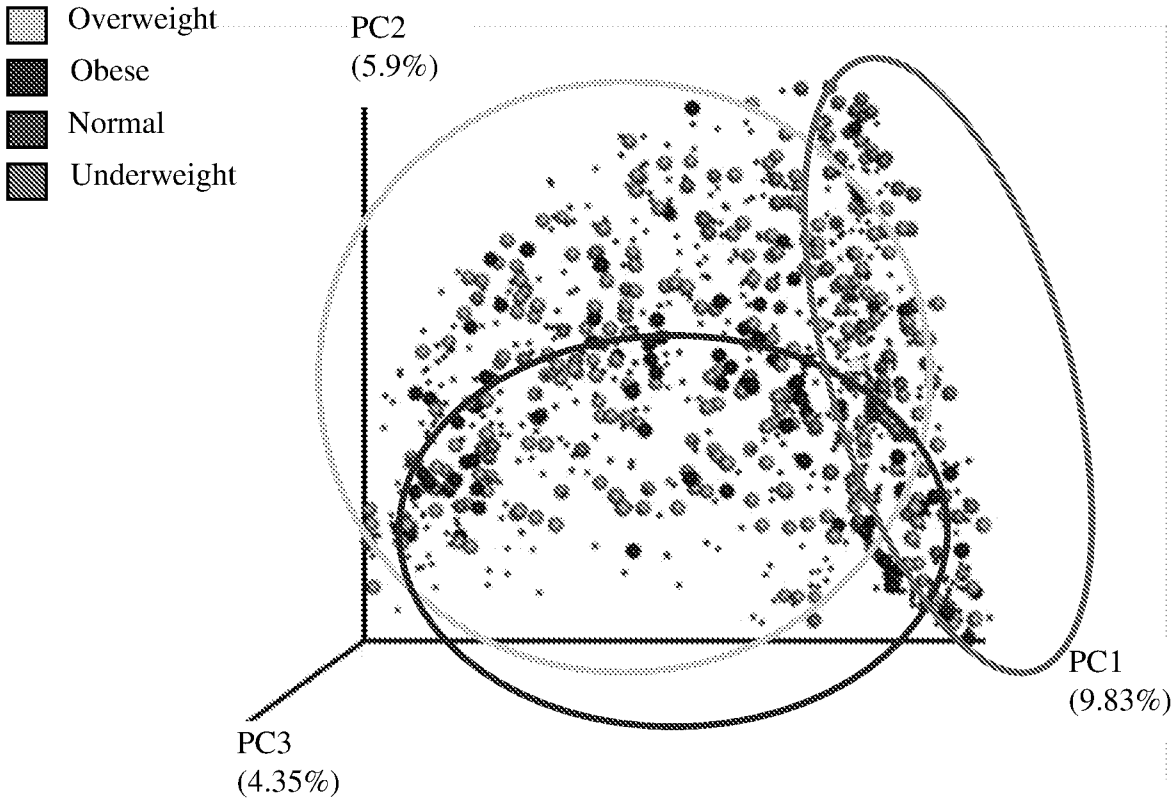

FIGURE 4

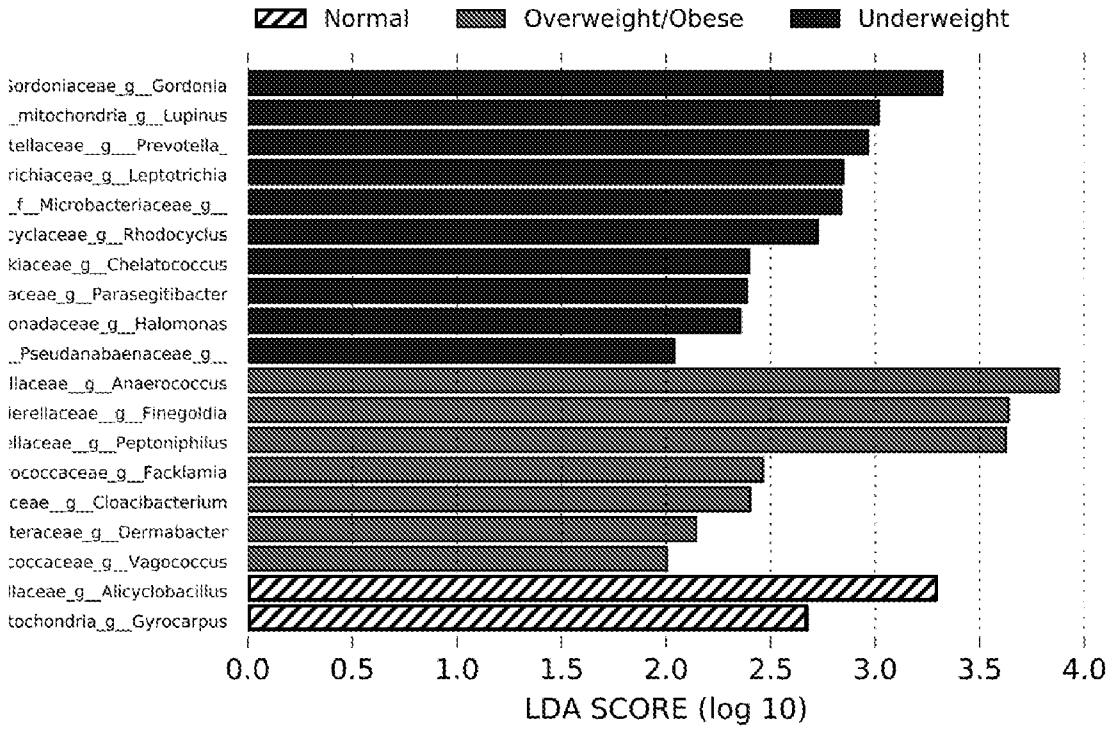

FIGURE 5A

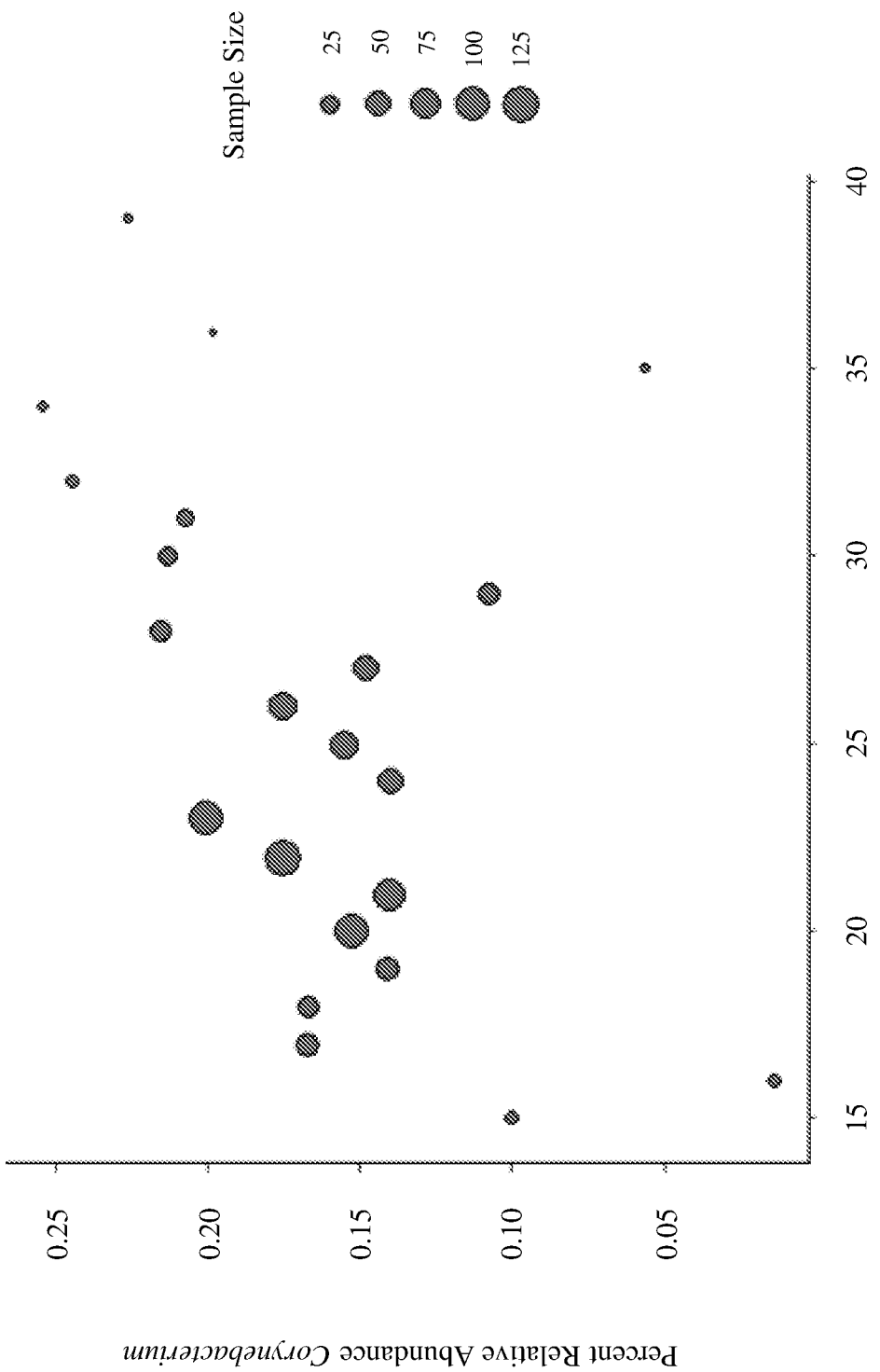
Sample Size
25
50
75
100
125
Percent Relative Abundance *Corynebacterium*
0.25
0.20
0.15
0.10
0.05
15
20
25
30
35
40
BMI

