Title: Metagenomic Sequencing Detects Respiratory Pathogens in Hematopoietic Cellular Transplant Patients

Abstract

Rationale: Current microbiologic diagnostics often fail to identify the etiology of lower respiratory tract infections (LRTI) in hematopoietic cellular transplant recipients (HCT), which precludes the implementation of targeted therapies.

Objectives: To address the need for improved LRTI diagnostics, we evaluated the utility of metagenomic next generation sequencing (mNGS) of bronchoalveolar lavage (BAL) to detect microbial pathogens in HCT patients with acute respiratory illnesses.

Methods: We enrolled 22 post-HCT adults ages 19-69 years with acute respiratory illnesses who underwent BAL at the University of Michigan between January 2012 and May 2013. mNGS was performed on BAL fluid to detect microbes and simultaneously assess the host transcriptional response. Results were compared against conventional microbiologic assays.

Measurements and Main Results: Standard of care clinical diagnostics identified microbes in seven patients (32%), six of which were considered pathogens by treating physicians, and all of which were detected by mNGS. Previously unrecognized LRTI pathogens were also identified in six patients for whom standard testing was negative (human coronavirus 229E, human rhinovirus A, Corynebacterium propinquum and Streptococcus mitis); findings were confirmed by independent PCR and 16S rRNA sequencing. Relative to patients without infection, patients
with infection had increased expression of immunity related genes ($p=0.022$) and significantly lower diversity of their respiratory microbiome ($p=0.017$).

Conclusions: Compared to conventional diagnostics, mNGS enhanced detection of pathogens in BAL fluid from HCT patients. Furthermore, our results suggest that combining unbiased microbial pathogen detection with assessment of host gene biomarkers of immune response may hold promise for enhancing the diagnosis of post-HCT respiratory infections.

**Supplemental Data, Methods and Text**

**Antimicrobial Use**

All study subjects had received prophylactic antimicrobials prior to bronchoscopy with the agents listed in Table 1. In addition, empiric broad spectrum antimicrobials were initiated in seventeen patients (77%) upon hospitalization, prior to BAL, and included vancomycin ($n=6$, patients 3, 5, 8, 19, 25, 25), cefepime ($n=4$, patients 10, 11, 22, 23), vancomycin + cefepime ($n=4$, patients 1, 7, 13, 18), cefepime + tobramycin ($n=1$, patient 24), and vancomycin + cefepime + tobramycin ($n=1$, patient 6) as described in Table 1. Two patients (9%) received exclusively pathogen-targeted antivirals that included ganciclovir for HHV-6 in patient 36 and ribavirin for RSV in patient 10. One patient (patient 5) received trimethoprim/sulfamethoxazole targeting *Stenotrophomonas maltophilia* in addition to prophylactic vancomycin. Four patients (15%) received no antimicrobials aside from pre-existing prophylactic agents.

**Clinical Microbiologic Testing**

Standard of care clinical microbiologic testing of BAL was performed for all patients at the University of Michigan Clinical Microbiology Laboratory. Testing included quantitative bacterial, mycobacterial, fungal and cytomegalovirus (CMV) shell vial cultures; Prodesse
ProFlu-HMPV+ multiplex respiratory viral PCR (Hologic) targeting influenza A/B, respiratory syncytial virus (RSV) and human metapneumovirus (HMPV); human herpesvirus-6 (HHV-6) PCR; Aspergillus galactomannan assay, and silver staining for Pneumocystis jirovecii.

Bacterial cultures were inoculated on 5% sheep blood agar, chocolate agar and MacConkey agar and incubated at 37˚C with 5% CO₂ for three days. Fungal cultures were inoculated on inhibitory mold agar, brain heart infusion (BHI) blood plates and BHI blood plates with chloramphenicol and gentamycin, and were incubated at 32˚C for four weeks. Mycobacterial cultures were processed with NaOH and inoculated into BacT/Alert MP bottles (Biomerieux) and Lowenstein Jensen slants and incubated at 35˚C for six weeks. CMV shell vial cultures were inoculated into 2% re-feed media and incubated at 35˚C for 48 hours.

For bacterial cultures, organisms were identified using Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) mass spectrometry and in equivocal cases, the VITEK microbial identification system (Biomerieux) and/or API plates were used. CMV cultures were performed in shell vial tissue (HS27 Ready Cell), fluorescently stained and evaluated for inclusion bodies by microscope.

The clinical laboratory reported growth of >10,000 CFU of any organism, regardless of interpreted pathogenicity. In this cohort, however, no bacterial or fungal microbes considered to represent commensal, non-pathogenic flora were reported by the clinical microbiology laboratory for any of the patients. In this study, BAL microbiologic results were considered to be negative in cases where no growth was observed by culture and all other diagnostics were also negative.

A subset of patients received additional non-BAL diagnostics per discretion of the treating physicians (Table 1) including the above described multiplex viral PCR performed on nasopharyngeal (NP) swabs, as well as blood cultures, serum PCR for herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), CMV and HHV-6, and Clostridium difficile toxin stool PCR.
Metagenomic Next Generation Sequencing

Total nucleic acid was extracted from 250µl of patient BAL fluid and a water control using bead-based lysis and the Zymo Viral DNA/RNA Kit (Zymo Research). In order to identify transcriptionally active organisms, RNA was isolated from 50µl of the extracted nucleic acid by treating with Turbo DNase (ThermoFisher) at 37°C for 20 minutes. The resulting RNA was subsequently purified using the Zymo RNA Clean and Concentrate system (Zymo Research) and then reverse transcribed using random-hexamer priming and the Ovation RNaseq system (Nugen) to generate complementary DNA. The remaining 50uL of total nucleic acid underwent DNA extraction by first incubating with RNAse A at 37°C for 20 minutes and then purifying the product using the Zymo DNA Clean and Concentrate system (Zymo Research). DNA and cDNA were then carried forward for adapter addition and barcoding using the Nextera system (Illumina) and the latter was depleted of human mitochondrial rRNA sequences using DASH as previously described (S1). After size-selection (350-450 nucleotides) using the BluePippin system (Sage), libraries were amplified, quantitated and paired-end sequenced on Illumina HiSeq 4000 or 2500 sequencers.

