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Early View

Original article

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TITLE:
Functional lower airways genomic profiling of the microbiome to capture active microbial metabolism

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2) Acquisition of data: BGW, YL, AS, KJ, AG, SB, EG, IS, LNS.
3) Analysis and interpretation of data: BGW, JT, MS, MW, MW, YH. KS, LZ, LT, EG, IS, LNS
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Abstract

Rationale

Microbiome studies of the lower airway based on bacterial 16S rRNA gene sequencing assess microbial community structure but can only infer functional characteristics. Microbial products, such as short chain fatty acids (SCFAs), in the lower airways have significant impact on the host's immune tone. Thus, functional approaches to the analyses of the microbiome are necessary.

Methods

Here we used upper and lower airway samples from a research bronchoscopy smoker cohort. In addition, we validated our results in an experimental mouse model.

Measurements

We extended our microbiota characterization beyond 16S rRNA gene sequencing with the use of whole genome (WGS) and RNA metatranscriptome sequencing. Short chain fatty acids (SCFA) were also measured in lower airway samples and correlated with each of the sequencing datasets. In the mouse model, 16S rRNA gene and RNA metatranscriptome sequencing were performed.

Main Results

Functional evaluations of the lower airway microbiota using inferred metagenome, WGS and metatranscriptome were dissimilar. Comparison with measured levels of SCFAs shows that the inferred metagenome from the 16S rRNA gene sequencing data was

poorly correlated, while better correlations were noted when SCFAs levels were compared with WGS and metatranscriptome. Modeling lower airway aspiration with oral commensals in a mouse model showed that the metatranscriptome most efficiently captures transient active microbial metabolism, which was overestimated by 16S rRNA gene sequencing.

Conclusions

Functional characterization of the lower airway microbiota through metatranscriptome identify metabolically active organisms capable of producing metabolites with immunomodulatory capacity such as SCFAs.

Abstract: 243/250

Introduction

Characterization of the lower airway microbiota by 16S rRNA gene sequencing has revealed that the lower airways are frequently enriched with oral commensals in healthy subjects [1-7], most likely due to micro-aspiration. The presence of oral commensals in the lower airways has also been identified in multiple pulmonary diseases such as cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease and lung cancer [7-11]. However, the viability of organisms identified in lower airway samples using targeted gene sequencing is uncertain and most investigations have been limited to just taxonomic description of the lower airway microbiota and its association with host phenotypes [1,2,7,12-14]. Whole genome shotgun (WGS) and RNA metatranscriptome sequencing can directly capture gene content and active transcription, respectively. These techniques have the potential to provide a more precise functional assessment of the lower airway microbiome[15-17]. Due to the limited microbial biomass in the lower airways, these methods are challenging and have not yet been fully evaluated in comparison to standard microbial profiling and inferred functional content based on 16S rRNA gene sequencing.

Functionally active microbes can produce microbial products of relevance to the host and may modify host functions [13,14,18]. For example, short chain fatty acids (SCFAs) cannot be produced by mammalian cells (with the exception of acetate) but are produced by facultative and obligate anaerobes in hypoxic conditions [19-24]. SCFAs produced by the gut microbiota induce regulatory T cells that modify asthma, inflammatory bowel disease and cancer [19-24]. These SCFAs have also been identified in the lower airways and, with 16S rRNA gene sequencing, our group has shown that its presence is associated with

enrichment of the lower airway microbiota with oral commensals [13]. To better characterize functional aspects of the lower airway microbiome, we explored the use of WGS and RNA metatranscriptome approaches to uncover active microbial metabolism of immunologically relevant metabolites, such as SCFAs.

Methods

Participants and samples

For this study samples were used from 21 healthy participants, that were recruited for research bronchoscopy as part of our ongoing Chronic Obstructive Pulmonary Disease and Smoker Control cohort. All participants signed informed consent and the protocol was approved by the New York University and Bellevue Hospital Center (New York, NY) institutional review boards (IRB# S14-01546). Further details are in the **Supplementary Methods**.

Sample Processing

DNA was extracted from all samples using Qiagen DNA Mini Kit spin column protocol (Qiagen). RNA extraction was carried out with the miRNeasy Micro Kit (Qiagen). Bacterial burden was measured by Droplet Digital PCR. All samples had high-throughput sequencing of bacterial 16S rRNA gene amplicons, WGS and RNA metatranscriptome sequencing. Sequence data was filtered for bacteria only. Additionally, to identify active bacterial metabolism, SCFAs were measured by mass spectrometry. Further details on sample processing can be found in the **Supplementary Methods**.

Mouse Experiment

Three mice were inoculated with PBS while the remaining 17 mice were inoculated with a mixture of human oral commensals (MOC) consisting of *Prevotella, Streptococcus and Veillonella.* BAL samples were sent for 16S rRNA gene sequencing and RNA

metatranscriptome sequencing. The NYU Institutional Animal Care & Use approved the animal studies (IACUC# s16-00032). Further details are in the **Supplementary Methods**.

Statistical Analysis

For association with discrete factors, we used non-parametric tests (Mann-Whitney or Kruskal-Wallis ANOVA). We used the *vegan* package in R to construct Principal Coordinate Analysis (PCoA) based on Bray-Curtis distances [25,26]. To cluster microbiome communities into exclusive 'metacommunities' we used a Dirichlet Multinomial Mixture (DMM) Model[27,28]. To evaluate differences between groups within each sequence data type, we evaluated differential expression with DESeq2 [29] with a false discover rate (FDR) <0.05 [30]. All data is publicly available in Sequence Read Archive (SRA) under accession numbers PRJNA603592, PRJNA573853 and PRJNA603675. All codes utilized for the analysis included in this manuscript are available at:

https://github.com/segalmicrobiomelab/functional_microbiomics

Further details on statistical analysis are in the **Supplementary Methods.**

Results

We recruited 21 healthy smokers for this study; lower airway samples from two subjects did not yield an adequate cDNA library for metatranscriptome and were excluded from the analysis, leaving a study cohort of 19 subjects (**Table 1**). 16S rRNA gene sequencing characterized the microbiota present in background (BKG) controls, upper (UA) and lower [bronchoalveolar lavage (BAL)] airway samples. Hierarchical clustering of the most abundant taxa shows that the microbiota in UA and BKG samples are differentially contained within the two dominant clusters (**Figure 1A**). Some BAL samples were more similar to the UA, composed of taxa commonly identified as oral commensals such as *Veillonella*, *Prevotella* and *Streptococcus,* whereas other samples were more similar to BKG samples dominated by taxa such as *Methylobacterium*, *Actinobacillus* and *Lactobacillus.* We confirmed by DMM that BAL samples clustered into 2 distinct groups (**Figure 1B**). Samples that clustered with UA samples were enriched with Supraglottic Predominant Taxa (BAL.16S.SPT) while samples that clustered with BKG samples were enriched with Background Predominant Taxa (BAL.16S.BPT).[1,2] This last cluster represent a group of samples with lower microbial biomass and with a taxonomic composition where most of the identified taxa are likely coming from methodological contamination and not from “true” lower airway microbes. Significant differences between all sample types were determined by both α (Shannon Index, **Figure 1C**) and β diversity (Bray-Curtis distance, **Figure 1D**); these microbial community metrics further supported qualifying BAL.16S.SPT samples as more similar to UA samples. The median bacterial load, as determined by droplet digital (ddPCR), was ~1,000-fold higher for UA and 10-fold higher for BAL as compared to BKG samples (**Figure 1E**). However, three of the

BAL samples clearly had higher bacterial burden, with levels similar to those found in UA samples; they were all identified as BAL.16S.SPT based on taxonomic composition (**Figure 1E**). To explore functional aspects using the 16S rRNA gene sequence data, we inferred metagenomic composition by PICRUSt[31]. Comparison of the inferred metagenome between BAL.16S.SPT and BAL.16S.BPT samples suggested that there should be several KEGGs and associated functional pathways differentially expressed between these two clusters (**Figure 1F, Supplementary Data 1**). While this analysis infers microbial function, it possible to directly measure microbial function through the use of other new next generation sequencing methods and metabolomics.

Evaluation of the lower airway metagenome and metatranscriptome

To further characterize functional aspects of the airway microbiota we profiled the metagenome by WGS and the metatranscriptome by RNA sequencing. For this analysis, all BAL and UA samples were used while only 2 BKG samples had RNA sequencing libraries that passed quality control. Importantly, rarefaction analysis for the WGS and RNA data showed plateauing of the curves at a lower depth than the one accomplished in this investigation (**Supplementary Figure 2**). Within the WGS and RNA sequence data, UA and BKG samples were significantly different from each other, based on α and β-diversity (**Figures 1G/H and Supplementary Figures 1A/B**), similar to the 16S rRNA gene sequence data, while BAL samples were either similar to the UA or BKG. Using each Bray-Curtis distance matrix for 16S rRNA gene sequence, WGS, and RNA metatranscriptome data we compared the paired distances between BAL and UA

samples. The 16S rRNA gene data indicated a clear separation of what we identified as BAL.16S.SPT and BAL.16S.BPT but this distinction was lost in WGS and RNA metatranscriptome data (**Figure 1I)**. Importantly, β diversity analyses on both WGS and RNA sequencing data showed that all BAL samples identified as BAL.16S.BPT remained similar to BKG samples. However, among BAL samples identified as BAL.16S.SPT, both WGS and RNA sequencing identified a subset of samples that clearly showed greater similarity to UA samples while others showed greater similarity to BKG samples (**Figures 1G-H**). Interestingly, 2/3 BAL samples that had the greatest similarities with UA samples in WGS data also had the greatest similarities with UA samples in the RNA metatranscriptome data (**Figure 1I**).

Taxonomic signature differences between sequencing data types

To evaluate similarities of taxonomic annotation at a global level we used PROCRUSTES with Monte-Carlo simulation. While there was high correlation in β-diversity between WGS and RNA taxonomic assignment (p=0.001), there was no significant correlation when 16S rRNA gene sequencing data was compared with WGS or RNA data (**Supplementary Figure 3**).

Based on 16S rRNA gene sequencing, several taxa were significantly enriched (FDR <0.05) in samples identified as BAL.SPT as compared with BAL.BPT (**Figure 2A, Supplementary Data 2**) with a number of known oral commensals, such as *Prevotella*, *Veillonella* and *Streptococcus*, enriched in BAL.SPT. Further differences identified in

taxonomic signatures between sequencing data types are discussed in the **Supplementary Results**.

Functional overlap and differences across sequencing data types

Using GSEA to compare the functional annotations across the sequencing data types, we identified significant overlap between the data obtained (>1000 overlapping KOs for each comparison, **Figure 3A**). In order to compare the differentially enriched pathways identified (with DESeq2) between BAL.16S.SPT and BAL.16S.BPT we overlapped the fold change of the functional pathways (summarized to Level 3 of annotation). We identified some concordance in the directionality of the fold change, most identified as enriched in BAL.16S.SPT (**Figure 3B**). For example, fatty acid biosynthesis, as well as purine and pyrimidine metabolism were significantly enriched in all three sequence datasets. However, the presence of statistical significance (identified in the figure by the presence of color) differed by the method used. Further, other functional pathways showed discordant directionality. For example, genes belonging to the fatty acid metabolism pathway appeared to be significantly depleted in BAL.16S.SPT samples by the inferred metagenome but significantly enriched in WGS and non-significantly enriched in RNA sequencing data (**Figure 3B**). Since several genes annotated to fatty acid biosynthesis and fatty acid metabolism are part of the production of SCFAs (end products of microbial metabolism associated with enrichment of the lower airway microbiota with

oral anaerobes[13]) we measured the levels of these products directly using mass spectrometry.

Further differences identified in functional signatures between sequencing data types are discussed in the **Supplementary Results**.

SCFA levels are different in upper and lower airways

Initially SCFA levels in ex vivo cultures were analyzed (see **Supplementary Results)**. We then evaluated SCFA levels in the 19 UA and BAL samples and 4 BKG samples. The levels of 4/7 SCFAs were significantly higher in UA samples when compared to BKG samples: acetate, propionate, isovalerate, and butyrate (**Figure 4**). However, the levels of 3 other SCFAs measured were similar when comparing UA with BKG samples: hexanoate, valerate and octanoate (data not shown). These data suggest that some SCFAs are not produced by oral commensals or that their measurement lack a dynamic range above BKG. Among BAL samples, there were 3 SCFAs with levels statistically higher than BKG samples: acetate, propionate, and isovalerate—all of which were exponentially higher in UA samples. However, three BAL samples identified as BAL.16S.SPT had significantly higher levels of these 3 SCFAS (**Figure 4**). These concentrations are comparable to what we have previously published as measurable in the lower airways of a separate cohort and found to be correlated with a T-reg phenotype, blunted IL-17 and IFN gamma response.[13] The remaining BAL samples had similar levels to BKG (regardless of their 16S.SPT/16S.BPT grouping). Importantly, the levels of these SCFAs in BAL samples did not correlate with levels in UA samples (p=ns for all

comparisons, **Supplementary Figure 7**) suggesting that microaspiration of upper airway secretions containing these metabolites was not the main source of SCFAs in the lung. To further test whether levels of SCFAs are dependent on lower airway microbial metabolism we correlated the findings from the different genomic datasets with the measured SCFAs.

The RNA metatranscriptome correlates with measured SCFAs in the lower airways

At a global compositional level (β-diversity), the levels of these 4 SCFAs were not statistically significantly associated with the 16S rRNA gene sequencing data but ¾ were statistically significantly associated with the WGS and RNA metatranscriptome data (**Figure 5A**). This is likely to be driven by the 3 BAL samples with high levels of measured SCFAs identified by mass spectrometry (**Figure 4)**, as this correlation is not seen with BAL.BPT samples. Furthermore, rarefying the three datasets lead to no significant change in the correlations.

Since DMM clustering on 16S rRNA gene sequencing data did not distinguish BAL samples with high and low SCFAs levels, we performed DMM analysis of the WGS and RNA metatranscriptome data (see **Supplementary Results**) again identifying two separate clusters among BAL samples.

As validation, we focused on 3 KOs with direct SCFA annotation: K01738 for acetate, K00925 for propionate and K01034 for butyrate. KO enrichment differences could be identified between sample types with the RNA metatranscriptome but not with the inferred metagenome (16S rRNA data) or the WGS data (**Figure 5B-D**). KOs in the RNA

metatranscriptome were significantly elevated in UA samples and at very low levels in BKG samples. Importantly, the BAL samples identified in DMM clustering as being compositionally similar to UA had significantly higher levels of these KOs when compared with the remaining BAL samples which clustered with BKG samples ($p<0.03$ for all comparisons, **Figure 5D**). We then evaluated the taxonomic annotation available for these 3 KOs in the RNA metatranscriptome data and noted that the taxonomic source for these genes was predominantly oral commensals such as *Streptococcus* and *Veillonella* (**Figure 5E**). Thus, the RNA metatranscriptome has better resolution (when compared to 16S rRNA gene sequencing) for the identification of enriched genes involved in the metabolism of SCFAs present in oral anaerobes and supports the presence of viable (RNA measurable) and metabolically active (metabolites elevated above BKG) bacteria in the lower airway airways.

By identifying potential contaminants (coming from DNA/RNA present in bronchoscope or added through sample processing) within each sequencing method using the *decontam* package[32] (see **Supplementary Results**), we ensured that these microbial patterns identified were related to signals present in the lower airways.

The RNA signature is lost earlier than the DNA signature in a mouse model of aspiration

It is possible that the improved resolution of RNA metatranscriptome in the identification of active microbial metabolism in the lower airways is due to differences in DNA and RNA clearance over time. To evaluate the stability and functional dynamics of aspirated oral commensals in the lower airways, we used a mouse model. For this, mice were inoculated with a mixture of human oral commensals (MOC) consisting of *Prevotella*

melaninogenica, *Streptococcus mitis* and *Veillonella parvula* cohoused with a PBS control group. Mice were sacrificed at 1Hr, 4Hr, 1Day, 3Day and 7Day post-inoculation (**Figure 6A**), and BAL samples were sent for 16S rRNA gene and RNA metatranscriptome sequencing. β diversity analysis on 16S rRNA gene sequencing data shows that BAL samples remain similar to MOC for at least 1 day and become more similar to PBS by day 3 with a concordant decrease in the relative abundance of oral commensals (**Figure 6B-C-D**). However, in the analysis based on RNA metatranscriptome, BAL samples remain similar to MOC until the 4-hour timepoint and become more similar to PBS by day 1 with a concordant rapid loss of the RNA signal from oral commensals (**Figure 6E-F-G**). These data support that discrepancies between these sequencing data can be time dependent and likely reflect the loss of viable (and transcriptionally active) microbes.

Discussion

Functional characterization of the lower airway microbiota has been attempted in a limited number of studies. In most of these, the inferred metagenome was used [2,33]. Few have attempted metagenomic analyses [15]. The purpose of this study was to evaluate different sequence data types in the evaluation of the functional microbiome of the lower airways and to use the measurement of SCFAs as an independent biological outcome, a direct measure of bacterial metabolism. Our analysis showed that, among lower airway samples with enrichment of oral commensals, determined by taxonomic assignment of 16S rRNA gene sequencing, the use of WGS or RNA metatranscriptomic sequencing provide a distinct representation of functional aspects of the lower airway microbiota. Importantly, by pairing our sequence data with SCFA measurement we showed that in lower airway samples with oral commensal enrichment, based on 16S rRNA gene sequencing, there is a subset with evidence of active microbial metabolism indicative of viability of the lower airway microbiota. This active microbial metabolism in the lower airways has been shown to influence lower airway immunity[34]. Further support for dissimilarity between 16S rRNA gene and RNA metatranscriptomic sequencing is provided with a mouse model of aspiration of oral commensal, demonstrating time dependent differences likely related to loss of metabolically active microbes as the lower airways clear them.

With the introduction of next generation sequencing we have discovered complex microbial communities within several different mucosae [35-38]. For each of these environments, the microbial-host interplay has an impact on mucosal homeostasis in health and disease [37-42]. Within the lower airways, several studies have shown that complex microbial communities significantly impact the mucosal host immune tone

[1,2,14,43,44]. For example, we have previously shown that lower airway enrichment with oral commensals leads to an increased lower airway inflammatory tone, characterized by a Th-17-like inflammatory phenotype [2]. Thus, it is increasingly important to describe these environments beyond just the presence/absence of bacteria but to look at the functional implications of these bacteria. A common technique used to evaluate bacterial function is to infer the metagenome from 16S rRNA gene sequencing data. Major concerns associated with this approach is the poor strain resolution of 16S rRNA gene sequencing and the dependence on existing reference databases of annotated microbes, which can bias the results. Direct measurement of microbial genes can be accomplished by WGS and RNA metatranscriptome sequencing. In this study, we used all three methods to evaluate taxonomic and functional signatures in the lower airways. As previously described, we identified a subset of subjects that had a lower airway microbiota enriched with oral commensals such as *Prevotella*, *Veillonella,* and *Streptococcus* [2]. Enrichment with oral commensals in a subset of samples that were identified as BAL.SPT based on 16S rRNA gene sequencing, were also found in WGS and RNA sequencing data but, importantly, not in all of them. This enrichment with supraglottic taxa in the lower airways and its impact on host immune tone also has implications in disease states, as we have previously shown[2]. Thus, the information we glean from each of these data types is variable and potentially important when combined in a multi-omic approach. In addition, we have shown performing multi-omic analysis on lower airways samples is a feasible approach that provides deeper insight into the lower airway micro-environment.

As validation for such an approach we focused on SCFAs. Several papers have identified SCFAs as the products of bacterial metabolism[45,46]; the role these metabolites play in

disease has been extensively studied in the gastrointestinal microbiota [20,21,23,24] and thought to be beneficial in inflammatory bowel disease and bowel cancer [47-50]. Within the lower airways, we have described that levels of these metabolites are associated with oral commensal enrichment (as defined by 16S rRNA gene sequencing) and have significant immunomodulatory effects on T cells [13]. In our prior investigation we also noted that not all subjects that had enrichment of the lower airway microbiota with oral commensals had elevated levels of SCFAs[13]. This suggests that functional characterization of the lower airway microbiota cannot be fully determined based solely on 16S rRNA gene sequencing data. We therefore integrated our WGS and RNA data with the measurement of SCFAs in UA, BAL and BKG samples. As expected, SCFAs were highest in UA samples consistent with the presence of oral anaerobes in these high biomass samples. Within BAL samples, a small subset of samples had detectable concentrations of acetate, propionate and isovalerate levels similar to the UA samples, identified as Supraglottic Predominant Taxa (BAL.SPT) samples based on 16S rRNA gene sequencing. Other BAL samples also identified as BAL.SPT based on 16S rRNA gene sequencing had low/below the limit of detection SCFA levels that were comparable with BAL.BPT and BKG samples. In contrast, the RNA metatranscriptome showed better sample type differentiation concordant with detected levels of SCFAs. In a recent report evaluating samples from 13 subjects, SCFAs levels did not correlate with bacterial burden in BAL samples.[51]In the current investigation we identified associations between SCFAs and the lower airway RNA metatranscriptome, suggesting that it is this active microbial translation that can be associated with levels of SCFAs. Importantly, taxonomic evaluation of these KOs identified that the bacteria expressing these genes were oral

commensals such as *Streptococcus*, *Prevotella* and *Veillonella*. Thus, these data suggest that in these samples, although oral commensals might have reached the lower airways and left traces of their genomic DNA, these bacteria have been cleared and are neither transcriptionally active nor capable of producing SCFAs at the time of sampling. This is further supported with a preclinical model of aspiration, where mice were exposed to a mixture of human oral commensals and sacrificed at different time points post exposure showing rapid loss of an RNA metatranscriptome signal from these microbes and longer persistence of 16S rRNA gene signal. Considering the known immunomodulatory effects of SCFAs and other microbial metabolites, both possibly beneficial and detrimental depending on the different human conditions, improved understanding of the value of different sequencing methods will be key to gain functional insights of the lower airway microbiome.

There are several limitations to this study. Firstly, in our analysis we did not remove any potential contaminants, which we found as the predominant taxa identified in many of the lower airway samples. Removing taxa identified as contaminant is frequently done in many microbiome studies hoping to remove contamination. However, there are many sources of noise that includes DNA contamination from the reagents/bronchoscope and stochastic sequencing noise [52,53]. Further, in low biomass samples background removal can be quite variable within different sequencing datasets and its effect on the resulting new dataset is unclear. A recent guideline on lung microbiome research has not recommended background removal[54] so our analysis was limited to just identifying possible contaminants. Importantly, none of the oral commensals associated with active microbial metabolism were identified as background contaminant. In addition, our sample

size was small and further validation will require a larger cohort. The lack of good correlation between 16S rRNA gene sequencing and WGS data may seem quite surprising since both are based on similar DNA template. However, similarity between two genomic datasets will be dependent on: a) their ability to detect “true” bacterial signals present in a biological sample (a well-recognized challenge in low biomass samples) and b) the background contamination due to differences in library preparation and sequencing techniques.[52,53] We also recognize that this approach could impose a significant increase in sequencing cost compared with the traditional 16S rRNA gene sequencing. However, improved accuracy in identifying active microbial metabolism in the lower airways can potentially lead to novel mechanistic insights about microbial metabolites with significant potential effects on the host, such as SCFAs. Future investigations should focus on determining the value of this improved accuracy by evaluating the potential implications for the host immune tone, an undertake that should be designed with a larger cohort. Thus, we acknowledge that in the current investigation we did not attempt to evaluate host factors. Instead, we focused on functional evaluation of the lower airway microbiota using SCFAs as proof of concept. It is important to note that we are already facing an increase in literature suggesting that “near bedside” metagenomics is feasible (both technically and computationally) and have potential clinical implications in terms of rapid detection of pathogens when compared with culture-based approaches and ability to detect resistant genes [55,56]. In this setting, our data supports that RNA sequencing could provide a better resolution of what microbial functions are active at a given time and may therefore contribute to the development of more targeted therapy. We also acknowledge that concentrations of acetate, which are not specific to microbes, can be influenced by

the host and the environment, including water. For our assay, we used freshly opened HPLC-grade water which did not have detectable acetate above that in the BKG samples. Dilution of BAL can affect the levels of SCFAs but should not affect compositional data such as metagenome/metatranscriptome. Future investigation may consider estimating BAL dilution factors, noting that there is still controversy in the literature about the accuracy the best method for this[57,58]. Also, variability between sequence data type may be due to differences in measured targets (target amplicon vs. WGS vs. RNA) as well as technical differences. For example, it is expected that deeper sequence depth will be needed to characterize the whole genome than to characterize taxonomic composition based on 16S rRNA gene sequencing and infer the metagenome using that data. The low bacterial biomass of the lower airway environment represents a critical challenge for the evaluation of the lower airway microbiome, both taxonomically and functionally. It is likely that this is an exponentially bigger problem for the WGS metagenome and RNA metatranscriptome. Although we aimed to achieve more sequence depth for our WGS metagenome and RNA metatranscriptome data, it is not surprising that differences may be more difficult to assess and that there is a greater level of background intrusion in these samples using these methods. However, the correlation of these data with SCFA levels suggest a more accurate functional evaluation can be achieved with WGS metagenome and RNA metatranscriptome data than with 16S rRNA gene sequencing data. Finally, the analyses presented here focused on fatty acid metabolism as a surrogate for bacterial activity. The highest level of precision and differential functional expression for lower airway samples identified by using RNA metatranscriptome data suggest that this might be a preferable functional method. However, it is likely that other

microbial functional pathways may be important to study in health and disease and future investigations should focus on experimental approaches to expand the observations made as proof of concept here.