FIGURE 5B

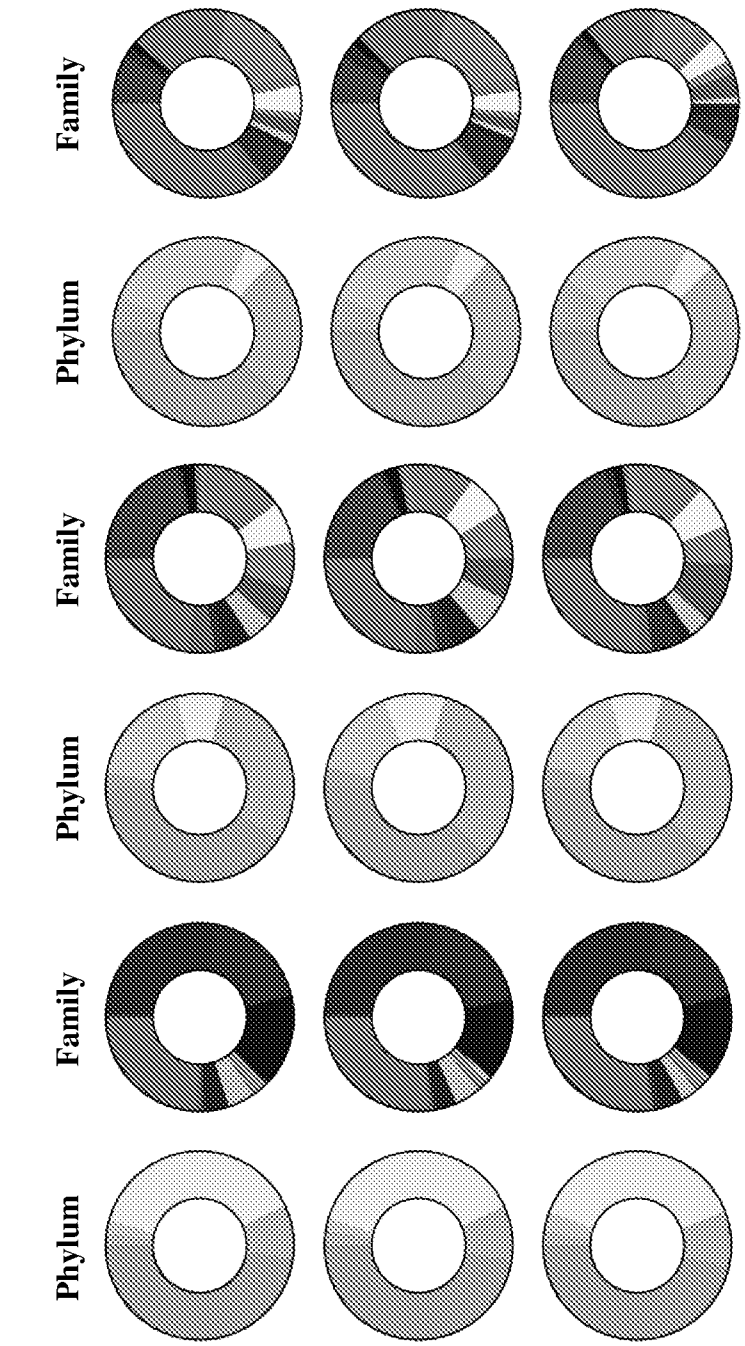

FIGURE 6A

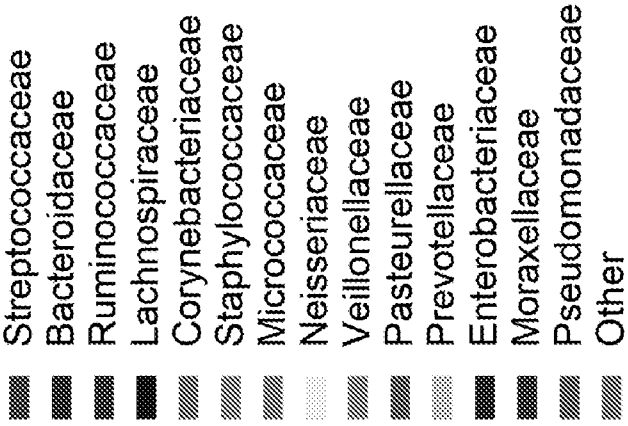

FIGURE 6B

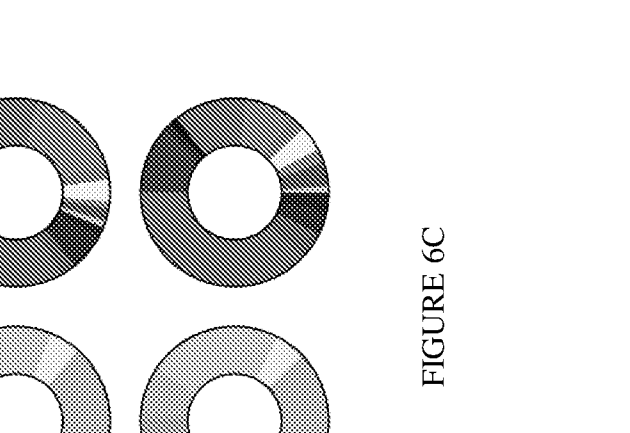

FIGURE 6C

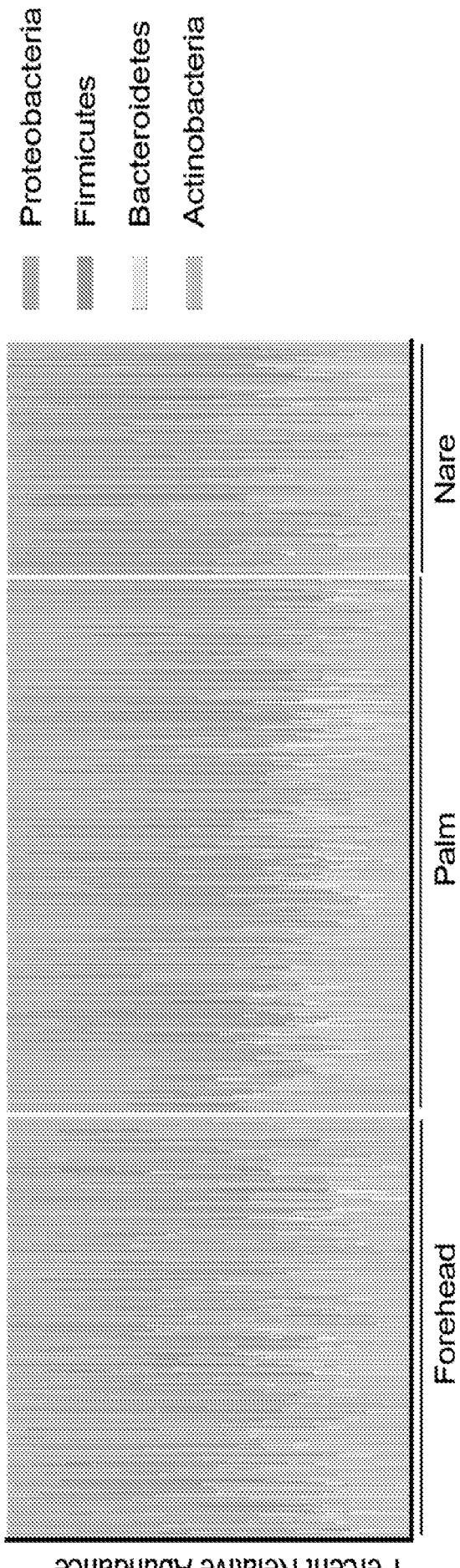

FIGURE 7A

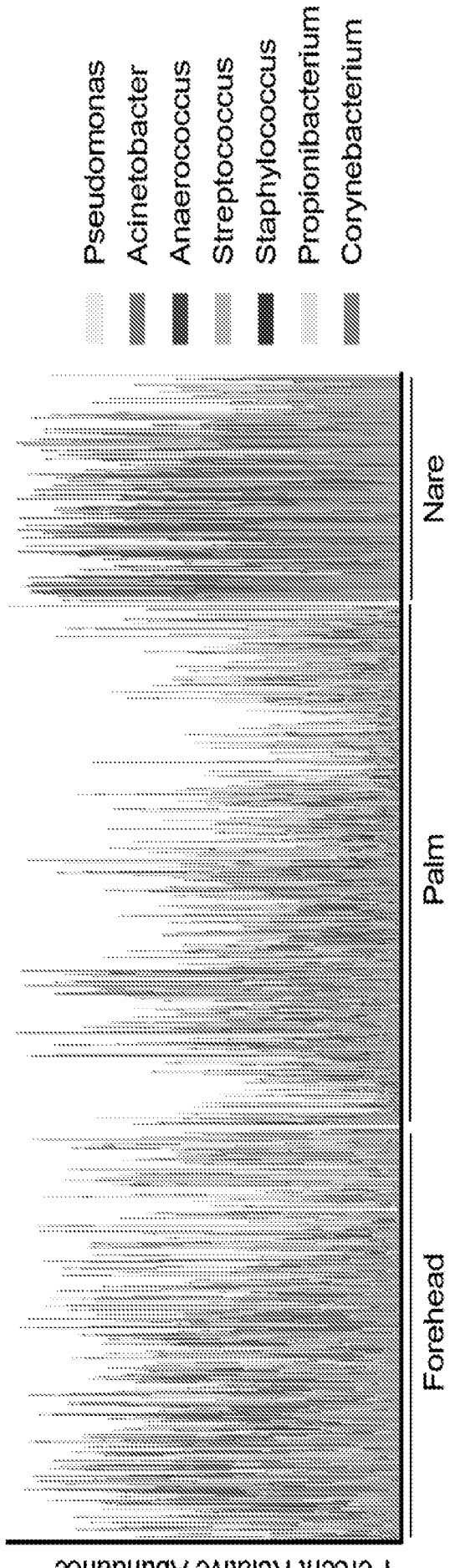

FIGURE 7B

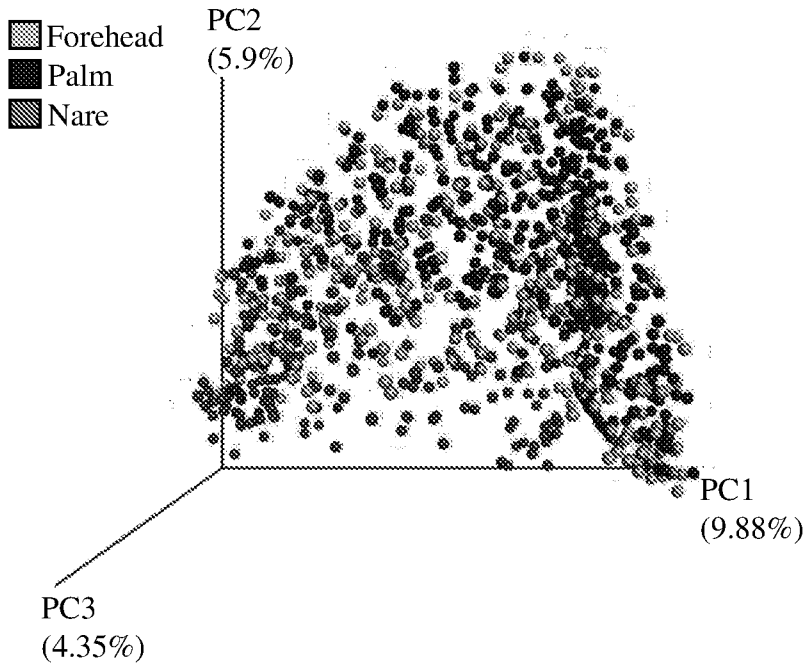

FIGURE 7C

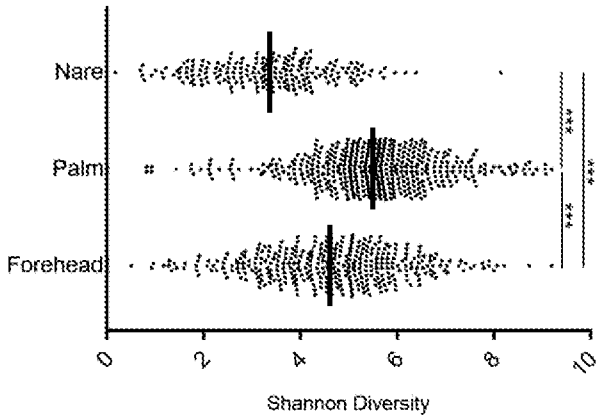

FIGURE 7D

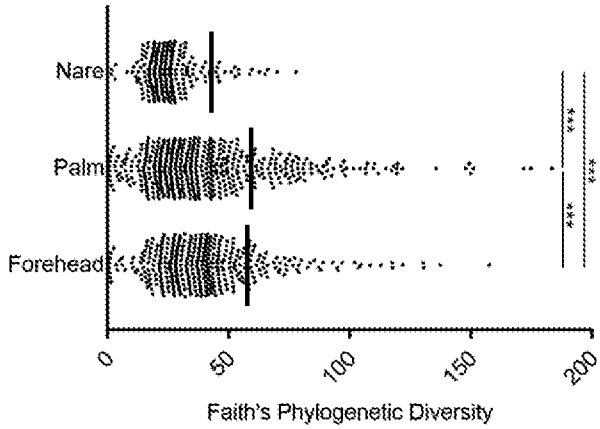

FIGURE 7E

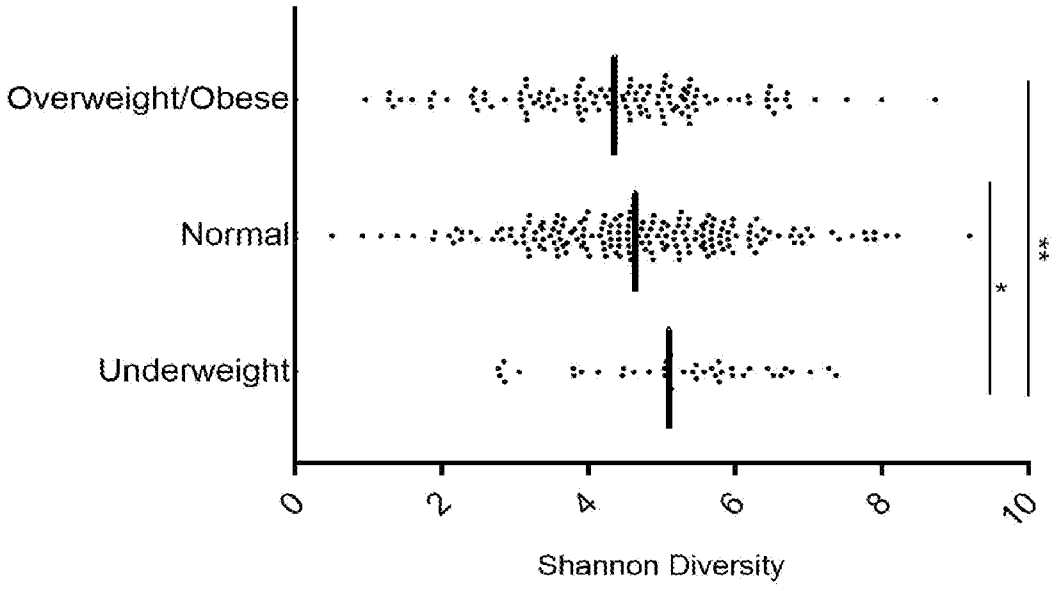

FIGURE 8A

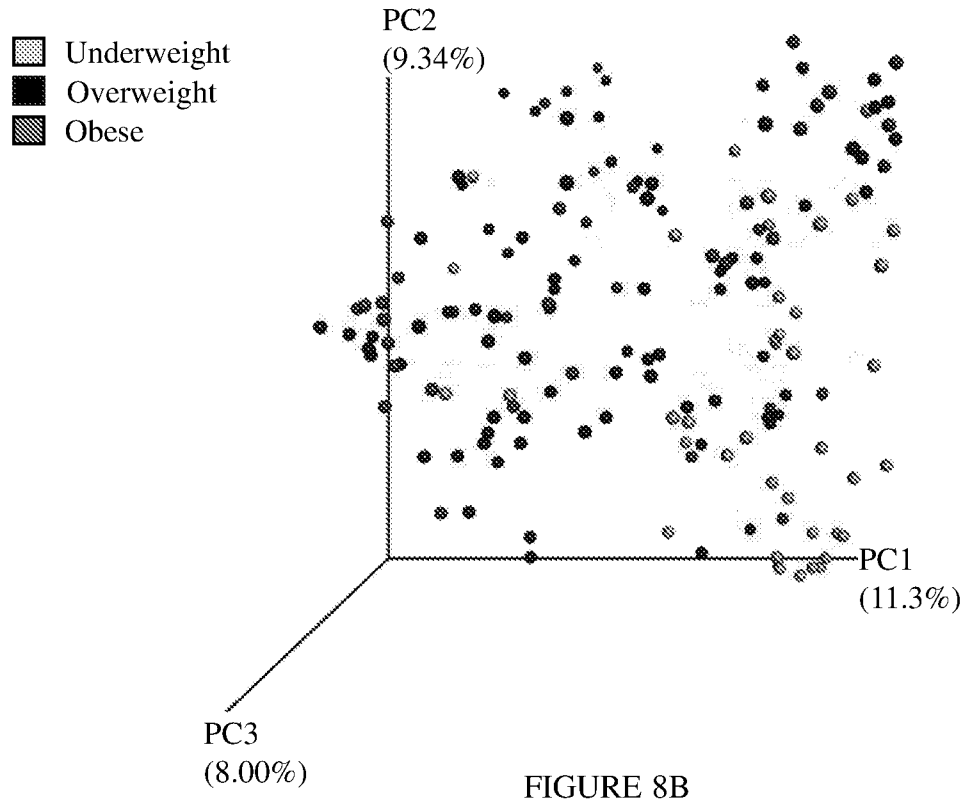

FIGURE 8B

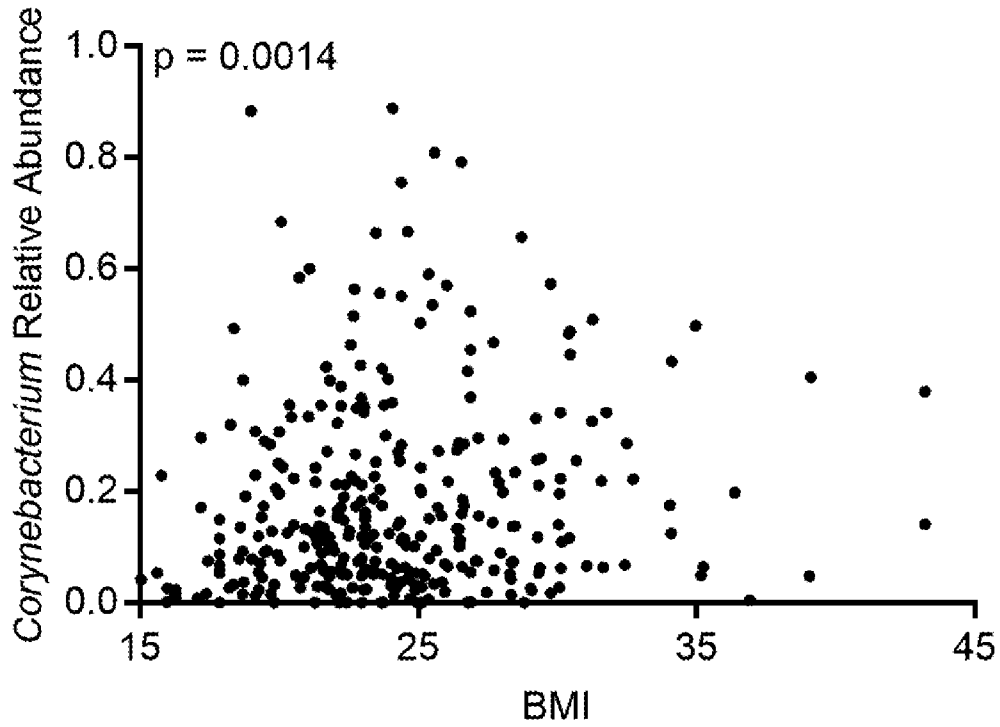

FIGURE 8C

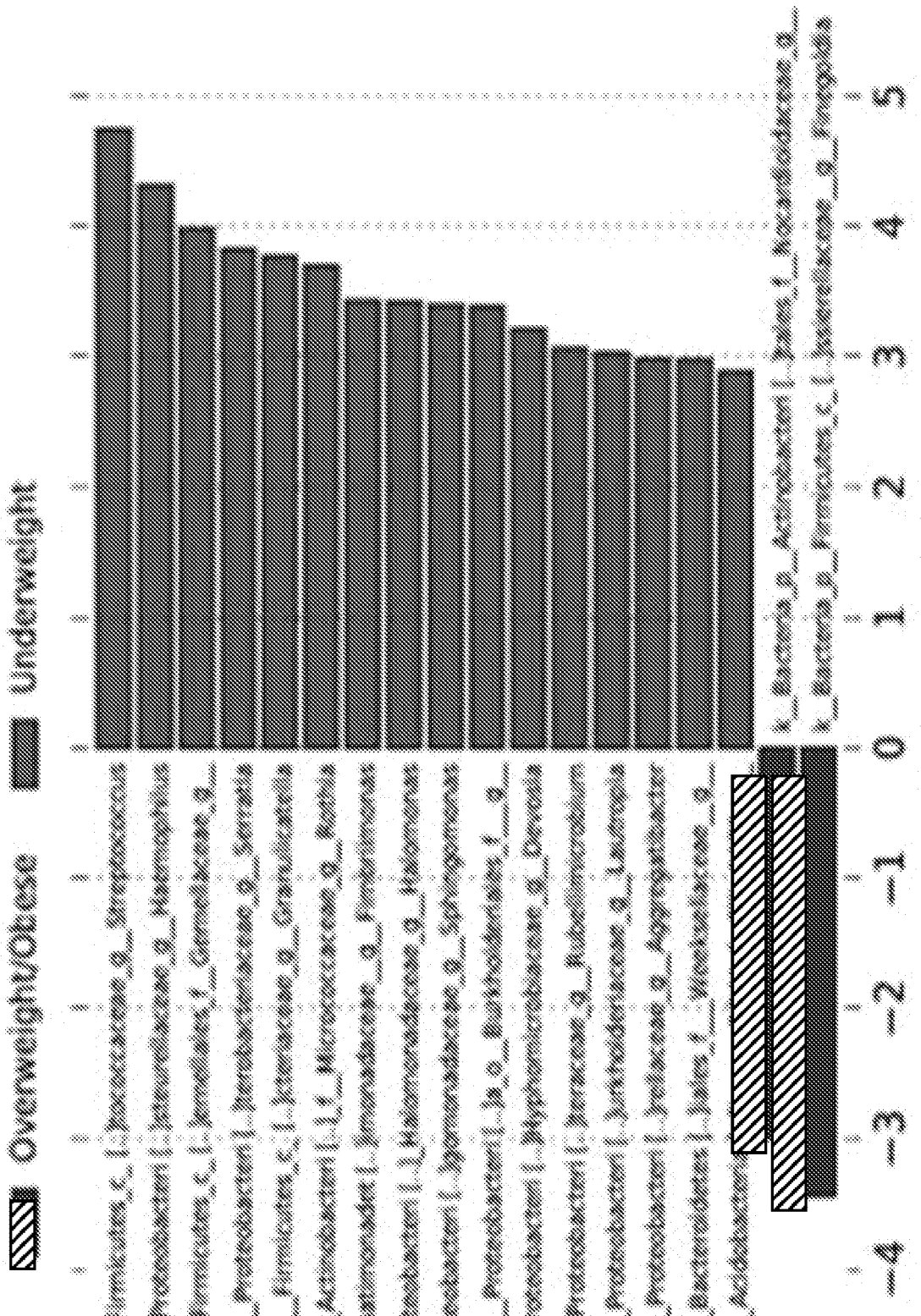
Overweight/Obese
Underweight
