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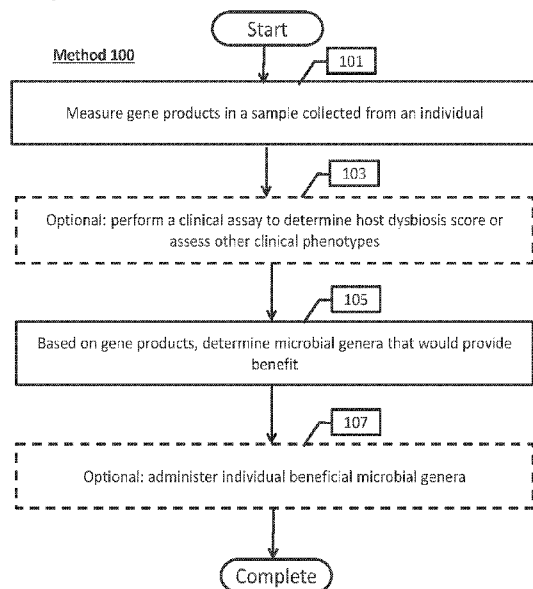
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(54) Title: SYSTEMS AND METHODS FOR ASSESSMENT OF MICROBIOME AND TREATMENTS THEREOF

Fig. 1



(57) Abstract: Systems and methods for assessing microbio-
me-host interactions are described. Several microbial genera have
been found to provide benefit for a variety of medical disorders
and phenotypes. Microbial genera can be provided as a composi-
tion to provide a particular benefit. Microbial genera can be ad-
ministered to an individual to alter expression of gene products
such as cytokines. Microbial genera can be administered to an in-
dividual as a treatment for a medical disorder.

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SYSTEMS AND METHODS FOR ASSESSMENT OF MICROBIOME AND TREATMENTS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Ser. No. 63/507,687, entitled "Systems and Methods for Assessment of Microbiome and Treatments Thereof," filed June 12, 2023, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002] The disclosure is generally directed towards systems and methods for assessment of microbiome, and more specifically directed towards systems and methods for analyzing the effect of microbial genera on host health and treatments thereof.

BACKGROUND

[0003] Human microbiomes are composed of remarkably dynamic microbial communities that live in and on various body sites, including the gut, skin, nasal cavity, and oral cavity. At each site, the microbial and host cell interactions exhibit territory-specific complexity. The molecular foundations of microbial ecology and their interactions with the host are being elucidated with new technology-enabled multi-omics profiling, shedding light on their role in both normal physiological processes. For instance, increasing evidence has shown that the microbiome can play an important role in regulating the host's immune system, while the immune system maintains the key feature of host-microbes symbiosis. This cross-talk between the microbiome and the immune system can provide an understanding of various biological phenomena such as aging and the pathogenesis of diseases such as inflammatory bowel disease (IBD), cardiovascular disease, and type 2 diabetes mellitus (T2DM). Studying the mechanisms underpinning such interactions has the potential to provide novel insights into the development of microbiome-targeted therapeutic interventions.

SUMMARY

[0004] In some aspects, the techniques described herein relate to a method for administering microbial genera to an individual, including: measuring levels of a set of one or more gene products in a biological sample of the individual; determining that an amount of one gene product of the set of gene products is above a threshold or is below a threshold; and when the amount of the one gene product is above a threshold, administering to the individual one or more microbial genera negatively correlated with the one gene product, or when the amount of the one gene product is below a threshold, administering to the individual one or more microbial genera positively correlated with the one gene product.

[0005] In some aspects, the techniques described herein relate to a method further including: measuring a microbial genera composition of a microbiome; wherein the composition of microbial genera is utilized to assist in selecting the one or more microbial genera to be administered.

[0006] In some aspects, the techniques described herein relate to a method, wherein the one gene product and the one or more correlated microbial genera to be administered is listed within Table 1.

[0007] In some aspects, the techniques described herein relate to a method, wherein the one gene product is: BDNF, EGF, Eotaxin, INF- α , INF- γ , IL-1 β , IL-6, IL-10, IL-12, IL-17, IL-22, IL-23, MCP-1, RANTES, TGF- β , or TNF- α .

[0008] In some aspects, the techniques described herein relate to a method, wherein the one gene product is Eotaxin, wherein Eotaxin is greater than threshold, wherein the is administered one or more of the following microbial genera: *Desulfovibrio* or *Escherichia_Shigella*.

[0009] In some aspects, the techniques described herein relate to a method, wherein the one gene product is INF- α , wherein INF- α is greater than threshold, wherein the is administered one or more of the following microbial genera: *Blautia* or *Dialister*.

[0010] In some aspects, the techniques described herein relate to a method, wherein the one gene product is INF- γ , wherein INF- γ is greater than threshold, wherein the is

administered one or more of the following microbial genera: Blautia, Dialister, or Fusicatenibacter.

[0011] In some aspects, the techniques described herein relate to a method, wherein the one gene product is IL-1 β , wherein IL-1 β is greater than threshold, wherein the is administered one or more of the following microbial genera: Agathobacter, Butyricimonas, Collinsella, Desulfovibrio, Faecalibacterium, Lachnospira, Prevotella, Roseburia, Slackia, Subdoligranulum, or Sutterella.

[0012] In some aspects, the techniques described herein relate to a method, wherein the one gene product is IL-6, wherein IL-6 is greater than threshold, wherein the is administered one or more of the following microbial genera: Collinsella, Dialister, or Fusicatenibacter.

[0013] In some aspects, the techniques described herein relate to a method, wherein the one gene product is IL-12, wherein IL-12 is greater than threshold, wherein the is administered one or more of the following microbial genera: Butyricimonas, Collinsella, or Fusicatenibacter.

[0014] In some aspects, the techniques described herein relate to a method, wherein the one gene product is IL-17, wherein IL-17 is greater than threshold, wherein the is administered one or more of the following microbial genera: Dialister, Subdoligranulum, or Senegalimassilia.

[0015] In some aspects, the techniques described herein relate to a method, wherein the one gene product is IL-23, wherein IL-23 is greater than threshold, wherein the is administered one or more of the following microbial genera: Butyricimonas, Dialister, Holdemanella, or Senegalimassilia.

[0016] In some aspects, the techniques described herein relate to a method, wherein the one gene product is MCP-1, wherein MCP-1 is greater than threshold, wherein the is administered one or more of the following microbial genera: Blautia, Desulfovibrio, Dialister, or Slackia.

[0017] In some aspects, the techniques described herein relate to a method, wherein the one gene product is RANTES, wherein RANTES is greater than threshold, wherein

the is administered one or more of the following microbial genera: Butyricimonas, Collinsella, Holdemanella, or Lawsonibacter.

[0018] In some aspects, the techniques described herein relate to a method, wherein the one gene product is TNF- α , wherein TNF- α is greater than threshold, wherein the is administered one or more of the following microbial genera: Agathobacter, Butyricimonas, Collinsella, Desulfovibrio, or Frisingicoccus.

[0019] In some aspects, the techniques described herein relate to a method, wherein the one gene product is TNF- α , wherein TNF- α is greater than threshold, wherein the is administered one or more of the following microbial genera: Agathobacter, Butyricimonas, Collinsella, Desulfovibrio, or Frisingicoccus.

[0020] In some aspects, the techniques described herein relate to a method, wherein the one gene product is BDNF, wherein BDNF is less than threshold, wherein the is administered one or more of the following microbial genera: Barnesiella, Eggerthella, Lachnospira or Parabacteroides.

[0021] In some aspects, the techniques described herein relate to a method, wherein the one gene product is EGF, wherein EGF is less than threshold, wherein the is administered one or more of the following microbial genera: Anaerostipes, Barnesiella, Eggerthella, Intestinibacter, Neglecta, Parabacteroides, or Romboutsia.

[0022] In some aspects, the techniques described herein relate to a method, wherein the one gene product is IL-10, wherein IL-10 is less than threshold, wherein the is administered one or more of the following microbial genera: Hungatella or Monoglobus.

[0023] In some aspects, the techniques described herein relate to a method, wherein the one gene product is IL-17, wherein IL-17 is less than threshold, wherein the is administered one or more of the following microbial genera: Adlercreutzia, Barnesiella, Butyricoccus, Cloacibacillus, Dysosmobacter, or Faecalicatena.

[0024] In some aspects, the techniques described herein relate to a method, wherein the one gene product is IL-22, wherein IL-22 is less than threshold, wherein the is administered one or more of the following microbial genera: Anaerotignum, Butyrivibrio, Cloacibacillus, Dysosmobacter, Frisingicoccus, Gordonibacter, Negativibacillus, Phocaea, Pseudoflavonifractor, Raoultibacter, or Turicibacter.

[0025] In some aspects, the techniques described herein relate to a method, wherein the one gene product is TGF- β , wherein TGF- β is less than threshold, wherein the is administered one or more of the following microbial genera: Acutalibacter, Akkermansia, Clostridium_sensu_stricto, Clostridium_XVIII, Flavonifractor, Holdemania, or Hungatella.

[0026] In some aspects, the techniques described herein relate to a method, wherein the one or more microbial genera are to be orally administered.

[0027] In some aspects, the techniques described herein relate to a method, wherein the one or more genera is provided in a probiotic food, a probiotic beverage, a liquid solution composition, a gel composition, an oil composition, an emulsion composition, a capsule, an enteric-coated capsule, a dragee, a gavage, a lyophilized powder, a freeze-dried powder, or a combination thereof.

[0028] In some aspects, the techniques described herein relate to a method, wherein the one or more microbial genera are to be rectally administered.

[0029] In some aspects, the techniques described herein relate to a method, wherein the one or more genera is provided in a probiotic liquid, a probiotic gel, a probiotic suppository, a probiotic fecal transplant, a probiotic enema, a probiotic catheter, a lyophilized powder, a freeze-dried powder, or a combination thereof.

[0030] In some aspects, the techniques described herein relate to a method for administering microbial genera to an individual, including: measuring levels of a set of one or more analytes in a biological sample of the individual; determining that the measurement of one analyte is not within a healthy range; and administering to the individual one or more microbial genera to individual for the purpose of altering the level of the one analyte into the healthy range, wherein the one or more microbial genera is correlated with the analyte.

[0031] In some aspects, the techniques described herein relate to a method further including: measuring a microbial genera composition of a microbiome; wherein the composition of microbial genera is utilized to assist in selecting the one or more microbial genera to be administered.

[0032] In some aspects, the techniques described herein relate to a method, wherein the one analyte and the one or more correlated microbial genera to be administered is listed within Table 2.

[0033] In some aspects, the techniques described herein relate to a method, wherein the one analyte is selected from: LDL cholesterol, non-HDL cholesterol, or HDL/LDL cholesterol ratio, wherein the one or more microbial genera to be administered includes *Haemophilus*.

[0034] In some aspects, the techniques described herein relate to a method, wherein the *Haemophilus* is to be topically administered.

[0035] In some aspects, the techniques described herein relate to a method, wherein the *Haemophilus* is provided in a probiotic suppository, a probiotic oil, a probiotic emulsion, a probiotic ointment, a probiotic lotion, a probiotic powder, a probiotic cream, a lyophilized powder, a freeze-dried powder, or a combination thereof.

[0036] In some aspects, the techniques described herein relate to a method, wherein the one analyte is A1C, wherein the one or more microbial genera to be administered includes *Akkermansia*.

[0037] In some aspects, the techniques described herein relate to a method, wherein the one or more microbial genera are to be orally administered.

[0038] In some aspects, the techniques described herein relate to a method, wherein the one or more genera is provided in a probiotic food, a probiotic beverage, a liquid solution composition, a gel composition, an oil composition, an emulsion composition, a capsule, an enteric-coated capsule, a dragee, a gavage, a lyophilized powder, a freeze-dried powder, or a combination thereof.

[0039] In some aspects, the techniques described herein relate to a method, wherein the one or more microbial genera are to be rectally administered.

[0040] In some aspects, the techniques described herein relate to a method, wherein the one or more genera is provided in a probiotic liquid, a probiotic gel, a probiotic suppository, a probiotic fecal transplant, a probiotic enema, a probiotic catheter, a lyophilized powder, a freeze-dried powder, or a combination thereof.

[0041] In some aspects, the techniques described herein relate to a method for treating an individual for a medical condition by administering microbial genera, including: administering to the individual one or more microbial genera to individual, wherein the one or more microbial genera is correlated with a gene product associated with the condition.

[0042] In some aspects, the techniques described herein relate to a method, wherein the medical condition is psoriasis and the one or more microbial genera is: *Finegoldia*, *Brevibacterium*, *Halomonas*, *Methylobacterium*, *Moraxella*, *Paracoccus*, *Dolosigranulum*, *Neisseria*, *Methylobacterium*, *Enhydrobacter*, *Peptoniphilus*, or *Roseomonas*.

[0043] In some aspects, the techniques described herein relate to a method, wherein the one or more microbial genera are to be topically administered.

[0044] In some aspects, the techniques described herein relate to a method, wherein the one or more microbial genera are provided in a probiotic suppository, a probiotic oil, a probiotic emulsion, a probiotic ointment, a probiotic lotion, a probiotic powder, a probiotic cream, a lyophilized powder, a freeze-dried powder, or a combination thereof.

[0045] In some aspects, the techniques described herein relate to a method, wherein the medical condition is inflammatory bowel disease and the one or more microbial genera is: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Fusicatenibacter*, *Dialister*, *Subdoligranulum*, *Senegalimassilia*, or *Holdemanella*.

[0046] In some aspects, the techniques described herein relate to a method, wherein the medical condition is rheumatoid arthritis and the one or more microbial genera is: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Subdoligranulum*, or *Senegalimassilia*.

[0047] In some aspects, the techniques described herein relate to a method, wherein the medical condition is systemic lupus erythematosus and the one or more microbial genera is: *Blautia*, *Dialister*, *Fusicatenibacter*, *Collinsella*, *Subdoligranulum*, or *Senegalimassilia*.

[0048] In some aspects, the techniques described herein relate to a method, wherein the medical condition is hypertension and the one or more microbial genera is:

Agathobacter, Butyricimonas, Collinsella, Desulfovibrio, Frisingicoccus, Dialister, Fusicatenibacter, Subdoligranulum, or Senegalimassilia.

[0049] In some aspects, the techniques described herein relate to a method, wherein the medical condition is atherosclerosis and the one or more microbial genera is: Agathobacter, Butyricimonas, Collinsella, Desulfovibrio, Frisingicoccus, Dialister, Fusicatenibacter, Hungatella, or Monoglobus.

[0050] In some aspects, the techniques described herein relate to a method, wherein the medical condition is depression or anxiety and the one or more microbial genera is: Agathobacter, Butyricimonas, Collinsella, Desulfovibrio, Frisingicoccus, Dialister, Fusicatenibacter, Hungatella, or Monoglobus.

[0051] In some aspects, the techniques described herein relate to a method, wherein the medical condition is autism and the one or more microbial genera is: Desulfovibrio, Escherichia_Shigella, Blautia, Dialister, Slackia, Butyricimonas, Collinsella, Holdemanella, Lawsonibacter, Fusicatenibacter, Acutalibacter, Akkermansia, Clostridium_sensu_stricto, Clostridium_XVIII, Flavonifractor, Holdemania, or Hungatella.

[0052] In some aspects, the techniques described herein relate to a method, wherein the medical condition is schizophrenia and the one or more microbial genera is: Agathobacter, Butyricimonas, Collinsella, Desulfovibrio, Frisingicoccus, Dialister, Fusicatenibacter, Hungatella, or Monoglobus.

[0053] In some aspects, the techniques described herein relate to a method, wherein the medical condition is metabolic disease and the one or more microbial genera is: Barnesiella, Frisingicoccus, Butyrivibrio, Adlercreutzia, Butyricoccus, Cloacibacillus, Dysosmobacter, Faecalicatena, Anaerotignum, Cloacibacillus, Dysosmobacter, Gordonibacter, Negativibacillus, Phoceia, Pseudoflavonifractor, Raoultibacter, or Turicibacter.

[0054] In some aspects, the techniques described herein relate to a method, wherein the one or more microbial genera is: Barnesiella, Frisingicoccus, or Butyrivibrio.

[0055] In some aspects, the techniques described herein relate to a method, wherein the medical condition is type 2 diabetes or obesity and the one or more microbial genera is: Agathobacter, Butyricimonas, Collinsella, Desulfovibrio, Frisingicoccus, Dialister,

Fusicatenibacter, Hungatella, Monoglobus, Faecalibacterium, Lachnospira, Prevotella, Roseburia, Slackia, Subdoligranulum, or Sutterella.

[0056] In some aspects, the techniques described herein relate to a method, wherein the medical condition is leaky gut syndrome and the one or more microbial genera is: Blautia, Dialister, Fusicatenibacter, Agathobacter, Butyricimonas, Collinsella, Desulfovibrio, Frisingicoccus, Faecalibacterium, Lachnospira, Prevotella, Roseburia, Slackia, Subdoligranulum, Sutterella, Hungatella Monoglobus, Acutalibacter, Akkermansia, Clostridium_sensu_stricto, Clostridium_XVIII, Flavonifractor, Holdemania, Anaerostipes, Barnesiella, Eggerthella, Intestinibacter, Neglecta, Parabacteroides, or Romboutsia.

[0057] In some aspects, the techniques described herein relate to a method, wherein the one or more microbial genera are to be orally administered.

[0058] In some aspects, the techniques described herein relate to a method, wherein the one or more genera is provided in a probiotic food, a probiotic beverage, a liquid solution composition, a gel composition, an oil composition, an emulsion composition, a capsule, an enteric-coated capsule, a dragee, a gavage, a lyophilized powder, a freeze-dried powder, or a combination thereof.

[0059] In some aspects, the techniques described herein relate to a method, wherein the one or more microbial genera are to be rectally administered.

[0060] In some aspects, the techniques described herein relate to a method, wherein the one or more genera is provided in a probiotic liquid, a probiotic gel, a probiotic suppository, a probiotic fecal transplant, a probiotic enema, a probiotic catheter, a lyophilized powder, a freeze-dried powder, or a combination thereof.

[0061] In some aspects, the techniques described herein relate to a method of determining microbial genera host immune response, including: providing immune responsive organoids in culture; adding a microbial genus culture supernatant to the immune responsive organoids in culture; and measuring one or more gene products to determine organoid response to the microbial genus culture supernatant.

[0062] In some aspects, the techniques described herein relate to a method for administering a probiotic treatment, including: providing a culture of an immune

responsive organoids of an individual; contacting the culture of immune responsive organoids with a culture product of a microbial genus or a combination of microbial genera; determining that the microbial genus or the combination of microbial genera yield a desired response by the immune responsive organoids; and based on the response by the immune responsive organoids, determining a treatment regimen for the individual that includes administration of the microbial genus or the combination of microbial genera.

BRIEF DESCRIPTION OF THE DRAWINGS

[0063] The description and claims will be more fully understood with reference to the following figures and data graphs, which are presented as exemplary embodiments of the disclosure and should not be construed as a complete recitation of the scope.

[0064] Figure 1 provides a flow diagram of an example of a method to assess microbiome-host interactions to infer treatments.

[0065] Figure 2 provides a flow diagram of an example of a co-culture organoid assay to assess microbiome-host interactions.

[0066] Figure 3 provides an example of a method to culture microbial isolates from a microbiome, which can be utilized in co-culture organoid assays.

[0067] Figures 4A to 4E provide results of an assessment of the immune response of an organoid culture in response to six different microbial samples.

[0068] Figure 5 provides principal component analysis of the results of the immune response of an organoid culture in response to six different microbial samples, inclusive of the results provided in Figs. 4A to 4E.

[0069] Figures 6A to 6F provide schematics and data charts depicting study of longitudinal profiles of the microbiome at four body sites. Figure 6A provides a schematic of the study design. Figure 6B provides data showing overlap of sample numbers among different omics types. Figure 6C provides data showing Proportion of stress, insulin resistant and healthy samples. Figure 6D provides UMAP of microbiome samples by body site. Figure 6E provides data showing density distribution of microbiome richness and evenness. Figure 6F provides data showing Rank prevalence curve of microbiome genera with the 100 highest longitudinal prevalence at each body site.

[0070] Figures 7A to 7M data charts showing ecological dynamics of microbiome from the four body sites. Figure 7A provides Relative Abundance of Representative Genera Displayed on UMAP. Figure 7B provides Principal Coordinate Analysis Distribution of Samples Differing in Insulin Status. Figure 7C provides Intraclass Correlation of Microbiome at Each Taxonomy Level. Figure 7D provides Microbiome Variance Explained by Individuality, Season, and Residuals. Figure 7E provides Variance in Microbiome Explained by Diet. Figure 7F provides Seasonal effect of Microbiome. Significance for richness (ACE) and evenness (Pielou) is reported for each site: stool (ACE $p < 0.0001$, Pielou $p = 0.4$), skin (ACE $p = 0.016$, Pielou $p = 0.016$), oral (ACE $p < 0.0001$, Pielou $p = 0.017$), and nasal (ACE $p = 0.0003$, Pielou $p = 0.39$). Figure 7G provides Variance in Microbiome Explained by Exposome. Figure 7H provides Shifts in Diversity and Evenness Between IR and IS Individuals. Figure 7I provides Prevalence by Relative Abundance Plot. Figure 7J provides Relationship Between the Number of Core Microbiome Genera, Steady-State Plasma Glucose, and Body Mass Index. Figure 7K provides Number of Core Microbiome Genera in Insulin Sensitive and Insulin Resistant Individuals. Figure 7L provides Rank Prevalence Curve of the Microbiome at Each Body Site. Figure 7M provides Effect Size of Taxa Differing in Relative Abundance Between Insulin Sensitive and Insulin Resistant Individuals. Significance is indicated as * for p -value < 0.05 , and ** for p -value < 0.01 . Significance is indicated as * for p -value < 0.05 , and ** for p -value < 0.01 .

[0071] Figures 8A to 8C provide data charts showing that the individuality of the microbiome differs significantly across genera and body sites. Figure 8A provides Bray Curtis dissimilarity comparisons within individuals, families, and between unrelated participants. Figure 8B provides DMI Scores. Figure 8C provides Average DMI Radar Plot by Body Site and Phylum, with significant Kruskal-Wallis test results for *Actinobacteria*, *Bacteroidetes*, Firmicutes, *Proteobacteria*, and Other phyla. Significance indicated by asterisks: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

[0072] Figures 9A and 9B provide data charts of DMI distribution across sites and health status. Figure 9A provides Histogram Distribution of Degree of Microbial Individuality and Family Score. For DMI: Nasal vs. Oral: $p=0.29263$, Nasal vs. Skin:

$p=0.38261$, Oral vs. Skin: $p=0.00016$, Nasal vs. Stool: $p=0.000027$, Oral vs. Stool: $p=0.000002$, and Skin vs. Stool: $p<0.000001$. For FS: Nasal vs. Oral: $p=0.076$, Nasal vs. Skin: $p=0.001$, Oral vs. Skin: $p=0.033$, Nasal vs. Stool: $p<0.001$, Oral vs. Stool: $p<0.001$, and Skin vs. Stool: $p=0.000011$. Figure 9B provides Comparative Analysis of Microbiome Individuality Across Different Insulin Sensitivity States. The Degree of Personalization, a relative abundance weighted sum up of Degree of Microbial Individuality, calculated for each individual at the four body sites was compared between individuals of different insulin sensitivity states. The p-value from Two-Sided Wilcoxon rank sum tests between insulin sensitive and insulin resistant individuals was shown. IR: insulin resistant; IS: insulin sensitive.

[0073] Figures 10A to 10F provide data charts showing temporal stability of microbiomes associated with individuality and stress events. Figure 10A provides correlations of taxa-recurrence with mean DMI for stool, skin, oral, and nasal samples. Figure 10B provides linear regression data between dissimilarity and collection date interval. Figure 10C provides beta coefficient of individual-based correlation between sample pair's BC distances and the collection date intervals. Figure 10D provides correlations of microbiome abundances within and between body sites. Figure 10E provides DMI differences between correlated and non-correlated genera. Figure 10F provides data showing microbiome shifts during health and stress events over three months. Significance indicated by asterisks: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

[0074] Figures 11A to 11H provide data charts of longitudinal dynamics and the relations with DMI. Figure 11A provides Strain Replacement Rate in Insulin Sensitive and Insulin Resistant Individuals. Figure 11B provides Time-Related Stability Correlation Between Body Sites in Insulin Sensitive Groups. Figure 11C provides Time-Related Stability Correlation Between Body Sites in Insulin Resistant Groups. The same illustration of Figure S3B for insulin resistant (IR) group. Figure 11D provides Degree of Microbial Individuality (DMI) Comparison Between Bacteria Genera Correlated and Uncorrelated Between Body Sites. Significance levels are annotated as follows: * for adjusted p-values < 0.05 , ** for adjusted p-values < 0.01 , *** for adjusted p-values < 0.001 .**** for adjusted p-values < 0.0001 . Figure 11E provides Microbial Evenness

Change During Respiratory Viral Infection Among Insulin Sensitive and Insulin Resistant Individuals. Figures 11F to 11H provides Microbial Relative Abundance Change During Respiratory Viral Infection. Their trends during infection are visually inspected and grouped into (Fig. 11F) temporarily increased during infection, (Fig. 11G) mixed trends of increase and decrease, (Fig. 11H) temporarily decreased during infection.

[0075] Figures 12A to 12C provide data charts showing systematic connections between circulating cytokines and microbiomes. Figure 12A provides data showing cytokine-related genera percentages by phylum. Figure 12B provides a density plot of significant cytokine-microbiome correlation coefficients, compared by genera prevalence. Figure 12C provides correlation coefficients by body site and phylum. p-values for positive versus negative associations were annotated in the middle. Significance indicated by asterisks: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

[0076] Figures 13A to 13D provide data charts of microbiome-cytokine interactions. Figure 13A provides Relationship Between the Microbiome and Cytokine Based on Their Correlation Coefficient. Figure 13B provides Phyla Composition of Core, Middle, and Opportunistic Genera of Microbiome. Figure 13C provides Correlation between Genera of Stool Proteobacteria and Plasma Cytokines Divided by Prevalence. Figure 13D provides The Correlation between Body Mass Index and Plasma Leptin and Granulocyte-Macrophage Colony-Stimulating Factor.

[0077] Figures 14A and 14B provide data on microbiome plasma analytics correlation. Figure 14A provides Collinearity of Metabolome, Lipidome, and Proteome. Figure 14B provides Different Interactome of the Stool Microbiome and Internal Plasma Analytics

[0078] Figures 15A to 15E provide data charts showing interactions between plasma metabolites, lipids, proteomics, and microbiome over time. Figure 15A provides a correlation Network that shows links between microbiome genera relative abundance and plasma analytics, color-coded by type (Microbiomes: Dark yellow, Blue, Dark red, Green; Plasma analytics: Dark blue, Orange, Red). Figure 15B provides data showing plasma analytics-microbiome relative abundance correlation summary of Fig. 15A. Figure 15C provides correlations between genera and the metabolite ethyl glucuronide. Figure 15D

provides data showing plasma analytics-microbiome relative richness. Figure 15E provides correlations between genera and the metabolite p-Cresol glucuronide.

[0079] Figure 16 provides data on microbiome-host correlations. Distribution of Correlation Coefficients for Microbiome Interactions Across Four Body Sites.

[0080] Figures 17A to 17E provide data showing causal inference decodes microbiome-driven phenotypic dynamics mediated by internal molecules and cytokines. Figure 17A provides a data summary of microbiome and phenotype mediation analysis. Comparisons between IS and IR regarding each mediated effect were performed using a Fisher exact t test. Figure 17B provides data showing *Akkermansia*'s Mediation Effect on Blood A1C Level via Plasma IL-15. Figure 17C provides data showing *Akkermansia*'s Mediation Effect on Blood A1C Level in Insulin Sensitive Individuals. Figure 17D provides data showing *Haemophilus*'s Mediation Effect on Plasma Triglycerides Level. Figure 17E provides data showing *Haemophilus*'s Mediation Effect on Plasma Triglycerides Level in Insulin Sensitive Individuals.

BRIEF DESCRIPTION OF THE TABLES

[0081] The description and claims will be more fully understood with reference to the following tables, which are presented as exemplary embodiments of the disclosure and should not be construed as a complete recitation of the scope.

[0082] Table 1 provides data of gene products that were significantly associate with a microbial genus, as determined by their correlation between the product and the microbial genus within a host microbiome.

[0083] Table 2 provides data of circulatory clinical phenotypes that were significantly associate with a microbial genus, as determined by their correlation between the phenotype measured in blood and the microbial genus within a host microbiome. The phenotype abbreviations are described in Table 3.

[0084] Table 3 provides circulatory clinical phenotypes assessed and their abbreviations.

DETAILED DESCRIPTION

[0085] Turning now to the drawings and data, the various embodiments of the disclosure are related to assessment of microbiome-host interactions and therapeutic applications thereof. In many embodiments, associations between microbial genera of a microbiome and their effect upon host gene expression are exploited to assess and/or to treat individuals, which may be useful for various medical disorders. In several embodiments, a microbial genus or a combination of microbial genera that have been found to be beneficial are utilized as supplements and/or medications that can be administered as probiotic supplement or as a treatment, including a prophylactic treatment and/or a prescribed treatment. In many embodiments, a supplement and/or treatment is associated with a particular health benefit, such as improvement of a clinical phenotype or a medical condition.

[0086] In several embodiments, a biological sample (e.g., blood sample) derived from a patient can be diagnostically assessed by examining the products of expressed gene products therein to determine a composition of microbial genera within a microbiome, which can be associated with a clinical phenotype or medical condition, and which microbial genera would be beneficial. In many embodiments, a microbiome sample derived from a patient can be assessed by examining which microbial genera are present, which can provide a determination of whether the patient could benefit from an administration of beneficial microbial genera. Utilizing the gene product data and/or the microbial genera data, a determination can be made on how to alter a patient's microbiome to improve the patient's expression of gene products to improve the individual's condition. In several embodiments, the individual's microbiome is altered by administering beneficial microbial genera.

[0087] As described in detail herein, it is now known that particular microbial genera can specifically alter a host's gene expression, especially genes related to immune response and inflammation. Provided in Table 1 is a list of genes whose expression levels are significantly correlated with various microbial genera, establishing a linkage between microbiome composition and the host's response to that composition. It has been further

discovered that administration of microbial genera can induce specific expression of a host's genes (see Examples and Data herein).

[0088] Provided in Table 2 is a list of circulatory clinical phenotypes that are significantly correlated with various microbial genera, establishing a linkage between a microbiome composition and the clinical phenotype. Assessments of gene product expression and/or clinical data can thus infer microbial genera composition within a gene host. Further, microbial genera can be provided to a patient to induce healthier gene product expression or improvements in clinical phenotypes. In several embodiments, these linkages between the microbial genera and the host response are exploited to provide assessments of and/or treatments to a host.

[0089] In several embodiments, a biological sample of a patient is assessed to determine the expression levels of various gene products, including immune system modulators, cytokines, chemokines, hormones, growth factors, and other signaling molecules. In many embodiments, the gene products that are assessed have known association with one or more microbial genera that can be found within an individual's microbiome and thus based on the gene product expression, the composition of a host's microbiome can be predicted.

[0090] Several medical disorders are known to develop at least in part by unhealthy expression of immune system modulators, cytokines, chemokines, hormones, growth factors, and other signaling molecules. These medical disorders include (but are not limited to) autoimmune disorders (including autoinflammatory disorders), cardiovascular disorders, mental health disorders, and metabolic disorders. These medical disorders have also been linked to altered microbiomes of the host. Based on the discovery that expression of these genes is significantly correlated and influenced by particular microbial genera, assessments and treatments for these disorders can be prescribed. In several embodiments, a patient can be administered bacterial genera as a probiotic supplement, a prophylaxis, or a treatment for a medical condition, which can be prescribed by a clinical assessment. In some embodiments, a microbial genus or a combination of microbial genera that are beneficial to a healthier condition (e.g., healthy clinical phenotype) can be administered to as a probiotic supplement to an individual, with or without any clinical

diagnostic assessment performed. In some embodiments, a microbial genus or a combination of microbial genera that are beneficial to medical condition can be administered as a treatment to a patient diagnosed with a medical condition. In some embodiments, an individual's biological sample is assessed for gene products as a diagnostic to determine which microbial genus or combinations of microbial genera would be beneficial; in some embodiments, based on the patient's gene product expression in the biological sample, the patient is administered the microbial genus or combinations of microbial genera that can alter gene expression. In some embodiments, an individual's microbiome sample is assessed to determine microbiome composition as a diagnostic to determine whether the patient would benefit from increasing beneficial microbial genera within the patient's microbiome; in some embodiments, the patient is administered a beneficial microbial genus or a beneficial combination of microbial genera to reestablish a healthy balance of microbiome populations.

[0091] To better understand microbial genera effects on a host, in accordance with several embodiments, a co-culture assay comprising an immune responsive organoid and microbial genera can be utilized. In many embodiments, bacterial isolates are generated from a microbiome sample and cultured; a bacterial isolate can be applied to the immune responsive organoid to assess the immune response the isolate stimulates. Examples of immune responsive organoids found to work well in this system are tonsil organoids, lymph node organoids, and spleen organoids. In some embodiments, tonsil tissue, lymph node tissue, or spleen tissue is extracted from a human donor and cultured. In some embodiments, an immune responsive organoid is developed via differentiation of pluripotent cells in culture. Immune responsive organoids can be challenged with a bacterial isolate. In some embodiments, the immune response (e.g., cytokine expression, immune cell activation) of an immune responsive organoid culture is assessed. In some embodiments, gene expression products (e.g., RNA, proteins/peptides) of an immune responsive organoid culture are assessed.

Assessment of Gene Products to Infer Microbiome Interactions

[0092] Several embodiments of the disclosure are directed to exploiting the correlation between microbial genera, host gene product expression, and medical condition. In several embodiments, an individual can be assessed to determine expression levels of gene products to infer presence and levels of particular microbial genera within the patient's microbiome. In many embodiments, gene product expression levels can be utilized to determine which microbial genera would be beneficial to be administered to the individual. In some embodiments, the composition of a patient's microbiome is assessed to determine which microbial genera would be beneficial to be administered to the individual. In several embodiments, a patient is administered a beneficial microbial genus or a combination of beneficial microbial genera, which may improve the health of the individual.

Detection of Gene Products Associated with Microbial Genera

[0093] Provided in Fig. 1 is an example of a method to determine microbial genera that would provide benefit to a patient. The method can be utilized in various applications that involve the association of microbial genera, host gene product expression, and phenotype. In accordance with numerous embodiments, the method is utilized to determine which microbial genera could be administered to alter host gene expression and thus improve recipient health.

[0094] Method 100 can begin with measuring (101) gene products in a biological sample that is collected from a patient. Assessment of gene products can be useful for various purposes related to host-microbiome interactions and health status, as will be discussed in greater detail below. Generally, gene products can infer a microbiome composition, an imbalance of a particular class of gene products (e.g., cytokines), or an appropriate treatment of beneficial microbial genera.

[0095] An individual (or patient) can be any individual for assessing the health as related to their microbiome. In some implementations, an individual has been diagnosed with a medical condition. Medical conditions that may be of interest include any clinical phenotype, medical disorder, or any other health-related condition that has a relationship

with host-microbiome. Examples of classes of medical disorders that may be of interest include autoimmune disorders (including autoinflammatory disorders), cardiovascular disorders, mental health disorders, and metabolic disorders. These disorders are also marked with unhealthy expression of immune system modulators, cytokines, chemokines, hormones, growth factors, and other signaling molecules, which may be related to host-microbiome interactions. In some implementations, a patient is considered healthy or is otherwise not diagnosed with a medical disorder. Screening of individuals may be part of routine screening or performed upon a diagnosis that related to a disorder (e.g., having symptoms indicative of a disorder). Accordingly, measuring gene products can be useful in assessing the individual's health status as it is related to the microbiomes (and composition thereof) of the individual.

[0096] The biological sample derived from an individual can be any biological sample that would have gene products. Examples of biological samples include (but are not limited to) blood, plasma, serum, lymph, cerebral spinal fluid, urine, stool, saliva, spittle, nasal fluid, vaginal fluid, pulmonary fluid, sweat, and swabs of a cavity (e.g., nasal, oral, urethral, vaginal, rectal, or ear canal). In some implementations, the biological sample source is local to the microbiome to be assessed. Various microbiomes that may be assessed include (but are not limited to) microbiomes of the gastrointestinal tract, the oral cavity, the nasal cavity, skin, a wound, lungs, urethral canal, vaginal canal, ocular surface, and ear canal. For example, assessment of the nasal cavity microbiome may be achieved by assessing the local nasal fluids or a nasal swab. Circulatory fluid samples (e.g., blood and plasma) are useful in assessing a number of microbiomes, including microbiomes of the gut, nasal cavity, oral cavity, and skin (see addendum and Table 1).

[0097] The gene products within a biological sample can be any analyte that can be influenced by expression of a gene. The gene products can also have an association with microbiome-host interaction in which various genera can influence the expression levels. These gene products include (but are not limited to) RNA, proteinaceous species (e.g., proteins and peptides), and metabolites. Classes of analytes that are useful include (but are not limited to) gene products of: immune system modulators, cytokines, chemokines,

hormones, growth factors, and other signaling molecules. Gene products found to associate with presence and microbial genera are provided in Table 1.

[0098] Method 100 can optionally perform (103) a clinical assay to determine host dysbiosis or assess other clinical phenotypes. As described herein, several clinical phenotypes are influenced by various microbiota, such as dysbiosis and circulating analytes (Table 2). These assessments can assist in determining which microbial genera would be beneficial to provide as a supplement to the individual. For assessing dysbiosis, the diversity and/or amount of microbiota within a microbiome sample can be assed. For assessing clinical phenotypes, a biological sample (e.g., blood, plasma, CSF) can be analyzed for circulating analytes. Other clinical assessments can also be performed that provide a phenotype that is correlated with particular microbiota genera.

[0099] In some implementations, the method further determines a composition of a microbiome of the individual. The composition of a microbiome can more help further determine whether a health status is related to a relative ratio of microbial genera, and often referred to an imbalance of microbial genera when influencing undesired health phenotypes. Certain medical conditions and health statuses significantly correlate with microbiome composition. For example, as described herein, type 2 diabetes and insensitivity to insulin significantly correlates with low microbiome diversity and particular microbial genera in the microbiomes of the gut, the oral cavity, the nasal cavity, and skin. For example, it was found that butyrate-producing bacteria such as *Coprococcus*, *Parasutterella*, and *Butyricicoccus* were more likely to be in stool microbiome samples of insulin sensitive individuals; whereas diabetes-related opportunistic pathogens such as *Finegoldia* and *Acinetobacter* were more prevalent in skin microbiome samples of insulin resistant individuals.

[0100] Composition of a microbiome can be determined from a microbiome sample. Microbiome samples can be obtained from the microbiome source and excretions or waste of that source (e.g., stool sample to determine gastrointestinal tract microbiome). Accordingly, microbiome samples can be obtained from one the following sources (or an excretion or waste of): the gastrointestinal tract, the oral cavity, the nasal cavity, skin, a wound, lungs, urethral canal, vaginal canal, ocular surface, and ear canal.

[0101] To identify the composition of a microbiome from a microbiome sample, any biochemical methodology for identifying microbial genera can be utilized, which may be combined with computational and/or statistical analysis. Biochemical methodologies include high-throughput sequencing, biomarker analysis, and bacterial genus isolation techniques (see, e.g., J. Galloway-Pena and B. Hanson, *Dig Dis Sci.* 2020 Mar;65(3):674-685, the disclosure of which is hereby incorporated by reference).

[0102] Composition of a microbiome can also be determined from host biomarkers that can act as surrogates of microbiome composition. For example, a set of twelve cytokines was found to be able to predict the composition of the microbiome within a stool sample (see, D. Yang, et al., *Sci Rep.* 2019 Dec 27;9(1):20082, the disclosure of which is incorporated hereby by reference).

[0103] Method 100 determines (105) microbial genera that would provide benefit to the individual. Based on research described herein, it is now understood that many gene products within the circulatory system are significantly correlated with microbiomes of the gut, nasal cavity, oral cavity, and skin. Table 1 provides a list of circulating gene products that are correlated with various microbial genera. Furthermore, several microbial genera have been shown to specifically induce expression of gene products (see Examples and Data). It has further been shown that imbalances of gene products in circulation (e.g., cytokines) and/or imbalances in microbiome composition is associated with a number of disease states. Accordingly, the gene product expression and/or microbiome composition of an individual can provide insight on whether administration of particular microbial genera can improve health. In other words, an administration of particular microbial genera can be utilized to correct gene product expression that is involved in the pathology of many medical disorders. In some embodiments, it is determined that one or more circulatory gene products are not within a healthy range. In some embodiments, it is determined that one or more circulatory gene products are too high or too low, which can be established based on a threshold.

[0104] In one example, it has been established that insulin sensitive individuals have relatively high levels of IL-17 and IL-22 circulating in plasma whereas type 2 diabetics that are insulin resistant have little to no circulating IL-17 and IL-22. Cytokines IL-17 and

IL-22 have also been shown to be protective in leaky gut disorder. As can be inferred from Table 1, genus *Barnesiella* within the stool microbiome is highly and positively correlated with circulating IL-17 and genera *Frisingicoccus* and *Butyrivibrio* are highly and positively correlated with circulating IL-22. Based on this information, a combination of one or more of these microbial genera would provide benefit to individuals with low circulating IL-17 and/or IL-22, individuals lacking these genera in their gut microbiome, insulin resistant individuals, type 2 diabetics, individuals experiencing leaky gut, and/or overweight individuals (especially obese individuals).

[0105] And as noted, various clinical phenotypes are significantly correlated with microbiomes of the gut, nasal cavity, oral cavity, and skin. Table 2, for example, provides a list of circulating analytes that are correlated with various microbial genera. And thus clinical phenotypes can be utilized to assist in determining which microbial genera that would provide benefit to the individual.

[0106] In some embodiments, the benefit of certain microbial genera can be further established utilizing patient-derived immune responsive organoids. These organoids can be derived from a patient and utilized to assess a particular patient's response to administration of particular microbial genera. For example, tonsil organoids can be extracted from an insulin resistant patient with low circulating IL-17 and IL-22. The tonsil organoids can be maintained in culture and particular microbial genera, such as (for example) *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio*, can be added to the culture individually or as some combination thereof to determine their effect on stimulating the expression of IL-17 and IL-22. Based on the results, particular combinations of microbial genera can be identified that best induce IL-17 and IL-22 production specific to that patient in order to determine a patient-specific combination of microbial genera to administer to the patient to treat insulin resistance. An example of a method for assessing immune responsive organoids with microbial genera is discussed further below in the description of Fig. 2.

[0107] Method 100 can optionally administer beneficial microbial genera to the patient. With the determination that particular microbial genera can be beneficial to a patient, the patient can be administered the microbial genera. Certain microbial genera within

particular microbiomes have been found to significantly correlate with circulatory gene products (Table 1), and with circulatory analytes (Table 2). In some embodiments, an individual is administered one or more microbial genera to increase an amount of a circulatory gene product. In some embodiments, an individual is administered one or more microbial genera to decrease an amount of a circulatory gene product. In some embodiments, an individual is administered one or more microbial genera to alter the level of a clinical analyte or otherwise adjust a clinical phenotype. Further description of gene products (and clinical phenotypes) that can be altered by administering a certain microbial genera are discussed below.

[0108] Administration of the microbial genera can be accorded to the particular microbiomes that provide the benefit. For example, some microbial genera can provide benefit within the gastrointestinal tract while other microbial genera can provide benefit on the skin. Therefore, the administration of microbial genera that provides benefit to the gastrointestinal tract can be orally administered (for example) within food, a beverage, or enteric-coated capsule, or can be rectally administered (for example) within a suppository or fecal transfer. Administration of microbial genera that provides benefit on the skin can be administered topically (for example) via an ointment, a cream, a lotion, or a powder. Further description of modes of administration are discussed below.

[0109] While a specific example of a method for determining beneficial microbial genera for a patient are described above, one of ordinary skill in the art can appreciate that various steps of the process can be performed in different orders and that certain steps may be optional according to some embodiments of the description. As such, it should be clear that the various steps of the method could be used as appropriate to the requirements of specific applications. Furthermore, any of a variety of methods for determining beneficial microbial genera for a patient appropriate to the requirements of a given application can be utilized in accordance with various embodiments of the disclosure.

Administration of Beneficial Microbial Genera

[0110] Various embodiments are directed towards a treatment comprising an administration of beneficial microbial genera. In some embodiments, based on the knowledge that the pathology of certain medical conditions is related to an altered expression of gene products, this knowledge is leveraged to develop treatments for a medical disorder that can adjust the expression level of the gene products by administering microbial genera that have are significantly associated with the expression of those gene products. The administered microbial genera can increase or decrease gene product expression, as dependent on the positive or negative association of gene product expression with particular microbial genera and the desired outcome to yield expression levels commiserate with healthy pathologies.

[0111] In several embodiments, a treatment regimen is administered for a medical condition. In these embodiments, a patient can be diagnosed as having a particular medical condition and based on this diagnosis, the patient can be administered microbial genera.

[0112] An example of a procedure for diagnosis and treatment of a medical condition can be as follows:

- (a) diagnose an individual or determine that the individual has been diagnosed with a medical condition
- (b) administer to the individual beneficial microbial genera based on the medical condition diagnosis.

[0113] In one example, the medical condition is type 2 diabetes, insulin resistance, leaky gut disease, and/or obesity.

[0114] A number of medical conditions can be treated with administration of microbial genera. Generally, any medical condition associated with an interaction between the host and a microbiome can be treated. Classes of medical disorders that can be treated include autoimmune disorders (including autoinflammatory disorders), cardiovascular disorders, mental health disorders, and metabolic disorders. Autoimmune disorders that can be treated with microbial genera include (but are not limited to) psoriasis, ulcerative colitis, Crohn's disease, inflammatory bowel disease, rheumatoid arthritis, and systemic

lupus erythematosus. Cardiovascular disorders that can be treated with microbial genera include (but are not limited to) hypertension, pulmonary artery hypertension, heart failure, atherosclerosis, vascular inflammation, and thrombosis. Mental health disorders that can be treated with microbial genera include (but are not limited to) depression, anxiety, autism, and schizophrenia. Metabolic disorders that can be treated with microbial genera include (but are not limited to) type 2 diabetes, insulin resistance, leaky gut disease, and obesity.

[0115] Several cytokines have been shown to promote inflammation in psoriasis, including TNF- α , IL-12, IL-17, IL-22 and IL-23 (I. Sieminska, et al., The Immunology of Psoriasis—Current Concepts in Pathogenesis. *Clinic Rev Allerg Immunol* (2024), the disclosure of which is hereby incorporated by reference). In some embodiments, an individual having psoriasis is administered microbial genera to reduce one or more of: TNF- α , IL-12, IL-17, IL-22 or IL-23. Genera found to reduce TNF- α on the skin include *Finegoldia* (Table 1). Genera found to reduce IL-12 on the skin *Brevibacterium*, *Halomonas*, *Methylobacterium*, *Moraxella*, and *Paracoccus* (Table 1). Genera found to reduce IL-17 on the skin include *Dolosigranulum*, *Neisseria*, and *Methylobacterium* (Table 1). Genera found to reduce IL-22 on the skin include *Enhydrobacter*, *Moraxella*, *Paracoccus*, *Peptoniphilus*, and *Roseomonas* (Table 1). Genera found to reduce IL-23 on the skin include *Methylobacterium* and *Moraxella* (Table 1). Accordingly, in some embodiments, an individual having psoriasis is administered one or more of: *Finegoldia*, *Brevibacterium*, *Halomonas*, *Methylobacterium*, *Moraxella*, *Paracoccus*, *Dolosigranulum*, *Neisseria*, *Methylobacterium*, *Enhydrobacter*, *Peptoniphilus*, or *Roseomonas*. And in some embodiments, an individual having psoriasis is administered one or more of: *Methylobacterium*, *Moraxella*, or *Paracoccus*.

[0116] Several cytokines have known roles in inflammatory bowel disease (inclusive of ulcerative colitis and Crohn's disease); TNF- α , IL-12, IL-17, and IL-23 promote inflammation and IL-22 has shown to improve maintenance of the gut epithelial layer (h. Nakase, et al., *Autoimmun Rev.* 2022 Mar;21(3):103017, the disclosure of which is hereby incorporated by reference). In some embodiments, an individual having ulcerative colitis or Crohn's disease is administered microbial genera to reduce one or more of: TNF- α , IL-

12, IL-17, or IL-23. Genera found to reduce TNF- α in the gut include *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, and *Frisingicoccus* (Table 1). Genera found to reduce IL-12 in the gut include *Butyricimonas*, *Collinsella*, and *Fusicatenibacter* (Table 1). Genera found to reduce IL-17 in the gut include *Dialister*, *Subdoligranulum*, and *Senegalimassilia*. Genera found to reduce IL-23 in the gut include *Butyricimonas*, *Dialister*, *Holdemanella*, and *Senegalimassilia*. In some embodiments, an individual having ulcerative colitis or Crohn's disease is administered microbial genera to increase IL-22. Genera found to increase IL-22 in the gut include *Frisingicoccus*, *Butyrivibrio*, *Anaerotignum*, *Cloacibacillus*, *Dysosmobacter*, *Gordonibacter*, *Negativibacillus*, *Phoceae*, *Pseudoflavonifractor*, *Raoultibacter*, and *Turicibacter* (Table 1). Accordingly, in some embodiments, an individual having ulcerative colitis or Crohn's disease is administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Fusicatenibacter*, *Dialister*, *Subdoligranulum*, *Senegalimassilia*, or *Holdemanella*. And in some embodiments, an individual having ulcerative colitis or Crohn's disease is administered one or more of: *Butyricimonas*, *Collinsella*, *Frisingicoccus*, *Dialister*, or *Senegalimassilia*.

[0117] Gut microbiota has been shown to influence rheumatoid arthritis (T. Zhao, et al., Front Immunol. 2022 Sep 8;13:1007165, the disclosure of which is hereby incorporated by reference). Furthermore, several cytokines have been shown to promote inflammation in rheumatoid arthritis, including TNF- α , IL-6, and IL-17 (N. Kondo, et al., Int J Mol Sci. 2021 Oct 10;22(20):10922, the disclosure of which is hereby incorporated by reference). In some embodiments, an individual having rheumatoid arthritis is administered microbial genera to reduce one or more of: TNF- α , IL-6, or IL-17. Genera found to reduce TNF- α in the gut include *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, and *Frisingicoccus* (Table 1). Genera found to reduce IL-6 in the gut include *Collinsella*, *Dialister*, and *Fusicatenibacter* (Table 1). Genera found to reduce IL-17 in the gut include *Dialister*, *Subdoligranulum*, and *Senegalimassilia* (Table 1). Accordingly, in some embodiments, an individual having rheumatoid arthritis is administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Subdoligranulum*, or *Senegalimassilia*. And in some embodiments, an

individual having rheumatoid arthritis is administered one or more of: *Collinsella* or *Dialister*.

[0118] Gut microbiota has been shown to influence systemic lupus erythematosus (H. Yaigoub, et al., Clin Immunol. 2022 Nov;244:109109, the disclosure of which is hereby incorporated by reference). Furthermore, several cytokines have been shown to promote inflammation in systemic lupus erythematosus, including INF- α , INF- γ , IL-6, and IL-17 (K. Ohl and K. Tenbrock J Biomed Biotechnol. 2011;2011:432595, the disclosure of which is hereby incorporated by reference). In some embodiments, an individual having systemic lupus erythematosus is administered microbial genera to reduce one or more of: INF- α , INF- γ , IL-6, or IL-17. Genera found to reduce INF- α in the gut include *Blautia* and *Dialister*. Genera found to reduce INF- γ in the gut include *Blautia*, *Dialister*, and *Fusicatenibacter* (Table 1). Genera found to reduce IL-6 in the gut include *Collinsella*, *Dialister*, and *Fusicatenibacter* (Table 1). Genera found to reduce IL-17 in the gut include *Dialister*, *Subdoligranulum*, and *Senegalimassilia* (Table 1). Accordingly, in some embodiments, an individual having systemic lupus erythematosus is administered one or more of: *Blautia*, *Dialister*, *Fusicatenibacter*, *Collinsella*, *Subdoligranulum*, or *Senegalimassilia*. And in some embodiments, an individual having systemic lupus erythematosus is administered one or more of: *Blautia*, *Dialister*, and *Fusicatenibacter*.

[0119] Gut microbiota has been shown to influence hypertension (D. Yan, et al., Animal Model Exp Med. 2022 Dec;5(6):513-531, the disclosure of which is hereby incorporated by reference). Furthermore, several cytokines have been shown to promote inflammation in hypertension, including TNF- α , IL-6, and IL-17 (Z. Zhang, et al., Front Immunol. 2023 Jan 10;13:1098725, the disclosure of which is hereby incorporated by reference). In some embodiments, an individual having hypertension is administered microbial genera to reduce one or more of: TNF- α , IL-6, or IL-17. Genera found to reduce TNF- α in the gut include *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, and *Frisingicoccus* (Table 1). Genera found to reduce IL-6 in the gut include *Collinsella*, *Dialister*, and *Fusicatenibacter* (Table 1). Genera found to reduce IL-17 in the gut include *Dialister*, *Subdoligranulum*, and *Senegalimassilia* (Table 1). Accordingly, in some embodiments, an individual having hypertension is administered one or more of:

Agathobacter, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Subdoligranulum*, or *Senegalimassilia*. And in some embodiments, an individual having hypertension is administered one or more of: *Collinsella* or *Dialister*.

[0120] Gut microbiota has been shown to influence atherosclerosis (A. Al Samarraie, et al., Int J Mol Sci. 2023 Mar 12;24(6):5420, the disclosure of which is hereby incorporated by reference). Furthermore, some cytokines have been shown to promote inflammation in atherosclerosis, including TNF- α and IL-6, and some cytokines have been shown to protect from atherosclerosis, including IL-10 (P. Tsioufis, et al., Int J Mol Sci. 2022 Dec 14;23(24):15937, the disclosure of which is hereby incorporated by reference). In some embodiments, an individual having atherosclerosis is administered microbial genera to reduce one or more of: TNF- α or IL-6, and/or to increase IL-10. Genera found to reduce TNF- α in the gut include *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, and *Frisingicoccus* (Table 1). Genera found to reduce IL-6 in the gut include *Collinsella*, *Dialister*, and *Fusicatenibacter* (Table 1). Genera found to increase IL-10 in the gut include *Hungatella* and *Monoglobus* (Table 1). Accordingly, in some embodiments, an individual having atherosclerosis is administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Hungatella*, or *Monoglobus*. And in some embodiments, an individual having atherosclerosis is administered one or more of: *Collinsella* or *Dialister*.

[0121] Gut microbiota has been shown to influence depression and anxiety (A. Kumar, et al., Pharmaceuticals (Basel). 2023 Apr 9;16(4):565, the disclosure of which is hereby incorporated by reference). Furthermore, some cytokines have been shown to be circulating at high levels in depressed and anxious patients, including TNF- α and IL-6, and some cytokines have been shown to be neurotrophic, including BDNF (J.C. Felger and F.E. Lotrich, Neuroscience. 2013 Aug 29;246:199-229; and F. Santoft, et al., Brain Behav Immun Health. 2020 Feb 5;3:100045; the disclosures of which are hereby incorporated by reference). In some embodiments, an individual having depression or anxiety is administered microbial genera to reduce one or more of: TNF- α or IL-6, and/or to increase BDNF. Genera found to reduce TNF- α in the gut include *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, and *Frisingicoccus* (Table 1). Genera found to

reduce IL-6 in the gut include *Collinsella*, *Dialister*, and *Fusicatenibacter* (Table 1). Genera found to increase BDNF in the gut include *Barnesiella*, *Eggerthella*, *Lachnospira* and *Parabacteroides* (Table 1). Accordingly, in some embodiments, an individual having depression or anxiety is administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Hungatella*, or *Monoglobus*. And in some embodiments, an individual having depression or anxiety is administered one or more of: *Collinsella* or *Dialister*.

[0122] Gut microbiota has been shown to influence autism (M.A. Taniya, et al., *Front Cell Infect Microbiol.* 2022 Jul 22;12:915701, the disclosure of which is hereby incorporated by reference). Furthermore, some cytokines have been shown to be circulating at increased levels in autistic individuals having more severe symptoms, including Eotaxin, MCP-1, RANTES and IL-6, and some cytokines have been shown to be circulating at reduced levels in autistic individuals having more severe symptoms, including TGF- β (A. Masi, et al., *Neurosci Bull.* 2017 Apr;33(2):194-204, the disclosure of which is hereby incorporated by reference). In some embodiments, an individual having autism is administered microbial genera to reduce one or more of: Eotaxin, MCP-1, RANTES or IL-6, and/or to increase TGF- β . Genera found to reduce Eotaxin in the gut include *Desulfovibrio* and *Escherichia_Shigella* (Table 1). Genera found to reduce MCP-1 in the gut include *Blautia*, *Desulfovibrio*, *Dialister*, and *Slackia* (Table 1). Genera found to reduce RANTES in the gut include *Butyricimonas*, *Collinsella*, *Holdemanella*, and *Lawsonibacter* (Table 1). Genera found to reduce IL-6 in the gut include *Collinsella*, *Dialister*, and *Fusicatenibacter* (Table 1). Genera found to increase TGF- β in the gut include *Acutalibacter*, *Akkermansia*, *Clostridium_sensu_stricto*, *Clostridium_XVIII*, *Flavonifractor*, *Holdemania*, and *Hungatella* (Table 1). Accordingly, in some embodiments, an individual having autism is administered one or more of: *Desulfovibrio*, *Escherichia_Shigella*, *Blautia*, *Dialister*, *Slackia*, *Butyricimonas*, *Collinsella*, *Holdemanella*, *Lawsonibacter*, *Fusicatenibacter*, *Acutalibacter*, *Akkermansia*, *Clostridium_sensu_stricto*, *Clostridium_XVIII*, *Flavonifractor*, *Holdemania*, or *Hungatella*.

[0123] Gut microbiota has been shown to influence schizophrenia (K. Tsamakidis, et al., *Microorganisms.* 2022 May 29;10(6):1121, the disclosure of which is hereby

incorporated by reference). Furthermore, some cytokines have been shown to circulating at high levels in schizophrenic patients, including TNF- α and IL-6 (B. Dawidowski, et al., J Clin Med. 2021 Aug 27;10(17):3849, the disclosure of which is hereby incorporated by reference). In some embodiments, an individual having schizophrenia is administered microbial genera to reduce one or more of: TNF- α or IL-6. Genera found to reduce TNF- α in the gut include *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, and *Frisingicoccus* (Table 1). Genera found to reduce IL-6 in the gut include *Collinsella*, *Dialister*, and *Fusicatenibacter* (Table 1). Accordingly, in some embodiments, an individual having schizophrenia is administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Hungatella*, or *Monoglobus*. And in some embodiments, an individual having schizophrenia is administered one or more of: *Collinsella* or *Dialister*.

[0124] Cytokines IL-17 and IL-22 have shown to be associated with positive outcomes in metabolic disease (type 2 diabetes, insulin resistance and/or obesity). In some embodiments, the individual is administered beneficial microbial genera that increases IL-17 or IL-22. In some embodiments, the individual is administered one or more of: *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio*. Other genera were also found to increase IL-17 in the gut, including *Adlercreutzia*, *Butyricicoccus*, *Cloacibacillus*, *Dysosmobacter*, and *Faecalicatena* (Table 1). Other genera were also found to increase IL-22 in the gut, including *Anaerotignum*, *Cloacibacillus*, *Dysosmobacter*, *Gordonibacter*, *Negativibacillus*, *Phoceia*, *Pseudoflavonifractor*, *Raoultibacter*, and *Turicibacter* (Table 1). In some embodiments, the individual is administered one or more of: *Barnesiella*, *Frisingicoccus*, *Butyrivibrio*, *Adlercreutzia*, *Butyricicoccus*, *Cloacibacillus*, *Dysosmobacter*, *Faecalicatena*, *Anaerotignum*, *Cloacibacillus*, *Dysosmobacter*, *Gordonibacter*, *Negativibacillus*, *Phoceia*, *Pseudoflavonifractor*, *Raoultibacter*, or *Turicibacter*.

[0125] Several cytokines have been associated with negative outcomes related to obesity and type 2 diabetes including TNF- α , IL-6 and IL-1 β ; and some cytokines have been associated with positive outcomes including IL-10 (N. Esser, et al., Diabetes Res Clin Pract. 2014 Aug;105(2):141-50, the disclosure of which is hereby incorporated by reference). Genera found to reduce TNF- α in the gut include *Agathobacter*,

Butyricimonas, *Collinsella*, *Desulfovibrio*, and *Frisingicoccus* (Table 1). Genera found to reduce IL-6 in the gut include *Collinsella*, *Dialister*, and *Fusicatenibacter* (Table 1). Genera found to reduce IL-1 β in the gut include *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Faecalibacterium*, *Lachnospira*, *Prevotella*, *Roseburia*, *Slackia*, *Subdoligranulum*, and *Sutterella* (Table 1). Genera found to increase IL-10 in the gut include *Hungatella* and *Monoglobus* (Table 1). Accordingly, in some embodiments, an individual having type 2 diabetes or obesity is administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Hungatella*, *Monoglobus*, *Faecalibacterium*, *Lachnospira*, *Prevotella*, *Roseburia*, *Slackia*, *Subdoligranulum*, and *Sutterella*. And in some embodiments, an individual having type 2 diabetes or obesity is administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, or *Dialister*.

[0126] Leaky gut syndrome is a medical condition in which the epithelium lining of the gastrointestinal track is damaged, resulting in increased permeability of damaging substances to reach into the blood stream. Leaky gut results in greater damage to other organs of the body and is commonly associated with inflammatory disorders, cardiovascular disorders, neurological disorder and metabolic disorders (R.S. Aleman, et al., *Molecules*. 2023 Jan 7;28(2):619, the disclosure of which is hereby incorporated by reference). Some cytokines have been shown to increase intestinal permeability, including INF- γ , TNF- α and IL-1 β ; and some cytokines and factors have been shown to improve intestinal barrier function including IL-10, TGF- β , and EGF (F. Meyer, et al., *Autoimmun Rev.* 2023 Jun;22(6):103331; and X. Tang, et al., *Mediators Inflamm.* 2016;2016:1927348; the disclosures of which are hereby incorporated by reference. In some embodiments, an individual having leaky gut syndrome (or any medical disorder commonly associated with leaky gut syndrome) is administered microbial genera to reduce one or more of: INF- γ , TNF- α or IL-1 β , and or to increase one or more of: IL-10, TGF- β , or EGF. Genera found to reduce INF- γ in the gut include *Blautia*, *Dialister*, and *Fusicatenibacter* (Table 1). Genera found to reduce TNF- α in the gut include *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, and *Frisingicoccus* (Table 1). Genera found to reduce IL-1 β in the gut include *Agathobacter*, *Butyricimonas*, *Collinsella*,

Desulfovibrio, *Faecalibacterium*, *Lachnospira*, *Prevotella*, *Roseburia*, *Slackia*, *Subdoligranulum*, and *Sutterella* (Table 1). Genera found to increase IL-10 in the gut include *Hungatella* and *Monoglobus* (Table 1). Genera found to increase TGF- β in the gut include *Acutalibacter*, *Akkermansia*, *Clostridium_sensu_stricto*, *Clostridium_XVIII*, *Flavonifractor*, *Holdemania*, and *Hungatella* (Table 1). Genera found to increase EGF in the gut include *Anaerostipes*, *Barnesiella*, *Eggerthella*, *Intestinibacter*, *Neglecta*, *Parabacteroides*, and *Romboutsia*. Accordingly, in some embodiments, an individual having leaky gut syndrome (or any medical disorder commonly associated with leaky gut syndrome) is administered one or more of: *Blautia*, *Dialister*, *Fusicatenibacter*, *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Faecalibacterium*, *Lachnospira*, *Prevotella*, *Roseburia*, *Slackia*, *Subdoligranulum*, *Sutterella*, *Hungatella*, *Monoglobus*, *Acutalibacter*, *Akkermansia*, *Clostridium_sensu_stricto*, *Clostridium_XVIII*, *Flavonifractor*, *Holdemania*, *Anaerostipes*, *Barnesiella*, *Eggerthella*, *Intestinibacter*, *Neglecta*, *Parabacteroides*, or *Romboutsia*. And in some embodiments, an individual having leaky gut syndrome (or any medical disorder commonly associated with leaky gut syndrome) is administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, or *Hungatella*.

[0127] Various embodiments are directed to treatment regimens based on an assessment of expression of gene products of the patient to indicate which gene products are unhealthy in the patient. In these embodiments, a biological sample is acquired from an individual and examined for expression of gene products and based on the expression profile, a determination of whether gene product expression is within a healthy range can be made. When expression of gene products is determined not to be within a healthy range (or on the borders of a healthy range), the individual can be administered microbial genera to adjust gene product expression back into a healthy range. As provided in Table 1, many gene products within the circulatory system are significantly correlated with microbiome composition in the gastrointestinal tract (i.e., as indicated by stool microbiome), nasal cavity, oral cavity, and skin. Further, as described within the Examples and Data below, microbial genera can alter gene product expression patterns of immune

responsive organoids, suggesting that administration of beneficial microbial genera would alter a host's gene product expression back into a healthy range.

[0128] In several embodiments, an individual can be assessed for gene expression products and treated with microbial genera as follows:

- (a) collect a biological sample of an individual
- (b) determine that the gene product expression level
- (c) based on the gene product expression level, administer to the individual one or more microbial genera to adjust gene product expression level.