In summary, the evaluation of the lower airway microbiome with 16S rRNA gene sequencing is limited in assessing bacterial function and therefore in assessing the potential impact on disease/host. The use of functional microbiome approaches that measure bacterial genes (WGS) and bacterial transcripts (RNA metatranscriptome) provide evidence of viable and active bacterial metabolism in the lower airways and will likely define subgroups of lower airway microbiota with different implications for the host.

TABLE 1: Baseline characteristics of study population

	Cohort
n	19
Age	53.0 [49.5-58.0]
Female (%)	5 (26.3)
BMI	28.4 [22.1-31.6]
PFT	
FVC Percent Predicted	95 [86-104]
FEV_1 Percent Predicted	89 [79-102]
FEV_1/FVC	79 [69-83]
Smoking Status	
Former Smoker (%)	17 (89)
Current Smoker (%)	2(11)
Pack Years	20 [11-28]

Data expressed as Median[IQR] or counts(%)

References:

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Figure 1

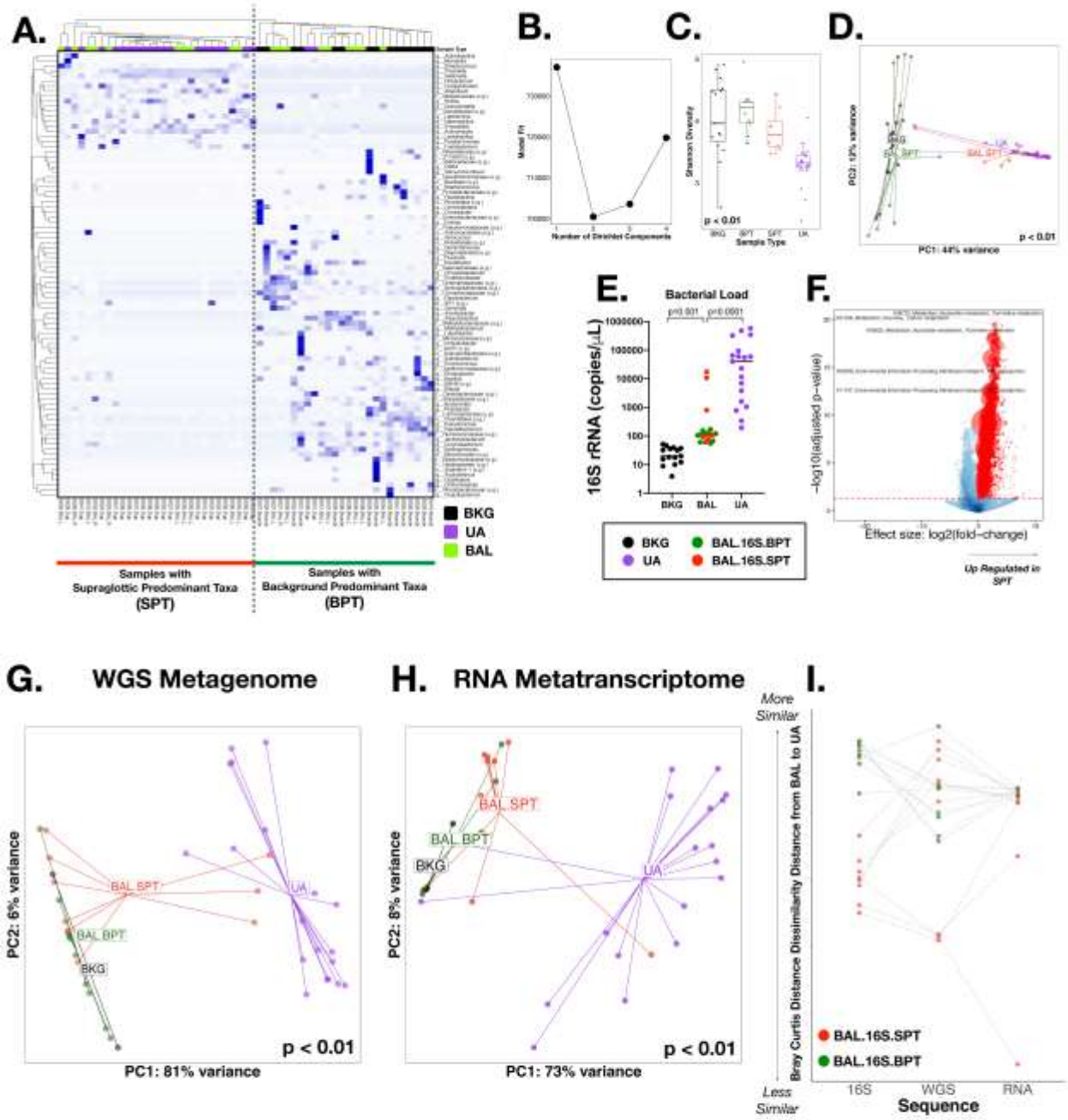


Figure 1: 16S rRNA gene, Whole genome (WGS) and RNA sequencing: Background (BKG), Upper Airway (UA) and Bronchoalveolar (BAL) samples were collected via bronchoscopy; 16S rRNA gene, Whole genome and RNA sequencing was performed. (**A**) A heatmap based on Bray-Curtis distance for the 16S rRNA gene sequencing, illustrates the top taxa for all samples. Hierarchical clustering showed two clear clusters, one with BKG samples and BAL samples similar to BKG (Background Predominant Taxa) and another with UA samples and BAL samples similar to UA (Supraglottic Predominant Taxa). (**B**) Dirichlet Multinomial Modelling (DMM) showed 2 clusters had the best model fit for the 16S rRNA gene sequencing. (**C**) α Diversity, measured by Shannon Index, showed significant (Wilcoxon) difference between all samples and lowest diversity in UA and among BAL samples that clustered to BAL.16S.SPT by DMM. (**D**) Beta Diversity, measured by Bray-Curtis, also indicates a significant (PERMANOVA) difference between all samples for 16S rRNA gene sequencing. (**E**) Bacterial load, measured by ddPCR showed highest levels in UA samples (Kruskal-Wallis). BAL Samples also had higher levels when compared to BKG samples. (**F**) The inferred metagenome was assessed using PiCRUST highlighting several significantly enriched pathways (colored in red). (**G**) β Diversity for WGS, measured by Bray-Curtis, showed a significant (PERMANOVA) difference between all samples, with UA samples separate from BKG and BAL.BPT samples. Three BAL.SPT samples clustered with UA Samples. (**H**) β Diversity for RNA, measured by Bray-Curtis, showed a significant (PERMANOVA) difference between all sample types. Two BAL.SPT samples clustered with UA samples. (**I**) **Z Transformed** Bray-Curtis Distance between BAL samples and paired UA samples showed clear separation of BAL.16S.BPT and BAL.16S.SPT samples in 16S rRNA gene sequencing. This separation was not as clear in WGS and RNA.

Figure 2

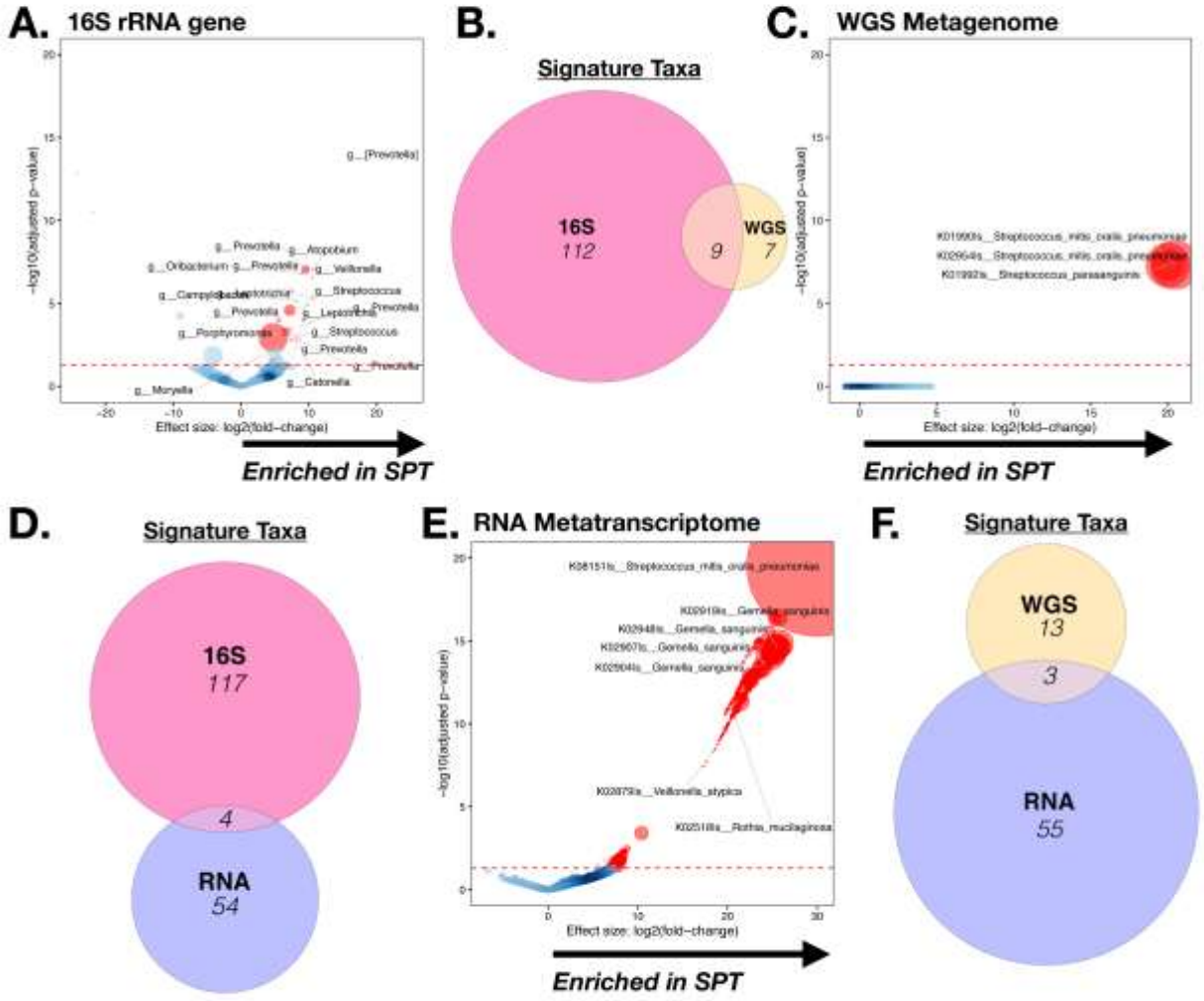
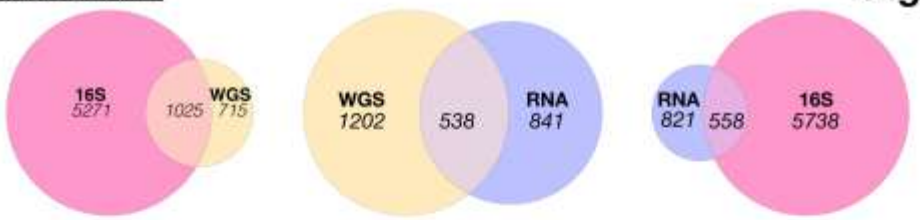


Figure 2: Taxonomic annotation of all three sequencing data types. DESEQ2 analysis of taxonomic annotation (at the genus level) between BAL.16S.SPT versus BAL. 16S.BPT samples (FDR <0.05) was performed on 16S rRNA gene sequencing data (**A**), WGS data (**C**) and RNA metatranscriptome data (**E**). Circle size is representative of relative abundance. Gene Set Enrichment Analysis (GSEA) was used to compare the taxonomic signatures identified as distinctly enriched in BAL.16S.SPT vs. BAL. 16S.BPT samples across the different sequencing platforms (**B**, **D**, **F**).

A. Signature KOs

Figure 3



B.

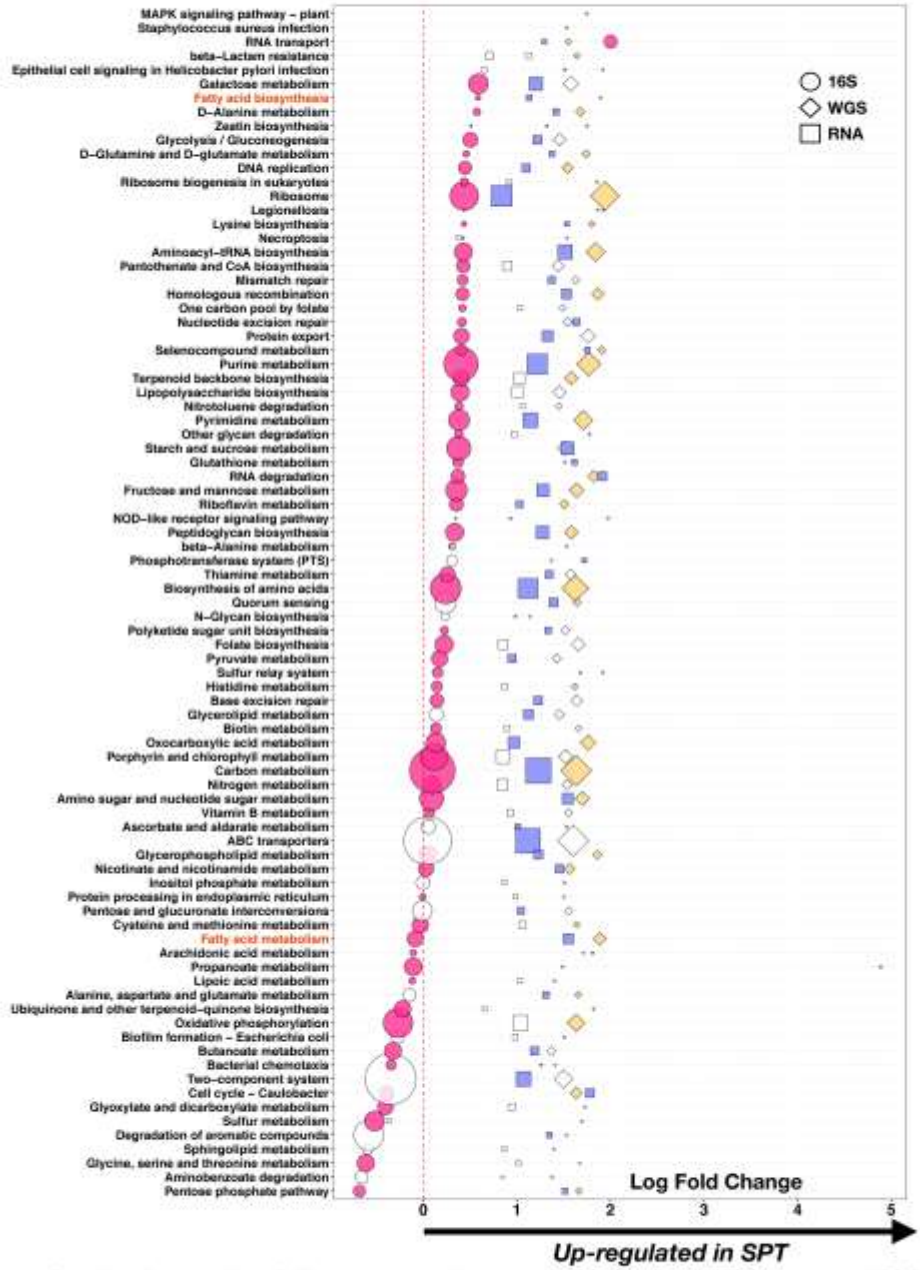


Figure 3: Functional annotation of all 3 sequencing data types. (**A**) Gene Set Enrichment Analysis (GSEA) comparing functional signatures identified across the different sequence data types as distinctly enriched in BAL.16S.SPT vs. BAL.16S.BPT samples based on KEGG Orthology (KO) annotation (differential enrichment performed based on DESEQ2 analysis). (**B**) KOs were summarized to associated pathways and differential expression between BAL.16S.SPT and BAL.16S.BPT are displayed as circles for 16S rRNA gene sequencing, diamonds for WGS and squares for RNA. Coloring indicates statistical significance (DESeq2 $p<0.05$) for each sequence data type and size is relative to the amount of KOs contributing to that pathway. Two pathways highlighted in red include Fatty Acid Biosynthesis, which shows concordance of directionality between the three sequence data types and Fatty Acid Metabolism, which shows discordance.

Figure 4

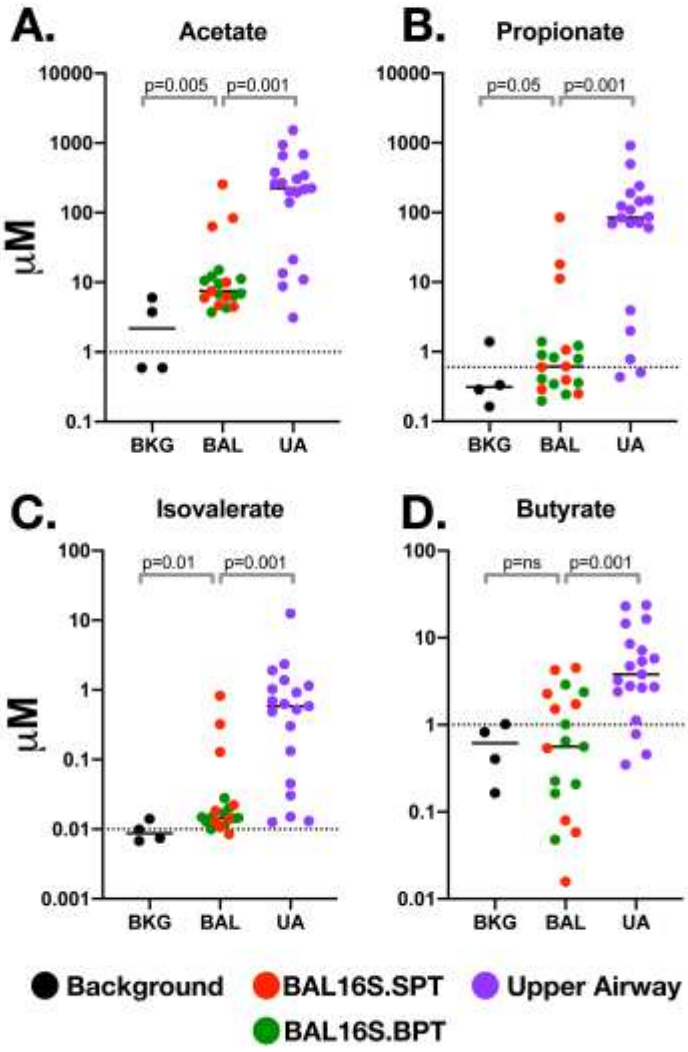


Figure 4: Concentrations of Short Chain Fatty Acid (SCFA) in bronchoscopy samples: A panel of SCFAs were measured and compared (Kruskal-Wallis) in Background (BKG), Upper Airway (UA) and Bronchoalveolar (BAL) samples by GC-MS. SCFA were derived from the linear phase of the standard curve leading to the following cutoffs values (dotted line): (**A**) 1μM for Acetate, (**B**) 0.6 μM for Propionate (**C**) 0.01 μM for Isovalerate and (**D**) 1μM for Butyrate.

Figure 5

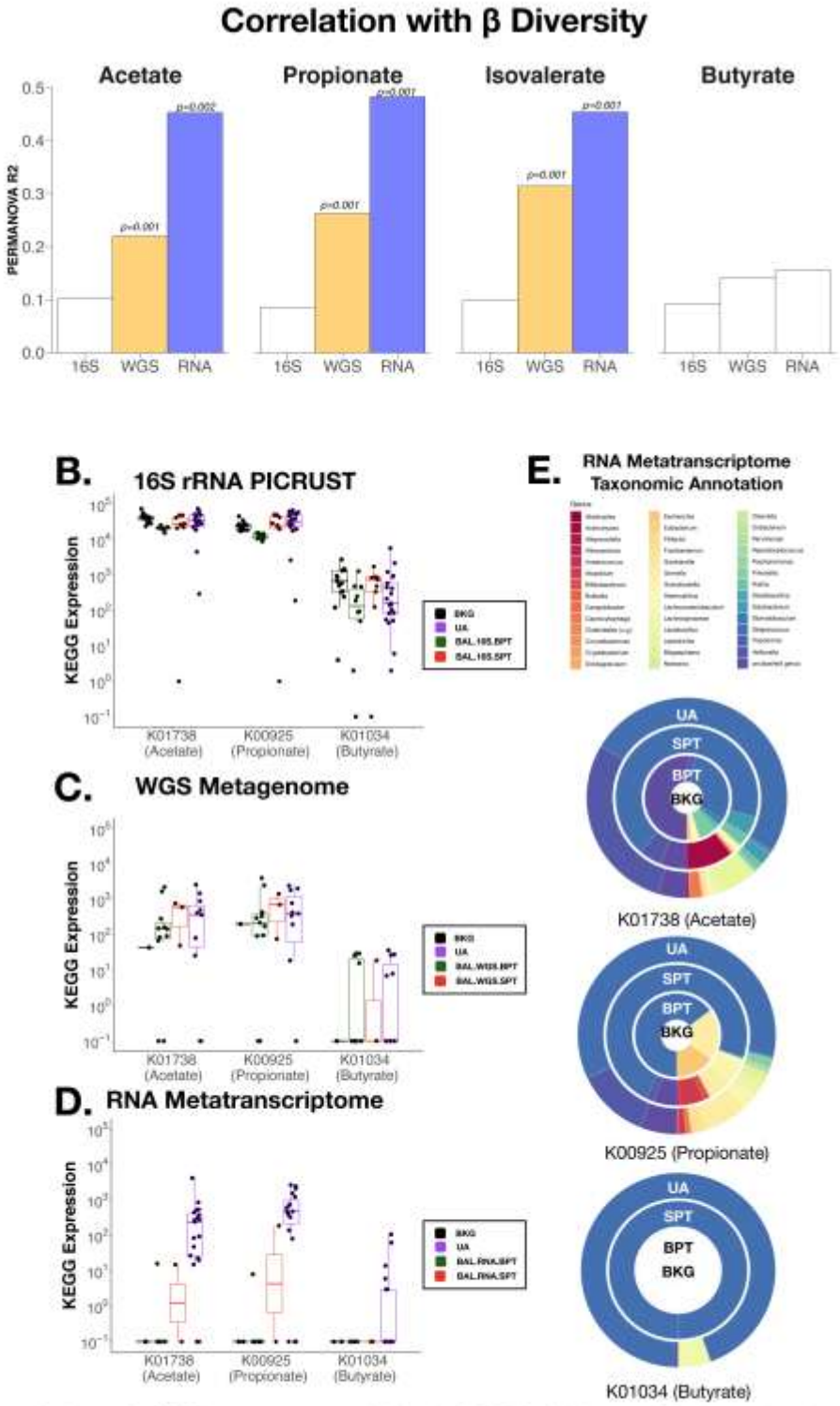


Figure 5: Diversity correlations with SCFA measurements: (**A**) Levels of SCFAs with Acetate, Propionate, Isovalerate and Butyrate were tested (PERMANOVA) against Beta Diversity distribution of data from all three sequencing techniques in BAL samples. Relative abundance of three KOs with direct annotation to measured SCFAs were compared across sample types: K01738 (Acetate), K00925 (Propionate) and K01034 (Butyrate) with (**B**) 16S rRNA gene sequencing, (**C**) Whole Genome Sequencing and (**D**) RNA metatranscriptome sequencing. **(E)** RNA metatranscriptome taxonomic annotation for these three SCFAs-associated KOs in UA, BAL.RNA.SPT, BAL.RNA.BPT and BKG samples are represented here. Each circle represents a different sample type and colors indicate a different taxonomic annotation.

