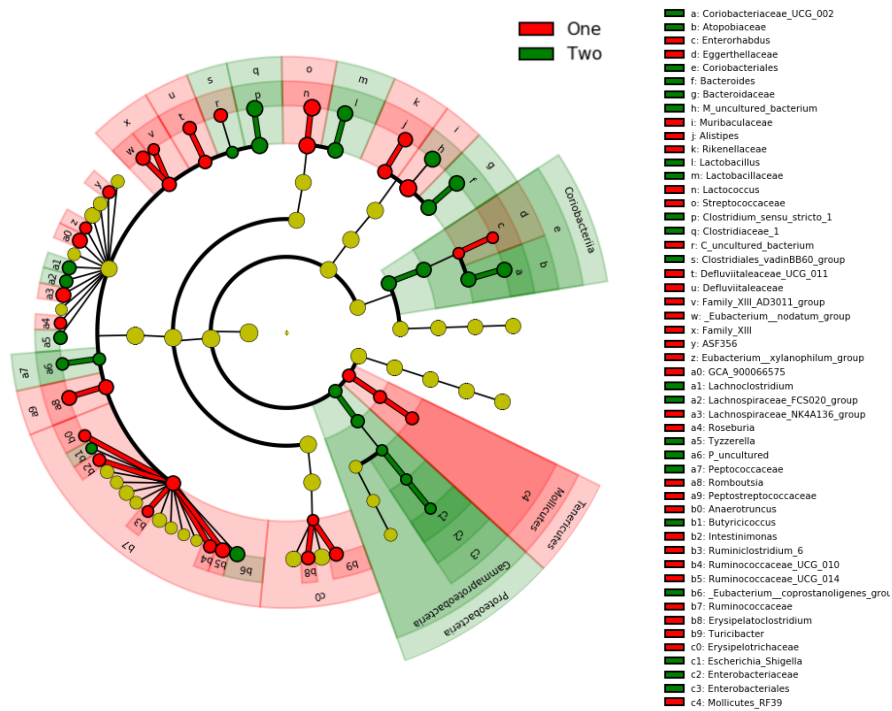


Supplemental Figure 1



Supplemental Figure 1: Cladogram generated from LEfSe analysis showing the most differentially abundant taxa enriched in microbiota; red indicating cohort 1 and green cohort 2.

Supplemental Table 1: Beta diversity Metrics: ANOSIM pairwise comparisons by diet, treatment, and cohort.

<b>Variable</b>	<b>Group 1</b>	<b>Group 2</b>	<b>Unweighted UF</b>	<b>Weighted UF</b>	<b>Bray-Curtis</b>	<b>Jaccard</b>
Diet	LF	HF	0.035	0.003	0.001	0.015
Tx	CON	MB	0.626	0.044	0.078	0.322
Cohort	C1	C2	0.001	0.002	0.001	0.001

Supplemental Table 2: Differentially abundant fecal microbiota genera between cohorts. Magnitude and directionality demonstrated by effect parameter (positive effect- increased in cohort 2; negative effect- decreased in cohort 2.) A cutoff of Benjamini-Hochberg adjusted  $p < 0.05$  for Welch's t or Wilcoxon rank sum tests were used to identify differentially regulated genera. (n=23-24/cohort)