Bioinformatics for Pathogen Detection

Detection of microbial pathogens was performed using a rapid informatics pipeline that incorporated Bayesian modeling to discriminate pathogens from background microbial sequences (Wilson, Odonovan et al., submitted). Briefly, this analytical pipeline employed PRICEseqfilter removal of low quality and low complexity sequences (S2), followed by subtractive alignment against the ENSEMBL GRCh38 human genome build using STAR and subsequent filtration using Bowtie2 for non-fungal eukaryotes, phage and other non-human tropic viruses (S3). All remaining sequences with > 92% similarity were the compressed using CD-HIT-DUP and subsequently
aligned against the NCBI nucleotide (nt) and non-redundant protein (nr) databases using GSNAPl and RAPSearch2, respectively (S4, S5).

Microbial sequences in each subject’s dataset were normalized to reads per million (rpM) alignments at the genus level against the NCBI nt database. We then calculated a Z-score for each microbial genus relative to a control group of 17 no-template water controls derived from sequencing runs performed in our laboratory over the past two years. The microbial constituents of this control group are summarized in Table S1. For taxonomic IDs that were not present in the background set, a Z-score of 100 was applied; for calculated Z-scores greater than 99, a maximum Z-score of 99 was applied.

Subsequently, we derived a microbial significance score by multiplying the RNAseq genus rpM by the summed nt and nr Z-scores \[\text{score} = \text{rpM}_{\text{genus}} \times (Z_{\text{nt-genus}} + Z_{\text{nr-genus}})\]. To further improve the specificity of microbial assignments, we required 1) microbes to be detected in both nucleotide (nt) and protein (nr) database alignments; 2) microbes to have a \(Z_{\text{nt}}\) and \(Z_{\text{nr}}\) > zero and 3) bacteria and fungi detected by RNAseq to also have detectable genomic sequence by DNAseq. To capture both DNA and RNA viruses, our model permitted detection of DNA viruses exclusively by DNAseq and RNA viruses exclusively by RNAseq. Finally, only genera with Z-scores > 0 were considered significant microbes.

For each patient, any microbes that passed these requirements were then processed using the following decision tree, summarized in Figure S1. Microbes identified were classified as confirmed pathogens if (a) both clinical testing and mNGS identified the microbe, (b) there existed literature evidence of pathogenicity in the lungs, and (c) the score was at least two-fold greater than that of any other microbe of the same type (virus, bacteria or fungus) identified in the patient. Microbes were considered new potential pathogens if mNGS alone identified the microbe and criteria (b) and (c) described above were met, otherwise they were considered unlikely or uncertain pathogens.
For all confirmed and new potential pathogens, as well as for all viruses, the corresponding most likely species was determined if a single species comprised the majority of related nt alignments. In equivocal cases, the MIDAS computational pipeline for quantifying bacterial species abundance was implemented (S6). For each RNA virus listed in Figure S1, we used PRICE (E2) to de novo assemble an initial genomic contig, and then employed Basic Local Alignment Search Tool (BLAST) to identify the closest phylogenetic match in the NCBI nt database (S7). We then aligned all viral sequences in the sample to this reference genome using the Geneious software package in order to obtain depth of coverage and percentage identity similarity (Figure S3). Microbial sequencing data are summarized in Table S3. Complete microbial sequencing reads are available in the NCBI SRA repository.

**Host Gene Expression Analyses**

Raw sequencing data underwent quality filtration and human genome alignment using STAR as described above. The average percent of reads uniquely mapping to the human transcriptome was 2.26% (mean 550,178 human reads per sample). Subjects with fewer than 250 unique genes indexed in the HGNC database and with ENSEMBL gene biotype of protein coding (patients 19, 24, 34, and 37) were excluded from analysis. Read count normalization was performed by cumulative sum scaling (S8) and genes expressed in fewer than 30% of samples or as outliers in only 10% of samples were removed from analysis. This normalization method was used to provide more stable estimates of expression at low read counts in the context of zero inflated data.

In a supervised approach, pathways related to immune functionality, with over 70% of their genes expressed by at least 10% of the samples, were selected from the molecular signatures database (S9). The sum of CSS normalized, scaled expression values for all genes in the pathway was taken for each sample, and are summarized in Table S5. Raw genecounts are provided in Table S6. Pathway expression from subjects with established LRTI pathogens, potential new
mNGS-identified pathogens, microbes or unclear significance and pathogen negative groups using a nonparametric Wilcoxon Rank Sum test.

Diversity Calculations

The Simpson Diversity Index (SDI) was utilized to assess alpha diversity of microbial taxa present in BAL fluids from subjects with established LRTI pathogens, potential new mNGS-identified pathogens, and microbes of unlikely or unclear significance (S10). The SDI formula is

\[ D = 1 - \left( \frac{\sum n(n-1)}{N(N-1)} \right) \]

where \( n = \) the total reads for each single organism and \( N = \) the total number of reads for all organisms combined. Genus rpM were used for calculations. SDI values for each subject are provided in Table S4.

Confirmatory Testing

Confirmatory testing for subjects found to be mNGS-positive for human rhinovirus was performed using reverse-transcriptase PCR targeting the 5'-untranslated region of human rhinovirus according to a previously published protocol from our laboratory (S11). Independent orthogonal confirmation of other microbial targets was performed by clinical reference laboratories (HCoV – Viracor; bacterial 16S rRNA gene sequencing, University of Washington Clinical Microbiology Laboratory).
**FIGURE LEGENDS**

**Figure S1. Overview of Pathogen Detection Workflow.** Total nucleic acid extracted from BAL fluid of HCT recipients underwent DNA and RNA sequencing. A custom bioinformatics pipeline simultaneously identified pathogens and assayed the human transcriptome. Pathogens meeting inclusion and exclusion criteria were ranked by microbial significance score \([\text{Score} = \text{rpM}_{\text{nt}} \times (Z_{\text{nt}} + Z_{\text{nr}})]\). To further improve the specificity of microbial assignments: we required 1) microbes to be detected in both nt and nr database alignments, 2) microbes to have a \(Z_{\text{nt}}\) and \(Z_{\text{nr}}\) greater than zero, and 3) bacteria and fungi detected by RNAseq to also have detectable genomic sequence by DNAseq. For each patient, any microbes that passed these requirements were then classified as either 1) confirmed pathogens, 2) new potential pathogens or 3) unlikely or uncertain pathogens.