k__Bacteria.p__Firmicutes.c__[.Thermoanaerobacter.o__Thermoanaerobacterales]
k__Bacteria.p__Proteobacteria.c__[.Thermodesulfovibrionia.o__Nitrospirales]
k__Bacteria.p__Firmicutes.c__[.Lachnospiraceae.g__Coprococcus]
k__Bacteria.p__Proteobacteria.c__[.Enterobacteriaceae.g__Serratia]
k__Bacteria.p__Firmicutes.c__[.Veillonellaceae.g__Granulicatella]
k__Bacteria.p__Actinobacteria.c__[.Micrococcaceae.g__Rothia]
k__Bacteria.p__Armatimonadetes.c__[.Armatimonadaceae.g__Armatimonas]
k__Bacteria.p__Proteobacteria.c__[.Helicobacteraceae.g__Helicobacter]
k__Bacteria.p__Proteobacteria.c__[.Spirochaetaceae.g__Spirochaeta]
k__Bacteria.p__Proteobacteria.c__[.Sphingomonadaceae.g__Sphingomonas]
k__Bacteria.p__Proteobacteria.c__[.Rhodocyclaceae.g__Azoarcus]
k__Bacteria.p__Proteobacteria.c__[.Enterobacteriaceae.g__Providencia]
k__Bacteria.p__Proteobacteria.c__[.Enterobacteriaceae.g__Escherichia.s__coli]
k__Bacteria.p__Actinobacteria.c__[.Intrasporangiaceae.g__Janibacter]
k__Bacteria.p__Proteobacteria.c__[.Enterobacteriaceae.g__Klebsiella]
k__Bacteria.p__Proteobacteria.c__[.Enterobacteriaceae.g__Enterobacter]
k__Bacteria.p__Actinobacteria.c__[.Intrasporangiaceae.g__Janibacter.s__terrae]
k__Bacteria.p__Firmicutes.c__[.Veillonellaceae.g__Megasphaera]
k__Bacteria.p__Actinobacteria.c__[.Intrasporangiaceae.g__Terrabacter]
−4
−3
−2
−1
0
1
2
3
4
5
LDA SCORE (log 10)