In many embodiments, the method is performed as part as a screening procedure of the individual. In some embodiments, the individual has not been diagnosed with a particular medical condition prior to the screening assay. In some embodiments, the screening procedure is performed to determine gene product expression associated with a particular medical condition. In some embodiments, the individual has been diagnosed with (or determined to be at risk for) a particular medical condition and the gene products assessed are related to the medical condition.

[0129] Various circulatory gene products that can be assessed are provided in Table 1. Numerous circulatory gene products that have been associated with various medical disorders, such as (for example) BDNF, EGF, Eotaxin, INF- α , INF- γ , IL-1 β , IL-6, IL-10, IL-12, IL-17, IL-22, IL-23, MCP-1, RANTES, TGF- β , and TNF- α . Accordingly, in some embodiments, a biological sample (e.g., blood, plasma, CSF) is assessed for one or more gene products listed within Table 1. And in some embodiments, a biological sample (e.g., blood, plasma, CSF) is assessed for one or more of the following gene products: BDNF, EGF, Eotaxin, INF- α , INF- γ , IL-1 β , IL-6, IL-10, IL-12, IL-17, IL-22, IL-23, MCP-1, RANTES, TGF- β , or TNF- α .

[0130] An individual can be administered one or more microbial genera to increase or to decrease a circulatory gene products, which can be based on assessment of circulatory gene product expression level. A gene product can be lowered by administering one or more microbial genera that are negatively correlated with the gene product (see Table 1). A gene product can be increased by administering one or more microbial genera that are positively correlated with the gene product (see Table 1).

[0131] To reduce levels of circulatory Eotaxin, an individual can be administered one or more of: *Desulfovibrio* or *Escherichia_Shigella* to the gastrointestinal tract. To reduce levels of circulatory INF- α , an individual can be administered one or more of: *Blautia* or *Dialister* to the gastrointestinal tract. To reduce levels of INF- γ , an individual can be administered one or more of: *Blautia*, *Dialister*, or *Fusicatenibacter* to the gastrointestinal tract. To reduce levels of circulatory IL-1 β , an individual can be administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Faecalibacterium*, *Lachnospira*, *Prevotella*, *Roseburia*, *Slackia*, *Subdoligranulum*, or *Sutterella* to the gastrointestinal tract. To reduce levels of circulatory IL-6, an individual can be administered one or more of: *Collinsella*, *Dialister*, or *Fusicatenibacter* to the gastrointestinal tract. To reduce levels of circulatory IL-12, an individual can be administered one or more of: *Butyricimonas*, *Collinsella*, or *Fusicatenibacter* to the gastrointestinal tract. To reduce levels of circulatory IL-17, an individual can be administered one or more of: *Dialister*, *Subdoligranulum*, or *Senegalimassilia* to the gastrointestinal tract. To reduce levels of circulatory IL-23, an individual can be administered one or more of: *Butyricimonas*, *Dialister*, *Holdemanella*, or *Senegalimassilia* to the gastrointestinal tract. To reduce levels of circulatory MCP-1, an individual can be administered one or more of: *Blautia*, *Desulfovibrio*, *Dialister*, or *Slackia* to the gastrointestinal tract. To reduce levels of circulatory RANTES, an individual can be administered one or more of: *Butyricimonas*, *Collinsella*, *Holdemanella*, or *Lawsonibacter* to the gastrointestinal tract. To reduce levels of circulatory TNF- α , an individual can be administered one or more of: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, or *Frisingicoccus* to the gastrointestinal tract.

[0132] To increase levels of circulatory BDNF, an individual can be administered one or more of: *Barnesiella*, *Eggerthella*, *Lachnospira* or *Parabacteroides* to the gastrointestinal tract. To increase levels of circulatory EGF, an individual can be administered one or more of: *Anaerostipes*, *Barnesiella*, *Eggerthella*, *Intestinibacter*, *Neglecta*, *Parabacteroides*, or *Romboutsia* to the gastrointestinal tract. To increase levels of circulatory IL-10, an individual can be administered one or more of: *Hungatella* or *Monoglobus* to the gastrointestinal tract. To increase levels of circulatory IL-17, an

individual can be administered one or more of: *Adlercreutzia*, *Barnesiella*, *Butyricicoccus*, *Cloacibacillus*, *Dysosmobacter*, or *Faecalicatena* to the gastrointestinal tract. To increase levels of circulatory IL-22, an individual can be administered one or more of: *Anaerotignum*, *Butyrivibrio*, *Cloacibacillus*, *Dysosmobacter*, *Frisingicoccus*, *Gordonibacter*, *Negativibacillus*, *Phoceia*, *Pseudoflavonifractor*, *Raoultibacter*, or *Turicibacter* to the gastrointestinal tract. To increase levels of circulatory TGF- β , an individual can be administered one or more of: *Acutalibacter*, *Akkermansia*, *Clostridium_sensu_stricto*, *Clostridium_XVIII*, *Flavonifractor*, *Holdemania*, or *Hungatella* to the gastrointestinal tract.

[0133] In one example, gene products IL-17 and IL-22 are assessed in an individual. Expression of IL-17 and IL-22 within the circulatory system has been associated with healthy insulin sensitivity and low or absent expression of these products has been associated with insulin resistance and type 2 diabetes. Accordingly, an individual can be orally or rectally administered one or more of: *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio* to improve IL-17 or IL-22 levels. When a biological sample of a patient is assessed and indicates that expression of IL-17 and/or IL-22 within the circulatory system is low or absent, the patient is administered beneficial microbial genera comprising one or more of: *Barnesiella*, *Frisingicoccus*, or *Butyrivibrio*.

[0134] Various embodiments are directed to treatment regimens based on an assessment of clinical phenotype readouts of common blood analytes. In these embodiments, a blood sample is acquired from an individual and examined for levels of blood analytes. Provided in Table 2 is a list of common blood analyte readouts that are significantly associated with microbial genera and the constituents that mediate the phenotypic result. When it is determined that a patient does not have a healthy level of one or more analytes, the individual can be administered beneficial microbial genera that can correct the level of the one or more analytes.

[0135] In several embodiments, an individual can be assessed for circulating metabolite levels and treated with microbial genera as follows:

- (a) collect a blood or serum sample of an individual
- (b) measure the level of one or more analytes in the sample

- (c) determine that the level of one or more analytes is not within a healthy range (or is near the borderline)
- (d) based on the level of one or more analytes, administer to the individual beneficial microbial genera to get the metabolite back into a healthy range.

In many embodiments, the method is performed as part as a screening procedure of the individual. In some embodiments, the individual has not been diagnosed with a particular medical condition prior to the screening assay. In some embodiments, the screening procedure is performed to determine analyte levels associated with a particular condition. In some embodiments, the individual has been diagnosed with (or determined to be at risk for) a particular medical condition and the analytes assessed are related to the medical condition.

[0136] Various circulatory analytes that can be assessed are provided in Table 3. Accordingly, in some embodiments, a biological sample (e.g., blood, plasma, CSF) is assessed for one or more analytes listed within Table 3.

[0137] An individual can be administered one or more microbial genera to increase or to decrease a circulatory analyte, which can be based on assessment of circulatory analytes. An analyte can be lowered by administering one or more microbial genera that are negatively correlated with the gene product (see Table 2). An analyte can be increased by administering one or more microbial genera that are positively correlated with the gene product (see Table 2).

[0138] In one example, skin microbiomes comprising the microbial genus *Haemophilus* are shown to be negatively correlated with unhealthy cholesterol (e.g., LDL and non-HDL) (Table 2). Thus, an individual can be topically administered *Haemophilus* to reduce unhealthy cholesterol levels. When the circulating analyte levels of an individual is assessed and indicates that the individual has high cholesterol, high LDL cholesterol, high non-HDL, and/or high LDL to HDL ratio, the individual can be administered beneficial microbial genera comprising *Haemophilus*.

[0139] In one example, gut microbiomes comprising the microbial genus *Akkermansia* are shown to be negatively correlated with A1C (Table 2). Thus, an individual can be orally or rectally administered *Akkermansia* to reduce A1C levels. When the circulating

analyte levels of an individual is assessed and indicates that the individual has high A1C, the individual can be administered beneficial microbial genera comprising *Akkermansia*.

[0140] Many other microbial genera have been found to promote healthy analyte levels and thus a method can be performed to administer microbial genera to promote healthy analyte levels in accordance with various embodiments.

[0141] Various embodiments are directed to treatment regimens based on an assessment of microbiome composition of the patient to indicate whether the patient could benefit from administration of microbial genera. In these embodiments, a microbiome sample is acquired from an individual and examined for microbiome composition, a determination of whether a healthy amount of beneficial microbial genera can be made. When it is determined that there is a lack of beneficial microbial genera, the individual can be administered beneficial microbial genera to introduce the beneficial microbial genera into the host's microbiome.

[0142] In several embodiments, an individual can be assessed for microbiome composition and treated with beneficial microbial genera as follows:

- (a) collect a microbiome sample of an individual
- (b) determine that the composition of the microbiome lacks beneficial genera
- (c) based on the composition of the microbiome, administer to the individual beneficial microbial genera to help promote a healthy microbiome composition.

In many embodiments, the method is performed as part as a screening procedure of the patient. In some embodiments, the patient has not been diagnosed with a particular medical condition prior to the screening assay. In some embodiments, the screening procedure is performed to determine microbiome composition associated with a particular medical condition. In some embodiments, the patient has been diagnosed with (or determined to be at risk for) a particular medical condition and the microbial genera assessed are related to the medical condition.

[0143] In one example, gastrointestinal microbiomes comprising microbial genera *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio* have been associated with healthy insulin sensitivity and gastrointestinal microbiomes having a low presence or an absence of these microbial genera has been associated with insulin resistance and type 2 diabetes.

When the gastrointestinal microbiome of a patient is assessed and indicates that microbiome comprises low presence or an absence of one or more of the microbial genera *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio*, the patient is administered beneficial microbial genera comprising one or more of: *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio*. In some embodiments, a gastrointestinal microbiome is assessed via a stool sample. Many other microbial genera have been found to help promote a healthy microbiome composition and thus a method can be performed to administer these microbial genera as determined by whether the composition of a microbiome lacks these beneficial genera in accordance with various embodiments.

[0144] Various embodiments are directed to treatment regimens based on an assessment of an immune responsive organoid derived from an individual to indicate whether the individual would benefit from administration of microbial genera. In these embodiments, immune responsive tissue (e.g., tonsil tissue) is extracted or otherwise generated from the patient and cultured. The immune responsive is treated with a microbial genus or a combination of microbial genera to determine if the microbial genus or the combination of microbial genera can induce healthy gene product response. When it is determined that the microbial genus or the combination of microbial genera can induce healthy gene product response, the individual can be administered the microbial genus or the combination of microbial genera can induce healthy gene product response.

[0145] In several embodiments, an individual can be assessed via an immune responsive organoid and treated with microbial genera as follows:

- (a) collect and culture or otherwise obtain a culture of immune responsive organoids of an individual
- (b) contact the culture of immune responsive organoids with a culture supernatant of a microbial genus or a combination of microbial genera
- (c) determine that the microbial genus or the combination of microbial genera yield a desired response by the immune responsive organoids
- (d) based on the response by the immune responsive organoids, administer to the individual the microbial genus or the combination of microbial genera.

In many embodiments, the method is performed as part as a screening procedure of the individual. In some embodiments, the individual has not been diagnosed with a particular medical condition prior to the screening assay. In some embodiments, the screening procedure is performed to determine microbiome composition associated with a particular medical condition. In some embodiments, the individual has been diagnosed with (or determined to be at risk for) a particular medical condition and the microbial genera assessed are related to the medical condition.

[0146] In one example, gastrointestinal microbiomes comprising microbial genera *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio* have been associated with healthy insulin sensitivity and gastrointestinal microbiomes having a low presence or an absence of these microbial genera has been associated with insulin resistance and type 2 diabetes. Accordingly, a culture of immune responsive organoids of a patient can be contacted with culture products of a microbial genus or a combination of microbial genera comprising one or more of *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio*. When the patient derived immune responsive organoid culture is assessed and indicates that the organoid culture produced a desired response by the microbial genus or the combination of microbial genera comprising one or more of *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio*, the patient is administered the microbial genus or the combination of microbial genera. In some embodiments, the immune responsive organoid culture is derived from an individual's tonsil tissue, lymph node tissue, or spleen tissue. Many other microbial genera have been found to provide a desired response by immune responsive organoids and can be utilized in accordance with various embodiments.

[0147] Various embodiments are directed to probiotic supplements based on microbial genera that have been determined to be beneficial. In these embodiments, a probiotic supplement can be produced or manufactured for administration to the general public. As discussed in greater detail below, the probiotic supplement can be produced in any means for microbial genera administration. Probiotic supplements can be sold with the intent that individuals of the general public are to self-administer beneficial microbial genera.

[0148] In one example, gastrointestinal microbiomes comprising microbial genera *Barnesiella*, *Frisingicoccus*, and *Butyrivibrio* have been associated with healthy insulin sensitivity and gastrointestinal microbiomes having a low presence or an absence of these microbial genera has been associated with insulin resistance and type 2 diabetes. Furthermore, gastrointestinal microbiomes comprising the microbial genus *Haemophilus* have been associated with low levels of cholesterol, especially unhealthy cholesterol (e.g., LDL and non-HDL). Accordingly, a probiotic supplement can be produced or manufactured with a microbial genus or a combination of microbial genera comprising one or more of *Barnesiella*, *Frisingicoccus*, *Butyrivibrio*, and *Haemophilus*. Individuals of the general public can administer the probiotic supplement, which may provide metabolic health benefits. Many other microbial genera have been found to provide health benefits and can be included a probiotic for general public administration in accordance with various embodiments.

[0149] Microbial genera can be administered by a variety of modes. Generally, the mode of administration relates to a local microbiome to be augmented by the microbial genera.

[0150] In some embodiments, administration of microbial genera to augment a gastrointestinal microbiome can comprise an oral administration or a rectal administration. Oral administration can comprise the administration of one or more of: a probiotic food, a probiotic beverage, a liquid solution composition, a gel composition, an oil composition, an emulsion composition, a capsule, an enteric-coated capsule, a dragee, a gavage, a lyophilized powder, a freeze-dried powder, a combination thereof, or any other means to orally administer microbial genera to the gastrointestinal tract. Rectal administration can comprise the administration of one or more of: a probiotic liquid, a probiotic gel, a probiotic suppository, a probiotic fecal transplant, a probiotic enema, a probiotic catheter, a lyophilized powder, a freeze-dried powder, a combination thereof, or any other means to rectally administer microbial genera to the gastrointestinal tract.

[0151] In some embodiments, administration of microbial genera to augment an oral microbiome can comprise an oral administration to the oral cavity. Oral administration to the oral cavity can comprise the administration of one or more of: a probiotic gel, a

probiotic suppository, a probiotic oil, a probiotic emulsion, a probiotic sublingual strip, a probiotic mouthwash, a lyophilized powder, a freeze-dried powder, a combination thereof, or any other means to orally administer microbial genera to the oral cavity.

[0152] In some embodiments, administration of microbial genera to augment a nasal microbiome can comprise a nasal administration to the nasal cavity. Nasal administration can comprise the administration of one or more of: a probiotic gel, a probiotic suppository, a probiotic oil, a probiotic emulsion, a probiotic inhaler, a probiotic nasal wash, a lyophilized powder, a freeze-dried powder, a combination thereof, or any other means to administer microbial genera to the nasal cavity.

[0153] In some embodiments, administration of microbial genera to augment a skin microbiome or a wound microbiome can comprise a topical administration to the skin. Topical administration can comprise the administration of one or more of: a probiotic gel, a probiotic suppository, a probiotic oil, a probiotic emulsion, a probiotic ointment, a probiotic lotion, a probiotic powder, a probiotic cream, a lyophilized powder, a freeze-dried powder, a combination thereof, or any other means to topically administer microbial genera to the skin or wound.

[0154] In some embodiments, administration of microbial genera to augment a pulmonary microbiome can comprise a pulmonary administration to the lungs. Pulmonary administration can comprise the administration of one or more of: a probiotic inhaler, a probiotic nebulizer, a lyophilized powder, a freeze-dried powder, a combination thereof, or any other means to administer microbial genera to the lungs.

[0155] In some embodiments, administration of microbial genera to augment a urethral microbiome can comprise a urethral administration to the urethral canal. Urethral administration can comprise the administration of one or more of: a probiotic gel, a probiotic suppository, a probiotic oil, a probiotic emulsion, a probiotic catheter, and any other means to administer microbial genera to the urethral canal.

[0156] In some embodiments, administration of microbial genera to augment a vaginal microbiome can comprise a vagina administration to the vaginal canal. Urethral administration can comprise the administration of one or more of: a probiotic gel, a probiotic suppository, a probiotic oil, a probiotic emulsion, a probiotic cream, a probiotic

ointment, a probiotic vaginal wash, a probiotic catheter, a lyophilized powder, a freeze-dried powder, a combination thereof, or any other means to administer microbial genera to the vaginal canal.

[0157] In some embodiments, administration of microbial genera to augment an ocular surface can comprise an ocular administration to the ocular surface. Ocular administration can comprise the administration of one or more of: a probiotic gel, a probiotic cream, a probiotic cream, a probiotic ocular drops, a probiotic ocular wash, a lyophilized powder, a freeze-dried powder, a combination thereof, or any other means to administer microbial genera to the ocular surface.

[0158] In some embodiments, administration of microbial genera to augment an ear canal can comprise an otic administration to the ear canal. Otic administration can comprise the administration of one or more of: a probiotic gel, a probiotic cream, a probiotic cream, a probiotic otic drops, a probiotic otic wash, a lyophilized powder, a freeze-dried powder, a combination thereof, or any other means to administer microbial genera to the ocular surface.

[0159] Provided herein are methods of treating various medical disorders in a recipient. In some embodiments, a recipient is administered beneficial microbiota as described herein. In some embodiments, the amount of bacterium for treatment is a therapeutically effective amount of the bacterium. In some embodiments, the bacterium for treatment is lyophilized. In some embodiments, the bacterium for treatment is freeze-dried. In some embodiments, the bacterium for treatment is lyophilized or freeze-dried and subsequently reconstituted.

[0160] In some embodiments, a bacterium is administered in a therapeutically effective amount as part of a course of treatment. As used in this context, to "treat" means to ameliorate or prevent at least one symptom of the disorder to be treated or to provide a beneficial physiological effect. A therapeutically effective amount can be an amount sufficient to prevent reduce, ameliorate or eliminate the symptoms of diseases or pathological conditions susceptible to such treatment. In certain embodiments, a therapeutically effective amount is an amount sufficient to (for example) reconstitute a

balanced microbiome, correct expression level of a gene product, correct level of an analyte, or improve a medical disorder phenotype.

[0161] Dosage, toxicity and therapeutic efficacy of a pharmaceutical composition can be determined, e.g., by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds that exhibit high therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0162] Data obtained from cell culture assays or animal studies can be used in formulating a range of dosage for use in humans. If a bacterium comprising a polypeptide is provided systemically, the dosage of effector polypeptides lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. A dose may be formulated in animal models to achieve a local environment concentration in a range that includes an IC₅₀. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by immunological based assays or liquid chromatography.

[0163] An "effective amount" is an amount sufficient to effect beneficial or desired results. For example, a therapeutically effective amount is one that achieves the desired therapeutic effect. This amount can be the same or different from a prophylactically effective amount, which is an amount necessary to prevent onset of disease or disease symptoms. An effective amount can be administered in one or more administrations, applications or dosages. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject

with a therapeutically effective amount of a bacterium described herein can include a single treatment or a series of treatments. For example, several divided doses may be administered daily, one dose, or cyclic administration of the compounds to achieve the desired therapeutic result.

[0164] Frequency of administration for a bacterium, inclusive of the various beneficial microbiota described herein, can be at least once a year, at least once every six months, at least once every five months, at least once every four months, at least once every three months, at least once every two months, at least once a month, at least once every four weeks, at least once every three weeks, at least once every two weeks, at least once a week, at least twice a week, at least three times a week, at least four times a week, at least five times a week, at least six times a week, daily, two times per day, three times per day, four times per day, five times per day, six times per day, eight times per day, nine times per day, ten times per day, eleven times per day, twelve times per day, at least once every 12 hours, at least once every 6 hours, at least once every 2 hours, at least once every hour, at least once every 30 min, at least once every 20 min, or at least once every 10 min. Administration can also be continuous and adjusted to maintaining a level of the compound within any desired and specified range.

[0165] A bacterium may be administered in an amount effective to yield a desired result, such as correcting gene product expression level within the subject, reduction of inflammation, improvement in glucose sensitivity, improvement of a neurological symptom, reduction of HDL cholesterol levels, etc. Examples of bacterial doses of colony forming units (CFU) include from about 1×10^5 to about 1×10^{13} , from about 1×10^6 to about 1×10^{10} , from about 1×10^5 to about 1×10^7 , from about 1×10^6 to about 1×10^8 , from about 1×10^7 to about 1×10^9 , from about 1×10^8 to about 1×10^{10} , from about 1×10^9 to about 1×10^{11} , from about 1×10^{10} to about 1×10^{12} , and from about 1×10^{11} to about 1×10^{13} . In various embodiments, the dosage is about 1×10^6 CFUs, the dosage is about 1×10^7 CFUs, the dosage is about 1×10^8 CFUs, the dosage is about 1×10^9 CFUs, the dosage is about 1×10^{10} CFUs, the dosage is about 1×10^{11} CFUs, the dosage is about 1×10^{12} CFUs, or the dosage is about 1×10^{13} CFUs. In reference to bacterial CFU dosage, about is $\pm 50\%$.

[0166] A bacterium can be grown utilizing techniques for cultivation of bacteria, which is appreciated in the art. Generally, a microbiota can be enriched and/or isolated from a microbiome sample. To isolate specific microbial genera, a microbiome can be sorted using a cell sorter or a dilution technique to yield single cells within a field or within a individual wells of plate. Upon expansion of colonies, the taxonomies of microbial colonies can be identified by any appropriate technique (e.g., sequencing). Alternatively, direct targeting of particular taxa can be achieved using a selective antibody. Various cultures may need optimization of media and/or a co-culture system. For further details and examples of particular methodologies to cultivate microbiome-derived bacteria, see X. Wan, et al., *Microorganisms*. 2023 Apr 20;11(4):1080, the disclosure of which is hereby incorporated by reference.

[0167] Microbial cultures can be lyophilized and/or freeze dried, which can yield a shelf-stable powder. Lyophilized and/or freeze-dried bacteria can be administered in that form or reconstituted prior to administration. In some embodiments, a composition for storage and/or administration comprises a lyophilized bacterium. In some embodiments, a composition for storage and/or administration comprises a freeze-dried bacterium. In some embodiments, a composition comprising a lyophilized and/or freeze-dried bacterium can further comprise one or more protectant agents, which can enhance the survivability of the bacterium. Examples of protectant agents include (but are not limited to) dimethylsulfoxide (Me₂SO), glycerol, blood serum, serum albumin, skimmed milk powder, whey protein, peptone, yeast extract, sucrose, glucose, trehalose, lactose, methanol, polyvinylpyrrolidone (PVP), sorbitol, sodium ascorbate, and malt extract.

Assessing Effect of Microbial Strains on Host Immune Response

[0168] Several embodiments are directed to assessing the effect microbial genera on the immune response of its host. In many embodiments, an immune responsive organoid culture system is utilized to assess the effect of microbial genera. Any organoid culture system capable of indicating an immune response can be utilized. In some embodiments, a tonsil organoid system is utilized. In some embodiments, a lymph node organoid system is utilized. In some embodiments, a spleen tissue organoid system is utilized. Immune

responsive culture systems and methods are described in U.S. Appl. No. 18/094,851, the disclosure of which is hereby incorporated by reference.

[0169] Provided in Fig. 2 is an example of a method to assess microbial genera effect on gene host expression. The method utilizes an immune responsive organoid culture system that is co-cultured with microbial genera. The co-culture system can assess the effect the microbial genera on the immune system, including T-cell activation, humoral response, and gene product expression.

[0170] Method 200 can begin by providing (201) immune responsive organoids in culture. An immune responsive organoid is an in vitro cluster of immune cells, which can be derived from lymphoid tissue or differentiated from stem cells. In many embodiments, the cluster of immune cells comprises one or more of: T-cells, antigen presenting cells, dendritic cells, and B-cells. T-cells can comprise CD8+ T-cells and/or CD4+ T-cells. B-cells can comprise CD38+ B-cells and/or CD27+ B-cells.

[0171] In some embodiments, the immune responsive organoids are derived from lymphoid tissue, including (but not limited to) tonsils, lymph nodes, and spleen. In some embodiments, the immune responsive organoids are derived from tonsil tissue, which can be collected from a donor as a biopsy or as whole tonsils (e.g., tonsillectomy). In some embodiments, the immune responsive organoids are derived from lymph nodes, which can be collected from a donor as a biopsy or as whole lymph nodes (e.g., lymphadenectomy). In some embodiments, the immune responsive organoids are derived from spleen, which can be collected from a donor as a biopsy. In some embodiments, the immune responsive organoids are collected from a patient, which may be used for patient-specific response assessment. Tissue and cells can be cryopreserved until ready for culture.

[0172] To culture immune responsive organoids, the lymphoid tissue is dissociated, washed, and dispersed into low-attachment tissue-culture wells. In some embodiments, tissue-culture wells with permeable membranes can be utilized to facilitate the collection and/or exchange of media of the organoid culture. The dissociated tissue can be kept in an appropriate medium, can be allowed to reaggregate, and can be developed into immune responsive organoids. To assist in immune cell culture, factors for promoting

immune cell health and/or maturity can be provided, such as (for example) B-cell activating factor and one or more adjuvants (e.g., aluminum hydroxide).

[0173] Method 200 adds (203) a microbial culture or a microbial culture supernatant to the organoid culture. Microbial genera isolates (or a population of mixed microbial genera) can be collected and isolated from a microbiome sample. The isolated microbial genera isolates (or a population of mixed microbial genera) can be further cultured. A singular isolated microbial genera isolate, a mixture of genera isolates, or a population of mixed microbial genera can be utilized as a microbial culture for assessment. The organoid culture can be contacted with a live microbial culture, an attenuated or killed microbial culture, or a supernatant of microbial culture to induce a response of the organoids. Any microbiome sample can be utilized. Microbiome samples can be obtained from the microbiome source and excretions or waste of that source (e.g., stool sample). Culturing of microbial genera isolates (or population of mixed microbial genera) can be extracted and cultured as described herein.

[0174] Provided in Fig. 3 is one example of a method yield a microbial genera culture supernatant product. The method can collect microbial genera isolates and then grow in a liquid culture. The culture can be pelleted via centrifugation and supernatant is extracted and filtered. The filtered supernatant is collected, which can be added to the organoid culture.

[0175] Returning to Fig. 2, method 200 measures (205) organoid response. After adding microbial genera culture supernatant to the organoid culture, stimulation of the organoid culture is allowed to continue for a period of time. In some embodiments, the stimulation period is between 12 hours and up to 672 hours (4 weeks). In various embodiments, the stimulation period is about 12 hours, the stimulation period is about 24 hours, the stimulation period is about 48 hours, the stimulation period is about 72 hours, the stimulation period is about 96 hours, the stimulation period is about 120 hours, the stimulation period is about 144 hours, the stimulation period is about 168 hours, the stimulation period is about 240 hours, the stimulation period is about 336 hours, the stimulation period is about 504 hours, or the stimulation period is about 672 hours. In

some embodiments, addition of microbial genera culture supernatant to the organoid culture is repeated over the course of the stimulation period.

[0176] After a period of stimulation, the organoids are assessed for responsiveness. In some embodiments, the supernatant of the organoid culture is utilized for assessment. In some embodiments, the cells of the organoid culture are utilized for assessment. In some embodiments, cell lysates of the organoid culture are utilized for assessment. In some embodiments, nucleic acids of the organoid culture are utilized for assessment. In some embodiments, gene products of the organoid culture are utilized for assessment.

[0177] Any assessment of immune response can be performed. In some embodiments, gene products are assessed to determine which genes were activated. In some embodiments, activation of T-cells is assessed. In some embodiments, humoral response (e.g., antibody production) is assessed. In some embodiments, cytokine and/or chemokine response is assessed.

[0178] While a specific example of a method for assessing microbial genera using an immune response organoid co-culture is described above, one of ordinary skill in the art can appreciate that various steps of the process can be performed in different orders and that certain steps may be optional according to some embodiments of the description. As such, it should be clear that the various steps of the method could be used as appropriate to the requirements of specific applications. Furthermore, any of a variety of methods for microbial genera using an immune response organoid co-culture appropriate to the requirements of a given application can be utilized in accordance with various embodiments of the disclosure.

EXAMPLES AND DATA

[0179] Provided in Figs. 4A to 4E is the results of immune response of six microbial strains utilized in the tonsil co-culture assay. The immune response measured is the induced expression of cytokines: IL-1A (Fig. 4A); IL-1RA (Fig. 4B); CCL3 (Fig. 4C); M-CSF (Fig. 4D); and IL-6 (Fig. 4E). The six microbial strains tested are as follows: strain 1 is *Clostridia.spp*; strain 2 is *Coprococcus.spp*; strain 3 is *E. coli.spp*; strain 4 is *Bacteriodes.spp*; strain 5 is *Prevotella.spp*; and strain 6 is a mix of *Roseburia.spp*. Used

as controls are phosphate buffered saline (PBS), culture media; staphylococcal enterotoxin B (SEB); toll-like receptor agonist (TLR), and live attenuated influenza vaccine (LIAV). As can be seen in the results, the various microbial strains each yielded a unique response for each cytokine. These results show that specific strains can induce specific immune responses. Further, the immune response of a microbiome is influenced by the strains within its composition and a change in composition can yield a different result. This indicates that introduction of specific strains can be administered to an individual to promote certain immune responses in order to achieve certain clinical phenotypes or treat medical disorders.

[0180] Provided in Fig. 5 is principal component analysis of the tonsil co-culture assay results. These results show that the tonsil co-culture system can generate strain specific immune response that is highly repeatable and phylogenetically relevant. The results of the different individuals for each strain all clustered together. Further, *Bacteroides* and *Prevotella* are known to be very close phylogenetically, and as the results show, these two genera clustered close to one another.

STUDY: LONGITUDINAL PROFILING OF THE MICROBIOME AT FOUR BODY SITES REVEALS CORE STABILITY AND INDIVIDUALIZED DYNAMICS DURING HEALTH AND DISEASE

[0181] The human microbiome comprises highly dynamic microbial communities inhabiting various body sites, engaging in intricate host-microbial interactions that display territory-specific complexity. Advancements in multi-omics technologies have catalyzed the elucidation of the molecular mechanisms underlying microbial ecology and their interactions with host, unveiling the critical roles of the microbiome in normal physiological processes such as aging as well as diseases including inflammatory bowel disease (IBD), cardiovascular disease, and type 2 diabetes mellitus (T2DM).

[0182] The etiology and pathogenesis of insulin resistance and T2DM have been closely linked to the human microbiome. Patients with impaired insulin and glucose homeostasis exhibit shifted microbiome composition in the gut, skin, and other body sites, reflecting an ecological dysbiosis characterized by altered microbial alpha diversity,

decreased compositional stability, and greater inter-individual variability. Compromised mucosal and skin barrier integrity, often associated with insulin resistance, may potentiate microbial translocation, thereby exacerbating systemic inflammation. Although human microbiome studies are often, by necessity, observational, a causal relationship between microbiome dysbiosis and impaired glucose/insulin homeostasis has been demonstrated through human microbiome manipulation.

[0183] While prior studies on the microbiome and glucose homeostasis have been informative, they exhibit certain limitations. Firstly, these studies often lack dense longitudinal sampling, essential for capturing stability features, thus limiting fundamental insights into host-microbe interactions. Secondly, they primarily focus on the microbiome from a single host site, overlooking the importance of simultaneous multi-region sampling for assessing microbiome site-specific dynamics, and their interplay across various host microenvironments. Lastly, most studies do not concurrently measure host clinical and molecular phenotypes, impeding the exploration of the molecular relationships underpinning health and disease-related host-microbiome interactions.

[0184] Collaborative initiatives like the Integrative Human Microbiome Project (iHMP) and Integrative Personal Omics Profiling (iPOP) offer avenues to surmount previous studies' limitations by investigating well-characterized human longitudinal cohorts. In this study, we examined the relationships between multi-site microbiomes and host health in the context of prediabetes, through characterizing the microbiome collected from four body sites in 86 adults for over six years and examining their associations with host omics and clinical characteristics. We describe unique longitudinal trajectories for microbiomes across different body sites, demonstrating their responsiveness to both host-specific and environmental factors. We found that personalized microbiomes exhibit greater stability than communal microbes, highlighting the resilience of the individualized microbiome. Nonetheless, these systems remain vulnerable to disturbances like viral infections, which may precipitate dysbiosis linked to metabolic dysfunctions. Furthermore, our analysis revealed associations between site-specific microbiomes and clinical parameters such as cytokine profiles and insulin sensitivity, highlighting the intertwined nature of immune activity and metabolic well-being.

Results

Description of the study design

[0185] We analyzed stool, skin, oral, and nasal microbiome from a human cohort of 86 participants for up to six years ($1,126.6 \pm 455.8$ days). (Fig. 6A). The cohort comprised 41 males and 45 females, aged between 29 and 75 years old (55 ± 9.8 years old), with BMIs ranging from 19.1 to 40.8 kg/m² (28.31 ± 4.44 kg/m²). Sampling occurred quarterly, with an additional 3-7 samples collected within five weeks (12% of the total) during periods of stress, such as respiratory illness, vaccination, or antibiotic use. The 16S ribosomal RNA gene sequencing method employed in this study targeted a variable region to facilitate the detection of amplicon sequence variants (ASVs), enabling the identification and differentiation of most bacterial taxa at the genus and species levels.

[0186] A unique feature of this cohort is the multi-omics phenotyping of participants at each timepoint (Fig. 6B). Untargeted proteomics (302 proteins), untargeted metabolomics (724 annotated metabolic features), targeted lipidomics (846 annotated lipids), and 62 targeted cytokine and growth factor measurements were performed, along with 51 clinical markers, including C-reactive protein (CRP), fasting glucose (FG), hemoglobin A1C (HbA1C), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) from plasma samples. (Fig. 6A). Glucose control assessments, comprising an annual oral glucose tolerance test for all participants and a gold-standard steady-state plasma glucose (SSPG) measurement for 58 individuals, classified 28 individuals as insulin-sensitive (IS) and 30 as insulin-resistant (IR) (Fig. 6C). Overall, we analyzed a total of 3,058 visits, 5,432 biological samples (1,467 plasma samples, 926 stool samples, 1,116 skin samples, 1,001 oral samples, and 922 nasal samples) generating a total of 118,124,374 measurements.

Microbial Demographics and Personalization Across Body Sites: Unraveling the Impact of Diet and Environment

[0187] We initially examined the overall demographics of the microbiome at each of the four body sites (Figs. 6D and 7A). Extending previous studies, we observed a

separation between body sites, including a clear boundary of the skin and nasal samples, highlighting the pronounced territory specificity of each microbiome.

[0188] Micro-biotypes, like enterotypes in the stool microbiome, are present in all body sites, with their community structure predominantly influenced by specific taxa. The stool microbiome primarily exhibited a gradient of abundance distributions between *Bacteroidetes* and *Firmicutes*, except for a few samples with high *Prevotella*. The recently identified core genus *Phocaeicola* had minimal impact on the overall *Bacteroidetes/Firmicutes* gradient, but samples with high *Phocaeicola* and *Bacteroides* were clearly separated. (Fig. 7A) The oral microbiome was primarily composed of *Prevotella*, *Streptococcus*, *Veillonella*, *Haemophilus*, *Neisseria*, and *Leptotrichia*. The skin and nasal microbiome samples jointly displayed a triangular distribution, primarily driven by three dominant genera: *Cutibacterium*, *Corynebacterium*, and *Staphylococcus* (Figs. 6D and 7A). The distribution of microbial genera remained consistent with findings from other cohorts, irrespective of participant diversity in insulin sensitivity in our study. (Fig. 7B). Our study, however, extends these observations by longitudinally comparing inter- and intra-individual covariance across all four body sites within the same cohort.

[0189] Intraclass (intra-individual) correlation coefficient (ICC) analysis confirmed that microbial personalization is more pronounced at the ASV level than at broader taxonomic resolutions (Fig. 7C), highlighting stronger individualization with finer taxonomy resolution. Notably, despite similar ecological characteristics and dominant bacterial constituents, the nasal microbiome manifested greater personalization than the skin microbiome (Fig. 7D), presumably because nasal microbiome dynamics are more host dependent.

[0190] While environmental factors like season and diet can influence the human microbiome, our results suggest that the impact of seasonality on the gut microbiome is relatively modest. Likely due to its direct external exposure, the skin microbiome exhibited the largest seasonal dynamic. This was followed by the oral microbiome, which may be shaped by seasonal dietary changes, as it explained more dietary variance than other sites (Fig. 7E). We also observed a significant fluctuation of the skin and oral microbiome evenness: these two communities both become more even during summer with an

increased number of different microbes (Fig. 7F) possibly triggered by environmental changes such as temperature and humidity. Based on two participants with accessible environmental and chemical exposure data, we found stronger exposome-skin microbiome covariance than in other body sites (Fig. 7G) with noticeable environmental impacts on internal sites like oral and stool microbiomes. By modeling the microbial dynamics across seasons, we found more pronounced alterations in skin and nasal microbiomes than in stool and oral microbiomes. These findings not only extend our knowledge of gut microbiome specificity and individuality to other body sites but also broaden our understanding of environmental influences on microbiomes, with diet shaping oral microbiomes and environmental exposure impacting skin and nasal microbiomes.

Microbiome from Distinct Body Sites are Ecologically Unique and Altered in Insulin Resistance

[0191] Beyond the influence of personal and environmental factors, we observed distinct ecological attributes among the microbiome at the four body sites (Fig. 6E). The stool microbiome exhibited the greatest richness and evenness, underscoring its essential complexity and functional significance. In contrast, the skin microbiome displayed a more skewed population due to its lower evenness compared to the nasal microbiome, despite their similar richness distributions. These ecological features, which often shift with disease progression, aligned with previous findings of IR-related gut dysbiosis, characterized by a significant decrease in stool microbiome's alpha diversity ($t = 2.8462$, $p\text{-value} = 0.0067$). Furthermore, shifts in the richness-evenness scatter plots for all four body sites (Fig. 7H) suggested systemic dysbiosis in IR individuals, highlighted by significantly higher skin microbiome richness ($t = -2.9102$, $p\text{-value} = 0.0057$) (Fig. 7H) and evenness ($t = -2.4393$, $p\text{-value} = 0.019$) (Fig. 7H). These shifts indicate that IR-associated dysbiosis extends beyond the gut microbiome.

[0192] Importantly, extending longitudinal observations from single body sites, we define a "core microbiome" as microbes consistently present over time, representing potentially indispensable genera at each body sites. Interestingly, we found that stool and

oral microbiomes maintain more than 25 highly prevalent core genera, whereas nasal and skin microbiomes only had three (Fig. 6F). Importantly, some core genera have low relative abundance, (e.g., *Coprococcus* Mean Prevalence = 80.75%; Mean Relative Abundance = 0.544%), demonstrating the potential significance of low-abundance strains (Fig. 7I). Intriguingly, the richness of core genera in stool and oral microbiome is negatively associated with steady-state plasma glucose (SSPG) (Spearman Rho = -0.52, p-value = 0.00047) and BMI (Spearman Rho = -0.40, p-value = 0.005), respectively (Fig. 7J), indicating that IR and obesity may be associated with a loss of core microbiomes at these sites.

[0193] We further explored the microbiome ecology variations between insulin resistant (IR) and insulin sensitive (IS) individuals. IR subjects had a significantly higher number of skin core genera ($t = -2.5856$, p-value = 0.014) and a lower number of stool core genera ($t = 2.9659$, p-value = 0.0051) compared to IS individuals (Fig. 7K). Notably, several butyrate-producing bacteria (i.e., *Coprococcus*, *Parasutterella*, and *Butyricicoccus*) were decreased in IR stool core microbiomes, whereas diabetes-related opportunistic skin pathogens (e.g., *Fingoldia* and *Acinetobacter*) were enriched in the skin core microbiome of IR individuals. In addition, we found a clear divergence of the rank prevalence curves in stool and skin microbiome (Fig. 7L), demonstrating a global microbial prevalence shift in IR individuals at these two sites.

[0194] Additionally, several taxa differed significantly between IR and IS individuals in relative abundance. The stool microbiome of IR individuals showed an increase of genus *Phocaeicola* (LEfSe_effect size: 0.03; BH-adjusted p-value = 0.017) and a reduction of the genus Unclassified *Ruminococcaceae* (LEfSe_effect size: 0.017; BH-adjusted p-value = 0.0039), whereas the skin microbiome exhibited a decrease in the genus *Cutibacterium* (LEfSe_effect size: 0.069; BH-adjusted p-value = 0.007) and an increase of the genus *Peptoniphilus* (LEfSe_effect size: 0.0076; BH-adjusted p-value = 0.0022), which has been previously associated with diabetes-related skin dysbiosis and necrotizing infections (Fig. 7M). No such differences were observed in oral and nasal microbiomes. These findings further indicate that skin and stool microbiome stability is altered in IR individuals. Overall, our results reveal that IR participants exhibit a stool

microbiome with reduced richness and butyrate-producing bacteria, and a skin microbiome more susceptible to opportunistic pathogens.

Distinct Taxon-Specific Stability and Individuality in Microbiomes Across Body Sites: A Potential Pathway for Personalized Interventions

[0195] We next examined microbiome stability at the genus level across body sites, hypothesizing stability is taxon- and site-specific. We defined a metric "Degree of Microbial Individuality" (DMI) for each genus, which quantifies similarity within an individual relative to the population; a high DMI means the microbes taxa is highly individual-specific. We also calculated a "Family Score" (FS) to evaluate microbial dissimilarity within households. Expanding observations of the stool microbiome, skin, oral and nasal microbiome also demonstrated significantly less intra-individual and within-family variation compared to the variation observed between different individuals (Fig. 8A). Intra-individually, the rate of complete ASV turnover within a genus over time was highest in the nasal microbiome (35.5% of cases), followed by skin (24.4%), stool (24.2%), and oral sites (2.7%). This finding underscores significant intra-individual ecological dynamics at the sub-genus level within microbiomes, despite overall community stability.

[0196] The DMI, irrespective of relative abundance, was high in the stool microbiome (Fig. 8B), particularly within the *Bacteroidetes* phylum (Fig. 8C), possibly due to its pronounced adaptive evolution and substantial colonization resistance. Furthermore, the stool microbiome had the lowest FS, whereas oral and nasal microbiomes shared greater similarity within households (Fig. 9A), likely due to common living environments or direct microbiome exchanges.

[0197] Our data revealed substantial DMI variance across body sites, potentially attributable to inherent niche-specific taxonomic complexities. For example, *Corynebacterium* in nasal and *Bacteroides* in stool showed the highest DMI, respectively. These results suggest that specific microbial taxa, adapting to their respective niches, may exhibit enhanced individualization. Therefore, the microbial community at each body site is largely shaped by niche-specific interactions. In contrast, environmental genera

such as *Klebsiella* and *Haemophilus* displayed uniformly low DMI across all examined body sites, indicating that external environmental factors exerts a relatively weaker influence on the individuality of the native host microbiome. Interestingly, after adjusting individuals' collective DMI by each genera's relative abundance, we found a notable increase of individuality in the stool microbiomes of IR individuals (Fig. 9B), likely due to the increased *Bacteroidetes* among IR individuals.

[0198] Overall, the DMI and FS metrics for each specific genus offer an overarching perspective on microbial host specificity. Meanwhile, they provide crucial insights into the taxonomic composition of the community and potential influences of environmental factors on the host's microbiome. Additionally, the DMI measurements provide important ecological characteristics about micro-biotypes, including 'enterotype' in stool microbiome or 'cutotypes' in skin microbiome.

[0199] Microbiome stability is highly personalized. Consequently, we explored the relationship between microbial individuality and stability across body sites. We first examined the genus recolonization rate, measured by ASV consistency when a genus is detectable after being undetected in one or more consecutive samples. The overall recolonization rate (measured by $1 - \text{Pairwise Jaccard Distance}$) was significantly associated with DMI on all three body sites except for the oral microbiome (Fig. 10A), which intrinsically maintains a high recolonization rate. Such correlations were strongest in the nasal microbiome (Fig. 10A), potentially explaining the high ICC observed above. Surprisingly, no difference in recolonization rate was found between IR and IS individuals. (Fig. 11A). Our results suggest that highly individualized strains are more likely to recolonize, validating a hypothesis raised by fecal transplantation studies and implying its potential efficacy in treating IR-related dysbiosis.

[0200] The longitudinal data also enabled tracking of microbiome stability over time by quantifying the dissimilarity between sample pairs in relation to collection date-intervals, which was reported to be higher in IBD-related gut dysbiosis. Our analysis revealed that the stool microbiome changed more slowly over time, with the nasal site exhibiting the fastest rate of change ($p\text{-value} < 0.001$) (Fig. 10B). Additionally, IR individuals showed significantly lower stability in stool and skin microbiomes than IS individuals, as evidenced

by linear mixed models (Stool p -value: 1.82×10^{-06} , Skin p -value: 2.84×10^{-12}), corroborating our findings of greater microbial abundance disparities in these two body sites between IR and IS participants. (Fig. 7M).

Intra- and Inter-Individual Correlations of Microbiome Dynamics Across Body Sites: Implications for Microbial Interdependence and Territory Specificity

[0201] We next investigated whether microbiome dynamics were intra-individually co-associated across body sites, both at the community level and for individual taxa. Hierarchical clustering demonstrated a strong link in personal microbiome dynamics between the skin and nasal sites, whereas the dynamics of the stool microbiome was less correlated with other body sites. (Fig. 10C). The inter-site correlation of microbiome stability indicates systemic microbial coordination, potentially regulated by the common mucosal system. Comparison between IS and IR individuals revealed that both groups had a strong skin-nasal link, but a skin-oral correlation was exclusive to IS individuals. (Figs. 11B and 11C). This implies that IR status undermines the stability of the skin or oral microbiome, possibly due to the compromised host regulation of microbiome stability or due to impaired mucosal immunity related to IR, a key factor for between-body-sites microbial interactions.

[0202] Since the microbiome often operates as inter-dependent guilds, we questioned which body sites demonstrate the highest microbial inter-dependency. We found that 18.23% of all stool genus pairings (5,671) were significantly correlated within individuals, mostly *Firmicutes* (Fig. 10D). Surprisingly, co-association was highest in the oral microbiome (50.17%), followed by skin (47.51%) and nasal (38.36%), highlighting strong synergistic interactions among microbiome members at each body site.

[0203] We further investigated the microbial crosstalk between body sites by searching for sample-wise microbial collinearity. Members from the skin and nasal sites were the most correlated (15.57% of all possible pairs) (Fig. 10D). However, remarkable territory specificity was still evident among core microbiomes of each body site. For instance, three predominant core genera - *Corynebacterium*, *Staphylococcus*, and *Cutibacterium* - exhibited no longitudinal correlation between skin and nasal sites.

Similarly, oral *Prevotella*'s abundance did not correlate with its abundance in the stool microbiome, consistent with our observation of high FS in oral but not stool *Prevotella*. Our results suggest translocation cases likely do not involve the niche-specific core taxa. Moreover, genera that are more interdependent exhibit lower DMI compared to less interdependent genera (Figs. 10E and 11D), indicating that highly individualized microbiomes exhibit greater temporal stability. Expanding on our findings of microbiotypes across body sites (Fig 7A), we observed that dominant taxa driving these biotypes exhibit significant inter-individual correlations. Examples include significant correlations of *Cutibacterium* levels in one's skin with their *Cutibacterium* level in nasal (beta = 0.56, BH-adjusted *p*-value = 0.0012), their *Bacteroides* in stool (beta = 0.52, BH-adjusted *p*-value = 0.0038), and their *Leptotrichia* in oral microbiomes (beta = 0.43, BH-adjusted *p*-value = 0.0088). Conversely, individuals with high Unclassified *Ruminococcaceae* in stool correlates with low *Veillonella* in oral microbiome (beta = -0.35, BH-adjusted *p*-value = 0.015). These findings suggest that the establishment of microbiotypes are regulated by personalized factors.

Acute Events Impact Microbiome Dynamics Across Body Sites and are Influenced by Insulin Resistance

[0204] Three strong perturbation events - infection, vaccination, and antibiotic usage - are known to cause stool microbiome disruptions. Within a three-month period, the stool microbiome of IR individuals exhibited greater temporal shifts between healthy visits and perturbations than IS individuals (Fig. 10F). This pattern, however, was not consistently discernible across other body sites, suggesting a site-specific microbiome response to these events. Unlike IS individuals, IR individuals displayed reduced stool microbiome evenness and lacked the perturbation in nasal microbiome during respiratory infection (Fig. 11E), possibly due to higher IR-associated mucosal inflammation masking or superseding infection-induced local microbiome changes observed in IS individuals. During the course of infection, we identified a transient increase in several genera such as *Alistipes* in the stool, *Peptoniphilus* on the skin, Unclassified *Prevotellaceae* in the oral cavity, and *Oribacterium* in the nasal cavity. Conversely, we noticed a decrease in the

presence of *Clostridium* cluster IV in the stool, Unclassified *Clostridia* in the oral cavity, and Unclassified *Neisseriales* in the nasal cavity (Figs. 11F-11H). Although the extent to which transient microbial shifts contribute to IR-related dysbiosis is not clear, the notable increase of core microbiomes in IR skin samples (Fig. 7K) may suggest a correlation between acute perturbations and long-term changes in the core microbiome composition. Overall, our findings indicate that dysbiosis can manifest differently across body sites, potentially through site-specific mechanisms. For instance, IR-related temporary disruptions in the stool microbiome seem to be characterized by a loss of core microbiome species producing short chain fatty acids. In contrast, in less complex skin and nasal microbiomes, dysbiosis might involve the acquisition of opportunistic pathogenic species such as *Peptoniphilus*.

The Interplay Between Host Immune System and Microbiome Across Body Sites: Insights Into Insulin Resistance and Inflammation

[0205] The dynamics of microbial stability are likely linked to multiple host regulatory mechanisms, particularly the immune system. Using a bayes model, we examined the longitudinal interplay between 62 host circulating cytokines/chemokines, growth factors and microbiome abundance at all four body sites. Based on credible interval, we identified 477 stool, 226 skin, 318 oral, and 221 nasal significant microbiome-cytokine associations that are body-site-specific. The stool and oral microbiome showed a significantly broader microbiome interaction spectrum than skin and nasal microbiome.. Interestingly, the cytokines associated with epithelial/endothelial growth and vascular inflammation (*i.e.*, EGF, VCAM-1, IL-22), IL-1 family members (*i.e.*, IL-1b, IL-1Ra), and leptin demonstrated the highest number of interactions with the microbiome. We further identified a subgroup of cytokines including IL-1b, IL-1Ra, MCP3(CCL-7), and IL-23 as the strongest correlative cytokines with the microbiome via effect size (Fig. 13A). The clear pattern of body-site-specific interactions may contribute to the taxa niche-specificity. For example, *Moraxella* shows a negative correlation with 23 cytokines on the skin, yet only with three in the nasal cavity. This reduced microbe-immune interaction in the nasal cavity may explain the higher prevalence of *Moraxella* in nasal.

[0206] We next examined whether certain phyla are more frequently interacting with cytokines, potentially influencing their stability and individuality. Members of the *Firmicutes* phylum (primarily *Clostridia*) were significantly overrepresented among cytokine-correlated microbes across all body sites ($X_{\text{stool}}^2 = 19.343$, $P_{\text{stool}} = 1.092 \times 10^{-5}$; $X_{\text{skin}}^2 = 10.418$, $P_{\text{skin}} = 0.0012$; $X_{\text{oral}}^2 = 30.935$, $P_{\text{oral}} = 2.668 \times 10^{-8}$; $X_{\text{nasal}}^2 = 31.396$, $P_{\text{nasal}} = 2.104 \times 10^{-8}$) (Fig. 12A). This interaction may account for *Firmicutes*' higher FS and lower DMI in the stool microbiome compared to other phyla. Additionally, an increase of *Firmicutes* is associated with conditions like obesity-related gut dysbiosis, IBD-related oral dysbiosis, and psoriasis-related skin dysbiosis, which share inflammation as a common factor.

[0207] Interestingly, cytokines appear to play a pivotal role in shaping an individual's core microbiome and in curbing the colonization of non-commensal bacteria, including many from the *Proteobacteria* phylum. At all four body sites we found that opportunistic microbes demonstrated a stronger correlation with cytokines than core microbiomes (stool: $W = 1,715$, $p\text{-value} = 1.181 \times 10^{-12}$, skin: $W = 223$, $p\text{-value} = 0.004041$, oral: $W = 1,055$, $p\text{-value} = 7.877 \times 10^{-6}$, nasal: $W = 482$, $p\text{-value} = 0.004691$) (Fig. 12B). This correlation is largely driven by *Proteobacteria* rather than *Firmicutes*, as *Proteobacteria* consistently constitutes a larger segment of the opportunistic microbiome compared to the core microbiome (Fig. 13B). *Proteobacteria* often carry potent lipopolysaccharides (LPS) and instigate the downstream immune cascade. Our study revealed that the correlations between cytokines and *Proteobacteria* abundance are mostly negative, except for *Proteobacteria* members in the nasal microbiome (Fig. 12C). The negative correlation of *Proteobacteria* is stronger in stool ($W = 25,315$, $p\text{-value} = 0.04439$), skin ($W = 4,995$, $p\text{-value} = 0.005214$), and oral sites ($W = 9,443$, $p\text{-value} = 9.649 \times 10^{-5}$), but weaker in nasal sites ($W = 5,218$, $p\text{-value} = 0.2693$). Furthermore, all cytokine correlations ($n = 10$) from opportunistic stool *Proteobacteria* are negative, while many high prevalence *Proteobacteria* members exhibit positive correlations with cytokines (Fig. 13C). Our results suggest that inflammation might contribute to the adaptation of more prevalent *Proteobacteria*.

[0208] The host response by cytokines and chemokines may be linked with the observed richness of bacterial genera, in addition to their relative abundance. We therefore examined the correlation between cytokines and the richness of the 20 most diverse genera per body site. The richness of several prevalent stool microbiome genera within the *Bacteroidetes* phylum, such as *Prevotella*, *Phocaeicola*, and *Parabacteroides*, form a cluster with primarily negative associations, echoing our finding that the relative abundances of *Bacteroidetes* members are more likely to be negatively correlated with cytokines (Fig. 12C). Also, leptin and GM-CSF, both strongly associated with BMI (Fig. 13D), show the strongest overall correlation with richness. Furthermore, we discovered that seven skin genera positively correlated with a cytokine cluster, indicating that the richness of specific skin genera (e.g., *Rothia*, *Veillonella*, *Streptococcus*) is positively associated with the level of plasma cytokines. Consequently, the observed increase in the skin microbiome richness in IR individuals (Fig. 16A) may suggest a diminished host selection of the skin microbiome during inflammatory periods.

[0209] Overall, our analysis elucidates the interplay between chronic low-grade inflammation and microbial dynamics across various body sites. It connects the immune system with microbiome composition and individualization, and shed lights on how these dynamics are both influenced by and contribute to insulin resistance.

The Microbiome is Highly Connected with Host Molecules: Unraveling the Role in Insulin Resistance and Inflammation

[0210] To comprehensively explore the relationship between the microbiome and internal host molecules and its role in IR, we analyzed the correlations between microbiome genera and plasma proteins, lipids, and metabolites in the host. We first modularized the lipidomics data to address its high collinearity (Fig. 14A), then applied a linear mixed model to residualize all omics data, reducing between-individual variation and emphasizing longitudinal intra-individual relationships.

[0211] Interestingly, the microbiome-host molecule interaction network partitions according to internal molecular composition rather than body sites of the microbiome (Fig. 15A), suggesting that certain taxa are primarily influenced by internal molecules

interactions over influencing host molecular composition. Notably, three enterotypes driving taxa: *Bacteroides*, *Prevotella*, and Unclassified *Ruminococcaceae*, exhibit a clear preference for the lipidome, proteome, and metabolome regions, respectively (Fig. 15A). The close association between *Prevotella* and proteins has been previously documented, as well as the relationship between *Bacteroides* and lipids. However, our findings reinforce this understanding to include both additional taxa and multiple body sites, suggesting that these connections are not only site- and taxa-specific but also systemic and robust.

[0212] Many taxa-molecule interactions were consistent across body sites, validating the robustness of these relationships. The skin microbiome exhibited the broadest connectivity in the microbe-lipidome association, whereas the stool microbiome was mainly connected to the metabolome and proteome, as expected (Fig. 15B). Proteome pathway annotation further supported these connections and their potential functional implications. The skin microbiome-related proteins were enriched for pathways regulating lipid transport and metabolism, whereas the stool, nasal, and oral microbiomes were more strongly connected to the host immune response, including complement activation and humoral immune response. The oral microbiome exhibited significant associations with proteins linked with regulation of proteolysis, hydrolase activity, and enzyme, peptidase, and lipase inhibitor activity. Strikingly, the complexity of the network between the stool microbiome and host molecular relationships was significantly reduced in individuals with IR (Fig. 14B), indicating a loss of balance in these individuals.

[0213] Our study reveals several metabolites, such as alcohol associated metabolite ethyl glucuronide, interact with microbiomes across all four body sites, demonstrating a more global effects of alcohol beyond the gut and oral microbiome. Notably, skin *Neisseria* and *Klebsiella*, recognized for their acetaldehyde- and ethanol-producing potential, showed a positive correlation with plasma ethyl glucuronide level (Fig. 15C). Conversely, *Faecalimonas*, typically an acetate-producing bacteria and sensitive to alcohol, exhibited a significant negative correlation with ethyl glucuronide. Furthermore, *Desulfovibrio*, a key genus promoting microbiome-related metabolic syndrome, was

positively correlated with ethyl glucuronide. These findings suggest that alcohol metabolism is associated with microbial dysbiosis across various body sites.

[0214] We also observed notable interactions between microbiome genera richness, a recognized indicator of host metabolic status, and internal plasma analytics. These interactions were most pronounced in the stool microbiome, likely due to its high richness. (Figs. 15D). Intriguingly, we discovered a positive association between p-Cresol glucuronide, a bacteriostatic metabolite produced exclusively by the anaerobic gut microbiome and linked to insulin resistance, and the richness of Unclassified *Ruminococcaceae* and *Oscillibacter* in the stool. Conversely, it was negatively associated with genera typically considered metabolically beneficial, such as *Roseburia*. (Fig. 15E) These findings suggest that p-Cresol glucuronide may influence the development of insulin resistance-related dysbiosis by altering host tolerance to certain genera belonging to *Clostridia*.

[0215] In conclusion, our results not only validate several previous findings but also generate many novel host-microbial associations, enhancing our understanding of the complex interplay between the human microbiome, metabolites, and host health.

Elucidating Microbiome-Mediated Effects on Clinical Phenotypes: A Comprehensive Mediation Analysis across Four Body Sites

[0216] We next investigated potential causal linkages between microbes, host molecules and clinical phenotypes using mediation analysis. This method measures the contribution of mediators, such as plasma omics or cytokines/chemokines, to the assumed microbiome-clinical phenotype connection, providing confidence levels by inverting the roles of mediator and dependent variable. Using this assumption, we identified 330 directionally significant mediation effects involving microbial taxa across all sites, with 207 and 164 of these mediation effects detected in IS and IR participants, respectively (Fig. 17A). These outcomes suggest potential microbiome-host causality exist and vary with IR status, though unaccounted confounders remain possible.

[0217] Compared to IS, we observed a significant decrease in cytokine-mediated effects of stool microbiome on hematologic parameters (p-value = 0.002) (Figs. 17B and

17C) and metabolome-mediated effects of stool microbiome on immune phenotypes (p-value = 0.002) in IR individuals. Furthermore, there was an absence of lipidome-mediated associations between skin microbiome and host plasma lipids/cholesterol in IR participants (p-value = 0.031), suggesting a dysregulation in specific microbiome-metabolic interactions related to hematologic/immune and lipid/cholesterol homeostasis in IR (Figs. 17D and 17E). In contrast, the oral microbiome mediated a large proportion of immune profiles via the modulation of lipidome (p-value = 0.035) and cytokines (p-value = 0.0001) in IR relative to IS participants, primarily through a negative relationship among major oral core microbiomes such as *Veillonella*. These causal relationships align with previous findings suggesting that diabetes-related oral dysbiosis may arise from a combination of the loss of core commensal oral taxa and an increase in the pathogenicity of resident oral bacteria during impaired glucose metabolism.

Conclusions

[0218] This study presents a systematic analysis of longitudinal multi-site microbiome ecology and host dynamics. With date-matched microbiome and host omics, we not only expand our knowledge of the stability and individuality of microbiome from various body sites, but also provide mechanism-generating hypotheses on host-microbiome interactions in the context of prediabetes. We demonstrate a number of novel observations: 1) There is a “core” microbiome that is highly stable over time and an opportunistic microbiome that is highly variable and more potent to the immune system; these are niche-specific. 2) Correlations between microbiomes across body sites and extensive interactions with host factors indicate systemic coordination and interactions across the human body. 3) Highly individualized microbiomes are associated with distinct environmental factors (i.e., season, diet, chemical and biological exposome) in a niche-specific manner. However, these effects do not override the variance contributed by individuals, suggesting that the host is still the largest confounding factor for the variation observed in the microbiome. 4) Individuals with IR have a less stable microbiome with more diverse microbiome members on skin, possibly associated with upper respiratory infection, as well as significantly altered host-microbiome interactions.

[0219] Our study revealed that the stool and oral microbiomes exhibit the highest level of individualization, likely due to the unique influence of personalized dietary habits and host-specific factors, such as IR, impacting the digestive system. Meanwhile, the skin and nasal microbiomes are less individualized, possibly owing more to individual environmental exposure. We observed site-specific impact of environmental factors, such as season, on the microbiomes of these four body sites. For instance, a decrease in stool microbiome richness in late summer corresponded with previous findings of worsened insulin sensitivity during this period. Similarly, we noted a decline in the richness and evenness of the oral microbiome from late summer through winter, suggesting a potential influence of environmental factors like the availability of fresh food and changes in sunlight durations. Meanwhile, changes in humidity from January to April might explain the richness increase in skin and decrease in nasal microbiome. These observations underscore the critical role of the host in modulating the microbiome in response to environmental fluctuations.

[0220] Leveraging dense longitudinal sampling, we were able to quantify the stability and degree of individuality of the microbiomes at different body sites. The strong correlation between microbiome stability and individuality suggests an active role of the host in the establishment of commensal bacterial populations. Notably, this individuality appears to be taxon-specific, pointing to the possibility that the stability of an individual's microbiome may be influenced by the dominant bacterial taxa they carry. For instance, the higher DMI in stool *Bacteroidetes* links traditional *Bacteroidetes/Firmicutes* ratio or enterotypes to new insights in the context of metabolic disorders. Furthermore, microbiotypes across different body sites within the same individual correlate. Individuals with high levels of *Bacteroides* in the stool also have high *Cutibacterium* on the skin and *Prevotella* in the oral microbiome. Combined with our findings on the correlation between microbiome individuality and stability, the low-level engagement between the core microbiome and cytokines, and the clear host molecular type-specific patterns in the host-microbiome interactome, we propose that the colonization and adaptation of bacteria across multiple body sites is not random but precisely regulated by host factors.

[0221] Niche-specific traits often emerge through multi-site comparisons; for instance, we identified unique characteristics of the oral microbiome. The recurrence rate of oral bacteria does not increase with DMI, possibly due to a stable and conserved community structure within the oral microbiome. This, coupled with the oral microbiome's high intra-site interdependence and minimal correlation with other body sites, underscores its specialization. The unique oral environment, shaped by factors such as saliva, teeth, gums, tongue, and distinct nutrient availability, likely contributes to this specialization.

[0222] Microbial individuality and stability are closely related to the host immune system, which is well known to interact with microbes at multiple body sites. This interaction modulates both the colonization of microbes, as well as their functional benefits (e.g., epithelium barrier integrity maintenance). Our Bayesian model reveals that the interactions between the microbiome and cytokines, while present, are subtle. Certain genera exhibit an approximate 1.5-fold change in response to cytokine variations. The interaction between inflammatory cytokines and the microbiome demonstrated that low prevalence genera (*i.e.*, stool *Proteobacteria*) are likely reduced during host inflammatory events. We also revealed a systematic relationship between cytokines and the genera complexity of the microbiome at each body site. Notably, the diversity within a subset of the skin microbiome positively correlates, while that within the stool microbiome negatively correlates with the same group of cytokines. Given the established association of IR with low-grade chronic inflammation, the observed changes in diversity among IR individuals might be related to their unique cytokine profiles.

[0223] We also identified a list of interactions between host plasma biomolecules and microbiomes. We also find many correlations across body sites with host factors; for example, the correlated *Bacteroides* in the stool and *Cutibacterium* in the skin are both closely related to lipid metabolism. Our multi-omics analyses suggest potential causality of host factors in these relationships, reinforcing the idea of host-driven systematic microbial coordination across body sites as proposed in gut-brain axis and gut-lung axis theories. Since many of the metabolites, lipids and proteins are signaling molecules (e.g., chemokines, hormones, peptides), these molecules may play important roles in

organismal communication across the entire host-microbiome ecosystem. Importantly, this interaction presumably occurs individually, and significantly altered at disease stage.