**Figure S2.** Expression of a Host Immune Response Multi-Gene Metric Correlates with Detection of LRTI Pathogens. Each data point represents a single patient for whom the composite immune response gene metric is plotted on the y-axis. Subjects are grouped according to confirmed pathogen (red triangles) vs. unlikely or uncertain pathogen (black circles). Patients with confirmed pathogens had significantly higher multi-gene metric expression relative to patients with only microbes of unlikely pathogenicity (33.1, IQR 20.7-75.1, n=7 vs. 94.9, IQR 93.8-105.6, n=6, \(p=0.022\)). Raw data are provided in Tables S5 and S6.

**Figure S3.** Viral Genomes Assembled from Patient Cohort

**Legend:** Viral sequences from five patients assembled against the closest matched NCBI reference genome. Percent similarity to closest matched genome in NCBI nt database and depth of sequencing coverage are indicated for each virus.
Table S1. Microbial Taxa Detected in Water Controls

**Legend:** Microbial taxa present in 17 water control samples derived from sequencing runs performed in our laboratory over the past two years were used to control for laboratory background contaminants. For samples analyzed in this study, genus Z-scores relative to this control group were calculated based on rpM sequence alignments to the nt and nr databases, and subsequently utilized to determine the microbial significance score for each genus \[\text{Score} = \text{rpM}_{\text{genus}} \times (Z_{\text{nt-genus}} + Z_{\text{nr-genus}})\].

Table E2. Hematopoietic Cellular Transplantation Data

**Legend:** Hematopoietic cellular transplantation clinical characteristics are listed and include the following. **Disease:** ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; AUL, acute undifferentiated leukemia; CLL, chronic lymphoblastic leukemia; MF, myelofibrosis; MM, multiple myeloma; MPD, myeloproliferative disorder and NHL, non-H Hodgkin lymphoma. Absolute neutrophil (ANC) and lymphocyte (ALC) counts, respectively. **Disease status:** Active; CR1, complete remission 1; CR2 complete remission 2, PR1 partial response 1; PR2 partial response 2; PD progressive disease; Untreated. **Conditioning:** Flu, fludaribine; Mel, melphalan; Cy, cytarabine; TBI, total body irradiation; Bu4, busulfan 12.8mg/kg; Bu2, busulfan 6.4mg/kg; TLI, total lung irradiation; R-BEAM, rituximab + BCNU + etoposide + Cy + M. Cell Source: PB, peripheral blood; BM, bone marrow. **Immunosuppression:** CS, corticosteroids, ETAN, etanercept, TAC, tacrolimus, SIR sirolimus.

Table S3. Microbial Taxa Identified by Metagenomic Next Generation Sequencing

**Legend:** The top 20 ranked taxa identified by RNA sequencing (RNAseq) and DNA sequencing (DNAseq) are listed in the first and second columns, respectively, and include those genera...
identified by alignment against both NCBI nt and nr databases with a Znt and Znr > 0. The third column lists those taxa which met criteria for significance that required bacteria and fungi to be detected by both RNAseq and DNAseq, whereas DNA viruses could be detected only by DNAseq and RNA viruses detected only by RNAseq. Data listed sequencing reads per million aligning to the NCBI nucleotide (nt) database at the genus level (rpM), Z-score derived based upon sequence alignments to the NCBI nt database at the genus level (Znt) and microbial significance score calculated based upon rpM x (Znt + Znr). Significant microbes were then classified based on pathogenicity as follows: **Confirmed pathogen:** Microbes detected by both conventional diagnostics and by mNGS with established pathogenicity in the lungs; **New potential pathogen:** Previously occult microbes detected by mNGS with established pathogenicity in the lungs or potential pulmonary pathogenicity with a score 2-fold greater than any other microbe. **Unlikely or uncertain pathogen:** Microbes detected by any method but: a) not known to exist as pulmonary pathogens, b) potential pathogens but scoring 2-fold less than the top ranking microbe, c) determined to be clinically insignificant by the treatment team or d) DNA virus of uncertain pathogenicity present in low abundance (< 5 rpM).

**Table S4. Simpson Diversity Index of Transcriptionally Active Microbes**

**Legend:** Simpson Diversity Index (SDI) was used to assess the alpha diversity of patient lung microbial communities at the genus level according to the following formula: $SDI = 1 - \left( \frac{\sum n(n-1)}{N(N-1)} \right)$, where $n=$ the total reads for each single genus and $N=$ the total number of reads for all genera combined.

**Table S5. Expression Values for Composite Host Immune Response Gene Metric**

**Legend:** A. Summed expression values for genes in each of six *a. priori* selected immunity pathways from the molecular signatures database as well as a composite multigene metric consisting of all genes represented in the immune-related gene sets. Group median expression
levels were compared using the nonparametric Wilcoxon Rank Sum test. Patients 19, 24, 34, and 37 were excluded due to insufficient human transcripts. B. Genes represented in the composite host immune response metric.

Table S6. Human Gene Count Data

Legend: Gene counts obtained by alignment against the ENSEMBL GRCh38 human genome build are listed. Genes and associated ENSEMBL ID are listed in rows and subjects are grouped by columns.


Figure S1

BAL

RNA Sequencing + DNA Sequencing

\[ \text{Rank taxa by score} = \text{rpM} \times (Z_{nt} + Z_{nr}) \]

Inclusion Criteria
1. Genus identified by nt and nr database alignments
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

Significant Microbe List

Confirmed Pathogens

New Potential Pathogens

Unlikely Pathogens

Confirm by PCR
Pt 01: Human Metapneumovirus B, 98.7% identity to GI:604624629

Pt-06: Human Coronavirus 229E, 99.1% identity to GI:1060650118

Pt-10: Human Respiratory Syncytial Virus B, 98.4% identity to GI:352963156

Pt-14: Human Rhinovirus A, 99.3% identity to GI:217316448

Pt-18: Human Rhinovirus A, 99.2% identity to GI:217316448
Table S1. Microbial Taxa Detected in Water Controls

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Established Pathogens

New Potential Pathogens Identified by NGS

Microbes of Uncertain or Unlikely Pathogenicity

No
### Table S3. Microbial Taxa Identified by Metagenomic Next Generation Sequencing

**Patient 01**

Total RNAseq Reads: 24,062,560  
Total RNAseq Non-Human Reads: 44,525 (0.19%)  
Total DNAseq Reads: 7,411,372  
Total DNAseq Non-Human Reads: 1,003 (0.01%)