Taxa	effect	Welch.BH	Wilcox.BH
Bacteroidetes;Bacteroidia;Bacteroidales;Bacteroidaceae;Bacteroides	4.300	0.0000	0.0000
Firmicutes;Clostridia;Clostridiales;Ruminococcaceae;[Eubacterium] coprostanoligenes group	4.150	0.0000	0.0000
Actinobacteria;Coriobacteriia;Coriobacteriales;Atopobiaceae;Coriobacteriaceae UCG-002	3.799	0.0000	0.0000
Firmicutes;Clostridia;Clostridiales;Ruminococcaceae;Ruminococcaceae UCG-010	-3.042	0.0000	0.0000
Bacteroidetes;Bacteroidia;Bacteroidales;Rikenellaceae;Alistipes	-2.880	0.0000	0.0000
Firmicutes;Clostridia;Clostridiales;Lachnospiraceae;Roseburia	-1.954	0.0000	0.0000
Firmicutes;Clostridia;Clostridiales;Lachnospiraceae;GCA-900066575	-1.945	0.0000	0.0000
Bacteroidetes;Bacteroidia;Bacteroidales;Muribaculaceae;uncultured bacterium	1.892	0.0000	0.0000
Firmicutes;Clostridia;Clostridiales;Lachnospiraceae;Lachnospiraceae FCS020 group	1.716	0.0000	0.0000
Firmicutes;Clostridia;Clostridiales;Deffluviitaleaceae;Deffluviitaleaceae UCG-011	-1.384	0.0000	0.0000
Actinobacteria;Coriobacteriia;Coriobacteriales;Eggerthellaceae;Enterorhabdus	-1.206	0.0001	0.0000
Firmicutes;Clostridia;Clostridiales;Lachnospiraceae;ASF356	-1.142	0.0002	0.0000
Firmicutes;Clostridia;Clostridiales;Clostridiales vadinBB60 group;uncultured bacterium	-1.088	0.0001	0.0000
Firmicutes;Clostridia;Clostridiales;Family XIII;[Eubacterium] nodatum group	-1.041	0.0003	0.0000
Firmicutes;Clostridia;Clostridiales;Peptococcaceae;uncultured	0.974	0.0151	0.0000
Firmicutes;Clostridia;Clostridiales;Ruminococcaceae;Intestinimonas	-0.926	0.0022	0.0002
Bacteroidetes;Bacteroidia;Bacteroidales;Muribaculaceae;__	-0.855	0.0002	0.0003
Firmicutes;Bacilli;Lactobacillales;Lactobacillaceae;Lactobacillus	0.774	0.0010	0.0016
Firmicutes;Clostridia;Clostridiales;Lachnospiraceae;Lachnospiraceae Lachnospiraceae	0.694	0.0042	0.0058
Firmicutes;Clostridia;Clostridiales;Ruminococcaceae;Ruminococcaceae UCG-014	-0.694	0.0030	0.0007
Firmicutes;Clostridia;Clostridiales;Lachnospiraceae;[Eubacterium] xylanophilum group	-0.687	0.0203	0.0154
Firmicutes;Erysipelotrichia;Erysipelotrichales;Erysipelotrichaceae;Erysipelatoclostridium	-0.668	0.0083	0.0045
Firmicutes;Clostridia;Clostridiales;Ruminococcaceae;Butyrivibrio	0.664	0.0177	0.0091
Firmicutes;Clostridia;Clostridiales;Family XIII;Family XIII AD3011 group	-0.602	0.0395	0.0308
Firmicutes;Clostridia;Clostridiales;Ruminococcaceae;Ruminococcaceae Ruminococcaceae	0.591	0.0083	0.0137
Firmicutes;Erysipelotrichia;Erysipelotrichales;Erysipelotrichaceae;Turicibacter	-0.585	0.0368	0.0608
Firmicutes;Clostridia;Clostridiales;Clostridiales vadinBB60 group;__	0.581	0.0235	0.0173
Tenericutes;Mollicutes;Mollicutes RF39;__;__	-0.571	0.0069	0.0016
Proteobacteria;Gammaproteobacteria;Betaproteobacteriales;Burkholderiaceae;Parasutterella	0.555	0.0067	0.0570
Firmicutes;Clostridia;Clostridiales;Clostridiaceae 1;Clostridium sensu stricto 1	0.521	0.0033	0.0064
Firmicutes;Clostridia;Clostridiales;Peptostreptococcaceae;Romoutsia	-0.505	0.0081	0.0043

Supplemental Table 3: Effect of diet, treatment, and cohort on levels of bacterial metabolites in feces. Data expressed as nmol/g, mean  $\pm$  SEM n=6 for each group.