[0224] Intriguingly, we found *Klebsiella* on skin was positively associated with metabolites of alcohol. This indicates that alcohol intake may change the host into a *Klebsiella*-tolerant environment, resulting in the adaptation and expansion of pathogenic *Klebsiella*. This observation supports previous findings in alcohol-associated pneumonia, where alcohol consumption and increased susceptibility to *Klebsiella* in the lungs may be a result of either intestinal *Klebsiella*-specific T-cell sequestration or alcohol-related impairment of tryptophan catabolite production/processing in the gut microbiome, which restricts pulmonary immune cell trafficking.

[0225] Insulin resistance (IR) appears to disrupt the intricate balance between the host and microbiome, demonstrated by an unstable, dysbiotic microbiome in IR individuals. In our study, we discovered marked differences in the microbiome composition, diversity, and core members of the stool and skin microbiomes in IR individuals compared to their insulin-sensitive counterparts. Notably, the systematic shift in microbiome prevalence indicates an entire microbial community's transformation instead of the abnormality of a few isolated members (Fig. 7L). This dysbiosis can potentially alter the complex host-microbiome interaction in IR subjects. Consistently, we detected reduced host-microbe coordination and a missing association between oral and skin microbiome stability. Further, our mediation analysis validates our result about the reduced gut microbiome-cytokine interaction in IR individuals, and revealed heightened pro-inflammatory signals linked to the microbiomes of the upper respiratory tract (oral and nasal microbiome) in IR individuals. Our in-depth exploration of acute microbiome changes during infection provides additional substantiation for this theory. We observed a significant increase in IR-enriched skin genera such as *Peptoniphilus* and *Intrasporangium* (Fig. 11D) during the course of a respiratory viral infection, while a decline in specific genera in the stool microbiome known for butyrate production, like *Clostridium_IV*, *Lawsonibacter*, and *Intestinimonas*. While these findings do not explicitly validate the hypothetical link between respiratory viral infection, chronic metabolic dysregulation, and related complications,

they suggest that infection-related microbial shifts may be associated with, or even cause, the dysbiosis and complications of metabolic syndrome.

Methods

Microbiome Sample Collection and Sequencing

[0226] Stool samples were self-collected by participants and other samples were collected by study coordinators following iPOP study standard operating procedures (SOP), as adapted from HMP_SOP corresponding sections (HMP_MOP_Version12_0_072910). Briefly, retroauricular areas were rubbed with pre-moistened swabs under pressure for skin sampling, anterior nares for nasal sampling, and rear of the oropharynx for oral sampling. Samples are stored at -80 C immediately after arrival. Stool and nasal samples were further processed and sequenced in-house at the Jackson Laboratory for Genomic Medicine (JAX-GM, Farmington, CT, USA), while oral and skin samples were sent to uBiome (uBiome, San Francisco, CA, USA) for further processing.

[0227] After 30 minutes of beads-beating lysis, skin and oral samples were processed using a silica-guanidinium thiocyanate-based nucleic acid isolation protocol on a liquid-handling robot. The 16S rRNA variable region V4 was amplified by 35 cycles of PCR. The DNA from each sample was barcoded and combined to create a sequencing library. The sequencing library was then purified using columns and microfluidic DNA fractionation to reduce unwanted DNA fragments. Bio-Rad MyiQ was used to quantify the DNA concentration of the library using the Kapa iCycler qPCR kit (Bio-Rad Laboratories, Hercules, CA, USA). Sequencing was performed on the Illumina NextSeq 500 Platform (Illumina, San Diego, CA, USA) via 2 * 150 bp paired-end sequencing protocol.

[0228] Raw sequencing data from the stool samples and nasal samples are acquired. Briefly, 16S rRNA gene from V1~V3 hyper-variable region was barcoded and sequenced on the Illumina MiSeq sequencing platform through a V3 2 × 300 sequencing protocol. The same cutoff used in skin and oral sequencing data was applied to stool and nasal sequencing data in demultiplexing. After demultiplexing, reads with Q-scores less than 35 and ambiguous bases (Ns) are trimmed for additional analysis.

Microbiome data processing

[0229] Demultiplexed sequenced samples were saved as FASTQ files using BCL2FASTQ software (Version 2.20, Illumina, CA, USA). Sequences with barcode mismatches, primer mismatches exceeding one, or Q-scores below 30 were excluded. Due to low overlap between forward and reverse reads according to FLASH (Version 1.2.11), only forward reads were selected for further processing.

[0230] Microbiome sequencing data from four body sites were combined and processed using the DADA2 R package (version 1.16). Sequences were filtered to remove ambiguous bases (maxN=0) and those with more than two expected errors (maxEE=2). After filtering, inter-sample composition analysis was performed based on the learned error rate. An amplicon sequence variant (ASV) table was constructed, and chimeras were removed using the DADA2 workflow consensus method. Reads passing all filters were aligned against a trained database of target 16S rRNA gene sequences and taxonomic annotations derived from Version 18 of The Ribosomal Database Project (RDP) Taxonomy release (Aug 14, 2020). Relative ASV abundance was determined by dividing the count associated with that taxon by the total number of filtered reads. Samples with depths below 1,000 reads were removed due to insufficient sequencing depths following the HMP consortium standard. The Local Outlier Factor (LOF) of each point was calculated on a sequencing depth to richness (observed ASV) plot, and samples with a LOF greater than 3 (n=7) were removed due to an abnormal richness-sequencing depth relationship. The average sample sequencing depth after quality control was 23,554 for stool microbiome, 74,515 for skin microbiome, 132,912 for oral microbiome, and 24,899 for nasal microbiome. Batch effects were estimated using PERMANOVA analysis when both batch and subject ID were included, with results showing that the total variance explained by the 23 batches was 2% for stool, 3% for nasal, 0.6% for oral, and 3.6% for skin samples. The batch effects were considered small, and no correction for batch effects was applied in the analysis.

Lipidomics analyses

[0231] Lipid extraction and data generation was performed as follows. Briefly, complex lipids were extracted from 40 μ L of EDTA-plasma using a mixture of methyl tertiary-butyl ether, methanol, and water, followed by biphasic separation. Lipids were then analyzed using the Lipidizer platform, which consists of a DMS device (SelexION Technology, Framingham, MA, USA) and a QTRAP 5500 (Sciex). Lipids were quantified using a mixture of 58 labeled internal standards provided with the platform (cat# 5040156, Sciex, Redwood City, CA, USA), and lipid abundances were reported in nmol/g.

[0232] To address the high collinearity of the lipidomic data, a customized clustering method was designed. Specifically, the lipidomics data were divided into six clusters using Fuzzy c-means clustering (R package “Mfuzz” (version 3.15)). For the lipids within each cluster, correlations were computed, and lipids with high correlative relationships (Spearman correlation > 0.8 and BH-adjusted p-values < 0.05) were grouped into the same module. Community analysis (‘fastgreedy.community’ function from R package “igraph” (v1.3.5)) was employed to detect the modules. For lipids not assigned to any of the modules, their original lipid species annotations were used for downstream analysis.

Metabolomics Analyses

[0233] Untargeted metabolic profiling was performed using a broad-spectrum LC-MS platform using a combination of reverse-phase liquid chromatography (RPLC) and hydrophilic interaction liquid chromatography (HILIC) separations and high-resolution MS. Briefly, plasma metabolites were extracted following solvent precipitation using a mixture of ice-cold acetone, acetonitrile, and methanol (1:1:1, v/v). Hydrophilic metabolites were separated on a ZIC-HILIC (2.1 $\times$ 100 mm, 3.5 μ m, 200 Å; Merck Millipore) while hydrophobic metabolites were separated on a Zorbax SBaq columns (2.1 $\times$ 50 mm, 1.7 μ m, 100 Å; Agilent Technologies). Data was acquired on a Thermo Q Exactive plus mass spectrometer for HILIC and a Thermo Q Exactive mass spectrometer for RPLC. Raw data were processed using Progenesis QI (v2.3, Nonlinear Dynamics, Waters) and metabolites were formally identified by matching fragmentation spectra and retention time to analytical-grade standards or matching experimental MS/MS to

fragmentation spectra in publicly available databases. A total of 726 annotated metabolites were retained for downstream analysis.

Proteomics Analyses

[0234] Plasma proteins were characterized using a TripleTOF 6600 system (Sciex) via liquid chromatography-mass spectrometry (LC-MS) with SWATH acquisition. In every injection, 8- μ g of tryptic peptides, derived from undepleted plasma, were loaded onto a ChromXP C18 column (0.3 $\times$ 150 mm, 3 μ m, 120 Å, Sciex). The separation of peptides was achieved through a 43-minute gradient ranging from 4% to 32% B. High sensitivity MS/MS mode was utilized to construct variable Q1 window SWATH Acquisition methods (100 windows) with Analyst TF Software (v1.7). Scoring of peak groups was performed with PyProphet (v2.0.1) and alignment of peak groups with TRIC, each adhering to stringent confidence thresholds (1% FDR at peptide level; 10% FDR at protein level). The abundance of proteins was calculated as the cumulative sum of the three most abundant peptides.

Luminex Multiplex Assays for Targeted Cytokine, Chemokine, and Growth Factors

[0235] The evaluation of circulating cytokines, chemokines, and growth factors was undertaken employing established procedures from the Stanford Human Immune Monitoring Center (HIMC). Specifically, EDTA-plasma was scrutinized using a Human 62-plex Luminex multiplex assay, consisting of conjugated antibodies (Affymetrix, Santa Clara, California). The raw data obtained from the assay were normalized against the median fluorescence intensity (MFI) value. Subsequently, variance stabilizing transformation (VST) was applied to the data to eradicate the batch effect. Measurements featuring background noise (CHEX) exceeding five standard deviations from the mean (mean $\pm$ 5 $\times$ SD) were omitted from the data.

Exposome and Associated Environmental Analyses

[0236] The process of data collection for the exposome and associated environmental elements proceeded accordingly. The chemical exposome was sampled using the RTI

MicroPEM V3.2 personal exposure monitor (RTI International, Research Triangle Park, NC, USA) for two participants. The MicroPEM, an active air sampling apparatus, operates by circulating air at a rate of 0.5 L/min. It was modified to house a customized cartridge containing 200 mg of zeolite adsorbent beads (Sigma 2-0304, Sigma-Aldrich Corp., St. Louis, MO USA) positioned at the airflow's termination to gather both hydrophobic and hydrophilic compounds. Each sampling session spanned approximately five days. Post-session, the cartridge was detached and preserved at -80 °C until subsequent processing. Chemical extraction involved the resuspension of zeolite beads in a sterile Eppendorf LoBind tube filled with 1 mL of Mass Spec grade methanol. Following a 20-minute incubation period at room temperature, the samples were subjected to a 20-minute centrifugation process at 22,000 g, also at room temperature. The samples were then analyzed using a Waters UPLC-coupled Exactive Orbitrap Mass Spectrometer (Thermo, Waltham, MA, USA), yielding a collection of 158 exposome chemicals. Environmental data, on the other hand, were sourced from several origins. Parameters such as temperature, humidity, and sampling flow rate were directly recorded by the MicroPEM. GPS coordinates of the participants provided geographical data. Additional meteorological and demographic information was obtained from public data repositories including the Climate Data Online (CDO), the US Census Bureau, and local weather stations. This culminated in the collection of 10 environmental feature data points.

Dietary Analyses

[0237] A total of 25 food items were included in a questionnaire that was completed voluntarily by participants during their routine visit in the study, using a diet questionnaire. The frequency of consuming each food item was scored in downstream analysis. For breads, biscuits, cakes, pies and pastries, we score the frequency from 0~4, with the associated frequency per day: 0) less than 1, 1)1 per day, 2)2~3 per day, 3)4~5 per day, 4)6 or more. For other foods we ask the participants to state the frequency from 6+ times per day to less than once per month.

Insulin-Suppression Test

[0238] A subset of eligible consenting participants (N=58) underwent an Insulin-suppression Test (IST), as a measure of insulin-mediated glucose uptake, to evaluate the insulin sensitivity status. Following a 12-hour overnight fast, participants were administered an infusion comprising 0.27 ug/m² min of octreotide, 25m U/m² min of insulin, and 240 mg/m² min of glucose over a three-hour period during their visit to Stanford's Clinical and Translational Research Unit (CTRU). Blood samples were procured at ten-minute intervals during the final half-hour of the infusion, resulting in a total of four blood draws. These samples were analyzed to determine plasma glucose and insulin levels. The mean value of the four steady-state plasma glucose (SSPG) and insulin concentrations were subsequently calculated. Participants were then categorized based on their SSPG values: those with SSPG < 150 mg/dl were classified as insulin sensitive (IS) (n=28), while those with SSPG ≥ 150 mg/dl were classified as insulin resistant (IR) (n =30). Participants who were unable to provide measurements due to personal or medical circumstances were allocated to an indeterminate group (Unknown) (n= 28).

Clinical Lab Test

[0239] Clinical lab tests were performed at the Stanford Clinical Lab. The test includes a metabolic panel, complete blood count panel, glucose, HbA1C, insulin measurements, hsCRP, IgM, lipid panel, kidney panel, liver panel.

UMAP for Microbiome Distribution

[0240] The distribution of the microbiome was visualized using Uniform Manifold Approximation and Projection (UMAP), facilitated by the R package "Seurat (Version 4.0)". Prior to the application of UMAP, the count data were first normalized to relative abundance and scaled to represent one million reads per sample. A total of 1524 variable features were identified and encapsulated within a Seurat object. From this point, a distance matrix was produced through the utilization of the R package "Vegan (Version 2.6-2)", employing Bray Curtis dissimilarity. This distance matrix was subsequently

transformed via Principal Coordinate Analysis (PCoA). The first ten dimensions from the PCoA (out of a total of 1094 generated) were used to determine neighboring relationships. The UMAP projection was then calculated, with default settings employed. This projection was made possible by invoking Python's UMAP via reticulate. The final UMAP results were visualized using the first two dimensions.

[0241] Intraclass correlation Coefficient (ICC) was calculated from Linear Mixed Models, in which we modeled random intercepts but a fixed slope, allowing different personal levels between individuals. We first linearly transformed each analyte (when applicable) and standardized the total variation to 1 before applying 'lmer' function from R package "lme4 (V1.1-30)", with the formula as:

$$Exp \sim 1 + Days + (1|SubjectID)$$

Where Exp was the linearly transformed and standardized values of each analyte, Days was the length of time individuals participated in the study, SubjectID was the subject ID associated with each participant.

[0242] We then used ICC as the proportion of total variation explained by subject structure in the cohort by $V_{\text{subjectID}}/V_{\text{total}}$, in which V was the variance from the corresponding component extracted by Var_{Corr} and V_{total} was 1.

Permutation Test on Bray Curtis Distance Comparison

[0243] The Bray-Curtis (BC) distance was used to quantify the degree of similarity between two microbiome samples, with the ASV serving as the unit for calculating dissimilarity for the complete microbiome sample or for specific taxa. Similarity metrics were calculated pairwise for both intra-individual and inter-individual comparisons. A permutation test was employed to estimate the null distribution while accounting for the varying sample sizes of each participant. The null hypothesis being tested was that there is no difference between intra-individual and inter-individual distances.

[0244] For each microbial genus, a test statistic was calculated as the mean difference in BC distances between intra-individual and inter-individual comparisons. To estimate the null distribution, all sample labels were randomly permuted, and the BC distances

were computed pairwise. This process was repeated 10,000 times, generating a null distribution of test statistics.

[0245] P-values were then calculated by determining the proportion of permuted test statistics that were at least as extreme as the observed test statistic. In the case of multiple comparisons, such as for different microbial genera, p-values were adjusted using the BH procedure to control the false discovery rate. Statistical significance was determined using a threshold of BH adjusted p-value < 0.1.

[0246] Degree of Microbial Individuality (DMI) was measured as the mathematical difference between a given genus regarding their populational median of the inter-individual BC distance and the median of the intra-individual BC distance. To assess the robustness and variability of the DMI estimates, we employed a bootstrap resampling technique.

[0247] First, we summarized the between-sample distance of genera with longitudinal prevalence greater than 10% at a given body site. The distance of sample pairs was then allocated into inter-individual or intra-individual groups. For each genus, we resampled the data with replacement and computed the DMI using the following formula:

$$DMI_i = BC_{inter-individual} - BC_{intra-individual}$$

[0248] This resampling process was repeated multiple times to obtain a distribution of DMI estimates, which enabled us to assess the variability and robustness of our results.

[0249] By employing the bootstrap resampling technique, we aimed to gain insights into the reliability of our DMI calculations and understand how sensitive they were to potential variations in the data. This approach provided a more comprehensive understanding of the degree of microbial individuality across various body sites and taxa. To ensure the accuracy of our results, we considered a DMI to be reliable only if that DMI's standard deviation (SD) of the bootstrapped distribution is less than 15 times of the mean DMI. This criterion helped to filter out any DMI estimates that might be influenced by high variability or uncertainty in the data. Detail of the bootstrap result was included in our supplementary materials, where we used column "confidence" to distinguish DMI values with high or low reliability. The total number of genera reported per region after bootstrapping included: 105 for stool, 35 for skin, 63 for oral, and 33 for nasal samples.

[0250] To quantify the cumulative DMI for each individual, the DMI score was multiplied by the average relative abundance of each genus for a given individual. This generated a weighted DMI (abundance_dmi) that represented the product of the DMI score and the genus's relative abundance. The total DMI for each individual was computed by summing these weighted DMI values across all genera. This approach offered a comprehensive measure of the overall DMI per individual, accounting for the contribution of each genus weighted by its relative abundance in the individual's microbiome.

Family Score

[0251] To assess the impact of a shared living environment on microbiome variability, we introduced a metric called the Family Score (FS). The FS represents the relative influence of a shared environment on the inter-individual dissimilarity of a given genus within cohabitating pairs. We began by excluding genera with a longitudinal prevalence of less than 10%, leaving 141 for stool, 119 for skin, 41 for oral, and 33 for nasal samples. For each remaining genus, we computed the "within-family" inter-individual Bray-Curtis (BC) distance between cohabiting pairs. We also calculated the median inter-individual BC distance (BC inter-individual) and intra-individual BC distance (BC intra-individual). Using these values, we computed the FS for a given genus 'i' with the following formula:

$$\text{Family Score } i = (BC_{\text{inter-individual}} - BC_{\text{intra-family}}) / (BC_{\text{inter-individual}} - BC_{\text{intra-individual}})$$

[0252] This formula normalizes the FS to a scale that allows for comparisons across families and non-families. An FS of 0 indicates that the shared living environment has no impact on inter-individual dissimilarity, while an FS of 1 suggests that living in the same environment causes inter-individual dissimilarity to resemble intra-individual dissimilarity. We truncated the FS at 0 and 1 to maintain consistency in the comparison scale. Any FS values greater than or equal to 1 were assigned a value of 1, and values less than or equal to 0 were assigned a value of 0.

Classification of The Microbiome Genera by Their Longitudinal Prevalence

[0253] The microbiome genera were categorized as the core microbiome, opportunistic microbiome, and middle group based on their longitudinal prevalence. Calculation of prevalence was based on the presence or absence of reads from each sample. For each sample, the relative abundance of each genus was first transformed to 1 if it was greater than 0; then, the proportion of 1 for each genus in each participant was determined as the longitudinal prevalence. Then the genera were assigned to a group based on their longitudinal prevalence: core microbiome: longitudinal prevalence > 80%; middle group: $20\% \leq \text{longitudinal prevalence} \leq 80\%$; opportunistic microbiome: longitudinal prevalence < 20%.

Body Site-Specific Longitudinal Model for Bray-Curtis distance

[0254] To estimate the effect of body site on the change in BC distance over time, we used a linear mixed effects regression with the BC distance as the response variable implemented in the “lme4” package in R. The BC distance of all pairwise samples was transformed to a more normally distributed dataset. The transformation method used was the log-log transformation, which has been widely used in survival analysis studies. Specifically, the transformation was performed by applying the formula:

$$\text{transformed_dist} = \log_{10}(-\log_{10}(1-\text{dist}))$$

[0255] A total of eight different transformations were evaluated (variations of logarithmic, square root, arcsine, and ratio transformations of the original distance) to identify the most suitable transformation for our analysis. To assess the normality of the transformed distances, an Anderson-Darling test was performed, and the best method was selected by Anderson-Darling’s statistics A.

[0256] Fixed effects included an interaction between the body site and time, and with a random intercept for each individual. Time was normalized to the days from the first sample for each individual. The model was optimized using the “nloptwrap” method and nested models were compared by likelihood ratio test using the “lmerTest” package in R. Differences in the slopes of the body sites over time were assessed by F-test with

Satterthwaites's degrees of freedom. For the comparisons between body sites, the model was constructed as:

$$dist \sim -1 + diffdays * dataset + (1 | subject_id)$$

[0257] For the comparison between IR and IS participants, the model was constructed as:

$$dist \sim -1 + IRIS * diffdays + (1 | subject_id) + (1 + IRIS | subject_id)$$

Where *dist* was the pairwise BC distance, *diffdays* was the date interval between two samples, *subject_id* was the subject ID associated with each participant, and *IRIS* was the insulin sensitivity status of each participant.

Bayesian Mixed-Effects Model for Microbial Taxa and Cytokine Interactions

[0258] We utilized a Bayesian negative-binomial longitudinal mixed-effects model to analyze the interactions between microbial taxa and cytokines. This model choice addresses several key characteristics of our data: the compositional nature of microbiome data, the presence of zero-inflation and high skewness in cytokine measurements, and the repeated measurements of both cytokine and microbiome data in our study cohort (n=62 with longitudinal, date-matching measurements). The model's capacity to handle the highly skewed cytokine data was a critical factor in its selection, especially given the dramatic range of cytokine surges observed in our dataset, ranging from a 10.8-fold increase for MIP1B to as much as a 618-fold increase for LEPTIN. Each genus's reads count was modeled as a sparse-matrix response variable, with a plasma cytokine level MFI quantity and time as fixed effects and a random intercept for each individual, following the formula:

$$M_i = X_i \beta + Z_i b_i + \epsilon_i$$

Where M_i is a vector of the genus-level microbe relative abundances for each participant i , X_i is the design matrix for the fixed effects, β . Each row of matrix X_i contains the terms (1) time (days post-study start), D_i , and (2) cytokine measurements, Y_i , from 1 to n . Z_i is the random effects design vector of 1's denoting a random intercept, b_i is a scalar for each participant, and ϵ_i is a zero-centered error term.

[0259] Posterior sampling was performed using four chains, 5,000 iterations per sample, and a 1,000-iteration burn-in of a No-U-Turn Sampler implemented in the “brms (Version 2.18.0)” package in R. The iteration plots and posterior predictive distributions were visually inspected for chain convergence. Microbe genera and cytokines above the limit of detection in less than 10% of the samples were excluded from the analysis. A microbe-cytokine association was considered significant if the 95% credible interval on the fit coefficient of the cytokine term did not include zero.

[0260] In our model, the beta represents the effect size. We estimated the variance explained by the model using the “bayes_R2” function from the brms package, and this information is included in the final table. While we provide p-values for each pair, as inferred from a method detailed previously, and the subsequent BH-adjusted p-values, it's important to note that these are supplementary. In our Bayesian analysis, the determination of significance is based on the commonly practiced use of credible intervals derived from Markov Chain Monte Carlo (MCMC) sampling.

Correlation Network Analysis

[0261] Correlation network analysis was conducted to construct a network between the microbiome (from stool, skin, oral, and nasal samples) and internal multi-omics data (proteome, metabolome, and lipidome) from plasma. Initially, time points with unmatched collection dates for each pair of microbiome and internal omics data were excluded. Subjects with fewer than five samples for a specific microbiome type were also removed from the corresponding correlation analysis.

[0262] The microbiome data, which included relative abundance or observed ASV richness at the genus level, was processed by retaining only genera detected in at least 10% of all samples. Centered log ratio (CLR) normalization was applied to address compositionality in microbiome data using the R package “compositions” (Version 2.0-4). Proteome, metabolome, and lipidome module data were log₂ transformed.

[0263] To account for repeated sampling from the same subject, a linear mixed-effects model was utilized, incorporating subject ID as a random effect using the R package “lme4” (Version 1.1-30). Spearman correlations were then calculated, and p-values were

adjusted using the Benjamini & Hochberg method. For correlation network construction, BH adjusted p-values < 0.2 were included. In the linear mixed model assessing longitudinal effects, the estimated correlation coefficient served as the measure of effect size (Fig. 16A).

[0264] To gauge the robustness of the point estimation for the proportion of microbiome genera that are significantly correlated, we employed a bootstrapping approach. Specifically, we determined the percentage of significantly correlated genera by dividing the number of significantly correlated pairs by the total possible pairs. We bootstrapped this procedure 20 times to obtain mean and standard deviation values for the percentage of significantly correlated microbiome genera. These values were then used to compare the scale of interdependency of microbiome across different body sites. To ascertain if one body site exhibits a significantly greater interdependency compared to another, we employed the two-sided Wilcoxon rank-sum test. The significance of these comparisons was determined using p-values adjusted for multiple testing using the BH correction.

[0265] The estimation of inter-individual microbiome-wide correlation was conducted utilizing the SparCC method (R package discordant, Version 1.25.0), a methodology specifically tailored for compositional data. To prepare the microbiome relative abundance data for this analysis, the data were multiplied by 20000 and subsequently rounded, a process designed to convert proportions into data resembling counts. Following this, the SparCC method was employed to compute the correlation matrix. This matrix was then transformed into a long format data frame, with each row representing a pair of genera and their corresponding correlation coefficient. To assess the statistical significance of the observed correlations, a permutation test was implemented. For each pair of genera, the sample labels were randomly permuted, and the permuted SparCC correlation coefficient was calculated. We executed this procedure 10,000 times to produce a null distribution of SparCC correlation coefficients. Following this, we counted the instances where our observed correlation coefficient was encompassed within this null distribution. A finding was deemed "non-significant" if the correlation coefficient from any of the 10,000 permutations was more extreme than the coefficient from our original analysis, and subsequent raw p-value was computed based on the permutation results.

Results with the BH adjusted p-value < 0.1 from this permutation was included in our final report.

[0266] The inter-omics correlation network was visualized using the R packages "ggraph" (Version 2.0.5), "igraph" (Version 1.3.2), and "tidygraph" (Version 1.2.1) under the "kk" layout.

Pathway Enrichment for Proteins Correlated with the Microbiome

[0267] The enrichment of pathways corresponding to proteins associated with the microbiome from four different body sites was achieved via the R package "clusterProfiler (Version 3.15)". The proteins in question served as input for pathway enrichment, specifically through Gene Ontology (GO) processes, enabling the identification of statistically significant pathways. The determination of these pathways was reliant on Fisher's exact test.

[0268] GO terms of interest were isolated based on their Benjamini-Hochberg adjusted p-values; terms with p-values below 0.05 were retained for ensuing analyses. For the GO terms that demonstrated significant enrichment, the R package "simplifyEnrichment" was employed. This package facilitated the calculation of similarities between each pair of GO terms. The construction of a network only incorporated edges that exhibited similarities exceeding 0.70.

[0269] In order to discern modules within the correlation network, community analysis was undertaken utilizing the R package "igraph (Version 1.3.4)". To encapsulate each module, only the GO term that presented with the smallest Benjamini-Hochberg adjusted p-value was preserved.

Mediation Analysis

[0270] A mediation analysis was conducted to investigate the potential influence of microbiomes from stool, skin, oral, and nasal sources on phenotypes through internal multi-omics data, including proteome, metabolome, lipidome, and cytokine. Phenotype data were obtained via clinical laboratory tests of plasma samples. The associations between the microbiome and phenotype (Direct Effect), as well as internal omics data

(Indirect Effect), were initially determined as outlined in the 'Correlation network analysis' section. Only significant associations (BH adjusted p-values < 0.2) were considered for subsequent mediation analysis. The linear regression model from R package "mediation" was employed for the mediation analysis. Ultimately, pairs with significant Average Causal Mediation Effects (ACME, p-values < 0.05) were reported, representing the microbiome's impact on phenotype measurements through internal multi-omics.

[0271] To control the false discovery rate (FDR), a reverse mediation analysis was performed by exchanging the mediator with effects (i.e., the microbiome influencing internal omics data via phenotype), and pairs with significant ACME in reverse mediation (p-values < 0.05) were excluded from the final results. Comparisons between body sites and insulin sensitivity statuses were conducted for each dataset using the Fisher exact test. Initially, it was hypothesized that the true meditative effect of each mediated pathway (e.g., genus $i \sim$ cytokine $j \sim$ immune k) was considerably large ($n = 1 \times 10^8$). Subsequently, the presence of a significantly different meditative linkage between the designated comparison pairs was assessed.

Principal Variance Component Analysis (PVCA)

[0272] To assess the variation in microbiome data based on individual and season, the principal variance component analysis (PVCA) was performed via R package "pvca (Version 3.15)". The PVCA is a combination of the principal component analysis and variance components analysis, which were originally employed to assess batch effects in microarray data and widely used for microbiome related variance decompositions. For microbiome samples in each body site, the season was determined by subtracting the date of collection from the first day of the year (from 1-365 days). Each sample's participant ID and season were then entered into the PVCA as variables. Then, the "ggtern (Version 3.3.5)" R package was used to visualize the data.

Deconvolute the Environmental Effect on the Microbiome

[0273] *Exposome and Diet Data Analysis:* To investigate the influence of exposome and diet data on the microbiome from different body sites, exposome data (chemical and

environmental) were collected and processed as previously described. Diet data were collected and detailed in the methods section above. As an example, the analysis process for exposome chemical data is described below.

[0274] Microbiome samples with matching exposome chemical data within a 3-day period were selected for subsequent analysis ($N_{\text{Chemical}} = 8$, $N_{\text{Environmental}} = 32$ ($N_{\text{Participant1}} = 13$; $N_{\text{Participant2}} = 19$)). Microbiome data were normalized using the centered log ratio (CLR, “clr” function from R package “compositions”), and exposome data were log2-transformed and auto-scaled. Principal component analysis (PCA) was performed on both microbiome and exposome data. Principal components (PCs) from the microbiome and exposome were further analyzed, with PCs accounting for over 80% of cumulative explained variation being included. A linear regression model was constructed using PCs of microbiome data as the dependent variable (Y) and corresponding exposome PCs as the independent variable (X). The R² value was extracted to represent the exposome's contribution to microbiome data. The same method was applied to evaluate the dietary effect on the microbiome from four body sites.

[0275] *Seasonal Effects on Microbiome:* Z-score normalized microbial data or microbial diversity was systematically analyzed using Generalized Additive Mixed Models (GAMMs). For each genus of interest, the model was formulated as:

$$\text{genera/diversity} \sim \text{IRIS} + \text{s}(\text{Time}, \text{bs} = \text{"cc"}) + (1|\text{Subject_ID}), \text{knots} = \text{list}(\text{TimeOfYear} = \text{c}(0, 366))$$

[0276] In this model, the response variable ‘genera’ represents the z-score normalized microbial relative abundance. The fixed effects components include the status of insulin sensitivity (IRIS) and a cyclic cubic spline smoother for the Time variable, encapsulating potential cyclical patterns across the year (from 0 to 366). The term (1|Subject_ID) includes a random intercept for each subject, to account for within-subject correlation.

[0277] The model was fitted using the Restricted Maximum Likelihood (REML) method for robust estimation of smoothing parameters in a complex and unbalanced design and incorporated the use of 'lmeControl' function from the 'nlme' package in R to handle the optimization process of the mixed-effects models. This was conducted by specifying 'optim' as the optimizer for the model fit.

[0278] The resulting model provides insight into the temporal dynamics of gene expression and its relationship with insulin sensitivity status (IRIS), considering the random effects associated with each subject. The graphical representation of these models for each genus and p value for smooth terms were saved for further exploration.

[0279] *The Effects of Infection on Microbiome:* The analysis of the effects of infection on the microbiome involved genera that were significantly altered during infection periods. The methodology implemented was informed by a previous method for estimating infection processes based on self-reported symptoms.

[0280] The infection status was classified into longitudinal categories: pre-healthy (-H) state, event early (EE) state, event late (EL) state, recovery (RE) state, and post-healthy (+H) state. The pre-healthy state comprised the healthy baselines observed within 186 days preceding the onset of the infection event. The EEs state was characterized by visits occurring between day 1 and day 6 of the event. The EL state spanned visits on days 7 to 14 since the onset of the event. The recovery state included visits within the 15–40-day period since the event's inception, and the post-healthy state encompassed visits within the 186 days following the event.

[0281] The categorization of these states was designed as a continuous progression from the pre-healthy to post-healthy state, with the average duration of an infection event being 88 days. 58 infection events were detected among 32 participants (IS: 7 participants, IR:12 participants, Unknown:13 participants) in our study. Each event was assigned a unique identification consisting of the subject ID and the event number. The progression of infection states within an event was tracked in the order of pre-healthy, event early, event late, recovery, and post-healthy.

[0282] In order to assess the effects of these infection states and insulin sensitivity status on microbiome genera, GAMM was constructed:

$$genera \sim IRIS + s(Infection_status, bs = "cc", k = 5) + (1|event)$$

[0283] In this model, '*genera*' represents the z-score normalized microbial relative abundance, IRIS indicates the insulin sensitivity status of each participant, and '*Infection_status*' is a smoothing function of the longitudinal infection states with cyclic

cubic regression splines. The term '(1|event)' is a random intercept for each infection event.

[0284] For the evenness changes during infection among insulin resistant (IR) and insulin sensitive (IS) individuals, the model was reformulated as follows:

$$\text{evenness} \sim s(\text{Infection_status}, \text{bs} = "cc", k = 5) + (1|\text{event})$$

[0285] In this adjusted model, 'evenness' denotes the outcome variable, specifically the Subject ID based Z-score transformed Pielou's evenness measure of the microbiome sample, indicating the diversity of the microbial community. The remaining components of the model and their interpretations align with the previously described model.

Table 1. Microbial Genera Correlated with Gene Products

Gene Product	Microbial Genus	Correlation Coefficient	Microbiome
VCAM1	Anaerostipes	0.000289651	stool
VCAM1	Ruminococcus	0.000294312	stool
VCAM1	Odoribacter	0.000253657	stool
VCAM1	Dorea	0.000240125	stool
IL22	Frisingicoccus	0.00610077	stool
IL22	Unclassified_Muribaculaceae	0.007980052	stool
IL22	Butyrivibrio	0.009078662	stool
VCAM1	Ruminococcus2	0.000224485	stool
IL17A	Barnesiella	0.023720287	stool
BDNF	Anaerotignum	-0.000134791	stool
BDNF	Barnesiella	0.000227538	stool
BDNF	Eggerthella	0.00033774	stool
BDNF	Lachnospira	0.000135762	stool
BDNF	Parabacteroides	0.000120461	stool
BDNF	Phoea	-0.000214052	stool
BDNF	Ruthenibacterium	-0.000180588	stool
CD40L	Barnesiella	0.001579901	stool
CD40L	Cloacibacillus	0.002375157	stool
CD40L	Eggerthella	0.000993913	stool
CD40L	Faecalicatena	0.0016263	stool
CD40L	Holdemania	0.00067425	stool
CD40L	Neglecta	0.000900094	stool
CD40L	Oxalobacter	-0.001681997	stool
CD40L	Raoultibacter	0.002963052	stool
CD40L	Turicibacter	0.001288915	stool
EGF	Anaerostipes	0.000423086	stool
EGF	Anaerotignum	-0.000497834	stool
EGF	Barnesiella	0.001868111	stool
EGF	Eggerthella	0.001494512	stool
EGF	Intestinibacter	0.001263134	stool
EGF	Neglecta	0.000878965	stool
EGF	Parabacteroides	0.000457256	stool
EGF	Romboutsia	0.001349344	stool
EGF	Unclassified_Clostridiales	0.000926419	stool
EGF	Unclassified_Erysipelotrichaceae	0.002032961	stool
EGF	Unclassified_Firmicutes	0.002128915	stool

ENA78	Lacrimispora	-0.001144014	stool
EOTAXIN	Desulfovibrio	-0.010848097	stool
EOTAXIN	Escherichia_Shigella	-0.011180209	stool
EOTAXIN	Turicibacter	0.007628332	stool
EOTAXIN	Unclassified_Bacteroidales	-0.012845766	stool
FASL	Acidaminococcus	0.036081167	stool
FASL	Agathobacter	-0.008003902	stool
FASL	Clostridium_sensu_stricto	0.015969159	stool
FASL	Eggerthella	0.015722457	stool
FASL	Faecalicatena	0.028892863	stool
FASL	Flavonifractor	0.011491978	stool
FASL	Holdemanella	-0.045713024	stool
FASL	Holdemania	0.017860593	stool
FASL	Longicatena	0.027755531	stool
FASL	Ruminococcus2	0.006084543	stool
FASL	Ruthenibacterium	0.011902919	stool
FGFB	Butyricimonas	-0.010787169	stool
FGFB	Clostridium_sensu_stricto	0.013916096	stool
FGFB	Flavonifractor	0.008273645	stool
FGFB	Holdemania	0.013875107	stool
FGFB	Prevotella	-0.032855335	stool
FGFB	Unclassified_Firmicutes	0.024536687	stool
GCSF	Bilophila	0.010484907	stool
GCSF	Dialister	-0.030073788	stool
GCSF	Eggerthella	0.014013278	stool
GCSF	Escherichia_Shigella	0.020662677	stool
GCSF	Ihubacter	0.007380794	stool
GCSF	Ruminococcus2	0.004680606	stool
GCSF	Sutterella	-0.02891904	stool
GMCSF	Agathobacter	0.007003765	stool
GMCSF	Anaerotignum	0.006011156	stool
GMCSF	Butyrivibrio	0.069231687	stool
GMCSF	Desulfovibrio	-0.03320304	stool
GMCSF	Frisingicoccus	0.025944554	stool
GMCSF	Intestinibacter	-0.014766296	stool
GMCSF	Raoultibacter	-0.023021936	stool
GMCSF	Terrisporobacter	-0.042799336	stool
GMCSF	Unclassified_Muribaculaceae	0.087674902	stool
GROA	Agathobacter	-0.005591251	stool
GROA	Clostridium_sensu_stricto	0.008285412	stool

GROA	Dialister	-0.031243623	stool
GROA	Eggerthella	0.009090599	stool
GROA	Unclassified_Erysipelotrichaceae	0.011331288	stool
GROA	Unclassified_Firmicutes	0.01713992	stool
HGF	Akkermansia	0.014304115	stool
HGF	Parabacteroides	0.004479667	stool
HGF	Phascolarctobacterium	-0.005971741	stool
HGF	Ruminococcus	0.007984103	stool
HGF	Slackia	-0.034037925	stool
HGF	Unclassified_Alphaproteobacteria	0.025250546	stool
HGF	Unclassified_Bacteroidales	-0.05148197	stool
HGF	Unclassified_Eggerthellaceae	-0.012234568	stool
ICAM1	Acidaminococcus	0.001479992	stool
ICAM1	Butyricimonas	-0.001105617	stool
ICAM1	Clostridium_IV	-0.000721899	stool
ICAM1	Lachnospiraceae	-0.001897297	stool
ICAM1	Oscillibacter	-0.000379454	stool
ICAM1	Phascolarctobacterium	-0.000402251	stool
ICAM1	Phocaeicola	-0.000251424	stool
ICAM1	Unclassified_Lachnospiraceae	-0.000201871	stool
IFNA	Blautia	-0.002232792	stool
IFNA	Dialister	-0.015688163	stool
IFNB	Acetivibrio	0.002765402	stool
IFNB	Adlercreutzia	0.002297885	stool
IFNB	Cloacibacillus	0.004086069	stool
IFNB	Faecalicatena	0.005571887	stool
IFNB	Holdemania	0.001867272	stool
IFNB	Raoultibacter	0.004661352	stool
IFNB	Unclassified_Muribaculaceae	-0.040033926	stool
IFNG	Blautia	-0.004210135	stool
IFNG	Dialister	-0.041802762	stool
IFNG	Fusicatenibacter	-0.005871796	stool
IFNG	Unclassified_Bacteroidales	-0.037519118	stool
IFNG	Unclassified_Firmicutes	0.025713731	stool
IL10	Collinsella	-0.010893793	stool
IL10	Hungatella	0.017801879	stool
IL10	Monoglobus	0.016451797	stool
IL12P40	Akkermansia	0.00497678	stool
IL12P40	Parabacteroides	0.002189194	stool
IL12P40	Raoultibacter	0.007935895	stool

IL12P70	Butyricimonas	-0.021850854	stool
IL12P70	Collinsella	-0.014728946	stool
IL12P70	Fusicatenibacter	-0.006471325	stool
IL12P70	Monoglobus	0.023234982	stool
IL13	Faecalimonas	0.035950575	stool
IL13	Oscillibacter	-0.005869153	stool
IL13	Unclassified_Muribaculaceae	-0.084113381	stool
IL13	Unclassified_Ruminococcaceae	-0.005025178	stool
IL15	Butyricimonas	-0.017000417	stool
IL15	Clostridium_sensu_stricto	0.00994687	stool
IL15	Collinsella	-0.011125976	stool
IL15	Faecalibacterium	-0.003933203	stool
IL15	Lachnospira	-0.004659097	stool
IL15	Turicibacter	0.013486613	stool
IL17A	Dialister	-0.038411954	stool
IL17A	Subdoligranulum	-0.005612308	stool
IL17F	Adlercreutzia	0.001200576	stool
IL17F	Butyricicoccus	0.000779244	stool
IL17F	Cloacibacillus	0.002639199	stool
IL17F	Dysosmobacter	0.000850256	stool
IL17F	Faecalicatena	0.003677757	stool
IL17F	Hungatella	0.003150082	stool
IL17F	Senegalimassilia	-0.005303245	stool
IL17F	Unclassified_Bacteroidales	-0.004999527	stool
IL17F	Unclassified_Muribaculaceae	-0.022204281	stool
IL18	Agathobacter	-0.00259136	stool
IL18	Dialister	-0.010787712	stool
IL18	Eggerthella	0.004819637	stool
IL18	Holdemanella	-0.013650035	stool
IL18	Prevotella	-0.011707982	stool
IL18	Ruminococcus2	0.002009433	stool
IL18	Unclassified_Firmicutes	0.008573517	stool
IL18	Unclassified_Muribaculaceae	-0.024601534	stool
IL1A	Dialister	-0.006025285	stool
IL1A	Hungatella	0.004128605	stool
IL1A	Intestinibacter	0.003735435	stool
IL1A	Ruminococcus2	0.001251757	stool
IL1A	Unclassified_Erysipelotrichaceae	0.005375817	stool
IL1A	Unclassified_Firmicutes	0.00526722	stool
IL1B	Agathobacter	-0.009659334	stool

IL1B	Barnesiella	0.015296511	stool
IL1B	Butyricimonas	-0.03082052	stool
IL1B	Cloacibacillus	0.030460049	stool
IL1B	Clostridium_sensu_stricto	0.015346376	stool
IL1B	Collinsella	-0.029731761	stool
IL1B	Desulfovibrio	-0.061177261	stool
IL1B	Faecalibacterium	-0.006410001	stool
IL1B	Lachnospira	-0.010507807	stool
IL1B	Prevotella	-0.036501256	stool
IL1B	Roseburia	-0.00537989	stool
IL1B	Slackia	-0.027556117	stool
IL1B	Subdoligranulum	-0.006387575	stool
IL1B	Sutterella	-0.039244818	stool
IL1RA	Butyricimonas	-0.026253837	stool
IL1RA	Clostridium_IV	-0.050491305	stool
IL1RA	Clostridium_XIVa	0.038351727	stool
IL1RA	Desulfovibrio	-0.070357111	stool
IL1RA	Dialister	-0.109064526	stool
IL1RA	Faecalimonas	0.096776199	stool
IL1RA	Lachnospira	-0.019977394	stool
IL1RA	Monoglobus	0.045541088	stool
IL1RA	Subdoligranulum	-0.024036921	stool
IL1RA	Unclassified_Bacteroidales	-0.1330559	stool
IL1RA	Unclassified_Erysipelotrichaceae	0.058537554	stool
IL1RA	Unclassified_Muribaculaceae	-0.182611396	stool
IL2	Butyrivibrio	0.034238689	stool
IL2	Coprococcus	0.006414868	stool
IL2	Holdemanella	0.03885044	stool
IL2	Paraprevotella	0.010400522	stool
IL2	Pseudoflavonifractor	-0.020516513	stool
IL2	Roseburia	-0.003983732	stool
IL2	Unclassified_Bacteroidales	-0.047511913	stool
IL2	Veillonella	-0.030407825	stool
IL21	Beduinibacterium	0.007984823	stool
IL21	Butyricicoccus	0.00329297	stool
IL21	Cuneatibacter	-0.005288291	stool
IL21	Faecalibacillus	-0.005162563	stool
IL21	Faecalibacterium	-0.002960464	stool
IL21	Intestinibacter	0.00900859	stool
IL21	Romboutsia	0.006404378	stool

IL21	Ruminococcus	-0.003852243	stool
IL21	Subdoligranulum	-0.004750763	stool
IL21	Turicibacter	0.008994764	stool
IL21	Unclassified_Erysipelotrichaceae	0.013012289	stool
IL22	Anaerotignum	0.000771414	stool
IL22	Cloacibacillus	0.00294123	stool
IL22	Dysosmobacter	0.000764219	stool
IL22	Gordonibacter	0.00192863	stool
IL22	Negativibacillus	0.001708288	stool
IL22	Parabacteroides	-0.000478617	stool
IL22	Phoceia	0.001334783	stool
IL22	Pseudoflavonifractor	0.002145118	stool
IL22	Raoultibacter	0.002464405	stool
IL22	Turicibacter	0.002225878	stool
IL22	Unclassified_Alphaproteobacteria	0.002452588	stool
IL22	Unclassified_Burkholderiales	-0.003991865	stool
IL23	Butyricimonas	-0.013497129	stool
IL23	Dialister	-0.033766465	stool
IL23	Erysipelatoclostridium	0.028103072	stool
IL23	Flavonifractor	0.007633745	stool
IL23	Holdemanella	-0.032277119	stool
IL23	Holdemania	0.01700053	stool
IL23	Longicatena	0.027334691	stool
IL23	Senegalimassilia	-0.030973044	stool
IL23	Unclassified_Muribaculaceae	-0.054285013	stool
IL27	Butyricimonas	-0.013065102	stool
IL27	Collinsella	-0.011423826	stool
IL27	Dialister	-0.036483623	stool
IL27	Flavonifractor	0.010396319	stool
IL27	Fusicatenibacter	-0.006137989	stool
IL27	Holdemanella	-0.037308444	stool
IL27	Unclassified_Proteobacteria	-0.043066812	stool
IL31	Butyrivibrio	-0.246452667	stool
IL31	Clostridium_XIVa	0.03819049	stool
IL31	Eggerthella	0.046603173	stool
IL31	Erysipelatoclostridium	0.065610275	stool
IL31	Faecalicatena	0.069554405	stool
IL31	Fusicatenibacter	-0.022859541	stool
IL31	Holdemanella	-0.104590275	stool
IL31	Holdemania	0.054223213	stool

IL31	Longicatena	0.06886041	stool
IL4	Butyricimonas	-0.010692544	stool
IL4	Dialister	-0.030502205	stool
IL4	Flavonifractor	0.007980374	stool
IL4	Unclassified_Muribaculaceae	-0.06461488	stool
IL5	Butyrivibrio	0.045894662	stool
IL5	Coprobacter	-0.011987386	stool
IL5	Howardella	-0.039054478	stool
IL5	Turicibacter	0.019756964	stool
IL5	Unclassified_Bacteroidales	-0.04143017	stool
IL6	Clostridium_sensu_stricto	0.021221282	stool
IL6	Collinsella	-0.019841523	stool
IL6	Dialister	-0.054231042	stool
IL6	Eggerthella	0.022271917	stool
IL6	Fusicatenibacter	-0.008950338	stool
IL6	Holdemania	0.026083473	stool
IL6	Hungatella	0.035489712	stool
IL6	Monoglobus	0.027373901	stool
IL6	Unclassified_Firmicutes	0.03705534	stool
IL7	Acutalibacter	0.011197703	stool
IL7	Butyricimonas	-0.009176703	stool
IL7	Coprobacter	-0.008076931	stool
IL7	Dialister	-0.014839058	stool
IL7	Erysipelatoclostridium	-0.020961458	stool
IL7	Frisingicoccus	-0.015192341	stool
IL7	Pseudoflavonifractor	-0.010556299	stool
IL7	Raoultibacter	0.011083634	stool
IL7	Unclassified_Alphaproteobacteria	-0.017041608	stool
IL7	Unclassified_Eggerthellaceae	0.007622815	stool
IL8	Dialister	-0.02679321	stool
IL8	Faecalicatena	0.012642395	stool
IL8	Holdemania	0.006846535	stool
IL8	Ruminococcus2	0.002864058	stool
IL8	Unclassified_Firmicutes	0.01378914	stool
IL9	Clostridium_sensu_stricto	0.013934699	stool
IL9	Dialister	-0.059939758	stool
IL9	Eggerthella	0.01495402	stool
IL9	Faecalicatena	0.029652432	stool
IL9	Flavonifractor	0.009902202	stool
IL9	Holdemania	0.015877777	stool

IL9	Hungatella	0.028869072	stool
IL9	Longicatena	0.0248893	stool
IL9	Ruthenibacterium	0.00927959	stool
IL9	Unclassified_Firmicutes	0.040655211	stool
IP10	Dialister	-0.008666218	stool
IP10	Mediterraneibacter	-0.00184684	stool
LEPTIN	Agathobacter	0.000102584	stool
LEPTIN	Barnesiella	-0.000217943	stool
LEPTIN	Catabacter	-0.000158317	stool
LEPTIN	Desulfovibrio	-0.000457887	stool
LEPTIN	Faecalicatena	-0.000267062	stool
LEPTIN	Frisingicoccus	0.000304507	stool
LEPTIN	Howardella	-0.00035646	stool
LEPTIN	Intestinibacter	-0.000290552	stool
LEPTIN	Odoribacter	-0.000105252	stool
LEPTIN	Phascolarctobacterium	-0.000108387	stool
LEPTIN	Sutterella	-0.000310315	stool
LEPTIN	Terrisporobacter	-0.000464882	stool
LEPTIN	Unclassified_Muribaculaceae	0.001262933	stool
LIF	Anaerotignum	-0.006190125	stool
LIF	Neglecta	0.008592342	stool
LIF	Raoultibacter	0.024629824	stool
LIF	Turicibacter	0.013787659	stool
MCP1	Barnesiella	0.001193502	stool
MCP1	Blautia	-0.000409801	stool
MCP1	Butyrivibrio	0.004282364	stool
MCP1	Desulfovibrio	-0.004630613	stool
MCP1	Dialister	-0.003993384	stool
MCP1	Slackia	-0.005349208	stool
MCP1	Unclassified_Alphaproteobacteria	0.002163889	stool
MCP3	Agathobacter	-0.010622037	stool
MCP3	Butyricimonas	-0.021831162	stool
MCP3	Desulfovibrio	-0.045141037	stool
MCP3	Faecalibacterium	-0.009753873	stool
MCP3	Flavonifractor	0.014013267	stool
MCP3	Fusicatenibacter	-0.010116411	stool
MCP3	Lachnospira	-0.014441714	stool
MCP3	Oscillibacter	-0.009298859	stool
MCP3	Slackia	-0.04393316	stool
MCP3	Subdoligranulum	-0.015052353	stool

MCP3	Unclassified_Bacteroidales	-0.064689541	stool
MCP3	Unclassified_Muribaculaceae	-0.125439768	stool
MCSF	Agathobacter	-0.003590619	stool
MCSF	Clostridium_sensu_stricto	0.006483421	stool
MCSF	Dialister	-0.027310146	stool
MCSF	Flavonifractor	0.003740888	stool
MCSF	Holdemanella	-0.022839033	stool
MCSF	Holdemania	0.007804654	stool
MCSF	Unclassified_Firmicutes	0.013616732	stool
MCSF	Unclassified_Muribaculaceae	-0.027765095	stool
MIG	Cuneatibacter	-0.002139919	stool
MIG	Dialister	-0.010380744	stool
MIG	Escherichia_Shigella	0.009869947	stool
MIG	Faecalibacterium	-0.000970212	stool
MIG	Holdemanella	-0.009424729	stool
MIG	Hungatella	0.009125534	stool
MIP1A	Butyricicoccus	0.001949442	stool
MIP1A	Cuneatibacter	-0.002633422	stool
MIP1A	Faecalibacillus	-0.003266799	stool
MIP1A	Faecalibacterium	-0.001633972	stool
MIP1A	Flavonifractor	0.002119382	stool
MIP1A	Unclassified_Erysipelotrichaceae	0.006708773	stool
MIP1B	Agathobacter	-0.001043384	stool
MIP1B	Dialister	-0.007532884	stool
MIP1B	Hungatella	0.003600485	stool
MIP1B	Unclassified_Erysipelotrichaceae	0.002894411	stool
MIP1B	Unclassified_Firmicutes	0.003569358	stool
NGF	Faecalimonas	0.050207171	stool
NGF	Flavonifractor	0.014295134	stool
NGF	Hungatella	0.03392372	stool
PAI1	Colidextribacter	0.000606969	stool
PAI1	Dialister	-0.00094413	stool
PAI1	Longicatena	-0.000493216	stool
PAI1	Paraprevotella	0.00040653	stool
PAI1	Prevotella	-0.00073446	stool
PAI1	Roseburia	9.22327E-05	stool
PAI1	Unclassified_Alphaproteobacteria	0.00045124	stool
PAI1	Unclassified_Lachnospiraceae	9.33283E-05	stool
PDGFBB	Anaeromassilibacillus	-0.001835699	stool
PDGFBB	Anaerotruncus	-0.002773335	stool

PDGFBB	Beduinibacterium	-0.007295546	stool
PDGFBB	Butyricimonas	-0.00381083	stool
PDGFBB	Collinsella	-0.002381736	stool
PDGFBB	Dialister	-0.008340663	stool
PDGFBB	Eisenbergiella	-0.002032026	stool
PDGFBB	Frisingicoccus	-0.009340087	stool
PDGFBB	Gordonibacter	-0.005633074	stool
PDGFBB	Oscillibacter	-0.001154277	stool
PDGFBB	Pseudoflavonifractor	-0.003678912	stool
PDGFBB	Raoultibacter	-0.004965421	stool
PDGFBB	Unclassified_Muribaculaceae	-0.022520768	stool
RANTES	Bacteroides	0.000140813	stool
RANTES	Butyricimonas	-0.000423609	stool
RANTES	Collinsella	-0.000568929	stool
RANTES	Erysipelatoclostridium	0.00136417	stool
RANTES	Holdemanella	-0.001284575	stool
RANTES	Holdemania	0.000555785	stool
RANTES	Lawsonibacter	-0.000349005	stool
RANTES	Unclassified_Proteobacteria	-0.000956901	stool
RESISTIN	Anaerotignum	-0.000243468	stool
RESISTIN	Clostridium_IV	-0.000496477	stool
RESISTIN	Eggerthella	0.000709653	stool
RESISTIN	Flavonifractor	-0.000296407	stool
RESISTIN	Fournierella	-0.00139654	stool
RESISTIN	Holdemanella	-0.00151956	stool
RESISTIN	Parasutterella	-0.000426515	stool
RESISTIN	Slackia	-0.000942794	stool
SCF	Agathobacter	-0.006881125	stool
SCF	Anaerotignum	-0.0093102	stool
SCF	Barnesiella	0.022484608	stool
SCF	Clostridium_sensu_stricto	0.014134588	stool
SCF	Fusicatenibacter	-0.004950778	stool
SCF	Holdemanella	-0.023566395	stool
SCF	Lachnotalea	0.023699046	stool
SCF	Monoglobus	0.022295137	stool
SCF	Parabacteroides	0.005498003	stool
SCF	Parasutterella	-0.012974796	stool
SCF	Romboutsia	0.011882799	stool
SCF	Unclassified_Firmicutes	0.040747134	stool
SDF1A	Butyricicoccus	0.001558823	stool

SDF1A	Intestinibacter	0.004462932	stool
SDF1A	Terrisporobacter	0.005914262	stool
SDF1A	Turcibacter	0.004454183	stool
SDF1A	Unclassified_Erysipelotrichaceae	0.005934726	stool
TGFA	Agathobacter	-0.006753947	stool
TGFA	Clostridium_XIVa	0.012391071	stool
TGFA	Dialister	-0.0450502	stool
TGFA	Dorea	-0.003431423	stool
TGFA	Dysosmobacter	0.006047134	stool
TGFA	Eggerthella	0.012607949	stool
TGFA	Faecalicatena	0.022443056	stool
TGFA	Fusicatenibacter	-0.003710445	stool
TGFA	Holdemania	0.009896751	stool
TGFA	Hungatella	0.022073461	stool
TGFA	Senegalimassilia	-0.075490403	stool
TGFA	Unclassified_Bacteroidales	-0.042081433	stool
TGFA	Unclassified_Muribaculaceae	-0.187095623	stool
TGFB	Acutalibacter	0.021000784	stool
TGFB	Akkermansia	0.024640204	stool
TGFB	Clostridium_sensu_stricto	0.021636562	stool
TGFB	Clostridium_XVIII	0.019400084	stool
TGFB	Flavonifractor	0.009468295	stool
TGFB	Holdemania	0.013110007	stool
TGFB	Howardella	-0.047880193	stool
TGFB	Hungatella	0.020967933	stool
TGFB	Odoribacter	-0.009816867	stool
TGFB	Unclassified_Bacteroidales	-0.053067158	stool
TGFB	Unclassified_Muribaculaceae	-0.105134821	stool
TNFA	Agathobacter	-0.004577381	stool
TNFA	Akkermansia	0.008155313	stool
TNFA	Barnesiella	0.009203345	stool
TNFA	Butyricimonas	-0.007475865	stool
TNFA	Cloacibacillus	0.016399493	stool
TNFA	Clostridium_sensu_stricto	0.008382473	stool
TNFA	Collinsella	-0.006431388	stool
TNFA	Desulfovibrio	-0.018853045	stool
TNFA	Frisingicoccus	-0.011810401	stool
TNFA	Romboutsia	0.005618619	stool
TNFA	Unclassified_Bacteroidales	-0.022473161	stool
TNFB	Clostridium_sensu_stricto	0.008322313	stool

TNFB	Holdemanella	-0.03683056	stool
TNFB	Holdemania	0.007640474	stool
TNFB	Unclassified_Firmicutes	0.014967865	stool
TRAIL	Butyricicoccus	0.001997998	stool
TRAIL	Faecalibacterium	-0.000983721	stool
TRAIL	Flavonifractor	0.002117492	stool
TRAIL	Intestinibacter	0.004806593	stool
TRAIL	Ruminococcus2	0.001373216	stool
TRAIL	Turicibacter	0.004260526	stool
TRAIL	Unclassified_Erysipelotrichaceae	0.007607594	stool
TRAIL	Unclassified_Muribaculaceae	-0.023857717	stool
VCAM1	Agathobacter	0.000273746	stool
VCAM1	Alistipes	0.000254529	stool
VCAM1	Bacteroides	0.000224947	stool
VCAM1	Butyrivibrio	-0.000943235	stool
VCAM1	Coprococcus	0.000196485	stool
VCAM1	Desulfovibrio	-0.000753207	stool
VCAM1	Lachnospira	0.000268678	stool
VCAM1	Oscillibacter	0.000242672	stool
VCAM1	Streptococcus	-0.000311343	stool
VCAM1	Unclassified_Firmicutes	-0.000680261	stool
VCAM1	Unclassified_Ruminococcaceae	0.000289439	stool
VEGF	Dialister	-0.003822994	stool
VEGF	Erysipelatoclostridium	0.004728722	stool
VEGF	Faecalibacillus	-0.001168741	stool
VEGF	Flavonifractor	0.001022455	stool
VEGF	Hungatella	0.00292533	stool
VEGF	Ruminococcus2	0.000779398	stool
VEGF	Unclassified_Bacteroidales	-0.006816505	stool
VEGFD	Anaerotignum	0.003832907	stool
VEGFD	Bacteroides	0.002143678	stool
VEGFD	Barnesiella	0.01437816	stool
VEGFD	Beduinibacterium	0.008664877	stool
VEGFD	Eisenbergiella	0.005127058	stool
VEGFD	Faecalicatena	0.018001987	stool
VEGFD	Flavonifractor	0.004483783	stool
VEGFD	Ihubacter	0.006086828	stool
VEGFD	Negativibacillus	0.006386131	stool
VEGFD	Neglecta	0.006741434	stool
VEGFD	Ruthenibacterium	0.005388215	stool

VEGFD	Unclassified_Clostridiales_Incertae_Sedis_XIII	0.007334668	stool
BDNF	Abiotrophia	0.000536338	skin
BDNF	Anaerococcus	0.000240646	skin
BDNF	Moraxella	-0.000931689	skin
BDNF	Porphyromonas	0.000530736	skin
BDNF	Sphingomonas	-0.000427629	skin
BDNF	Streptococcus	0.000225882	skin
CD40L	Brucella	-0.00106773	skin
CD40L	Halomonas	-0.002694922	skin
CD40L	Lactococcus	0.00269535	skin
CD40L	Moraxella	-0.008926067	skin
EGF	Actinomyces	0.002249684	skin
EGF	Bradyrhizobium	-0.001314709	skin
EGF	Fusobacterium	0.003410263	skin
EGF	Lactococcus	0.003356359	skin
EGF	Leptotrichia	0.002780075	skin
EGF	Moraxella	-0.007639462	skin
EGF	Pelomonas	-0.001277298	skin
EGF	Porphyromonas	0.002372244	skin
EGF	Rothia	0.002299633	skin
EGF	Schaalia	0.002182672	skin
EGF	Streptococcus	0.001258973	skin
EGF	Unclassified_Carnobacteriaceae	0.003541909	skin
EGF	Veillonella	0.002263307	skin
ENA78	Dolosigranulum	-0.0047828	skin
ENA78	Fusobacterium	-0.002116835	skin
ENA78	Haemophilus	-0.000920996	skin
ENA78	Neisseria	-0.001293509	skin
ENA78	Veillonella	-0.000913979	skin
EOTAXIN	Pseudomonas	-0.005396801	skin
EOTAXIN	Sphingomonas	-0.005638281	skin
FASL	Corynebacterium	-0.010841753	skin
FASL	Lactococcus	0.064922338	skin
FASL	Streptococcus	0.016504821	skin
FGFB	Lactococcus	0.044853458	skin
FGFB	Moraxella	-0.093970033	skin
GCSF	Lactococcus	0.041899607	skin
GMCSF	Aminobacter	0.014207141	skin
GMCSF	Anaerococcus	0.017811879	skin
GMCSF	Campylobacter	0.024517325	skin

GMCSF	Cutibacterium	-0.00358289	skin
GMCSF	Dolosigranulum	-0.123327575	skin
GMCSF	Neisseria	-0.022440691	skin
GMCSF	Peptoniphilus	0.023031005	skin
GROA	Halomonas	-0.040425571	skin
GROA	Moraxella	-0.062225623	skin
GROA	Peptoniphilus	-0.015012382	skin
HGF	Chryseobacterium	-0.036510872	skin
HGF	Dolosigranulum	-0.044836415	skin
HGF	Enhydrobacter	0.029199049	skin
HGF	Moraxella	-0.038953227	skin
IFNA	Corynebacterium	-0.007556344	skin
IFNB	Unclassified_Lachnospiraceae	-0.003840154	skin
IFNG	Moraxella	-0.06979999	skin
IL10	Brevibacterium	-0.049186389	skin
IL10	Campylobacter	0.026478821	skin
IL10	Lactococcus	0.037683932	skin
IL10	Leptotrichia	0.019257116	skin
IL10	Moraxella	-0.069576979	skin
IL10	Streptococcus	0.012144904	skin
IL12P40	Porphyromonas	0.006360168	skin
IL12P70	Brevibacterium	-0.063391215	skin
IL12P70	Halomonas	-0.060542662	skin
IL12P70	Lactococcus	0.054771409	skin
IL12P70	Methylobacterium	-0.024517658	skin
IL12P70	Moraxella	-0.137579399	skin
IL12P70	Paracoccus	-0.067589566	skin
IL12P70	Streptococcus	0.01348681	skin
IL13	Corynebacterium	-0.015871068	skin
IL13	Lactococcus	0.057176479	skin
IL15	Aeribacillus	-0.031672897	skin
IL15	Fingoldia	-0.027252272	skin
IL15	Halomonas	-0.032028406	skin
IL15	Peptoniphilus	-0.02609808	skin
IL17A	Dolosigranulum	-0.046545847	skin
IL17A	Neisseria	-0.019510939	skin
IL17F	Enhydrobacter	0.002458215	skin
IL17F	Methylobacterium	-0.003797254	skin
IL17F	Unclassified_Lachnospiraceae	-0.003649868	skin
IL18	Abiotrophia	0.011307895	skin