Figure 6

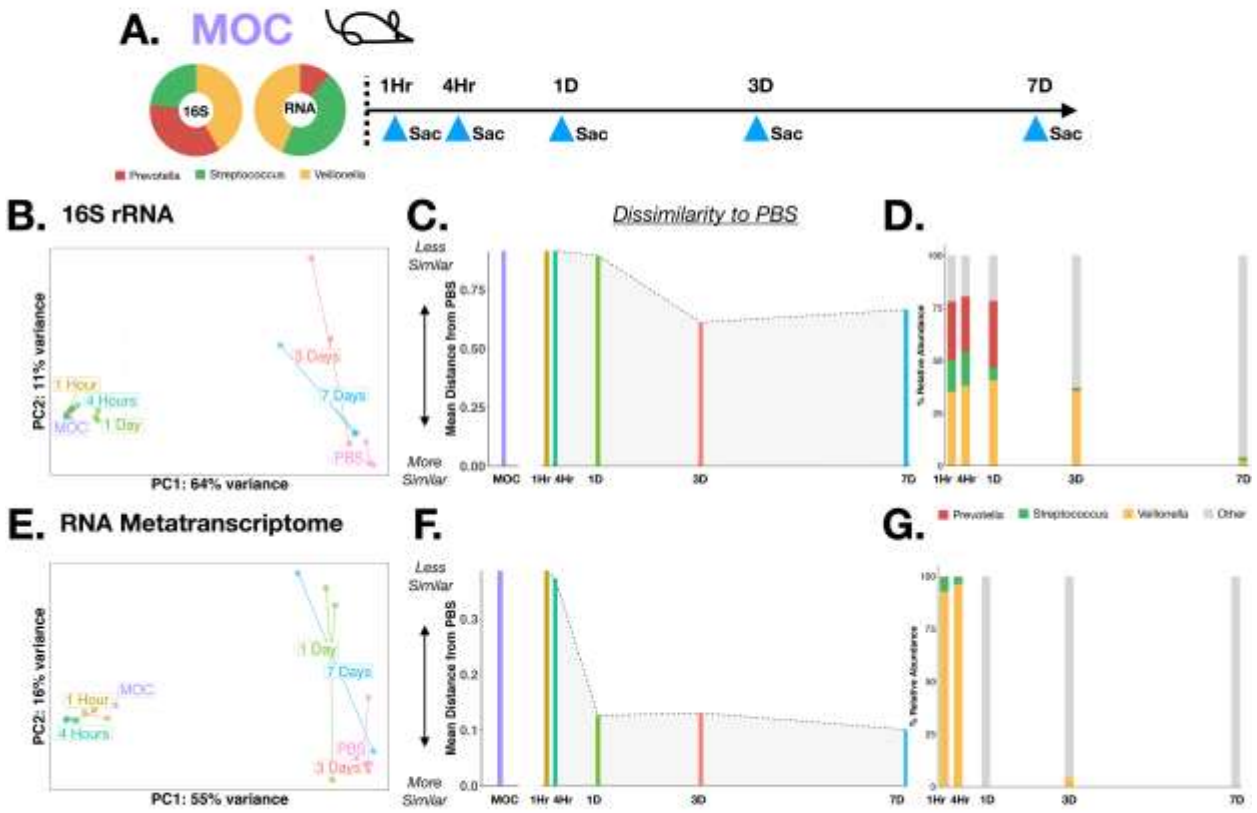


Figure 6: Mouse experiment with 16S rRNA gene and RNA metatranscriptome sequencing: (A) Visual schematic of the experiment, mice (n=17) were inoculated with a mixture of *Prevotella*, *Streptococcus* and *Veillonella* (MOC) and sacrificed at specific time intervals: 1 Hour, 4 Hours, 1 Day, 3 Days, 7 Days. BAL samples were analyzed by 16S rRNA gene sequencing (**B-D**) and RNA metatranscriptome sequencing (**E-G**). Principle coordinate analysis was performed with Bray-Curtis Distances by time point (**B, E**). Mean inter-group distance between sample time point and PBS was calculated (**C, F**). Relative abundance for taxa annotated to *Prevotella*, *Streptococcus* and *Veillonella* were calculated for each time point (**D, G**)

Supplementary Materials:

TITLE:
Functional lower airways genomic profiling of the microbiome to capture active microbial metabolism

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Participants and samples

Inclusion criteria included >50 years old with significant smoking history. Exclusion criteria included recent infection or antibiotic use in the prior three months, no inhaler therapy, no diabetes, cardiovascular or renal disease. On all participants we performed research bronchoscopy to collect bronchoalveolar lavage (BAL) samples, upper airway (UA, which were either supraglottic or oral rinse) and bronchoscope control (BKG) as previously described [1, 2]. Technical background controls (DNA free water passed through DNA/RNA isolation kit) were included.

DNA/RNA isolation:

DNA was extracted from all samples using Qiagen DNA Mini Kit spin column protocol (Qiagen). RNA extraction was carried out with the miRNeasy Micro Kit (Qiagen). RNA was eluted in either 15 or 30µl. RNA quantity and integrity were tested with TapeStation 4200 (Agilent) for all samples. RNA quality control was established using an RNA Integrity Number (RIN) cut-off >5. The BAL of two subjects did not yield quality RNA (RIN < 5). Among BKG samples, only one yielded RNA with sufficient quality and quantity to undergo library and sequencing for the metatranscriptome. The Illumina Ribo-Zero Gold rRNA Removal Kit (Epidemiology) was used to deplete the rRNA from the samples with a modified low input version.

Bacterial Burden assessment

We measured bacterial burden in all samples using a QX200 Droplet Digital PCR System (BioRad, Hercules, CA). For this, primers were 5'- GCAGGCCTAACACATGCAAGTC-3' (63F) and 5'- CTGCTGCCTCCCGTAGGAGT-3' (355R). Cycling conditions included 1 cycle at 95°C for 5 minutes, 40 cycles at 95°C for 15 seconds and 60°C for 1 minute, 1 cycle at 4°C for 5 minutes, and 1 cycle at 90°C for 5 minutes all at a ramp rate of 2°C/second. The BioRad C1000 Touch Thermal Cycler was used for PCR cycling. Droplets were quantified using the Bio-Rad Quantisoft software. Two replicates were used per sample. Negative control specimens (detailed in the text) were used and were run alongside samples.

Microbial community characterization using 16S rRNA gene sequencing (16S rRNA):

High-throughput sequencing of bacterial 16S rRNA gene amplicons encoding the V4 region was performed as previously described.[2] Each unique barcoded amplicon was generated in pairs of 25µl reactions with the following reaction conditions: 11µl PCR-grade H2O, 10µl Hot MasterMix (5 Prime Cat# 2200410), 2µl of forward and reversed barcoded primer (5µM, 515F= 5'-GTGCCAGCMGCCGCGGTAA-3', and 806R= 5'-GGACTACHVGGGTWTCTAAT-3'), and 2µl template DNA. Amplification and detection of the 16S rRNA gene by qPCR was performed with the StepOne™ Real-time PCR System (Applied Biosystems, Foster City, CA, USA). The PCR reaction condition for amplification of DNA were: initial denaturing at 94°C for 3 min followed by 35 cycles of denaturation at 94°C for 45 seconds, annealing at 58°C for 1 minute, and extension at 72°C for 90 seconds, with a final extension of 10 min at 72°C. Amplicons were quantified using Agilent 2200 TapeStation system and pooled. Purification was then performed

using Ampure XT (Beckman Coulter Cat# A63882) as per the manufacturer instructions. Reagent controlled samples and mock mixed microbial DNA were sequenced and analyzed in parallel with the samples. Sequence was performed on the Illumina MiSeq (150bp read length, paired-end protocol) in one single run.

The 16S rRNA gene sequences were analyzed using the Quantitative Insights into Microbial Ecology (QIIME 1.9) package [3]. Reads were demultiplexed and quality filtered with default parameters. We required > 1,000 reads in any sample, a threshold that was achieved with all samples (31,524 [23,128 – 77,405] reads). Reads were demultiplexed and quality filtered with default parameters. Sequences were then clustered into operational taxonomic units (OTUs) using a 97% similarity threshold with UCLUST [4] and annotated using the Greengenes 16S rRNA gene reference dataset [5]. For each sample, the proportion of reads at the OTU or genus levels was used as a measure of the relative abundance of each type of bacteria in a specimen. No OTU was removed from the analysis. To infer the genomic potential of the microbial communities identified by 16S rRNA gene sequencing we computationally predicted the metagenome using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt).[6] This software tool uses the obtained 16S rRNA sequence data to predict the functional profile of a bacterial community based on a database of existing reference genomes.

Microbial community characterization using Whole genome shotgun sequencing (WGS):

Extracted DNA was used as input into the NexteraXT library preparation kit following the manufacturer's protocol. Libraries were purified using the Agencourt AMPure XP beads (Beckman Coulter, Inc.) to remove fragments below 200 bp. The purified libraries were quantified using the Qubit dsDNA High Sensitivity Assay kit (Invitrogen) and the average fragment length for each library was determined using a High Sensitivity D1000 ScreenTape Assay (Agilent). Samples were added in an equimolar manner to form two sequencing pools. The sequencing pools were quantified using the KAPA Library Quantification Kit for Illumina platforms. The pools were then sequenced on the Illumina NextSeq500 (2x150 bp) in one single run.

The metagenomic sequences were filtered to remove the adaptor sequences, and human sequences by using Trimmomatic [7], SortMeRNA [8] and DeconSeq [9]. In addition, fungal and viral sequences were removed. The median sequence read count for raw reads was 32.5M (IQR=18.11M) per sample. After rRNA removal, the median read count was 30.2M (IQR=16.90M), and after human read removal it was 886368 [IQR: 1217360 – 3264527]. The remaining metagenomic sequences were processed for functional and taxonomic annotation using the HUMAnN2 pipeline [10] with the UniRef90 database [11]. The gene assignments were regrouped by KEGG terms and joined into a gene table.

Microbial community characterization using RNA metatranscriptomic sequencing (RNA)

NEB Ultra II RNA Library Prep kit was used for library preparation and each library was subjected to 14-17 cycles of PCR in a manner proportional to RNA input mass. Adaptor concentration was diluted 1:100 or 1:200 to maintain appropriate sample and adaptor

ratio. Library molarity was quantified on the LightCycler 480 (Roche) using the KAPA Library Quantification Kit. Each library was diluted to 20µM before pooling (5 libraries/pool, each pool intended for one lane of the flowcell) and the molarity of each pool was remeasured using the same assays before further dilution to 2µM in preparation for clustering. Two BAL samples failed to amplify and did not generate a typical fragment size distribution; they were excluded from sequencing. Sequence was performed in one single run using HiSeq 2500 in High Output mode with a TruSeq SBS v3-HS kit (2x100 paired-end approach).

Metatranscriptome sequences were filtered to remove the adaptor sequences, ribosomal RNA and human sequences by using Trimmomatic, SortMeRNA, and DeconSeq [7-9]. In addition, fungal and viral sequences were removed. The median read count for the raw reads was 84.8M (IQR=26.86M) per sample. After rRNA removal, the median read counts were 60M (IQR=14.30M); after removing the human reads, it was 1794919 [IQR: 766116 – 58743048]. The first three bases on the reverse sequences were removed using Seqtk due to low quality. The remaining metatranscriptomic sequences were processed for functional and taxonomic annotation using the HUMAnN2 pipeline [10] with the UniRef90 database [11]. The gene assignments were regrouped by KEGG terms and joined into one gene table.

Measurement of Short Chain Fatty Acids

Each sample (50µl) was diluted to 100µl with HPLC-grade water. A solution of hydrochloric acid (30mM) plus isotopically-labeled acetate (150µM), butyrate (10µM),

and hexanoate (2µM) in water was added to each sample and vortexed. Methyl tert-butyl ether (MTBE; 300µl) was added to each sample, and the mixture was vortexed (10 s) to emulsify, then held at 4°C for 5 min, and vortexed again (10 s). Samples were centrifuged (1 min) to separate the solvent layers. The MTBE layer was then removed and transferred to an autosampler vial for GC-MS analysis. A small volume (10µl) of the MTBE layer was removed from each sample and pooled in a separate autosampler vial for quality control purposes. A series of calibration standards were prepared along with samples to quantify metabolites.

GC-MS analysis was performed on an Agilent 69890N GC- 5973 MS detector (Agilent, Santa Clara, CA USA) using the following parameters: sample (1µl) was injected with a 1:10 split ratio on a ZB-WAXplus, 30m_ 0.25mm x 0.25 mm (Phenomenex Cat# 7HG-G013-11) GC column, with helium as the carrier gas at a flow rate: 1.1 ml/min. The injector temperature was 240°C, and the column temperature was isocratic at 310°C. Data were processed using MassHunter Quantitative analysis version B.07.00 (Agilent). Two replicated injections of five standards were used to create a linear calibration curve with accuracy better than 80% for each standard. Each detected SCFA was normalized to the nearest isotope labeled internal standard and quantitated from the linear phase of the standard curve. Normalization between sample type, by measuring urea, was not performed due previously published limitations with this method [12-14].

Mouse Experiment

Twenty female C57BL/6J mice (8-14 weeks of age, 18-22 grams/mouse) were purchased from a vendor (Jackson Research Laboratories, Bar Harbor, ME Cat#000664). All mice were allowed 2 weeks of acclimation to their facilities prior to the start of experiments and mice with different experimental condition arm were cohoused to limit potential cage effect on the microbiome and host immune tone.

Three mice were inoculated with PBS while the remaining 17 mice were inoculated with a mixture of human oral commensals (MOC) consisting of *Prevotella, Streptococcus and Veillonella.* The mice were anesthetized using isoflurane via VetFlo Anesthesia machine (Kent Scientific, Torrington, CT) sedated to 10-15 breaths per minute and monitored for any distress. The mice were then placed on an intubation platform and with blunt forceps, their tongue was gently pulled ventrally until the pharynx was exposed [15]. A human otoscope with a 2 mm ear cone (Welch Allyn 3.5V Hill-Rom, Inc., Skaneateles Falls, NY Model #20200) was introduced into the oral airway to expose and visualize the murine vocal cords and a gel-loading pipette tip loaded with a 50 ml aliquot was introduced through the vocal cords of the mouse and deployed into the lower airway. Then, the mouse was removed from the platform to recover from anesthesia on a heat pad. Mice were monitored every 2-4 hours following intra-tracheal challenge. The MOC exposed mice were sacrificed at each time point: 1Hr (n=4), 4Hr (n=4), 1Day (n=3), 3Day (n=3) and 7Day (n=3) (**Figure 6A**). The PBS exposed mice were all sacrificed at 1Hr. BAL samples were sent for 16S rRNA gene sequencing and RNA metatranscriptome sequencing. The animal studies described in these experiments were approved by the Institutional Animal Care and Use Committee at the

respective institutions (New York University School of Medicine IACUC# s16-00032). Laboratory animal care policies follow the Public Health Service Policy on Humane Care and Use of Laboratory Animals.

Statistical Analysis

For association with discrete factors, we used non-parametric tests (Mann-Whitney or Kruskal-Wallis ANOVA). We used the *vegan* package in R to construct Principal Coordinate Analysis (PCoA) based on Bray-Curtis distances [16, 17] and PERMANOVA to test statistical differences based on β-diversity. To cluster microbiome communities into exclusive 'metacommunities' we used a Dirichlet Multinomial Mixture Model using the R package *DirichletMultinomial* [18, 19]. For tests of association with continuous variables, we used non-parametric Spearman correlation tests. To evaluate differences between groups within each sequence data type, we evaluated differential expression with DESeq2 [20] with a false discover rate (FDR) <0.05 [21]. To compare the sequencing methods, we used Gene Set Enrichment Analysis (GSEA, [22]) and PROCRUSTES (an analytical pipeline that can overlay paired sample β diversity distribution obtained by two different sequence data types). Summary of KOs for pathway analysis was performed by aligning KOs with associated pathways from the KO Database (https://www.genome.jp/kegg/ko.html). With KOs with multiple pathways, the read count for that KO was added to each pathway. Data was then summarized for each pathway. Further analysis was also done to identify contaminants from the three different sequencing datasets. To perform this, a prevalence-based method using the R package *decontam[23],* with a threshold of 0.7, was used. In this process, all reads from BKG

(bronchoscope control) samples were identified as negative controls and prevalence of each sequence feature in all other sample types was identified as contaminants. All data is publicly available in Sequence Read Archive (SRA) under accession numbers PRJNA603592, PRJNA573853 and PRJNA603675. All codes utilized for the analysis included in this manuscript are available at:

https://github.com/segalmicrobiomelab/functional_microbiomics

Supplementary Results:

Taxonomic signature differences between sequencing data types

To evaluate similarities of taxonomic annotation at a global level we used PROCRUSTES with Monte-Carlo simulation. While there was high correlation in β-diversity between WGS and RNA taxonomic assignment (p=0.001), there was no significant correlation when 16S rRNA gene sequencing data was compared with WGS or RNA data (**Supplementary Figure 3**).

Based on 16S rRNA gene sequencing, several taxa were significantly enriched (FDR <0.05) in samples identified as BAL.SPT as compared with BAL.BPT (**Figure 2A, Supplementary Data 2**) with a number of known oral commensals, such as *Prevotella*, *Veillonella* and *Streptococcus*, enriched in BAL.SPT. Using 16S rRNA gene sequencing SPT/BPT assignment, we evaluated the taxonomic differences identified with the other sequencing methods. Comparing BAL.16S.SPT to BAL.16S.BPT, there were fewer significantly enriched taxa within the WGS (**Figure 2C, Supplementary Data 2**), most of

which were annotated to the genus *Streptococcus*. However, in the RNA sequencing data, there were a number of taxa significantly enriched in BAL.16S.SPT samples as compared with BAL.16S.BPT samples, including *Veillonella*, *Rothia*, and *Streptococcus* **(Figure 2E, Supplementary Data 2).** Using Gene-Set-Enrichment Analysis (GSEA), we compared the different sequencing methods for 16S.SPT/16S.BPT signatures in BAL samples (at the genus level) and identified very little overlap (**Figures 2B**, **2D** and **2F**).

Functional overlap and differences across sequencing data types

We used PROCRUSTES to evaluate similarities in global functional annotation between sequence datasets. Monte-Carlo simulation showed that there was statistically significant overlap between the three datasets ($p<0.01$ for all comparisons, **Supplementary Figure 4**). The 16S rRNA gene sequence data was used to infer the predictive metagenome allowing us to identify several KEGG Orthology (KO) pathways that should be enriched in BAL.16S.SPT samples (**Figure 1F**). We then used WGS and RNA sequencing KEGG annotated data to explore functional capacity on measured genes between BAL.16S.SPT and BAL.16S.BPT. WGS data revealed few differentially enriched pathways between BAL.16S.SPT and BAL.16S.BPT, most of which were associated with Ribosome function (**Supplementary Figure 5A, Supplementary Data 3**). A larger number of differentially enriched KEGGs were identified in the RNA metatranscriptome data, all enriched in BAL.16S.SPT samples. Among these pathways we identified lipid metabolism and fatty acid metabolism as enriched (**Supplementary Figure 5B, Supplementary Data 3**).

Ex Vivo analysis of Short Chain Fatty Acids

We first evaluated our ability to detect SCFA production by oral anaerobes frequently found in the lower airways. To this end, we measured SCFA levels in an *ex vivo* culture of *Veillonella parvula* grown under anaerobic conditions. Compared to media alone, the supernatant of *Veillonella parvula* had higher levels of 3/7 SCFAs: acetate, propionate and isovalerate (**Supplementary Figure 6A**). Given the concern of volatility of SCFAs and use of these metabolites by mammalian cells in human biological samples we then measured SCFA levels after the addition of butyrate and propionate to BAL cells *ex vivo*. Levels of butyrate and propionate remained measurable for at least 1 and 3 hours, respectively (**Supplementary Figure 6B-C**) which exceeds the time normally taken to process samples from our bronchoscopies (usually < 1hr).

Further Clustering of Samples by Sequencing Method

Clustering for each of these data types show 2 clusters as the best fit (**Supplementary Figure 8A & C**). However, within WGS only 3 BAL samples clustered with UA samples (BAL.WGS.SPT, **Supplementary Figure 8B**), while with the RNA metatranscriptome only 2 BAL samples clustered with UA samples (BAL.RNA.SPT, **Supplementary Figure 8D**), all of which were the samples with the highest levels of SCFAs, as shown in **Figure 4**.

Decontamination Analysis

In both the 16S rRNA and RNA Metatranscriptome, contaminants were identified as BPT taxa such as *Flavobacterium* and *Propionibacterium (***Supplementary Figure 9A, B, &**

Supplementary Table 4*)*. SPT taxa such as *Streptococcus* and *Veillonella* were not identified as contaminants. In the WGS dataset, contaminants were genes that were unmapped or ungrouped and thus did not have a taxonomic annotation (**Supplementary Figure 9C & Supplementary Table 4**).

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Supplemental Information

Supplementary Figure 1: α Diversity for WGS Metagenome and RNA Metatranscriptome data. Shannon Index of (**A**) WGS Metagenome and (**B**) RNA Metatranscriptome data.

Supplementary Figure 2: Rarefaction analysis for each sequencing datasets. Each line represents a sample and the dash line represents the mean for all samples. Sequence depth (x axis) is compared with OTU or KO annotation (y axis). (A) 16S rRNA gene sequencing (B) Whole Genome Sequencing (C) RNA Metatranscriptome.

Supplementary Figure 3: Comparison of global taxonomic composition across different sequencing data types. PROCRUSTES analysis, using Bray-Curtis Distance matrices, was used to compare taxonomic annotation for the three data types. Monte-Carlo simulation test was used for statistical significance. (**A**) Comparison between 16S rRNA gene sequencing and WGS Metagenome (Monte-Carlo p-value=ns). (**B**) Comparison between 16S rRNA gene sequencing and RNA Metatranscriptome (Monte-Carlo p-value=ns). (**C**) Comparison between WGS Metagenome and RNA Metatranscriptome (Monte-Carlo p-value <0.01).

Supplementary Figure 4: Comparison of global functional composition across different sequencing data types. PROCRUSTES analysis, with Bray-Curtis Distance matrices, was used to compare functional annotation across the sequencing data types.

Monte-Carlo simulation test was used for statistical significance. (**A**) Comparison between 16S rRNA gene sequencing and WGS Metagenome (Monte-Carlo p-value<0.01). (**B**) Comparison between 16S rRNA gene sequencing and RNA Metatranscriptome (Monte-Carlo p-value<0.01). (**C**) Comparison between WGS Metagenome and RNA Metatranscriptome (Monte-Carlo p-value <0.01).

Supplementary Figure 5: Functional signatures identified as differentially enriched in BAL.SPT on WGS Metagenome and RNA Metatranscriptome data. DESEQ2 analysis of WGS Metagenome (**A**) and RNA Metatranscriptome (**B**) functional annotation identified KOs differentially enriched in BAL.16S.SPT vs. BAL.BPT.16S samples (FDR<0.05). Circle size is representative of KEGG Expression.

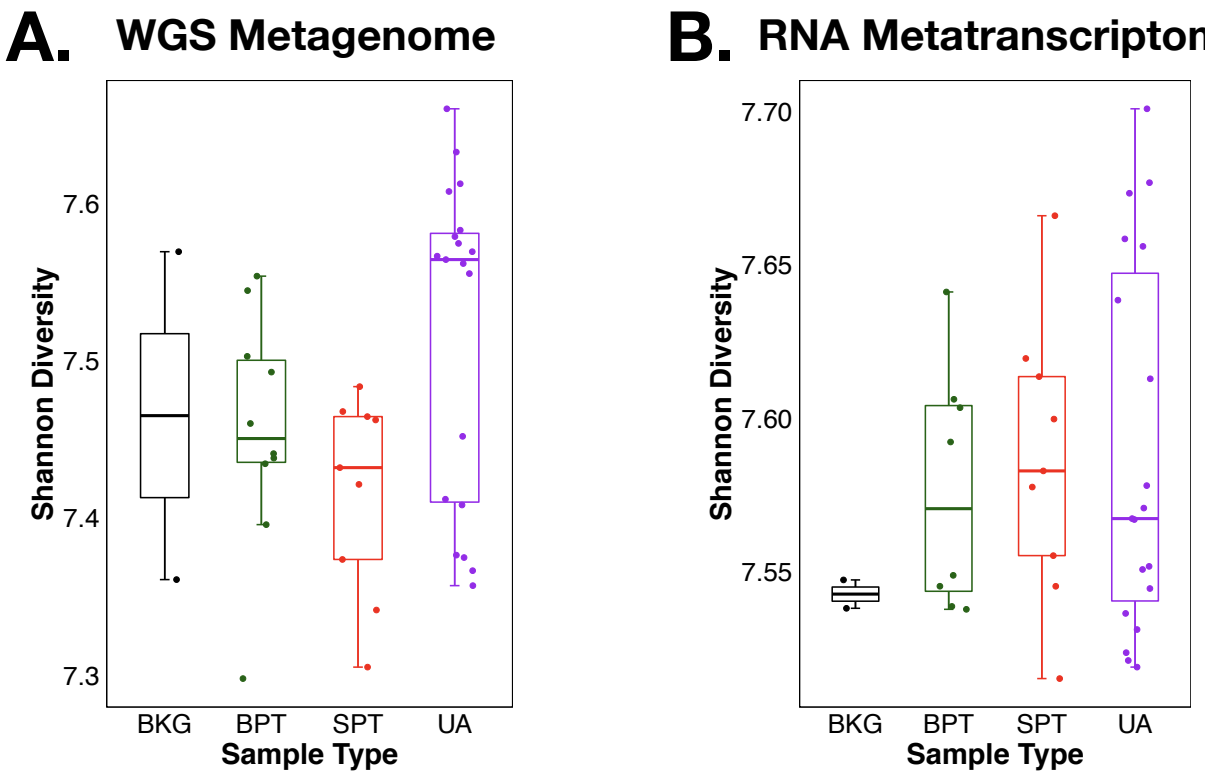
Supplementary Figure 6: Ex-Vivo measurement of Short Chain Fatty Acids (SCFAs) levels. (A) Levels of SCFAs in supernatant of *Veillonella parvula* in culture media were compared with media alone. Longitudinal change in levels of Butyrate (**B**) or Propionate (**C**) after ex vivo addition to BAL cells.

Supplementary Figure 7: Comparison of levels of SCFAs in UA and BAL samples. Correlation analysis using spearman rho showed no significant association between levels of SCFAs detected in UA and BAL samples.

Supplementary Figure 8: Clustering of WGS Metagenome and RNA Metatranscriptome: Dirichlet Multinomial Modelling (DMM) of all samples was performed separately for WGS Metagenome (**A**) and RNA Metatranscriptome (**C**). In both cases, 2 clusters were identified as the best model fit. Principle Co-ordinate analysis of WGS metagenome (**B**), based on Bray-Curtis Distance, using DMM clustering of BAL samples showed that only three BAL Samples clustered with UA samples. Principle Co-ordinate analysis of RNA metatranscriptome (**C**), based on Bray-Curtis Distance, using DMM clustering of BAL samples showed that only two BAL Samples clustered with UA samples.

Supplementary Figure 9: Identifying Potential Contaminants. Using *decontam* with a threshold of 0.7, contaminants were identified based on their prevalence in BAL and Upper Airway (UA) samples when compared to Background (BKG) samples. The top taxa, identified as contaminants, median relative abundance, is displayed for the (A) 16S rRNA gene sequencing (**B**) Whole Genome Sequencing and (**C**) RNA Metatranscriptome.