FIGURE 8D

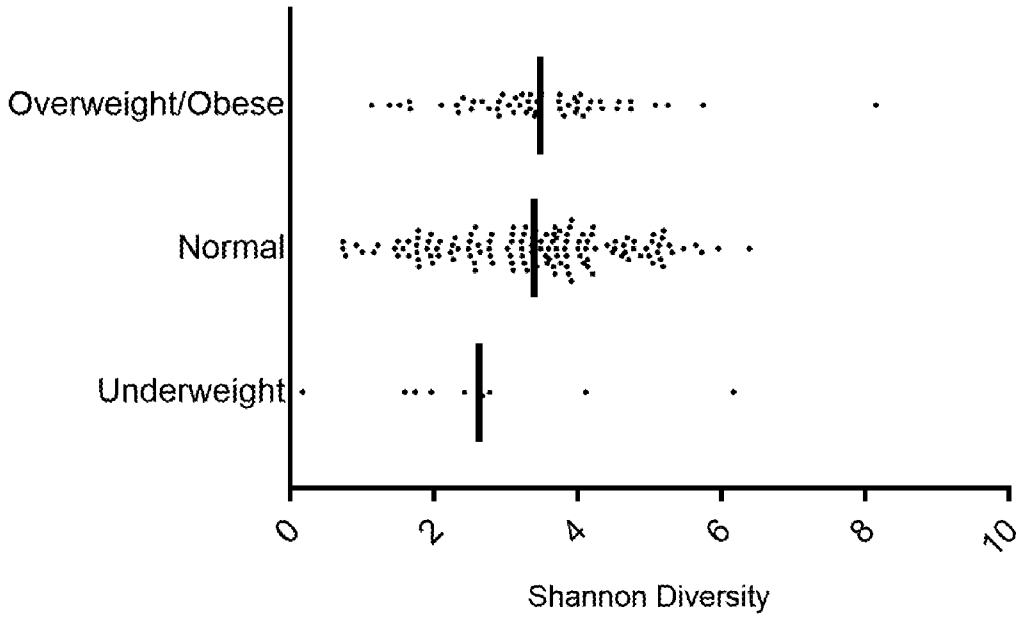

FIGURE 9A

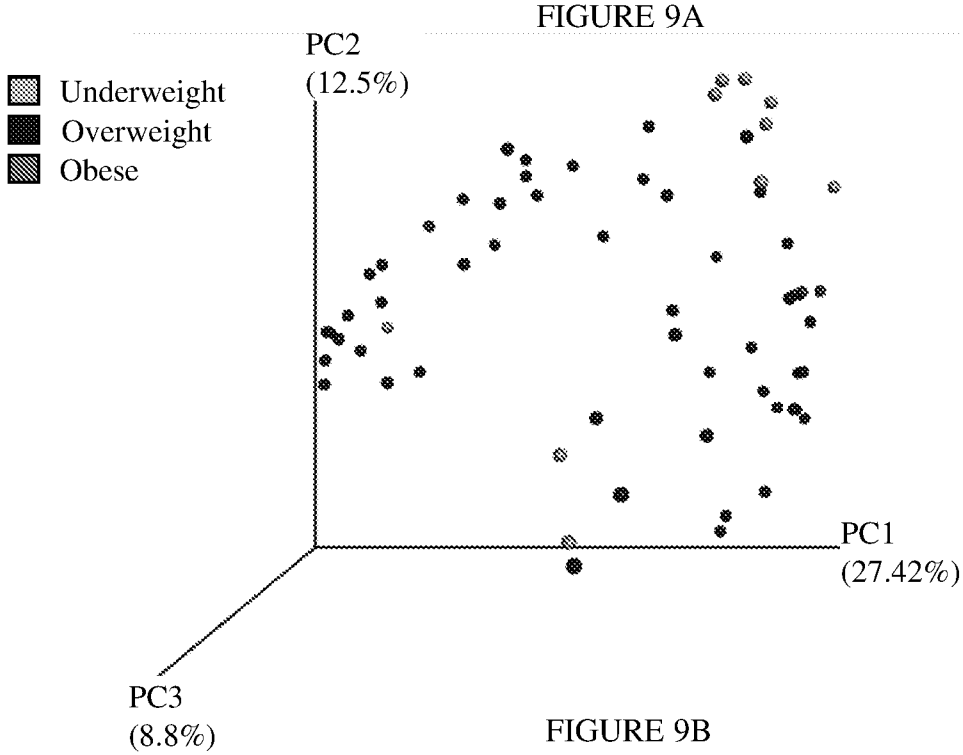

FIGURE 9B

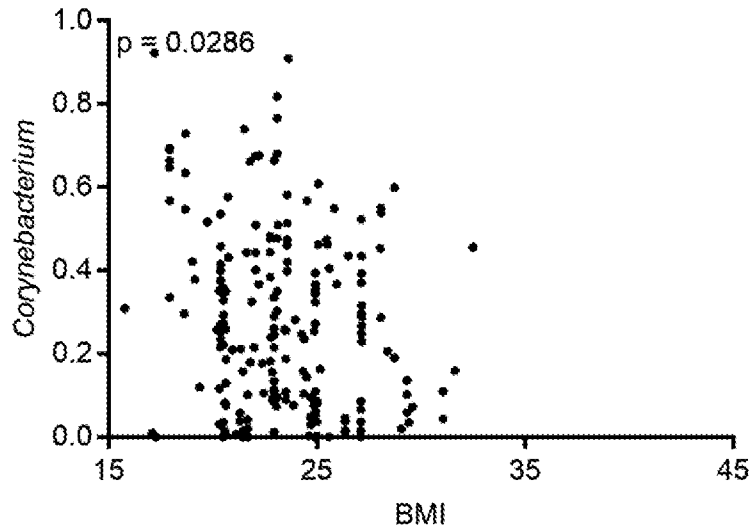

FIGURE 9C

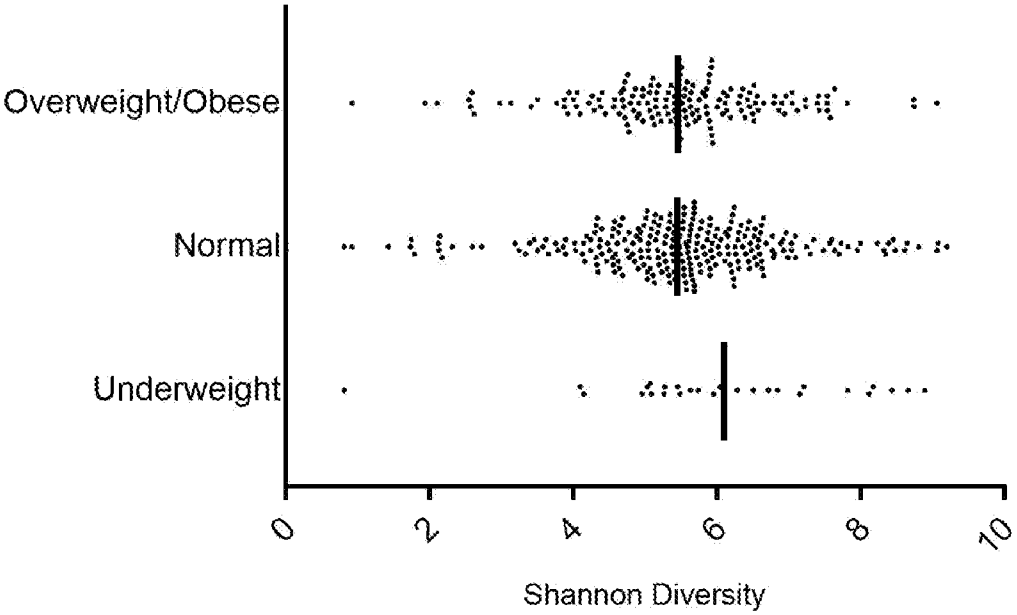

FIGURE 10A

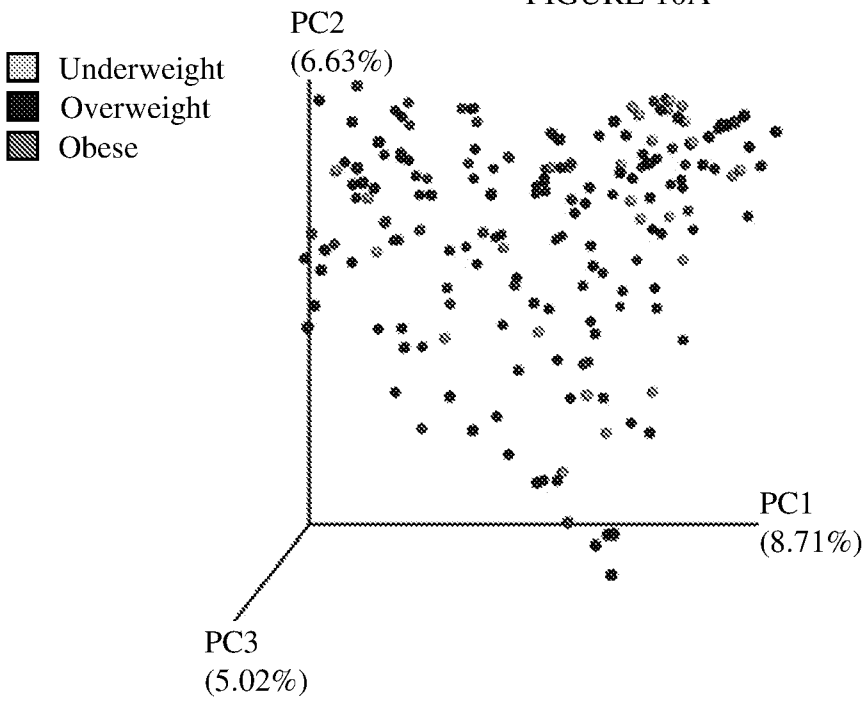

FIGURE 10B

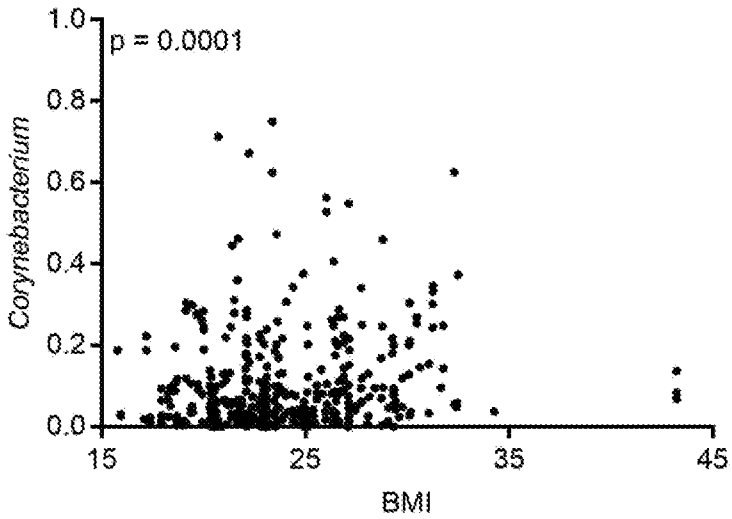

FIGURE 10C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2020/050955

A. CLASSIFICATION OF SUBJECT MATTER
IPC (20200101) C12Q 1/6888, C12N 1/20, C12Q 1/689, A61P 3/10, C12R 1/01
CPC (20180501) C12Q 1/6888, C12N 1/20, C12Q 1/689, A61P 3/10, C12R 1/01
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (20200101) C12Q 1/6888, C12N 1/20, C12Q 1/689, A61P 3/10, C12R 1/01
CPC (20180501) C12Q 1/6888, G01N 2800/04, C12N 1/20, C12Q 1/689, A61P 3/10, C12R 1/01, C12Q 1/689

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Databases consulted: Google Patents, Google Scholar, Orbit

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016271189 A1 Whole Biome, Inc. 22 Sep 2016 (2016/09/22) the whole document	1,9-13,17,18
Y	the whole document	2-8,14-16
Y	KWASZEWSKA, Anna; SOBI?-GLINKOWSKA, Maria; SZEWCZYK, Eligia M. Cohabitation—relationships of corynebacteria and staphylococci on human skin. Folia microbiologica, 2014, 59.6: 495-502. KWASZEWSKA, Anna; SOBI?-GLINKOWSKA, Maria; SZEWCZYK, Eligia M. 01 Jun 2014 (2014/06/01) the whole document	2-8,14-16
P,X	BRANDWEIN, Michael, et al. Beyond the gut: Skin microbiome compositional changes are associated with BMI. Human Microbiome Journal, 2019, 13: 100063. BRANDWEIN, Michael, et al. 16 Sep 2019 (2019/09/16) the whole document	1-18