IL18	Halomonas	-0.011812797	skin
IL18	Moraxella	-0.021004399	skin
IL1A	Lactococcus	0.007706777	skin
IL1A	Pseudomonas	0.003046704	skin
IL1B	Aeribacillus	-0.07534059	skin
IL1B	Brevibacterium	-0.142097894	skin
IL1B	Dolosigranulum	-0.16688471	skin
IL1B	Finegoldia	-0.106428477	skin
IL1B	Halomonas	-0.123795018	skin
IL1B	Methylobacterium	-0.033700085	skin
IL1B	Moraxella	-0.293060203	skin
IL1B	Paracoccus	-0.128626856	skin
IL1B	Peptoniphilus	-0.053372477	skin
IL1B	Roseomonas	-0.182387176	skin
IL1B	Stenotrophomonas	-0.022909701	skin
IL1RA	Capnocytophaga	0.075797217	skin
IL1RA	Leptotrichia	0.053332377	skin
IL1RA	Methylobacterium	-0.092822155	skin
IL1RA	Neisseria	0.06078996	skin
IL1RA	Porphyromonas	0.094852877	skin
IL1RA	Rothia	0.05054727	skin
IL1RA	Schaalia	0.063780455	skin
IL1RA	Streptococcus	0.035656216	skin
IL1RA	Unclassified_Carnobacteriaceae	0.068561682	skin
IL1RA	Veillonella	0.057185686	skin
IL2	Bradyrhizobium	0.008282689	skin
IL2	Cutibacterium	-0.003483211	skin
IL2	Lactococcus	0.040668194	skin
IL2	Leptotrichia	0.015461369	skin
IL2	Lysinibacillus	0.010746802	skin
IL2	Pelomonas	0.006176818	skin
IL2	Prevotella	0.014644666	skin
IL2	Pseudomonas	0.008017963	skin
IL2	Rhodococcus	0.01880483	skin
IL2	Schaalia	0.01337165	skin
IL2	Unclassified_Lachnospiraceae	0.015329283	skin
IL21	Cutibacterium	-0.002341251	skin
IL21	Delftia	0.005503342	skin
IL21	Dolosigranulum	-0.047492974	skin
IL21	Klebsiella	0.016352581	skin

IL21	Pseudomonas	0.006226291	skin
IL21	Roseomonas	0.018052352	skin
IL22	Capnocytophaga	0.003625285	skin
IL22	Enhydrobacter	-0.004384481	skin
IL22	Gemella	0.003502605	skin
IL22	Moraxella	-0.007510545	skin
IL22	Paracoccus	-0.006981724	skin
IL22	Peptoniphilus	-0.002505765	skin
IL22	Ralstonia	0.001546725	skin
IL22	Roseomonas	-0.010177682	skin
IL22	Unclassified_Lachnospiraceae	0.003622051	skin
IL22	Unclassified_Streptophyta	-0.002661779	skin
IL23	Lactococcus	0.059220651	skin
IL23	Methylobacterium	-0.035917612	skin
IL23	Moraxella	-0.099789273	skin
IL27	Corynebacterium	-0.014913073	skin
IL27	Methylobacterium	-0.031641477	skin
IL31	Methylobacterium	-0.049203418	skin
IL4	Abiotrophia	0.032970221	skin
IL4	Corynebacterium	-0.01076371	skin
IL4	Lactococcus	0.042721409	skin
IL4	Moraxella	-0.083367918	skin
IL4	Streptococcus	0.015022031	skin
IL5	Lactococcus	0.039164576	skin
IL5	Methylobacterium	-0.01844986	skin
IL5	Moraxella	-0.06031857	skin
IL5	Paracoccus	-0.042923713	skin
IL5	Rhodococcus	0.023806997	skin
IL6	Halomonas	-0.063255172	skin
IL6	Methylobacterium	-0.039003661	skin
IL7	Actinomyces	-0.014537947	skin
IL8	Abiotrophia	0.01824409	skin
IL8	Halomonas	-0.021054629	skin
IL8	Lactococcus	0.023149301	skin
IL9	Halomonas	-0.060233905	skin
IL9	Methylobacterium	-0.020064695	skin
IP10	Citrobacter	-0.005030939	skin
LEPTIN	Anaerococcus	0.000153095	skin
LEPTIN	Dolosigranulum	-0.001040612	skin
LEPTIN	Klebsiella	-0.000400793	skin

LEPTIN	Neisseria	-0.000308455	skin
LEPTIN	Unclassified_Bacteroidales	-0.000314769	skin
LIF	Aeribacillus	-0.051735808	skin
LIF	Granulicatella	-0.04863437	skin
LIF	Kocuria	-0.070152451	skin
LIF	Lactococcus	0.023663895	skin
LIF	Moraxella	-0.104828469	skin
MCP1	Acinetobacter	-0.0014207	skin
MCP1	Citrobacter	-0.001728757	skin
MCP1	Methylobacterium	-0.003183579	skin
MCP1	Pelomonas	-0.001141264	skin
MCP1	Sphingomonas	-0.002231019	skin
MCP3	Finegoldia	-0.043778993	skin
MCP3	Lactococcus	0.078233309	skin
MCP3	Leptotrichia	0.036035256	skin
MCP3	Moraxella	-0.17495995	skin
MCSF	Halomonas	-0.026712434	skin
MCSF	Lactococcus	0.02980974	skin
MIG	Delftia	0.004391035	skin
MIG	Kocuria	-0.017850201	skin
MIG	Pseudomonas	0.003876705	skin
MIP1A	Cutibacterium	-0.001121333	skin
MIP1A	Delftia	0.00343345	skin
MIP1A	Dolosigranulum	-0.023522846	skin
MIP1A	Klebsiella	0.007911926	skin
MIP1A	Pseudomonas	0.002996885	skin
MIP1B	Delftia	0.002253734	skin
MIP1B	Enhydrobacter	0.005202562	skin
MIP1B	Moraxella	-0.010333042	skin
MIP1B	Pseudomonas	0.002183103	skin
NGF	Corynebacterium	-0.019446557	skin
PAI1	Delftia	0.000239771	skin
PAI1	Lactobacillus	-0.000743643	skin
PAI1	Paracoccus	-0.000640769	skin
PAI1	Phocaeicola	0.0007489	skin
PDGFBB	Acinetobacter	-0.003693594	skin
PDGFBB	Dolosigranulum	-0.013931988	skin
PDGFBB	Unclassified_Streptophyta	0.004520648	skin
RANTES	Abiotrophia	0.001275105	skin
RANTES	Microbacterium	0.000708712	skin

RESISTIN	Moraxella	-0.003455011	skin
RESISTIN	Rhodococcus	0.000786873	skin
RESISTIN	Unclassified_Bacteroidales	0.00083942	skin
SCF	Lactococcus	0.041166218	skin
SCF	Methylobacterium	-0.018670405	skin
SCF	Moraxella	-0.077987501	skin
SCF	Streptococcus	0.012234258	skin
SDF1A	Delftia	0.003174991	skin
SDF1A	Klebsiella	0.008003942	skin
SDF1A	Lactococcus	0.008294058	skin
SDF1A	Pseudomonas	0.002912504	skin
TGFB	Lactococcus	0.048851688	skin
TGFB	Moraxella	-0.080605673	skin
TGFB	Streptococcus	0.014542255	skin
TNFA	Finegoldia	-0.02062196	skin
TNFA	Peptoniphilus	-0.01358227	skin
TNFA	Rhodococcus	0.016616302	skin
TNFB	Halomonas	-0.027845642	skin
TNFB	Lactococcus	0.022860952	skin
TNFB	Moraxella	-0.049603537	skin
TNFB	Streptococcus	0.007354676	skin
TRAIL	Klebsiella	0.008800696	skin
TRAIL	Pseudomonas	0.003784475	skin
VEGF	Gemella	0.003111662	skin
VEGF	Lactococcus	0.006401278	skin
VEGF	Streptococcus	0.001944397	skin
VEGFD	Moraxella	-0.035335148	skin
VCAM1	Haemophilus	0.000407326	oral
VCAM1	Unclassified_Lachnospiraceae	0.000210808	oral
VCAM1	Leptotrichia	0.000357607	oral
VCAM1	Lachnoanaerobaculum	0.000165234	oral
VCAM1	Eubacterium	0.000132735	oral
VCAM1	Unclassified_Bacteroidales	0.000227899	oral
VCAM1	Solobacterium	0.000207138	oral
VCAM1	Porphyromonas	0.000236611	oral
BDNF	Abiotrophia	0.000227987	oral
BDNF	Alloprevotella	-0.000219159	oral
BDNF	Corynebacterium	0.000170397	oral
BDNF	Megasphaera	-9.7278E-05	oral
BDNF	Parvimonas	-0.000136724	oral

BDNF	Schaalia	5.0213E-05	oral
BDNF	Unclassified_Bacteroidetes	-0.00026859	oral
BDNF	Unclassified_Firmicutes	-0.000306633	oral
BDNF	Unclassified_Prevotellaceae	-0.000188389	oral
CD40L	Actinomyces	0.000381225	oral
CD40L	Schaalia	0.000240751	oral
CD40L	Unclassified_Firmicutes	-0.001456959	oral
CD40L	Unclassified_Flavobacteriaceae	-0.002872674	oral
CD40L	Unclassified_Neisseriaceae	-0.001628685	oral
EGF	Aminipila	0.001273356	oral
EGF	Corynebacterium	0.000789445	oral
EGF	Delftia	0.001457457	oral
EGF	Eikenella	-0.001049189	oral
EGF	Filifactor	0.001173733	oral
EGF	Metamycoplasma	0.001128587	oral
EGF	Peptoanaerobacter	0.001389923	oral
EGF	Schaalia	0.000385966	oral
EGF	Treponema	0.000947267	oral
EGF	Unclassified_Bacteroidetes	-0.001121719	oral
EGF	Unclassified_Peptostreptococcaceae	0.000815529	oral
EGF	Veillonella	-0.000157882	oral
ENA78	Alloprevotella	-0.000709671	oral
ENA78	Lautropia	-0.000695151	oral
ENA78	Neisseria	-0.000352324	oral
ENA78	Oribacterium	0.00016911	oral
ENA78	Parvimonas	-0.000612741	oral
ENA78	Streptococcus	0.000148155	oral
ENA78	Tannerella	-0.000816861	oral
ENA78	Unclassified_Bacteroidales	-0.000458744	oral
ENA78	Unclassified_Bacteroidetes	-0.001667417	oral
ENA78	Unclassified_Lachnospiraceae	0.000377041	oral
ENA78	Unclassified_Peptostreptococcaceae	-0.001313326	oral
EOTAXIN	Eikenella	-0.008430216	oral
EOTAXIN	Kingella	-0.005648613	oral
FASL	Solobacterium	0.004757717	oral
FGFB	Solobacterium	0.002897835	oral
FGFB	Unclassified_Clostridia	-0.006673433	oral
GCSF	Corynebacterium	0.0127401	oral
GCSF	Unclassified_Bacteroidales	0.007086948	oral
GMCSF	Aminipila	-0.024788404	oral

GMCSF	Gemella	0.005202844	oral
GMCSF	Kingella	0.011956984	oral
GMCSF	Lautropia	-0.00767403	oral
GMCSF	Neisseria	-0.006901037	oral
GMCSF	Peptoanaerobacter	-0.033285442	oral
GMCSF	Rothia	0.004604207	oral
GMCSF	Streptococcus	0.003699778	oral
GMCSF	Unclassified_Neisseriaceae	-0.023027122	oral
GMCSF	Unclassified_Peptostreptococcaceae	-0.018954052	oral
GMCSF	Veillonella	0.002808365	oral
GROA	Actinomyces	0.002612423	oral
GROA	Porphyromonas	-0.002695966	oral
GROA	Solobacterium	0.002180571	oral
GROA	Unclassified_Clostridia	-0.003796987	oral
GROA	Unclassified_Flavobacteriaceae	-0.026317675	oral
GROA	Unclassified_Selenomonadaceae	0.002455312	oral
HGF	Actinomyces	0.004949589	oral
HGF	Unclassified_Firmicutes	-0.01022495	oral
ICAM1	Peptoanaerobacter	0.000829929	oral
ICAM1	Unclassified_Flavobacteriales	0.000491406	oral
ICAM1	Unclassified_Pasteurellaceae	0.000588531	oral
IFNA	Unclassified_Bacteroidales	0.003654078	oral
IFNA	Unclassified_Firmicutes	-0.007879864	oral
IFNB	Actinomyces	0.00108778	oral
IFNB	Neisseria	-0.00154155	oral
IFNB	Schaalia	0.000545933	oral
IL10	Abiotrophia	0.009596782	oral
IL10	Anaerosinus	0.009878953	oral
IL10	Corynebacterium	0.008634493	oral
IL10	Unclassified_Bacteroidales	0.007814707	oral
IL10	Unclassified_Clostridia	-0.009214702	oral
IL10	Unclassified_Firmicutes	-0.015769493	oral
IL10	Unclassified_Selenomonadaceae	0.005510079	oral
IL12P40	Actinomyces	0.001676426	oral
IL12P40	Delftia	0.004738213	oral
IL12P40	Lancefieldella	0.001241499	oral
IL12P40	Unclassified_Clostridia	-0.003978607	oral
IL12P70	Abiotrophia	0.013489312	oral
IL12P70	Unclassified_Bacteroidales	0.010219085	oral
IL12P70	Unclassified_Selenomonadaceae	0.006144919	oral

IL13	Unclassified_Bacteroidales	0.007344111	oral
IL15	Actinomyces	0.003715882	oral
IL15	Filifactor	0.015642026	oral
IL15	Lancefieldella	0.003435306	oral
IL15	Mogibacterium	0.003335591	oral
IL15	Neisseria	-0.005084625	oral
IL15	Solobacterium	0.004015731	oral
IL15	Unclassified_Bacteroidales	0.006365923	oral
IL15	Unclassified_Clostridia	-0.009707922	oral
IL15	Unclassified_Firmicutes	-0.029124371	oral
IL15	Unclassified_Neisseriaceae	-0.021778666	oral
IL17A	Aggregatibacter	-0.007300695	oral
IL17A	Alloprevotella	-0.011815708	oral
IL17A	Lautropia	-0.009106726	oral
IL17A	Mogibacterium	0.003349902	oral
IL17A	Neisseria	-0.00665637	oral
IL17A	Oribacterium	0.002837625	oral
IL17A	Parvimonas	-0.007091575	oral
IL17A	Solobacterium	0.003896905	oral
IL17A	Unclassified_Lachnospiraceae	0.005437351	oral
IL17A	Unclassified_Neisseriaceae	-0.014850467	oral
IL17A	Unclassified_Pasteurellaceae	-0.016054601	oral
IL17F	Actinomyces	0.000573654	oral
IL17F	Capnocytophaga	-0.000702477	oral
IL17F	Fusobacterium	-0.000798732	oral
IL17F	Lautropia	-0.001015996	oral
IL17F	Neisseria	-0.001162507	oral
IL17F	Schaalia	0.000379876	oral
IL17F	Unclassified_Weeksellaceae	-0.000604571	oral
IL18	Rothia	0.001255488	oral
IL18	Unclassified_Clostridia	-0.002751973	oral
IL18	Unclassified_Firmicutes	-0.005513137	oral
IL1A	Solobacterium	0.000833766	oral
IL1A	Unclassified_Clostridia	-0.002644823	oral
IL1A	Unclassified_Firmicutes	-0.003246132	oral
IL1B	Actinomyces	0.007403594	oral
IL1B	Anaerosinus	0.012109018	oral
IL1B	Butyrivibrio	0.009535833	oral
IL1B	Filifactor	0.031306234	oral
IL1B	Lancefieldella	0.005506451	oral

IL1B	Mogibacterium	0.005557435	oral
IL1B	Neisseria	-0.00818248	oral
IL1B	Peptoanaerobacter	-0.076443021	oral
IL1B	Treponema	0.014828413	oral
IL1B	Unclassified_Bacteroidales	0.009720854	oral
IL1B	Unclassified_Clostridia	-0.020171161	oral
IL1B	Unclassified_Firmicutes	-0.073332553	oral
IL1B	Unclassified_Flavobacteriaceae	-0.085685593	oral
IL1B	Unclassified_Leptotrichiaceae	0.015549258	oral
IL1B	Unclassified_Neisseriaceae	-0.052892625	oral
IL1B	Unclassified_Selenomonadaceae	0.009114823	oral
IL1RA	Alloprevotella	-0.024944078	oral
IL1RA	Alloscardovia	0.038919029	oral
IL1RA	Eubacterium	-0.014903577	oral
IL1RA	Tannerella	-0.025385628	oral
IL1RA	Unclassified_Bacteroidales	0.0201885	oral
IL1RA	Unclassified_Burkholderiales	-0.084595619	oral
IL1RA	Unclassified_Clostridia	-0.028806125	oral
IL1RA	Unclassified_Firmicutes	-0.036707081	oral
IL1RA	Unclassified_Leptotrichiaceae	-0.026226813	oral
IL2	Alloprevotella	-0.010289366	oral
IL2	Capnocytophaga	0.005377537	oral
IL2	Catonella	0.003929783	oral
IL2	Granulicatella	0.010655905	oral
IL2	Unclassified_Bacteroidales	0.008088224	oral
IL2	Unclassified_Neisseriaceae	-0.019207951	oral
IL21	Actinomyces	0.003075282	oral
IL21	Cardiobacterium	-0.01080457	oral
IL21	Schaalia	0.001596649	oral
IL21	Treponema	-0.008469958	oral
IL21	Unclassified_Bacteroidetes	-0.011103072	oral
IL21	Unclassified_Clostridia	-0.007876087	oral
IL21	Unclassified_Firmicutes	-0.011828411	oral
IL21	Unclassified_Peptostreptococcaceae	-0.013667303	oral
IL21	Unclassified_Weeksellaceae	-0.004704863	oral
IL22	Abiotrophia	0.001572578	oral
IL22	Granulicatella	0.001017178	oral
IL22	Treponema	0.001019606	oral
IL22	Unclassified_Clostridia	0.001050197	oral
IL22	Unclassified_Flavobacteriales	-0.002117511	oral

IL22	Unclassified_Weeksellaceae	0.000658343	oral
IL23	Solobacterium	0.004525337	oral
IL27	Unclassified_Bacteroidales	0.010786449	oral
IL27	Unclassified_Candidatus_Saccharibacteria	-0.006981277	oral
IL27	Unclassified_Clostridia	-0.008933948	oral
IL31	Schaalia	-0.005117797	oral
IL4	Abiotrophia	0.01229669	oral
IL4	Corynebacterium	0.008086489	oral
IL4	Solobacterium	0.004094872	oral
IL4	Unclassified_Bacteroidales	0.00715592	oral
IL4	Unclassified_Firmicutes	-0.013613186	oral
IL5	Alloprevotella	-0.011900289	oral
IL5	Aminipila	-0.035540357	oral
IL5	Peptoanaerobacter	-0.043721175	oral
IL5	Unclassified_Bacteroidales	0.009902087	oral
IL5	Unclassified_Flavobacteriaceae	-0.046735808	oral
IL5	Unclassified_Neisseriaceae	-0.024668682	oral
IL5	Unclassified_Peptostreptococcaceae	-0.016600838	oral
IL6	Filifactor	0.024266547	oral
IL6	Unclassified_Bacteroidales	0.008494245	oral
IL6	Unclassified_Selenomonadaceae	0.006057722	oral
IL7	Schaalia	-0.001367961	oral
IL7	Unclassified_Neisseriaceae	-0.008251868	oral
IL8	Solobacterium	0.00173429	oral
IP10	Cardiobacterium	0.001947322	oral
IP10	Unclassified_Bacteroidales	0.00077437	oral
IP10	Unclassified_Flavobacteriaceae	0.002750138	oral
LEPTIN	Abiotrophia	0.00012854	oral
LEPTIN	Aminipila	-0.000610415	oral
LEPTIN	Gemella	6.10446E-05	oral
LEPTIN	Lautropia	-0.000152152	oral
LEPTIN	Metamycoplasma	-0.000137774	oral
LEPTIN	Peptoanaerobacter	-0.000466643	oral
LEPTIN	Streptococcus	4.50976E-05	oral
LEPTIN	Unclassified_Bacteroidetes	-0.000180415	oral
LEPTIN	Unclassified_Carnobacteriaceae	3.99916E-05	oral
LEPTIN	Unclassified_Flavobacteriaceae	-0.000403145	oral
LEPTIN	Unclassified_Flavobacteriales	-0.00022052	oral
LEPTIN	Unclassified_Neisseriaceae	-0.000231105	oral
LEPTIN	Unclassified_Peptostreptococcaceae	-0.000233248	oral

LIF	Actinomyces	0.003464037	oral
LIF	Unclassified_Firmicutes	-0.060757536	oral
LIF	Unclassified_Neisseriaceae	-0.022203798	oral
MCP3	Corynebacterium	0.016270483	oral
MCP3	Filifactor	0.043454056	oral
MCP3	Granulicatella	0.015809268	oral
MCP3	Peptoanaerobacter	-0.030266065	oral
MCP3	Unclassified_Bacteroidales	0.011974481	oral
MCP3	Unclassified_Clostridia	-0.020930292	oral
MCP3	Unclassified_Firmicutes	-0.023199236	oral
MCSF	Solobacterium	0.002142003	oral
MCSF	Unclassified_Clostridia	-0.004125218	oral
MIG	Unclassified_Peptostreptococcaceae	0.001566813	oral
MIP1A	Cardiobacterium	-0.005762257	oral
MIP1A	Unclassified_Bacteroidetes	-0.005192318	oral
MIP1A	Unclassified_Clostridia	-0.004651399	oral
MIP1A	Unclassified_Weeksellaceae	-0.001462293	oral
MIP1B	Unclassified_Clostridia	-0.001652029	oral
MIP1B	Unclassified_Firmicutes	-0.002166973	oral
NGF	Corynebacterium	0.016572113	oral
PAI1	Abiotrophia	0.000225566	oral
PAI1	Catonella	0.00010295	oral
PAI1	Corynebacterium	0.000172079	oral
PAI1	Gemella	8.97915E-05	oral
PAI1	Kingella	-0.000362774	oral
PAI1	Oribacterium	5.69406E-05	oral
PAI1	Prevotella	-4.89425E-05	oral
PAI1	Unclassified_Peptostreptococcaceae	0.000328524	oral
PAI1	Unclassified_Weeksellaceae	9.75873E-05	oral
PDGFBB	Alloprevotella	-0.002713123	oral
PDGFBB	Eubacterium	-0.001048214	oral
PDGFBB	Gemella	-0.00098586	oral
PDGFBB	Haemophilus	-0.000726382	oral
PDGFBB	Peptoanaerobacter	-0.005040786	oral
PDGFBB	Peptostreptococcus	-0.001569688	oral
PDGFBB	Unclassified_Clostridia	-0.002574486	oral
PDGFBB	Unclassified_Selenomonadaceae	0.001140061	oral
PDGFBB	Unclassified_Weeksellaceae	-0.001068853	oral
RANTES	Aggregatibacter	-0.00036338	oral
RANTES	Butyrivibrio	0.00034021	oral

RANTES	Gemella	-0.000227705	oral
RANTES	Solobacterium	0.000228617	oral
RANTES	Unclassified_Carnobacteriaceae	-0.000148231	oral
RESISTIN	Alloscardovia	-0.000610584	oral
RESISTIN	Butyrivibrio	0.000347084	oral
RESISTIN	Treponema	0.000471021	oral
RESISTIN	Unclassified_Bacteroidales	0.000308967	oral
RESISTIN	Unclassified_Firmicutes	-0.000453316	oral
SCF	Corynebacterium	0.009412207	oral
SCF	Filifactor	0.015304901	oral
SCF	Unclassified_Neisseriaceae	-0.017494168	oral
SCF	Unclassified_Peptostreptococcaceae	0.012135136	oral
SDF1A	Capnocytophaga	-0.001445993	oral
SDF1A	Solobacterium	0.000956355	oral
SDF1A	Unclassified_Bacteroidetes	-0.003222062	oral
SDF1A	Unclassified_Clostridia	-0.00351094	oral
SDF1A	Unclassified_Firmicutes	-0.002935421	oral
SDF1A	Unclassified_Weeksellaceae	-0.001115404	oral
TGFA	Fusobacterium	-0.008134474	oral
TGFA	Neisseria	-0.006038188	oral
TGFB	Abiotrophia	0.013721658	oral
TGFB	Peptoanaerobacter	-0.036477679	oral
TGFB	Solobacterium	0.005986337	oral
TGFB	Unclassified_Firmicutes	-0.028114714	oral
TGFB	Unclassified_Neisseriaceae	-0.025885735	oral
TNFA	Actinomyces	0.004066688	oral
TNFA	Filifactor	0.013195861	oral
TNFA	Neisseria	-0.006159569	oral
TNFA	Slackia	-0.009075645	oral
TNFA	Unclassified_Bacteroidales	0.003557869	oral
TNFA	Unclassified_Clostridia	-0.0081526	oral
TNFA	Unclassified_Firmicutes	-0.014536987	oral
TNFA	Unclassified_Neisseriaceae	-0.007959898	oral
TNFA	Unclassified_Selenomonadaceae	0.003880596	oral
TNFB	Solobacterium	0.002479642	oral
TNFB	Unclassified_Bacteroidales	0.003825737	oral
TNFB	Unclassified_Selenomonadaceae	0.003027929	oral
TRAIL	Unclassified_Bacteroidetes	-0.003793605	oral
TRAIL	Unclassified_Clostridia	-0.003181023	oral
TRAIL	Unclassified_Firmicutes	-0.004572103	oral

TRAIL	Unclassified_Peptostreptococcaceae	-0.005887147	oral
TRAIL	Unclassified_Weeksellaceae	-0.001517907	oral
VCAM1	Actinomyces	0.000135823	oral
VCAM1	Campylobacter	0.000241768	oral
VCAM1	Capnocytophaga	0.000269748	oral
VCAM1	Catonella	0.00019482	oral
VCAM1	Gemella	0.000212821	oral
VCAM1	Lancefieldella	0.000139212	oral
VCAM1	Lautropia	0.000194642	oral
VCAM1	Mogibacterium	9.98376E-05	oral
VCAM1	Oribacterium	0.000223096	oral
VCAM1	Streptococcus	0.000284904	oral
VCAM1	Unclassified_Carnobacteriaceae	0.00018887	oral
VCAM1	Unclassified_Weeksellaceae	0.000187249	oral
VEGF	Actinomyces	0.000705117	oral
VEGF	Parvimonas	-0.001037787	oral
VEGF	Unclassified_Clostridia	-0.002261335	oral
VEGF	Unclassified_Firmicutes	-0.002232097	oral
VEGFD	Aggregatibacter	-0.005631654	oral
VEGFD	Alloprevotella	-0.010057538	oral
VEGFD	Delftia	0.008719631	oral
VEGFD	Filifactor	0.012164212	oral
VEGFD	Gemella	-0.002665731	oral
VEGFD	Haemophilus	-0.00225082	oral
VEGFD	Unclassified_Carnobacteriaceae	-0.002765905	oral
VCAM1	Streptococcus	0.000372235	nasal
IL5	Unclassified_Betaproteobacteria	0.042569492	nasal
MIP1A	Stenotrophomonas	0.00916581	nasal
BDNF	Blautia	0.000443376	nasal
BDNF	Paenibacillus	0.000468971	nasal
BDNF	Peptoniphilus	-0.000176299	nasal
BDNF	Roseomonas	0.000382978	nasal
BDNF	Unclassified_Candidatus_Saccharibacteria	0.000269608	nasal
CD40L	Micrococcus	-0.002063026	nasal
EGF	Bacillus	-0.002923033	nasal
EGF	Massilia	-0.001759001	nasal
EGF	Pelomonas	-0.002694101	nasal
EGF	Phocaeicola	0.002849445	nasal
EGF	Porphyromonas	-0.001426774	nasal
EGF	Roseomonas	0.002576263	nasal

EOTAXIN	Capnocytophaga	-0.007955161	nasal
EOTAXIN	Corynebacterium	0.001765317	nasal
EOTAXIN	Lautropia	-0.009483537	nasal
EOTAXIN	Unclassified_Candidatus_Saccharibacteria	-0.00620504	nasal
FASL	Dolosigranulum	-0.039545052	nasal
FGFB	Dolosigranulum	-0.034689697	nasal
GCSF	Dolosigranulum	-0.036204977	nasal
GCSF	Kingella	-0.028502658	nasal
GCSF	Roseomonas	0.032091027	nasal
GMCSF	Corynebacterium	-0.005049111	nasal
GMCSF	Dolosigranulum	-0.027119031	nasal
GMCSF	Massilia	0.015009875	nasal
GMCSF	Microbacterium	0.012587308	nasal
GMCSF	Moraxella	-0.039542931	nasal
GMCSF	Staphylococcus	0.006930242	nasal
GMCSF	Unclassified_Neisseriales	0.017483648	nasal
GROA	Lautropia	-0.022507692	nasal
HGF	Moraxella	0.034814936	nasal
HGF	Roseomonas	0.024888288	nasal
HGF	Unclassified_Betaproteobacteria	0.019626633	nasal
ICAM1	Kocuria	-0.000952276	nasal
ICAM1	Microbacterium	-0.000973196	nasal
ICAM1	Peptoniphilus	-0.001002897	nasal
IFNA	Dolosigranulum	-0.026480576	nasal
IFNA	Roseomonas	0.015316732	nasal
IFNB	Micrococcus	-0.003533718	nasal
IFNB	Unclassified_Betaproteobacteria	-0.00417	nasal
IFNG	Dolosigranulum	-0.045816673	nasal
IFNG	Moraxella	-0.042874252	nasal
IL10	Dolosigranulum	-0.03201302	nasal
IL10	Micrococcus	-0.017851652	nasal
IL10	Streptococcus	0.009006942	nasal
IL12P70	Micrococcus	-0.028640037	nasal
IL12P70	Staphylococcus	0.007753609	nasal
IL13	Dolosigranulum	-0.039799387	nasal
IL13	Kingella	-0.049642499	nasal
IL13	Staphylococcus	0.004935136	nasal
IL15	Micrococcus	-0.021841153	nasal
IL15	Streptococcus	0.007239795	nasal
IL17A	Corynebacterium	-0.003180329	nasal

IL17A	Dolosigranulum	-0.016580313	nasal
IL17F	Capnocytophaga	-0.001961637	nasal
IL17F	Micrococcus	-0.002255052	nasal
IL17F	Negativicoccus	0.003467024	nasal
IL18	Dolosigranulum	-0.008009746	nasal
IL18	Kocuria	-0.006775793	nasal
IL18	Staphylococcus	0.001318094	nasal
IL1A	Dolosigranulum	-0.008152849	nasal
IL1A	Peptoniphilus	-0.003622319	nasal
IL1A	Stenotrophomonas	0.00779035	nasal
IL1B	Bacillus	-0.039285349	nasal
IL1B	Pelomonas	-0.090738554	nasal
IL1B	Streptococcus	0.012419908	nasal
IL1RA	Kingella	-0.071394616	nasal
IL1RA	Lactobacillus	-0.072841629	nasal
IL1RA	Unclassified_Betaproteobacteria	0.074169	nasal
IL2	Brevundimonas	0.011301183	nasal
IL2	Cutibacterium	0.004491992	nasal
IL2	Finegoldia	-0.017861032	nasal
IL2	Lachnoanaerobaculum	-0.032919513	nasal
IL2	Lawsonella	-0.022843043	nasal
IL2	Massilia	0.009920733	nasal
IL2	Microbacterium	0.011154585	nasal
IL2	Micrococcus	-0.041783419	nasal
IL2	Negativicoccus	0.029060551	nasal
IL2	Unclassified_Betaproteobacteria	0.03597751	nasal
IL2	Unclassified_Neisseriales	0.011199161	nasal
IL21	Capnocytophaga	-0.009886114	nasal
IL21	Dolosigranulum	-0.017016524	nasal
IL21	Neisseria	-0.009344016	nasal
IL21	Pelomonas	-0.016458409	nasal
IL21	Porphyromonas	-0.01010965	nasal
IL21	Stenotrophomonas	0.016230269	nasal
IL22	Actinomyces	0.001551142	nasal
IL22	Dermabacter	-0.004477334	nasal
IL22	Dolosigranulum	-0.002327801	nasal
IL22	Gemella	0.001507788	nasal
IL22	Phocaeicola	-0.003467661	nasal
IL22	Porphyromonas	0.002350317	nasal
IL22	Schaalia	0.002510326	nasal

IL22	Unclassified_Clostridiales	-0.004708921	nasal
IL23	Dolosigranulum	-0.042782173	nasal
IL23	Peptoniphilus	-0.009986695	nasal
IL23	Roseomonas	0.025901987	nasal
IL27	Dolosigranulum	-0.047700774	nasal
IL27	Roseomonas	0.031520225	nasal
IL27	Staphylococcus	0.00542153	nasal
IL31	Lachnoanaerobaculum	0.044758665	nasal
IL31	Lactococcus	-0.065411315	nasal
IL31	Neisseria	0.03126298	nasal
IL31	Peptoniphilus	-0.059003042	nasal
IL31	Prevotella	0.027054605	nasal
IL31	Rothia	0.035324275	nasal
IL31	Streptococcus	0.030754901	nasal
IL31	Veillonella	0.036125615	nasal
IL4	Dolosigranulum	-0.039844983	nasal
IL5	Brevundimonas	0.015313487	nasal
IL5	Cutibacterium	0.006251825	nasal
IL5	Finegoldia	-0.013044924	nasal
IL5	Massilia	0.013385158	nasal
IL5	Microbacterium	0.013221515	nasal
IL5	Micrococcus	-0.02061677	nasal
IL5	Negativicoccus	0.026672655	nasal
IL5	Unclassified_Neisseriales	0.01498203	nasal
IL5	Unclassified_Streptophyta	0.00743235	nasal
IL6	Streptococcus	0.017770743	nasal
IL7	Haemophilus	0.011392856	nasal
IL7	Klebsiella	-0.010543803	nasal
IL8	Dolosigranulum	-0.016404322	nasal
IL8	Kocuria	-0.013139869	nasal
IL8	Peptoniphilus	-0.004483514	nasal
IL8	Prevotellamassilia	0.011833897	nasal
IL9	Dolosigranulum	-0.031977469	nasal
IL9	Kingella	-0.03314127	nasal
IL9	Micrococcus	-0.029252469	nasal
IP10	Kocuria	-0.009846899	nasal
LEPTIN	Agathobacter	-0.000417577	nasal
LEPTIN	Corynebacterium	-6.48766E-05	nasal
LEPTIN	Finegoldia	0.000149689	nasal
LEPTIN	Granulicatella	0.000152987	nasal

LEPTIN	Leptotrichia	0.000211631	nasal
LEPTIN	Moraxella	-0.000511293	nasal
LEPTIN	Schaalia	0.000218026	nasal
LEPTIN	Staphylococcus	7.03337E-05	nasal
LIF	Micrococcus	-0.027311315	nasal
MCP1	Capnocytophaga	-0.002303036	nasal
MCP1	Kingella	-0.002596795	nasal
MCP1	Lachnoanaerobaculum	-0.003162682	nasal
MCP1	Neisseria	-0.00147736	nasal
MCP1	Unclassified_Candidatus_Saccharibacteria	-0.001798903	nasal
MCP1	Unclassified_Streptophyta	0.000979849	nasal
MCP1	Zea	0.001737002	nasal
MCP3	Peptoniphilus	-0.019805892	nasal
MCSF	Dolosigranulum	-0.014061624	nasal
MCSF	Lawsonella	0.004281319	nasal
MCSF	Micrococcus	-0.014782555	nasal
MCSF	Peptoniphilus	-0.005196789	nasal
MIG	Abiotrophia	-0.007670908	nasal
MIG	Finegoldia	0.002427913	nasal
MIG	Fusobacterium	-0.005808301	nasal
MIG	Haemophilus	-0.005509633	nasal
MIG	Kingella	-0.010675088	nasal
MIG	Leptotrichia	-0.004640825	nasal
MIG	Stenotrophomonas	0.012265183	nasal
MIG	Veillonella	-0.003971203	nasal
MIP1A	Blautia	-0.010842443	nasal
MIP1A	Capnocytophaga	-0.004952892	nasal
MIP1A	Dolosigranulum	-0.008524427	nasal
MIP1A	Fusobacterium	-0.004473259	nasal
MIP1A	Klebsiella	-0.005610383	nasal
MIP1A	Lactobacillus	-0.007446599	nasal
MIP1A	Leptotrichia	-0.004455845	nasal
MIP1A	Neisseria	-0.004443855	nasal
MIP1A	Pelomonas	-0.009031677	nasal
MIP1A	Porphyromonas	-0.00643677	nasal
MIP1A	Unclassified_Lachnospiraceae	-0.00913657	nasal
MIP1A	Unclassified_Streptophyta	-0.00309214	nasal
MIP1B	Capnocytophaga	-0.002504904	nasal
MIP1B	Haemophilus	-0.003147552	nasal
MIP1B	Kingella	-0.00428603	nasal

MIP1B	Peptoniphilus	-0.002790509	nasal
MIP1B	Staphylococcus	0.000845688	nasal
MIP1B	Unclassified_Betaproteobacteria	0.004549639	nasal
NGF	Dolosigranulum	-0.044298686	nasal
NGF	Roseomonas	0.047226242	nasal
PAI1	Abiotrophia	0.000474854	nasal
PAI1	Finegoldia	-0.000296447	nasal
PAI1	Negativicoccus	-0.000722473	nasal
PDGFBB	Acinetobacter	-0.006537294	nasal
PDGFBB	Peptoniphilus	-0.002488672	nasal
PDGFBB	Unclassified_Clostridiales	-0.005881642	nasal
RANTES	Campylobacter	-0.000857606	nasal
RANTES	Kocuria	-0.001237001	nasal
RESISTIN	Klebsiella	0.000674271	nasal
RESISTIN	Moraxella	0.001374893	nasal
RESISTIN	Peptoniphilus	-0.000360478	nasal
SCF	Unclassified_Neisseriales	-0.014454018	nasal
SDF1A	Capnocytophaga	-0.005567839	nasal
SDF1A	Dolosigranulum	-0.00920301	nasal
SDF1A	Fusobacterium	-0.003690515	nasal
SDF1A	Kingella	-0.007360429	nasal
SDF1A	Peptoniphilus	-0.003325778	nasal
SDF1A	Porphyromonas	-0.004734855	nasal
SDF1A	Stenotrophomonas	0.009445661	nasal
TGFA	Kocuria	-0.02710462	nasal
TGFA	Lachnoanaerobaculum	0.011176634	nasal
TGFA	Micrococcus	-0.028207012	nasal
TGFA	Unclassified_Neisseriales	-0.017890993	nasal
TGFB	Dolosigranulum	-0.034489062	nasal
TGFB	Micrococcus	-0.033568752	nasal
TGFB	Staphylococcus	0.006733814	nasal
TNFA	Lautropia	-0.013305054	nasal
TNFA	Streptococcus	0.00634315	nasal
TNFB	Peptoniphilus	-0.006123412	nasal
TNFB	Streptococcus	0.005378276	nasal
TRAIL	Capnocytophaga	-0.006029025	nasal
TRAIL	Dolosigranulum	-0.010414052	nasal
TRAIL	Kingella	-0.007336625	nasal
TRAIL	Lactobacillus	-0.007196453	nasal
TRAIL	Lautropia	-0.0074415	nasal

TRAIL	Peptoniphilus	-0.003582894	nasal
TRAIL	Stenotrophomonas	0.009582553	nasal
VCAM1	Moraxella	0.000781511	nasal
VCAM1	Subdoligranulum	0.000956596	nasal
VEGF	Dolosigranulum	-0.003963652	nasal
VEGF	Peptoniphilus	-0.002042995	nasal

Table 2. Microbial Genera Correlated with Clinical Analytes

Microbial Genus	Analytes	Correlation Coefficient	Microbiome
Agathobacter	GLOB	-0.005356815	Gut
Agathobacter	TP	-0.005514113	Gut
Agathobacter	LYM	0.094716616	Gut
Agathobacter	PLT	-0.947360127	Gut
Agathobacter	CHOLHDL	0.010646257	Gut
Agathobacter	CR	0.003290014	Gut
Agathobacter	LDLHDL	0.008465834	Gut
Agathobacter	RDW	0.023020492	Gut
Agathobacter	CHOLHDL	0.011035142	Gut
Agathobacter	CR	0.001092536	Gut
Agathobacter	EOS	0.0277714	Gut
Agathobacter	LDLHDL	0.010609055	Gut
Ruminococcus	HGB	0.021276863	Gut
Akkermansia	A1C	-0.008338842	Gut
Akkermansia	BASO	-0.002921234	Gut
Akkermansia	CO2	0.025766098	Gut
Akkermansia	BASO	-0.003633019	Gut
Akkermansia	BASO	-0.002982775	Gut
Akkermansia	BUN	-0.054112981	Gut
Akkermansia	BASO	-0.00298568	Gut
Akkermansia	A1C	-0.027373098	Gut
Akkermansia	BASO	-0.002666482	Gut
Akkermansia	A1C	-0.01571406	Gut
Akkermansia	A1C	-0.01853334	Gut
Akkermansia	A1C	-0.010785664	Gut
Akkermansia	BASO	-0.00326816	Gut
Akkermansia	A1C	-0.008463498	Gut
Akkermansia	BUN	-0.052379875	Gut
Akkermansia	EOSAB	-0.002055755	Gut
Phascolarctobacterium	HDL	0.172236584	Gut
Phascolarctobacterium	RDW	0.018277776	Gut
Phascolarctobacterium	TP	0.005041736	Gut
Phascolarctobacterium	TP	0.008963111	Gut
Blautia	CR	-0.003055391	Gut
Blautia	CR	-0.002320667	Gut
Barnesiella	EGFR	0.161040459	Gut
Romboutsia	ALT	-0.436239518	Gut
Romboutsia	MCV	0.093117999	Gut

Romboutsia	ALKP	0.273234223	Gut
Akkermansia	BUN	-0.049426933	Gut
Akkermansia	EOSAB	-0.001510737	Gut
Akkermansia	EOSAB	-0.00254701	Gut
Akkermansia	BUN	-0.046467891	Gut
Akkermansia	EOSAB	-0.001729992	Gut
Akkermansia	CR	0.001103788	Gut
Akkermansia	A1C	-0.007396889	Gut
Sutterella	ALKP	-0.429706297	Gut
Sutterella	LDL	-0.466368944	Gut
Sutterella	NHDL	-0.479153298	Gut
Faecalibacillus	HDL	0.281626026	Gut
Faecalibacillus	ALKP	0.333992903	Gut
Faecalibacillus	TP	0.008335581	Gut
Faecalibacillus	HDL	0.31839612	Gut
Faecalibacillus	HDL	0.206317972	Gut
Faecalibacillus	CHOLHDL	0.016479411	Gut
Faecalibacillus	LDLHDL	0.013131203	Gut
Faecalibacillus	CHOLHDL	0.012839837	Gut
Faecalibacillus	LDLHDL	0.010923805	Gut
Faecalibacillus	ALKP	0.514056051	Gut
Faecalibacillus	TP	0.010130811	Gut
Faecalibacillus	HDL	0.15355654	Gut
Faecalibacillus	CHOLHDL	0.010354343	Gut
Faecalibacillus	LDLHDL	0.008950255	Gut
Faecalibacillus	CO2	0.028680837	Gut
Faecalibacillus	CHOLHDL	0.024170583	Gut
Faecalibacillus	LDLHDL	0.020013546	Gut
Faecalibacillus	TP	0.006137132	Gut
Faecalibacillus	ALKP	0.742056695	Gut
Faecalibacillus	HDL	0.290912852	Gut
Faecalibacillus	TP	0.014724029	Gut
Ruthenibacterium	BUN	0.064091712	Gut
Romboutsia	ALKP	0.25363153	Gut
Romboutsia	ALT	-0.265706744	Gut
Romboutsia	UALB	-0.102961194	Gut
Romboutsia	EGFR	-0.107613237	Gut
Romboutsia	ALKP	0.420223528	Gut
Romboutsia	ALKP	0.290241511	Gut
Romboutsia	ALKP	0.342089774	Gut
Intestinimonas	TBIL	-0.005185854	Gut
Ihubacter	ALCRU	0.89515941	Gut

Akkermansia	BASO	-0.003237466	Gut
Akkermansia	BASO	-0.003139056	Gut
Akkermansia	BUN	-0.121459953	Gut
Akkermansia	EOSAB	-0.004328684	Gut
Akkermansia	BASO	-0.005413098	Gut
Akkermansia	EOSAB	-0.002275303	Gut
Akkermansia	BASO	-0.00448212	Gut
Akkermansia	EOSAB	-0.003177104	Gut
Akkermansia	BASOAB	-0.000136196	Gut
Roseburia	PLT	1.884756707	Gut
Roseburia	GLOB	0.005426228	Gut
Fusicatenibacter	ALT	-0.150881618	Gut
Fusicatenibacter	ALKP	0.300319665	Gut
Fusicatenibacter	ALKP	0.368838714	Gut
Fusicatenibacter	CR	-0.002041458	Gut
Fusicatenibacter	ALKP	0.217076429	Gut
Fusicatenibacter	CR	-0.003037505	Gut
Fusicatenibacter	ALT	-0.213656361	Gut
Fusicatenibacter	ALT	-0.210714154	Gut
Fusicatenibacter	ALKP	0.89440186	Gut
Fusicatenibacter	ALKP	0.727390507	Gut
Agathobacter	ALT	0.083317973	Gut
Agathobacter	CR	0.003342294	Gut
Ruminococcus	MCH	0.085455661	Gut
Ruminococcus	MCV	0.285981967	Gut
Unclassified_Lachnospiraceae	ALKP	0.253137507	Gut
Unclassified_Lachnospiraceae	ALKP	0.737913061	Gut
Phascolarctobacterium	GLU	-0.336219345	Gut
Phascolarctobacterium	IGM	0.737993807	Gut
Phascolarctobacterium	MCHC	0.049722994	Gut
Phascolarctobacterium	RBC	0.01170495	Gut
Phascolarctobacterium	GLU	-0.198345589	Gut
Phascolarctobacterium	IGM	1.305597012	Gut
Phascolarctobacterium	TP	0.006728837	Gut
Oscillibacter	MONOAB	0.002699862	Gut
Oscillibacter	TGL	0.740307109	Gut
Roseburia	CA	-0.006976242	Gut
Roseburia	PLT	0.596631489	Gut
Roseburia	TP	-0.007858667	Gut
Roseburia	PLT	1.258949756	Gut
Roseburia	NEUTAB	-0.021826641	Gut
Roseburia	PLT	1.231061422	Gut

Roseburia	PLT	2.164453976	Gut
Faecalibacillus	ALKP	0.295260365	Gut
Faecalibacillus	MCH	0.037089741	Gut
Faecalibacillus	LDLHDL	0.030864842	Gut
Odoribacter	EGFR	0.134538457	Gut
Odoribacter	EGFR	0.420012646	Gut
Anaerobutyricum	K	-0.010093359	Gut
Veillonella	EGFR	-0.097224222	Gut
Butyricimonas	IGM	0.926843011	Gut
Butyricimonas	IGM	1.780763432	Gut
Intestinimonas	TBIL	-0.006805047	Gut
Intestinimonas	TBIL	-0.005513367	Gut
Intestinimonas	EGFR	-0.106150821	Gut
Intestinimonas	MCH	0.035854551	Gut
Staphylococcus	RDW	0.008745474	Skin
Staphylococcus	RDW	0.0127358	Skin
Staphylococcus	CR	-0.001412777	Skin
Haemophilus	LDL	-0.552175761	Skin
Haemophilus	MCV	-0.112268059	Skin
Haemophilus	MONO	0.037038648	Skin
Staphylococcus	UALB	0.084740197	Skin
Staphylococcus	CR	-0.001410136	Skin
Staphylococcus	UALB	0.055123076	Skin
Staphylococcus	CHOLHDL	-0.009663252	Skin
Staphylococcus	LDLHDL	-0.008713585	Skin
Staphylococcus	UALB	0.072100455	Skin
Staphylococcus	CA	-0.004023835	Skin
Staphylococcus	CR	-0.001798809	Skin
Staphylococcus	UALB	0.058360612	Skin
Staphylococcus	CHOLHDL	-0.005853482	Skin
Staphylococcus	LDLHDL	-0.005666458	Skin
Corynebacterium	RDW	0.021492961	Skin
Corynebacterium	ALKP	-0.353104807	Skin
Corynebacterium	ALKP	-0.250379265	Skin
Haemophilus	CHOL	-1.184949819	Skin
Haemophilus	CHOLHDL	-0.044596366	Skin
Haemophilus	LDL	-0.905490147	Skin
Haemophilus	LDLHDL	-0.027678253	Skin
Haemophilus	MONO	0.040062998	Skin
Haemophilus	NHDL	-1.670570802	Skin
Haemophilus	CHOLHDL	-0.027657663	Skin
Haemophilus	LDLHDL	-0.014087302	Skin

Haemophilus	MONO	0.048104022	Skin
Haemophilus	NHDL	-0.750586557	Skin
Haemophilus	CHOL	-1.515470111	Skin
Haemophilus	CHOLHDL	-0.01584292	Skin
Haemophilus	LDL	-1.009545706	Skin
Haemophilus	LDLHDL	-0.010557627	Skin
Haemophilus	TGL	-1.71789091	Skin
Haemophilus	CHOLHDL	-0.044939467	Skin
Haemophilus	LDLHDL	-0.039053518	Skin
Haemophilus	TGL	-2.048063105	Skin
Haemophilus	CHOLHDL	-0.040281071	Skin
Haemophilus	HCT	-0.054833432	Skin
Haemophilus	HGB	-0.024044714	Skin
Haemophilus	LDL	-1.800290082	Skin
Haemophilus	LDLHDL	-0.035628405	Skin
Haemophilus	NHDL	-2.068429393	Skin
Haemophilus	TGL	-1.350505754	Skin
Haemophilus	CHOL	-1.5163154	Skin
Haemophilus	CHOLHDL	-0.032933421	Skin
Haemophilus	LDL	-1.486704109	Skin
Haemophilus	LDLHDL	-0.028905258	Skin
Haemophilus	NHDL	-1.704188174	Skin
Haemophilus	TGL	-1.095257125	Skin
Haemophilus	CHOLHDL	-0.034238777	Skin
Haemophilus	LDL	-0.384774797	Skin
Haemophilus	LDLHDL	-0.02213169	Skin
Haemophilus	MONO	0.052060275	Skin
Haemophilus	NHDL	-0.913585247	Skin
Haemophilus	TGL	-2.654025634	Skin
Haemophilus	CHOL	-0.788921315	Skin
Haemophilus	CHOLHDL	-0.03909901	Skin
Haemophilus	LDL	-0.605950789	Skin
Haemophilus	LDLHDL	-0.02433314	Skin
Haemophilus	MONO	0.032082071	Skin
Haemophilus	NHDL	-1.25259791	Skin
Haemophilus	LDLHDL	-0.023703414	Skin
Haemophilus	CHOL	-1.400605195	Skin
Haemophilus	LDL	-1.378535264	Skin
Haemophilus	LDLHDL	-0.048029106	Skin
Haemophilus	NHDL	-2.334356144	Skin
Haemophilus	ALB	-0.004820878	Skin
Haemophilus	CHOLHDL	-0.009604306	Skin

Haemophilus	LDL	-1.145442623	Skin
Haemophilus	NHDL	-1.384082925	Skin
Haemophilus	TGL	-1.197854229	Skin
Haemophilus	CHOL	-1.229854033	Skin
Haemophilus	CHOLHDL	-0.016606184	Skin
Haemophilus	LDL	-0.948182064	Skin
Haemophilus	LDLHDL	-0.012691788	Skin
Haemophilus	MONO	0.059200055	Skin
Haemophilus	NHDL	-1.234534299	Skin
Haemophilus	TGL	-1.431591819	Skin
Haemophilus	CHOL	-0.832809521	Skin
Haemophilus	NHDL	-0.538145671	Skin
Haemophilus	TGL	-0.982939064	Skin
Haemophilus	ALB	-0.00609757	Skin
Haemophilus	CHOL	-1.111506293	Skin
Haemophilus	CHOLHDL	-0.033438598	Skin
Haemophilus	LDL	-0.86865389	Skin
Haemophilus	LDLHDL	-0.022509869	Skin
Haemophilus	CHOL	-0.897733137	Skin
Haemophilus	CHOLHDL	-0.032224568	Skin
Haemophilus	LDL	-0.987820008	Skin
Haemophilus	LDLHDL	-0.026138309	Skin
Haemophilus	TGL	-1.361095992	Skin
Haemophilus	CHOLHDL	-0.034019036	Skin
Haemophilus	LDL	-1.633912342	Skin
Haemophilus	LDLHDL	-0.029694779	Skin
Haemophilus	NHDL	-1.903920557	Skin
Haemophilus	TGL	-1.356348344	Skin
Haemophilus	CHOLHDL	-0.042593608	Skin
Haemophilus	LDL	-1.708706903	Skin
Haemophilus	LDLHDL	-0.036165692	Skin
Haemophilus	NHDL	-2.038593875	Skin
Haemophilus	TGL	-1.66687622	Skin
Haemophilus	CHOL	-0.993204136	Skin
Haemophilus	LDL	-0.784151651	Skin
Haemophilus	NHDL	-0.629352407	Skin
Haemophilus	CHOLHDL	-0.02542401	Skin
Haemophilus	LDL	-1.626746563	Skin
Haemophilus	LDLHDL	-0.025204375	Skin
Haemophilus	MONO	0.022267348	Skin
Haemophilus	TGL	-0.54389773	Skin
Corynebacterium	CR	-0.001386031	Skin

Pelomonas	ALKP	0.532263176	Skin
Pelomonas	ALKP	0.370851978	Skin
Pelomonas	LYMAB	0.014341238	Skin
Staphylococcus	CR	-0.002074128	Skin
Prevotella	CHOLHDL	-0.012825189	Skin
Prevotella	LDLHDL	-0.011565831	Skin
Prevotella	EGFR	0.243740531	Skin
Prevotella	CHOLHDL	-0.011196991	Skin
Prevotella	CHOLHDL	-0.021620369	Skin
Prevotella	LDLHDL	-0.017654933	Skin
Prevotella	CHOLHDL	-0.026013204	Skin
Prevotella	LDLHDL	-0.023019414	Skin
Prevotella	CHOLHDL	-0.027236858	Skin
Prevotella	LDLHDL	-0.023524247	Skin
Corynebacterium	RDW	0.009475153	Skin
Corynebacterium	IGM	-0.400012563	Skin
Unclassified_Carnobacteriaceae	TGL	-2.481816875	Skin
Dermabacter	EGFR	-0.285470223	Skin
Stenotrophomonas	LDL	0.764191091	Skin
Stenotrophomonas	IGM	0.991001056	Skin
Prevotella	ALKP	-0.15652465	Oral cavity
Prevotella	HGB	0.029486323	Oral cavity
Prevotella	ALB	0.00583	Oral cavity
Prevotella	ALKP	-0.418619358	Oral cavity
Veillonella	ALKP	-0.508347633	Oral cavity
Schaalia	ALB	-0.004443067	Oral cavity
Schaalia	TP	-0.010089685	Oral cavity
Unclassified_Candidatus_Saccharibacteria	IGM	-0.474202691	Oral cavity
Unclassified_Carnobacteriaceae	TBIL	0.002328499	Oral cavity
Oribacterium	NA.	0.065379937	Oral cavity
Lachnoanaerobaculum	CHOLHDL	0.012584583	Oral cavity
Streptococcus	HGB	0.015257364	Oral cavity
Alloprevotella	EOS	0.016789815	Oral cavity
Unclassified_Candidatus_Saccharibacteria	MONOAB	0.001547602	Oral cavity
Peptostreptococcus	HCT	-0.028997985	Oral cavity
Peptostreptococcus	HGB	-0.008646219	Oral cavity
Lachnoanaerobaculum	CHOLHDL	0.015445205	Oral cavity
Lachnoanaerobaculum	LDLHDL	0.01157626	Oral cavity
Actinomyces	CHOL	-0.293260336	Oral cavity
Actinomyces	LDL	-0.32525834	Oral cavity
Actinomyces	NHDL	-0.434097316	Oral cavity
Mogibacterium	CHOLHDL	-0.026897512	Oral cavity

Aggregatibacter	PLT	0.312489595	Oral cavity
Aggregatibacter	PLT	0.578788878	Oral cavity
Aggregatibacter	RDW	0.014594145	Oral cavity
Haemophilus	HDL	-0.190508736	Oral cavity
Haemophilus	HDL	-0.196987866	Oral cavity
Haemophilus	HDL	-0.266371409	Oral cavity
Streptococcus	ALB	-0.011971878	Oral cavity
Lancefieldella	CHOL	-0.667227301	Oral cavity
Snodgrassella	UALBCR	-0.248336142	Oral cavity
Streptococcus	HCT	0.036273824	Oral cavity
Streptococcus	HGB	0.013167246	Oral cavity
Schaalia	TP	-0.009800657	Oral cavity
Lancefieldella	LDL	-0.298115165	Oral cavity
Unclassified_Neisseriaceae	MONOAB	-0.001836822	Oral cavity
Unclassified_Neisseriaceae	NEUTAB	-0.016107387	Oral cavity
Lautropia	GLU	-0.358969323	Nasal cavity
Lautropia	GLU	-0.423151134	Nasal cavity
Lautropia	GLU	-0.279619676	Nasal cavity
Lautropia	GLU	-0.338142129	Nasal cavity
Lautropia	GLU	-0.387273523	Nasal cavity
Lautropia	GLU	-0.292268396	Nasal cavity
Phocaeicola	HSCR	-0.041976261	Nasal cavity
Phocaeicola	IGM	1.623351072	Nasal cavity
Phocaeicola	MCH	0.072360029	Nasal cavity
Phocaeicola	HSCR	-0.10974401	Nasal cavity
Phocaeicola	IGM	1.624552686	Nasal cavity
Phocaeicola	MCH	0.052501153	Nasal cavity
Phocaeicola	UALBCR	-0.334712619	Nasal cavity
Blautia	A1C	-0.012691739	Nasal cavity
Schaalia	CHOL	1.430885564	Nasal cavity
Schaalia	MCV	0.127753182	Nasal cavity
Schaalia	GLOB	0.006986732	Nasal cavity
Phocaeicola	IGM	1.601471146	Nasal cavity
Lawsonella	CR	-0.001367122	Nasal cavity
Granulicatella	BUN	0.217947353	Nasal cavity
Granulicatella	LDL	0.53512433	Nasal cavity
Granulicatella	BUN	0.161241793	Nasal cavity
Granulicatella	LDL	1.423163611	Nasal cavity
Granulicatella	BUN	0.162239148	Nasal cavity
Granulicatella	LDL	1.738518478	Nasal cavity
Phascolarctobacterium	CL	0.173394905	Gut
Phascolarctobacterium	CL	0.10624458	Gut

Phascolarctobacterium	CL	0.121383049	Gut
Phascolarctobacterium	CL	0.065287669	Gut
Phascolarctobacterium	CL	0.096273549	Gut
Phascolarctobacterium	CL	0.149290433	Gut
Phascolarctobacterium	MCHC	0.044032151	Gut
Parasutterella	HGB	0.032948873	Gut
Anaerobutyricum	K	-0.011092835	Gut
Anaerobutyricum	BASOAB	-0.000462188	Gut
Anaerobutyricum	K	-0.008745319	Gut
Mediterraneibacter	MCV	0.228864394	Gut
Beduinibacterium	GLOB	-0.006981216	Gut
Ruminococcus	LDLHDL	-0.021391415	Gut
Parasutterella	HGB	0.029976406	Gut
Parasutterella	MCV	0.186317022	Gut
Parasutterella	LYMAB	-0.017958071	Gut
Parasutterella	HGB	0.047267557	Gut
Parasutterella	LYMAB	-0.028772248	Gut
Parasutterella	HDL	0.472728498	Gut
Parasutterella	MCV	0.390153858	Gut
Parasutterella	HGB	0.030585611	Gut
Parasutterella	MCV	0.186072442	Gut
Unclassified_Eggerthellaceae	NHDL	-0.766389165	Gut
Unclassified_Eggerthellaceae	LDLHDL	-0.033611634	Gut
Delftia	LYMAB	0.014867311	Skin
Delftia	MCHC	0.072997638	Skin
Delftia	MCHC	0.048820318	Skin
Acinetobacter	HDL	-0.540550622	Skin
Haemophilus	EGFR	0.380519833	Skin
Haemophilus	MONOAB	0.005465883	Skin
Haemophilus	MONOAB	0.0063244	Skin
Unclassified_Candidatus_Saccharibacteria	PLT	2.352087922	Skin
Pseudomonas	MCV	-0.20151087	Skin
Pseudomonas	EGFR	-1.076587008	Skin
Pseudomonas	EGFR	-1.16913125	Skin
Prevotella	EOS	0.047309478	Oral cavity
Prevotella	EOSAB	0.003562748	Oral cavity
Prevotella	NA.	0.06870046	Oral cavity
Prevotella	ALKP	-0.501598926	Oral cavity
Prevotella	NA.	0.10579263	Oral cavity
Prevotella	TP	-0.006401312	Oral cavity
Prevotella	NA.	0.067488443	Oral cavity
Veillonella	EOS	0.098533185	Oral cavity

Veillonella	EOSAB	0.006158765	Oral cavity
Veillonella	EOS	0.09911502	Oral cavity
Veillonella	TGL	1.760510765	Oral cavity
Veillonella	ALB	-0.007241136	Oral cavity
Veillonella	EOS	0.060848705	Oral cavity
Veillonella	EOSAB	0.00500501	Oral cavity
Veillonella	EOS	0.076014919	Oral cavity
Veillonella	EOSAB	0.003259312	Oral cavity
Veillonella	EOS	0.08962076	Oral cavity
Veillonella	EOS	0.047704008	Oral cavity
Veillonella	EOSAB	0.003296531	Oral cavity
Veillonella	NA.	0.063894749	Oral cavity
Veillonella	EOS	0.094925097	Oral cavity
Veillonella	EOS	0.119795678	Oral cavity
Veillonella	EOS	0.062068522	Oral cavity
Veillonella	EOSAB	0.004830499	Oral cavity
Veillonella	TGL	1.882033584	Oral cavity
Veillonella	EOS	0.083361518	Oral cavity
Veillonella	EOSAB	0.006535404	Oral cavity
Veillonella	TGL	2.135351141	Oral cavity
Veillonella	EOS	0.06541934	Oral cavity
Veillonella	EOSAB	0.005553419	Oral cavity
Veillonella	EOS	0.095643056	Oral cavity
Veillonella	ALB	-0.010267975	Oral cavity
Veillonella	EOS	0.096020553	Oral cavity
Veillonella	EOS	0.094788314	Oral cavity
Veillonella	EOSAB	0.006187639	Oral cavity
Veillonella	NA.	0.099900377	Oral cavity
Veillonella	TGL	2.024843033	Oral cavity
Streptococcus	NA.	0.073507131	Oral cavity
Eggerthia	UALBCR	0.556805547	Oral cavity
Streptococcus	HCT	-0.147525531	Oral cavity
Streptococcus	HGB	-0.053722197	Oral cavity
Streptococcus	HCT	-0.145650564	Oral cavity
Streptococcus	HGB	-0.047071329	Oral cavity
Rothia	HCT	-0.122746945	Oral cavity
Rothia	RBC	-0.012792313	Oral cavity
Rothia	MCV	0.090899403	Oral cavity
Rothia	HCT	-0.138528011	Oral cavity
Rothia	HGB	-0.055769132	Oral cavity
Rothia	AST	0.230842036	Oral cavity
Rothia	HCT	-0.127149221	Oral cavity

Rothia	HGB	-0.042617532	Oral cavity
Rothia	HCT	-0.231970924	Oral cavity
Rothia	HCT	-0.200779662	Oral cavity
Rothia	HGB	-0.072142455	Oral cavity
Rothia	AST	0.221332298	Oral cavity
Tannerella	TBIL	0.005593862	Oral cavity
Tannerella	TGL	-1.17478603	Oral cavity
Tannerella	TBIL	0.004828695	Oral cavity
Tannerella	TBIL	0.006939616	Oral cavity
Parvimonas	HSCR	0.036569603	Oral cavity
Parvimonas	TBIL	0.009333738	Oral cavity
Parvimonas	HSCR	0.043641236	Oral cavity
Parvimonas	RDW	0.014568879	Oral cavity
Parvimonas	HSCR	0.045892021	Oral cavity
Parvimonas	RDW	0.01998389	Oral cavity
Parvimonas	HSCR	0.057464364	Oral cavity
Parvimonas	HSCR	0.069440926	Oral cavity
Parvimonas	HSCR	0.070898033	Oral cavity
Parvimonas	TBIL	0.004959719	Oral cavity
Parvimonas	HSCR	0.042502018	Oral cavity
Parvimonas	HSCR	0.050527355	Oral cavity
Parvimonas	HSCR	0.062010967	Oral cavity
Parvimonas	TBIL	0.005478911	Oral cavity
Parvimonas	HSCR	0.071178123	Oral cavity
Parvimonas	RDW	0.016014332	Oral cavity
Parvimonas	RDW	0.020865824	Oral cavity
Parvimonas	HSCR	0.057033827	Oral cavity
Parvimonas	RDW	0.014153768	Oral cavity
Veillonella	TGL	1.881798538	Oral cavity
Parvimonas	HSCR	0.051863861	Oral cavity
Parvimonas	TBIL	0.012949337	Oral cavity
Parvimonas	HSCR	0.03706207	Oral cavity
Parvimonas	TBIL	0.010596901	Oral cavity
Leptotrichia	NEUTAB	0.033878608	Nasal cavity
Leptotrichia	WBC	0.045915247	Nasal cavity
Corynebacterium	WBC	-0.028391453	Nasal cavity
Corynebacterium	EGFR	-0.313840112	Nasal cavity
Corynebacterium	NEUTAB	-0.026996399	Nasal cavity
Corynebacterium	WBC	-0.050732114	Nasal cavity
Corynebacterium	EGFR	-0.281132985	Nasal cavity
Corynebacterium	NEUTAB	-0.053888213	Nasal cavity
Corynebacterium	NEUTAB	-0.037715524	Nasal cavity