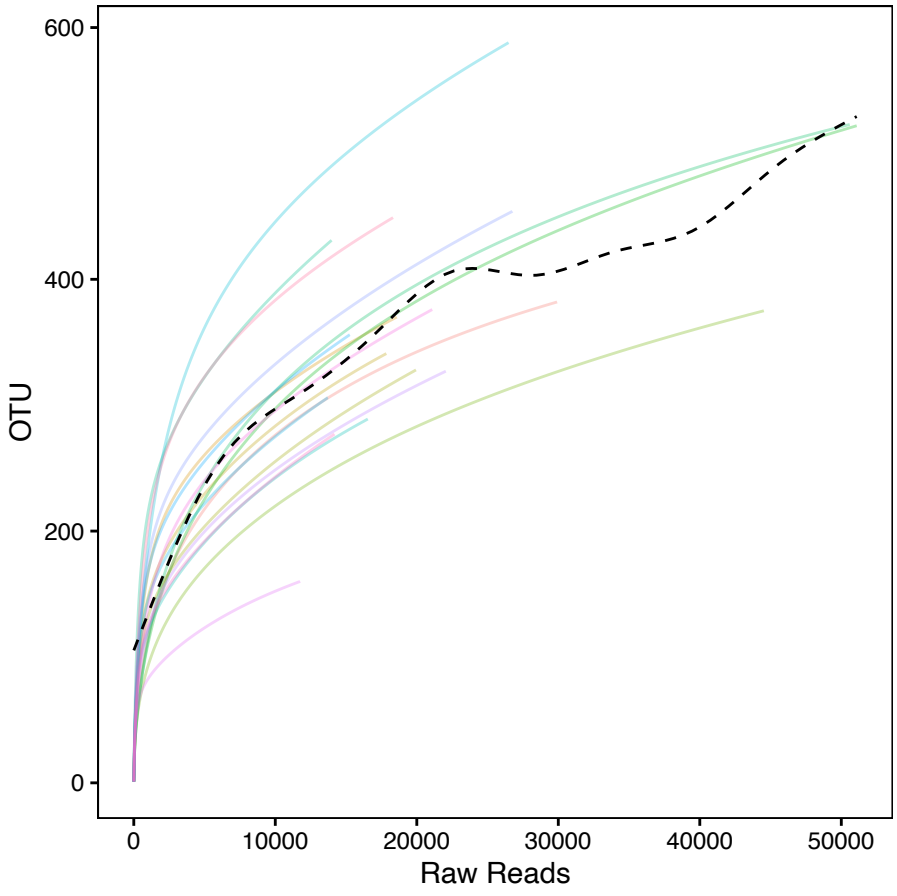
SFigure 1


A.
WGS Metagenome
Shannon Diversity
7.6
7.5
7.4
7.3
BKG
BPT
SPT
UA
Sample Type
B.
RNA Metatranscriptome
Shannon Diversity
7.70
7.65
7.60
7.55
BKG
BPT
SPT
UA
Sample Type