#### Microbial Taxa by RNAseq (Top 20)

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<tr>
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#### Microbial Taxa by DNAseq (Top 20)

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#### Inclusion/Exclusion Criteria for Significant Microbe List

1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

#### Significant Microbe List

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<thead>
<tr>
<th>Genus</th>
<th>Species Class</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
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#### Microbe Classification:

1. **Confirmed pathogens**  
   (known pathogens identified on conventional and mNGS)
2. **New potential pathogens**  
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)
3. **Unlikely pathogens**  
   a) limited/no literature evidence of pulmonary pathogenicity  
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample  
   c) determined to be clinically insignificant by treatment team  
   d) low-abundance DNA virus (<5 rpM)

#### Final Patient Classification:

- [X] Confirmed LRT Infection
- [ ] Likely LRT Infection
- [ ] No LRT Infection
**Patient 03**

**Total RNAseq Reads:** 17,038,966  
**Total RNAseq Non-Human Reads:** 202,806 (1.19%)  

**Total DNAseq Reads:** 1,663,778  
**Total DNAseq Non-Human Reads:** 2,039 (0.12%)  

**Microbial Taxa by RNAseq (Top 20)**

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**Microbial Taxa by DNAseq (Top 20)**

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**Significant Microbe List**

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<td>Flavobacterium</td>
<td>F. indicum</td>
<td>Unlikely Pathogen3b</td>
<td>1.00</td>
</tr>
<tr>
<td>Chryseobacterium</td>
<td>C. SIRB126</td>
<td>Unlikely Pathogen3b</td>
<td>0.85</td>
</tr>
<tr>
<td>Aeromonas</td>
<td>A. hydrophiila</td>
<td>Unlikely Pathogen3b</td>
<td>0.16</td>
</tr>
<tr>
<td>Chroococcidiopsis</td>
<td>C. spp.</td>
<td>Unlikely Pathogen3b</td>
<td>0.14</td>
</tr>
<tr>
<td>Dechloromonas</td>
<td>D. aromatica</td>
<td>Unlikely Pathogen3b</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Microbe Classification:**

1. **Confirmed pathogens**  
   (known pathogens identified on conventional and mNGS)

2. **New potential pathogens**  
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)

3. **Unlikely pathogens**  
   a) limited/no literature evidence of pulmonary pathogenicity  
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample  
   c) determined to be clinically insignificant by treatment team  
   d) low-abundance DNA virus (<5 rpM)

**Final Patient Classification:**  
☐ Confirmed LRT Infection  
☐ Likely LRT Infection  
☒ No LRT Infection

**Inclusion/Exclusion Criteria for Significant Microbe List**

1. Genus identified by alignment against NCBI nt and nr databases  
2. Genus Znt and Znr > 0  
3. Bacteria and Fungi detected by both RNAseq and DNAseq  
4. DNA viruses may be detected only by DNAseq  
5. RNA viruses may be detected only by RNAseq
Patient 05

Total RNAseq Reads: 12,443,364
Total RNAseq Non-Human Reads: 25,525 (0.21%)

Total DNAseq Reads: 17,654,287
Total DNAseq Non-Human Reads: 18,586 (0.11%)

Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus</td>
<td>205055.6</td>
<td>1030.43</td>
<td>99</td>
</tr>
<tr>
<td>Stenotrophomonas</td>
<td>10757.81</td>
<td>1430.56</td>
<td>7.39</td>
</tr>
<tr>
<td>Pseudoalteromonas</td>
<td>579.7572</td>
<td>57.86</td>
<td>9.85</td>
</tr>
<tr>
<td>Vibrio</td>
<td>86.2752</td>
<td>24.51</td>
<td>1.07</td>
</tr>
<tr>
<td>Psychromonas</td>
<td>71.7696</td>
<td>12.46</td>
<td>5.76</td>
</tr>
<tr>
<td>Psychrobacter</td>
<td>43.1321</td>
<td>38.17</td>
<td>0.73</td>
</tr>
<tr>
<td>Myroides</td>
<td>27.649</td>
<td>12.86</td>
<td>2.15</td>
</tr>
<tr>
<td>Alternaria</td>
<td>23.2408</td>
<td>4.18</td>
<td>5.56</td>
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<tr>
<td>Streptococcus</td>
<td>19.5092</td>
<td>114.76</td>
<td>0.09</td>
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<tr>
<td>Xanthomonas</td>
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<td>20.33</td>
<td>0.18</td>
</tr>
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<td>Genistelloides</td>
<td>15.84</td>
<td>0.16</td>
<td>99</td>
</tr>
<tr>
<td>Paraphaeosphaeria</td>
<td>8</td>
<td>0.08</td>
<td>100</td>
</tr>
<tr>
<td>Alkanindiges</td>
<td>7.8448</td>
<td>0.16</td>
<td>48.78</td>
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<td>Arthrobacter</td>
<td>6.912</td>
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<td>0.45</td>
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<td>Exiguobacterium</td>
<td>5.688</td>
<td>4.74</td>
<td>1.06</td>
</tr>
<tr>
<td>Niabella</td>
<td>5.025</td>
<td>4.02</td>
<td>0.84</td>
</tr>
<tr>
<td>Vagococcus</td>
<td>4.0752</td>
<td>0.24</td>
<td>16.98</td>
</tr>
<tr>
<td>Bacillus</td>
<td>3.8668</td>
<td>8.44</td>
<td>0.5</td>
</tr>
<tr>
<td>Curvularia</td>
<td>3.9264</td>
<td>0.48</td>
<td>8.18</td>
</tr>
<tr>
<td>Cellulomonas</td>
<td>3.4465</td>
<td>3.05</td>
<td>0.15</td>
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</table>

Microbial Taxa by DNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenotrophomonas</td>
<td>28710.75</td>
<td>1717.15</td>
<td>8.9</td>
</tr>
<tr>
<td>Xanthomonas</td>
<td>23.1264</td>
<td>26.28</td>
<td>0.27</td>
</tr>
<tr>
<td>Nitrosomonas</td>
<td>2.5568</td>
<td>1.36</td>
<td>2.01</td>
</tr>
<tr>
<td>Myxococcus</td>
<td>2.514</td>
<td>4.19</td>
<td>0.42</td>
</tr>
<tr>
<td>Pseudoxanthomonas</td>
<td>1.9136</td>
<td>3.68</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus</td>
<td>Human rhinovirus A</td>
<td>New Pathogen</td>
<td>1.00</td>
</tr>
<tr>
<td>Stenotrophomonas</td>
<td>S. maltophilia</td>
<td>Confirmed Pathogen</td>
<td>0.05</td>
</tr>
</tbody>
</table>