Corynebacterium	WBC	-0.062186969	Nasal cavity
Corynebacterium	WBC	-0.025718864	Nasal cavity
Corynebacterium	NEUTAB	-0.027386027	Nasal cavity
Corynebacterium	EGFR	-0.472979258	Nasal cavity
Corynebacterium	WBC	-0.026126619	Nasal cavity
Corynebacterium	WBC	-0.055569147	Nasal cavity
Corynebacterium	NEUTAB	-0.036071286	Nasal cavity
Corynebacterium	WBC	-0.068875961	Nasal cavity
Corynebacterium	NEUTAB	-0.059974995	Nasal cavity
Corynebacterium	NEUTAB	-0.02497876	Nasal cavity
Corynebacterium	WBC	-0.035517784	Nasal cavity
Corynebacterium	NEUTAB	-0.022312095	Nasal cavity
Corynebacterium	NEUTAB	-0.036974896	Nasal cavity
Corynebacterium	WBC	-0.066767283	Nasal cavity
Corynebacterium	EGFR	-0.300750257	Nasal cavity
Corynebacterium	NEUTAB	-0.047263975	Nasal cavity
Corynebacterium	EGFR	-0.317532569	Nasal cavity
Corynebacterium	EGFR	-0.323855092	Nasal cavity
Corynebacterium	WBC	-0.036123049	Nasal cavity
Corynebacterium	EGFR	-0.366640462	Nasal cavity
Corynebacterium	NEUTAB	-0.025894117	Nasal cavity
Corynebacterium	WBC	-0.045364563	Nasal cavity
Corynebacterium	WBC	-0.037314036	Nasal cavity
Schaalia	CHOLHDL	0.049759841	Nasal cavity
Schaalia	CHOL	2.57570761	Nasal cavity
Schaalia	CHOLHDL	0.041296826	Nasal cavity
Schaalia	LDL	1.931521106	Nasal cavity
Schaalia	CHOL	1.97963853	Nasal cavity
Schaalia	NHDL	1.900519514	Nasal cavity
Schaalia	CHOL	2.685406899	Nasal cavity
Schaalia	LDL	1.737995581	Nasal cavity
Schaalia	NHDL	2.264858863	Nasal cavity
Schaalia	CHOL	1.894260468	Nasal cavity
Schaalia	CHOLHDL	0.04324007	Nasal cavity
Schaalia	LDL	1.469065339	Nasal cavity
Schaalia	NHDL	2.121599277	Nasal cavity
Agathobacter	EOS	-0.066357989	Gut
Agathobacter	WBC	-0.038338712	Gut
Agathobacter	LDLHDL	0.042777411	Gut
Ruminococcus	HCT	0.093828618	Gut
Ruminococcus	MCV	0.193004955	Gut
Ruminococcus	ALB	0.008351637	Gut

Ruminococcus	MCHC	0.084694643	Gut
Ruminococcus	MCV	0.160296844	Gut
Ruminococcus	ALT	0.705559653	Gut
Ruminococcus	ALT	0.226408437	Gut
Ruminococcus	IGM	-0.600776622	Gut
Ruminococcus	ALB	0.009347043	Gut
Ruminococcus	MCV	0.283824914	Gut
Clostridium_IV	A1C	0.019008417	Gut
Clostridium_IV	HDL	0.362556056	Gut
Clostridium_IV	HDL	0.26251623	Gut
Unclassified_Lachnospiraceae	MCH	0.112518327	Gut
Unclassified_Lachnospiraceae	MCV	0.353413137	Gut
Phascolarctobacterium	ALT	-0.533525298	Gut
Phascolarctobacterium	CR	-0.004052644	Gut
Phascolarctobacterium	GLOB	0.013654171	Gut
Phascolarctobacterium	ALT	-0.498806886	Gut
Phascolarctobacterium	ALT	-0.389225113	Gut
Phascolarctobacterium	CA	-0.010269818	Gut
Phascolarctobacterium	CR	-0.002028435	Gut
Oscillibacter	MCV	0.287806796	Gut
Romboutsia	MCV	0.109922511	Gut
Romboutsia	MCH	0.043827829	Gut
Romboutsia	MCH	0.051105717	Gut
Romboutsia	MCHC	0.061195951	Gut
Romboutsia	MCV	0.137396335	Gut
Collinsella	HDL	-1.119353876	Gut
Collinsella	MCV	-0.280660786	Gut
Neglecta	MONOAB	0.004089111	Gut
Unclassified_Firmicutes	NEUTAB	-0.028878222	Gut
Unclassified_Firmicutes	NEUTAB	-0.01891224	Gut
Unclassified_Firmicutes	WBC	-0.021599353	Gut
Lawsonibacter	RDW	-0.035634689	Gut
Phocaeicola	ALB	-0.013056044	Gut
Phocaeicola	CL	-0.313190325	Gut
Phocaeicola	CHOLHDL	-0.03326046	Gut
Phocaeicola	LDLHDL	-0.030638292	Gut
Agathobacter	BASOAB	0.000433963	Gut
Agathobacter	NEUT	-0.25326201	Gut
Agathobacter	MONO	0.028944461	Gut
Oscillibacter	ALKP	-0.555071655	Gut
Oscillibacter	LDL	-0.8375149	Gut
Oscillibacter	LDL	-0.895893694	Gut

Romboutsia	CL	0.30071509	Gut
Collinsella	HDL	-0.453022451	Gut
Collinsella	LYMAB	0.022386475	Gut
Collinsella	RDW	-0.044607896	Gut
Collinsella	TBIL	0.004510922	Gut
Dorea	MCH	-0.255919713	Gut
Victivallis	NEUT	-0.435511769	Gut
Victivallis	NEUT	-0.354486107	Gut
Victivallis	RDW	-0.066573375	Gut
Phocaeicola	IGM	1.005207043	Gut
Phocaeicola	RDW	0.069599197	Gut
Phocaeicola	RDW	0.057354406	Gut
Roseburia	ALB	-0.008458927	Gut
Roseburia	CR	-0.00435502	Gut
Roseburia	ALB	-0.006224646	Gut
Roseburia	TBIL	-0.006398253	Gut
Roseburia	TBIL	-0.006450848	Gut
Roseburia	TBIL	-0.006846036	Gut
Roseburia	CR	-0.003294947	Gut
Roseburia	BASO	0.007308602	Gut
Roseburia	CR	-0.003807951	Gut
Mediterraneibacter	AST	-0.232971219	Gut
Mediterraneibacter	CHOLHDL	-0.047788597	Gut
Mediterraneibacter	LDLHDL	-0.040362901	Gut
Phocaeicola	RDW	0.064140948	Gut
Phocaeicola	ALB	-0.017454994	Gut
Phocaeicola	IGM	1.352846359	Gut
Alistipes	IGM	-0.917252788	Gut
Agathobacter	AG	-0.059083894	Gut
Agathobacter	LDL	1.053129173	Gut
Agathobacter	LDLHDL	0.052072106	Gut
Agathobacter	NHDL	1.395366306	Gut
Agathobacter	PLT	-1.894565612	Gut
Agathobacter	MCV	-0.156724538	Gut
Agathobacter	BUN	-0.108703705	Gut
Agathobacter	EOS	-0.059361291	Gut
Agathobacter	LDLHDL	0.02150706	Gut
Agathobacter	BASOAB	0.000318323	Gut
Agathobacter	EOS	-0.142110197	Gut
Agathobacter	LDLHDL	0.018957759	Gut
Agathobacter	BASOAB	0.000579081	Gut
Agathobacter	EOS	-0.1092004	Gut

Agathobacter	NHDL	1.157841736	Gut
Ruminococcus	HDL	-0.496617171	Gut
Clostridium_IV	A1C	0.026213567	Gut
Clostridium_IV	RDW	0.043925119	Gut
Faecalibacterium	ALKP	-0.601245281	Gut
Oscillibacter	HDL	-0.745604325	Gut
Oscillibacter	HDL	-0.825734418	Gut
Oscillibacter	MONO	0.068024731	Gut
Roseburia	BASO	0.005282745	Gut
Roseburia	CR	-0.006667451	Gut
Roseburia	TBIL	-0.009774855	Gut
Roseburia	CR	-0.006545447	Gut
Roseburia	ALB	-0.015166839	Gut
Roseburia	CR	-0.00799078	Gut
Roseburia	NA.	-0.35730465	Gut
Roseburia	TP	-0.020309534	Gut
Roseburia	CR	-0.005324318	Gut
Roseburia	EOS	-0.172943301	Gut
Collinsella	HGB	0.032659549	Gut
Collinsella	TBIL	0.006976783	Gut
Collinsella	TBIL	0.017783203	Gut
Collinsella	HDL	-0.58981017	Gut
Collinsella	MCHC	-0.081585003	Gut
Collinsella	MCV	-0.290771115	Gut
Collinsella	LYMAB	0.019474294	Gut
Collinsella	MCV	-0.185026952	Gut
Collinsella	MCHC	-0.063974885	Gut
Collinsella	MCV	-0.184602076	Gut
Dorea	EGFR	0.436877028	Gut
Dorea	EGFR	0.329919944	Gut
Neglecta	WBC	0.043601464	Gut
Odoribacter	NEUT	0.393006321	Gut
Unclassified_Muribaculaceae	CHOL	0.92515022	Gut
Unclassified_Muribaculaceae	LDLHDL	0.023104293	Gut
Butyricimonas	K	-0.018828132	Gut
Butyricimonas	EGFR	0.286388444	Gut
Anaerotruncus	RBC	-0.021273879	Gut
Anaerotruncus	HCT	-0.200038524	Gut
Anaerotruncus	RBC	-0.021474344	Gut
Cutibacterium	NEUT	0.161512133	Skin
Cutibacterium	NEUT	0.250581244	Skin
Cutibacterium	NEUT	0.274702185	Skin

Cutibacterium	NEUT	0.238289923	Skin
Staphylococcus	RDW	0.015129358	Skin
Streptococcus	NEUT	0.3829266	Skin
Escherichia/Shigella	NEUTAB	-0.052602057	Skin
Unclassified_Bacillaceae_1	MCH	-0.131672552	Skin
Unclassified_Bacillaceae_1	MCV	-0.454006248	Skin
Cutibacterium	IGM	-0.968923788	Skin
Cutibacterium	RDW	0.014480371	Skin
Cutibacterium	IGM	-0.521261201	Skin
Cutibacterium	IGM	-0.479430037	Skin
Staphylococcus	UALB	0.106506672	Skin
Staphylococcus	UALB	0.128362956	Skin
Staphylococcus	UALB	0.059341499	Skin
Haemophilus	CHOLHDL	-0.036436192	Skin
Haemophilus	TGL	-2.094857441	Skin
Haemophilus	CHOLHDL	-0.048402988	Skin
Haemophilus	CHOLHDL	-0.025452846	Skin
Haemophilus	TGL	-1.81502573	Skin
Haemophilus	TGL	-2.194921869	Skin
Gemella	MCV	0.35092088	Skin
Gemella	MCV	0.552148984	Skin
Gemella	RDW	0.106175664	Skin
Gemella	RDW	0.055288612	Skin
Cutibacterium	IGM	-0.532233187	Skin
Staphylococcus	MCV	0.070300765	Skin
Staphylococcus	EGFR	0.103004848	Skin
Anaerococcus	LYM	0.223412568	Skin
Anaerococcus	LYM	0.169102942	Skin
Delftia	A1C	0.017395891	Skin
Delftia	LYM	-0.128532879	Skin
Delftia	NEUT	-0.581369812	Skin
Delftia	TBIL	-0.005632438	Skin
Delftia	NEUT	-0.376737636	Skin
Delftia	EOS	-0.049368948	Skin
Delftia	MCV	-0.167981044	Skin
Delftia	NEUT	-0.211674029	Skin
Delftia	ALKP	0.412429198	Skin
Stenotrophomonas	AST	-0.518211312	Skin
Stenotrophomonas	MONO	0.108079915	Skin
Stenotrophomonas	AST	-0.373166104	Skin
Stenotrophomonas	MONO	0.078142581	Skin
Unclassified_Candidatus_Saccharibacteria	EOS	0.024227216	Oral cavity

Unclassified_Candidatus_Saccharibacteria	IGM	0.440843675	Oral cavity
Unclassified_Candidatus_Saccharibacteria	IGM	0.830510535	Oral cavity
Unclassified_Candidatus_Saccharibacteria	IGM	0.695987075	Oral cavity
Gemella	fpg_mg_ml	0.005658297	Oral cavity
Catonella	MCV	-0.23912178	Oral cavity
Butyrivibrio	ALB	0.006782488	Oral cavity
Butyrivibrio	CA	-0.007761113	Oral cavity
Unclassified_Prevotellaceae	CR	-0.001869638	Oral cavity
Unclassified_Neisseriaceae	PLT	1.129148922	Oral cavity
Streptococcus	NA.	0.360452595	Oral cavity
Streptococcus	CA	0.030654801	Oral cavity
Streptococcus	CA	0.017257938	Oral cavity
Streptococcus	CA	0.029069067	Oral cavity
Streptococcus	CA	0.014939285	Oral cavity
Streptococcus	CA	0.020409531	Oral cavity
Streptococcus	CL	0.219259739	Oral cavity
Streptococcus	NA.	0.317809345	Oral cavity
Streptococcus	CA	0.021338504	Oral cavity
Streptococcus	NA.	0.270463965	Oral cavity
Streptococcus	NA.	0.345022098	Oral cavity
Streptococcus	NA.	0.230160815	Oral cavity
Unclassified_Candidatus_Saccharibacteria	HDL	0.275441944	Oral cavity
Capnocytophaga	BUN	0.109489712	Oral cavity
Unclassified_Neisseriaceae	NEUTAB	-0.033335892	Oral cavity
Unclassified_Neisseriaceae	NEUTAB	-0.032398653	Oral cavity
Unclassified_Neisseriaceae	NEUTAB	-0.061861693	Oral cavity
Capnocytophaga	BUN	0.209308767	Oral cavity
Capnocytophaga	BUN	0.063484954	Oral cavity
Capnocytophaga	BUN	0.121137266	Oral cavity
Catonella	MCV	-0.143843177	Oral cavity
Unclassified_Neisseriaceae	NEUTAB	-0.025544871	Oral cavity
Unclassified_Flavobacteriales	UALBCR	0.313222805	Oral cavity
Lachnospira	UALBCR	1.498977923	Nasal cavity

Table 3. Abbreviations of Analytes of Table 2.

Analyte Abbreviation	Clinical Circulatory Phenotype Measurement	Class
A1C	Hemoglobin A1C	Glucose/Insulin
AG	albumin/globulin	Kidney/Hepatic
ALB	Albumin Blood Test	Kidney/Hepatic
ALCRU	Aluminum/Creatinine Ratio, Random, Urine	Kidney
ALKP	Alkaline Phosphatase	Hepatic
ALT	alanine aminotransferase	Hepatic
AST	aspartate aminotransferase	Hepatic
BASO	Basophils	Immune
BASOAB	Basophils Absolute Number	Immune
BUN	blood urea nitrogen	Kidney
CA	calcium blood test	Electrolyte
CHOL	complete cholesterol test	Cholesterol/Lipid
CHOLHDL	High-density lipoprotein (HDL) cholesterol ratio	Cholesterol/Lipid
CL	Chloride Blood Test	Electrolyte
CO2	Carbon Dioxide (CO2) in Blood	Hematologic
CR	creatinine	Kidney
EGFR	estimated Glomerular Filtration Rate	Kidney
EOS	Eosinophils	Immune
EOSAB	Eosinophils Absolute Number	Immune
GLOB	globulin	Kidney/Hepatic
GLU	Glucose	Glucose/Insulin
HCT	hematocrit	Hematologic
HDL	High-density lipoprotein (HDL) cholesterol	Cholesterol/Lipid
HGB	Hemoglobin	Hematologic
HSCRP	High-sensitivity C-reactive protein	Immune
IGM	Immunoglobulin M	Immune
INSF	Insulin, Fasting	Glucose/Insulin
K	potassium	Electrolyte
LDL	Low-density lipoprotein (LDL) cholesterol	Cholesterol/Lipid
LDLHDL	LDL to HDL ratio	Cholesterol/Lipid
LYM	Lymphocytes	Immune
LYMAB	Lymphocytes Absolute Number	Immune
MCH	mean corpuscular hemoglobin	Hematologic
MCHC	corpuscular hemoglobin concentration	Hematologic
MCV	Mean Corpuscular Volume	Hematologic
MONO	Monocytes	Immune
MONOAB	Monocytes Absolute Number	Immune
NA.	sodium	Electrolyte

NEUT	Neutrophils	Immune
NEUTAB	Neutrophils Absolute Number	Immune
NHDL	non-high-density lipoprotein cholesterol	Cholesterol/Lipid
PLT	platelet count	Hematologic
RBC	red blood cell count	Immune
RDW	red cell distribution width	Hematologic
TBIL	Total bilirubin	Hepatic
TGL	triglycerides	Cholesterol/Lipid
TP	total protein	Kidney/Hepatic
UALB	Microalbumin test	Kidney
UALBCR	Urine Albumin-Creatinine Ratio	Kidney
WBC	whitebloodcell	Immune

WHAT IS CLAIMED IS:

1. A method for administering microbial genera to an individual, comprising:
measuring levels of a set of one or more gene products in a biological sample of the individual;
determining that an amount of one gene product of the set of gene products is above a threshold or is below a threshold; and
when the amount of the one gene product is above a threshold, administering to the individual one or more microbial genera negatively correlated with the one gene product, or when the amount of the one gene product is below a threshold, administering to the individual one or more microbial genera positively correlated with the one gene product.
2. The method of claim 1 further comprising:
measuring a microbial genera composition of a microbiome; wherein the composition of microbial genera is utilized to assist in selecting the one or more microbial genera to be administered.
3. The method of claim 1 or 2, wherein the one gene product and the one or more correlated microbial genera to be administered is listed within Table 1.
4. The method of claim 3, wherein the one gene product is: BDNF, EGF, Eotaxin, INF- α , INF- γ , IL-1 β , IL-6, IL-10, IL-12, IL-17, IL-22, IL-23, MCP-1, RANTES, TGF- β , or TNF- α .
5. The method of claim 4, wherein the one gene product is Eotaxin, wherein Eotaxin is greater than threshold, wherein the is administered one or more of the following microbial genera: *Desulfovibrio* or *Escherichia_Shigella*.

6. The method of claim 4, wherein the one gene product is INF- α , wherein INF- α is greater than threshold, wherein the is administered one or more of the following microbial genera: *Blautia* or *Dialister*.
7. The method of claim 4, wherein the one gene product is INF- γ , wherein INF- γ is greater than threshold, wherein the is administered one or more of the following microbial genera: *Blautia*, *Dialister*, or *Fusicatenibacter*.
8. The method of claim 4, wherein the one gene product is IL-1 β , wherein IL-1 β is greater than threshold, wherein the is administered one or more of the following microbial genera: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Faecalibacterium*, *Lachnospira*, *Prevotella*, *Roseburia*, *Slackia*, *Subdoligranulum*, or *Sutterella*.
9. The method of claim 4, wherein the one gene product is IL-6, wherein IL-6 is greater than threshold, wherein the is administered one or more of the following microbial genera: *Collinsella*, *Dialister*, or *Fusicatenibacter*.
10. The method of claim 4, wherein the one gene product is IL-12, wherein IL-12 is greater than threshold, wherein the is administered one or more of the following microbial genera: *Butyricimonas*, *Collinsella*, or *Fusicatenibacter*.
11. The method of claim 4, wherein the one gene product is IL-17, wherein IL-17 is greater than threshold, wherein the is administered one or more of the following microbial genera: *Dialister*, *Subdoligranulum*, or *Senegalimassilia*.
12. The method of claim 4, wherein the one gene product is IL-23, wherein IL-23 is greater than threshold, wherein the is administered one or more of the following microbial genera: *Butyricimonas*, *Dialister*, *Holdemanella*, or *Senegalimassilia*.

13. The method of claim 4, wherein the one gene product is MCP-1, wherein MCP-1 is greater than threshold, wherein the is administered one or more of the following microbial genera: *Blautia*, *Desulfovibrio*, *Dialister*, or *Slackia*.
14. The method of claim 4, wherein the one gene product is RANTES, wherein RANTES is greater than threshold, wherein the is administered one or more of the following microbial genera: *Butyricimonas*, *Collinsella*, *Holdemanella*, or *Lawsonibacter*.
15. The method of claim 4, wherein the one gene product is TNF- α , wherein TNF- α is greater than threshold, wherein the is administered one or more of the following microbial genera: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, or *Frisingicoccus*.
16. The method of claim 4, wherein the one gene product is TNF- α , wherein TNF- α is greater than threshold, wherein the is administered one or more of the following microbial genera: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, or *Frisingicoccus*.
17. The method of claim 4, wherein the one gene product is BDNF, wherein BDNF is less than threshold, wherein the is administered one or more of the following microbial genera: *Barnesiella*, *Eggerthella*, *Lachnospira* or *Parabacteroides*.
18. The method of claim 4, wherein the one gene product is EGF, wherein EGF is less than threshold, wherein the is administered one or more of the following microbial genera: *Anaerostipes*, *Barnesiella*, *Eggerthella*, *Intestinibacter*, *Neglecta*, *Parabacteroides*, or *Romboutsia*.
19. The method of claim 4, wherein the one gene product is IL-10, wherein IL-10 is less than threshold, wherein the is administered one or more of the following microbial genera: *Hungatella* or *Monoglobus*.

20. The method of claim 4, wherein the one gene product is IL-17, wherein IL-17 is less than threshold, wherein the is administered one or more of the following microbial genera: *Adlercreutzia*, *Barnesiella*, *Butyricicoccus*, *Cloacibacillus*, *Dysosmobacter*, or *Faecalicatena*.

21. The method of claim 4, wherein the one gene product is IL-22, wherein IL-22 is less than threshold, wherein the is administered one or more of the following microbial genera: *Anaerotignum*, *Butyrivibrio*, *Cloacibacillus*, *Dysosmobacter*, *Frisingicoccus*, *Gordonibacter*, *Negativibacillus*, *Phoceia*, *Pseudoflavonifractor*, *Raoultibacter*, or *Turicibacter*.

22. The method of claim 4, wherein the one gene product is TGF- β , wherein TGF- β is less than threshold, wherein the is administered one or more of the following microbial genera: *Acutalibacter*, *Akkermansia*, *Clostridium_sensu_stricto*, *Clostridium_XVIII*, *Flavonifractor*, *Holdemania*, or *Hungatella*.

23. The method of any one of claims 1-22, wherein the one or more microbial genera are to be orally administered.

24. The method of claim 23, wherein the one or more genera is provided in a probiotic food, a probiotic beverage, a liquid solution composition, a gel composition, an oil composition, an emulsion composition, a capsule, an enteric-coated capsule, a dragee, a gavage, a lyophilized powder, a freeze-dried powder, or a combination thereof.

25. The method of any one of claims 1-22, wherein the one or more microbial genera are to be rectally administered.

26. The method of claim 23, wherein the one or more genera is provided in a probiotic liquid, a probiotic gel, a probiotic suppository, a probiotic fecal transplant, a probiotic enema, a probiotic catheter, a lyophilized powder, a freeze-dried powder, or a combination thereof.
27. A method for administering microbial genera to an individual, comprising:
measuring levels of a set of one or more analytes in a biological sample of the individual;
determining that the measurement of one analyte is not within a healthy range;
and
administering to the individual one or more microbial genera to individual for the purpose of altering the level of the one analyte into the healthy range, wherein the one or more microbial genera is correlated with the analyte.
28. The method of claim 27 further comprising:
measuring a microbial genera composition of a microbiome; wherein the composition of microbial genera is utilized to assist in selecting the one or more microbial genera to be administered.
29. The method of claim 27 or 28, wherein the one analyte and the one or more correlated microbial genera to be administered is listed within Table 2.
30. The method of any one of claims 27-29, wherein the one analyte is selected from: LDL cholesterol, non-HDL cholesterol, or HDL/LDL cholesterol ratio, wherein the one or more microbial genera to be administered comprises *Haemophilus*.
31. The method of claim 30, wherein the *Haemophilus* is to be topically administered.

32. The method of claim 31, wherein the *Haemophilus* is provided in a probiotic suppository, a probiotic oil, a probiotic emulsion, a probiotic ointment, a probiotic lotion, a probiotic powder, a probiotic cream, a lyophilized powder, a freeze-dried powder, or a combination thereof.

33. The method of any one of claims 27-29, wherein the one analyte is A1C, wherein the one or more microbial genera to be administered comprises *Akkermansia*.

34. The method of claim 33, wherein the one or more microbial genera are to be orally administered.

35. The method of claim 34, wherein the one or more genera is provided in a probiotic food, a probiotic beverage, a liquid solution composition, a gel composition, an oil composition, an emulsion composition, a capsule, an enteric-coated capsule, a dragee, a gavage, a lyophilized powder, a freeze-dried powder, or a combination thereof.

36. The method of claim 33, wherein the one or more microbial genera are to be rectally administered.

37. The method of claim 36, wherein the one or more genera is provided in a probiotic liquid, a probiotic gel, a probiotic suppository, a probiotic fecal transplant, a probiotic enema, a probiotic catheter, a lyophilized powder, a freeze-dried powder, or a combination thereof.

38. A method for treating an individual for a medical condition by administering microbial genera, comprising:

administering to the individual one or more microbial genera to individual, wherein the one or more microbial genera is correlated with a gene product associated with the condition.

39. The method of claim 38, wherein the medical condition is psoriasis and the one or more microbial genera is: *Finegoldia*, *Brevibacterium*, *Halomonas*, *Methylobacterium*, *Moraxella*, *Paracoccus*, *Dolosigranulum*, *Neisseria*, *Methylobacterium*, *Enhydrobacter*, *Peptoniphilus*, or *Roseomonas*.

40. The method of claim 39, wherein the one or more microbial genera are to be topically administered.

41. The method of claim 40, wherein the one or more microbial genera are provided in a probiotic suppository, a probiotic oil, a probiotic emulsion, a probiotic ointment, a probiotic lotion, a probiotic powder, a probiotic cream, a lyophilized powder, a freeze-dried powder, or a combination thereof.

42. The method of claim 38, wherein the medical condition is inflammatory bowel disease and the one or more microbial genera is: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Fusicatenibacter*, *Dialister*, *Subdoligranulum*, *Senegalimassilia*, or *Holdemanella*.

43. The method of claim 38, wherein the medical condition is rheumatoid arthritis and the one or more microbial genera is: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Subdoligranulum*, or *Senegalimassilia*.

44. The method of claim 38, wherein the medical condition is systemic lupus erythematosus and the one or more microbial genera is: *Blautia*, *Dialister*, *Fusicatenibacter*, *Collinsella*, *Subdoligranulum*, or *Senegalimassilia*.

45. The method of claim 38, wherein the medical condition is hypertension and the one or more microbial genera is: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Subdoligranulum*, or *Senegalimassilia*.

46. The method of claim 38, wherein the medical condition is atherosclerosis and the one or more microbial genera is: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Hungatella*, or *Monoglobus*.

47. The method of claim 38, wherein the medical condition is depression or anxiety and the one or more microbial genera is: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Hungatella*, or *Monoglobus*.

48. The method of claim 38, wherein the medical condition is autism and the one or more microbial genera is: *Desulfovibrio*, *Escherichia_Shigella*, *Blautia*, *Dialister*, *Slackia*, *Butyricimonas*, *Collinsella*, *Holdemanella*, *Lawsonibacter*, *Fusicatenibacter*, *Acutalibacter*, *Akkermansia*, *Clostridium_sensu_stricto*, *Clostridium_XVIII*, *Flavonifractor*, *Holdemania*, or *Hungatella*.

49. The method of claim 38, wherein the medical condition is schizophrenia and the one or more microbial genera is: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Hungatella*, or *Monoglobus*.

50. The method of claim 38, wherein the medical condition is metabolic disease and the one or more microbial genera is: *Barnesiella*, *Frisingicoccus*, *Butyrivibrio*, *Adlercreutzia*, *Butyricicoccus*, *Cloacibacillus*, *Dysosmobacter*, *Faecalicatena*, *Anaerotignum*, *Cloacibacillus*, *Dysosmobacter*, *Gordonibacter*, *Negativibacillus*, *Phoceia*, *Pseudoflavonifractor*, *Raoultibacter*, or *Turicibacter*.

51. The method of claim 50, wherein the one or more microbial genera is: *Barnesiella*, *Frisingicoccus*, or *Butyrivibrio*.

52. The method of claim 38, wherein the medical condition is type 2 diabetes or obesity and the one or more microbial genera is: *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Dialister*, *Fusicatenibacter*, *Hungatella*, *Monoglobus*, *Faecalibacterium*, *Lachnospira*, *Prevotella*, *Roseburia*, *Slackia*, *Subdoligranulum*, or *Sutterella*.

53. The method of claim 38, wherein the medical condition is leaky gut syndrome and the one or more microbial genera is: *Blautia*, *Dialister*, *Fusicatenibacter*, *Agathobacter*, *Butyricimonas*, *Collinsella*, *Desulfovibrio*, *Frisingicoccus*, *Faecalibacterium*, *Lachnospira*, *Prevotella*, *Roseburia*, *Slackia*, *Subdoligranulum*, *Sutterella*, *Hungatella*, *Monoglobus*, *Acutalibacter*, *Akkermansia*, *Clostridium_sensu_stricto*, *Clostridium_XVIII*, *Flavonifractor*, *Holdemania*, *Anaerostipes*, *Barnesiella*, *Eggerthella*, *Intestinibacter*, *Neglecta*, *Parabacteroides*, or *Romboutsia*.

54. The method of any one of claims 42-53, wherein the one or more microbial genera are to be orally administered.

55. The method of claim 54, wherein the one or more genera is provided in a probiotic food, a probiotic beverage, a liquid solution composition, a gel composition, an oil composition, an emulsion composition, a capsule, an enteric-coated capsule, a dragee, a gavage, a lyophilized powder, a freeze-dried powder, or a combination thereof.

56. The method of any one of claims 42-53, wherein the one or more microbial genera are to be rectally administered.

57. The method of claim 56, wherein the one or more genera is provided in a probiotic liquid, a probiotic gel, a probiotic suppository, a probiotic fecal transplant, a probiotic enema, a probiotic catheter, a lyophilized powder, a freeze-dried powder, or a combination thereof.

58. A method of determining microbial genera host immune response, comprising:
providing immune responsive organoids in culture;
adding a microbial genus culture supernatant to the immune responsive organoids in culture; and
measuring one or more gene products to determine organoid response to the microbial genus culture supernatant.
59. A method for administering a probiotic treatment, comprising:
providing a culture of an immune responsive organoids of an individual;
contacting the culture of immune responsive organoids with a culture product of a microbial genus or a combination of microbial genera;
determining that the microbial genus or the combination of microbial genera yield a desired response by the immune responsive organoids; and
based on the response by the immune responsive organoids, determining a treatment regimen for the individual that comprises administration of the microbial genus or the combination of microbial genera.

Fig. 1

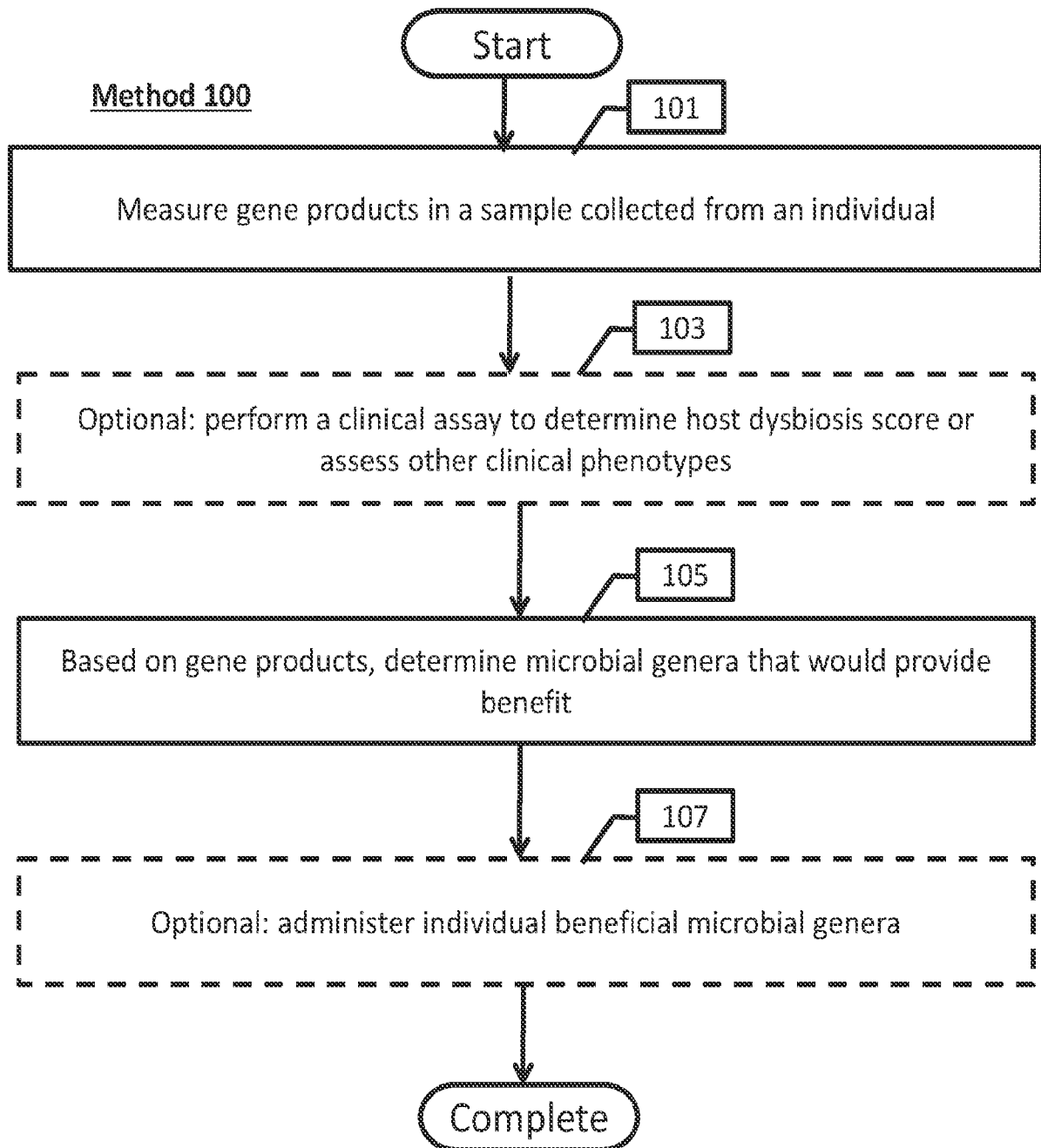


Fig. 2

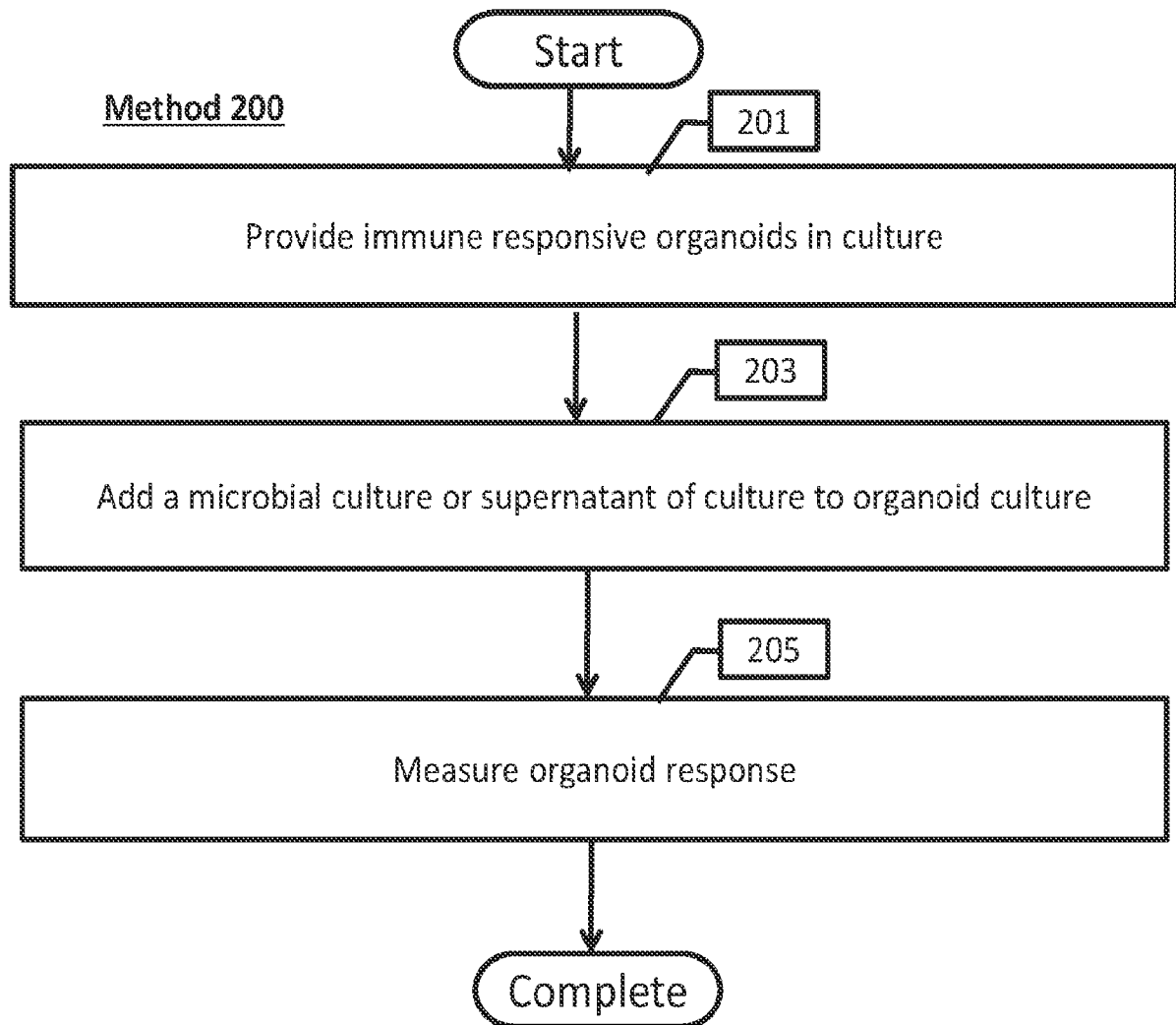
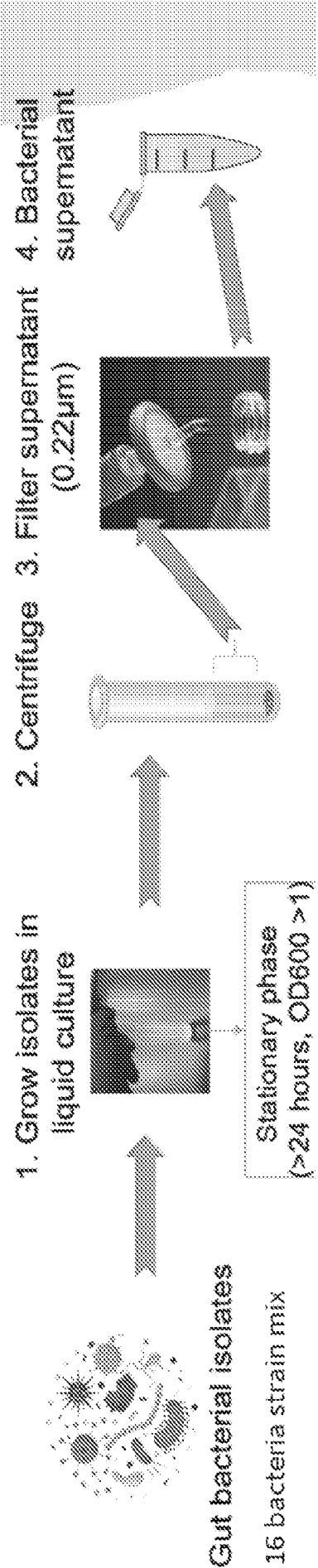
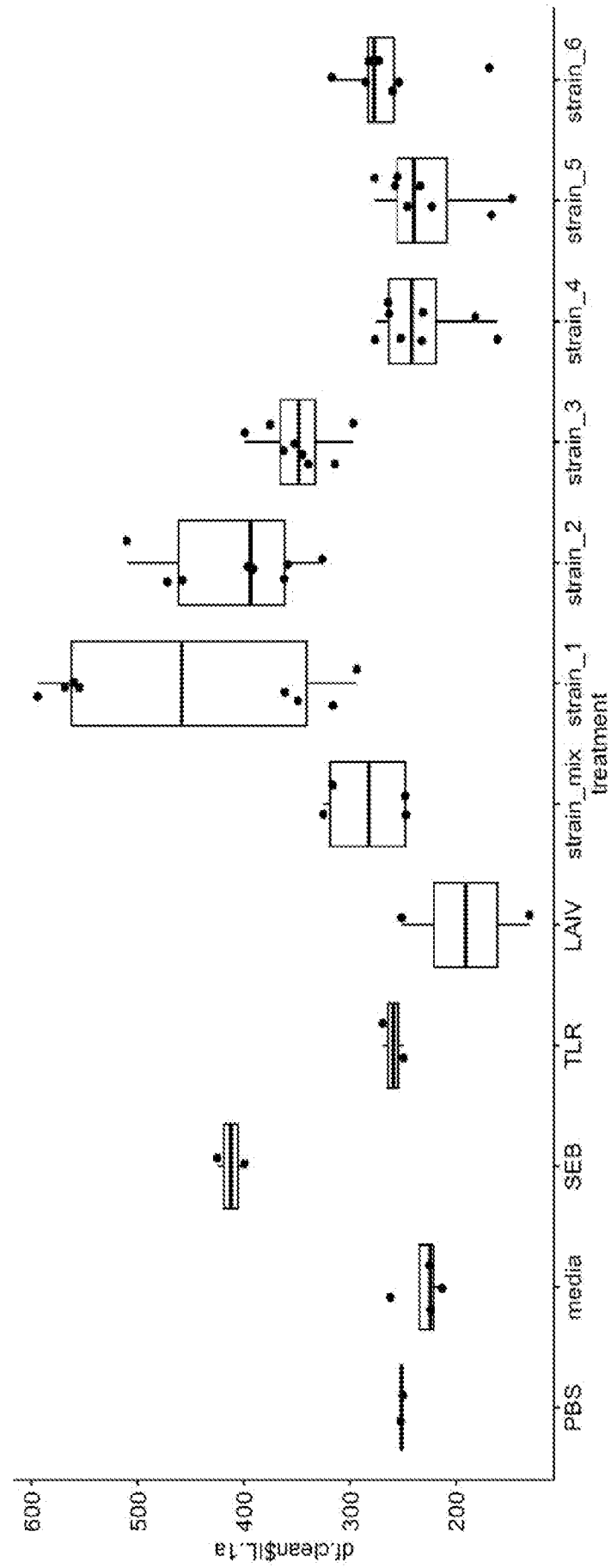


Fig. 3



ALL



IL-1RA

Fig. 4B

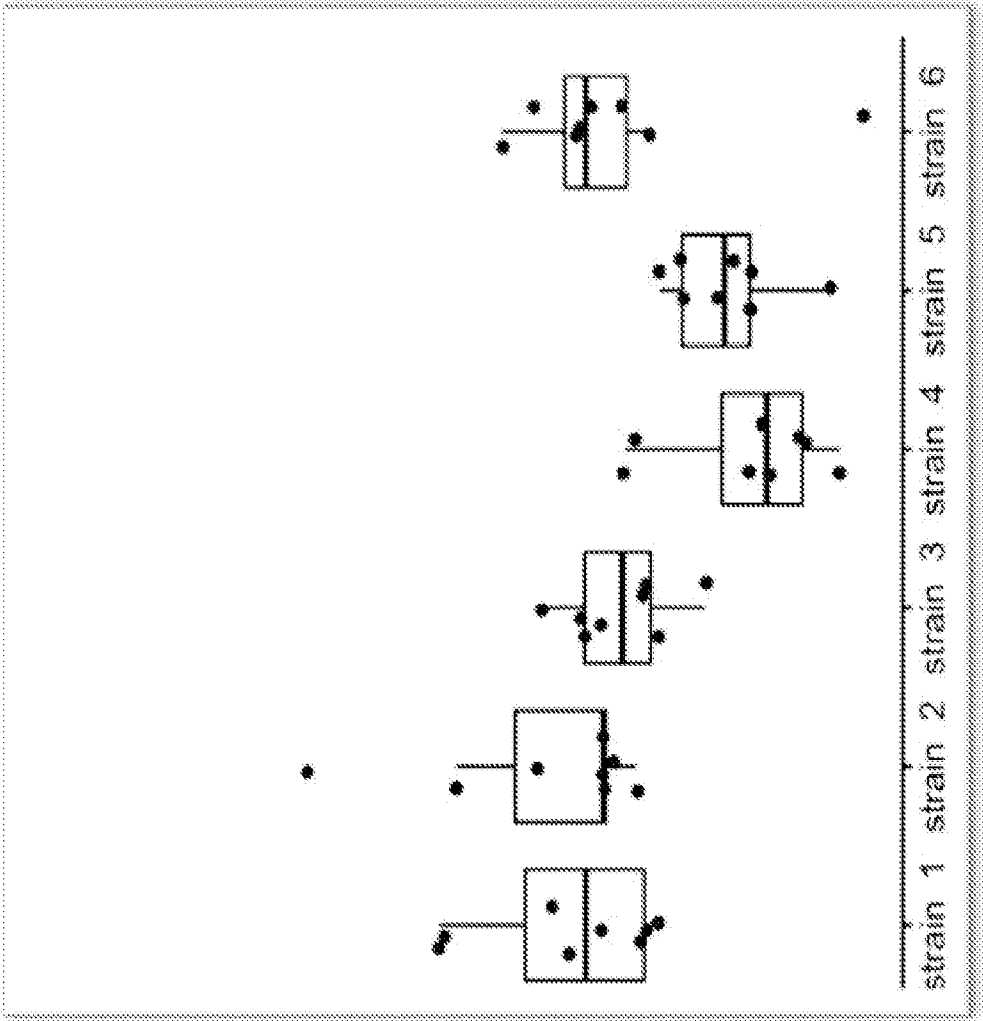


Fig. 4C

CCL3

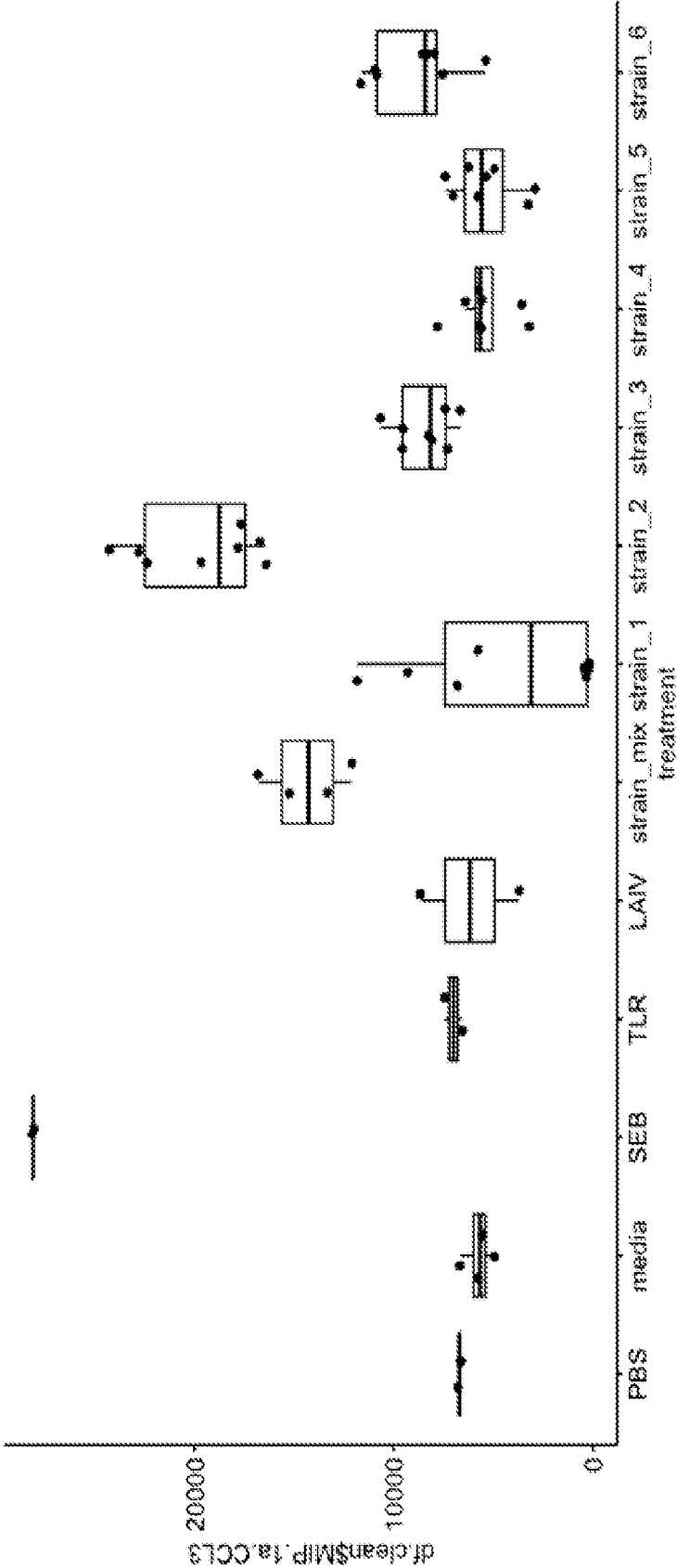


Fig. 4D

M-CSF

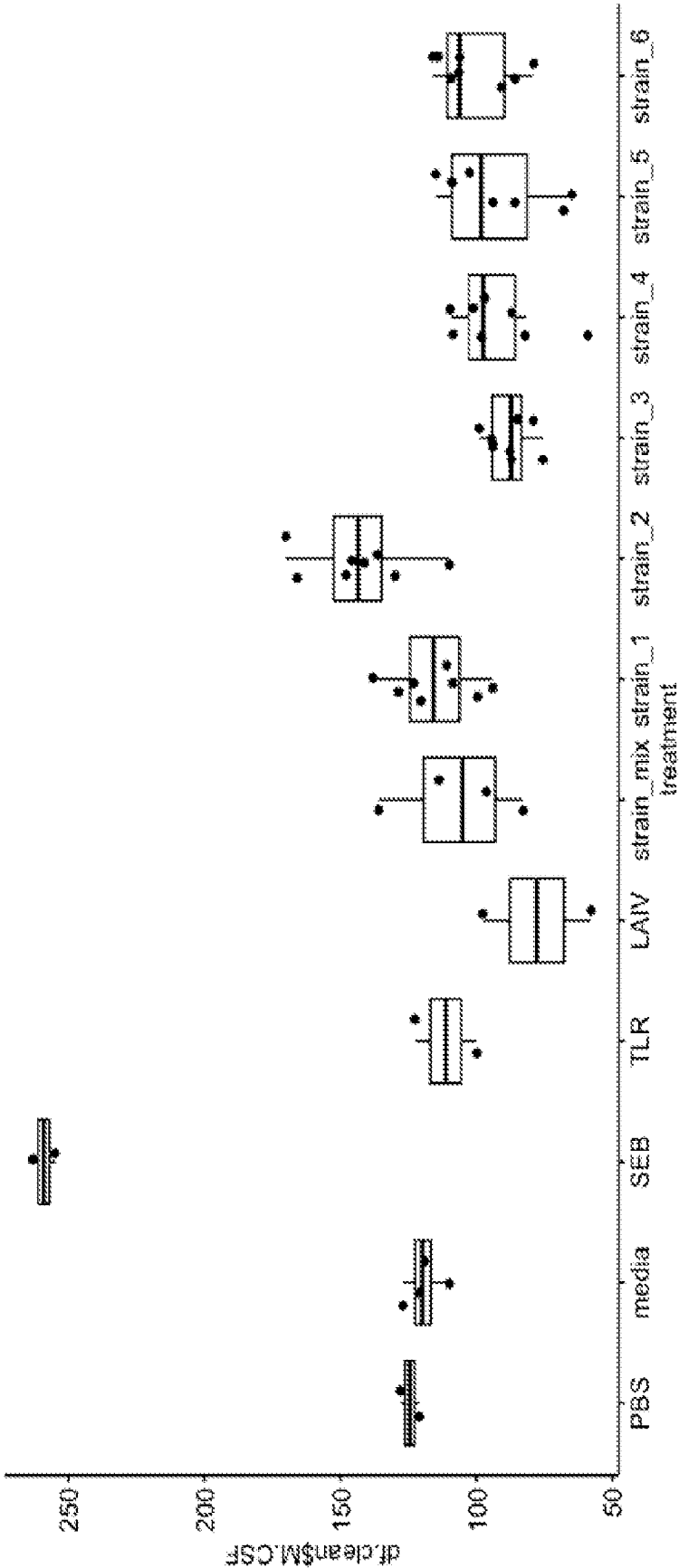


Fig. 4E

IL-6

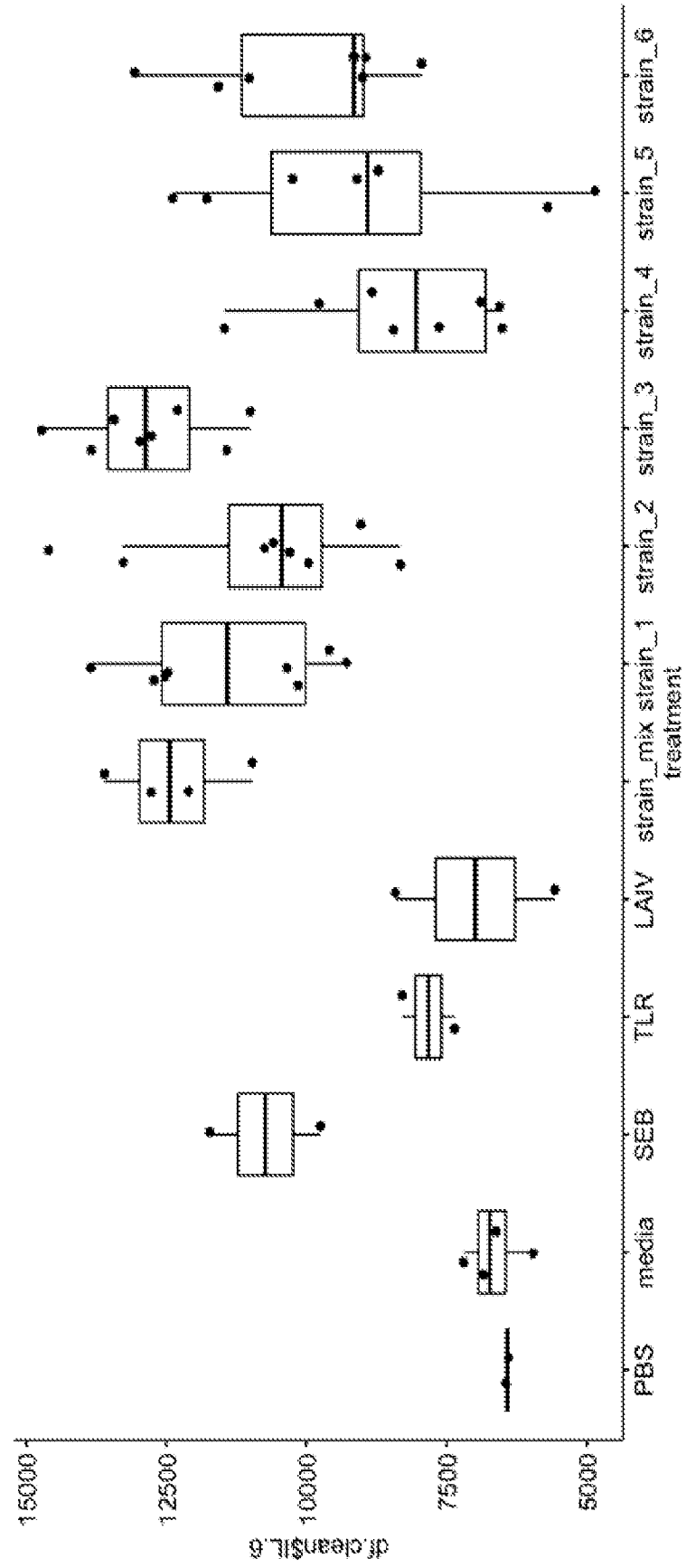


Fig. 5

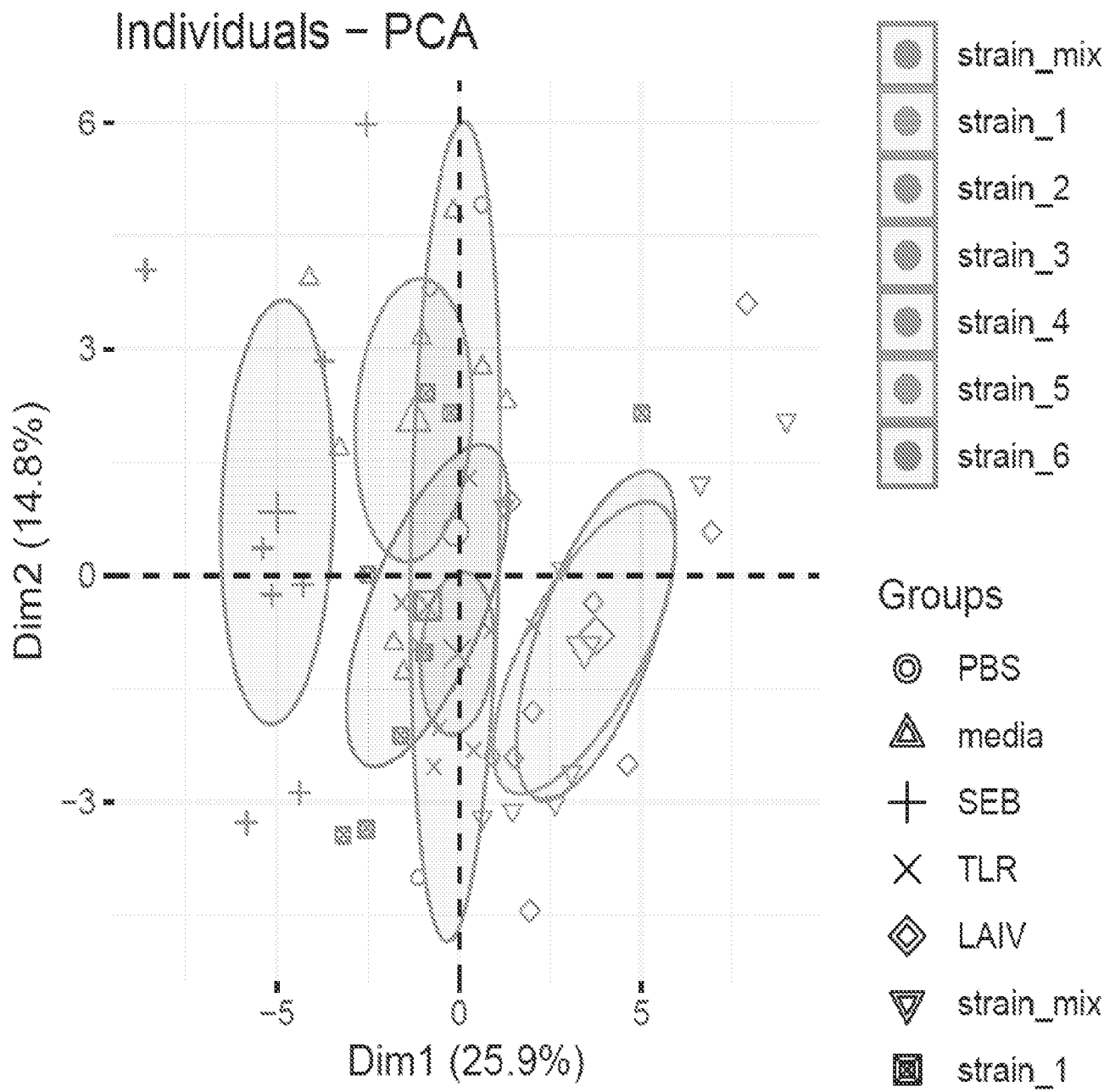


Fig. 6A

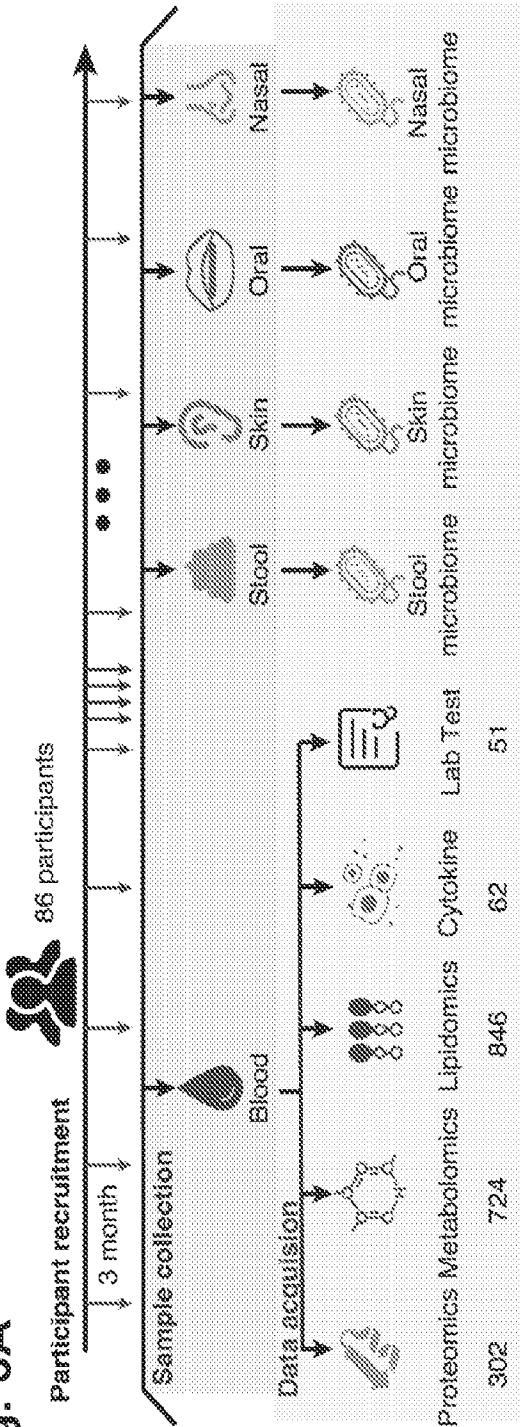


Fig. 6B

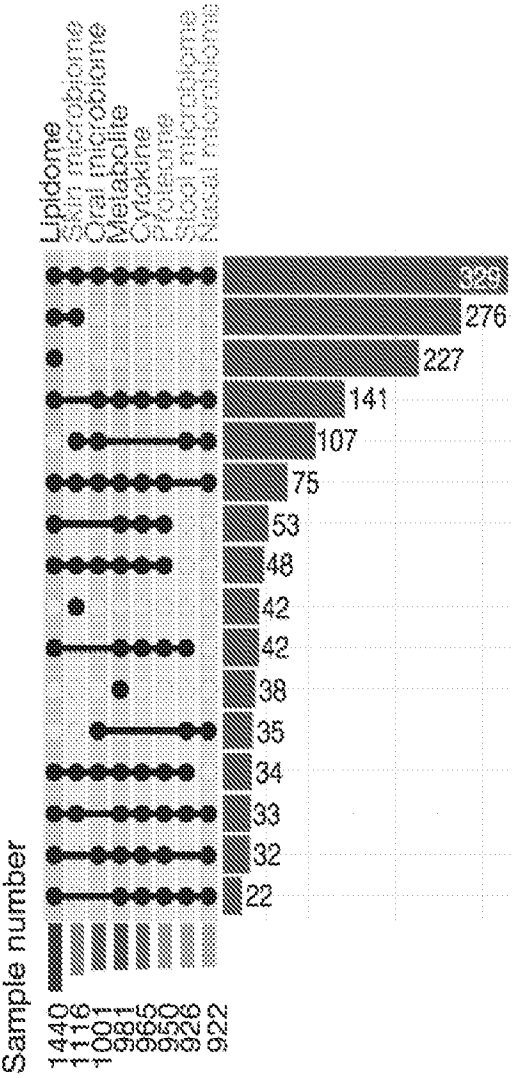


Fig. 6C

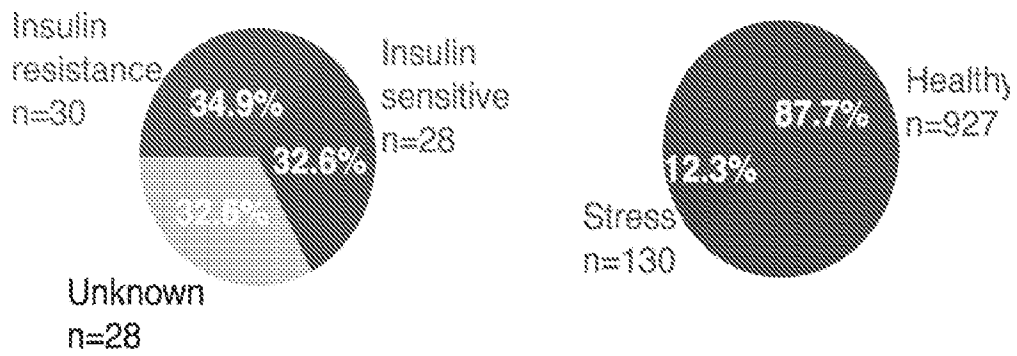


Fig. 6D

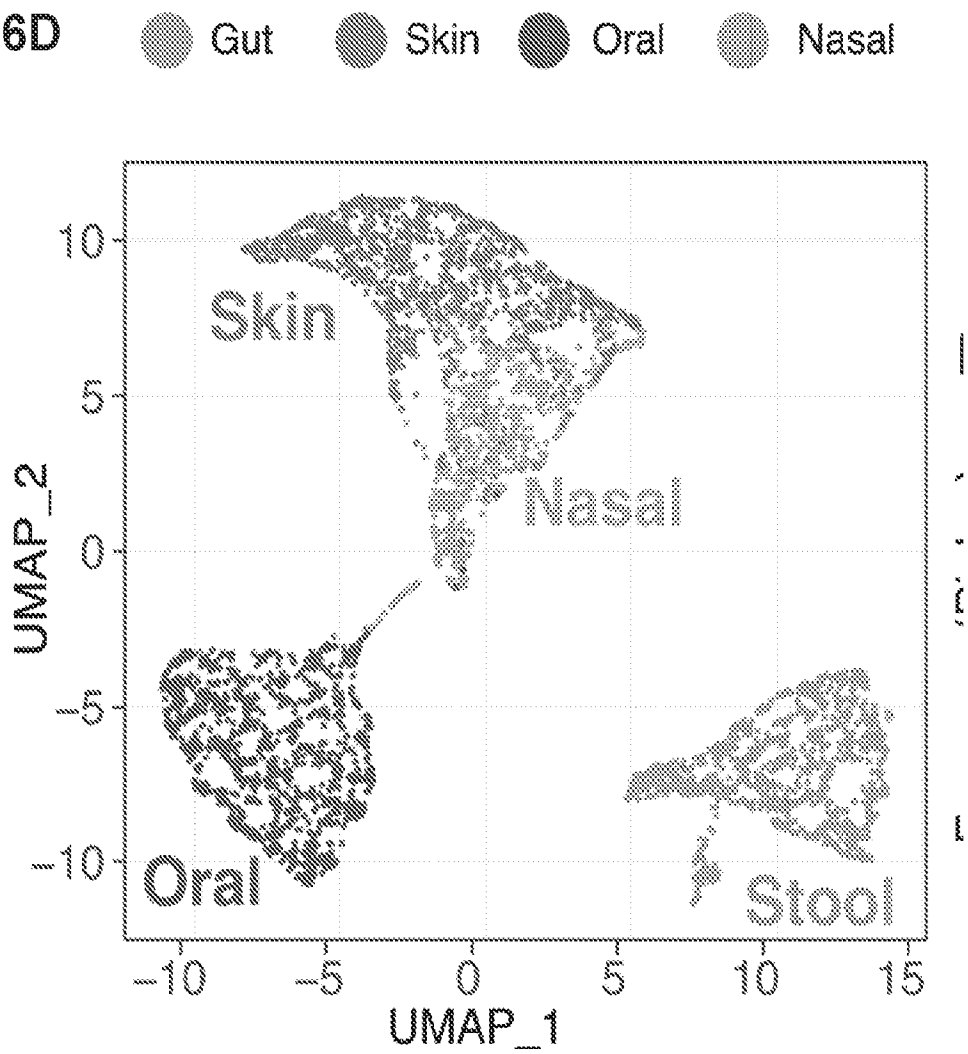


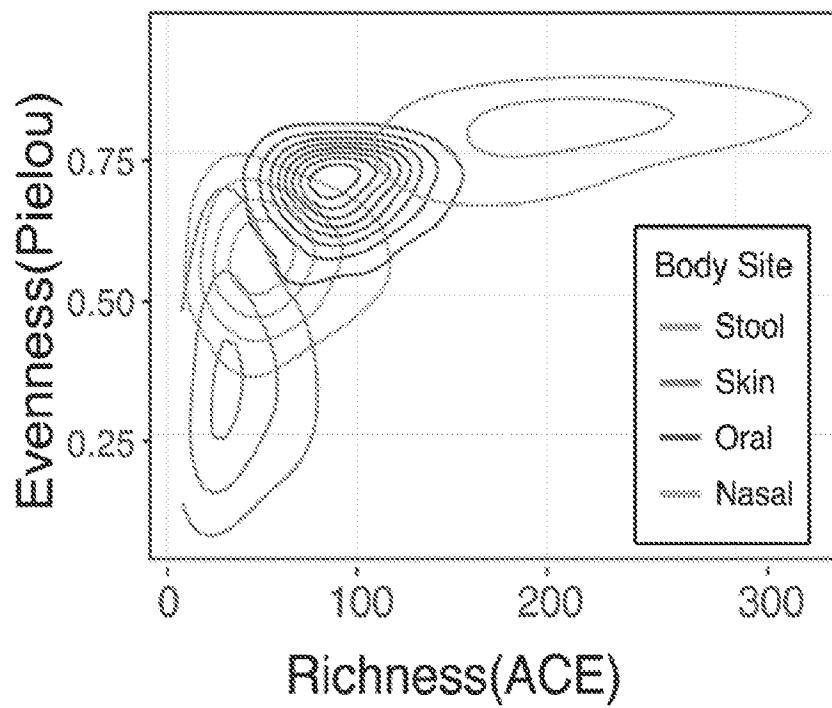
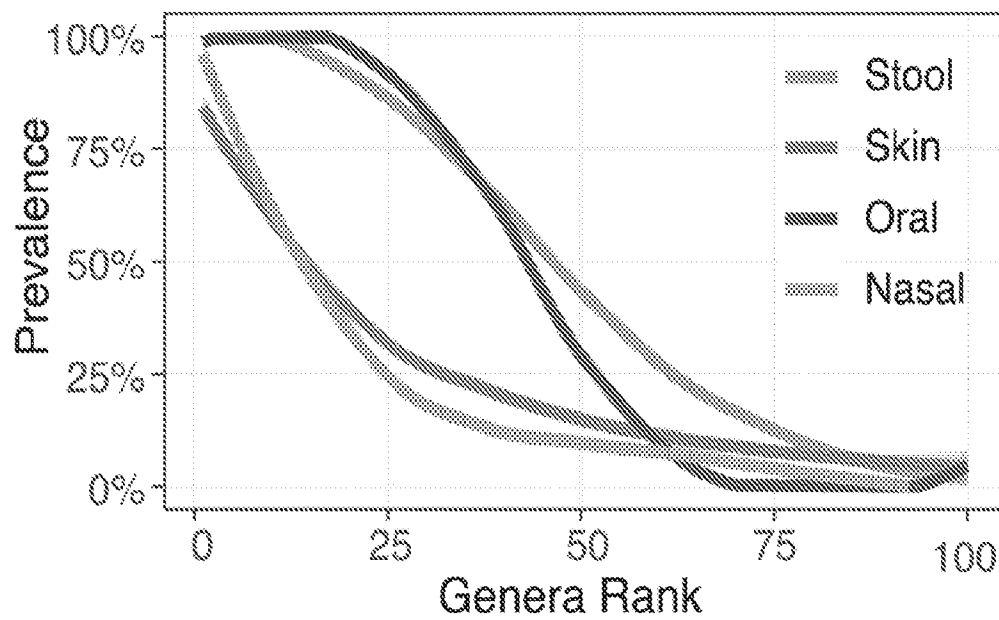
Fig. 6E**Fig. 6F**