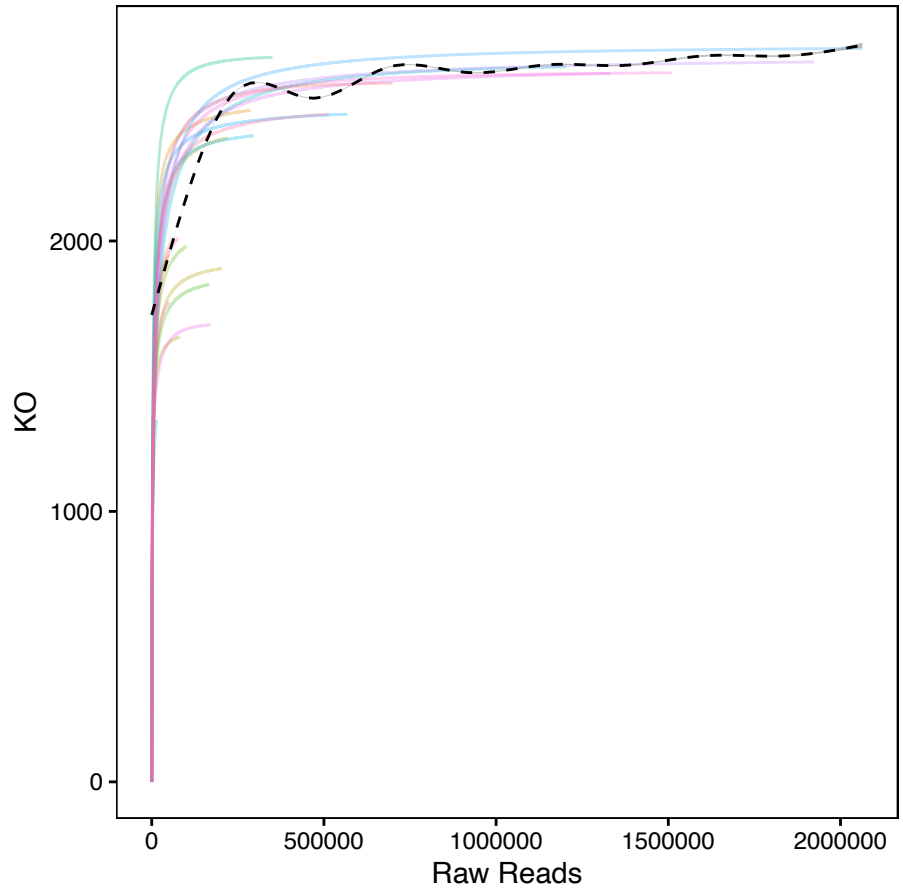
SFigure 2

Rarefaction Analysis

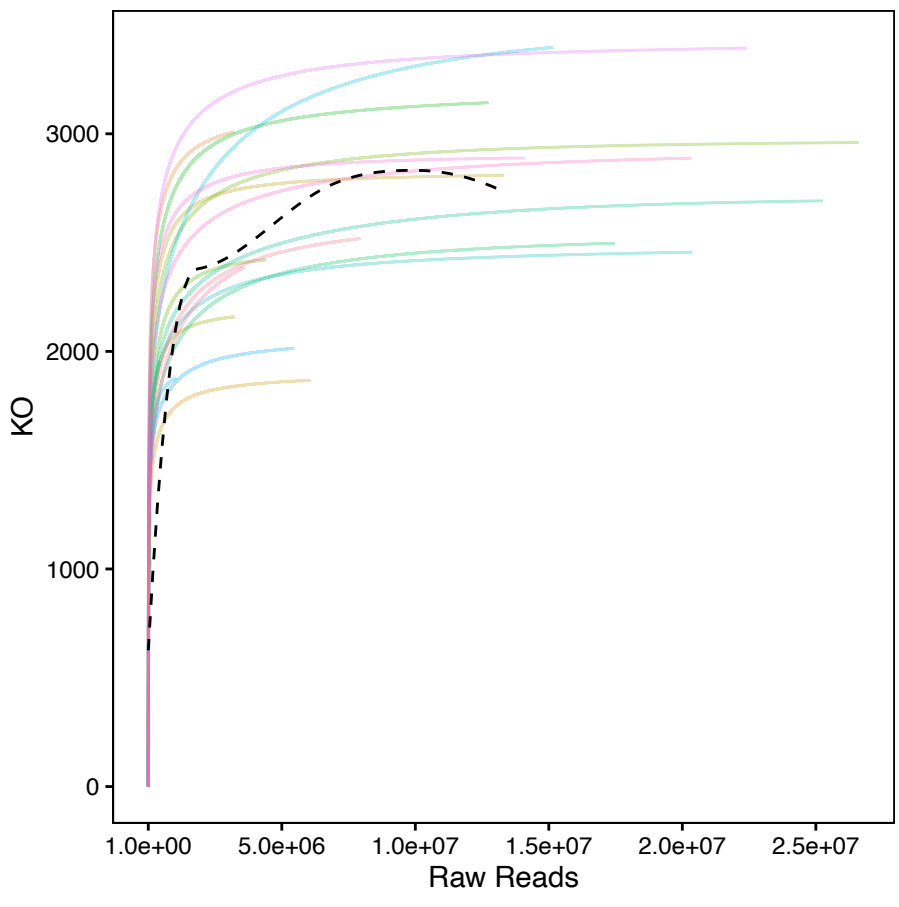
A. 16S



B. WGS



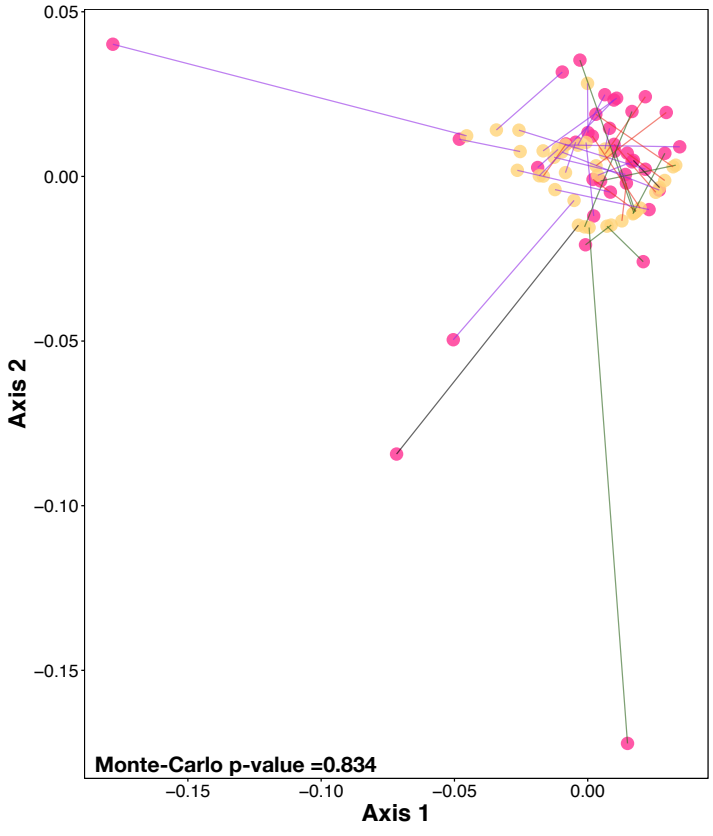
C. RNA



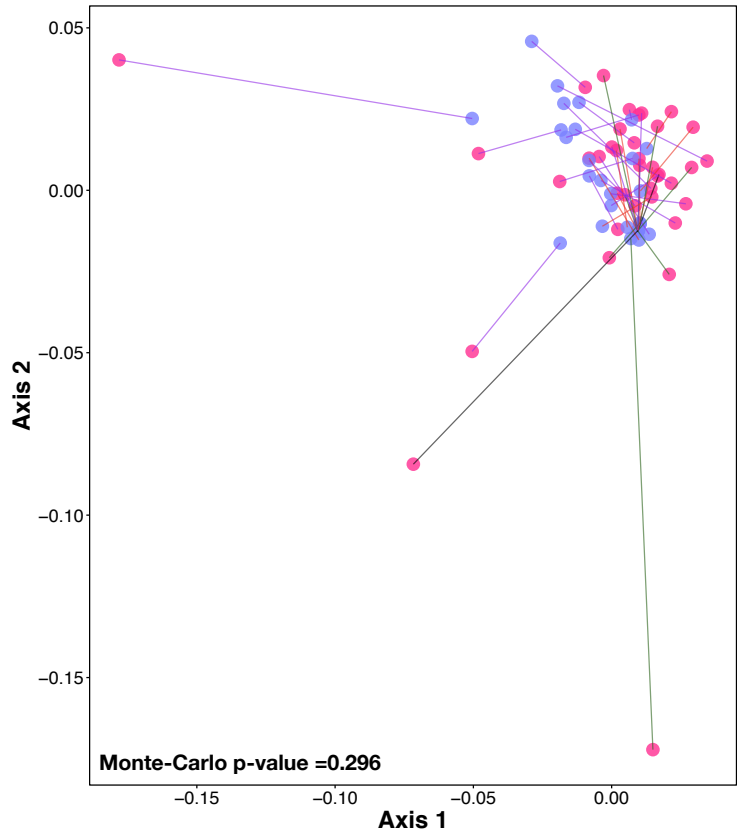
SFigure 3

Taxonomic Annotation

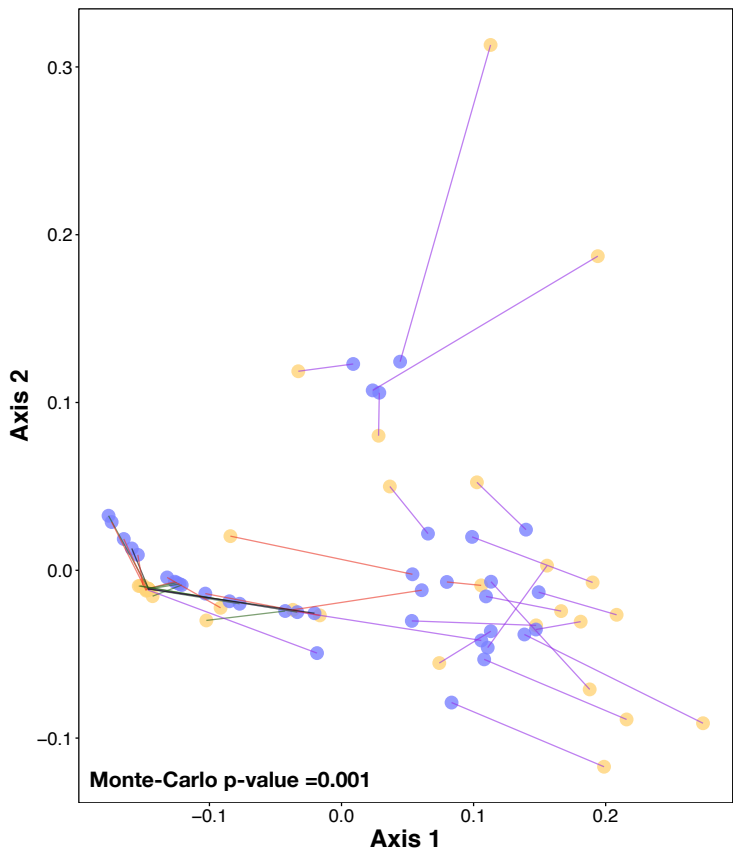
A. 16S vs. WGS

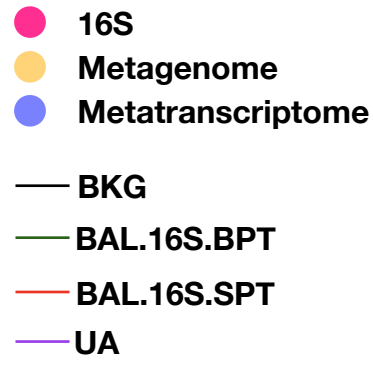


B. 16S vs. RNA



C. WGS vs. RNA

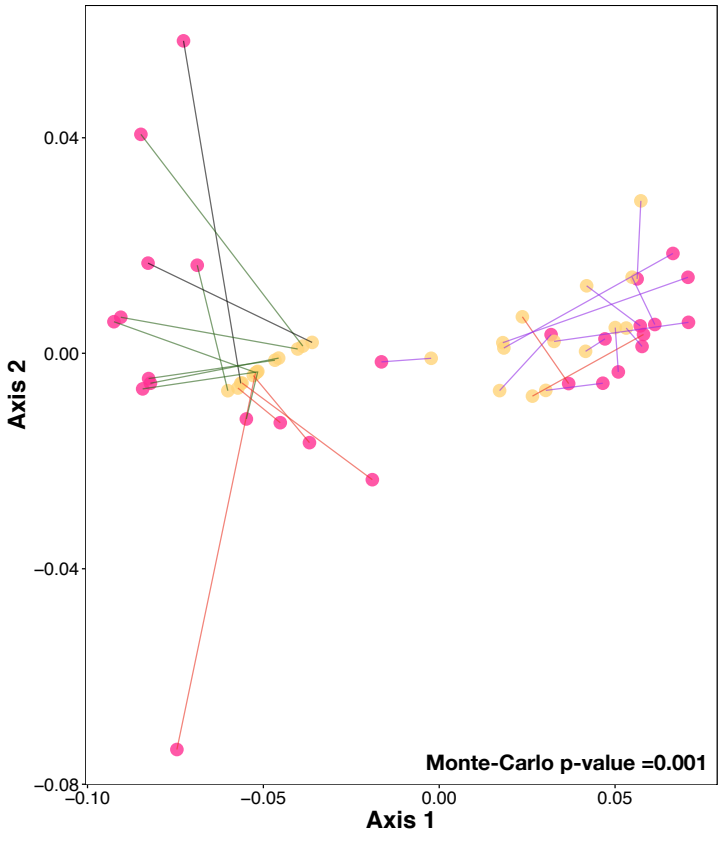




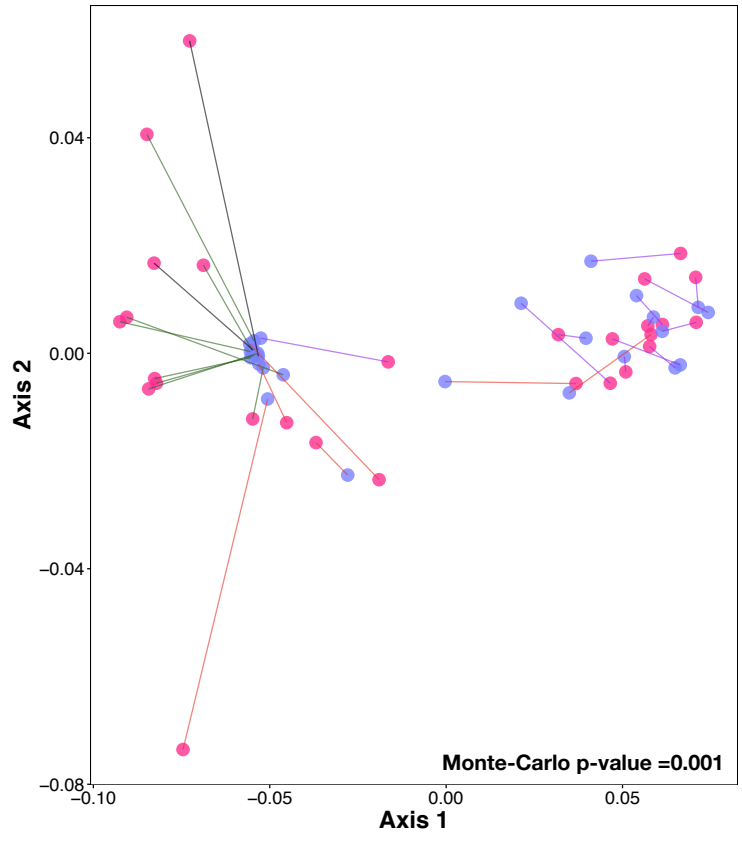
SFigure 4

Functional Annotation

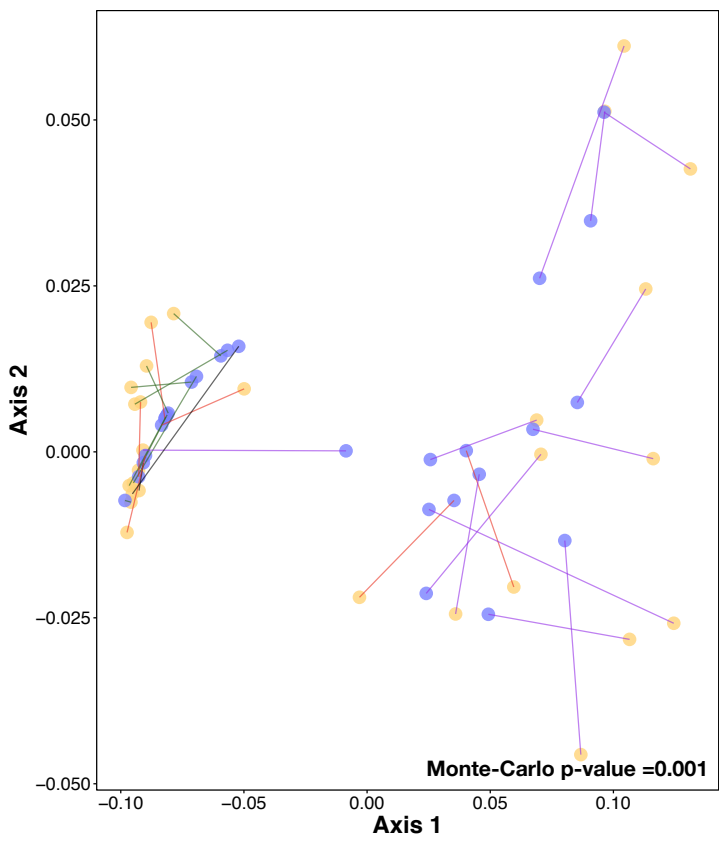
A. 16S vs. WGS

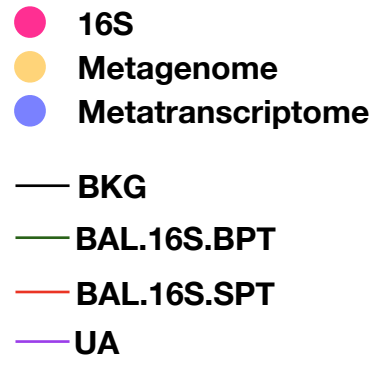


B. 16S vs. RNA

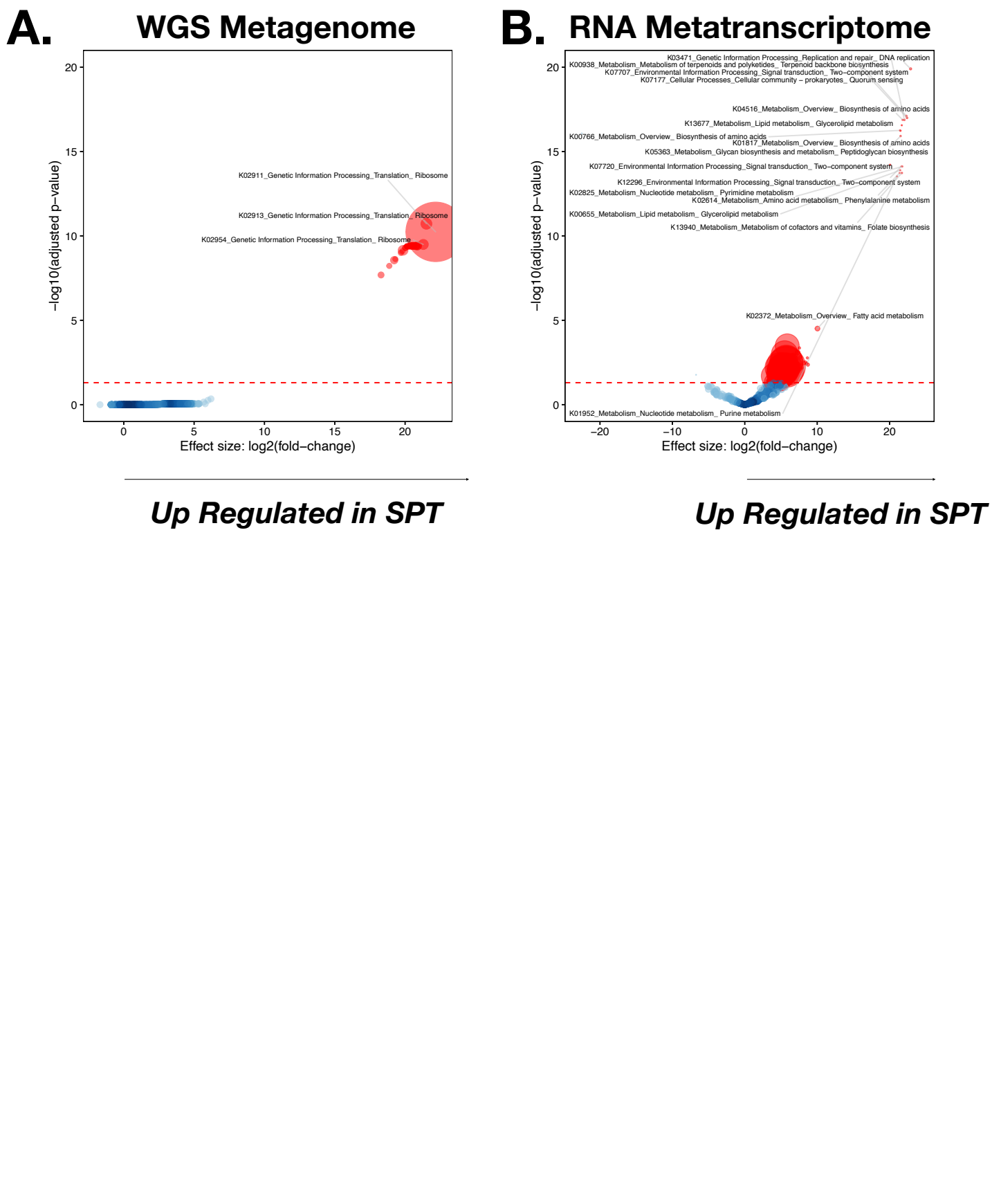


C. WGS vs. RNA

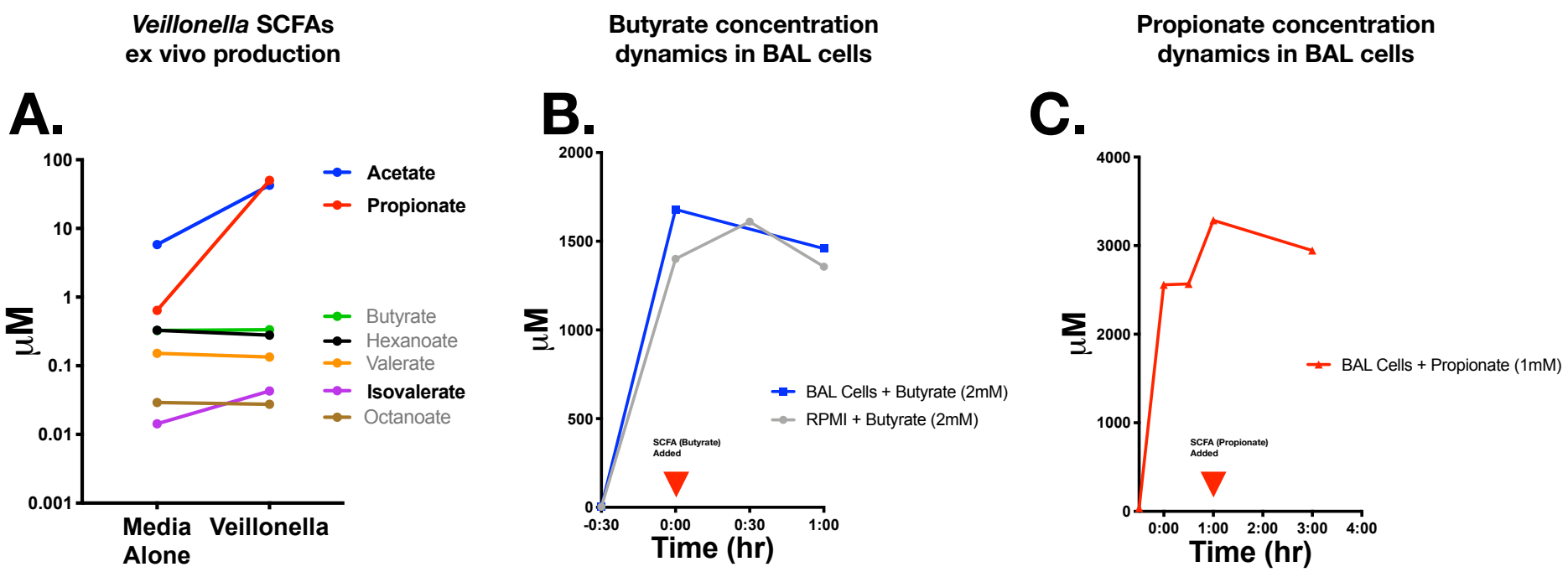




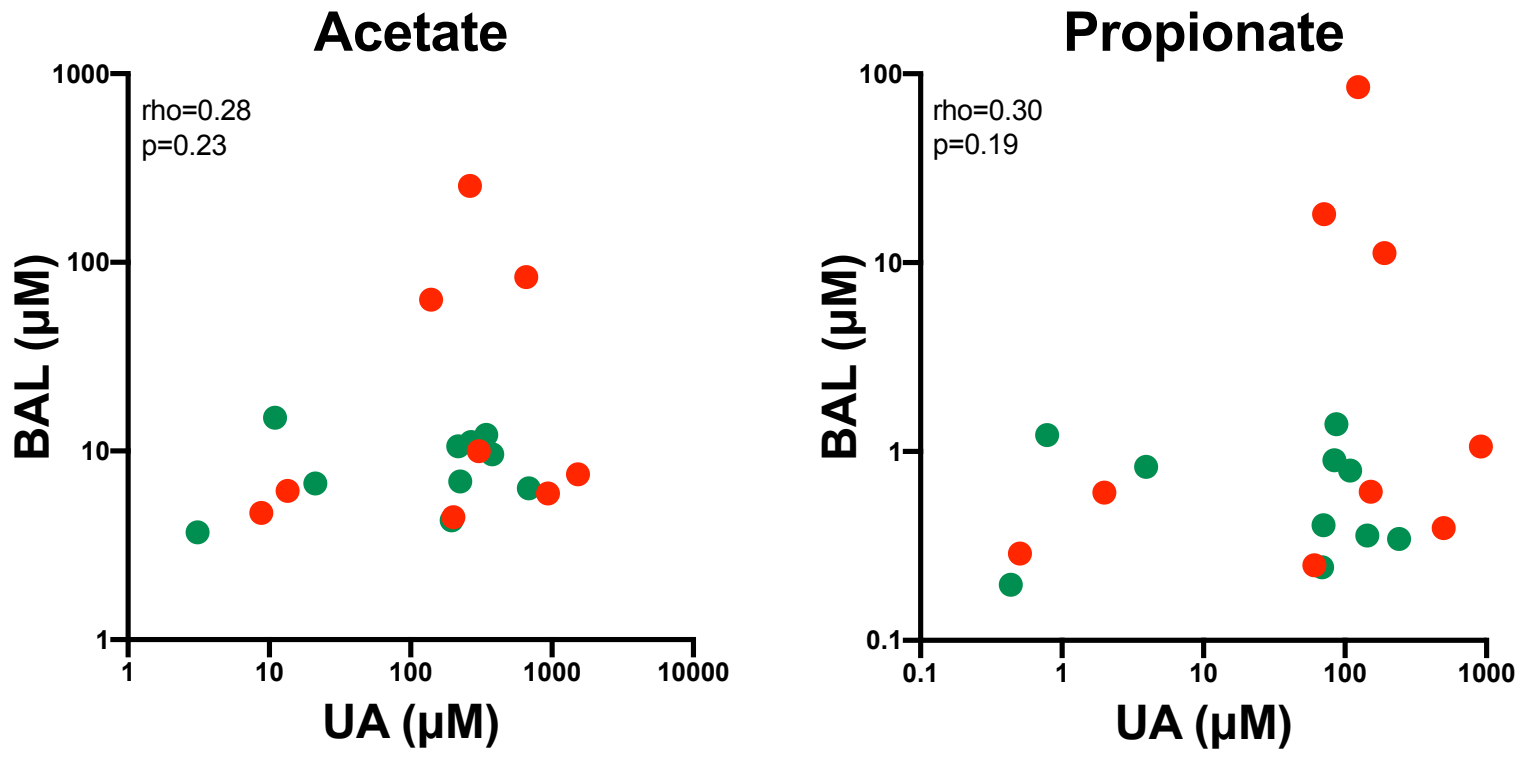
SFigure 5


A.
WGS Metagenome
K02911_Genetic Information Processing_Translation_ Ribosome
K02913_Genetic Information Processing_Translation_ Ribosome
K02954_Genetic Information Processing_Translation_ Ribosome
−log10(adjusted p−value)
Effect size: log2(fold−change)
Up Regulated in SPT
B.
RNA Metatranscriptome
K03471_Genetic Information Processing_Replication and repair_ DNA replication
K00938_Metabolism_Metabolism of terpenoids and polyketides_ Terpenoid backbone biosynthesis
K07707_Environmental Information Processing_Signal transduction_ Two−component system
K07177_Cellular Processes_Cellular community − prokaryotes_ Quorum sensing
K04516_Metabolism_Overview_ Biosynthesis of amino acids
K13677_Metabolism_Lipid metabolism_ Glycerolipid metabolism
K00766_Metabolism_Overview_ Biosynthesis of amino acids
K01817_Metabolism_Overview_ Biosynthesis of amino acids
K05363_Metabolism_Glycan biosynthesis and metabolism_ Peptidoglycan biosynthesis
K07720_Environmental Information Processing_Signal transduction_ Two−component system
K12296_Environmental Information Processing_Signal transduction_ Two−component system
K02825_Metabolism_Nucleotide metabolism_ Pyrimidine metabolism
K02614_Metabolism_Amino acid metabolism_ Phenylalanine metabolism
K00655_Metabolism_Lipid metabolism_ Glycerolipid metabolism
K13940_Metabolism_Metabolism of cofactors and vitamins_ Folate biosynthesis
K02372_Metabolism_Overview_ Fatty acid metabolism
K01952_Metabolism_Nucleotide metabolism_ Purine metabolism
−log10(adjusted p−value)
Effect size: log2(fold−change)
Up Regulated in SPT

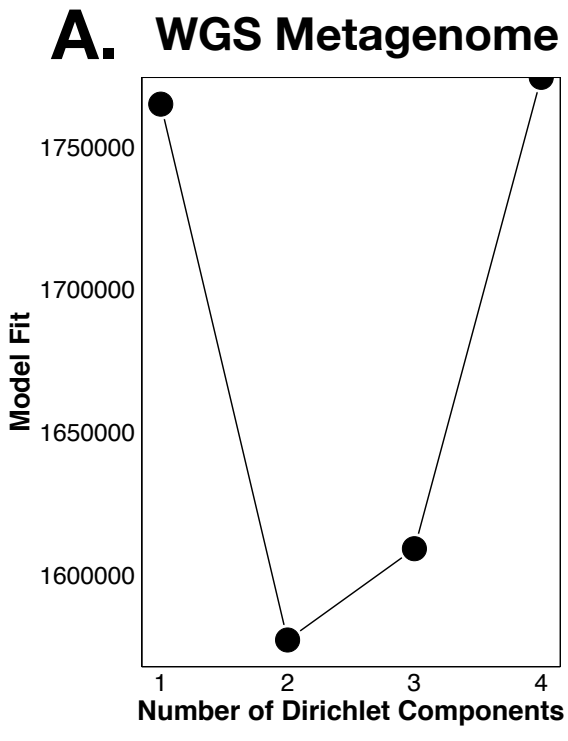
SFigure 6

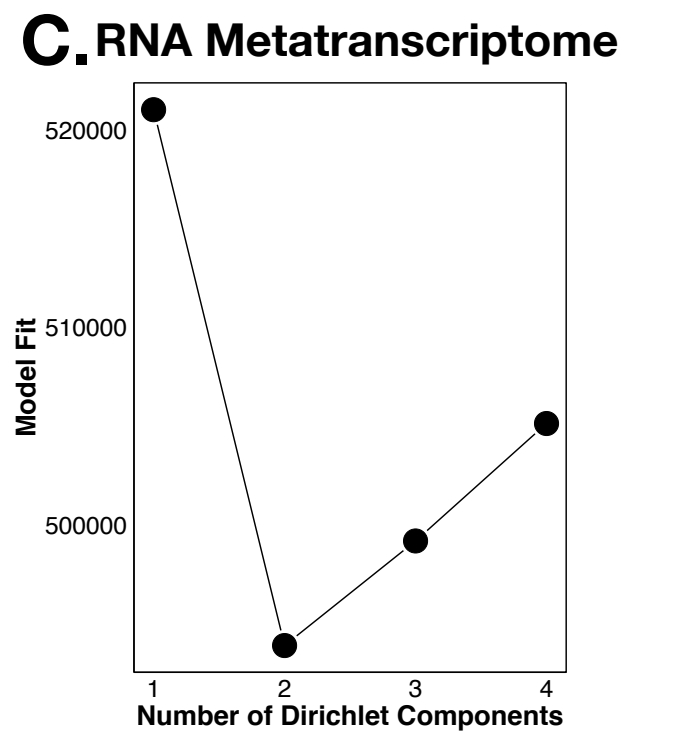

Veillonella SCFAs
ex vivo production
A.
100
10
1
0.1
0.01
0.001
µM
Media Alone
Veillonella
Acetate
Propionate
Butyrate
Hexanoate
Valerate
Isovalerate
Octanoate
Butyrate concentration
dynamics in BAL cells
B.
2000
1500
1000
500
0
µM
-0:30
0:00
0:30
1:00
Time (hr)
SCFA (Butyrate)
Added
BAL Cells + Butyrate (2mM)
RPMI + Butyrate (2mM)
Propionate concentration
dynamics in BAL cells
C.
4000
3000
2000
1000
0
µM
0:00
1:00
2:00
3:00
4:00
Time (hr)
SCFA (Propionate)
Added
BAL Cells + Propionate (1mM)

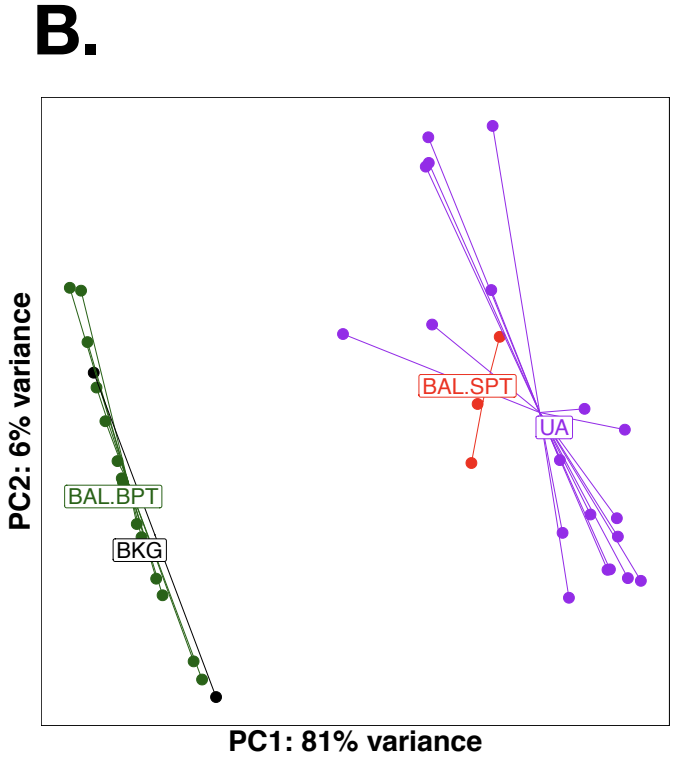
SFigure 7

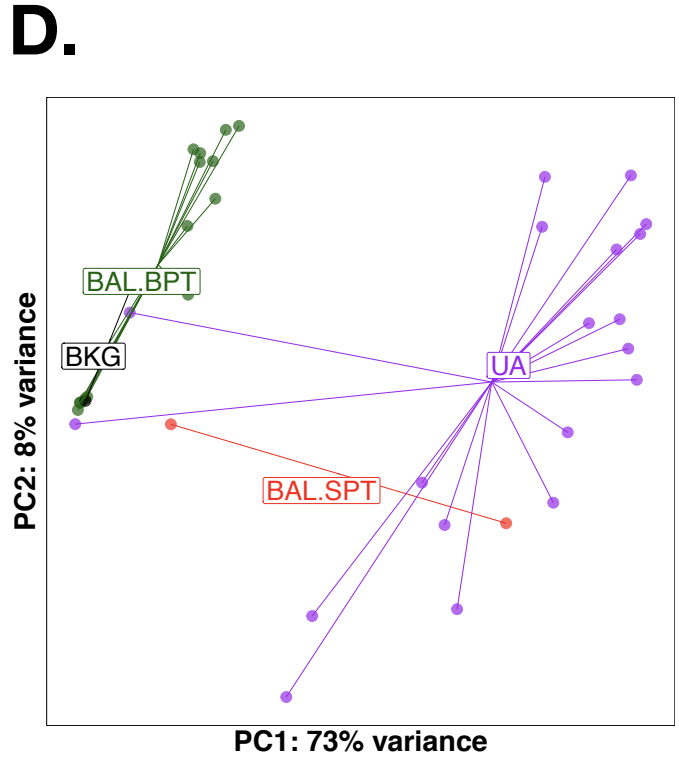

Acetate
rho=0.28
p=0.23
BAL (µM)
1000
100
10
1
1
10
100
1000
10000
UA (µM)
Propionate
rho=0.30
p=0.19
BAL (µM)
100
10
1
0.1
0.1
1
10
100
1000
UA (µM)
Isovalerate
rho=-0.04
p=0.85
BAL (µM)
1
0.1
0.01
0.01
0.1
1
10
100
UA (µM)
Butyrate
rho=0.10
p=0.66
BAL (µM)
10
1
0.1
0.01
0.1
1
10
100
UA (µM)
BAL16S.SPT
BAL16S.BPT

SFigure 7

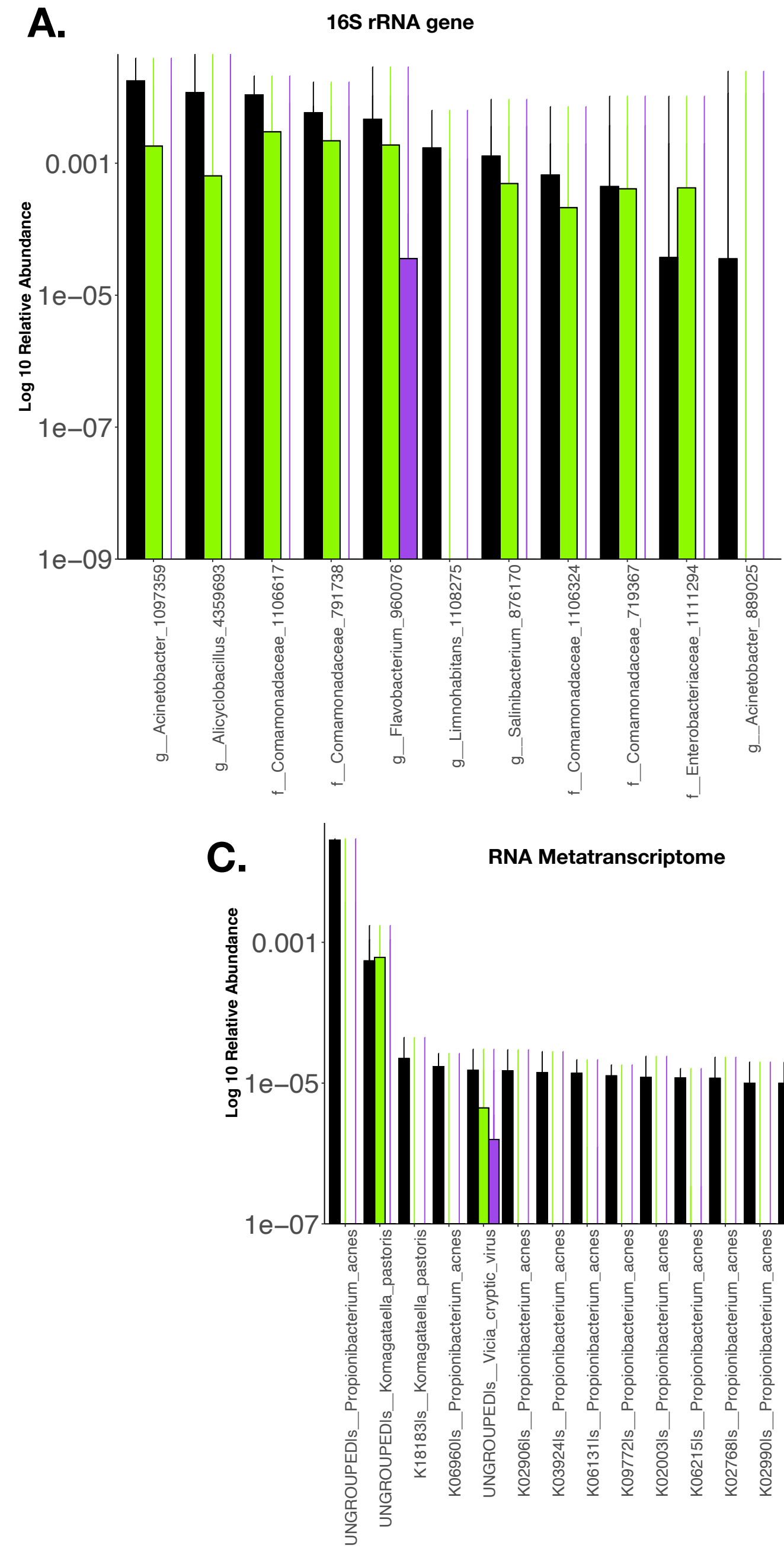

A.
WGS Metagenome
1750000
1700000
1650000
1600000
Model Fit
1
2
3
4
Number of Dirichlet Components


C.
RNA Metatranscriptome
520000
510000
500000
Model Fit
1
2
3
4
Number of Dirichlet Components


B.
PC2: 6% variance
BAL.BPT
BKG
BAL.SPT
UA
PC1: 81% variance


D.
PC2: 8% variance
BAL.BPT
BKG
UA
BAL.SPT
PC1: 73% variance

SFigure 9


A.
16S rRNA gene
Log 10 Relative Abundance
0.001
1e−05
1e−07
1e−09
g__Acinetobacter_1097359
g__Alicyclobacillus_4359693
f__Comamonadaceae_1106617
f__Comamonadaceae_791738
g__Flavobacterium_960076
g__Limnohabitans_1108275
g__Salinibacterium_876170
f__Comamonadaceae_1106324
f__Comamonadaceae_719367
f__Enterobacteriaceae_1111294
g__Acinetobacter_889025
B.
WGS Metagenome
Log 10 Relative Abundance
0.1
0.001
1e−05
1e−07
UNMAPPED
UNGROUPED
UNGROUPEDlunclassified
C.
RNA Metatranscriptome
BKG
UA
BAL
Log 10 Relative Abundance
0.001
1e−05
1e−07
UNGROUPEDls__Propionibacterium_acnes
UNGROUPEDls__Komagataella_pastoris
K18183ls__Komagataella_pastoris
K06960ls__Propionibacterium_acnes
UNGROUPEDls__Vicia_cryptic_virus
K02906ls__Propionibacterium_acnes
K03924ls__Propionibacterium_acnes
K06131ls__Propionibacterium_acnes
K09772ls__Propionibacterium_acnes
K02003ls__Propionibacterium_acnes
K06215ls__Propionibacterium_acnes
K02768ls__Propionibacterium_acnes
K02990ls__Propionibacterium_acnes
K07742ls__Propionibacterium_acnes
K03110ls__Propionibacterium_acnes
K00338ls__Propionibacterium_acnes
K10258ls__Komagataella_pastoris
K02519ls__Propionibacterium_acnes
K04047ls__Propionibacterium_acnes

Inferred Metagenome (PICRUST): Comparing SPT vs BPT		
KO_Number	logFC	adj.P.Val
K02190	5.279310797	2.15E-40
K02191	5.566761085	4.63E-39
K03340	4.907003047	4.63E-39
K00651	4.358818993	1.05E-38
K00625	3.800625828	1.39E-37
K01989	3.385486671	2.66E-37
K08567	5.45273698	4.29E-37
K07139	4.266565182	5.15E-37
K03319	4.534463608	4.62E-36
K03737	4.468823454	4.62E-36
K11707	4.793857392	1.01E-35
K11708	4.836003532	1.64E-35
K11709	4.825554497	3.66E-35
K11710	4.742922026	3.66E-35
K01611	3.592575929	9.67E-35
K00656	3.696246515	1.18E-34
K02823	3.808049975	1.86E-34
K06871	4.162023614	2.63E-34
K02824	3.92200464	2.63E-34
K03620	4.872519243	2.67E-34
K01938	3.6951719	2.75E-34
K05832	3.583939623	3.03E-34
K00478	-24.00926689	3.25E-34
K05833	3.676818297	4.23E-34
K00378	4.56958565	4.40E-34
K01751	4.220012755	6.01E-34
K12267	4.187922816	6.41E-34
K06895	3.392961307	7.60E-34
K01005	4.25485177	8.17E-34
K09951	3.844655808	8.24E-34
K11382	8.126251362	9.31E-34
K00868	3.774352891	1.06E-33
K03399	5.61075024	1.16E-33
K03152	4.043314377	2.26E-33
K06926	4.697187479	2.59E-33
K03523	3.419969068	3.30E-32
K01155	4.082596846	3.95E-32
K03498	3.248484551	4.06E-32

K14540	3.09094966	5.21E-32
K14761	3.238891448	6.02E-32
K14155	3.605539616	7.25E-32
K01914	4.036057182	8.04E-32
K00198	4.680417021	1.24E-31
K06890	3.14878243	1.90E-31
K06921	4.20304965	1.90E-31
K04068	3.843789766	2.67E-31
K09825	3.405542027	2.93E-31
K03602	2.754399302	3.45E-31
K03763	3.603035593	5.88E-31
K09772	3.48287164	8.58E-31
K03402	3.893452843	1.08E-30
K00005	4.157885747	1.30E-30
K03458	3.07473079	1.58E-30
K01270	3.808410194	1.87E-30
K01917	4.280357713	1.99E-30
K08722	5.171870069	2.66E-30
K01200	4.359590153	3.03E-30
K02006	3.29398416	3.26E-30
K13643	3.126889466	3.26E-30
K00763	2.637241134	5.80E-30
K02071	2.788131826	7.10E-30
K09002	5.396251451	7.72E-30
K12527	5.860381632	7.72E-30
K08161	6.009770563	9.59E-30
K01121	7.075615659	1.01E-29
K09762	3.477099989	1.10E-29
K02013	2.740155342	1.23E-29
K05919	4.534031113	1.44E-29
K09816	3.337615043	2.35E-29
K00926	4.150509603	3.41E-29
K09861	3.037600786	3.74E-29
K12942	4.278553006	4.54E-29
K06958	2.543901076	6.50E-29
K00991	2.960574301	7.55E-29
K03799	2.635906351	7.55E-29
K02614	2.809951339	8.16E-29
K01304	3.106201208	1.04E-28
K00527	3.438108389	1.19E-28
K09787	3.697680243	1.45E-28

K03655	2.867492207	1.71E-28
K03816	3.884615613	1.86E-28
K13888	2.84199664	2.11E-28
K09815	3.264113366	2.85E-28
K03780	5.258938139	2.95E-28
K03499	2.989361092	2.95E-28
K03779	5.255460333	2.95E-28
K03785	3.660845919	4.24E-28
K07024	3.139158863	4.45E-28
K09155	5.102685815	4.45E-28
K06281	3.252400941	4.70E-28
K03310	3.295995777	4.70E-28
K01409	2.52897051	6.09E-28
K02008	3.105457337	8.89E-28
K10041	3.461537492	9.28E-28
K07173	3.911508131	9.55E-28
K00610	4.20316002	9.58E-28
K07584	3.695999053	9.72E-28
K02371	3.245656993	1.16E-27
K12574	3.187165142	1.33E-27
K06282	3.191617593	1.37E-27
K09817	3.230947545	1.61E-27
K04069	3.156690132	1.70E-27
K05540	2.552943195	1.86E-27
K07085	3.489732877	2.31E-27
K03601	2.477423529	2.60E-27
K09457	2.998794608	3.37E-27
K01752	2.83176317	3.99E-27
K03839	4.118200124	4.70E-27
K13922	5.495953984	5.73E-27
K02073	2.71156119	5.73E-27
K11145	4.043623795	5.89E-27
K01495	2.600884697	6.77E-27
K08303	3.046423453	8.33E-27
K02072	2.545038557	1.26E-26
K06180	2.785302511	1.63E-26
K02821	3.467850487	1.77E-26
K00951	2.562791432	1.82E-26
K01258	3.433264944	2.03E-26
K00526	2.564753613	2.95E-26
K01515	2.483087218	3.41E-26