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<thead>
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<td>1.00</td>
</tr>
<tr>
<td>Stenotrophomonas</td>
<td>S. maltophilia</td>
<td>Confirmed Pathogen</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Inclusion/Exclusion Criteria for Significant Microbe List
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

Microbe Classification:
1. Confirmed pathogens
   (known pathogens identified on conventional and mNGS)
2. New potential pathogens
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)
3. Unlikely pathogens
   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

Final Patient Classification:
☒ Confirmed LRT Infection
☐ Likely LRT Infection
☐ No LRT Infection
**Microbial Taxa by RNAseq (Top 20)**

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphacoronavirus</td>
<td>1098110.00</td>
<td>5490.55</td>
<td>100</td>
</tr>
<tr>
<td>Prevotella</td>
<td>161993.70</td>
<td>818.15</td>
<td>99</td>
</tr>
<tr>
<td>Atopobium</td>
<td>2109.97</td>
<td>24.97</td>
<td>50.97</td>
</tr>
<tr>
<td>Actinomyces</td>
<td>1750.05</td>
<td>40.87</td>
<td>42.07</td>
</tr>
<tr>
<td>Veillonella</td>
<td>349.86</td>
<td>73.04</td>
<td>1.21</td>
</tr>
<tr>
<td>Neofusicoccum</td>
<td>275.58</td>
<td>14.69</td>
<td>18.76</td>
</tr>
<tr>
<td>Kineococcus</td>
<td>120.45</td>
<td>14.87</td>
<td>8.1</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>107.50</td>
<td>34.79</td>
<td>2.88</td>
</tr>
<tr>
<td>Actinobaculum</td>
<td>98.30</td>
<td>4.41</td>
<td>22.29</td>
</tr>
<tr>
<td>Scardovia</td>
<td>83.91</td>
<td>0.79</td>
<td>7.22</td>
</tr>
<tr>
<td>Bilfdobacterium</td>
<td>80.19</td>
<td>23.11</td>
<td>2.8</td>
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<tr>
<td>Neisseria</td>
<td>75.15</td>
<td>15.82</td>
<td>3.71</td>
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<tr>
<td>Paludibacter</td>
<td>49.42</td>
<td>2.69</td>
<td>18.37</td>
</tr>
<tr>
<td>Serratia</td>
<td>31.70</td>
<td>18.01</td>
<td>1.41</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>26.21</td>
<td>8.04</td>
<td>3.34</td>
</tr>
<tr>
<td>Mucinivorans</td>
<td>24.98</td>
<td>1.67</td>
<td>3.02</td>
</tr>
<tr>
<td>Simplexvirus</td>
<td>23.05</td>
<td>0.22</td>
<td>4.78</td>
</tr>
<tr>
<td>Porphyromonas</td>
<td>20.44</td>
<td>9.78</td>
<td>1.64</td>
</tr>
<tr>
<td>Actinoallomorus</td>
<td>20.35</td>
<td>0.52</td>
<td>39.14</td>
</tr>
<tr>
<td>Beutenbergia</td>
<td>19.94</td>
<td>5.65</td>
<td>3.53</td>
</tr>
</tbody>
</table>

**Microbial Taxa by DNAseq (Top 20)**

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevotella</td>
<td>1825004.01</td>
<td>9217.19</td>
<td>99</td>
</tr>
<tr>
<td>Veillonella</td>
<td>37689.01</td>
<td>692.94</td>
<td>11.88</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>30378.04</td>
<td>563.6</td>
<td>47.69</td>
</tr>
<tr>
<td>Atopobium</td>
<td>10466.28</td>
<td>52.86</td>
<td>99</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>6277.05</td>
<td>60.73</td>
<td>20.51</td>
</tr>
<tr>
<td>Simplexvirus</td>
<td>3442.70</td>
<td>17.3</td>
<td>99</td>
</tr>
<tr>
<td>Parabacteroides</td>
<td>2604.96</td>
<td>31.56</td>
<td>80.08</td>
</tr>
<tr>
<td>Megasphaera</td>
<td>2340.50</td>
<td>19.86</td>
<td>8.35</td>
</tr>
<tr>
<td>Odoribacter</td>
<td>2139.96</td>
<td>19.24</td>
<td>99</td>
</tr>
<tr>
<td>Alisptes</td>
<td>1933.75</td>
<td>52.86</td>
<td>99</td>
</tr>
<tr>
<td>Paludibacter</td>
<td>1796.95</td>
<td>17.69</td>
<td>99</td>
</tr>
<tr>
<td>Barnesiella</td>
<td>1678.53</td>
<td>40.07</td>
<td>40.89</td>
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<tr>
<td>Candidatus</td>
<td>1350.52</td>
<td>11.19</td>
<td>99</td>
</tr>
<tr>
<td>Porphyromonas</td>
<td>862.10</td>
<td>48.46</td>
<td>8.35</td>
</tr>
<tr>
<td>Tannerella</td>
<td>731.33</td>
<td>70.66</td>
<td>9.43</td>
</tr>
<tr>
<td>Brachyspira</td>
<td>289.52</td>
<td>2.91</td>
<td>99</td>
</tr>
<tr>
<td>Mucinivorans</td>
<td>158.62</td>
<td>24.94</td>
<td>2.09</td>
</tr>
<tr>
<td>Capnocytophaga</td>
<td>139.31</td>
<td>1.26</td>
<td>11.56</td>
</tr>
<tr>
<td>Scardovia</td>
<td>111.41</td>
<td>0.74</td>
<td>99</td>
</tr>
</tbody>
</table>

**Significant Microbe List**

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphacoronavirus</td>
<td>Human coronavirus 229E</td>
<td>Confirmed Pathogen</td>
<td>1.00</td>
</tr>
<tr>
<td>Prevotella</td>
<td>P. melaninogenica</td>
<td>Unlikely Pathogen 3+</td>
<td>0.05</td>
</tr>
<tr>
<td>Simplexvirus (DNA only)</td>
<td>Human herpesvirus 1 (HSV-1)</td>
<td>New Pathogen</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Inclusion/Exclusion Criteria for Significant Microbe List**
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
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   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