Fig. 7A

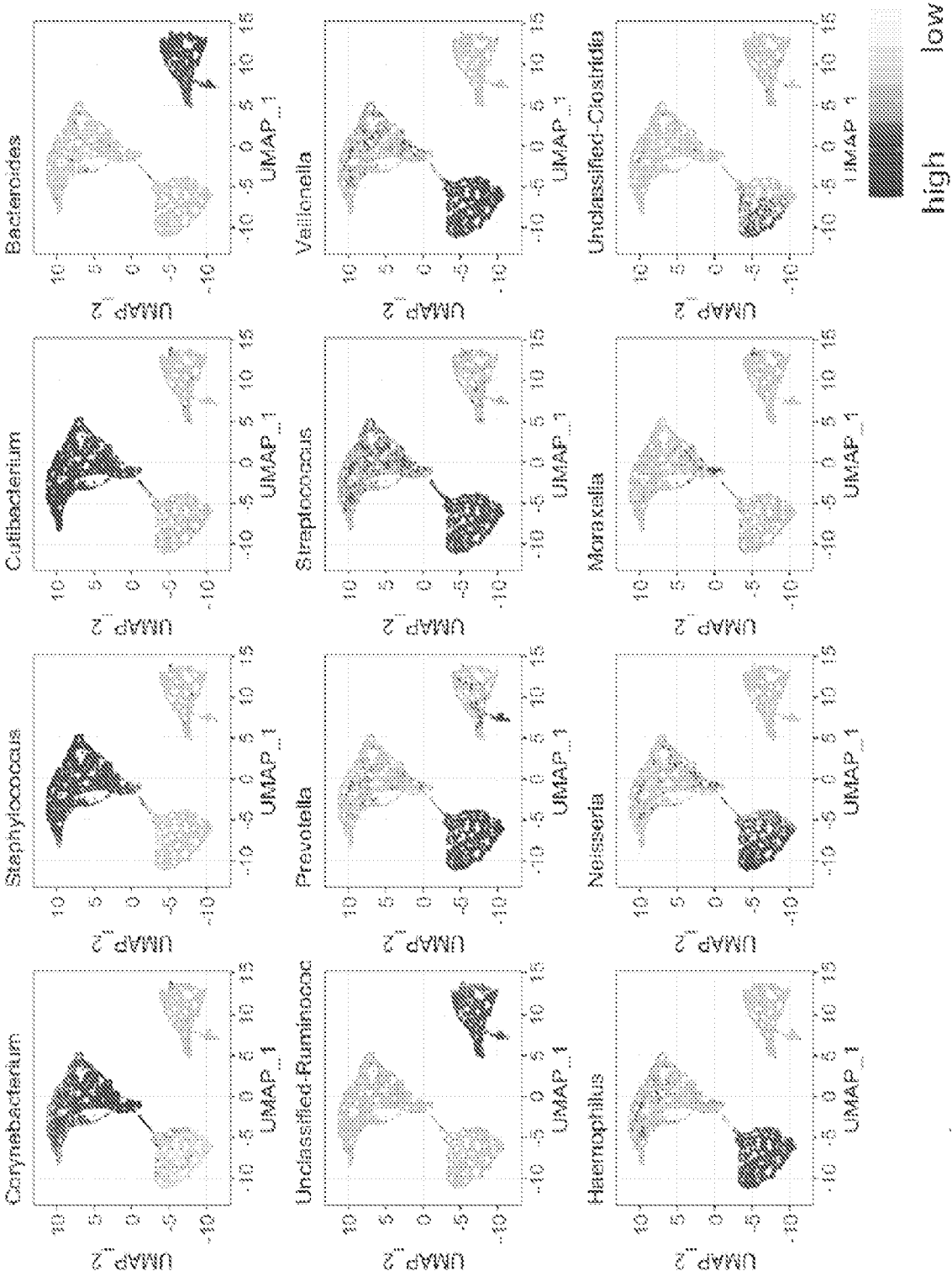


Fig. 7B

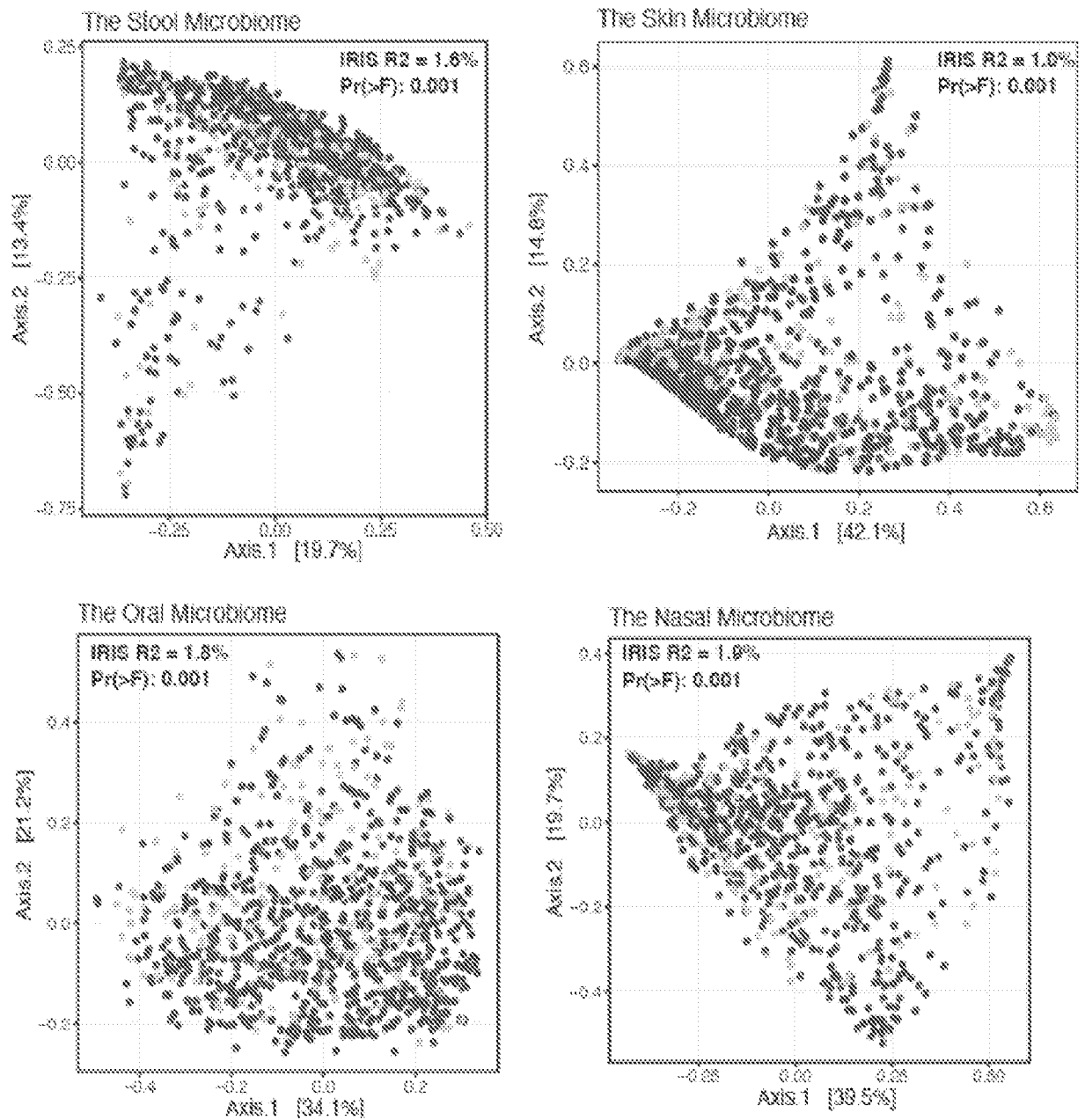


Fig. 7C

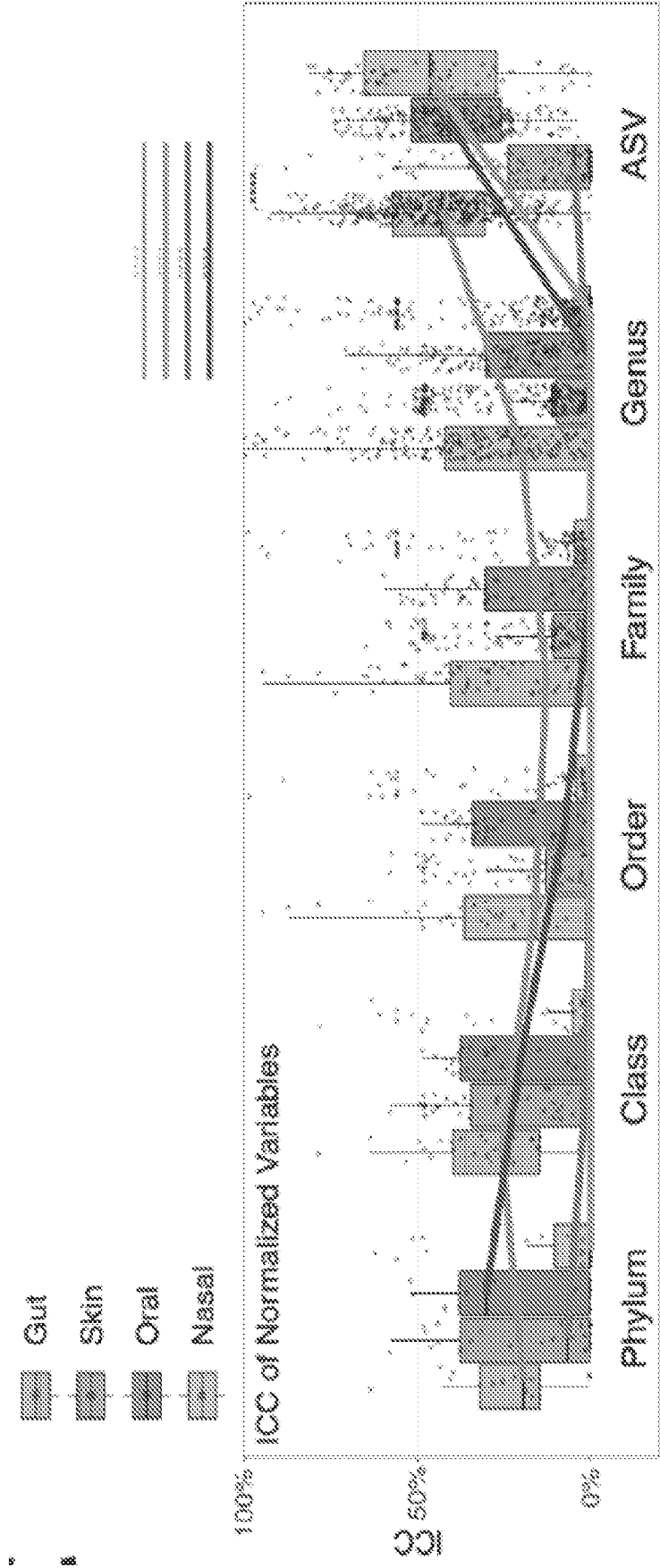
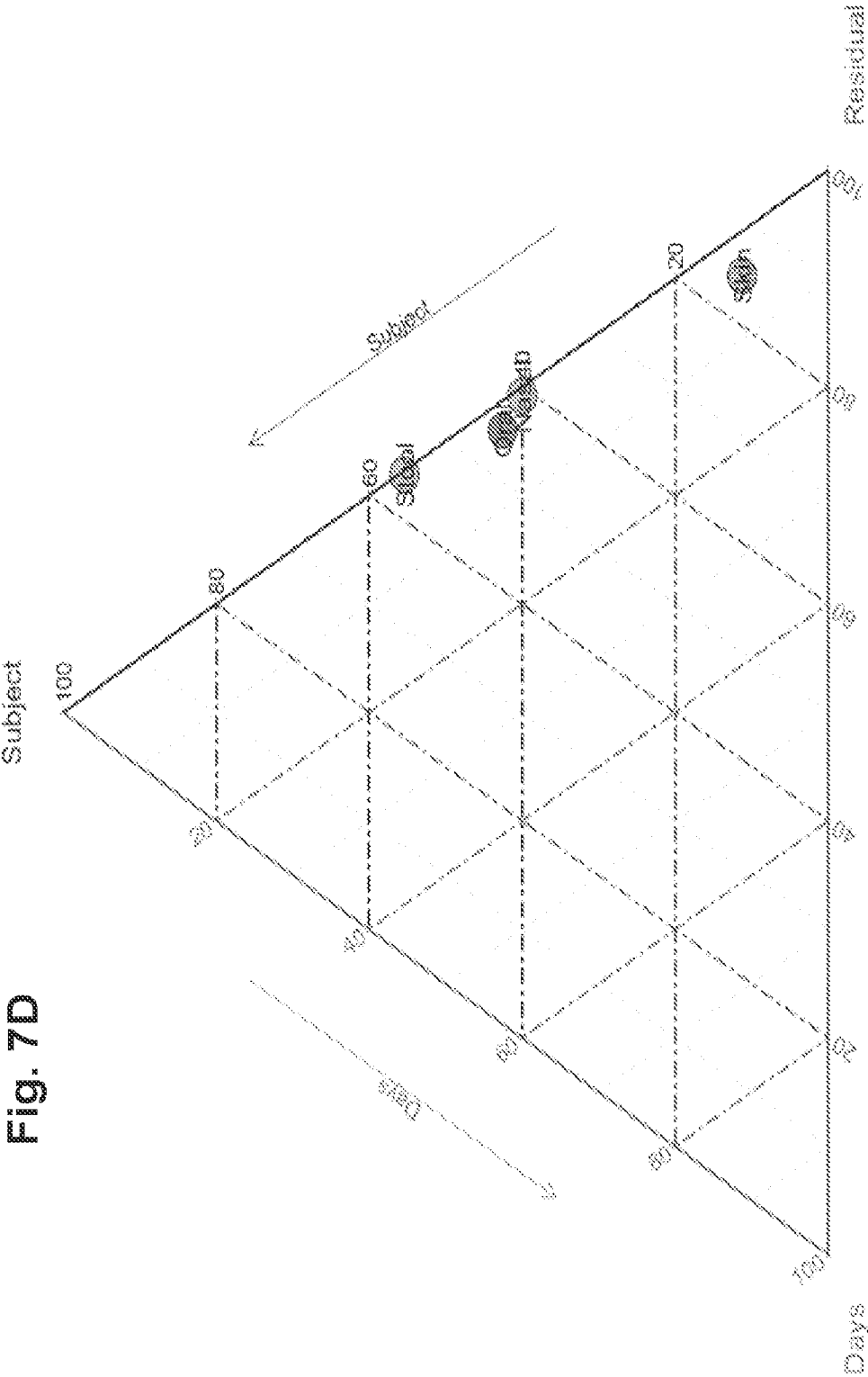


Fig. 7D



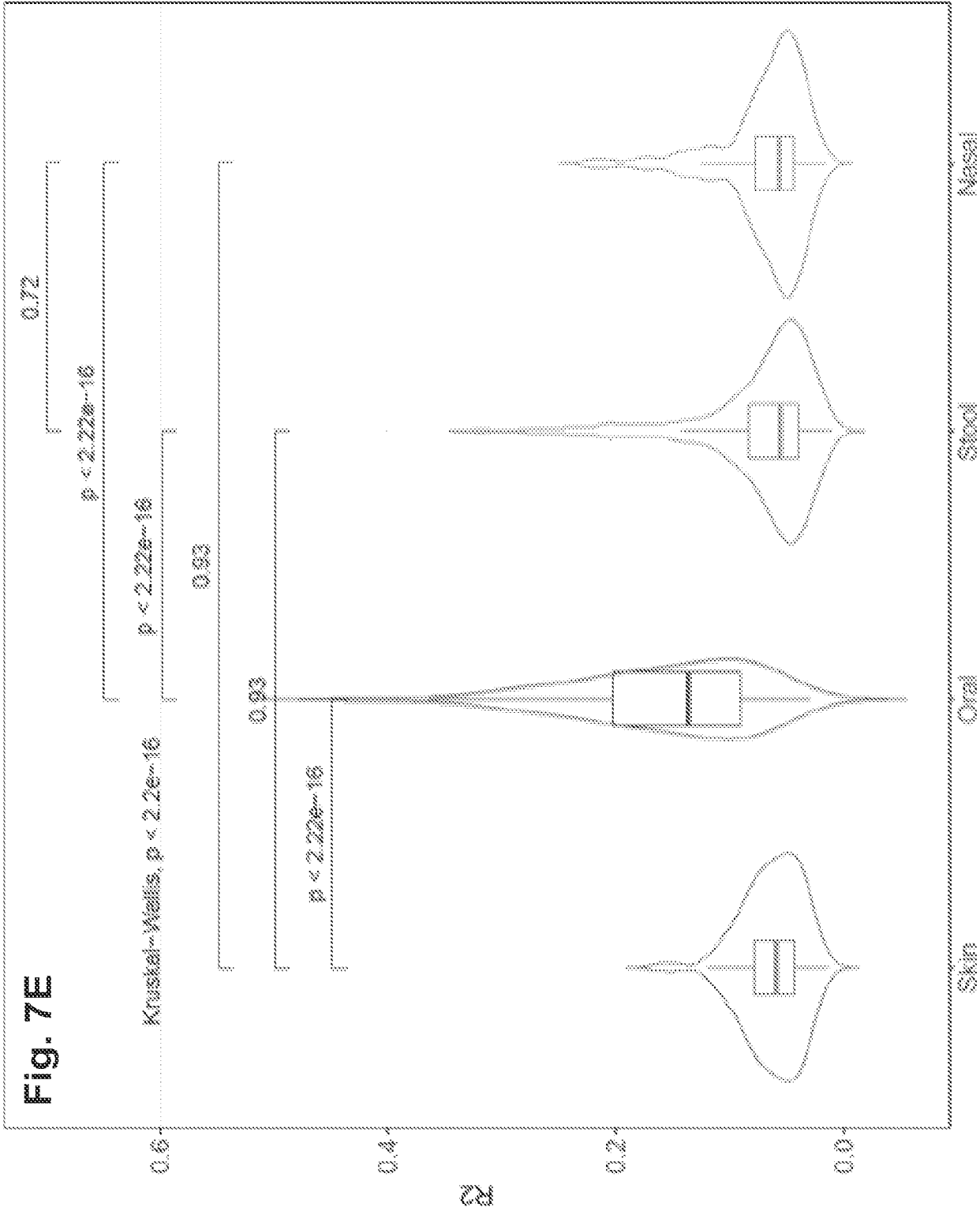


Fig. 7F

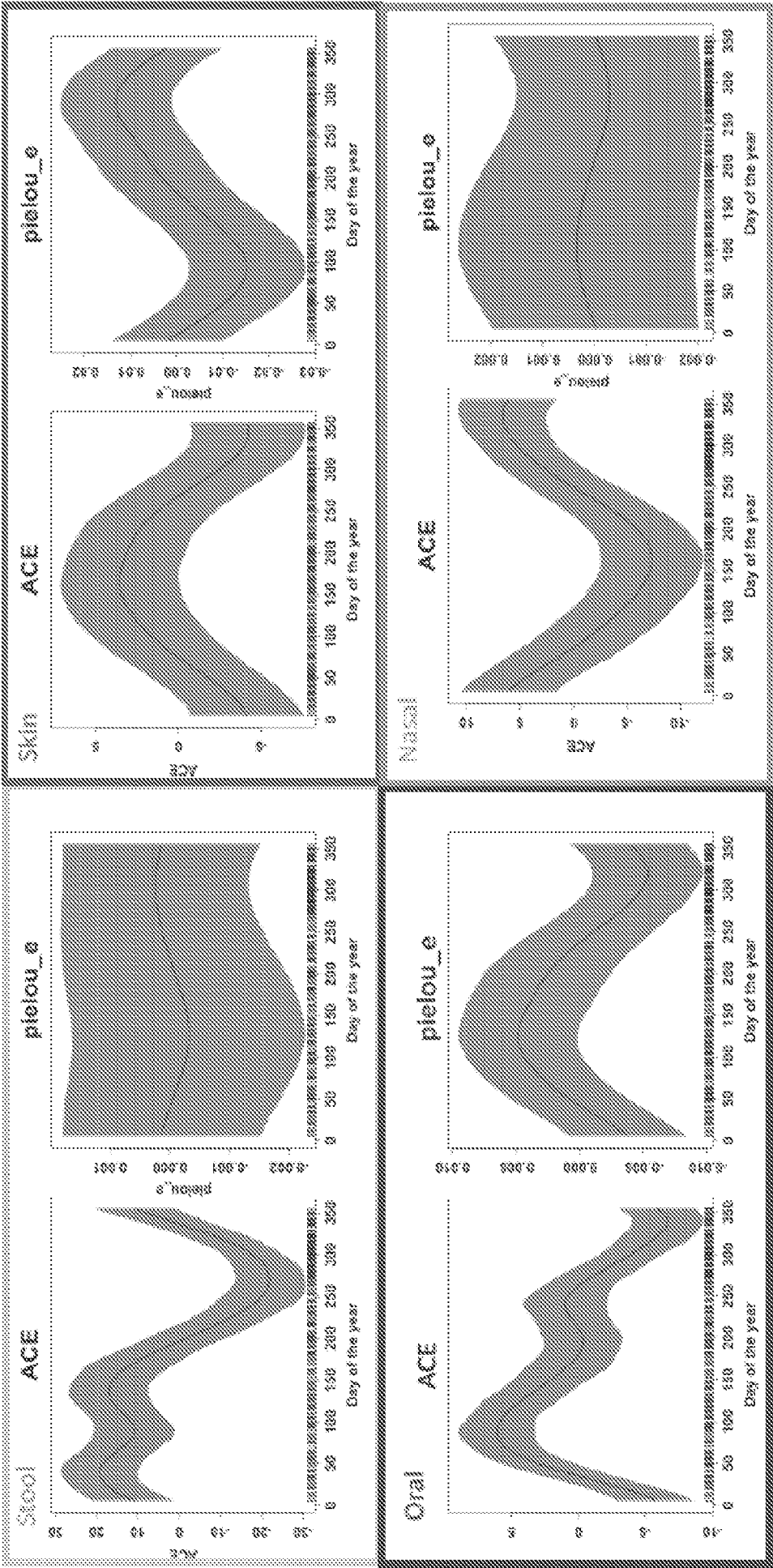
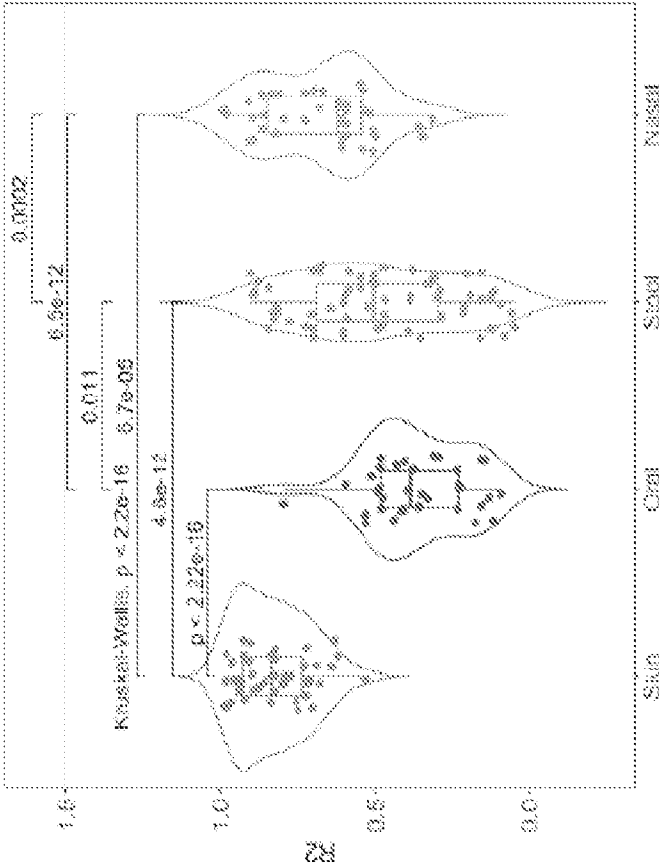


Fig. 7G

Participant 1



Participant 2

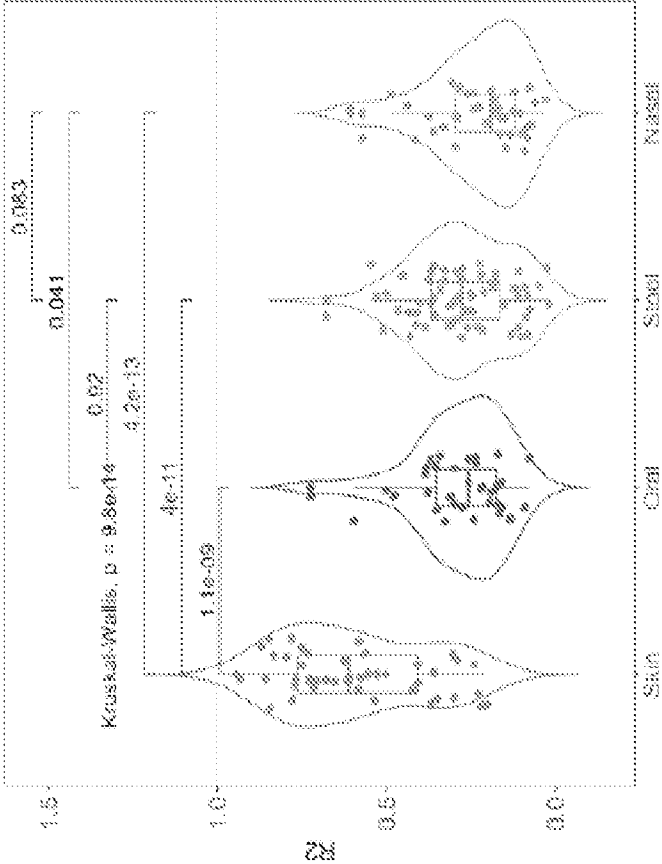


Fig. 7H

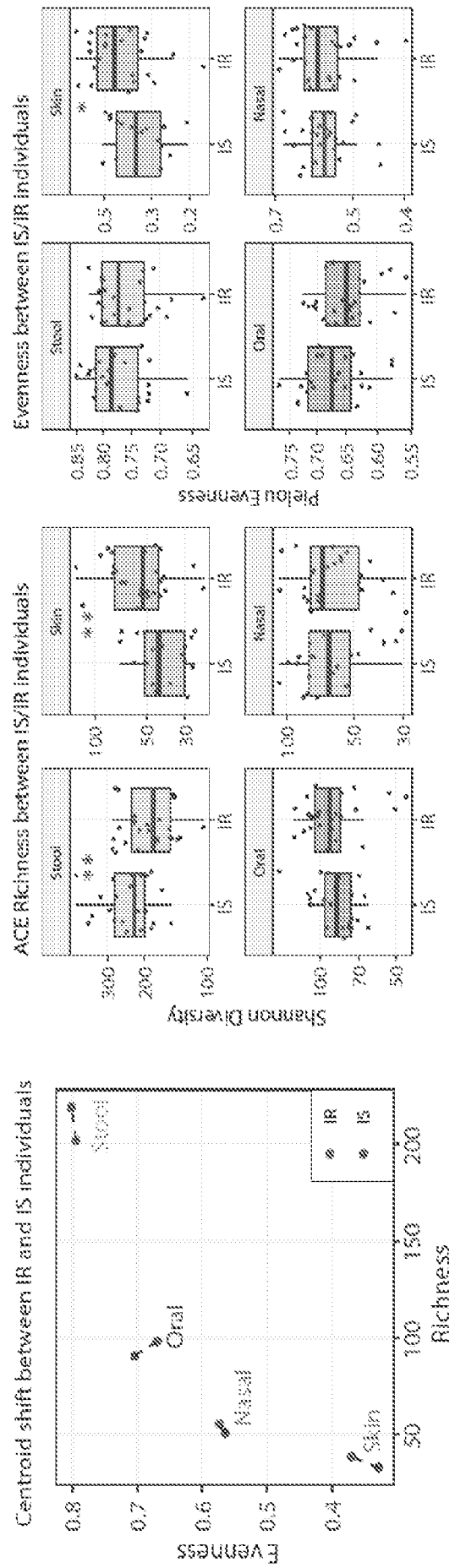


Fig. 71

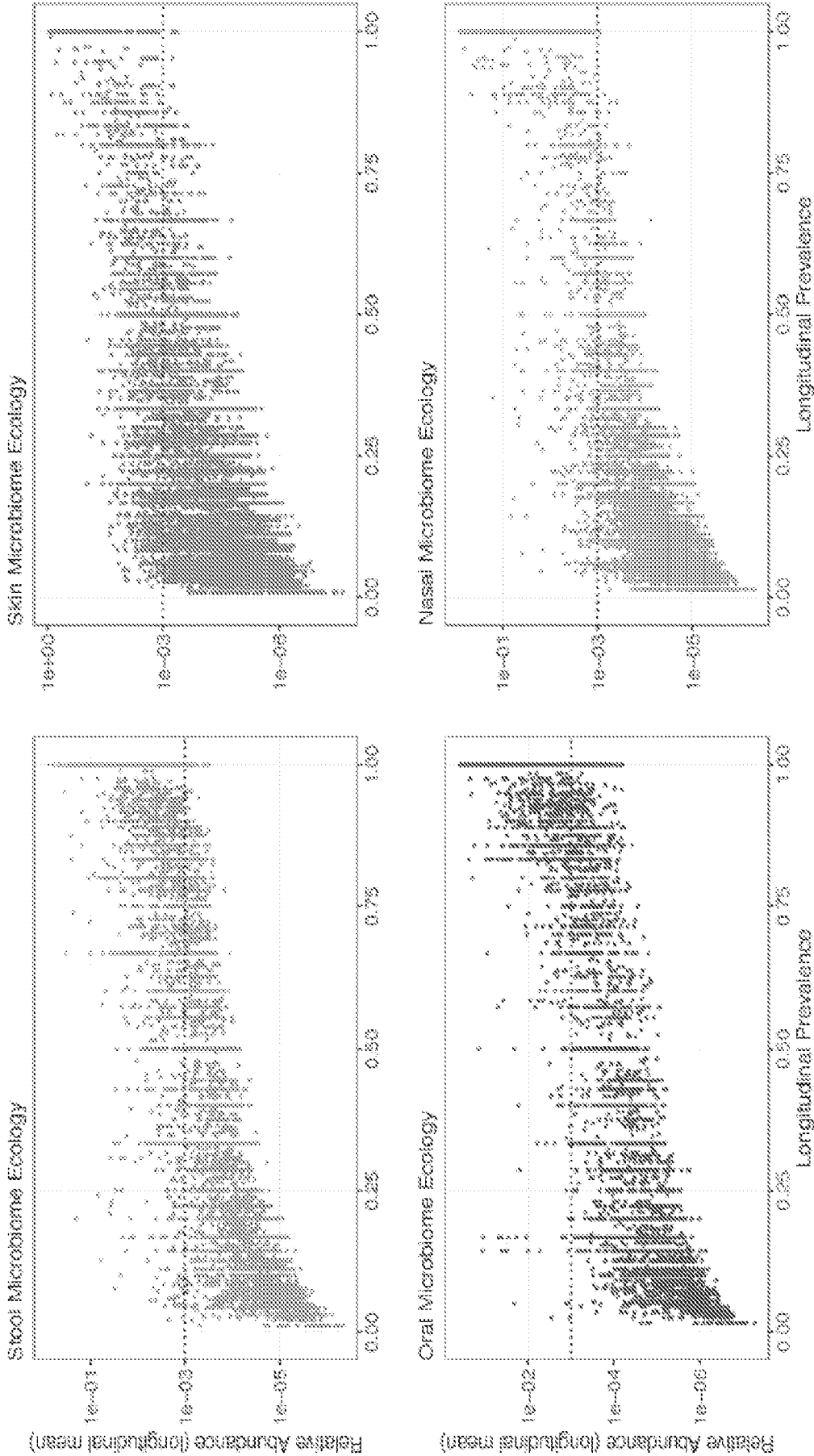


Fig. 7J

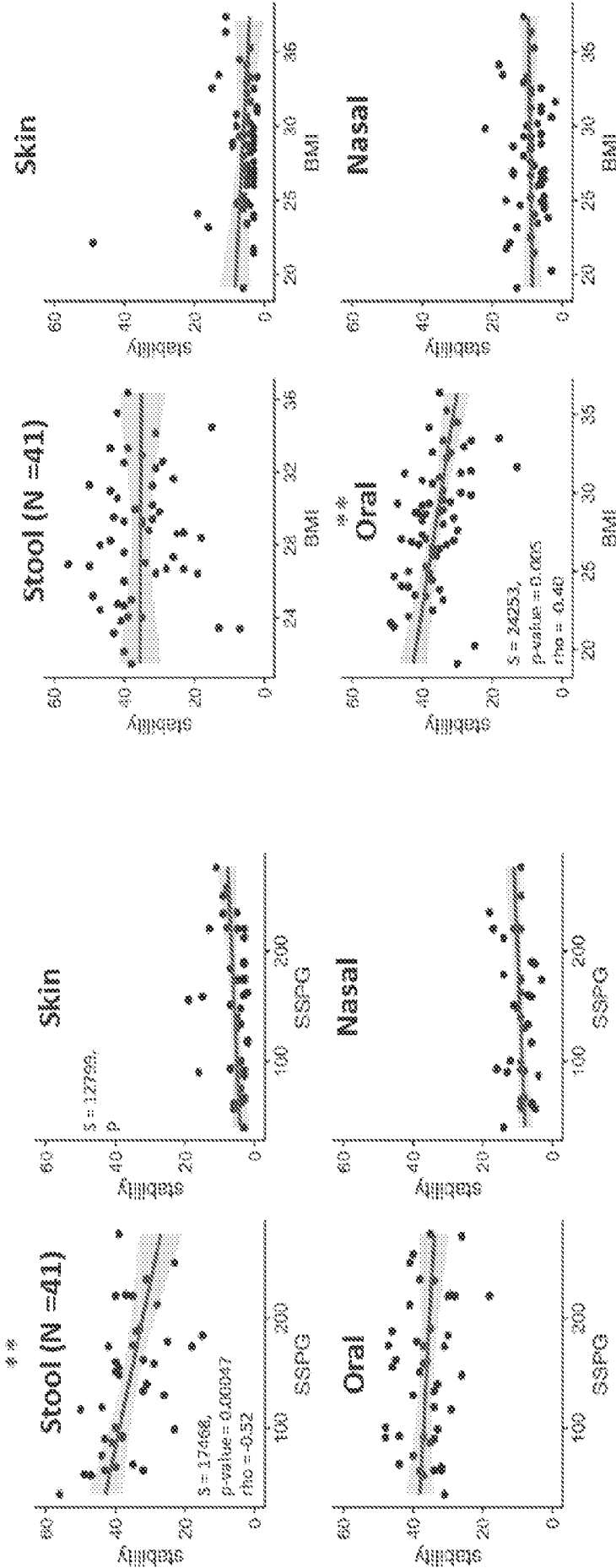
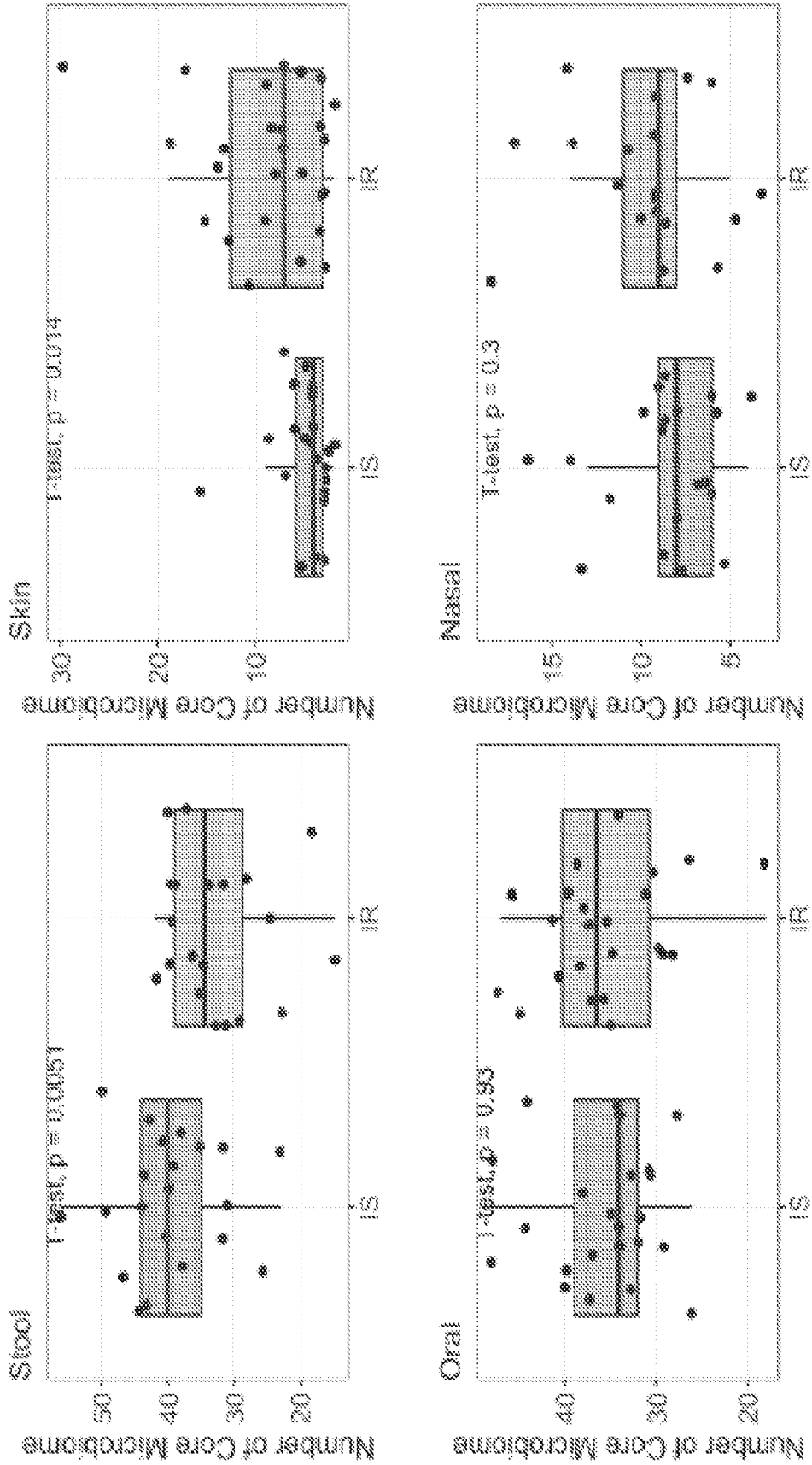


Fig. 7K



75

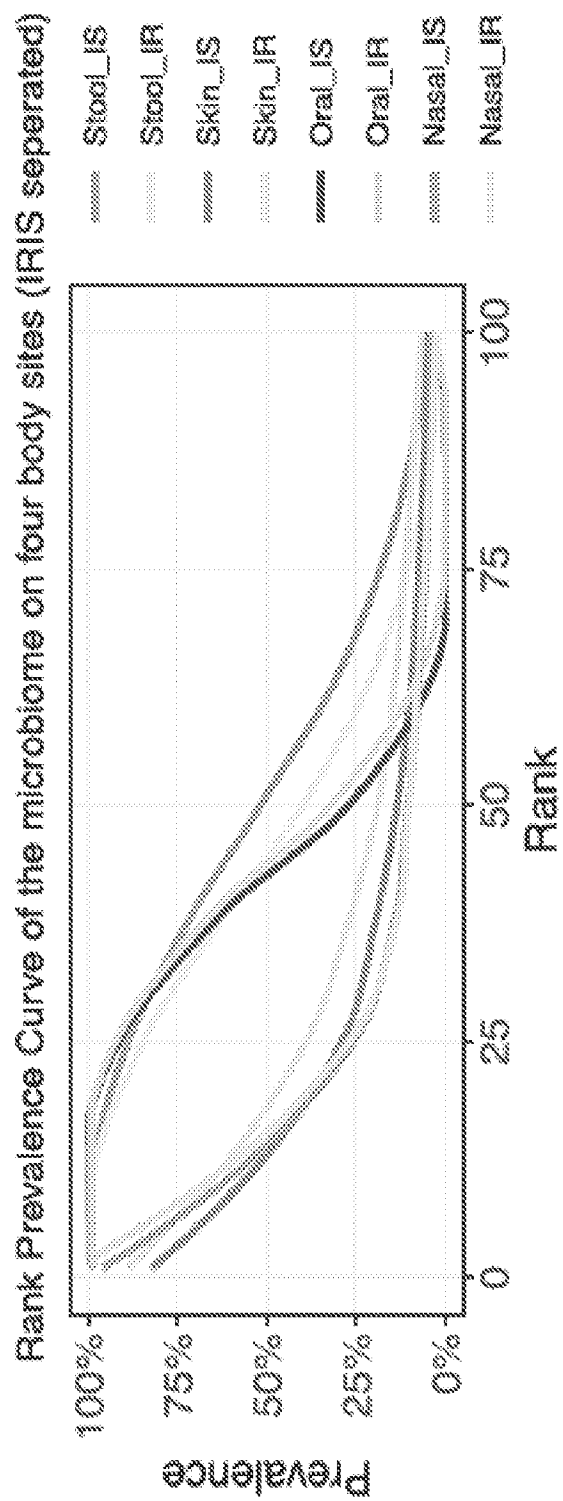


Fig. 7M

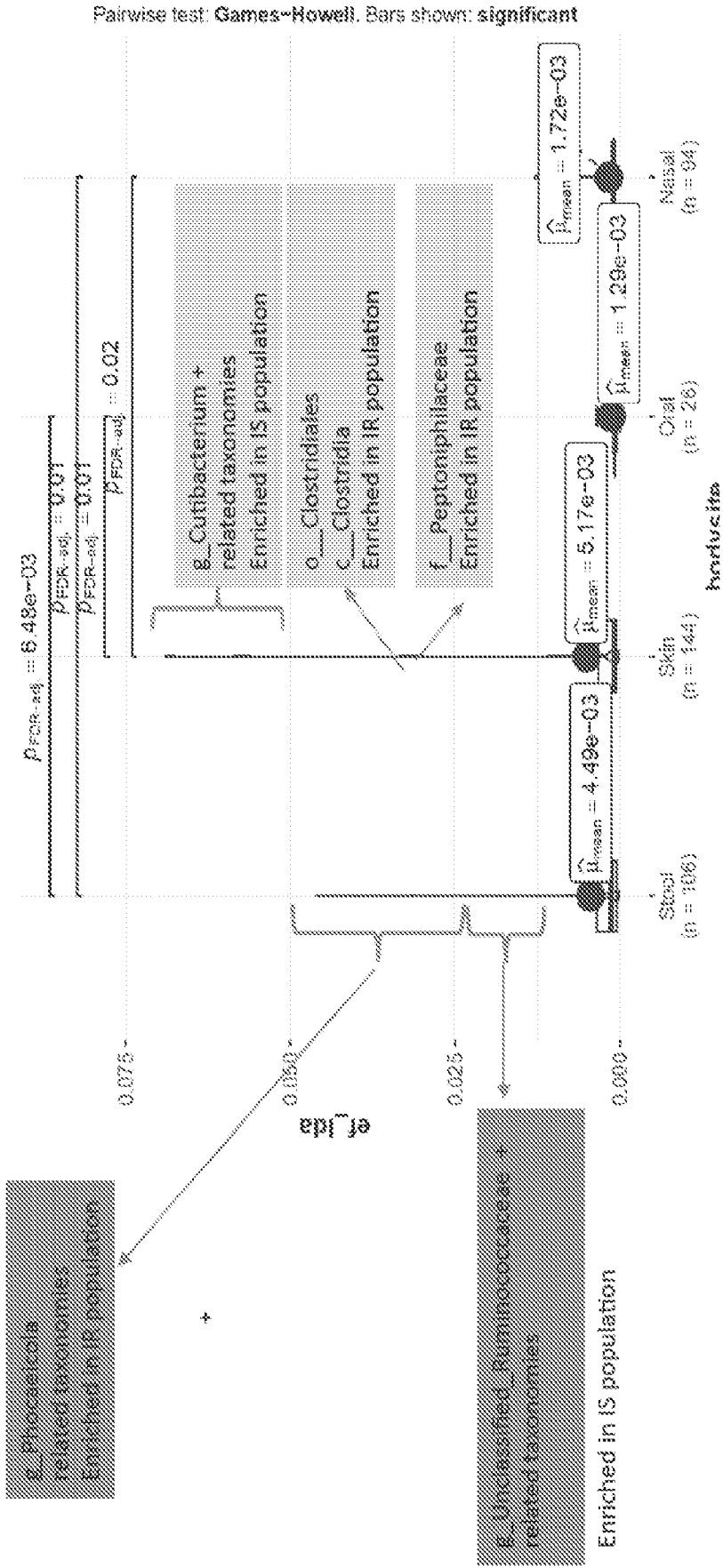


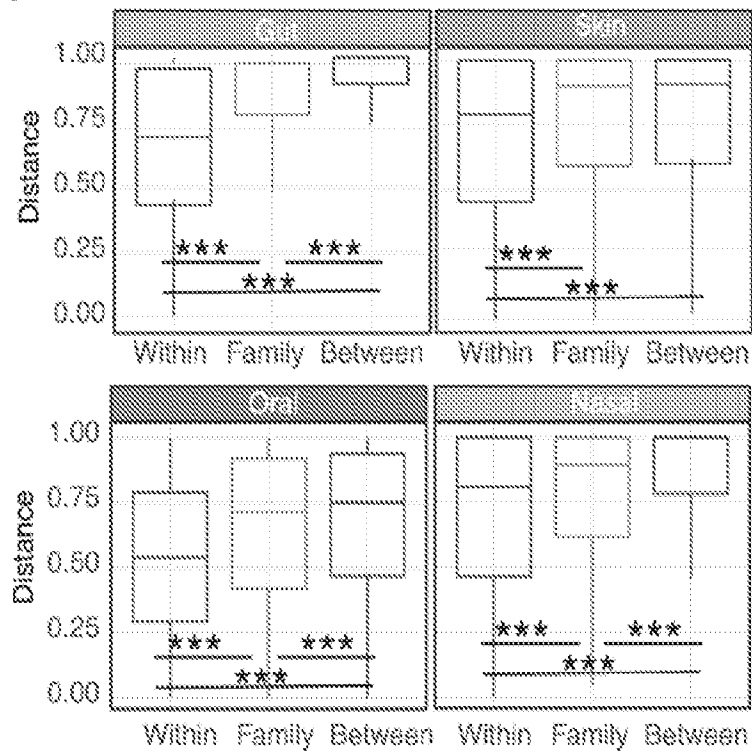
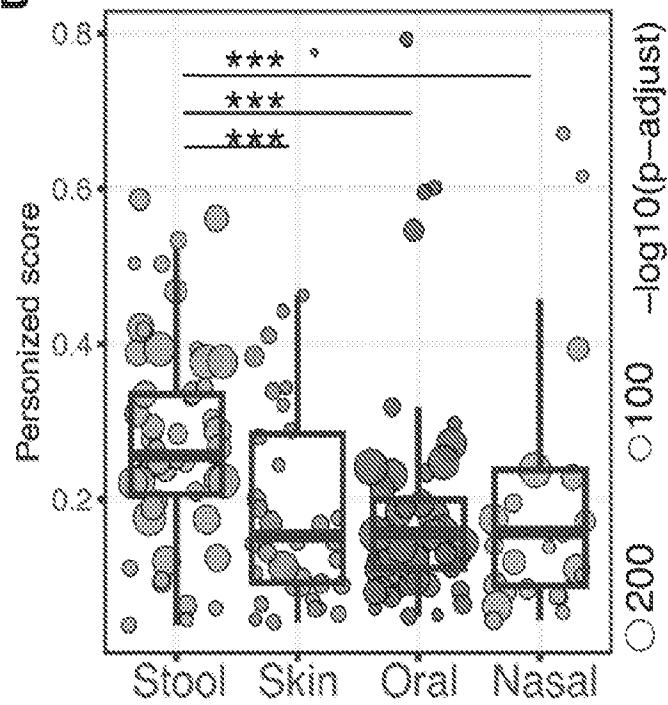
Fig. 8A**Fig. 8B**