K00364	3.892558713	4.01E-26
K09811	2.566822811	4.52E-26
K06901	2.722719544	4.78E-26
K02822	4.367875028	4.87E-26
K03784	3.332245685	4.90E-26
K00016	3.704078317	4.90E-26
K03326	5.906546826	4.90E-26
K01424	2.509511893	5.48E-26
K01243	2.633366781	5.82E-26
K03404	3.877299734	6.14E-26
K01607	2.633791045	6.14E-26
K07574	3.237946966	7.03E-26
K02188	3.227521115	7.43E-26
K12982	4.47403633	9.54E-26
K07010	2.763975029	1.12E-25
K00374	3.019862356	1.14E-25
K04654	2.918217969	1.27E-25
K03595	2.381738762	1.30E-25
K07133	3.723490675	1.33E-25
K02031	2.301142252	1.33E-25
K00231	3.198985931	1.37E-25
K01835	2.570529514	1.41E-25
K04655	2.869754651	1.49E-25
K02016	2.432107416	1.63E-25
K10974	3.841449009	1.69E-25
K04720	3.609498112	1.69E-25
K03389	3.453206675	1.83E-25
K00761	2.456429126	1.97E-25
K04652	2.880376364	2.67E-25
K02860	2.377011333	2.70E-25
K03531	2.457756585	2.70E-25
K04656	2.93740883	2.70E-25
K07791	4.913943629	2.93E-25
K06215	3.288242439	3.02E-25
K00891	2.418573512	3.66E-25
K01906	5.865137326	3.85E-25
K01493	3.053100697	3.89E-25
K03589	2.414670913	3.97E-25
K01960	4.133228966	3.97E-25
K03571	2.427065293	4.25E-25
K00370	3.006142089	4.27E-25

K09729	5.801165768	4.47E-25
K00373	2.973938856	4.47E-25
K12960	2.889187813	4.82E-25
K00876	2.823383981	5.29E-25
K02907	2.375415075	5.29E-25
K00756	3.261471523	5.36E-25
K03429	3.283884329	5.36E-25
K03565	2.44207375	5.48E-25
K00832	2.46555789	5.50E-25
K04096	2.500368581	6.19E-25
K00768	2.727479655	6.73E-25
K00602	2.500078533	8.06E-25
K09790	2.643588387	8.06E-25
K01489	2.599672663	8.15E-25
K00547	3.610286371	8.81E-25
K07082	2.357697721	9.94E-25
K00313	3.763573716	1.11E-24
K09748	2.366369936	1.17E-24
K02015	2.345590022	1.21E-24
K04095	4.520299927	1.31E-24
K01520	2.377964846	1.32E-24
K03386	2.424728429	1.32E-24
K03705	2.360508437	1.33E-24
K02919	2.314694534	1.33E-24
K04485	2.355385249	1.45E-24
K00174	3.266905601	1.48E-24
K01176	3.085239341	1.57E-24
K03311	3.385781486	1.58E-24
K03978	2.393610313	1.62E-24
K01924	2.326891943	1.84E-24
K00782	2.815053853	2.01E-24
K02238	2.353154259	2.27E-24
K00175	3.256654904	2.47E-24
K01776	2.347674185	2.75E-24
K02549	3.398171793	3.02E-24
K09812	2.488643041	3.13E-24
K00969	2.365240709	3.20E-24
K00950	2.518820299	3.30E-24
K01934	2.339430666	3.64E-24
K00018	2.870424544	3.71E-24
K00226	2.309180832	3.84E-24

K07742	2.818684227	4.24E-24
K07271	4.633502261	4.51E-24
K01193	3.707454898	4.56E-24
K02959	2.290765496	4.59E-24
K02358	2.282103538	4.68E-24
K02904	2.293254868	4.68E-24
K00760	2.414386985	4.72E-24
K03475	4.249566684	4.75E-24
K01464	3.045584933	4.82E-24
K01422	2.867179855	5.05E-24
K01879	2.379212414	5.11E-24
K00791	2.503627517	5.28E-24
K02619	2.749310456	5.28E-24
K00566	2.290585413	5.28E-24
K04094	2.908472162	5.44E-24
K00783	2.35903366	5.44E-24
K01878	2.379215439	5.70E-24
K03530	2.59158024	6.04E-24
K00371	2.928754602	6.05E-24
K06950	2.956298729	6.19E-24
K00262	2.808336543	6.58E-24
K00925	2.55513222	6.83E-24
K09952	4.695838033	7.20E-24
K02911	2.264821162	7.73E-24
K08483	2.530627151	8.14E-24
K00858	2.271510571	8.49E-24
K02770	3.017565408	8.63E-24
K07456	2.987444067	8.64E-24
K04651	2.763390891	1.04E-23
K00075	2.296134377	1.13E-23
K03385	4.254934824	1.14E-23
K00919	2.330962208	1.14E-23
K01163	4.744964943	1.18E-23
K03624	2.200696127	1.23E-23
K03773	3.285911433	1.26E-23
K02355	2.429219491	1.34E-23
K00882	2.916146189	1.36E-23
K04653	2.640200629	1.46E-23
K01923	2.243100612	1.55E-23
K02338	2.208669817	1.59E-23
K06178	2.201224359	1.60E-23

K06346	3.287524157	1.65E-23
K01610	2.702319352	1.84E-23
K11928	3.094604401	1.88E-23
K03073	2.273363746	1.90E-23
K01104	2.462534096	2.04E-23
K01185	3.8179338	2.08E-23
K02874	2.282981462	2.21E-23
K01615	5.984600652	2.28E-23
K02914	2.239834581	2.28E-23
K07040	2.405165449	2.49E-23
K03855	3.664540642	2.87E-23
K07568	2.493534729	2.95E-23
K07862	3.424531388	2.95E-23
K03075	2.283171903	3.26E-23
K02237	2.343501448	3.28E-23
K11753	2.24562769	3.33E-23
K03501	2.291301569	3.47E-23
K06949	2.372630561	3.75E-23
K03588	2.12581057	3.98E-23
K09698	3.785580274	4.17E-23
K03629	2.391180831	4.39E-23
K00790	2.242517464	4.45E-23
K07491	2.376266826	4.46E-23
K04567	2.431657916	4.51E-23
K03431	2.084918196	5.15E-23
K02340	2.261547166	5.50E-23
K02563	2.247123354	5.51E-23
K07447	2.256414728	5.75E-23
K02687	2.277996739	5.98E-23
K03536	2.26170374	6.01E-23
K03169	2.955326543	6.35E-23
K03789	2.269117828	6.64E-23
K00099	2.255907964	6.98E-23
K02495	2.37531424	6.98E-23
K00762	2.24078711	6.98E-23
K02113	2.232095137	7.71E-23
K03526	2.232678535	8.28E-23
K01591	2.256642935	8.28E-23
K11102	3.914167801	8.43E-23
K11754	2.161450434	8.48E-23
K07462	2.289707524	8.61E-23

K01491	2.222121844	8.99E-23
K02520	2.240249646	9.57E-23
K03545	2.219359169	9.58E-23
K07166	4.478976277	9.65E-23
K01876	2.232123893	1.04E-22
K03470	2.259703313	1.07E-22
K00997	2.27584422	1.12E-22
K00945	2.231132992	1.15E-22
K02909	2.134310942	1.18E-22
K01875	2.227366348	1.18E-22
K01008	2.663849615	1.18E-22
K06187	2.239140447	1.19E-22
K06199	2.309502176	1.19E-22
K02836	2.234044751	1.20E-22
K00525	2.328156768	1.20E-22
K03217	2.345682859	1.22E-22
K03977	2.232856276	1.22E-22
K02992	2.233737227	1.22E-22
K02939	2.23107054	1.22E-22
K03768	2.520478986	1.23E-22
K00177	3.850368588	1.23E-22
K02899	2.235520016	1.23E-22
K02996	2.234937686	1.23E-22
K03282	2.446159613	1.23E-22
K01933	2.22529465	1.23E-22
K00057	2.222334841	1.26E-22
K02835	2.230723988	1.26E-22
K01000	2.21817118	1.26E-22
K01951	2.220096217	1.26E-22
K01929	2.244713638	1.26E-22
K03630	2.233511582	1.28E-22
K06925	2.329779318	1.29E-22
K01744	2.790931209	1.35E-22
K03596	2.230711916	1.35E-22
K01925	2.222068844	1.38E-22
K03303	2.461187722	1.38E-22
K02888	2.231377241	1.39E-22
K02834	2.224131569	1.39E-22
K01756	2.217353236	1.39E-22
K01869	2.229013311	1.41E-22
K02341	2.223385989	1.43E-22

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K07318	2.461329016	0.000147926
K11180	-4.100106826	0.000147972

K01932	3.534997438	0.000148254
K06134	-3.520994913	0.000148443
K12941	-3.441786042	0.000149967
K09958	-2.824694763	0.000150359
K06432	-5.105902381	0.000151232
K06305	-4.686765612	0.000151901
K04496	-5.652802663	0.000152582
K01028	-2.037712075	0.000153143
K04712	-5.187429743	0.000153298
K06428	-5.105799237	0.000154598
K00032	-6.98516394	0.000154923
K11386	-5.638718187	0.000156508
K10679	-2.136713023	0.000156588
K03709	1.62616019	0.000157342
K01043	-2.940670869	0.000157522
K05928	-4.07692048	0.000158223
K12070	-3.776573648	0.00015843
K07653	-3.068549388	0.000158521
K12072	-3.219926595	0.0001586
K00840	-4.346537815	0.000158751
K07569	-16.72858662	0.000159666
K09929	2.280217003	0.000159973
K00769	1.587573372	0.000160359
K07787	-1.597418596	0.00016041
K13669	-5.817109388	0.000160545
K01640	-2.046542362	0.000161109
K07673	-2.573518041	0.000162211
K14165	-3.796031054	0.00016385
K09017	-1.015802599	0.000165724
K13580	-3.068093147	0.000166186
K14727	-3.319158999	0.000166685
K11811	-2.958017806	0.000166846
K07283	-3.558865767	0.000172944
K14335	-3.877182429	0.000174552
K01569	-3.850010172	0.00017518
K01093	-3.765507654	0.000176121
K11892	-1.900223774	0.000176299
K01137	-4.178173107	0.000176299
K06605	-3.090101192	0.000176299
K01003	-2.93414621	0.000176719
K01546	-2.269777041	0.000176734

K13895	-2.782467736	0.000178519
K00131	1.735322056	0.00018039
K03296	0.946958036	0.000183729
K08738	-3.697655451	0.00018419
K10221	-3.73547735	0.000184264
K00930	0.638967951	0.000185075
K08973	-1.697699888	0.000189024
K01547	-2.262289432	0.000191902
K13021	-4.163685172	0.000193488
K01965	-3.341025644	0.000193568
K02167	-3.836390602	0.00019369
K01548	-2.260383884	0.000194196
K06221	-2.460731989	0.000194862
K11618	2.199613196	0.000195986
K01451	-1.934499339	0.00019828
K00436	-3.482205414	0.000198349
K07116	-3.637467681	0.000198997
K08714	-2.724425443	0.000199647
K06140	-2.862099356	0.000201049
K07169	-3.624837965	0.000202622
K01178	-3.706266367	0.000203544
K02303	-2.221710541	0.000204203
K12254	-5.683071067	0.000204684
K07641	-3.37484198	0.000205493
K03556	-2.087131744	0.000205957
K02081	1.23236163	0.000206961
K01428	-2.184851769	0.000208654
K11384	-3.811413599	0.000208971
K02406	-1.040607109	0.000208987
K13013	-4.107300116	0.000209088
K11383	-6.081963905	0.000209895
K00207	-3.867811657	0.000210392
K11312	-1.939014967	0.000210852
K01483	-3.564211725	0.000211015
K00121	-1.069949567	0.000211855
K09938	-3.84407515	0.000212031
K07047	-1.367157093	0.000212267
K07104	-0.963535097	0.000214477
K10235	-5.796417806	0.000215205
K02613	-2.284728556	0.000215622
K13585	-5.874280663	0.000215977

K09461	-3.077011643	0.000217236
K13815	-5.747895434	0.000218222
K01227	3.019791608	0.000218222
K01502	-3.527987863	0.000218321
K01560	-1.462430543	0.000221415
K05793	-3.640848856	0.000222668
K05994	-4.292578282	0.000223196
K03222	-3.507803245	0.000223537
K13283	-4.566348574	0.000225531
K01962	0.812657897	0.00022606
K03392	-3.77335529	0.000227438
K07733	-2.016076703	0.000230455
K08279	-2.725082197	0.000231026
K02790	-4.109050256	0.000233529
K14162	-2.664792942	0.000233798
K06342	-5.054298447	0.000234861
K02618	-2.987155384	0.000238119
K03300	-1.29374018	0.000238483
K07050	1.626748988	0.000239521
K00549	0.948859754	0.000239521
K13593	-4.126973286	0.000243931
K00038	-1.96548523	0.000244149
K14161	-1.017923217	0.000244602
K02593	-3.750684906	0.000245118
K09835	-4.859298309	0.000247649
K12278	-3.663840256	0.000248462
K10016	-3.761842615	0.000248766
K01252	2.300154256	0.00025002
K12073	-3.835125346	0.000252072
K05951	-4.161064869	0.000253579
K03649	-2.091582329	0.000253734
K10007	1.810586687	0.000254401
K00218	-4.719949266	0.000254648
K01713	2.40413497	0.00025602
K09476	-5.52979694	0.000256247
K02351	-1.982063334	0.000258211
K00369	-4.927583278	0.000260977
K07675	-1.891751722	0.00026255
K14660	-4.723330815	0.000264926
K10926	-3.641895224	0.00026583
K01053	-3.172380888	0.000266443

K13894	-2.808777407	0.000268
K11686	-5.10586642	0.000269986
K11615	-4.889169132	0.000270651
K04021	-4.218610741	0.000270855
K11738	2.163457047	0.000272265
K02484	0.928382392	0.000273034
K01563	-3.567362659	0.000273164
K12279	-3.611072896	0.000274359
K12280	-3.610674961	0.000274735
K12282	-3.545823524	0.000275357
K05844	-1.315060306	0.000276087
K10714	-4.0077446	0.000276635
K03146	3.802029641	0.000278141
K14953	-6.196816136	0.000280133
K05779	-4.638851251	0.000281777
K07149	1.56046152	0.000282707
K14338	-3.69675969	0.000283411
K11013	4.12832471	0.000285112
K00145	0.607905671	0.000286009
K11624	-7.697249638	0.000288256
K10747	-7.161658489	0.000289154
K01555	-2.785973752	0.00028943
K10927	-3.680893499	0.000290039
K01082	-5.323047093	0.000291169
K07453	-6.290195458	0.000292295
K09131	-1.392105925	0.000293478
K00901	0.859370755	0.000293478
K06336	-5.078189235	0.000294035
K12953	-6.276930402	0.000297739
K12062	-3.55257522	0.000299422
K00167	-2.004480267	0.000300003
K00885	3.580910837	0.000301042
K13633	-3.157716358	0.000302473
K10938	-5.436499299	0.000303854
K03752	-1.13154424	0.000304584
K09950	-3.531499307	0.000305559
K08969	2.384543691	0.000307031
K07715	-3.414247589	0.000307708
K06195	-2.18990506	0.000307946
K03203	-1.972729699	0.000309454
K05889	-4.299390984	0.000309571

K02450	-3.425856402	0.000309709
K13410	-5.998761325	0.000310605
K12281	-4.056563525	0.000311219
K09846	-3.969467646	0.000314063
K03224	-3.445537135	0.000314063
K04088	-1.037929076	0.000315104
K01194	-2.305440995	0.000315916
K03669	-2.767512727	0.000316319
K13896	-2.791820376	0.00031837
K11443	-3.362379404	0.000319599
K10924	-3.638164365	0.000319824
K08286	-4.591464764	0.000320264
K03230	-3.434242728	0.000321235
K03489	3.037137979	0.00032213
K09164	-2.840967447	0.000322153
K09740	-3.695523336	0.000322153
K04091	-3.454315536	0.000323377
K09965	-3.614166279	0.000323478
K06860	1.811098676	0.000325205
K12285	-3.5724629	0.000325205
K03228	-3.431076362	0.000325205
K03229	-3.431076243	0.000325205
K03226	-3.430765918	0.000325205
K03227	-3.431076983	0.000325205
K02641	-4.835636667	0.000325205
K00499	-3.577510452	0.000328102
K05739	-4.73566191	0.000329633
K12537	-6.32904117	0.000330775
K10227	-3.553709906	0.000331295
K03290	3.723748256	0.000331578
K09844	-3.86629457	0.000331879
K01438	-1.319400622	0.000331879
K01239	1.297875651	0.000331978
K09845	-3.865057006	0.000333197
K02452	-3.425078579	0.000338761
K05977	-4.634970445	0.000339658
K11045	6.004062695	0.000340346
K04102	-3.526319224	0.000342547
K06197	-4.051577327	0.00034345
K12286	-3.642251167	0.000343494
K10796	3.51907015	0.000345206

K08983	-3.151205156	0.000346319
K08295	-3.025463142	0.000347925
K06214	-3.533358079	0.000349086
K12529	-5.289282826	0.000351074
K12681	-7.067631322	0.000353718
K04340	-7.06763153	0.000353718
K02266	-7.067631322	0.000353718
K00984	-2.561584736	0.000354398
K12276	-3.665242308	0.000360195
K08481	-3.297123385	0.000360505
K06412	1.34502086	0.000362559
K14048	-4.102659135	0.000362559
K03520	-3.697890559	0.000365569
K10022	-4.054075688	0.000365897
K14393	-1.805914576	0.000368022
K13591	-5.679817482	0.000368022
K03636	-1.094883423	0.000368791
K09794	1.305736136	0.000370159
K06922	3.062753977	0.000373274
K07669	-2.691235796	0.000373985
K01066	-1.146664334	0.000376446
K07397	-1.834629453	0.000381108
K00066	-3.578362247	0.000383674
K09954	-2.466269594	0.00038531
K02279	-1.506078886	0.000388079
K06049	-3.954074808	0.000388497
K01618	-3.73774389	0.000388696
K02573	1.975632517	0.000389694
K13688	-3.901217522	0.000390948
K07734	-2.638776032	0.000392506
K01208	2.678116912	0.000395863
K02805	-2.012107695	0.000396715
K01686	1.241019925	0.000397594
K07338	-3.883215404	0.000405692
K05795	-1.478375463	0.000405919
K03219	-3.42307189	0.00040597
K01905	-4.061826299	0.000406775
K08077	3.891144555	0.000411675
K13651	-4.546103153	0.000414834
K00632	-1.83395697	0.00041665
K07798	-1.522723558	0.000417109

K09134	1.498972635	0.000418883
K10711	-5.850214274	0.000422292
K03223	-3.873145795	0.000422901
K03891	-2.566388059	0.00042387
K05839	-4.458628612	0.00042452
K01812	1.197007454	0.000425081
K03837	2.18982212	0.000425081
K09914	-3.3407573	0.000427746
K11264	-4.709151067	0.000429885
K02407	-1.171651728	0.000438104
K03382	-2.46205217	0.000439374
K08927	-3.943331059	0.000439487
K11336	-3.943331059	0.000439487
K11335	-3.943331059	0.000439487
K11334	-3.943331059	0.000439487
K11333	-3.943331059	0.000439487
K02617	-4.021826842	0.000439516
K08217	1.519939172	0.000439936
K05597	-3.775920727	0.000440839
K04338	-3.502605739	0.000442199
K13926	-2.180164139	0.000442997
K02451	-3.758045862	0.000443248
K14261	-1.735209025	0.000444254
K11337	-3.939569334	0.000448079
K05555	-6.250978717	0.000450259
K05344	3.944574885	0.000450259
K08926	-3.935402123	0.000453822
K13991	-3.935402123	0.000453822
K08929	-3.935402123	0.000453822
K08928	-3.935402123	0.000453822
K02848	-4.011851836	0.000453822
K03890	-2.553842476	0.000453822
K07182	-2.71617304	0.000454662
K03445	1.971184032	0.000457233
K02046	-2.520997495	0.000460891
K00908	-4.051022557	0.000460891
K02424	-3.81615329	0.000462117
K02047	-2.519388094	0.000464856
K01216	-4.399057436	0.000466016
K11748	-2.487757132	0.000468332
K06718	-2.787430743	0.000468861

K14623	1.879036014	0.000471986
K06417	-4.480355938	0.000472134
K07711	-3.293185625	0.000476544
K07285	1.940128743	0.000477108
K07127	-2.582106635	0.000478337
K01429	-1.92164999	0.000478857
K05782	-2.21916177	0.000479124
K02826	-3.502160758	0.000479124
K06418	-4.75173074	0.000479432
K04058	-3.830056186	0.000480028
K05831	-6.031268699	0.000480028
K12071	-3.178832527	0.000481693
K00449	-2.421085687	0.000487521
K13875	-3.554577999	0.000487521
K07167	-3.560961095	0.000490157
K09019	1.668404528	0.000496669
K02391	-3.072748807	0.000496669

16S rRNA Gene Sequencing: Comparing SPT vs BPT		
Taxonomy	**logFC**	**adj.P.Val**
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__Lachnospiraceae.g__Oribacterium	12.29874287	1.85E-15
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__Veillonellaceae.g__Dialister	11.8679938	6.93E-13
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__Veillonellaceae.g__Veillonella	7.297055062	1.92E-09
k__Bacteria.p__Proteobacteria.c__Gammaproteobacteria.o__Pasteurellales.f__Pasteurellaceae.g__Aggregatibacter	10.05147915	1.82E-08
k__Bacteria.p__Fusobacteria.c__Fusobacteriia.o__Fusobacteriales.f__Leptotrichiaceae.g__Leptotrichia	9.455465319	4.34E-08
k__Bacteria.p__Bacteroidetes.c__Bacteroidia.o__Bacteroidales.f__Prevotellaceae.g__Prevotella	6.286654022	6.33E-08
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__Lachnospiraceae.g__Catonella	10.34253888	2.48E-07
k__Bacteria.p__Proteobacteria.c__Gammaproteobacteria.o__Pasteurellales.f__Pasteurellaceae.g__Haemophilus	8.286956407	2.46E-06
k__Bacteria.p__Proteobacteria.c__Gammaproteobacteria.o__Pasteurellales.f__Pasteurellaceae.g__	8.467775966	4.63E-06
k__Bacteria.p__Firmicutes.c__Bacilli.o__Lactobacillales.f__Streptococcaceae.g__Streptococcus	5.450722291	4.63E-06
k__Bacteria.p__Bacteroidetes.c__Flavobacteriia.o__Flavobacteriales.f__[Weeksellaceae].g__	10.09825898	7.90E-06
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__Lachnospiraceae.g__Moryella	9.023335731	8.09E-06
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__[Mogibacteriaceae].g__	8.131513343	1.81E-05
k__Bacteria.p__Bacteroidetes.c__Bacteroidia.o__Bacteroidales.f__Porphyromonadaceae.g__Tannerella	8.956131689	1.95E-05
k__Bacteria.p__Firmicutes.c__Bacilli.o__Gemellales.f__Gemellaceae.g__Gemella	8.539187351	0.00011136
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__Clostridiaceae.g__	6.29234279	0.00026097
k__Bacteria.p__Actinobacteria.c__Actinobacteria.o__Actinomycetales.f__Actinomycetaceae.g__Actinomyces	5.978505236	0.000263424
k__Bacteria.p__Synergistetes.c__Synergistia.o__Synergistales.f__Dethiosulfovibrionaceae.g__TG5	9.683458917	0.000265488
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__[Tissierellaceae].g__Parvimonas	7.785278714	0.000572087
k__Bacteria.p__Proteobacteria.c__Betaproteobacteria.o__Neisseriales.f__Neisseriaceae.g__Neisseria	5.990244096	0.001034573
k__Bacteria.p__Fusobacteria.c__Fusobacteriia.o__Fusobacteriales.f__Fusobacteriaceae.g__Fusobacterium	5.912241506	0.001089489
k__Bacteria.p__Bacteroidetes.c__Bacteroidia.o__Bacteroidales.f__Porphyromonadaceae.g__Porphyromonas	6.609957216	0.001391701
k__Bacteria.p__Proteobacteria.c__Gammaproteobacteria.o__Pasteurellales.f__Pasteurellaceae.g__Actinobacillus	5.827961853	0.001430698
k__Bacteria.p__Proteobacteria.c__Alphaproteobacteria.o__Rhizobiales.f__Methylobacteriaceae.g__Methylobacterium	-4.306512888	0.002070607
k__Bacteria.p__Proteobacteria.c__Epsilonproteobacteria.o__Campylobacterales.f__Campylobacteraceae.g__Campylobacter	5.927165879	0.002117494
k__Bacteria.p__Actinobacteria.c__Actinobacteria.o__Actinomycetales.f__Micrococcaceae.g__Rothia	6.490935164	0.002684089
k__Bacteria.p__Firmicutes.c__Bacilli.o__Lactobacillales.f__Lactobacillaceae.g__Lactobacillus	4.793542449	0.002684089
k__Bacteria.p__Actinobacteria.c__Coriobacteriia.o__Coriobacteriales.f__Coriobacteriaceae.g__Atopobium	6.685374725	0.002684089
k__Bacteria.p__Firmicutes.c__Bacilli.o__Gemellales.f__Gemellaceae.g__	5.41769618	0.003853158
k__Bacteria.p__Tenericutes.c__Mollicutes.o__Mycoplasmatales.f__Mycoplasmataceae.g__Mycoplasma	8.780473949	0.005979153
k__Bacteria.p__Firmicutes.c__Bacilli.o__Lactobacillales.f__Enterococcaceae.g__Enterococcus	5.776769215	0.008060167
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__Veillonellaceae.g__Megasphaera	7.790650542	0.010993315
k__Bacteria.p__Proteobacteria.c__Betaproteobacteria.o__Burkholderiales.f__Burkholderiaceae.g__Lautropia	8.505291464	0.013117887
k__Bacteria.p__Firmicutes.c__Bacilli.o__Bacillales.f__Planococcaceae.g__	4.159160919	0.030850745
k__Bacteria.p__Firmicutes.c__Clostridia.o__Clostridiales.f__[Mogibacteriaceae].g__Mogibacterium	5.175039943	0.030850745
k__Bacteria.p__Proteobacteria.c__Betaproteobacteria.o__Neisseriales.f__Neisseriaceae.g__Kingella	8.188455728	0.0378211
k__Bacteria.p__Actinobacteria.c__Coriobacteriia.o__Coriobacteriales.f__Coriobacteriaceae.g__	8.026721284	0.03959979
k__Bacteria.p__Proteobacteria.c__Betaproteobacteria.o__Neisseriales.f__Neisseriaceae.g__	4.496547256	0.045080934