**Final Patient Classification:**
☒ Confirmed LRT Infection
☐ Likely LRT Infection
☐ No LRT Infection
### Patient 07

Total RNAseq Reads: 30,269,269  
Total RNAseq Non-Human Reads: 4,860 (0.02%)

Total DNAseq Reads: 14,289,502  
Total DNAseq Non-Human Reads: 651 (0.00%)

### Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphacoronavirus</td>
<td>12792</td>
<td>63.96</td>
</tr>
<tr>
<td>Meyerozyma</td>
<td>40,5662</td>
<td>0.53</td>
</tr>
<tr>
<td>Macrococcus</td>
<td>6,4156</td>
<td>0.86</td>
</tr>
<tr>
<td>Desulfurella</td>
<td>1,062</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### Microbial Taxa by DNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphatorquevirus</td>
<td>43.0584</td>
<td>0.42</td>
</tr>
<tr>
<td>Simplexvirus</td>
<td>14.4256</td>
<td>0.14</td>
</tr>
<tr>
<td>Rothia</td>
<td>2.0188</td>
<td>7.21</td>
</tr>
</tbody>
</table>

### Inclusion/Exclusion Criteria for Significant Microbe List
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

### Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphacoronavirus</td>
<td>Human coronavirus 229E</td>
<td>New Potential Pathogen</td>
<td>1.00</td>
</tr>
<tr>
<td>Simplexvirus (DNA</td>
<td>Human herpesvirus 1 (HSV-1)</td>
<td>Unlikely Pathogen&lt;sup&gt;3d&lt;/sup&gt;</td>
<td>n/a</td>
</tr>
</tbody>
</table>

### Microbe Classification:

1. **Confirmed pathogens**  
   (known pathogens identified on conventional and mNGS)

2. **New potential pathogens**  
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)

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   d) low-abundance DNA virus (<5 rpM)

### Final Patient Classification:
- ☐ Confirmed LRT Infection
- ☒ Likely LRT Infection
- ☐ No LRT Infection
Total RNAseq Reads: 20,901,440
Total RNAseq Non-Human Reads: 4,113 (0.02%)

Total DNAseq Reads: 19,887,268
Total DNAseq Non-Human Reads: 1,220 (0.01%)

Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
<th>rpM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumovirus</td>
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<td>264.57</td>
</tr>
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<td>Nakaseomyces</td>
<td>2153.298</td>
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<td>18.42</td>
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<tr>
<td>Potyvirus</td>
<td>75.24</td>
<td>99</td>
<td>0.38</td>
</tr>
<tr>
<td>Alphatorquevirus</td>
<td>44.1137</td>
<td>2.59</td>
<td>0.43</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>19</td>
<td>100</td>
<td>0.19</td>
</tr>
<tr>
<td>Leeuwenhoekiella</td>
<td>4.9362</td>
<td>8.66</td>
<td>0.57</td>
</tr>
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</table>

Microbial Taxa by DNAseq (Top 20)

<table>
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<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
<th>rpM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakaseomyces</td>
<td>312.9558</td>
<td>2.94</td>
<td>3.07</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
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<td>1.28</td>
<td>1.66</td>
</tr>
<tr>
<td>Alphatorquevirus</td>
<td>72.989</td>
<td>4.27</td>
<td>0.7</td>
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</table>

Significant Microbe List

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<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumovirus</td>
<td>Respiratory syncytial</td>
<td>Confirmed Pathogen</td>
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</tr>
<tr>
<td></td>
<td>virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakaseomyces</td>
<td>Candida glabrata</td>
<td>Unlikely Pathogen³a</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Human herpes virus 5 (CMV)</td>
<td>Unlikely Pathogen³d</td>
<td>n/a</td>
</tr>
<tr>
<td>(DNA only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alphatorquevirus</td>
<td>n/a</td>
<td>Unlikely Pathogen³d</td>
<td>n/a</td>
</tr>
<tr>
<td>(DNA only)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inclusion/Exclusion Criteria for Significant Microbe List
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus $\text{Znt}$ and $\text{Znr} > 0$
3. Bacteria and Fungi detected by both RNAseq and DNAseq
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5. RNA viruses may be detected only by RNAseq

Microbe Classification:
1. **Confirmed pathogens**
   (known pathogens identified on conventional and mNGS)
2. **New potential pathogens**
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)
3. **Unlikely pathogens**
   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

Final Patient Classification:
☒ Confirmed LRT Infection
☐ Likely LRT Infection
☐ No LRT Infection
**Microbial Taxa by RNAseq (Top 20)**

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metapneumovirus</td>
<td>12276</td>
<td>61.38</td>
<td>100</td>
</tr>
<tr>
<td>Lodderomyces</td>
<td>4.074</td>
<td>0.97</td>
<td>0.89</td>
</tr>
<tr>
<td>Raoultella</td>
<td>1.4356</td>
<td>0.97</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Microbial Taxa by DNAseq (Top 20)**

- Inclusion/Exclusion Criteria for Significant Microbe List
  1. Genus identified by alignment against NCBI nt and nr databases
  2. Genus Znt and Znr > 0
  3. Bacteria and Fungi detected by both RNAseq and DNAseq
  4. DNA viruses may be detected only by DNAseq
  5. RNA viruses may be detected only by RNAseq

**Significant Microbe List**

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metapneumovirus</td>
<td>Human metapneumovirus</td>
<td>Confirmed Pathogen</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Microbe Classification:**

1. **Confirmed pathogens**
   (known pathogens identified on conventional and mNGS)
2. **New potential pathogens**
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)
3. **unlikely pathogens**
   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

**Final Patient Classification:**

- ✗ Confirmed LRT Infection
- ☐ Likely LRT Infection
- ☐ No LRT Infection
### Total RNAseq Reads: 28,238,985
Total RNAseq Non-Human Reads: 16,008 (0.06%)

### Total DNAseq Reads: 16,209,612
Total DNAseq Non-Human Reads: 720 (0.00%)

#### Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumovirus</td>
<td>173723</td>
<td>872.98</td>
<td>99</td>
</tr>
<tr>
<td>Rubrobacter</td>
<td>2</td>
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</tr>
<tr>
<td>Nakamurella</td>
<td>1</td>
<td>1.13</td>
<td>0.11</td>
</tr>
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</table>