Variable	Cohort1				Cohort2				3 way ANOVA P values						
	LF_CON	LF_MB	HF_CON	HF_MB	LF_CON	LF_MB	HF_CON	HF_MB	Cohort	Diet	Treatment	Cohort x Diet	Cohort x Treatment	Diet x Treatment	Cohort x Diet x Treatment
Acetic	858.04 $\pm$ 44.39	949.62 $\pm$ 148.98	813.02 $\pm$ 43.02	922.15 $\pm$ 170.15	1267.48 $\pm$ 292.7	1047.23 $\pm$ 227.37	949.52 $\pm$ 110.13	761.72 $\pm$ 83.52	0.307	0.155	0.659	0.262	0.200	0.915	0.975
Butyric	16.87 $\pm$ 7.54	19.47 $\pm$ 8.66	47.62 $\pm$ 10.13	88.23 $\pm$ 31.44	9.06 $\pm$ 4.02	22.08 $\pm$ 8.54	27.08 $\pm$ 9.48	112.63 $\pm$ 34.89	0.980	0.000	0.012	0.866	0.306	0.045	0.522
Isobutyric	32.1 $\pm$ 4.11	23.98 $\pm$ 3.07	37.68 $\pm$ 1.88	44.43 $\pm$ 9.56	17.57 $\pm$ 2.37	15.9 $\pm$ 1.88	30.43 $\pm$ 7.77	21.37 $\pm$ 5.12	0.001	0.006	0.435	0.618	0.545	0.629	0.154
Formic	486.1 $\pm$ 86.71	487.7 $\pm$ 60.56	415.88 $\pm$ 58.88	584.38 $\pm$ 94.98	647.88 $\pm$ 140.92	596.35 $\pm$ 98.52	485.12 $\pm$ 101.82	360.43 $\pm$ 27.81	0.661	0.163	0.982	0.113	0.194	0.722	0.365
Hexanoic	3.33 $\pm$ 0.46	3.18 $\pm$ 0.17	3.44 $\pm$ 0.23	2.4 $\pm$ 0.16	3.28 $\pm$ 0.16	3.07 $\pm$ 0.18	3.57 $\pm$ 0.62	2.97 $\pm$ 0.28	0.575	0.599	0.038	0.362	0.691	0.180	0.590
Propionic	102.13 $\pm$ 18.13	79.35 $\pm$ 17.62	81.86 $\pm$ 20.55	143.98 $\pm$ 40.54	88.77 $\pm$ 5.67	81.47 $\pm$ 7.77	92.88 $\pm$ 16.08	98.08 $\pm$ 28.89	0.467	0.306	0.557	0.709	0.513	0.129	0.256
Valeric	16.75 $\pm$ 3.71	12.18 $\pm$ 3.22	29.18 $\pm$ 2.19	31.48 $\pm$ 6.19	11.52 $\pm$ 1.79	11.47 $\pm$ 2.03	18.43 $\pm$ 3.19	22.75 $\pm$ 4.63	0.021	<0.0001	0.851	0.208	0.540	0.294	0.814
Isovaleric	30.98 $\pm$ 4.81	30.83 $\pm$ 5.54	35.18 $\pm$ 2.1	33.95 $\pm$ 3.64	17.82 $\pm$ 1.94	16.55 $\pm$ 1.37	24.85 $\pm$ 2.72	19.23 $\pm$ 4.8	<0.0001	0.115	0.439	0.821	0.605	0.610	0.759
Glyceric	45.27 $\pm$ 6.35	33.43 $\pm$ 5.2	29.96 $\pm$ 10.02	54.78 $\pm$ 10.27	27.08 $\pm$ 4.06	29.52 $\pm$ 6.73	33.13 $\pm$ 7.64	50.13 $\pm$ 15.09	0.349	0.196	0.200	0.412	0.797	0.046	0.380
Glycolic	17.17 $\pm$ 0.83	15.65 $\pm$ 1.23	18.62 $\pm$ 1.35	22.2 $\pm$ 1.86	15.72 $\pm$ 0.5	16.35 $\pm$ 1.06	15.27 $\pm$ 1.16	14.08 $\pm$ 1.57	0.001	0.146	0.673	0.005	0.467	0.363	0.059
Lactic	220 $\pm$ 54.76	145.8 $\pm$ 30.11	134.2 $\pm$ 45.34	77.67 $\pm$ 21.39	303.88 $\pm$ 86.69	179.03 $\pm$ 58.93	115.77 $\pm$ 52.2	66.22 $\pm$ 26.57	0.552	0.003	0.043	0.319	0.766	0.527	0.694
Pyruvic	104.08 $\pm$ 12.79	82.67 $\pm$ 9.19	87.72 $\pm$ 2.61	67.55 $\pm$ 8.68	122.13 $\pm$ 27.76	108.47 $\pm$ 16.44	95.88 $\pm$ 7.74	93.87 $\pm$ 10.63	0.066	0.088	0.174	0.822	0.534	0.757	0.802
Succinic	18.37 $\pm$ 3.03	19.85 $\pm$ 2.94	22.36 $\pm$ 4.74	16.97 $\pm$ 3.08	19.9 $\pm$ 5.36	13.78 $\pm$ 3.08	12.2 $\pm$ 1.59	17.2 $\pm$ 3.03	0.150	0.749	0.613	0.587	0.778	0.669	0.075
Indole-3 LA	0.38 $\pm$ 0.08	0.43 $\pm$ 0.08	0.32 $\pm$ 0.04	0.5 $\pm$ 0.08	0.52 $\pm$ 0.14	0.53 $\pm$ 0.16	1.33 $\pm$ 0.22	1.13 $\pm$ 0.18	<0.0001	0.001	0.906	0.001	0.297	0.826	0.381