WGS Metagenome Taxonomic Annotation: Comparing SPT vs BPT		
Taxonomy	**logFC**	**adj.P.Val**
g__Streptococcus.s__Streptococcus_mitis_oralis_pneumoniae	23.03964114	3.59E-05
g__Streptococcus.s__Streptococcus_peroris	23.03964114	3.59E-05
g__Prevotella.s__Prevotella_histicola	21.77598986	0.000150588
g__Streptococcus.s__Streptococcus_infantis	21.14866582	0.000272095

RNA Metatranscriptome Taxonomic An	WGS Metag	WGS Metagenome T
Taxonomy	**logFC**	**adj.P.Val**
g__Streptococcus.s__Streptococcus_vestibularis	25.62181459	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	26.46729854	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.5221295	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	26.54565459	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.89271147	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.659873	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	26.21015012	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.57507983	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.86362293	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.87207615	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.95906397	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.54836312	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.71627981	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	26.12484557	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.76714283	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	26.65836207	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	26.12868399	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	27.92448304	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	26.19042446	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.60095822	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.62684269	8.12E-06
g__Granulicatella.s__Granulicatella_adiacens	26.1434941	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	26.47833662	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.81282187	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.88286206	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.65910618	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.56357148	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.72500586	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.81014336	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.86145657	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	26.031785	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	26.36196567	8.12E-06
g__Bifidobacterium.s__Bifidobacterium_longum	25.56342118	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.59716272	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	26.32219034	8.12E-06

g__Streptococcus.s__Streptococcus_peroris	26.47742743	8.12E-06
g__Actinomyces.s__Actinomyces_odontolyticus	25.53776794	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.70592664	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.67461331	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.85255966	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.55657117	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.57899753	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	26.16159109	8.12E-06
g__Streptococcus.s__Streptococcus_peroris	25.93289678	8.12E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.50233728	8.14E-06
g__Streptococcus.s__Streptococcus_peroris	25.47468773	8.26E-06
g__Actinomyces.s__Actinomyces_graevenitzii	25.32784751	8.66E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.3776539	8.66E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.32965954	8.66E-06
g__Bifidobacterium.s__Bifidobacterium_longum	25.35520222	8.66E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.39685707	8.66E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.36877737	8.66E-06
g__Streptococcus.s__Streptococcus_peroris	25.35808095	8.66E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.28735651	8.86E-06
g__Streptococcus.s__Streptococcus_peroris	25.28089587	8.86E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.25234185	9.03E-06
g__Streptococcus.s__Streptococcus_peroris	25.2361678	9.05E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.18670181	9.29E-06
g__Streptococcus.s__Streptococcus_peroris	25.12560508	9.29E-06
g__Streptococcus.s__Streptococcus_sanguinis	25.12869105	9.29E-06
g__Granulicatella.s__Granulicatella_adiacens	25.13259713	9.29E-06
g__Streptococcus.s__Streptococcus_peroris	25.15213396	9.29E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.15464074	9.29E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.19495332	9.29E-06
g__Streptococcus.s__Streptococcus_peroris	25.11175984	9.31E-06
g__Streptococcus.s__Streptococcus_vestibularis	25.06954352	9.67E-06
g__Streptococcus.s__Streptococcus_sanguinis	24.9290647	1.08E-05
g__Actinomyces.s__Actinomyces_graevenitzii	24.9197449	1.08E-05
g__Actinomyces.s__Actinomyces_odontolyticus	24.9420795	1.08E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.91536903	1.08E-05
g__Streptococcus.s__Streptococcus_peroris	24.93292059	1.08E-05
g__Streptococcus.s__Streptococcus_peroris	24.94613364	1.08E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.90500456	1.08E-05

g__Streptococcus.s__Streptococcus_vestibularis	24.89116038	1.08E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.87221984	1.09E-05
g__Streptococcus.s__Streptococcus_peroris	24.83984959	1.12E-05
g__Streptococcus.s__Streptococcus_tigurinus	24.81605937	1.14E-05
g__Streptococcus.s__Streptococcus_peroris	24.79591163	1.14E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.79492874	1.14E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.7829962	1.15E-05
g__Streptococcus.s__Streptococcus_peroris	24.66728664	1.18E-05
g__Granulicatella.s__Granulicatella_adiacens	24.72731295	1.18E-05
g__Bifidobacterium.s__Bifidobacterium_longum	24.65786994	1.18E-05
g__Streptococcus.s__Streptococcus_peroris	24.69349113	1.18E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.6635987	1.18E-05
g__Granulicatella.s__Granulicatella_adiacens	24.69424017	1.18E-05
g__Streptococcus.s__Streptococcus_tigurinus	24.72684495	1.18E-05
g__Atopobium.s__Atopobium_rimae	24.72038259	1.18E-05
g__Streptococcus.s__Streptococcus_tigurinus	24.67968537	1.18E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.72684495	1.18E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.65863517	1.18E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.63281942	1.18E-05
g__Actinomyces.s__Actinomyces_odontolyticus	24.64154991	1.18E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.63060261	1.18E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.60167288	1.19E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.60167288	1.19E-05
g__Bifidobacterium.s__Bifidobacterium_longum	24.60542643	1.19E-05
unclassified	-23.73346147	1.21E-05
g__Bifidobacterium.s__Bifidobacterium_dentium	24.56591007	1.22E-05
g__Streptococcus.s__Streptococcus_peroris	24.50197718	1.30E-05
g__Streptococcus.s__Streptococcus_peroris	24.47189832	1.34E-05
unclassified	24.45582863	1.34E-05
g__Haemophilus.s__Haemophilus_parainfluenzae	24.45978181	1.34E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.43610649	1.36E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.40563011	1.39E-05
g__Granulicatella.s__Granulicatella_adiacens	24.40196298	1.39E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.38353513	1.41E-05
g__Atopobium.s__Atopobium_rimae	24.37697755	1.41E-05
g__Actinomyces.s__Actinomyces_graevenitzii	24.34480279	1.42E-05
g__Actinomyces.s__Actinomyces_graevenitzii	24.35427255	1.42E-05
g__Streptococcus.s__Streptococcus_tigurinus	24.34253649	1.42E-05

g__Streptococcus.s__Streptococcus_peroris	24.34161221	1.42E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.32866708	1.43E-05
g__Streptococcus.s__Streptococcus_peroris	24.24680139	1.46E-05
g__Granulicatella.s__Granulicatella_adiacens	24.276803	1.46E-05
g__Actinomyces.s__Actinomyces_odontolyticus	24.29761714	1.46E-05
g__Actinomyces.s__Actinomyces_odontolyticus	24.25697714	1.46E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.24680139	1.46E-05
g__Granulicatella.s__Granulicatella_adiacens	24.25292066	1.46E-05
g__Granulicatella.s__Granulicatella_adiacens	24.24965526	1.46E-05
g__Streptococcus.s__Streptococcus_peroris	24.27701155	1.46E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.276803	1.46E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.2589989	1.46E-05
g__Actinomyces.s__Actinomyces_graevenitzii	24.2305293	1.46E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.23208367	1.46E-05
g__Streptococcus.s__Streptococcus_tigurinus	24.2170215	1.47E-05
g__Actinomyces.s__Actinomyces_graevenitzii	24.2050389	1.48E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.16927257	1.50E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.17016099	1.50E-05
g__Actinomyces.s__Actinomyces_graevenitzii	24.16020936	1.50E-05
g__Atopobium.s__Atopobium_parvulum	24.16400976	1.50E-05
g__Actinomyces.s__Actinomyces_graevenitzii	24.16737688	1.50E-05
g__Streptococcus.s__Streptococcus_peroris	24.16482894	1.50E-05
g__Actinomyces.s__Actinomyces_graevenitzii	24.15128003	1.50E-05
g__Streptococcus.s__Streptococcus_peroris	24.14137322	1.51E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.12701707	1.53E-05
g__Haemophilus.s__Haemophilus_parainfluenzae	24.11591018	1.53E-05
g__Haemophilus.s__Haemophilus_parainfluenzae	24.11145146	1.53E-05
g__Granulicatella.s__Granulicatella_adiacens	24.10141161	1.54E-05
g__Streptococcus.s__Streptococcus_vestibularis	24.09243399	1.55E-05
g__Streptococcus.s__Streptococcus_tigurinus	24.08641331	1.55E-05
g__Streptococcus.s__Streptococcus_sanguinis	24.0804103	1.55E-05
g__Actinomyces.s__Actinomyces_graevenitzii	24.06837388	1.56E-05
g__Streptococcus.s__Streptococcus_peroris	24.06145951	1.56E-05
g__Granulicatella.s__Granulicatella_adiacens	24.04808944	1.58E-05
g__Bifidobacterium.s__Bifidobacterium_longum	24.00709646	1.65E-05
g__Granulicatella.s__Granulicatella_adiacens	23.98761914	1.67E-05
g__Granulicatella.s__Granulicatella_adiacens	23.9789581	1.67E-05
g__Granulicatella.s__Granulicatella_adiacens	23.97646809	1.67E-05

g__Actinomyces.s__Actinomyces_odontolyticus	23.94541439	1.69E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.94035544	1.69E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.94035544	1.69E-05
g__Granulicatella.s__Granulicatella_adiacens	23.95631425	1.69E-05
g__Granulicatella.s__Granulicatella_adiacens	23.94541439	1.69E-05
g__Granulicatella.s__Granulicatella_adiacens	23.92888924	1.71E-05
g__Streptococcus.s__Streptococcus_tigurinus	23.92038478	1.71E-05
g__Bifidobacterium.s__Bifidobacterium_longum	23.90982946	1.72E-05
g__Granulicatella.s__Granulicatella_adiacens	23.89659045	1.73E-05
g__Streptococcus.s__Streptococcus_sanguinis	23.89751688	1.73E-05
g__Streptococcus.s__Streptococcus_peroris	23.88312646	1.75E-05
g__Streptococcus.s__Streptococcus_tigurinus	23.87432037	1.75E-05
g__Streptococcus.s__Streptococcus_vestibularis	23.87269603	1.75E-05
g__Streptococcus.s__Streptococcus_tigurinus	23.86242161	1.76E-05
g__Atopobium.s__Atopobium_rimae	23.84601462	1.78E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.81314994	1.80E-05
g__Granulicatella.s__Granulicatella_adiacens	23.80346382	1.80E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.80579521	1.80E-05
g__Granulicatella.s__Granulicatella_adiacens	23.82526465	1.80E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.82035707	1.80E-05
g__Streptococcus.s__Streptococcus_vestibularis	23.80229803	1.80E-05
g__Streptococcus.s__Streptococcus_tigurinus	23.80416956	1.80E-05
g__Streptococcus.s__Streptococcus_vestibularis	23.79279998	1.81E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.78671692	1.82E-05
g__Atopobium.s__Atopobium_rimae	23.74373792	1.87E-05
g__Bifidobacterium.s__Bifidobacterium_dentium	23.73963035	1.87E-05
g__Streptococcus.s__Streptococcus_tigurinus	23.74910108	1.87E-05
g__Granulicatella.s__Granulicatella_adiacens	23.74237154	1.87E-05
g__Granulicatella.s__Granulicatella_adiacens	23.74780906	1.87E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.69032315	1.92E-05
g__Streptococcus.s__Streptococcus_peroris	23.70822193	1.92E-05
g__Haemophilus.s__Haemophilus_parainfluenzae	23.70685559	1.92E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.68194038	1.92E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.68614196	1.92E-05
g__Streptococcus.s__Streptococcus_vestibularis	23.68194038	1.92E-05
g__Streptococcus.s__Streptococcus_tigurinus	23.68299069	1.92E-05
g__Streptococcus.s__Streptococcus_tigurinus	23.68299069	1.92E-05
g__Granulicatella.s__Granulicatella_adiacens	23.66152812	1.93E-05

g__Actinomyces.s__Actinomyces_graevenitzii	23.66450294	1.93E-05
g__Haemophilus.s__Haemophilus_parainfluenzae	23.66875035	1.93E-05
g__Granulicatella.s__Granulicatella_adiacens	23.64596228	1.96E-05
g__Actinomyces.s__Actinomyces_graevenitzii	23.63426635	1.98E-05
g__Granulicatella.s__Granulicatella_adiacens	23.63022514	1.98E-05
g__Streptococcus.s__Streptococcus_peroris	23.60941514	1.99E-05
g__Actinomyces.s__Actinomyces_odontolyticus	23.61469889	1.99E-05
g__Actinomyces.s__Actinomyces_odontolyticus	23.61286488	1.99E-05
g__Bifidobacterium.s__Bifidobacterium_longum	23.61286488	1.99E-05
unclassified	-21.85454758	0.000377373
g__Veillonella.s__Veillonella_atypica	-19.88671138	0.002899617
unclassified	-19.88671138	0.002899617

WGS Metagenome Functional Annotation: Comparing SPT vs BPT		
KO_Number	**logFC**	**adj.P.Val**
K02954	7.880286074	1.08E-19
K07024	7.849171999	1.08E-19
K02015	7.440333937	2.45E-19
K02904	7.371861891	3.19E-19
K02982	7.335582204	7.46E-19
K02992	7.29004383	1.31E-18
K02013	7.146391284	1.36E-18
K02909	7.164261167	1.36E-18
K00790	7.129316093	1.43E-18
K02986	7.259597159	1.43E-18
K01624	7.058954642	1.72E-18
K02967	7.07076628	1.83E-18
K04567	7.031209506	2.19E-18
K01923	6.996606797	3.47E-18
K01951	6.978765541	3.47E-18
K01867	6.970576616	3.69E-18
K02988	7.013599904	3.96E-18
K00948	6.948240137	4.56E-18
K00059	6.921613069	5.27E-18
K02926	7.001034094	5.27E-18
K02946	6.908958228	5.27E-18
K16787	6.918901086	5.80E-18
K01866	6.880485971	6.68E-18
K00761	7.001470891	6.97E-18
K02895	6.891070688	6.97E-18
K09458	6.861637662	6.97E-18
K01756	6.859754203	7.08E-18
K00088	6.825489981	1.00E-17
K01142	6.847490565	1.04E-17
K00925	6.90826081	1.12E-17
K04043	6.807509447	1.47E-17
K01883	6.769610382	1.84E-17
K01933	6.751005796	1.92E-17
K01937	6.764034722	1.96E-17
K01810	6.737395567	2.11E-17
K00820	6.732578381	3.05E-17
K02906	6.842794201	3.32E-17
K16785	6.711523578	3.33E-17

K09903	6.707848948	3.80E-17
K02876	6.776823345	3.95E-17
K00927	6.675732836	4.89E-17
K01892	6.676611167	4.89E-17
K02428	6.778945735	8.15E-17
K02864	6.634896633	9.45E-17
K00384	6.64764186	9.63E-17
K00876	6.643394908	1.04E-16
K02793	6.686036839	1.07E-16
K03553	6.637421396	1.11E-16
K01696	6.645547869	1.52E-16
K02887	6.688807257	1.90E-16
K00645	6.65052788	2.38E-16
K01687	6.581323624	3.07E-16
K02959	6.613359362	3.70E-16
K00928	6.559604473	3.88E-16
K03703	6.55578241	3.96E-16
K03544	6.583176907	4.43E-16
K02794	6.584545605	5.66E-16
K03671	6.562191214	6.93E-16
K01889	6.598050711	7.92E-16
K03386	6.519964317	8.23E-16
K00615	6.511651943	8.87E-16
K00648	6.531081503	1.11E-15
K00868	6.497879431	1.54E-15
K02796	6.483674966	2.11E-15
K01939	6.462751266	2.58E-15
K02884	6.506120388	3.55E-15
K06131	6.463999128	3.83E-15
K02888	6.449221568	3.88E-15
K02109	6.437147581	5.28E-15
K00789	6.428013688	5.87E-15
K02313	6.423268897	6.17E-15
K00053	6.484596777	7.32E-15
K01938	6.433208115	7.59E-15
K03629	6.452246797	1.03E-14
K00762	6.394950127	1.06E-14
K01736	6.390251628	1.14E-14
K00566	6.377073333	1.57E-14
K00057	6.375678735	2.32E-14
K08303	6.377189494	2.45E-14

K00602	6.354125093	2.86E-14
K00600	6.369676889	3.77E-14
K02072	6.365876681	3.78E-14
K02016	6.38547982	4.93E-14
K01695	6.347394881	5.04E-14
K17828	6.341532858	6.56E-14
K01738	6.340077239	6.83E-14
K00826	6.331593299	8.41E-14
K11717	6.336077427	9.18E-14
K02495	6.324845184	1.01E-13
K01893	6.307236934	1.13E-13
K03110	6.296122536	1.13E-13
K01881	6.342195907	1.35E-13
K01658	6.281390271	1.65E-13
K03550	6.24465489	4.20E-13
K06949	6.232613519	5.46E-13
K03551	6.239903357	7.15E-13
K01673	6.216119675	8.69E-13
K01928	6.205491944	9.94E-13
K03596	6.196105638	1.55E-12
K01703	6.212792709	1.63E-12
K02111	6.200622566	1.64E-12
K01921	6.18555824	1.83E-12
K01735	6.179898933	2.33E-12
K02433	6.169473248	2.46E-12
K00991	6.179474942	2.49E-12
K02073	6.175499748	2.53E-12
K02961	6.188671879	3.17E-12
K02795	6.186188319	4.59E-12
K03685	6.175182217	4.80E-12
K01000	6.157140249	5.86E-12
K02939	6.168809048	5.96E-12
K01424	6.166118939	6.44E-12
K00760	6.139830961	7.21E-12
K01740	6.118433763	8.58E-12
K03584	6.151914605	1.07E-11
K09698	6.112812573	1.16E-11
K01875	6.119748096	1.18E-11
K01495	6.101578351	1.31E-11
K05592	6.098367669	1.41E-11
K04077	6.132375948	1.75E-11

K02036	6.079371473	2.61E-11
K01887	6.075109842	2.69E-11
K00764	6.062238142	3.59E-11
K01776	6.065074673	4.00E-11
K00766	6.061535118	4.18E-11
K00174	6.076489046	4.88E-11
K01661	6.049212434	5.66E-11
K06187	6.054207084	8.90E-11
K12574	6.042803825	9.23E-11
K02338	6.056162971	9.60E-11
K01714	6.024038332	1.04E-10
K00873	6.011737868	1.33E-10
K00847	6.025748343	1.70E-10
K03217	5.996890924	1.87E-10
K03526	6.00604962	1.88E-10
K03470	5.99076672	2.63E-10
K03531	6.012582968	2.74E-10
K00981	5.985107183	2.86E-10
K02945	6.006361928	3.00E-10
K01465	5.981693902	3.10E-10
K00075	5.967419167	4.09E-10
K09457	5.963011257	6.67E-10
K02340	5.948120856	6.96E-10
K03621	5.915701336	1.75E-09
K01439	5.909467065	1.77E-09
K01961	5.909524676	2.02E-09
K01803	5.898104425	2.40E-09
K01755	5.904177925	2.46E-09
K01206	5.898531412	2.80E-09
K00609	5.901792207	3.85E-09
K02341	5.875776292	4.07E-09
K00215	5.882355934	5.96E-09
K02113	5.852571119	7.03E-09
K03100	5.853165227	7.23E-09
K02314	5.863392184	7.38E-09
K01914	5.866540291	9.02E-09
K00052	5.851251572	1.02E-08
K01223	5.856017438	1.10E-08
K03655	5.859371179	1.12E-08
K01997	5.82978161	1.31E-08
K00850	5.828083373	1.40E-08

K01619	5.835280096	1.47E-08
K01653	5.816199231	1.76E-08
K02115	5.820780963	2.20E-08
K00800	5.808517093	2.27E-08
K00791	5.8157981	2.43E-08
K00806	5.805692461	2.64E-08
K17686	5.802808242	2.87E-08
K01520	5.479138644	2.96E-08
K00338	5.803576774	3.51E-08
K00963	5.797723351	3.96E-08
K01924	5.78295596	5.64E-08
K00625	5.759529731	6.06E-08
K02563	5.75386581	6.95E-08
K01091	5.746777589	8.38E-08
K01589	5.745798674	9.57E-08
K18682	5.74798018	9.80E-08
K01783	5.430879377	1.01E-07
K01929	5.738752587	1.19E-07
K01878	5.739224864	1.20E-07
K00941	5.738142454	1.39E-07
K01193	5.712223093	1.84E-07
K01775	5.707967001	2.03E-07
K03101	5.706471848	2.31E-07
K00763	5.708080503	2.63E-07
K15771	5.691822215	3.23E-07
K00560	5.681528217	3.63E-07
K00872	5.679925409	5.10E-07
K00651	5.664444642	6.54E-07
K09816	5.656935	7.74E-07
K06881	5.630792413	1.48E-06
K00831	5.615027485	1.57E-06
K03340	5.604656058	1.95E-06
K01885	5.602230397	2.08E-06
K07173	5.606389991	2.38E-06
K02825	5.600083014	2.61E-06
K03785	5.590190793	2.83E-06
K00882	5.575851143	3.35E-06
K09808	5.574618231	3.46E-06
K01468	5.575654678	3.99E-06
K00796	5.56671183	4.91E-06
K02435	5.551779008	5.57E-06

K00024	5.548305484	6.78E-06
K06861	5.541912598	7.01E-06
K01770	5.540794889	8.19E-06
K00864	5.515282988	1.27E-05
K00703	5.514513919	1.36E-05
K11071	5.495117886	1.80E-05
K07260	5.488055381	2.10E-05
K04042	5.485131281	2.21E-05
K11070	5.487968944	2.21E-05
K17320	5.490727227	2.30E-05
K02342	5.466198311	3.28E-05
K00297	5.464630329	3.30E-05
K00342	5.453851139	4.09E-05
K07177	5.46014874	4.10E-05
K10823	5.451962459	4.28E-05
K10773	5.44864656	5.02E-05
K03585	5.441916647	5.17E-05
K01880	5.441415955	5.35E-05
K01916	5.436783638	6.30E-05
K01358	5.428283824	6.91E-05
K04564	5.423269271	7.53E-05
K03601	5.412967687	9.11E-05
K01807	5.402718355	0.000109835
K06041	5.397601532	0.000119327
K15580	5.398193792	0.000119327
K01963	5.39453199	0.000128485
K01443	5.389528656	0.000142223
K01739	5.393046135	0.000142223
K03590	5.367012309	0.00022152
K09474	5.336884394	0.000353425
K16363	5.329745116	0.000392691
K03587	5.331102563	0.000411986
K01840	5.318923966	0.000477934
K02066	5.321599195	0.000487433
K03092	5.316018608	0.000527277
K14260	5.299763391	0.000632131
K09810	5.292361879	0.000728351
K01874	5.28716771	0.000816371
K17319	5.271109064	0.001005456
K00549	5.260465034	0.001169196
K03702	5.255336748	0.00126601

K00147	5.255886681	0.001266786
K01854	5.257080972	0.001287103
K07718	5.253243257	0.001292101
K00965	5.239009534	0.001576675
K15772	5.235984734	0.001680983
K02110	5.959477381	0.002067526
K00162	5.218825239	0.002093315
K01698	5.217689208	0.00211054
K05606	5.2184945	0.00215919
K15986	5.208458304	0.002370354
K01839	5.212024607	0.00240444
K00841	5.206950388	0.002519757
K03471	5.196926043	0.002731153
K14652	5.199969627	0.002731153
K01745	5.178953817	0.003464188
K01903	5.17531908	0.003813557
K00845	5.165808125	0.00407009
K01677	5.164895872	0.004083243
K03784	5.165066974	0.004139172
K02343	5.162328594	0.004199849
K00784	5.156156089	0.004745651
K00266	5.148998246	0.005135571
K00974	5.131742333	0.006064639
K00003	5.122503329	0.006683285
K13940	5.120505519	0.007012668
K19302	5.117672149	0.007113355
K01772	5.11677538	0.007181024
K01876	6.114074984	0.007502238
K11041	5.094874402	0.008839676
K04517	5.093070621	0.009185966
K02822	5.088322102	0.009732528
K01868	5.079212757	0.010614876
K00330	5.075065561	0.011002432
K03385	5.072383833	0.011002432
K00158	5.059784968	0.012637905
K11072	5.057249101	0.012947993
K00364	5.046065554	0.014252405
K02078	6.290172766	0.014345366
K01809	5.041450643	0.014402492
K00337	5.037960087	0.015148202
K00705	5.03810065	0.015203459