#### Microbial Taxa by DNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphatorquevirus</td>
<td>12</td>
<td>0.12</td>
<td>0.69</td>
</tr>
</tbody>
</table>

#### Inclusion/Exclusion Criteria for Significant Microbe List
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
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#### Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumovirus</td>
<td>Respiratory syncytial virus</td>
<td>Confirmed Pathogen</td>
<td>1.00</td>
</tr>
<tr>
<td>Alphatorquevirus</td>
<td>n/a</td>
<td>Unlikely Pathogen³a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

#### Microbe Classification:
1. **Confirmed pathogens**
   (known pathogens identified on conventional and mNGS)
2. **New potential pathogens**
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)
3. **Unlikely pathogens**
   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

#### Final Patient Classification:
- ☒ Confirmed LRT Infection
- ☐ Likely LRT Infection
- ☐ No LRT Infection
Patient 11

Total RNAseq Reads: 21,942,896
Total RNAseq Non-Human Reads: 2,173 (0.01%)

Total DNAseq Reads: 17,431,889
Total DNAseq Non-Human Reads: 11,111 (0.06%)

Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptotrichia</td>
<td>6771.739</td>
<td>48.17</td>
<td>41.58</td>
</tr>
<tr>
<td>Capnocytophaga</td>
<td>5550.233</td>
<td>160.69</td>
<td>13.77</td>
</tr>
<tr>
<td>Rhodotorula</td>
<td>3727.625</td>
<td>36.18</td>
<td>99</td>
</tr>
<tr>
<td>Roseburia</td>
<td>3463.977</td>
<td>40.7</td>
<td>47.64</td>
</tr>
<tr>
<td>Anoxybacillus</td>
<td>2913.95</td>
<td>56.78</td>
<td>40.83</td>
</tr>
<tr>
<td>Veillonella</td>
<td>2431.424</td>
<td>236.29</td>
<td>17.09</td>
</tr>
<tr>
<td>Oscillatoria</td>
<td>2252.605</td>
<td>53.14</td>
<td>42.39</td>
</tr>
<tr>
<td>Metarhizium</td>
<td>2178.84</td>
<td>20.1</td>
<td>9.4</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>1796.015</td>
<td>20.78</td>
<td>1.35</td>
</tr>
<tr>
<td>Neisseria</td>
<td>1574.922</td>
<td>70.09</td>
<td>17.09</td>
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<tr>
<td>Thermus</td>
<td>1243.362</td>
<td>30.67</td>
<td>20.84</td>
</tr>
<tr>
<td>Planococcus</td>
<td>1127.647</td>
<td>87.96</td>
<td>12.47</td>
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<tr>
<td>Trichoderma</td>
<td>1084.774</td>
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<td>41.49</td>
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<td>Sebaldella</td>
<td>952.5513</td>
<td>5.01</td>
<td>91.13</td>
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<tr>
<td>Streptococcus</td>
<td>780.8255</td>
<td>596.05</td>
<td>0.67</td>
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<tr>
<td>Fusarium</td>
<td>511.5532</td>
<td>52.04</td>
<td>7.29</td>
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<tr>
<td>Corynebacterium</td>
<td>492.9939</td>
<td>335.37</td>
<td>0.56</td>
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<td>Bacillus</td>
<td>437.6574</td>
<td>76.38</td>
<td>5.63</td>
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<td>Thiomonas</td>
<td>364.041</td>
<td>75.06</td>
<td>4.79</td>
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<tr>
<td>Kineococcus</td>
<td>285.7866</td>
<td>22.79</td>
<td>12.54</td>
</tr>
</tbody>
</table>

Microbial Taxa by DNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dechloromonas</td>
<td>182.6895</td>
<td>19.05</td>
<td>4.13</td>
</tr>
<tr>
<td>Castellaniella</td>
<td>6.1236</td>
<td>7.29</td>
<td>0.52</td>
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<tr>
<td>Tolumonas</td>
<td>1.4766</td>
<td>0.46</td>
<td>2.23</td>
</tr>
<tr>
<td>Alicycliphilus</td>
<td>1.3853</td>
<td>19.79</td>
<td>0.1</td>
</tr>
<tr>
<td>Aeromonas</td>
<td>1.1392</td>
<td>3.56</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>(none)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inclusion/Exclusion Criteria for Significant Microbe List
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

Microbe Classification:
1. Confirmed pathogens
   (known pathogens identified on conventional and mNGS)
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   (known pathogens identified on mNGS testing only and with a score
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   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a
      polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

Final Patient Classification:
☐ Confirmed LRT Infection
☐ Likely LRT Infection
☒ No LRT Infection
Total RNAseq Reads: 33,164,411
Total RNAseq Non-Human Reads: 290,432 (0.88%)

Total DNAseq Reads: 21,264,899
Total DNAseq Non-Human Reads: 3,499 (0.02%)

### Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corynebacterium</td>
<td>472779</td>
<td>12587.3</td>
<td>22.95</td>
</tr>
<tr>
<td>Actinobaculum</td>
<td>7656.13</td>
<td>77.28</td>
<td>99</td>
</tr>
<tr>
<td>Jonesia</td>
<td>3558.06</td>
<td>35.94</td>
<td>99</td>
</tr>
<tr>
<td>Saccharomonospora</td>
<td>2671.221</td>
<td>39.65</td>
<td>67.37</td>
</tr>
<tr>
<td>Actinomyces</td>
<td>1328.525</td>
<td>35.79</td>
<td>36.82</td>
</tr>
<tr>
<td>Streptomyces</td>
<td>1324.5</td>
<td>105.96</td>
<td>1.82</td>
</tr>
<tr>
<td>Gimesia</td>
<td>925.65</td>
<td>9.35</td>
<td>99</td>
</tr>
<tr>
<td>Arthrobacter</td>
<td>601.257</td>
<td>138.22</td>
<td>4.47</td>
</tr>
<tr>
<td>Arcanobacterum</td>
<td>350.8385</td>
<td>27.05</td>
<td>12.97</td>
</tr>
<tr>
<td>Caldocellulosiruptor</td>
<td>209.9925</td>
<td>10.37</td>
<td>20.25</td>
</tr>
<tr>
<td>Stackebrandta</td>
<td>181.5084</td>
<td>11.43</td>
<td>10.88</td>
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<tr>
<td>Trueperella</td>
<td>173.0352</td>
<td>83.19</td>
<td>2.08</td>
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<tr>
<td>Peptoclostridium</td>
<td>133.7096</td>
<td>33.68</td>
<td>4.13</td>
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<tr>
<td>Mycobacterium</td>
<td>119.7719</td>
<td>151.61</td>
<td>0.45</td>
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<tr>
<td>Microtetraspore</td>
<td>101.97</td>
<td>1.03</td>
<td>99</td>
</tr>
<tr>
<td>melanconiiella</td>
<td>96</td>
<td>0.96</td>
<td>100</td>
</tr>
<tr>
<td>Salinispora</td>
<td>75.198</td>
<td>12.45</td>
<td>6.04</td>
</tr>
<tr>
<td>Alphatorquevirus</td>
<td>68.6532</td>
<td>0.66</td>
<td>4.02</td>
</tr>
<tr>
<td>Mobiluncus</td>
<td>59.6778</td>
<td>5.46</td>
<td>10.93</td>
</tr>
<tr>
<td>Kineococcus</td>
<td>33.9575</td>
<td>7.99</td>
<td>4.25</td>
</tr>
</tbody>
</table>