Supplemental Table 4: Differentially abundant PICRUSt2 identified Metacyc pathways between cohorts. Magnitude and directionality demonstrated by effect parameter (positive effect- increased in cohort 2; negative effect- decreased in cohort 2.) A cutoff of Benjamini-Hochberg adjusted  $p < 0.05$  for Welch's t (we.eBH) or Wilcoxon rank sum (wi.eBH) tests were used to identify differentially regulated pathways. Specific pathway description and general category description of pathways are provided for each pathway. (n=23-24/cohort)

Pathway	effect	we.eBH	wi.eBH	Path Description	Path Category
PWY-6572	6.230	4.47E-17	1.22E-11	chondroitin sulfate degradation I (bacterial)	Polymeric Compound Degradation
PWY-6263	-4.314	1.32E-20	1.22E-11	superpathway of menaquinol-8 biosynthesis II	Cofactor, Prosthetic Group, Electron Carrier, and Vitamin Biosynthesis
PWY-7210	-3.947	1.71E-09	2.92E-07	pyrimidine deoxyribonucleotides biosynthesis from CTP	Nucleoside and Nucleotide Biosynthesis
PWY-7198	-3.791	1.06E-09	2.86E-07	pyrimidine deoxyribonucleotides de novo biosynthesis IV	Nucleoside and Nucleotide Biosynthesis
PWY-7371	-3.410	6.58E-18	1.22E-11	1,4-dihydroxy-6-naphthoate biosynthesis II	Cofactor, Prosthetic Group, Electron Carrier, and Vitamin Biosynthesis
P441-PWY	-1.541	3.26E-08	4.82E-07	superpathway of N-acetylneuraminate degradation	Carboxylate Degradation
GLYCOLYSIS-E-D	-1.527	3.75E-08	4.75E-07	superpathway of glycolysis and the Entner-Doudoroff pathway	superpathway of glycolysis and the Entner-Doudoroff pathway
PWY-5304	1.510	1.21E-06	5.38E-09	superpathway of sulfur oxidation (Acidianus ambivalens)	Inorganic Nutrient Metabolism
P461-PWY	-1.503	8.83E-08	7.39E-07	hexitol fermentation to lactate, formate, ethanol and acetate	Fermentation
PWY-6749	-1.498	1.13E-06	5.84E-06	CMP-legionamate biosynthesis I	Carbohydrate Biosynthesis
PWY-7003	-1.361	1.80E-07	3.25E-07	glycerol degradation to butanol	Fermentation
P23-PWY	-1.334	1.79E-06	1.06E-05	reductive TCA cycle I	C1 Compound Utilization and Assimilation
FUCCAT-PWY	-1.325	1.33E-06	2.73E-06	fructose degradation	Carbohydrate Degradation
LACTOSECAT-PWY	1.322	3.15E-04	7.45E-07	lactose and galactose degradation I	Carbohydrate Degradation
P125-PWY	-0.993	8.88E-05	2.79E-06	superpathway of (R,R)-butanediol biosynthesis	Fermentation
GLUCUROCAT-PWY	-0.979	1.44E-04	5.24E-04	superpathway of beta-D-glucuronosides degradation	Secondary Metabolite Degradation
PWY-6396	-0.975	4.40E-04	2.07E-06	superpathway of 2,3-butanediol biosynthesis	Fermentation
P163-PWY	-0.916	3.23E-04	2.73E-04	L-lysine fermentation to acetate and butanoate	Fermentation
GALACT-GLUCUROCAT-PWY	-0.847	6.67E-04	1.42E-03	superpathway of hexuronide and hexuronate degradation	superpathway of hexuronide and hexuronate degradation
RHAMCAT-PWY	0.844	4.35E-04	3.62E-04	L-rhamnose degradation I	Carbohydrate Degradation
GLUCARDEG-PWY	-0.814	3.42E-03	6.50E-04	D-glucarate degradation I	Secondary Metabolite Degradation
NAD-BIOSYNTHESIS-II	-0.803	1.38E-03	1.69E-03	NAD salvage pathway III (to nicotinamide riboside)	Cofactor, Prosthetic Group, Electron Carrier, and Vitamin Biosynthesis
PWY0-41	-0.770	8.75E-03	2.62E-02	allantoin degradation IV (anaerobic)	Amine and Polyamine Degradation