K00067	5.033942659	0.015447044
K01270	5.033942659	0.015447044
K00973	5.019409366	0.017307906
K02809	5.013367427	0.018096925
K02810	5.013367427	0.018096925
K02892	6.143980686	0.018433159
K02913	10.46148414	0.018750538
K01079	5.00413761	0.019542584
K02769	4.997757928	0.020384403
K02770	4.997757928	0.020384403
K02963	6.045008557	0.020477267
K02911	7.050756376	0.021399692
K01639	4.98835615	0.022261614
K01586	4.982526328	0.02304347
K00036	4.981647081	0.023316675
K01962	4.977054437	0.023997153
K01493	5.441350868	0.02458762
K01635	4.97111084	0.024867086
K02031	4.974218761	0.024867086
K01626	4.963568178	0.026552089
K02948	7.439304688	0.027226379
K02040	4.958522961	0.027400472
K02871	6.293335049	0.027533292
K00939	6.31095071	0.027922327
K01644	4.956009049	0.028004046
K01922	4.952387332	0.028117453
K02768	4.951817795	0.028117453
K03588	4.953522299	0.028117453
K00949	4.956425322	0.02821528
K03523	4.951151676	0.028842504
K00058	4.947396579	0.029276447
K09817	5.201914131	0.029379769
K01886	4.944712282	0.029472086
K11709	4.947509544	0.029519834
K00526	5.681989325	0.029718958
K02952	7.338333189	0.030144281
K03742	4.942904856	0.030144281
K00969	4.944348792	0.030260374
K18369	4.93874942	0.030663691
K02899	5.704221998	0.030801893
K04518	4.933298608	0.031298533

K12292	4.93441405	0.031298533
K01597	4.932355036	0.031619607
K07706	4.933077745	0.032032646
K10681	4.931097311	0.032798321
K03040	7.113928032	0.034456563
K02863	7.16852947	0.035066376
K00016	4.911629546	0.036016211
K06281	4.912537555	0.037825652
K01733	4.902140983	0.038279837
K15634	4.896026656	0.039826187
K02890	7.064942594	0.039874468
K03367	4.892293489	0.040196818
K02881	6.92648411	0.041379376
K00912	4.903044394	0.042615546
K01956	5.817233594	0.042949245
K02160	4.88581673	0.042982252
K02316	4.876343755	0.04453647
K02970	6.944981626	0.04453647
K02916	6.768003472	0.04481431
K00054	4.871158154	0.045383263
K02020	4.868581304	0.045572783
K01187	4.870079663	0.045889598
K16786	6.788943318	0.045889598
K02886	6.156002582	0.046165266
K03046	4.864228618	0.046325246
K00177	4.876800125	0.04679845
K02867	5.792051479	0.047805114

RNA Metatranscriptome Functional Annotation: Comparing SPT vs BPT		
KO_Number	**logFC**	**adj.P.Val**
K02470	21.11339779	1.72E-66
K05366	22.06025771	5.41E-61
K02035	23.31722871	5.90E-60
K03070	22.00548176	1.20E-58
K00382	20.93951148	1.35E-57
K03696	21.30626752	1.35E-57
K15581	20.59675139	1.02E-56
K12574	21.10003746	1.26E-56
K00527	21.56398679	1.87E-56
K02469	21.05373082	2.29E-53
K01924	21.18959857	3.33E-53
K00525	20.77934971	1.47E-52
K03043	21.89728387	3.37E-52
K04759	23.15135849	5.67E-52
K00790	21.25884962	7.77E-52
K03979	19.59186979	4.43E-51
K03046	22.52598123	1.29E-50
K05592	19.9248332	6.09E-50
K06147	21.17223455	7.72E-50
K08884	21.18450859	3.74E-48
K01439	20.5572525	3.99E-48
K07052	19.09841071	5.08E-48
K01000	20.50505566	7.53E-48
K00611	19.63354627	1.19E-47
K12573	20.53483231	9.26E-46
K08643	21.27149928	6.86E-44
K16787	19.70953248	1.24E-43
K03466	20.22347995	1.35E-43
K07462	20.17154349	7.00E-43
K03699	19.87978053	8.56E-43
K01950	20.8901023	1.11E-42
K00962	20.2578688	1.73E-41
K02057	20.09666828	6.79E-41
K01961	20.6331774	1.03E-40
K11749	18.7221659	1.39E-38
K00005	19.55556029	5.05E-38
K01534	20.02803906	4.48E-34
K00627	18.81082358	9.75E-33
K03969	18.56263835	1.61E-26
K00975	9.165904681	4.38E-12
K01265	6.781502365	1.31E-08

K00703	7.496269539	1.39E-08
K03531	6.804461013	4.35E-08
K02529	7.185585865	4.58E-08
K02357	7.32516224	7.72E-08
K02601	6.717647621	9.57E-08
K03625	6.737084541	3.33E-07
K09013	5.532143706	3.86E-07
K02913	4.977811652	5.62E-07
K16509	6.562733618	7.58E-07
K00651	6.843976169	7.64E-07
K02316	7.296323742	8.37E-07
K10794	6.781298722	8.37E-07
K01990	7.370298893	8.88E-07
K07024	6.505983866	8.88E-07
K00688	7.707244666	1.01E-06
K02970	5.562844084	1.24E-06
K00600	7.329777616	1.26E-06
K07335	6.112481004	1.28E-06
K00820	7.478900148	1.31E-06
K01358	7.11756243	1.31E-06
K06131	7.601925506	1.60E-06
K00432	6.012069181	1.70E-06
K02935	5.899242129	1.85E-06
K06286	6.577707511	1.85E-06
K15580	6.903426216	2.17E-06
K03544	6.23283178	2.18E-06
K00700	6.536648973	3.13E-06
K00939	5.743166404	3.22E-06
K03496	7.264407383	3.38E-06
K02564	5.850612735	3.56E-06
K01537	6.118115764	3.58E-06
K01595	6.388730972	3.64E-06
K00760	5.170095911	3.78E-06
K01738	7.034652934	3.91E-06
K01462	5.614355545	4.21E-06
K14982	5.959864604	4.37E-06
K00088	6.008874252	4.60E-06
K00648	6.439132516	4.60E-06
K09903	5.662592695	4.63E-06
K01938	6.58081351	4.90E-06
K03319	7.471755867	4.97E-06
K00384	6.559145012	5.15E-06
K00615	6.1271465	5.15E-06

K02356	5.725254449	5.15E-06
K09014	6.282021311	5.15E-06
K09811	6.105753232	5.15E-06
K00059	5.897971212	5.86E-06
K02078	5.469830682	6.47E-06
K15986	6.568741456	6.47E-06
K00705	6.533068078	6.74E-06
K02796	5.838180998	6.79E-06
K00554	5.317533793	7.10E-06
K00763	5.367805926	7.10E-06
K03977	6.16057784	7.10E-06
K08600	6.07330024	7.10E-06
K03778	5.846071698	7.39E-06
K04564	5.336652002	7.39E-06
K00948	6.802830464	7.90E-06
K04074	6.54387911	8.04E-06
K00789	5.920096806	8.42E-06
K02109	5.739431032	8.61E-06
K02867	4.577306528	8.61E-06
K15371	19.00595581	8.61E-06
K00560	5.482080319	9.20E-06
K01992	6.953441531	9.30E-06
K06207	5.993104095	9.39E-06
K02003	6.25628158	9.71E-06
K02888	5.940576894	9.71E-06
K02031	6.025457573	1.08E-05
K02838	4.999003969	1.23E-05
K05808	5.460354387	1.23E-05
K05878	18.62751207	1.30E-05
K12267	5.909495218	1.33E-05
K03768	5.77540998	1.43E-05
K01784	5.781341249	1.45E-05
K03431	6.467867084	1.45E-05
K06997	5.740096729	1.45E-05
K07386	8.000758363	1.45E-05
K03217	5.906559496	1.49E-05
K09812	5.537510739	1.53E-05
K03702	5.692572598	1.68E-05
K08483	5.794371062	1.69E-05
K00928	5.468079237	1.72E-05
K02115	5.767008009	1.91E-05
K01803	6.306819228	1.93E-05
K02217	6.057777428	1.93E-05

K03596	6.39502026	2.08E-05
K02113	5.354667507	2.12E-05
K01893	5.548612152	2.16E-05
K02914	4.553782221	2.16E-05
K07010	5.54570572	2.21E-05
K03590	5.596744103	2.24E-05
K00057	5.655536268	2.29E-05
K18682	6.331957127	2.33E-05
K03737	6.845424848	2.53E-05
K02836	5.231533194	2.77E-05
K04077	6.385532016	2.86E-05
K01740	6.270226699	2.92E-05
K02959	5.020934164	3.17E-05
K00162	5.615521843	3.28E-05
K01673	4.845779755	3.28E-05
K09685	5.328088037	3.28E-05
K01006	6.668436565	3.28E-05
K01710	5.601060077	3.28E-05
K02794	5.428594607	3.28E-05
K01951	6.271548259	3.52E-05
K01752	5.559180349	3.52E-05
K02014	7.444162388	3.59E-05
K01262	6.66706582	3.64E-05
K03655	6.097105368	3.95E-05
K06346	4.933313824	3.98E-05
K03744	5.016022821	4.16E-05
K00133	5.451561019	4.28E-05
K01142	5.26374593	4.28E-05
K01714	5.487979821	4.28E-05
K15770	5.981515459	4.28E-05
K07082	5.504500426	4.37E-05
K03073	5.512404314	4.47E-05
K02028	5.623757582	4.51E-05
K03438	5.736880871	4.85E-05
K00287	4.999579812	5.03E-05
K02314	5.527201486	5.14E-05
K04567	6.000800283	5.34E-05
K07738	4.932728633	5.82E-05
K10112	5.485063	5.87E-05
K03701	5.978995376	5.91E-05
K03168	6.128873423	6.32E-05
K00858	5.247543853	6.96E-05
K01443	5.153332309	6.96E-05

K01870	6.422505286	6.96E-05
K03569	6.002910936	6.96E-05
K09458	5.810458413	6.96E-05
K01104	5.479549463	7.32E-05
K01835	6.349176741	7.63E-05
K02319	-5.717284245	7.63E-05
K04488	5.54147446	7.63E-05
K11065	5.046547039	7.63E-05
K04068	4.886458816	8.05E-05
K02338	5.769787393	8.69E-05
K00645	5.717515332	8.94E-05
K01756	5.200422441	9.05E-05
K09772	5.003313189	9.13E-05
K11753	6.028545977	9.21E-05
K03601	5.35453649	9.39E-05
K01610	6.162078113	9.75E-05
K03734	4.973591645	0.000103181
K04069	4.47205174	0.000103181
K06471	-12.53415543	0.000104273
K03574	4.828795433	0.000105379
K00625	5.462372549	0.000105454
K11068	5.608801046	0.000106364
K02040	5.467270051	0.000110586
K03695	7.351667929	0.000112206
K04047	3.407138958	0.000114781
K07056	4.745621748	0.000114781
K15633	6.909046788	0.000114781
K08999	5.813957522	0.000115307
K01875	5.172871783	0.00012437
K06217	5.007981615	0.00012437
K01785	5.369313114	0.000131031
K02916	4.183792106	0.000135798
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K01060	2.536750433	0.15649065
K17836	-2.182684271	0.157100077
K04767	2.648018529	0.158902225
K07757	2.40740493	0.161923283
K13747	2.937911858	0.161954536
K03930	3.021153939	0.162070421
K08659	2.726949002	0.162944433
K13052	2.348595541	0.162944433
K03648	2.20132997	0.163092438
K00997	2.140441359	0.16474394
K02020	2.41768341	0.166194602
K15923	3.222572192	0.166886678
K03458	2.738637719	0.167204969
K02687	2.466003071	0.168390902
K00048	2.742354124	0.168845871
K05362	2.758168629	0.168991132
K14441	2.936000729	0.169092154
K02703	-5.641776926	0.169436054
K11071	2.506086105	0.169436054
K05823	2.926571757	0.170335751
K03525	2.492001973	0.172093436
K01676	3.161185713	0.17251981
K15977	2.468822809	0.173340706
K11358	2.693469301	0.17374313
K07407	2.973465205	0.174133542
K07224	2.872117418	0.175141597
K07322	2.585252783	0.175174408
K01681	2.711905191	0.176215722

K01079	2.520070607	0.176437563
K01571	3.149822562	0.176483543
K02982	1.218195077	0.176524507
K00613	2.718264156	0.176952162
K00348	2.583425721	0.179742165
K04516	2.140356628	0.180597687
K09780	2.336896402	0.181673678
K00001	2.165960037	0.181801351
K00782	2.42541317	0.182856514
K12524	2.860379921	0.182920724
K01716	-5.485964716	0.18484752
K01770	2.402665683	0.18484752
K02968	1.36451929	0.185176522
K03564	2.307195478	0.185176522
K07030	1.581059163	0.190395412
K03090	2.399763264	0.190641853
K03385	2.813503033	0.191206112
K16924	2.566196045	0.191841054
K12349	3.132665033	0.191958675
K00796	2.392234809	0.193019646
K01624	1.624412118	0.19400488
K00164	2.99083766	0.196034473
K16345	3.00700816	0.199274812
K10542	2.234484374	0.199305203
K01866	1.711930246	0.199939457
K07139	2.061546539	0.199939457
K02843	2.389287327	0.200798164
K02759	2.185853074	0.201496863
K00097	2.604401753	0.201692711
K03316	2.70828029	0.202239348
K01849	2.415196253	0.202668973
K02077	2.630973923	0.202691259
K04518	2.574838822	0.202691259
K03048	2.304702621	0.203999716
K09457	2.202794889	0.205560928
K01056	2.131337359	0.207184394
K05516	2.306968469	0.21033822
K03183	2.453476512	0.212065569
K07584	1.093679345	0.213957285
K03593	2.481932488	0.21685121
K00680	2.233215344	0.217402522
K00887	2.304246338	0.218284406
K00940	1.925747811	0.218284406

K01848	3.046284211	0.222412115
K03786	2.05446023	0.224000144
K09474	2.495568386	0.225470331
K04561	2.611937524	0.226548374
K19272	-1.564118607	0.227413935
K00281	3.007898504	0.22773342
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K00231	2.228881102	0.233638622
K01081	2.140380325	0.233638622
K07089	2.220512855	0.233638622
K10040	2.634066242	0.233638622
K01468	2.787692619	0.234016252
K01652	1.595564102	0.234016252
K17759	2.792951424	0.234016252
K01012	2.306863606	0.235129017
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K03687	1.380705376	0.236710448
K04773	2.76716253	0.236710448
K03457	2.575344394	0.240333125
K13643	2.462556954	0.240333125
K07483	-1.398577263	0.24120595
K00757	2.272787966	0.241671846
K01599	2.349860335	0.242514832
K01704	1.87517322	0.246749047
K01635	2.463842923	0.249131405
K13990	2.895264574	0.249162471
K01749	2.162032517	0.250522403
K07304	2.317326941	0.250685533
K07461	1.790800305	0.250685533
K00283	3.624039759	0.250737968
K00459	2.528690484	0.252126345
K00548	2.513998507	0.252126345
K02007	2.215185024	0.253135677
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K06409	2.637649869	0.254353039
K13677	2.024578597	0.25446247
K01934	1.866754117	0.259411101
K10716	2.386393068	0.259411101
K03270	2.072173261	0.260091672
K16789	2.285382954	0.262689832
K01572	2.427038012	0.263235746
K13542	2.825424051	0.263444459
K00919	2.076728822	0.264723824

K00052	1.958020284	0.265318239
K03169	2.225724817	0.265318239
K07707	2.439841012	0.265318239
K00336	2.397072905	0.269118399
K00330	2.056917162	0.269568605
K00373	2.41053314	0.269568605
K12268	2.699117935	0.270861249
K02160	2.167783802	0.271382822
K09125	2.073974979	0.271994186
K03790	1.637923249	0.273232973
K07387	2.383904175	0.273232973
K18888	2.54302863	0.273299282
K01858	2.563409662	0.275796031
K07391	2.42031737	0.278325644
K09765	-1.36184291	0.28089706
K16926	2.347304476	0.280932869
K16899	4.198992823	0.28336426
K01524	2.136753629	0.287208815
K01647	2.49992545	0.288495025
K01361	4.193183525	0.289546973
K10039	2.191327493	0.291232258
K11209	2.043278453	0.291589176
K13940	2.00796742	0.291589176
K09791	-2.944581397	0.292046691
K00549	2.171718866	0.292389503
K03605	1.865575727	0.292612881
K01207	1.974950806	0.292933362
K01151	1.93755747	0.296866511
K03082	1.948910472	0.298491783
K03713	1.400064301	0.298671904
K00337	1.980614815	0.299323857
K14742	2.271832265	0.301582927
K02377	2.432695983	0.3044314
K00363	2.344631799	0.304548712
K01626	1.631691488	0.304548712
K06282	2.384073496	0.307537984
K00567	1.904324265	0.310471544
K02484	2.619471413	0.313200048
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K03453	2.062470908	0.316708088
K02483	1.869132553	0.319931381
K00606	2.023924404	0.322202329
K03399	2.033896492	0.325178425

K08974	1.984509476	0.326616422
K02575	2.473454898	0.329178756
K04771	1.701451527	0.331962228
K00989	1.629385922	0.332601146
K00331	2.141363244	0.335374129
K04026	2.453003848	0.337761803
K01186	2.619230141	0.33834548
K18118	2.448151365	0.339048859
K01661	1.907926321	0.339587368
K00376	2.630543515	0.341501343
K11382	2.407261715	0.343401148
K00349	2.079153775	0.344027891
K06001	2.067725151	0.34513382
K00528	1.899077358	0.345754831
K01187	2.40545589	0.346402461
K01922	2.313082539	0.347741276
K01739	2.104412141	0.349062033
K01823	1.749117768	0.349260571
K02788	2.440772352	0.349260571
K09758	3.574312746	0.349910936
K07405	2.198142289	0.350095128
K05934	2.173521404	0.352263647
K00016	1.024677609	0.355350067
K06920	1.96779076	0.355727942
K12554	2.213364878	0.356407027
K01919	3.523150548	0.357056977
K19165	1.862902571	0.357056977
K19221	2.188635373	0.357056977
K00865	2.029310309	0.35935018
K01678	2.162782976	0.362142665
K07636	2.015200312	0.362142665
K10530	2.286826178	0.362142665
K11031	2.169982653	0.362499665
K01197	2.483948448	0.364020745
K08289	2.152940762	0.364108683
K00338	1.7870222	0.364259535
K03571	2.037574274	0.364259535
K03476	2.165711437	0.367861345
K02425	-3.481461829	0.368484581
K03210	0.906621061	0.368484581
K02230	2.10584	0.369013181
K06929	0.97776201	0.371300733
K03404	1.818661065	0.372172038

K09891	-3.481074857	0.38307401
K07177	2.047941314	0.383751743
K03705	1.224661252	0.38399175
K14445	2.2165536	0.38399175
K03743	2.223758012	0.384693593
K07776	1.965066746	0.385718879
K06136	-3.480915471	0.388244089
K07660	-3.480916076	0.388244089
K08305	-3.480909452	0.388244089
K07305	1.371816386	0.395077608
K07496	1.896657455	0.395077608
K07739	1.846864781	0.395077608
K01695	1.691773789	0.395513042
K07027	2.166513104	0.396513098
K03486	1.817074772	0.402017049
K07037	2.125128031	0.403246549
K03667	2.19410818	0.404312299
K00068	2.025421828	0.412066529
K03332	1.920733312	0.412882286
K07150	1.721566902	0.412883886
K01696	1.79234276	0.421146791
K03736	2.84431787	0.423017951
K18891	2.914824945	0.426278689
K02824	1.076652833	0.428489605
K00127	2.069239556	0.429304127
K03394	2.06139978	0.4355709
K07701	-2.582651094	0.435665723
K19134	2.744984724	0.435665723
K10974	2.743017429	0.437834087
K01486	1.984831802	0.442804973
K01786	1.96988067	0.443341346
K02075	2.021906355	0.445785128
K06926	3.020893339	0.44771486
K01480	2.112859189	0.44775798
K02074	2.129096303	0.450430807
K00135	2.994905931	0.450511105
K03491	2.995510537	0.450511105
K00013	2.951673922	0.457115544
K07034	2.043341072	0.464034709
K01834	0.77759687	0.46582343
K11720	1.844923845	0.474324512
K18216	1.997892063	0.477823361
K06915	2.138043671	0.481263876

K00158	0.993123208	0.487620597
K01654	2.727557859	0.491241481
K06889	1.274805043	0.491241481
K00370	2.652252804	0.503448671
K08167	2.622046924	0.508209304
K14645	1.996760489	0.509115386
K00691	1.888230712	0.511277702
K13288	1.356841728	0.511305425
K03735	2.580532203	0.513777572
K15987	1.980739897	0.514624144
K04030	1.784970247	0.527135535
K06940	0.865257445	0.529060188
K03558	-1.971907396	0.53043991
K06200	2.026129968	0.539404242
K01191	2.390810948	0.543927645
K15584	2.011827236	0.543927645
K18955	0.775118568	0.543927645
K05363	1.783969295	0.560970743
K07452	2.288218728	0.560970743
K00244	2.27288088	0.563256354
K07654	2.220642913	0.57221228
K01902	1.028880547	0.573215019
K18217	1.866307647	0.577881722
K15772	0.836911177	0.601308771
K03273	0.859312383	0.65865792
K03559	0.794160022	0.661363513
K03756	1.164302311	0.674491013
K11706	0.568065679	0.685071663
K15256	1.565701284	0.691549662
K07552	0.864032727	0.69874349
K11251	-0.740429793	0.70213885
K06925	-0.457219467	0.715614712
K01687	0.52057364	0.72886942
K00009	1.269273042	0.747421482
K00901	0.447204138	0.775294925
K01420	0.452696321	0.776437815
K02760	0.365359074	0.78316557
K01579	-0.515101077	0.786539808
K00053	0.296503776	0.801410561
K08151	-0.927051026	0.809436893
K01419	0.342763122	0.894903641
K06215	0.202105451	0.897117672
K07497	0.205571911	0.89726447

K09022	0.190824222	0.900579885
K00647	-0.184318509	0.921444338
K04086	0.086814334	0.946815939
K02037	0.069180296	0.96187613
K05311	0.021016098	0.995618083

16S rRNA Gene Sequencing Decontamination		
Taxa	**Freq**	**Contaminant**
g__Alicyclobacillus_4359693	0.022947413	TRUE
g__Flavobacterium_960076	0.023594421	TRUE
g__Acinetobacter_1097359	0.00822969	TRUE
f__Methylobacteriaceae_785526	0.011645502	TRUE
g__Methylobacterium_1007180	0.009964154	TRUE
o__Rhizobiales_951794	0.003680734	TRUE
g__Acinetobacter_889025	0.012775794	TRUE
f__Comamonadaceae_1106617	0.004264202	TRUE
f__Comamonadaceae_791738	0.003832526	TRUE
f__Enterobacteriaceae_1111294	0.003223772	TRUE
g__Limnohabitans_1108275	0.003193661	TRUE
f__Micrococcaceae_1081815	0.003367206	TRUE
f__Comamonadaceae_1106324	0.002536363	TRUE
g__Salinibacterium_876170	0.003126259	TRUE
f__Haliangiaceae_313833	0.002042938	TRUE
f__Comamonadaceae_719367	0.003293414	TRUE
g__Enhydrobacter_990864	0.001997074	TRUE
g__Bacillus_854050	0.001713149	TRUE
g__Corynebacterium_300811	0.001885315	TRUE

WGS Metagenome Sequencing Decontamination		
Taxa	**Freq**	**Contaminant**
UNMAPPED	0.60234084	TRUE
UNGROUPED	0.16047332	TRUE
UNGROUPED|unclassified	0.06478362	TRUE

RNA Metatranscriptome Sequencing Decontamination		
Taxa	**Freq**	**Contaminant**
UNGROUPED|s__Propionibacterium_acnes	0.00446081	TRUE
UNGROUPED|s__Komagataella_pastoris	0.00053986	TRUE
K18183|s__Komagataella_pastoris	1.47E-06	TRUE
K06960|s__Propionibacterium_acnes	9.79E-07	TRUE
UNGROUPED|s__Vicia_cryptic_virus	7.23E-06	TRUE
K02906|s__Propionibacterium_acnes	9.18E-07	TRUE
K03924|s__Propionibacterium_acnes	9.60E-07	TRUE
K06131|s__Propionibacterium_acnes	1.29E-06	TRUE
K09772|s__Propionibacterium_acnes	1.05E-06	TRUE
K02003|s__Propionibacterium_acnes	1.56E-06	TRUE
K06215|s__Propionibacterium_acnes	1.38E-06	TRUE
K02768|s__Propionibacterium_acnes	7.86E-07	TRUE
K02990|s__Propionibacterium_acnes	8.83E-07	TRUE
K07742|s__Propionibacterium_acnes	6.53E-07	TRUE
K03110|s__Propionibacterium_acnes	1.49E-06	TRUE
K00338|s__Propionibacterium_acnes	8.42E-07	TRUE
K10258|s__Komagataella_pastoris	4.99E-07	TRUE
K02519|s__Propionibacterium_acnes	6.72E-07	TRUE
K04047|s__Propionibacterium_acnes	1.10E-06	TRUE