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 Dec 2020	27 Dec 2020
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Email address: pctoffice@justice.gov.il	Authorized officer ORENSHTEIN-VILENSKY Liya Telephone No. 972-73-3927241

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2020/050955

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015259728 A1 WHOLE BIOME, INC. 17 Sep 2015 (2015/09/17) the whole document	1-18
A	US 2017020932 A1 Whole Biome Inc. 26 Jan 2017 (2017/01/26) the whole document	1-18
A	US 2017151290 A1 New York University 01 Jun 2017 (2017/06/01) the whole document	1-18
A	US 2019050534 A1 uBiome, Inc. 14 Feb 2019 (2019/02/14) the whole document	1-18

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 2015259728 A1	17 Sep 2015	US 2015259728 A1	17 Sep 2015
		US 10633714 B2	28 Apr 2020
		CN 105407728 A	16 Mar 2016
		GB 201602937 D0	06 Apr 2016
		GB 2535034 A	10 Aug 2016
		JP 2016525355 A	25 Aug 2016
		JP 6637885 B2	29 Jan 2020
		JP 2020072680 A	14 May 2020
		US 2020277658 A1	03 Sep 2020
		WO 2015013214 A2	29 Jan 2015
		WO 2015013214 A3	26 Mar 2015
US 2017020932 A1	26 Jan 2017	US 2017020932 A1	26 Jan 2017
		CA 2964480 A1	06 May 2016
		CN 108064132 A	22 May 2018
		EP 3212001 A1	06 Sep 2017
		EP 3212001 A4	25 Apr 2018
		GB 201707848 D0	28 Jun 2017
		GB 2551642 A	27 Dec 2017
		GB 2551642 B	23 Sep 2020
		JP 2017535597 A	30 Nov 2017
		SG 10201903823Q A	30 May 2019
		SG 11201703395P A	30 May 2017
		US 2016228476 A1	11 Aug 2016
		US 9486487 B2	08 Nov 2016
		US 2017027996 A1	02 Feb 2017
		US 10668116 B2	02 Jun 2020
		US 2019030095 A1	31 Jan 2019
		US 10675312 B2	09 Jun 2020
		US 2019070228 A1	07 Mar 2019