Fig. 8C

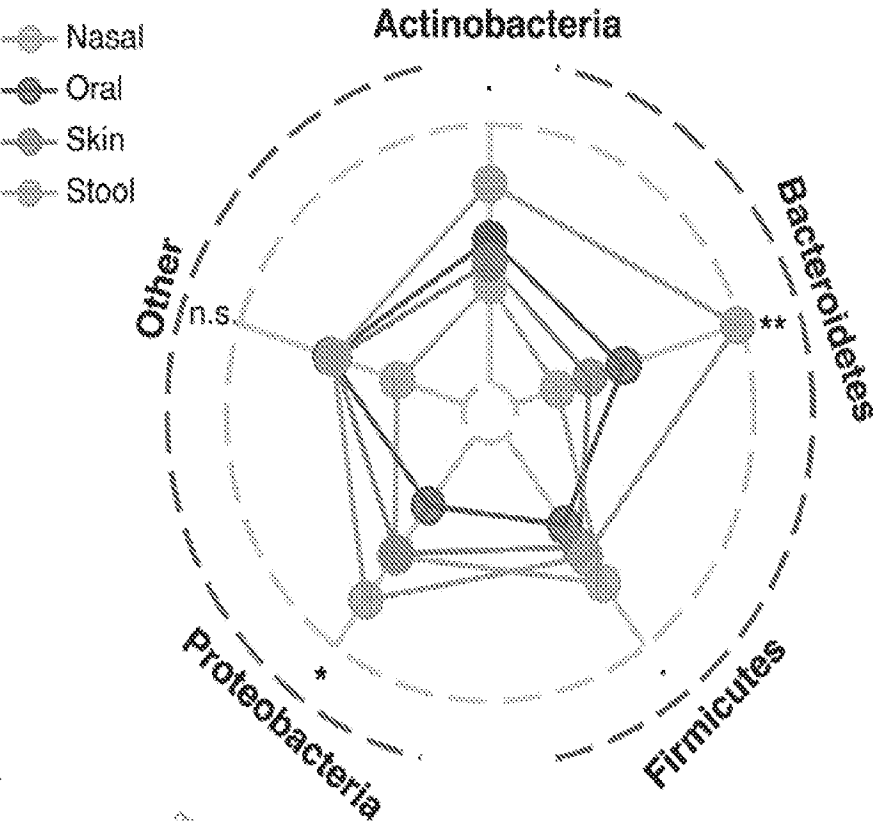


Fig. 9A

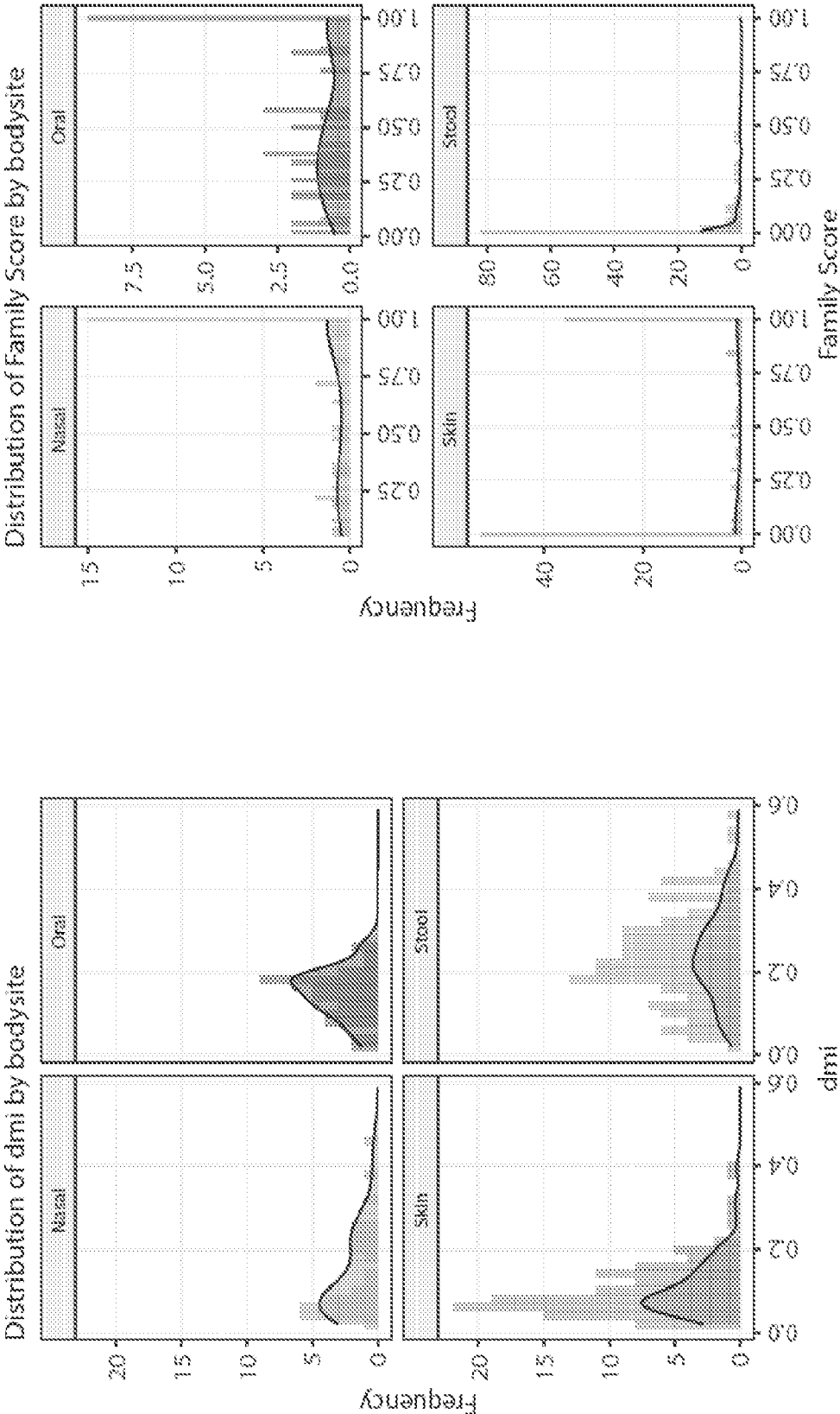


Fig. 9B

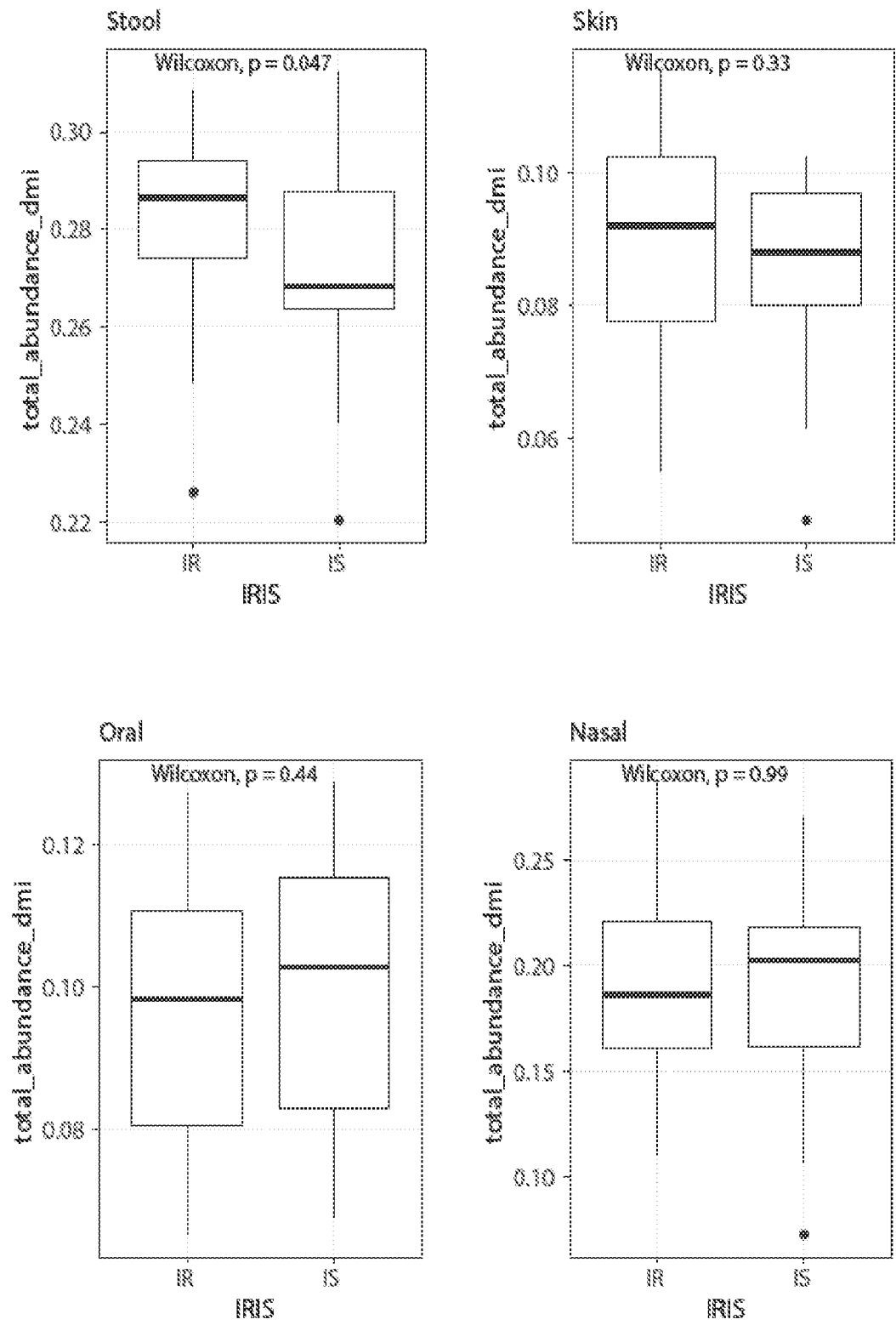


Fig. 10A

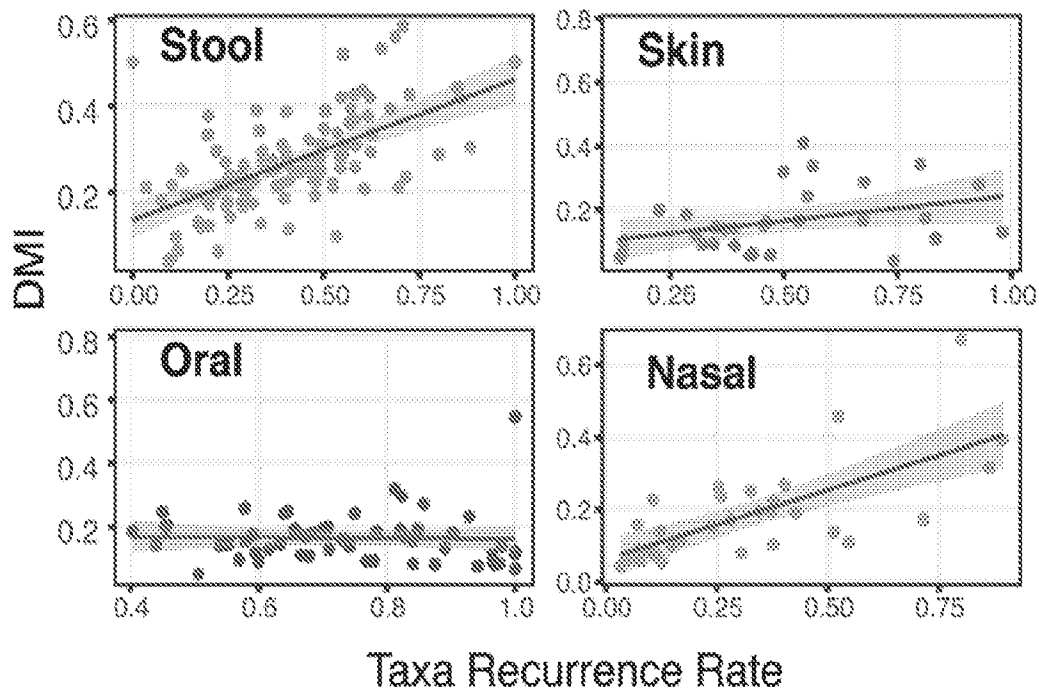


Fig. 10B

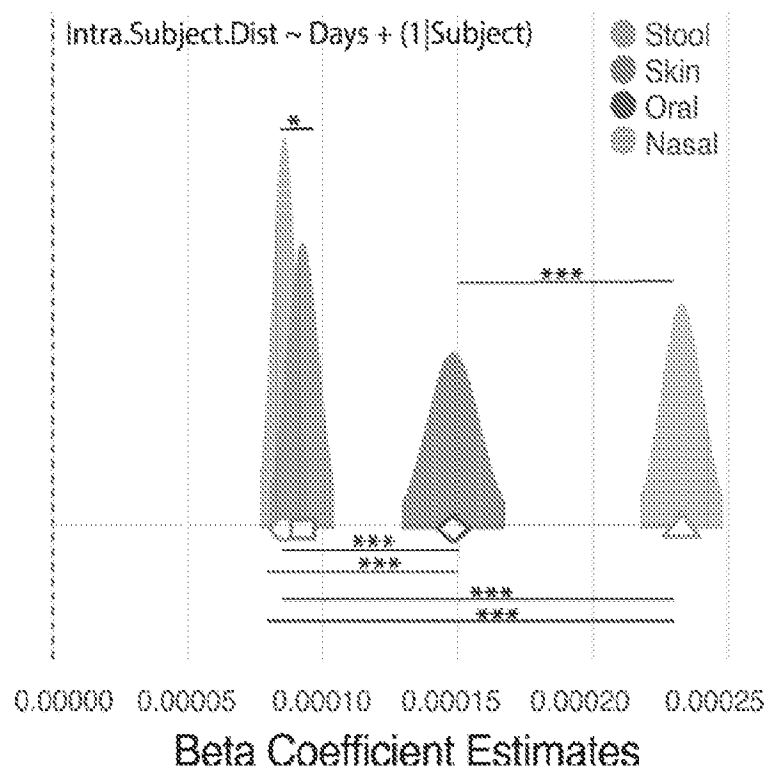


Fig. 10C

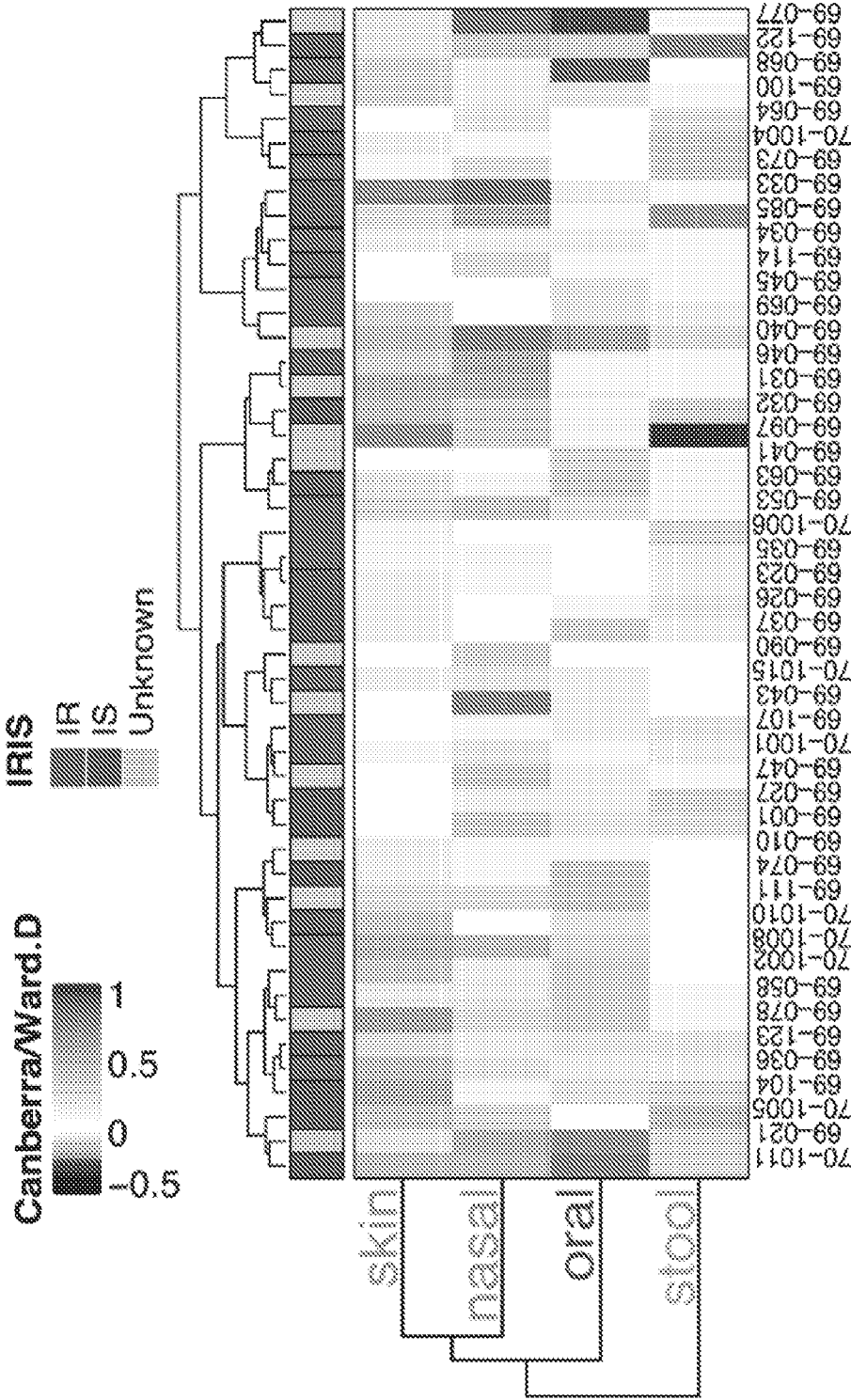


Fig. 10D

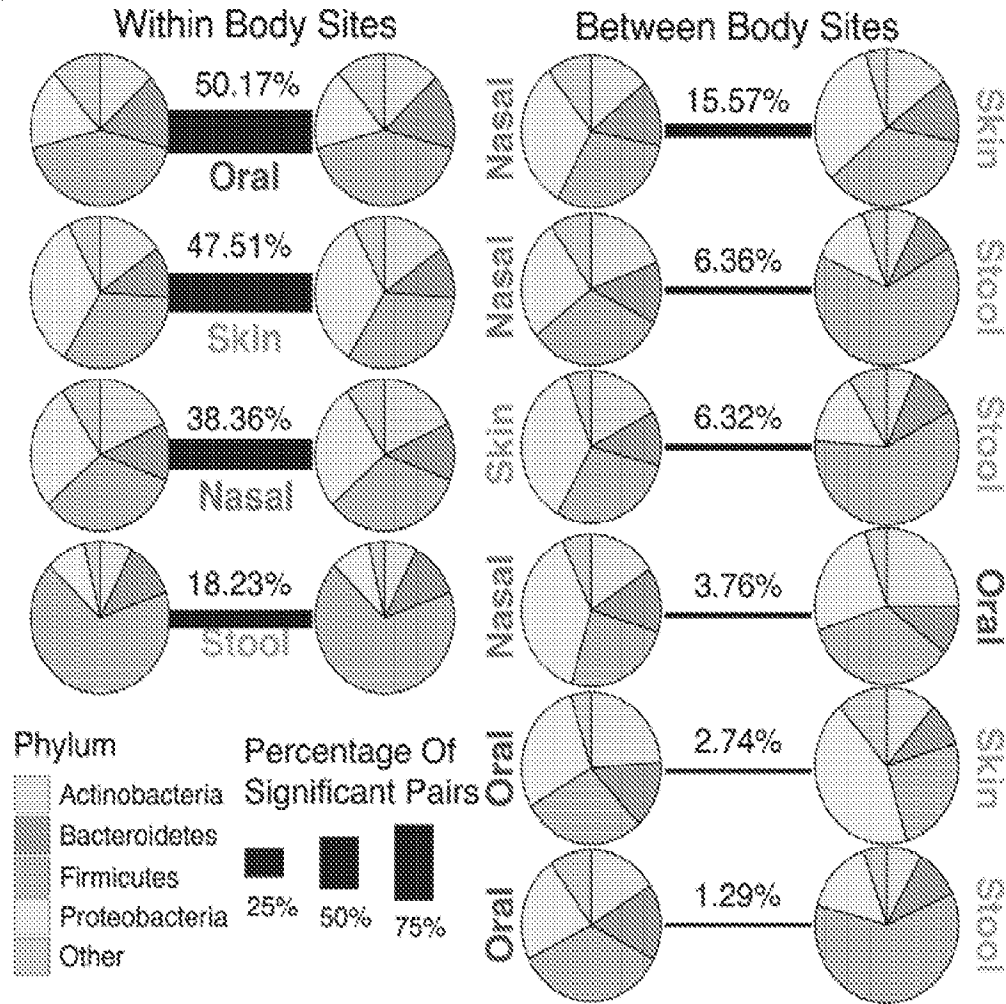


Fig. 10E

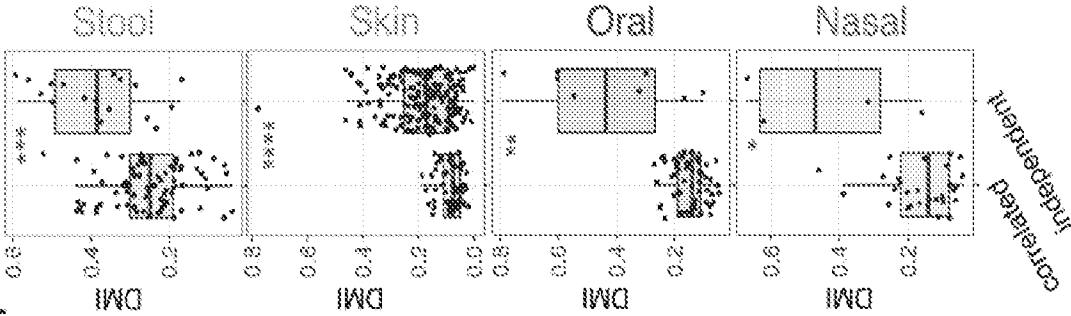


Fig. 10F

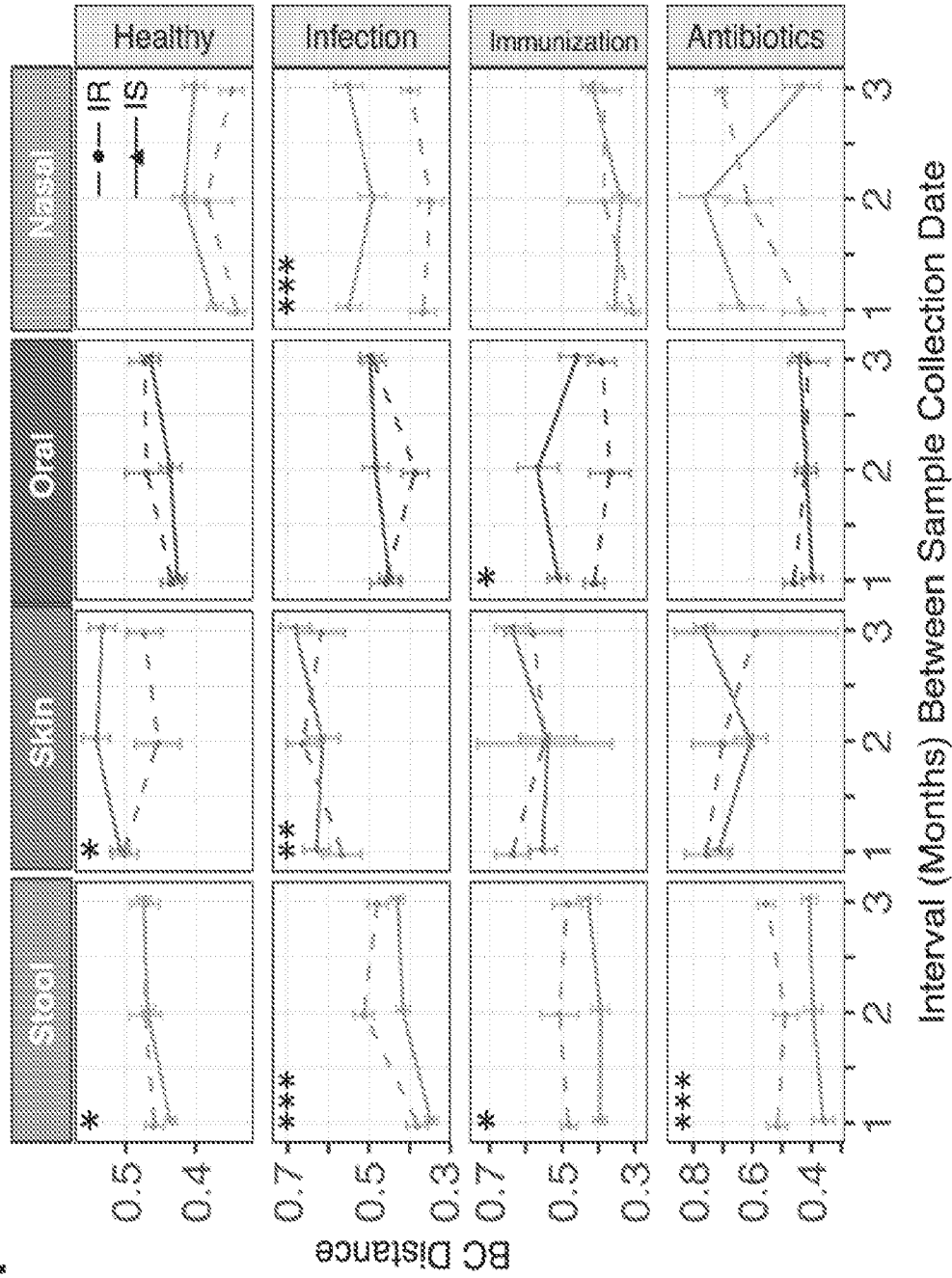


Fig. 11A

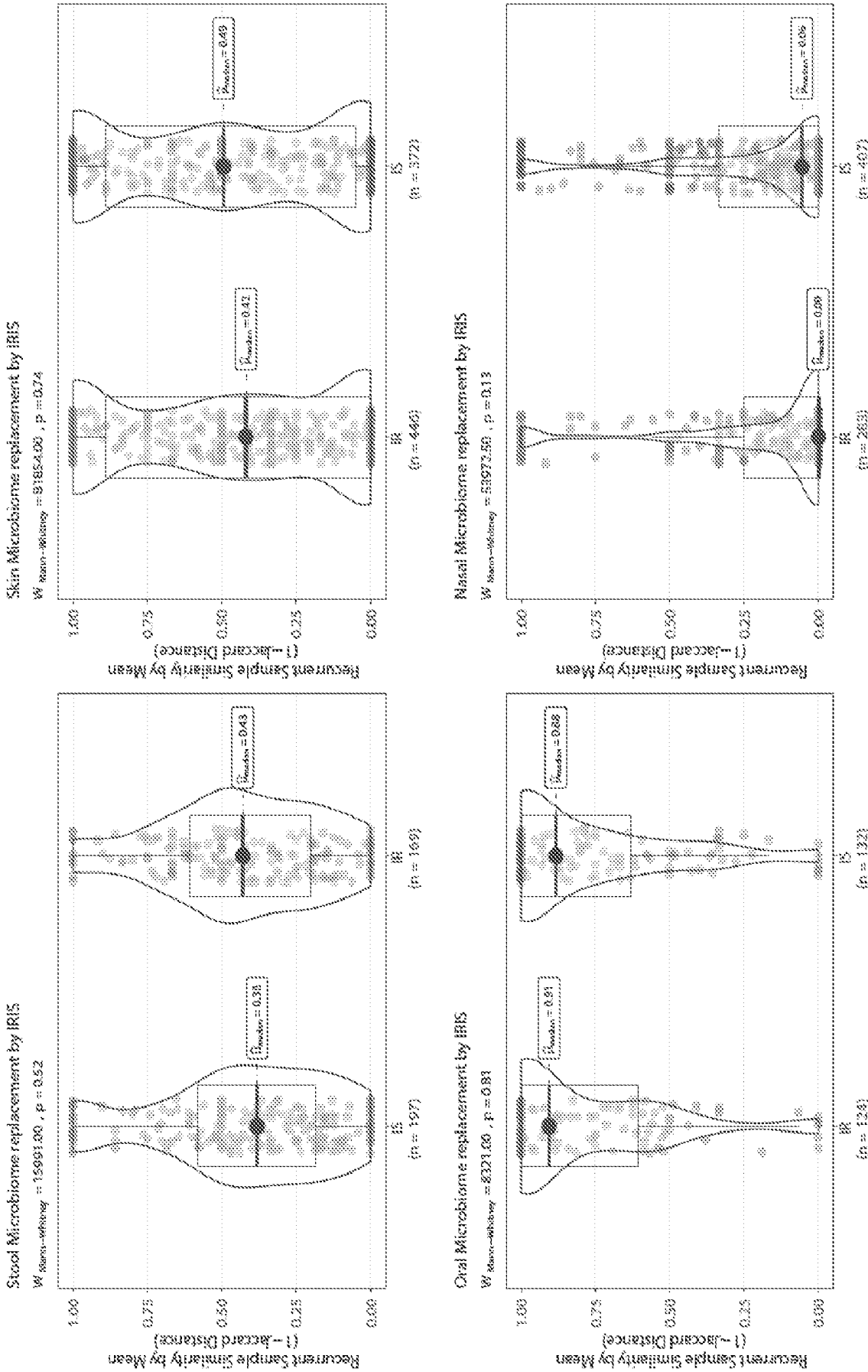


Fig. 11B (1/3)

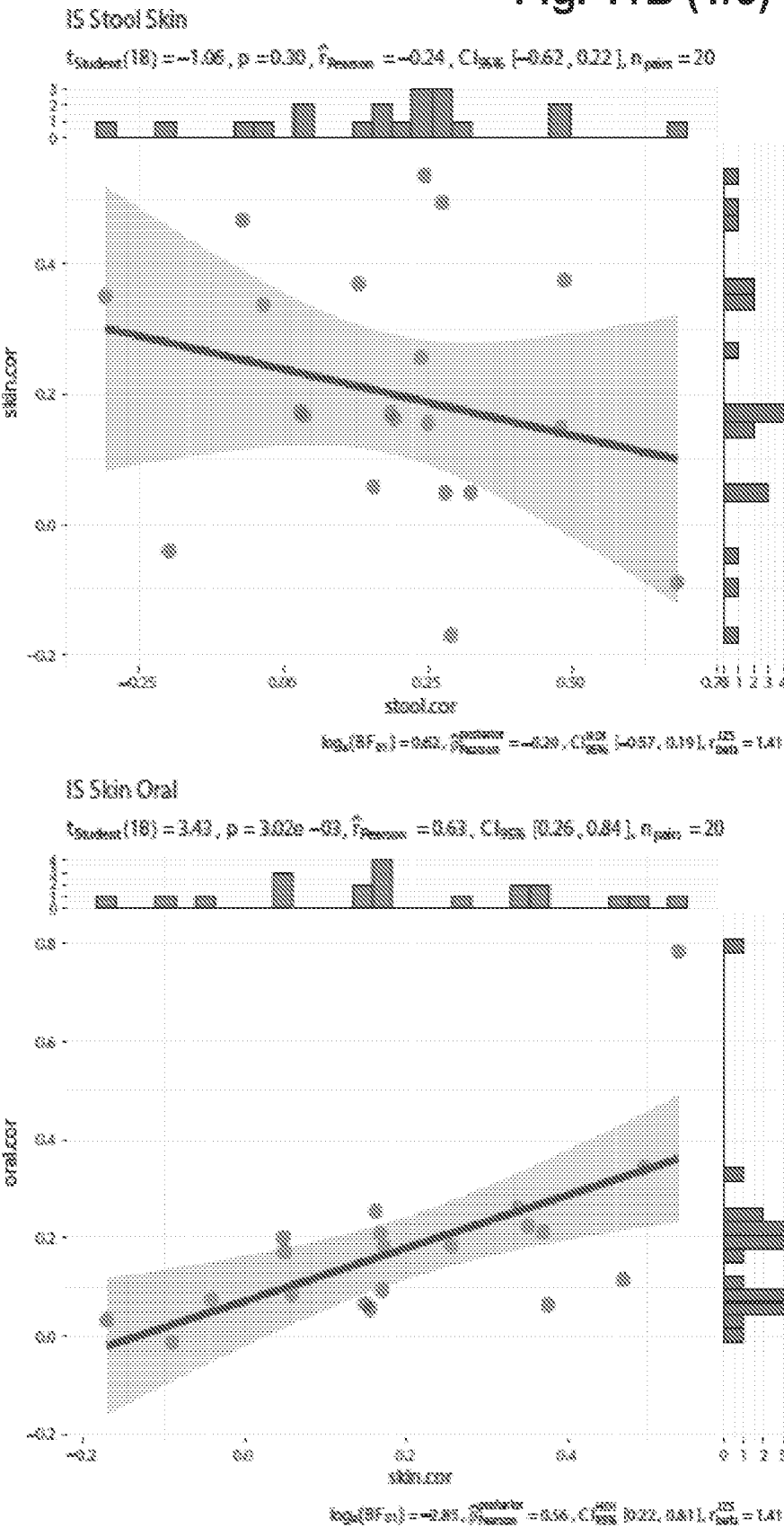
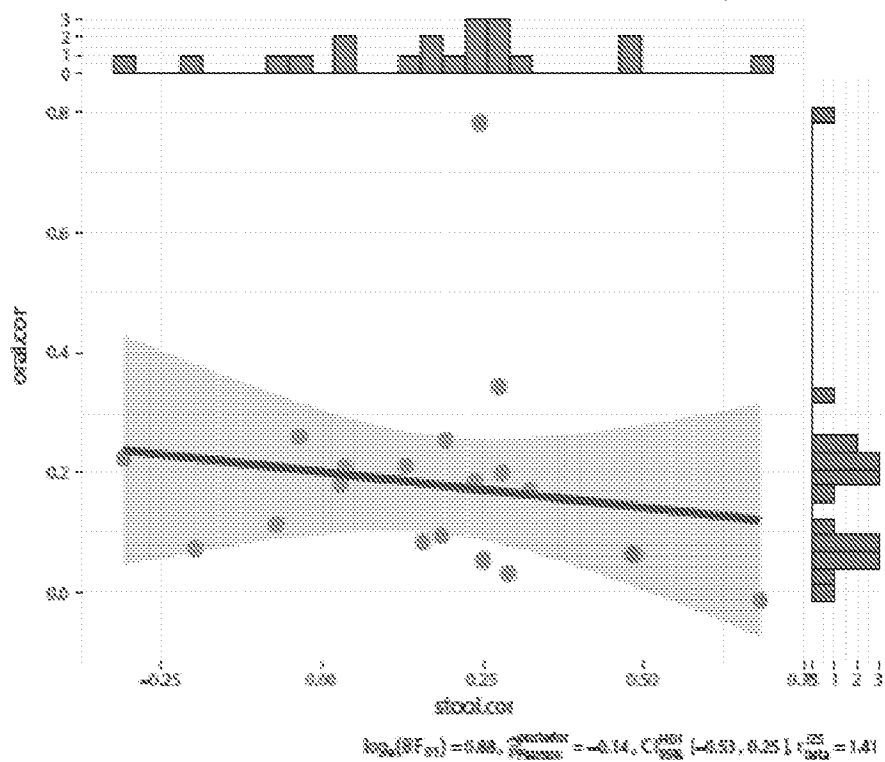


Fig. 11B (2/3)

IS Stool Oral

 $t_{\text{Student}}(18) = -0.76$, $p = 0.49$, $\hat{\rho}_{\text{Pearson}} = -0.16$, $CI_{95\%} [-0.57, 0.30]$, $n_{\text{pairs}} = 20$


IS Skin Nasal

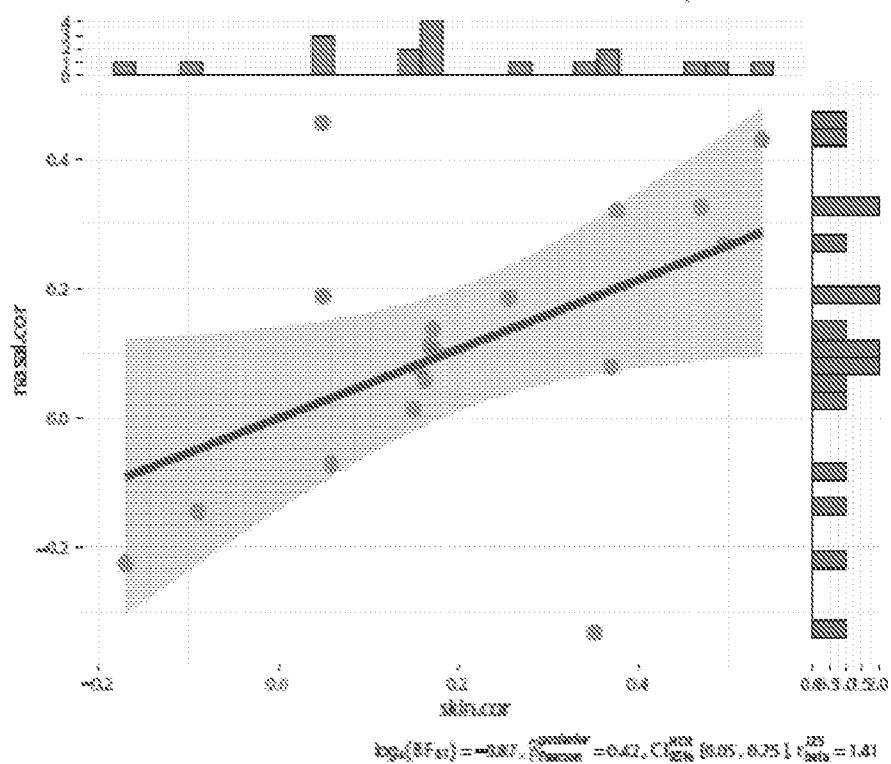
 $t_{\text{Student}}(16) = 2.26$, $p = 0.04$, $\hat{\rho}_{\text{Pearson}} = 0.49$, $CI_{95\%} [0.03, 0.78]$, $n_{\text{pairs}} = 18$


Fig. 11B (3/3)

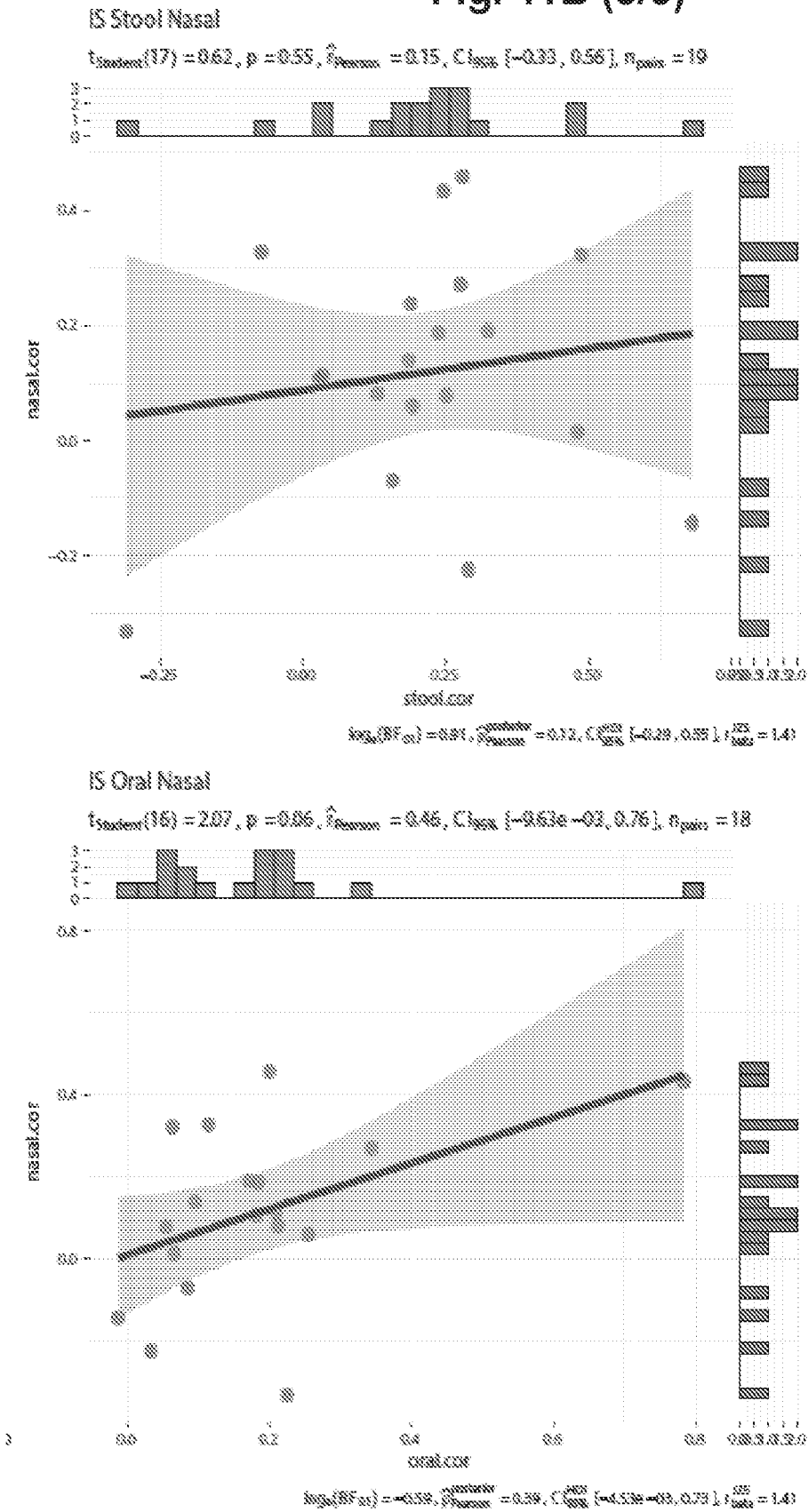


Fig. 11C (1/3)

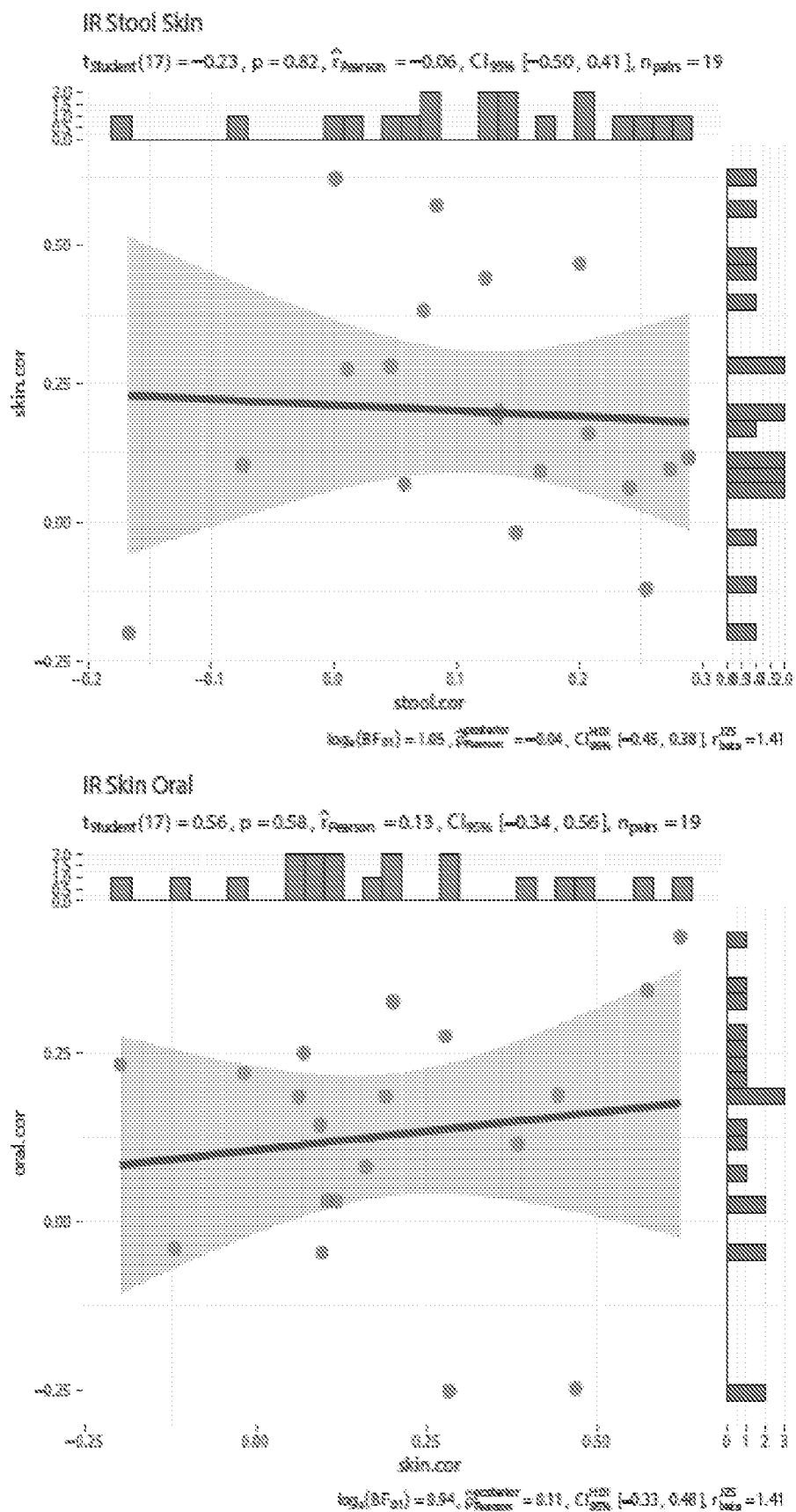


Fig. 11C (2/3)

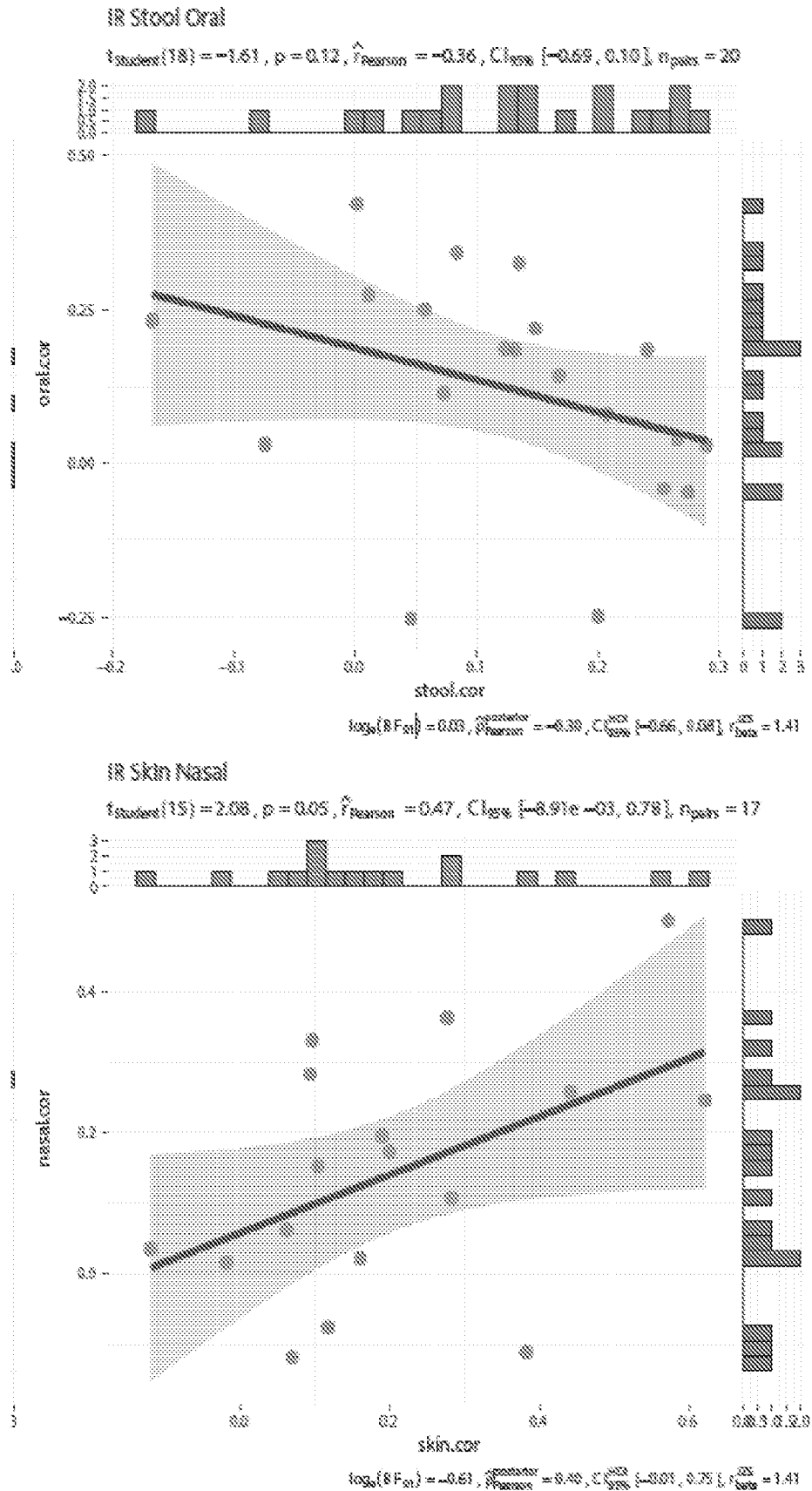


Fig. 11C (3/3)

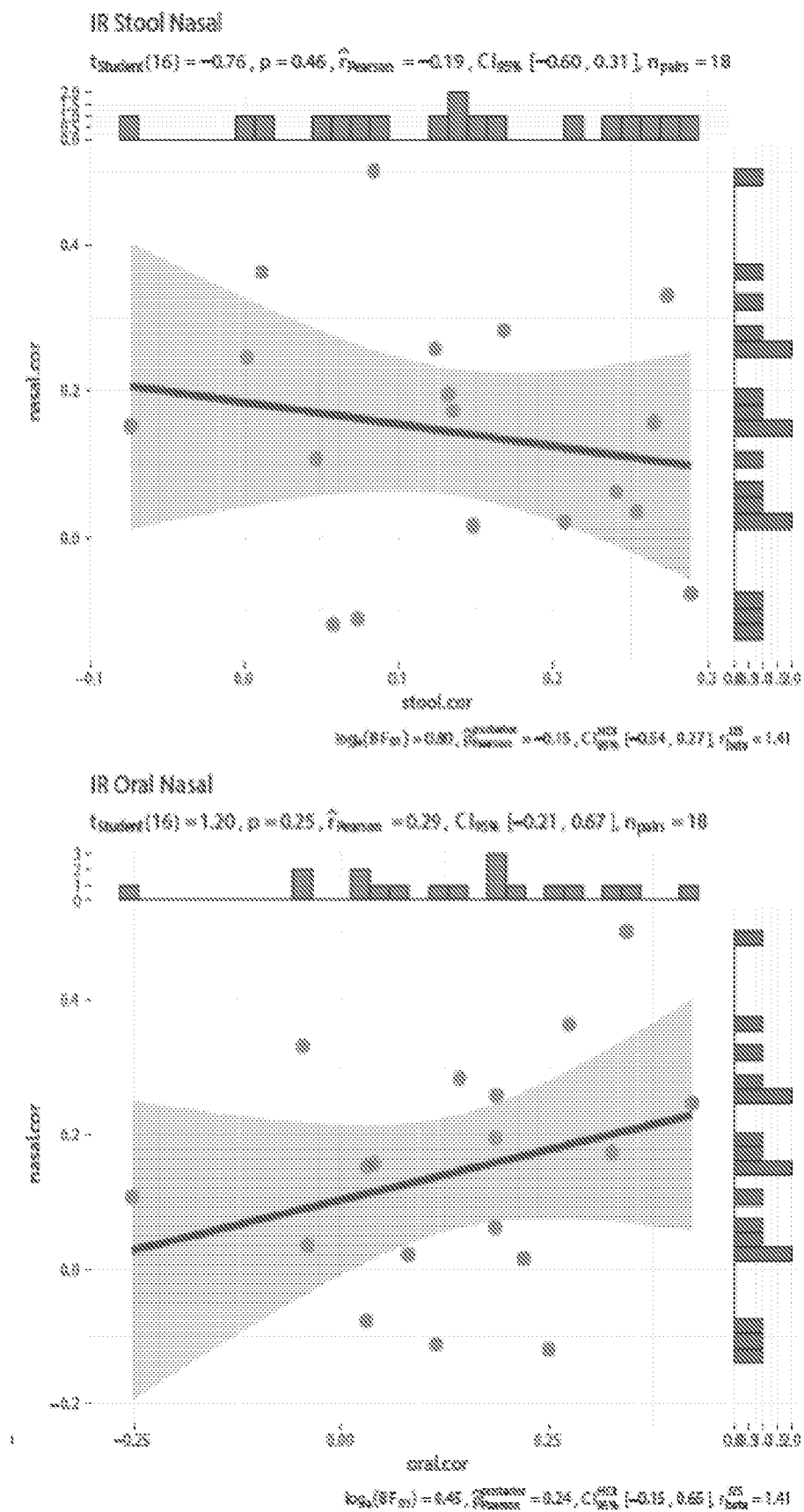


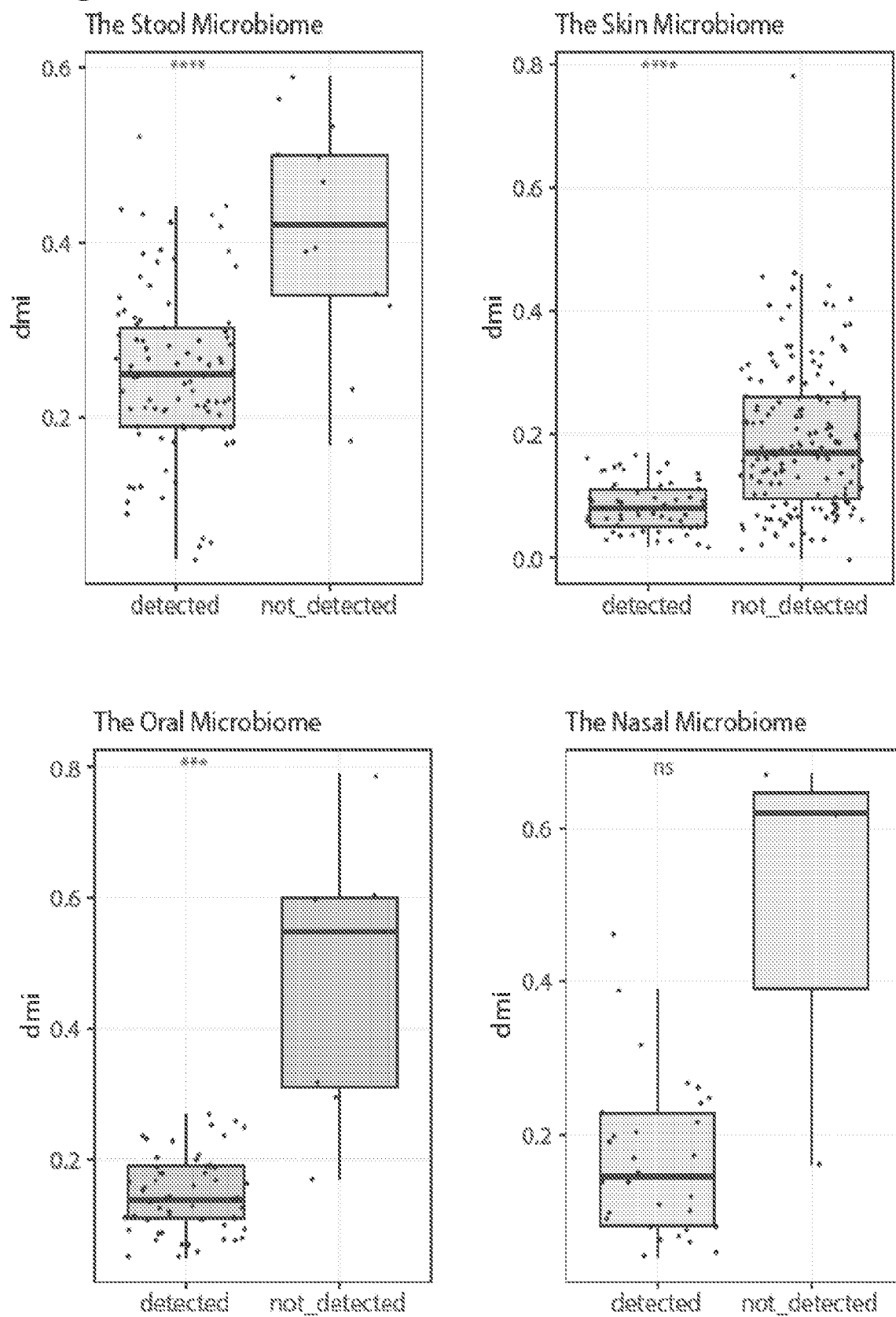
Fig. 11D

Fig. 11E

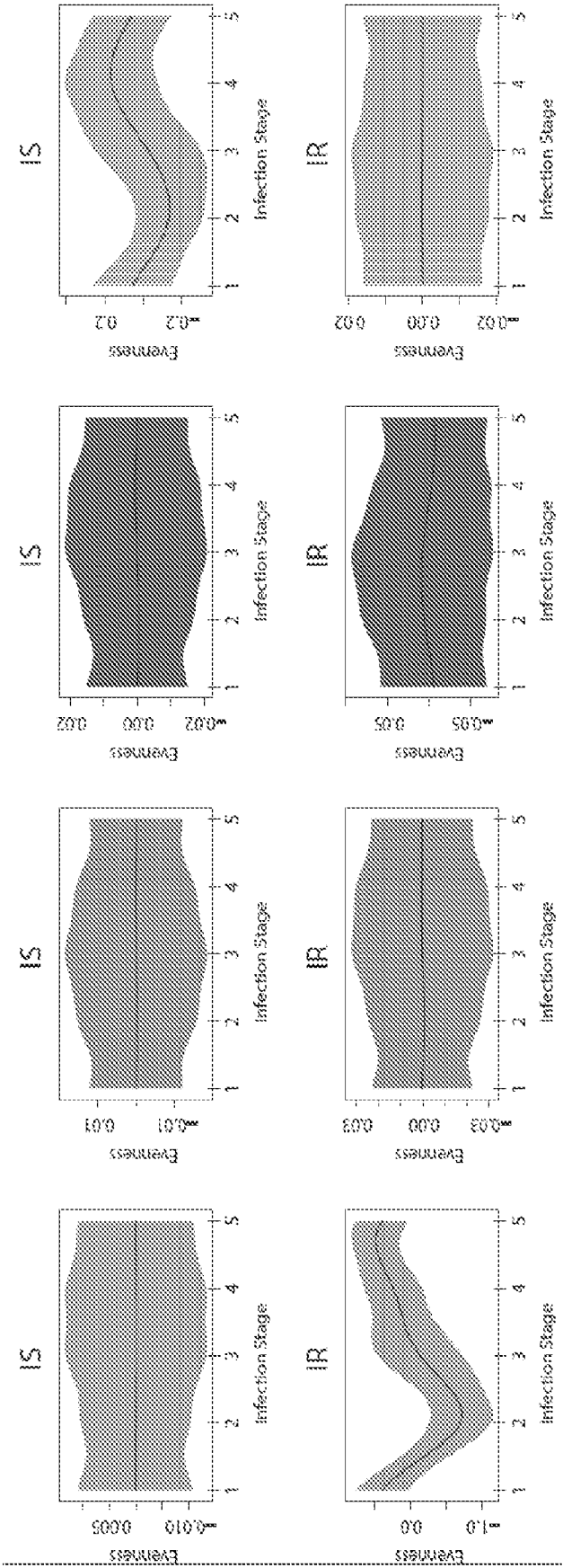


Fig. 11F

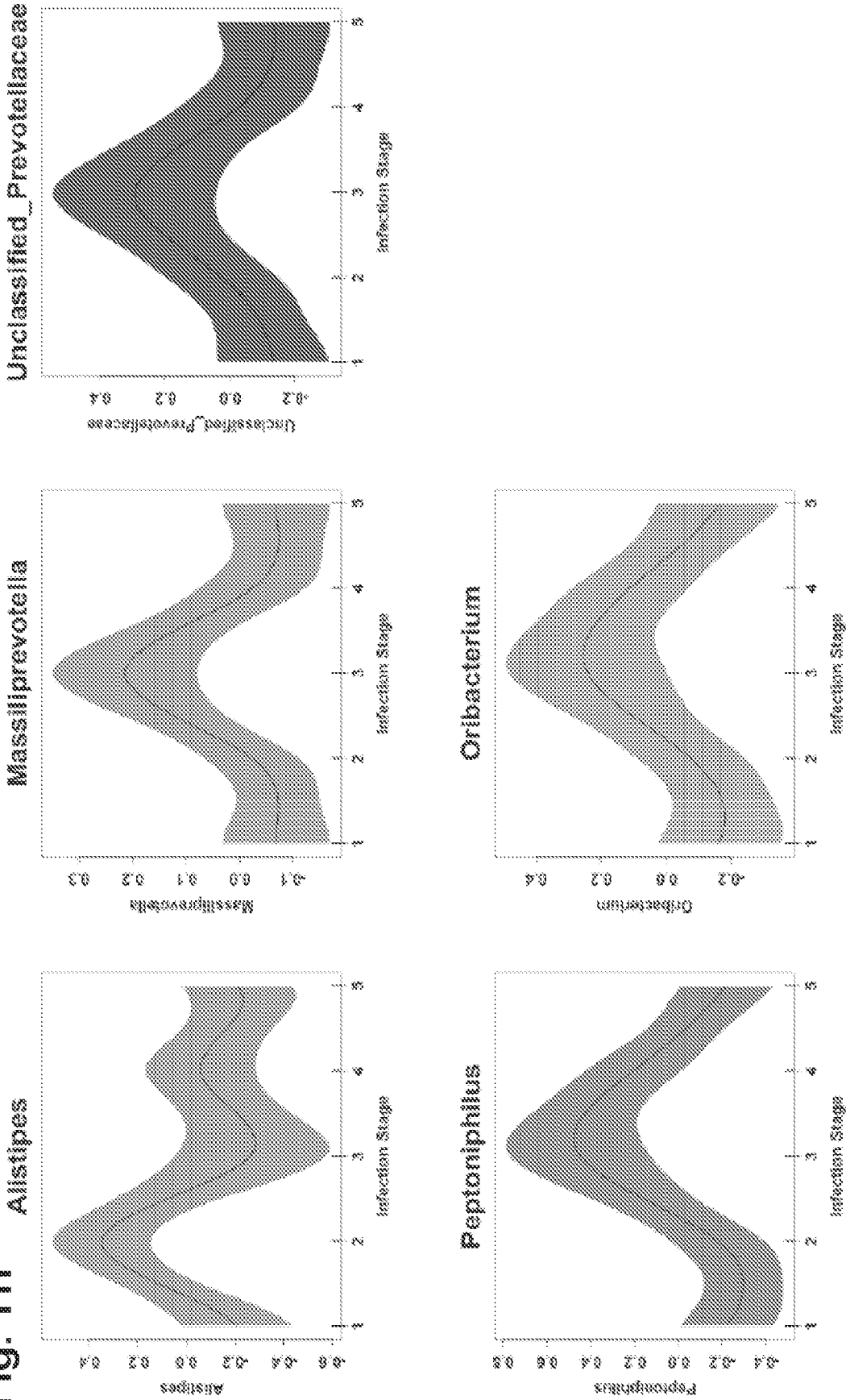


Fig. 11G

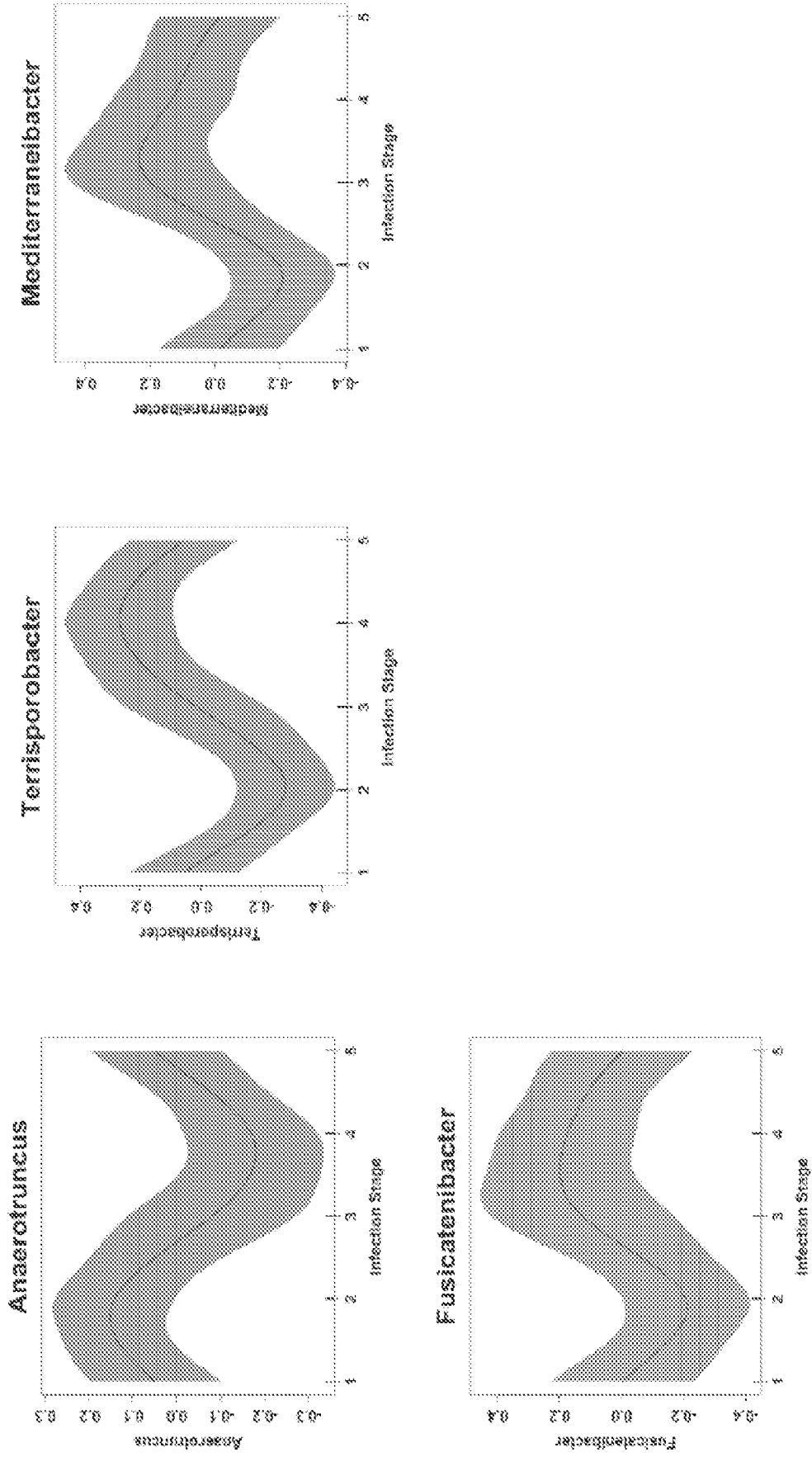


Fig. 11H

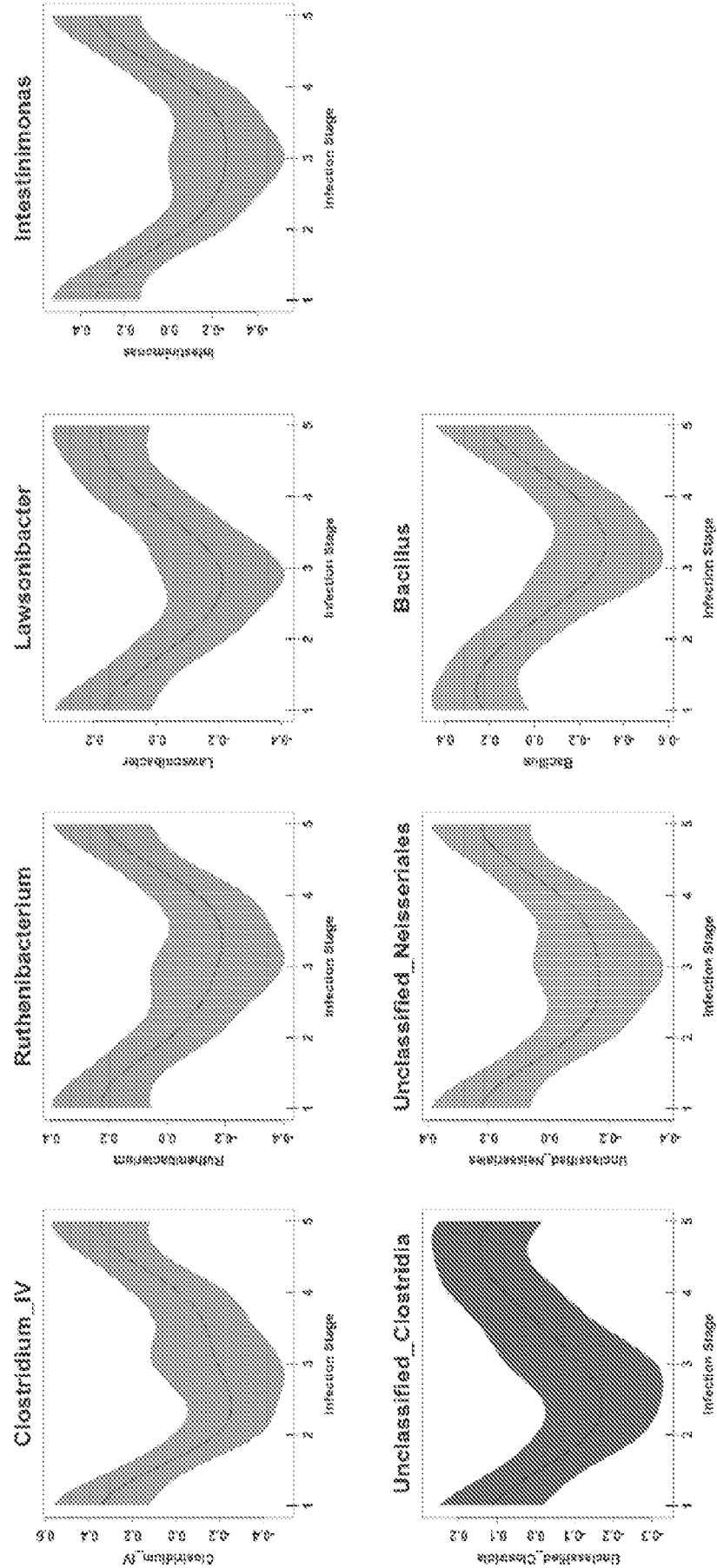


Fig. 12A

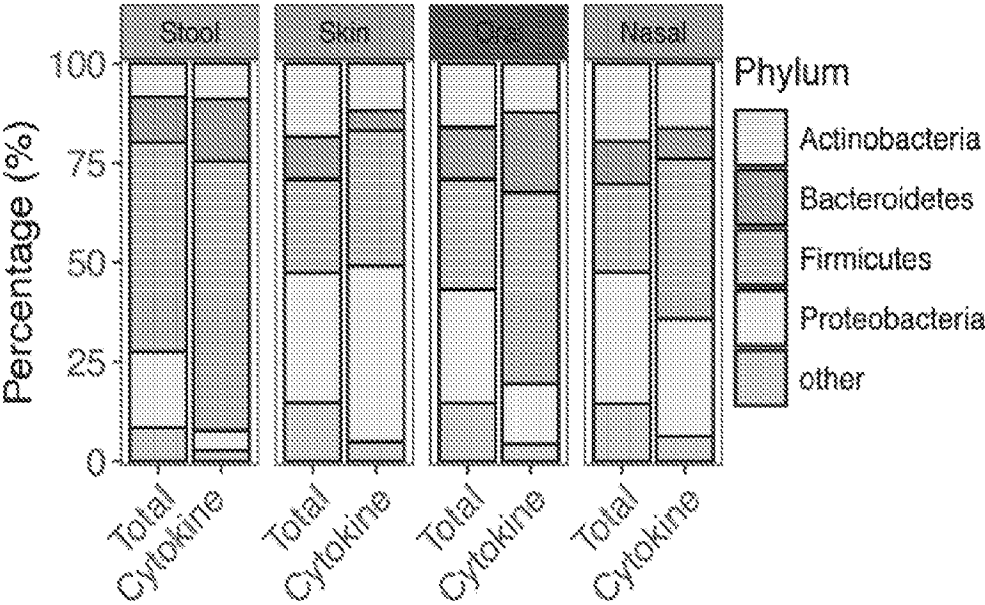


Fig. 12B

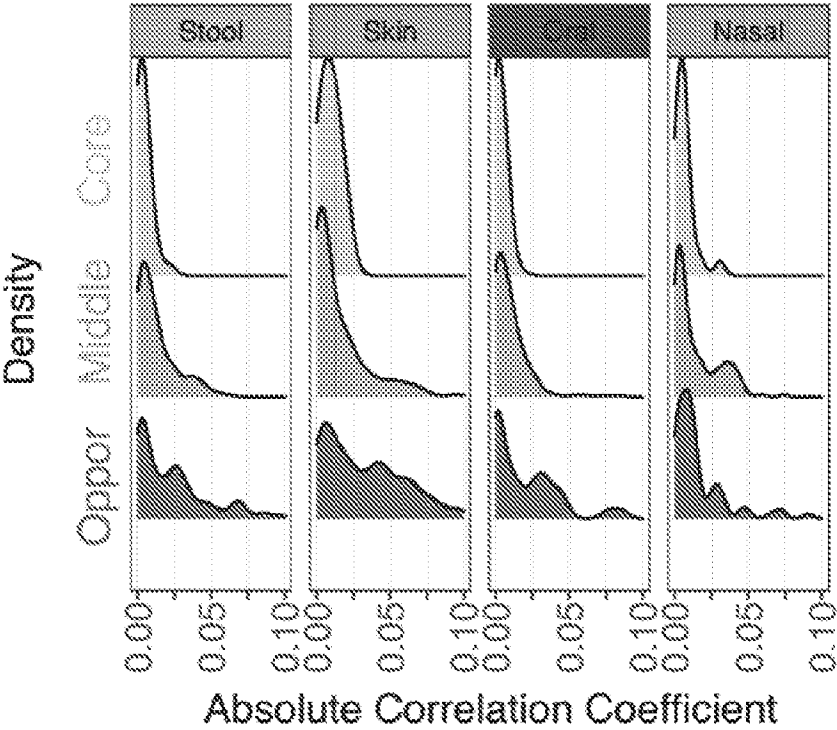
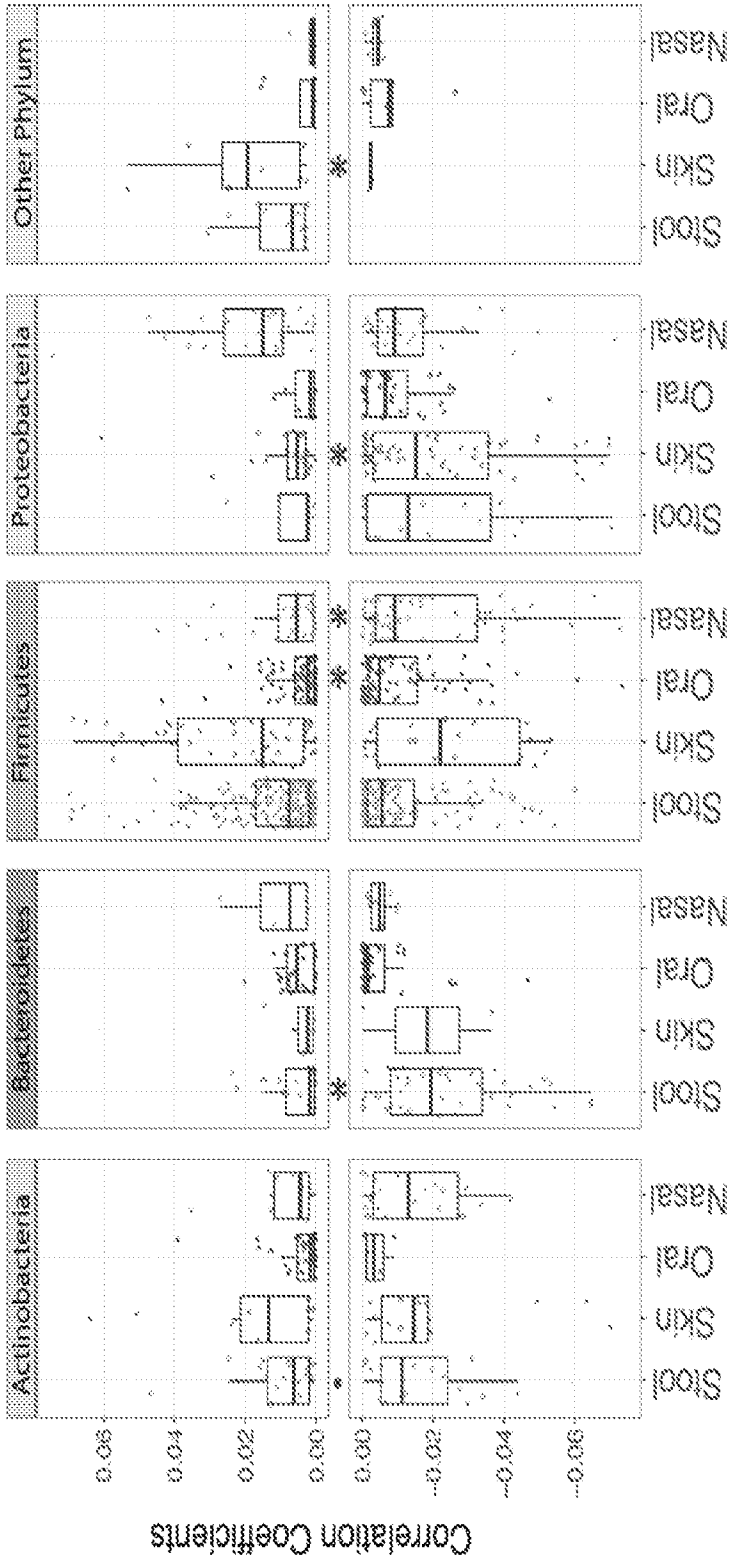