PWY0-1533	0.697	1.90E-02	6.99E-03	methylphosphonate degradation I	Inorganic Nutrient Metabolism
METH-ACETATE-PWY	-0.696	9.26E-03	3.53E-03	methanogenesis from acetate	Respiration
HEXITOLDEGSUPER-PWY	-0.691	1.16E-02	8.45E-03	superpathway of hexitol degradation (bacteria)	Secondary Metabolite Degradation
PWY-5705	-0.689	1.31E-02	4.29E-03	allantoin degradation to glyoxylate III	Amine and Polyamine Degradation
GLUCARGALACTSUPER-PWY	0.676	2.14E-02	9.88E-03	superpathway of D-glucarate and D-galactarate degradation	superpathway of D-glucarate and D-galactarate degradation
PWY-7237	0.675	1.04E-02	1.48E-02	myo-, chiro- and scyllo-inositol degradation	Secondary Metabolite Degradation
PWY-6478	-0.665	9.24E-03	1.96E-02	GDP-D-glycero-alpha-D-manno-heptose biosynthesis	Carbohydrate Biosynthesis
GALACTARDEG-PWY	0.654	2.16E-02	9.37E-03	D-galactarate degradation I	Secondary Metabolite Degradation
HEMESYN2-PWY	-0.641	1.41E-02	1.56E-02	heme b biosynthesis II (anaerobic)	Cofactor, Prosthetic Group, Electron Carrier, and Vitamin Biosynthesis
P162-PWY	-0.634	3.82E-03	3.78E-04	L-glutamate degradation V (via hydroxyglutarate)	Fermentation
PWY-6895	-0.626	1.96E-02	7.26E-04	superpathway of thiamine diphosphate biosynthesis II	Cofactor, Prosthetic Group, Electron Carrier, and Vitamin Biosynthesis
GALACTUROCAT-PWY	-0.626	1.25E-02	1.41E-02	D-galacturonate degradation I	Secondary Metabolite Degradation
PWY-6891	-0.622	1.11E-02	3.23E-03	thiazole biosynthesis II (aerobic bacteria)	Cofactor, Prosthetic Group, Electron Carrier, and Vitamin Biosynthesis
PWY-5913	0.597	3.63E-02	1.70E-02	partial TCA cycle (obligate autotrophs)	TCA cycle
PWY-7254	-0.589	2.57E-02	5.95E-03	TCA cycle VII (acetate-producers)	TCA cycle
PWY-5022	-0.586	7.34E-03	3.87E-03	4-aminobutanoate degradation V	Fermentation
PWY-5837	-0.581	1.79E-02	1.84E-02	2-carboxy-1,4-naphthoquinol biosynthesis	Cofactor, Prosthetic Group, Electron Carrier, and Vitamin Biosynthesis
PWY-5863	-0.580	1.76E-02	1.77E-02	superpathway of phyloquinol biosynthesis	Cofactor, Prosthetic Group, Electron Carrier, and Vitamin Biosynthesis
PWY-7242	-0.579	1.70E-02	1.73E-02	D-fructuronate degradation	Secondary Metabolite Degradation
PWY-6471	0.573	2.42E-02	3.85E-02	peptidoglycan biosynthesis IV (Enterococcus faecium)	Cell Structure Biosynthesis
PWY-7456	0.569	1.08E-02	1.35E-03	beta-(1,4)-mannan degradation	Polymeric Compound Degradation
PWY0-166	0.558	9.30E-03	2.51E-02	superpathway of pyrimidine deoxyribonucleotides de novo biosynthesis (E. coli)	Nucleoside and Nucleotide Biosynthesis
PWY-5005	-0.546	1.98E-02	4.03E-03	biotin biosynthesis II	Cofactor, Prosthetic Group, Electron Carrier, and Vitamin Biosynthesis
P164-PWY	-0.523	3.07E-02	4.40E-02	purine nucleobases degradation I (anaerobic)	Nucleoside and Nucleotide Degradation
REDCITCYC	-0.520	2.46E-02	1.60E-02	TCA cycle VIII (helicobacter)	TCA cycle
PWY-5677	-0.486	2.27E-02	1.29E-02	succinate fermentation to butanoate	Fermentation
PWY-6876	0.450	1.21E-02	2.82E-02	isopropanol biosynthesis (engineered)	isopropanol biosynthesis (engineered)
PWY0-1261	0.369	2.40E-02	3.65E-02	anhydromuropeptides recycling I	Secondary Metabolite Degradation