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 10842830 B2	24 Nov 2020
		US 2019030096 A1	31 Jan 2019
		US 10842831 B2	24 Nov 2020
		US 2019070227 A1	07 Mar 2019
		US 2020261517 A1	20 Aug 2020
		US 2020261518 A1	20 Aug 2020
		US 2020345796 A1	05 Nov 2020
		WO 2016070151 A1	06 May 2016
		WO 2016070151 A8	30 Jun 2016
		WO 2016070151 A9	29 Jun 2017
US 2016271189 A1	22 Sep 2016	US 2016271189 A1	22 Sep 2016
		CA 2976956 A1	22 Sep 2016
		EP 3270938 A1	24 Jan 2018
		EP 3270938 A4	19 Dec 2018
		GB 201716169 D0	15 Nov 2017
		GB 2553701 A	14 Mar 2018
		SG 11201707657U A	30 Oct 2017
		WO 2016149687 A1	22 Sep 2016
US 2017151290 A1	01 Jun 2017	US 2017151290 A1	01 Jun 2017
		US 2012058094 A1	08 Mar 2012
		US 9386793 B2	12 Jul 2016
		WO 2012024638 A2	23 Feb 2012
		WO 2012024638 A3	03 May 2012
US 2019050534 A1	14 Feb 2019	US 2019050534 A1	14 Feb 2019
		AU 2015335907 A1	13 Apr 2017
		AU 2016248050 A1	09 Nov 2017
		AU 2016248063 A1	09 Nov 2017
		AU 2016248115 A1	09 Nov 2017

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)		Publication Date
		AU 2016248120	A1	09 Nov 2017
		AU 2016248120	A8	06 Dec 2018
		AU 2016250096	A1	09 Nov 2017
		AU 2016250096	A8	06 Dec 2018
		AU 2016250100	A1	09 Nov 2017
		AU 2016250102	A1	09 Nov 2017
		AU 2016250104	A1	09 Nov 2017
		AU 2016250152	A1	09 Nov 2017
		AU 2016250159	A1	09 Nov 2017
		AU 2016321349	A1	26 Apr 2018
		AU 2016366656	A1	28 Jun 2018
		AU 2017229488	A1	20 Sep 2018
		AU 2017257785	A1	08 Nov 2018
		AU 2017295861	A1	24 Jan 2019
		AU 2017326564	A1	28 Mar 2019
		AU 2018288849	A1	06 Feb 2020
		AU 2018302175	A1	13 Feb 2020
		AU 2018318756	A1	05 Mar 2020
		AU 2018327227	A1	16 Apr 2020
		AU 2018329948	A1	16 Apr 2020
		AU 2018334252	A1	23 Apr 2020
		AU 2018359900	A1	21 May 2020
		AU 2019228079	A1	18 Jun 2020
		BR 112019000709	A2	14 May 2019
		BR 112019005025	A2	18 Jun 2019
		CA 2962466	A1	28 Apr 2016
		CA 3005987	A1	16 Mar 2017
		CA 3007503	A1	15 Jun 2017
		CA 3016891	A1	14 Sep 2017
		CA 3022294	A1	02 Nov 2017
		CA 3030792	A1	18 Jan 2018

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)		Publication Date
		CA 3036994	A1	22 Mar 2018
		CN 107075588	A	18 Aug 2017
		CN 107708714	A	16 Feb 2018
		CN 107708715	A	16 Feb 2018
		CN 107708716	A	16 Feb 2018
		CN 107709576	A	16 Feb 2018
		CN 107710205	A	16 Feb 2018
		CN 107835692	A	23 Mar 2018
		CN 107835859	A	23 Mar 2018
		CN 107849609	A	27 Mar 2018
		CN 107849616	A	27 Mar 2018
		CN 108283012	A	13 Jul 2018
		CN 108350510	A	31 Jul 2018
		CN 108472506	A	31 Aug 2018
		CN 108699586	A	23 Oct 2018
		CN 109152803	A	04 Jan 2019
		CN 109475305	A	15 Mar 2019
		CN 109715059	A	03 May 2019
		CN 111164224	A	15 May 2020
		CN 111164706	A	15 May 2020
		CN 111201323	A	26 May 2020
		CN 111247598	A	05 Jun 2020
		CN 111315884	A	19 Jun 2020
		CN 111315898	A	19 Jun 2020
		CN 111315899	A	19 Jun 2020
		CN 111465704	A	28 Jul 2020
		CO 2019001319	A2	19 Feb 2019
		CO 2019003713	A2	30 Apr 2019
		EA 201990294	A1	30 Aug 2019
		EA 201990520	A1	30 Sep 2019
		EP 3209803	A1	30 Aug 2017

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		EP 3209803 A4	13 Jun 2018
		EP 3283084 A1	21 Feb 2018
		EP 3283084 A4	19 Dec 2018
		EP 3283085 A1	21 Feb 2018
		EP 3283085 A4	10 Apr 2019
		EP 3283086 A1	21 Feb 2018
		EP 3283086 A4	24 Apr 2019
		EP 3283087 A1	21 Feb 2018
		EP 3283087 A4	13 Mar 2019
		EP 3283648 A1	21 Feb 2018
		EP 3283648 A4	20 Mar 2019
		EP 3283649 A1	21 Feb 2018
		EP 3283649 A4	20 Mar 2019
		EP 3283650 A1	21 Feb 2018
		EP 3283650 A4	10 Apr 2019
		EP 3283651 A1	21 Feb 2018
		EP 3283651 A4	05 Dec 2018
		EP 3283652 A1	21 Feb 2018
		EP 3283652 A4	05 Dec 2018
		EP 3283884 A1	21 Feb 2018
		EP 3283884 A4	20 Mar 2019
		EP 3347495 A1	18 Jul 2018
		EP 3347495 A4	21 Aug 2019
		EP 3386592 A1	17 Oct 2018
		EP 3386592 A4	22 May 2019
		EP 3426794 A1	16 Jan 2019
		EP 3426794 A4	13 Nov 2019
		EP 3448399 A1	06 Mar 2019
		EP 3448399 A4	13 May 2020
		EP 3484348 A1	22 May 2019
		EP 3512421 A1	24 Jul 2019

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		EP 3642357 A1	29 Apr 2020
		EP 3655971 A1	27 May 2020
		EP 3669377 A1	24 Jun 2020
		EP 3679135 A1	15 Jul 2020
		EP 3679162 A1	15 Jul 2020
		EP 3682036 A1	22 Jul 2020
		EP 3687375 A1	05 Aug 2020
		EP 3707280 A1	16 Sep 2020
		JP 2019521706 A	08 Aug 2019
		JP 2019528729 A	17 Oct 2019
		JP 2020528285 A	24 Sep 2020
		JP 2020528740 A	01 Oct 2020
		JP 2020530931 A	29 Oct 2020
		JP 2020532995 A	19 Nov 2020
		JP 2020533998 A	26 Nov 2020
		JP 2020535121 A	03 Dec 2020
		KR 20190033561 A	29 Mar 2019
		KR 20190055127 A	22 May 2019
		KR 20200045557 A	04 May 2020
		KR 20200047686 A	07 May 2020
		KR 20200049861 A	08 May 2020
		KR 20200051587 A	13 May 2020
		KR 20200054203 A	19 May 2020
		KR 20200059208 A	28 May 2020
		KR 20200096230 A	11 Aug 2020
		KR 20200128558 A	13 Nov 2020
		SG 11201900253T A	27 Feb 2019
		SG 11201901726Q A	28 Mar 2019
		SG 11201912798V A	30 Jan 2020
		SG 11202000340S A	27 Feb 2020
		SG 11202001335U A	30 Mar 2020

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		SG 11202001850Y A	30 Mar 2020
		SG 11202001853X A	30 Mar 2020
		SG 11202001860Q A	30 Mar 2020
		SG 11202002500S A	29 Apr 2020
		SG 11202002507U A	29 Apr 2020
		US 2016110515 A1	21 Apr 2016
		US 9703929 B2	11 Jul 2017
		US 2016232312 A1	11 Aug 2016
		US 9710606 B2	18 Jul 2017
		US 2016232280 A1	11 Aug 2016
		US 9754080 B2	05 Sep 2017
		US 2016230217 A1	11 Aug 2016
		US 9758839 B2	12 Sep 2017
		US 2016232313 A1	11 Aug 2016
		US 9760676 B2	12 Sep 2017
		US 2016224748 A1	04 Aug 2016
		US 10073952 B2	11 Sep 2018
		US 2017228514 A1	10 Aug 2017
		US 10169541 B2	01 Jan 2019
		US 2017270269 A1	21 Sep 2017
		US 10242160 B2	26 Mar 2019
		US 2017175172 A1	22 Jun 2017
		US 10246753 B2	02 Apr 2019
		US 2016224749 A1	04 Aug 2016
		US 10265009 B2	23 Apr 2019
		US 2017277843 A1	28 Sep 2017
		US 10268803 B2	23 Apr 2019
		US 2017277846 A1	28 Sep 2017
		US 10282520 B2	07 May 2019
		US 2017286619 A1	05 Oct 2017
		US 10289805 B2	14 May 2019