Fig. 12C



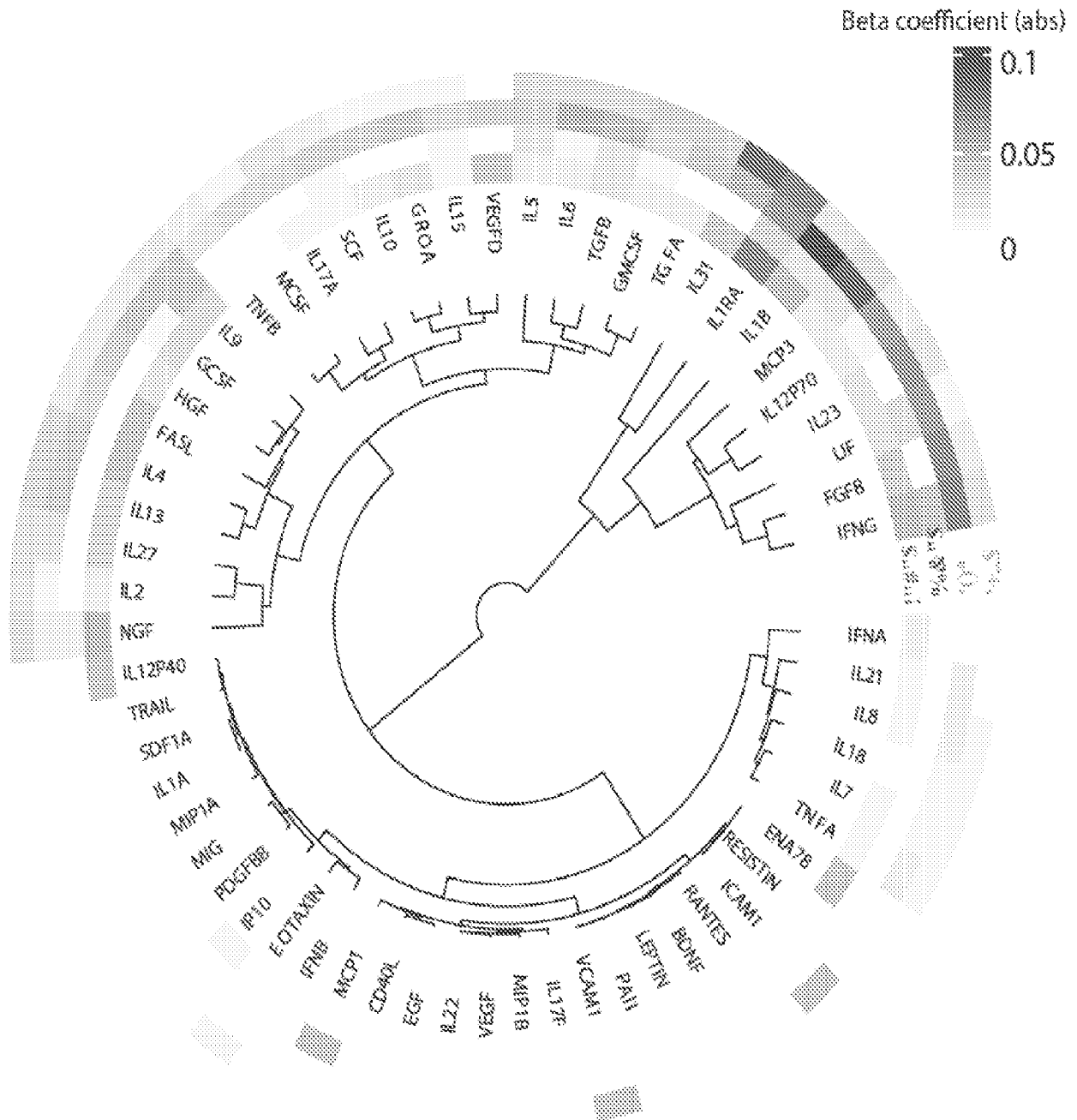


Fig. 13B

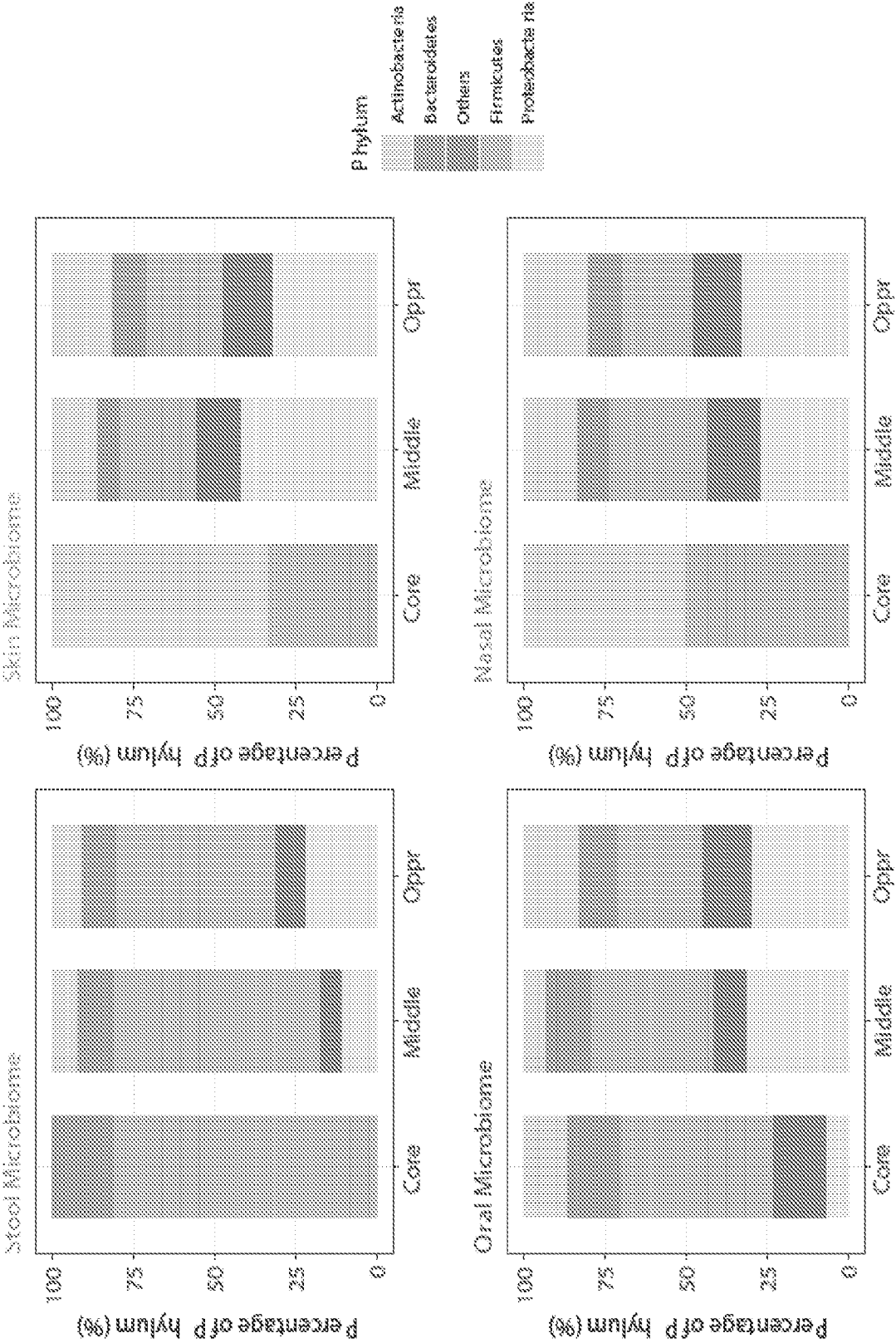


Fig. 13C

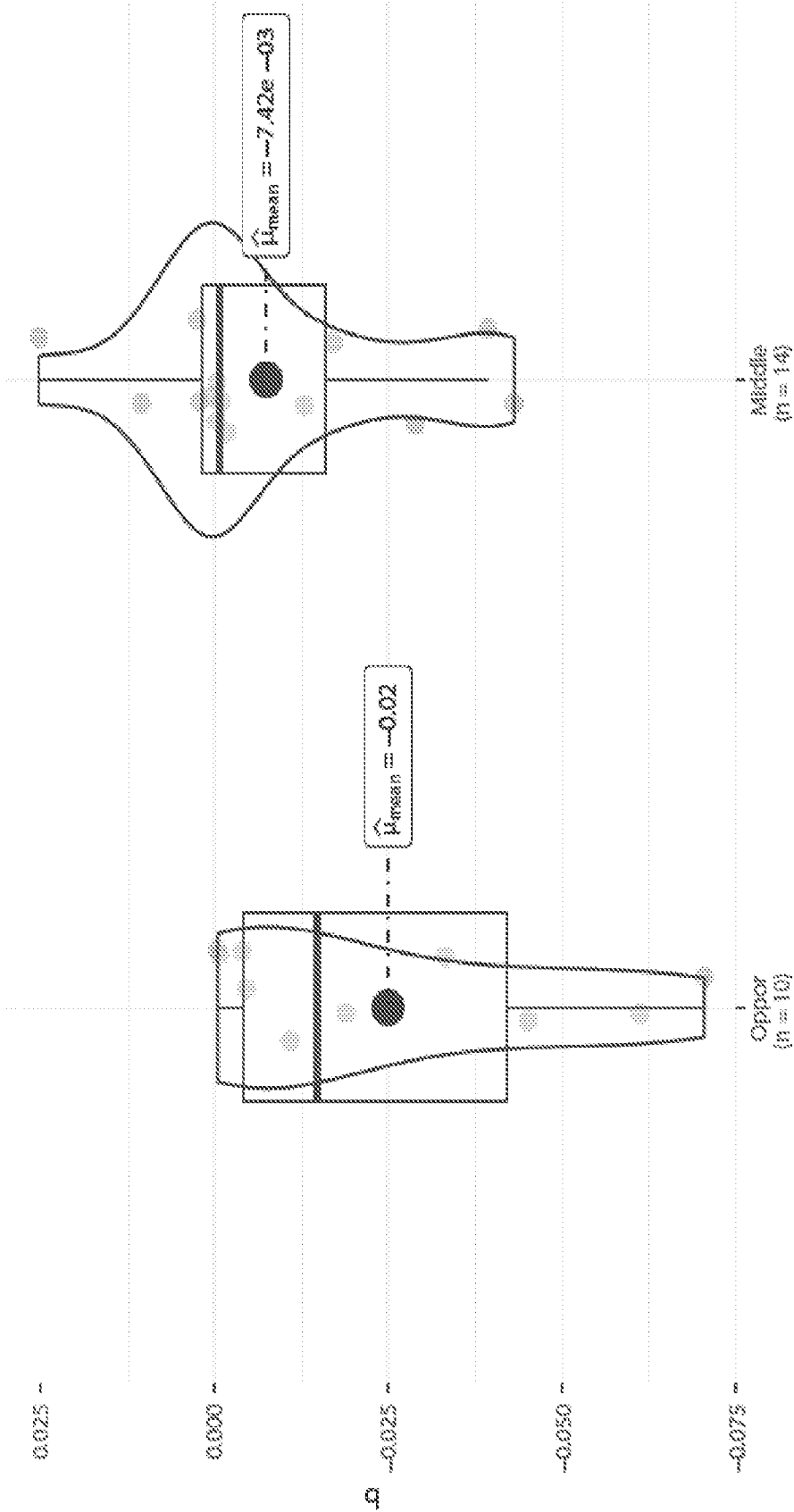


Fig. 13D (1/2)

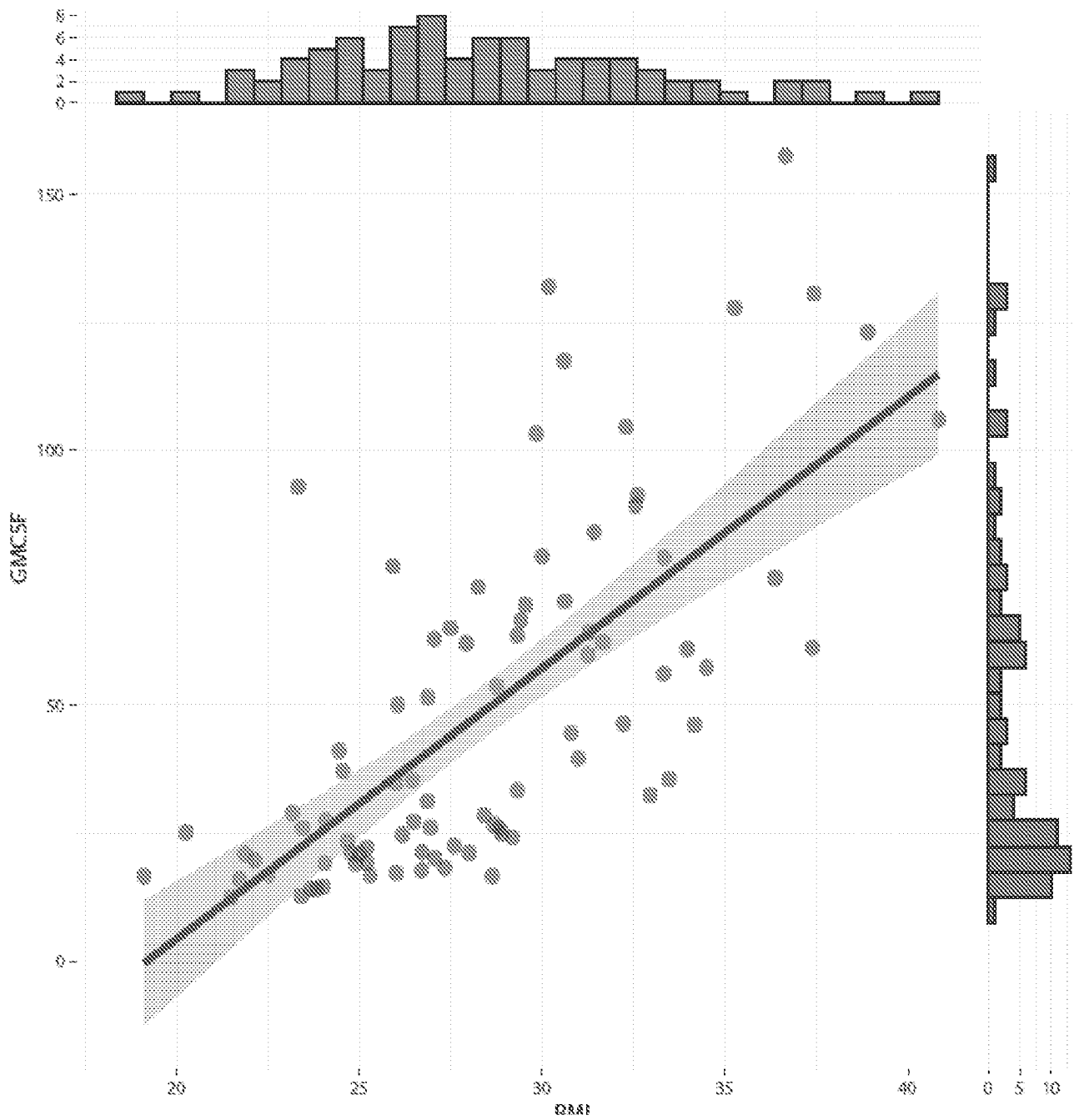


Fig. 13D (2/2)

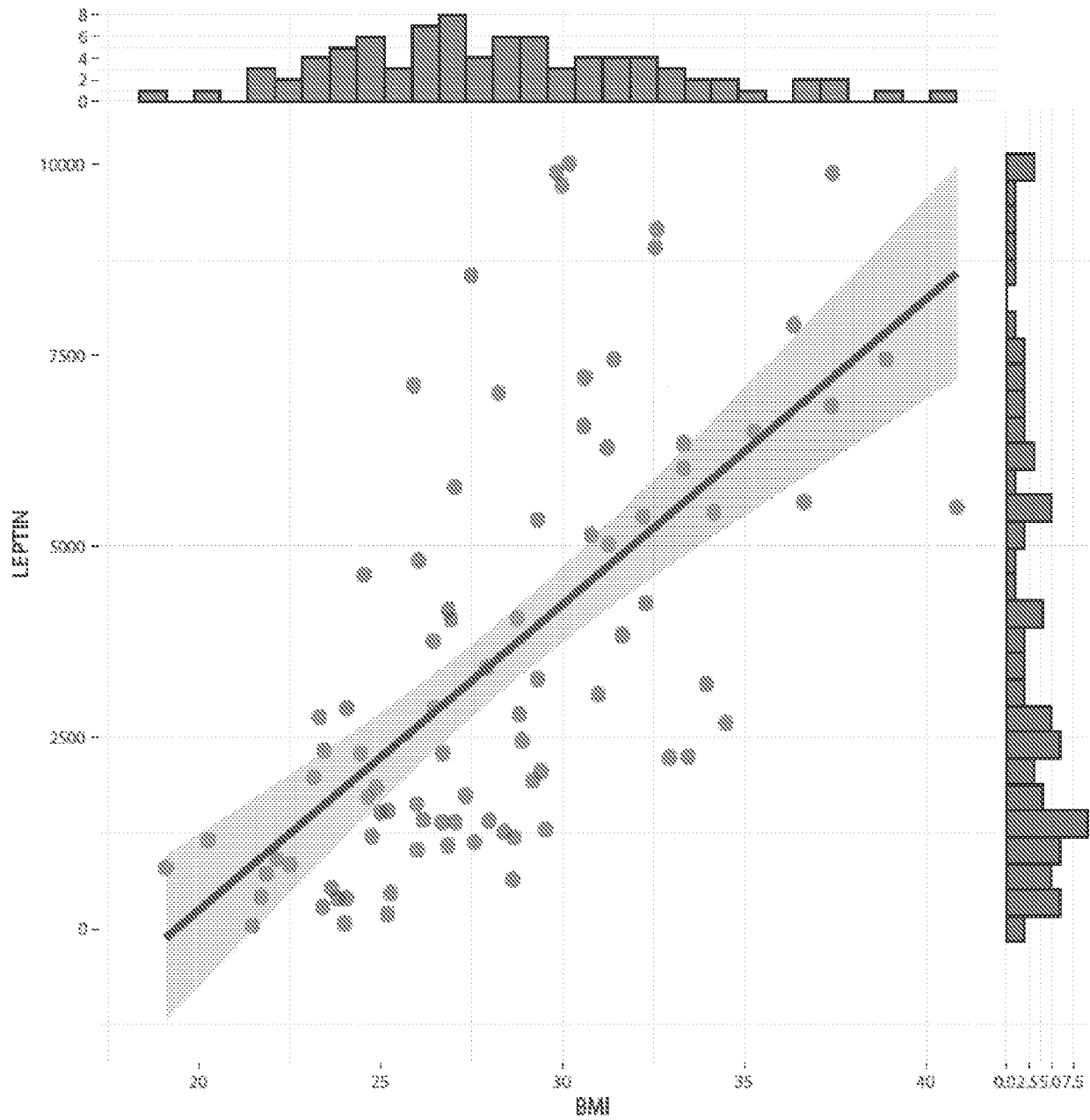
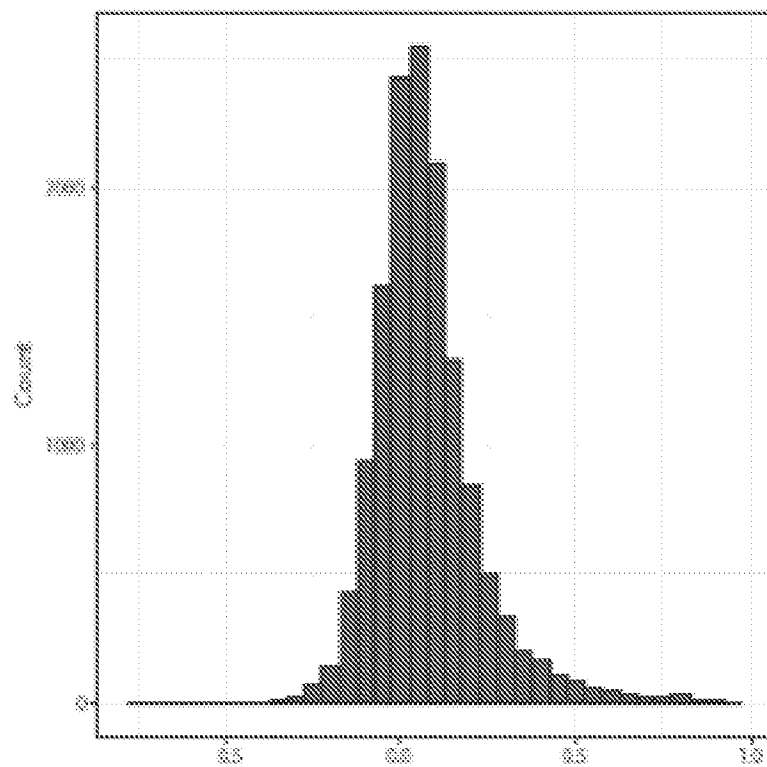


Fig. 14A (1/2)

Metabolome



Lipidome

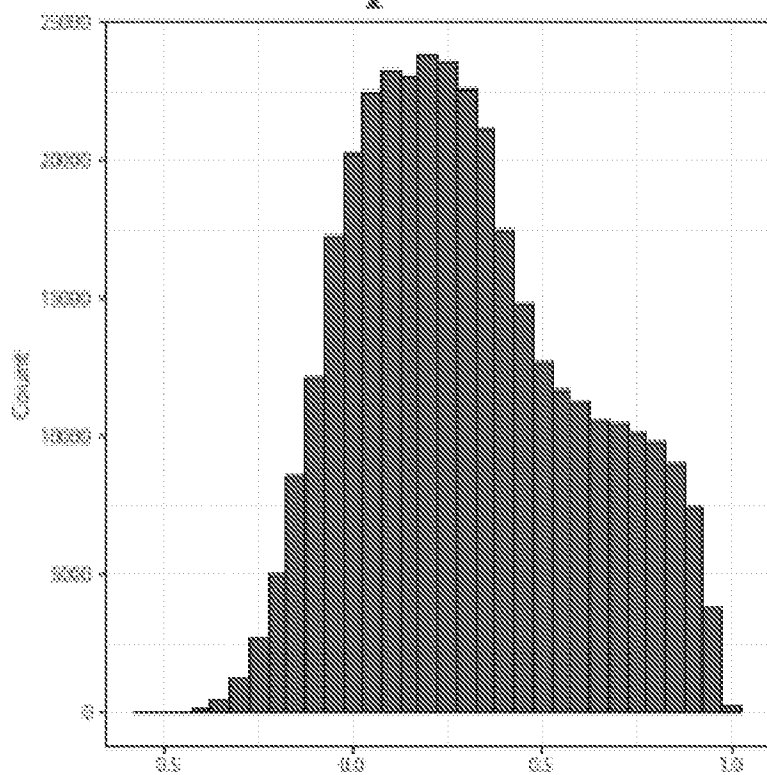


Fig. 14A (2/2)

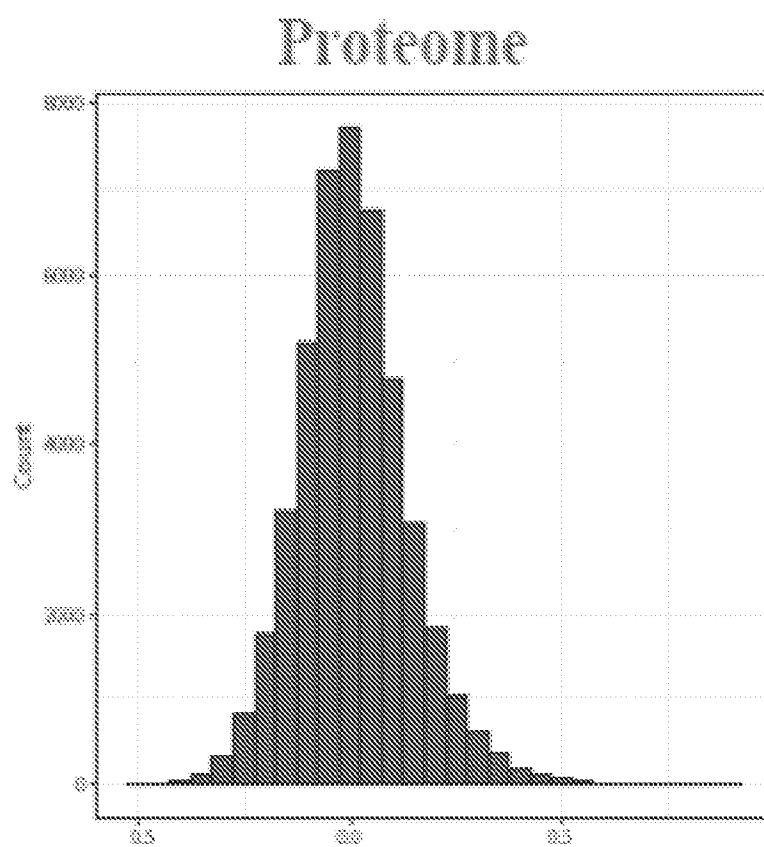


Fig. 14B

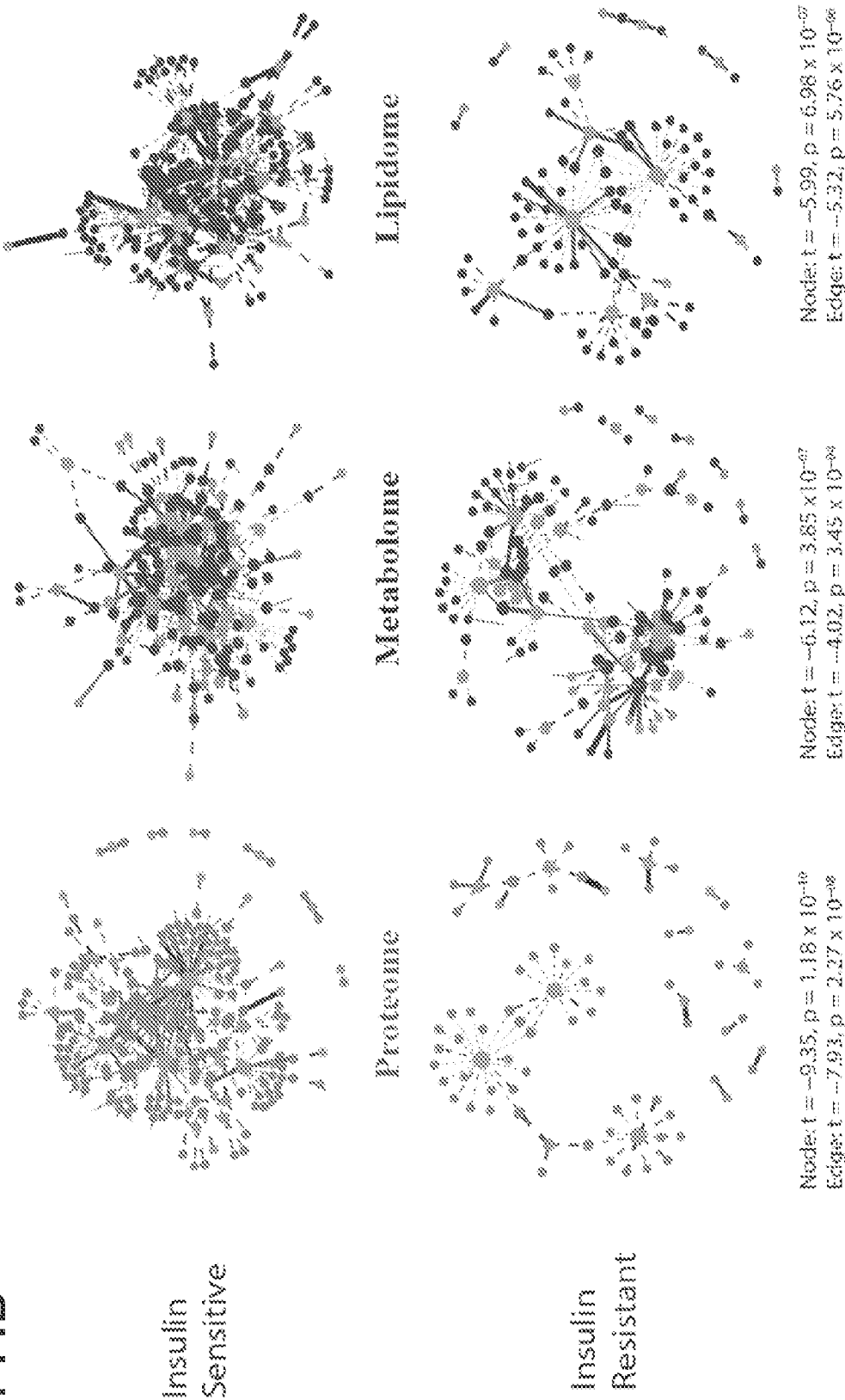


Fig. 15A

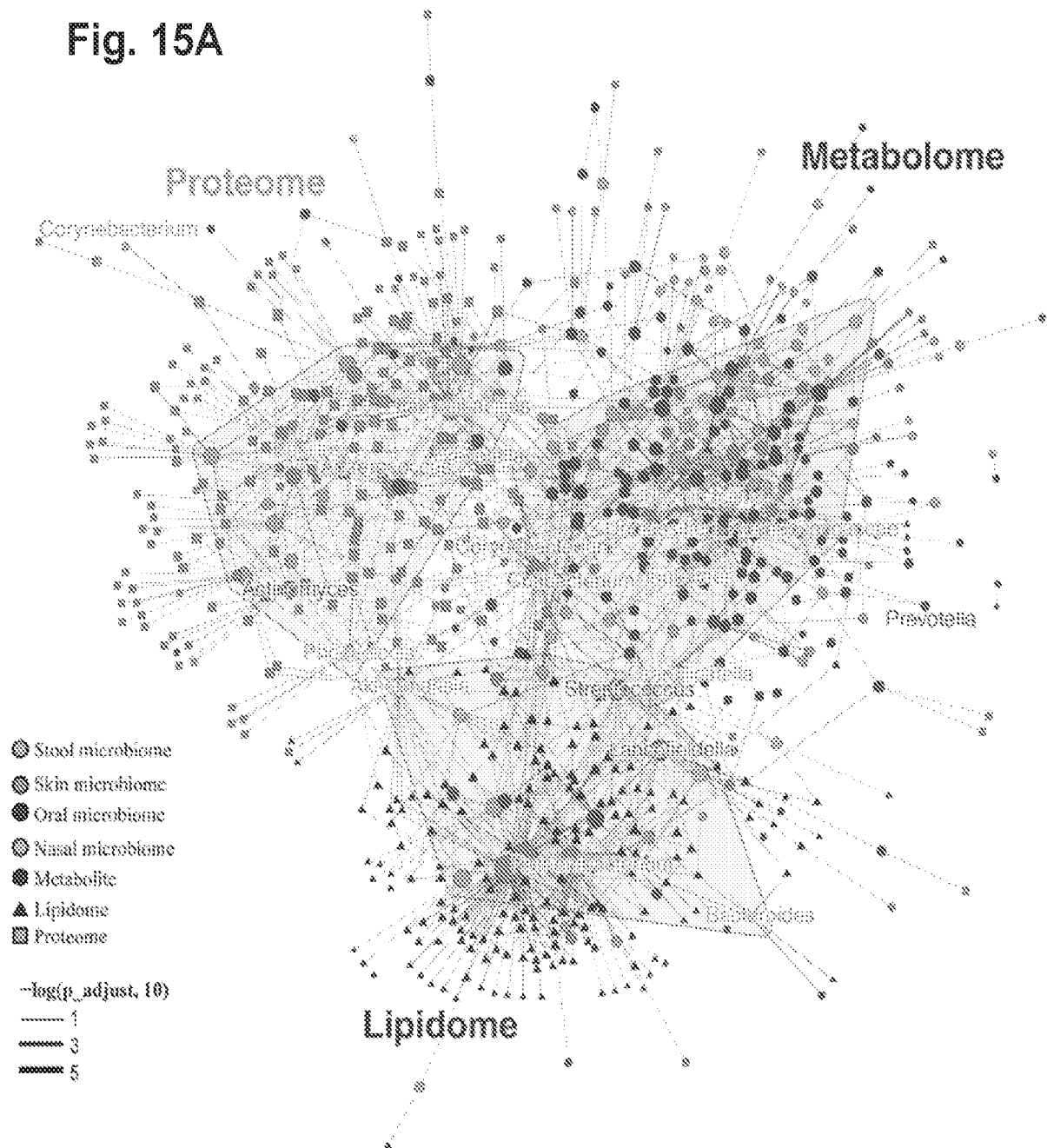


Fig. 15B

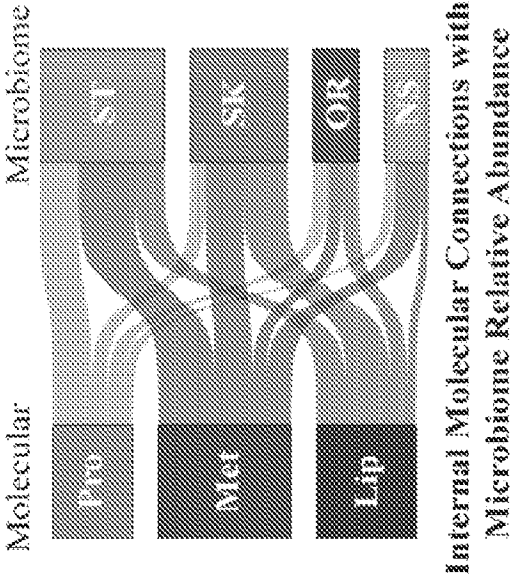


Fig. 15C

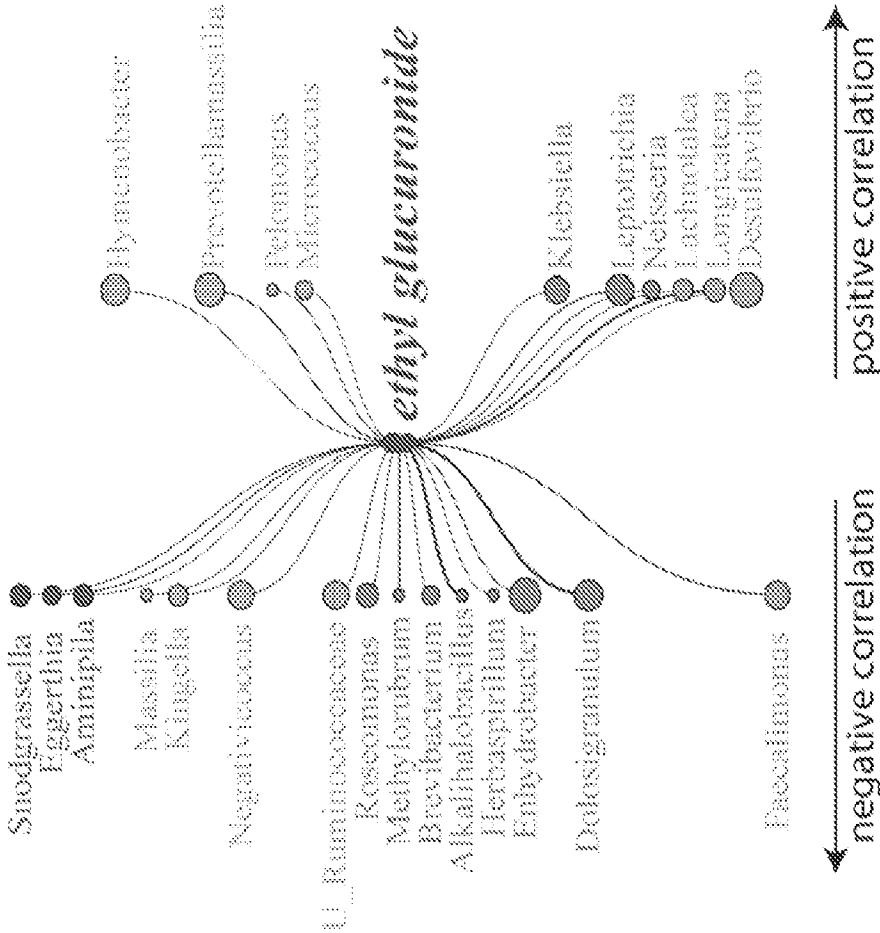


Fig. 15D

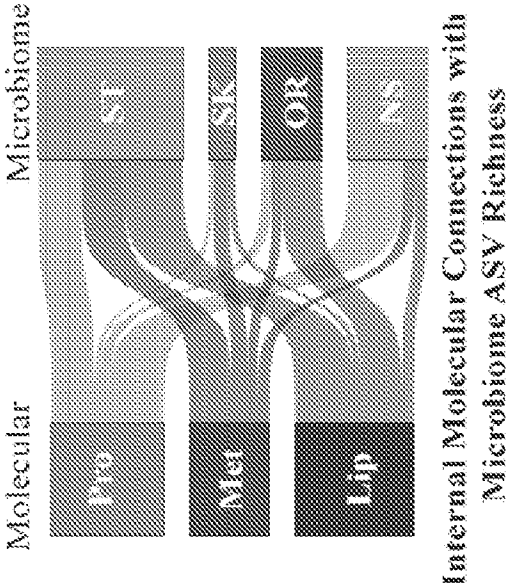


Fig. 15E

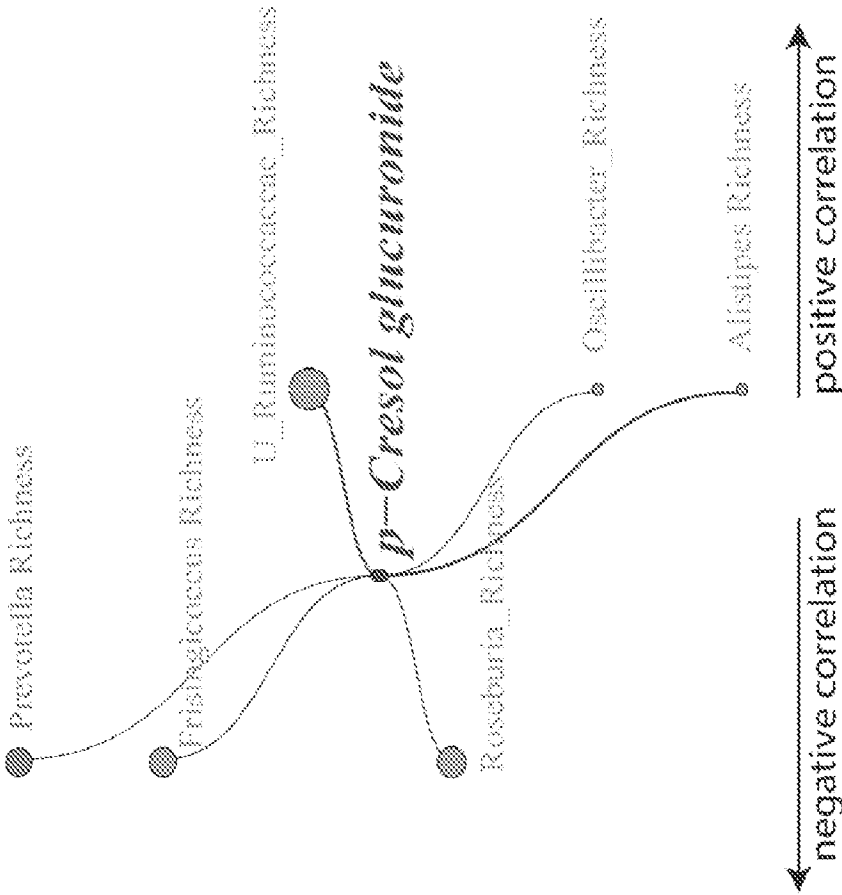


Fig. 16 (1/2)

Microbial correlation

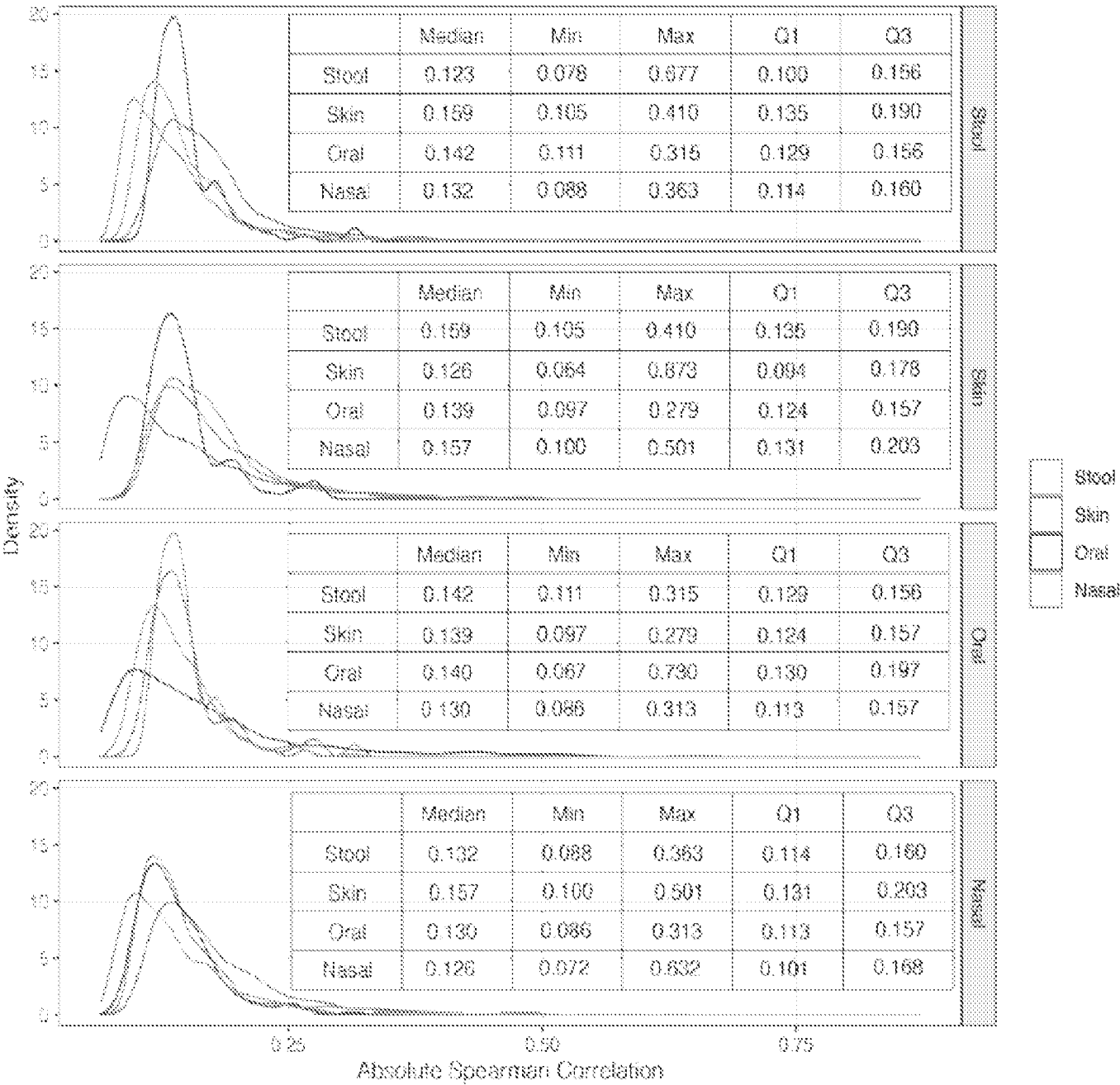


Fig. 16 (2/2)

Microbial-host correlation

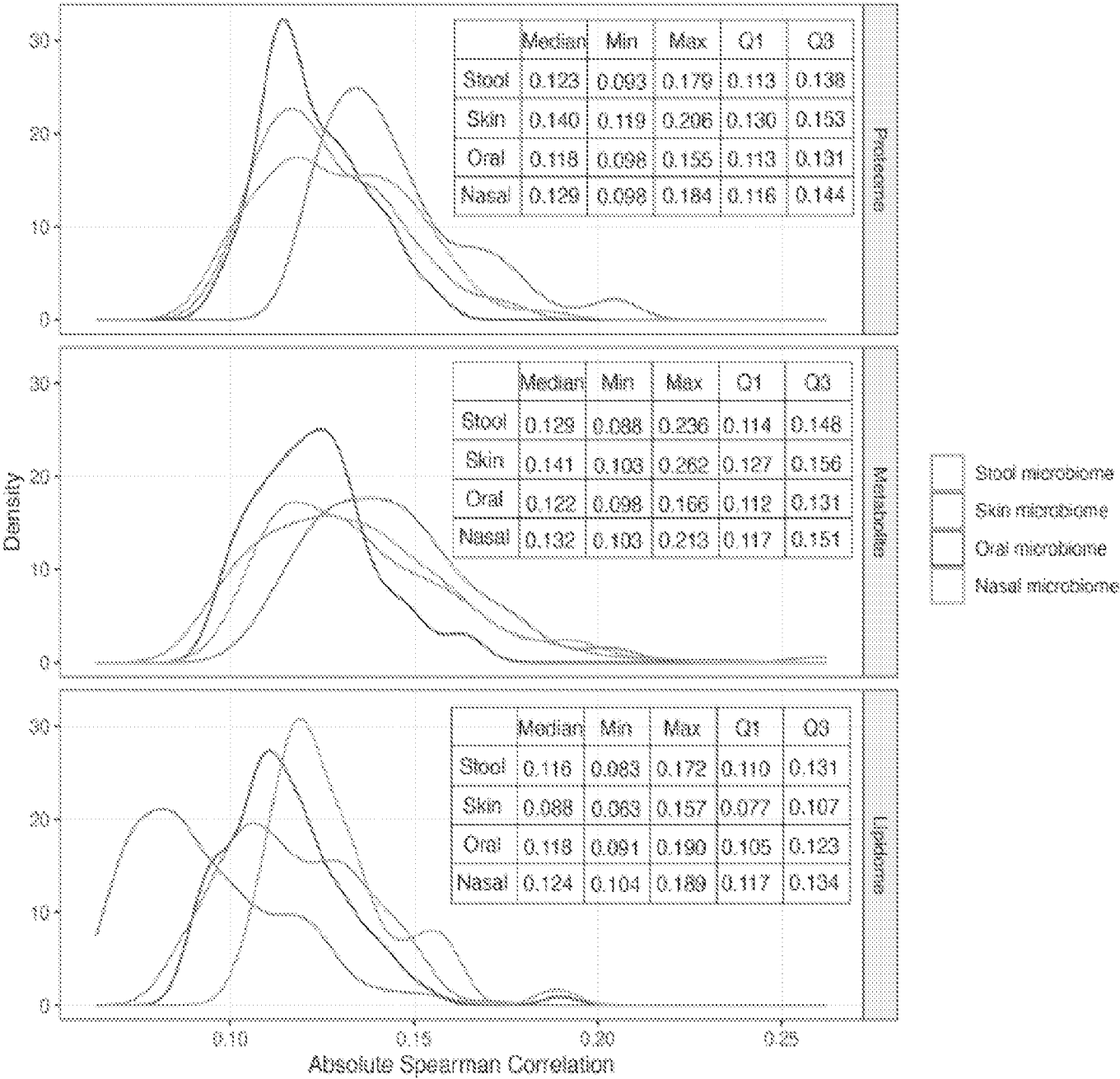


Fig. 17A

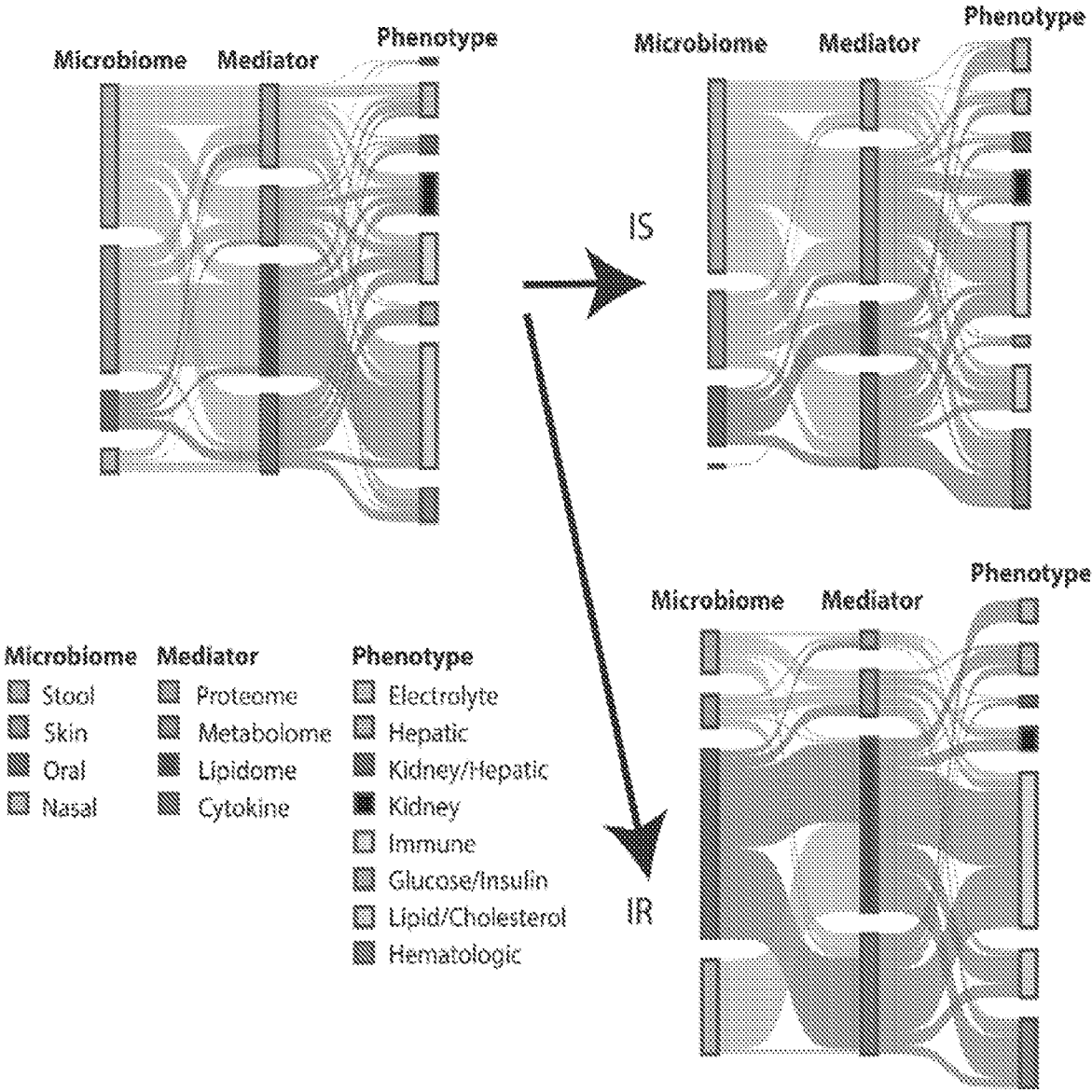


Fig. 17B

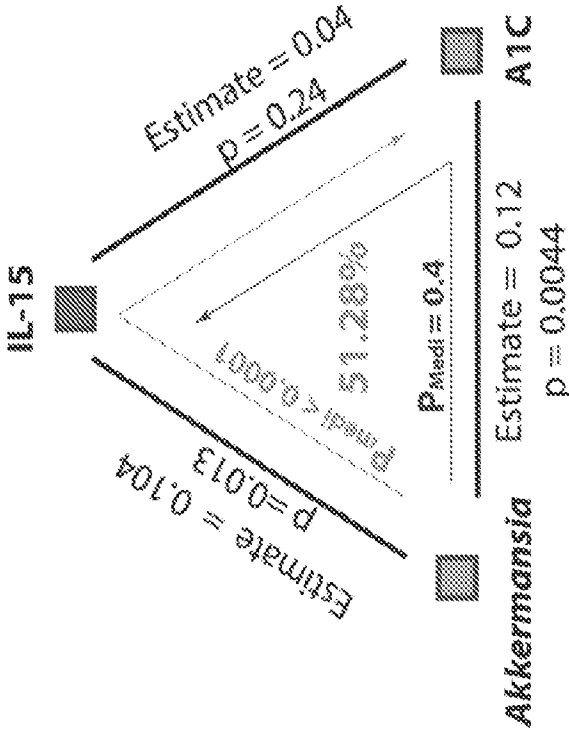


Fig. 17C

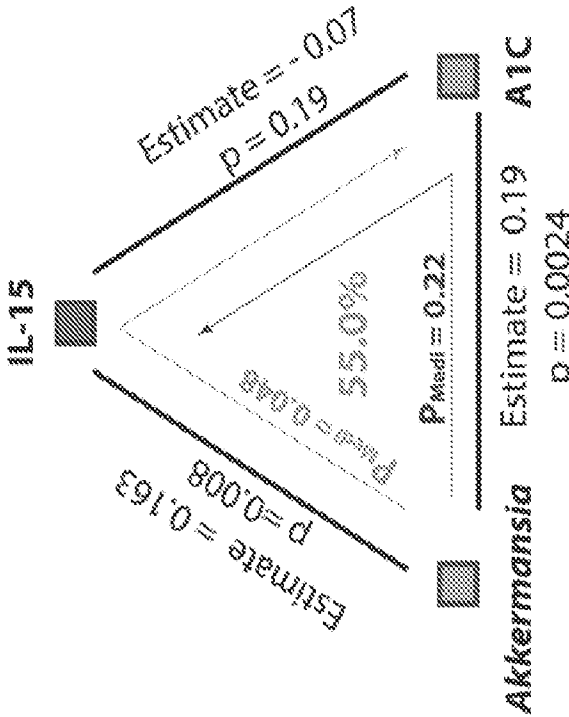


Fig. 17D

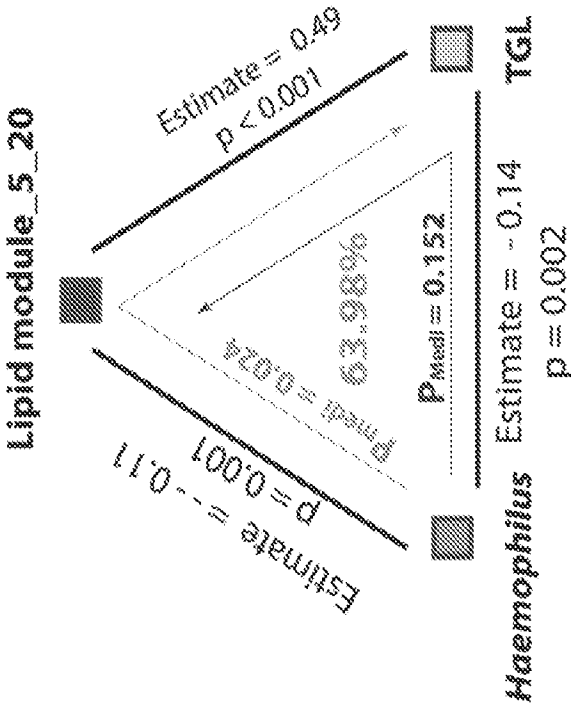
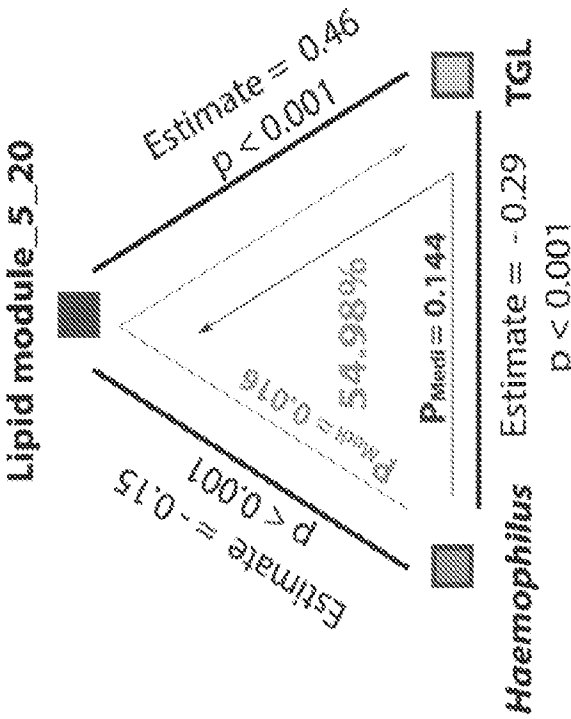


Fig. 17E



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033663

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **A61K 35/74** (2024.01); **A61K 45/06** (2024.01); **A61P 1/00** (2024.01); **A61P 19/02** (2024.01); **A61P 37/02** (2024.01)
CPC: **A61K 35/74**; **A61K 45/06**; **A61P 1/00**; **A61P 19/02**; **A61P 37/02**

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)

See Search History Document

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

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2022/0118030 A1 (EVELO BIOSCIENCES INC.) 21 April 2022 (21.04.2022) entire document	1-3
A	PESSI et al., Interleukin-10 generation in atopic children following oral Lactobacillus rhamnosus GG, Clinical and Experimental Allergy, Vol. 30, 2000, Pgs. 1804-1808	1-3
A	ZHOU et al., Lactobacillus salivarius Promotion of Intestinal Stem Cell Activity in Hens Is Associated with Succinate-Induced Mitochondrial Energy Metabolism, mSystems, Vol. 7, No. 6, 22 November 2022, Pgs. 1-14	1-3



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

09 August 2024 (09.08.2024)

Date of mailing of the international search report

05 November 2024 (05.11.2024)

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033663

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: **23-26, 30-37**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Group I+: claims 1-22 are drawn to methods for administering microbial genera to an individual, comprising: measuring levels of a set of one or more gene products in a biological sample of the individual; determining that an amount of one gene product of the set of gene products is above a threshold or is below a threshold; and when the amount of the one gene product is above a threshold, administering to the individual one or more microbial genera negatively correlated with the one gene product, or when the amount of the one gene product is below a threshold, administering to the individual one or more microbial genera positively correlated with the one gene product.

Group II: claims 27-29 are drawn to methods for administering microbial genera to an individual, comprising: measuring levels of a set of one or more analytes in a biological sample of the individual; determining that the measurement of one analyte is not within a healthy range; and administering to the individual one or more microbial genera to individual for the purpose of altering the level of the one analyte into the healthy range, wherein the one or more microbial genera is correlated with the analyte.

Group III: claims 38-57 are drawn to methods for treating an individual for a medical condition by administering microbial genera.

Group IV: claim 58 is drawn to a method of determining microbial genera host immune response.

Group V: claim 59 is drawn to a method for administering a probiotic treatment.

The first invention of Group I+ is restricted to a gene product selected to be VCAM1, a microbial genera selected to be Anaerostipes, and methods for administering microbial genera to an individual comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed gene product and microbial genera presented in the claims (see claim 3). It is believed that claims 1-3 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the gene product selected to be VCAM1 and the microbial genera selected to be Anaerostipes.

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

Applicant is invited to elect additional gene products and microbial genera to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a gene product selected to be VCAM1, a microbial genera selected to be Ruminococcus, and methods for administering microbial genera to an individual comprising the same. Additional gene products and microbial genera will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the “+” group(s) will result in only the first claimed invention to be searched/examined.

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

The Groups I+ formulas do not share a significant structural element requiring the selection of gene products and microbial genera where “the one gene product and the one or more correlated microbial genera to be administered is listed within Table 1.”

The special technical features of Groups I+, methods for administering microbial genera to an individual, comprising: measuring levels of a set of one or more gene products in a biological sample of the individual; determining that an amount of one gene product of the set of gene products is above a threshold or is below a threshold; and when the amount of the one gene product is above a threshold, administering to the individual one or more microbial genera negatively correlated with the one gene product, or when the amount of the one gene product is below a threshold, administering to the individual one or more microbial genera positively correlated with the one gene product, are not present in Groups II-V; the special technical features of Group II, methods for administering microbial genera to an individual, comprising: measuring levels of a set of one or more analytes in a biological sample of the individual; determining that the measurement of one analyte is not within a healthy range; and administering to the individual one or more microbial genera to individual for the purpose of altering the level of the one analyte into the healthy range, wherein the one or more microbial genera is correlated with the analyte, are not present in Groups I+ or III-V; the special technical features of Group III, methods for treating an individual for a medical condition by administering microbial genera, are not present in Groups I+, II, IV and V; the special technical feature of Group IV, a method of determining microbial genera host immune response, is not present in Groups I+, II, III and V; and the special technical feature of Group V, a method for administering a probiotic treatment, is not present in Groups I+ and II-IV.

Additionally, even if Groups I+ and II-V were considered to share the technical features of a method for administering microbial genera to an individual, comprising: measuring levels of a set, determining the measurement, administering to the individual one or more microbial genera correlated with a gene product; a culture of an immune responsive organoids; adding a microbial genus culture supernatant to the immune responsive organoids in culture; and measuring one or more gene products to determine organoid response to the microbial genus culture supernatant, these shared technical features do not represent a contribution over the prior art as disclosed by the publication entitled “Interleukin-10 generation in atopic children following oral Lactobacillus rhamnosus GG” by Pessi et al. (hereinafter, “Pessi”) and the publication entitled “Lactobacillus salivarius Promotion of Intestinal Stem Cell Activity in Hens Is Associated with Succinate-Induced Mitochondrial Energy Metabolism” by Zhou et al. (hereinafter, “Zhou”).

Pessi teaches a method for administering microbial genera to an individual (Lactobacillus rhamnosus GG at a daily dose was added for 4 weeks to the diets of nine children; abstract), comprising: measuring levels of a set (concentrations of interleukin-6 (IL-6), IL-10, IL-12, tumour necrosis factor- α (TNF α) and interferon- γ (IFN γ) in sera, as well as the production of IL-2, IL-4, IL-10 and IFN γ in mitogen-induced peripheral blood mononuclear cells, were assessed; abstract), determining the measurement (figure 1), administering to the individual one or more microbial genera correlated with a gene product (Lactobacillus rhamnosus GG at a daily dose was added for 4 weeks to the diets of nine children...enhanced IL-10 generation; abstract).

Zhou teaches a culture of an immune responsive organoids (intestinal organoid; abstract); adding a microbial genus culture supernatant to the immune responsive organoids in culture (L. salivarius supernatant was further confirmed to promote the intestinal organoids’ size, budding, and LGR5 expression; abstract); and measuring

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one or more gene products to determine organoid response to the microbial genus culture supernatant (LGR5 expression is increased after supernatant treatment as compared to control; figure 3).

The inventions listed in Groups I+ and II-V therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-3**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.