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 2017316169 A1	02 Nov 2017
		US 10290374 B2	14 May 2019
		US 2017308659 A1	26 Oct 2017
		US 10290375 B2	14 May 2019
		US 2017308660 A1	26 Oct 2017
		US 10290376 B2	14 May 2019
		US 2017316167 A1	02 Nov 2017
		US 10297351 B2	21 May 2019
		US 2016321416 A1	03 Nov 2016
		US 10311973 B2	04 Jun 2019
		US 2017277845 A1	28 Sep 2017
		US 10325071 B2	18 Jun 2019
		US 2017316166 A1	02 Nov 2017
		US 10325683 B2	18 Jun 2019
		US 2017308658 A1	26 Oct 2017
		US 10325684 B2	18 Jun 2019
		US 2018122510 A1	03 May 2018
		US 10325685 B2	18 Jun 2019
		US 2018070825 A1	15 Mar 2018
		US 10327641 B2	25 Jun 2019
		US 2018070827 A1	15 Mar 2018
		US 10327642 B2	25 Jun 2019
		US 2017286620 A1	05 Oct 2017
		US 10331857 B2	25 Jun 2019
		US 2017316168 A1	02 Nov 2017
		US 10332635 B2	25 Jun 2019
		US 2017308657 A1	26 Oct 2017
		US 10340045 B2	02 Jul 2019
		US 2017270270 A1	21 Sep 2017
		US 10346588 B2	09 Jul 2019
		US 2017270271 A1	21 Sep 2017

Patent document cited search report	Publication date	Patent family member(s)		Publication Date
		US 10346589	B2	09 Jul 2019
		US 2016314281	A1	27 Oct 2016
		US 10346592	B2	09 Jul 2019
		US 2017316152	A1	02 Nov 2017
		US 10347362	B2	09 Jul 2019
		US 2018090552	A1	29 Mar 2018
		US 10347366	B2	09 Jul 2019
		US 2018137930	A1	17 May 2018
		US 10347367	B2	09 Jul 2019
		US 2018137931	A1	17 May 2018
		US 10347368	B2	09 Jul 2019
		US 2018122514	A1	03 May 2018
		US 10347379	B2	09 Jul 2019
		US 2018122513	A1	03 May 2018
		US 10354756	B2	16 Jul 2019
		US 2018122515	A1	03 May 2018
		US 10354757	B2	16 Jul 2019
		US 2016228003	A1	11 Aug 2016
		US 10357157	B2	23 Jul 2019
		US 2017298418	A1	19 Oct 2017
		US 10358682	B2	23 Jul 2019
		US 2017262608	A1	14 Sep 2017
		US 10360346	B2	23 Jul 2019
		US 2017277847	A1	28 Sep 2017
		US 10360347	B2	23 Jul 2019
		US 2017277848	A1	28 Sep 2017
		US 10360348	B2	23 Jul 2019
		US 2018122887	A1	03 May 2018
		US 10366782	B2	30 Jul 2019
		US 2017286612	A1	05 Oct 2017
		US 10366789	B2	30 Jul 2019

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 2018122511 A1	03 May 2018
		US 10366793 B2	30 Jul 2019
		US 2017270272 A1	21 Sep 2017
		US 10380325 B2	13 Aug 2019
		US 2018114592 A1	26 Apr 2018
		US 10381112 B2	13 Aug 2019
		US 2018122512 A1	03 May 2018
		US 10381117 B2	13 Aug 2019
		US 2018070826 A1	15 Mar 2018
		US 10383519 B2	20 Aug 2019
		US 2018102187 A1	12 Apr 2018
		US 10388407 B2	20 Aug 2019
		US 2018286520 A1	04 Oct 2018
		US 10395777 B2	27 Aug 2019
		US 2016259909 A1	08 Sep 2016
		US 10409955 B2	10 Sep 2019
		US 2016232319 A1	11 Aug 2016
		US 10410749 B2	10 Sep 2019
		US 2016342735 A1	24 Nov 2016
		US 10755800 B2	25 Aug 2020
		US 2017024527 A1	26 Jan 2017
		US 10777320 B2	15 Sep 2020
		US 2017367640 A1	28 Dec 2017
		US 10786194 B2	29 Sep 2020
		US 2017367641 A1	28 Dec 2017
		US 10786195 B2	29 Sep 2020
		US 2017369933 A1	28 Dec 2017
		US 10787714 B2	29 Sep 2020
		US 2017308669 A1	26 Oct 2017
		US 10789334 B2	29 Sep 2020
		US 2017316151 A1	02 Nov 2017

Patent document cited search report	Publication date	Patent family member(s)		Publication Date
		US 10790042	B2	29 Sep 2020
		US 2017329896	A1	16 Nov 2017
		US 10790043	B2	29 Sep 2020
		US 2017357762	A1	14 Dec 2017
		US 10790060	B2	29 Sep 2020
		US 2017357763	A1	14 Dec 2017
		US 10790061	B2	29 Sep 2020
		US 2016319358	A1	03 Nov 2016
		US 10793907	B2	06 Oct 2020
		US 2017357767	A1	14 Dec 2017
		US 10795970	B2	06 Oct 2020
		US 2017344719	A1	30 Nov 2017
		US 10795971	B2	06 Oct 2020
		US 2017372027	A1	28 Dec 2017
		US 10795972	B2	06 Oct 2020
		US 2017053061	A1	23 Feb 2017
		US 10796783	B2	06 Oct 2020
		US 2017329895	A1	16 Nov 2017
		US 10796785	B2	06 Oct 2020
		US 2017329897	A1	16 Nov 2017
		US 10796786	B2	06 Oct 2020
		US 2017327864	A1	16 Nov 2017
		US 10796800	B2	06 Oct 2020
		US 2017357768	A1	14 Dec 2017
		US 10803147	B2	13 Oct 2020
		US 2017270268	A1	21 Sep 2017
		US 10803991	B2	13 Oct 2020
		US 2017327863	A1	16 Nov 2017
		US 10803992	B2	13 Oct 2020
		US 2017035346	A1	09 Feb 2017
		US 2017039347	A1	09 Feb 2017

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 2017235902 A1	17 Aug 2017
		US 2017277844 A1	28 Sep 2017
		US 2017329898 A1	16 Nov 2017
		US 2017329923 A1	16 Nov 2017
		US 2018137239 A1	17 May 2018
		US 2018342322 A1	29 Nov 2018
		US 2018362967 A1	20 Dec 2018
		US 2019019575 A1	17 Jan 2019
		US 2019078085 A1	14 Mar 2019
		US 2019080046 A1	14 Mar 2019
		US 2019085396 A1	21 Mar 2019
		US 2019136288 A1	09 May 2019
		US 2020123539 A1	23 Apr 2020
		US 2020202979 A1	25 Jun 2020
		US 2020263171 A1	20 Aug 2020
		US 2020286623 A1	10 Sep 2020
		US 2020303070 A1	24 Sep 2020
		US 2020392481 A1	17 Dec 2020
		WO 2016065075 A1	28 Apr 2016
		WO 2016168316 A1	20 Oct 2016
		WO 2016168336 A1	20 Oct 2016
		WO 2016168344 A1	20 Oct 2016
		WO 2016168344 A8	26 Jul 2018
		WO 2016168350 A1	20 Oct 2016
		WO 2016168352 A1	20 Oct 2016
		WO 2016168354 A1	20 Oct 2016
		WO 2016168355 A1	20 Oct 2016
		WO 2016168359 A1	20 Oct 2016
		WO 2016168359 A8	09 Aug 2018
		WO 2016168364 A1	20 Oct 2016
		WO 2016168370 A1	20 Oct 2016

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050955

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		WO 2017044901 A1	16 Mar 2017
		WO 2017100688 A1	15 Jun 2017
		WO 2017156031 A1	14 Sep 2017
		WO 2017189614 A1	02 Nov 2017
		WO 2018013865 A1	18 Jan 2018
		WO 2018053443 A1	22 Mar 2018
		WO 2018094376 A1	24 May 2018
		WO 2018112419 A1	21 Jun 2018
		WO 2018112437 A1	21 Jun 2018
		WO 2018112459 A1	21 Jun 2018
		WO 2018223146 A1	06 Dec 2018
		WO 2018237092 A1	27 Dec 2018
		WO 2019018580 A1	24 Jan 2019
		WO 2019036176 A1	21 Feb 2019
		WO 2019051130 A1	14 Mar 2019
		WO 2019051319 A1	14 Mar 2019
		WO 2019055874 A1	21 Mar 2019
		WO 2019090353 A1	09 May 2019
		WO 2019169395 A1	06 Sep 2019
		ZA 201900473 B	25 Sep 2019
		ZA 201901371 B	27 Nov 2019