### Microbial Taxa by DNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphatorquevirus</td>
<td>159.0232</td>
<td>1.46</td>
<td>8.92</td>
</tr>
<tr>
<td>Corynebacterium</td>
<td>39.6075</td>
<td>52.81</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corynebacterium</td>
<td>C.propinquum</td>
<td>New Pathogen</td>
<td>1.00</td>
</tr>
<tr>
<td>Alphatorquevirus</td>
<td>n/a</td>
<td>Unlikely Pathogen&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**Inclusion/Exclusion Criteria for Significant Microbe List**

1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
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   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking pathogenicity
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

**Final Patient Classification:**

☐ Confirmed LRT Infection
☒ Likely LRT Infection
☐ No LRT Infection
Total RNAseq Reads: 16,357,814  
Total RNAseq Non-Human Reads: 796,478 (4.87%)  
Total DNAseq Reads: 20,503,270  
Total DNAseq Non-Human Reads: 494 (0.00%)  

Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus</td>
<td>13114380.00</td>
<td>65901.4</td>
<td>99</td>
</tr>
<tr>
<td>Corynebacterium</td>
<td>1287944.00</td>
<td>21207.7</td>
<td>38.7</td>
</tr>
<tr>
<td>Coniosporium</td>
<td>93978.72</td>
<td>474.64</td>
<td>99</td>
</tr>
<tr>
<td>Actinobaculum</td>
<td>13557.06</td>
<td>136.94</td>
<td>99</td>
</tr>
<tr>
<td>Jonesia</td>
<td>7625.97</td>
<td>77.03</td>
<td>99</td>
</tr>
<tr>
<td>Marssonina</td>
<td>5053.25</td>
<td>51.11</td>
<td>81.91</td>
</tr>
<tr>
<td>Saccharomonospora</td>
<td>4202.73</td>
<td>49.76</td>
<td>84.62</td>
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<tr>
<td>Streptomycetes</td>
<td>3594.15</td>
<td>177.84</td>
<td>3.18</td>
</tr>
<tr>
<td>Schizosaccharomyces</td>
<td>2254.37</td>
<td>60.52</td>
<td>37.25</td>
</tr>
<tr>
<td>Arthrobacter</td>
<td>1915.37</td>
<td>241.84</td>
<td>7.92</td>
</tr>
<tr>
<td>Gimesia</td>
<td>1809.72</td>
<td>18.28</td>
<td>99</td>
</tr>
<tr>
<td>Atopobium</td>
<td>1494.82</td>
<td>27.08</td>
<td>55.28</td>
</tr>
<tr>
<td>Caldicellulosiruptor</td>
<td>1378.23</td>
<td>26.53</td>
<td>51.95</td>
</tr>
<tr>
<td>Leptosphaeria</td>
<td>907.69</td>
<td>122.33</td>
<td>6.4</td>
</tr>
<tr>
<td>Lasiodiplodia</td>
<td>581.13</td>
<td>5.87</td>
<td>99</td>
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<tr>
<td>Stackebrandlia</td>
<td>510.10</td>
<td>23.05</td>
<td>22.13</td>
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<tr>
<td>Salinispora</td>
<td>508.31</td>
<td>32.09</td>
<td>15.84</td>
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<tr>
<td>Arcanobacterium</td>
<td>503.82</td>
<td>32.4</td>
<td>15.55</td>
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<tr>
<td>Mycobacterium</td>
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<tr>
<td>Peptoclostridium</td>
<td>313.16</td>
<td>50.92</td>
<td>6.28</td>
</tr>
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</table>

Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus</td>
<td>Human rhinovirus A</td>
<td>New Pathogen</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Inclusion/Exclusion Criteria for Significant Microbe List
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   c) determined to be clinically insignificant by treatment team  
   d) low-abundance DNA virus (<5 rpM)

Final Patient Classification:
- [ ] Confirmed LRT Infection  
- ☒ Likely LRT Infection  
- [ ] No LRT Infection
Total RNAseq Reads: 15,084,501
Total RNAseq Non-Human Reads: 1,600,047 (10.61%)

**Microbial Taxa by RNAseq (Top 20)**

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus</td>
<td>6187228.00</td>
<td>31091.6</td>
</tr>
<tr>
<td>Bdellovibrio</td>
<td>49785.65</td>
<td>563.76</td>
</tr>
<tr>
<td>Rothia</td>
<td>34472.46</td>
<td>2081.67</td>
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<td>Janninobacterium</td>
<td>27174.28</td>
<td>583.64</td>
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<td>23884.65</td>
<td>172.03</td>
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<td>Lactobacillus</td>
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<td>Megamonas</td>
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<td>Herminimonas</td>
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<td>Bacillus</td>
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<tr>
<td>Rhodospiridium</td>
<td>6833.27</td>
<td>46.8</td>
</tr>
<tr>
<td>Wallemia</td>
<td>6037.02</td>
<td>30.49</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>5879.96</td>
<td>50.65</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>5722.61</td>
<td>998.71</td>
</tr>
<tr>
<td>Psychrobacter</td>
<td>5357.93</td>
<td>210.28</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>5298.44</td>
<td>49.99</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>5044.87</td>
<td>495.08</td>
</tr>
<tr>
<td>Totivirus</td>
<td>4761.44</td>
<td>369.39</td>
</tr>
<tr>
<td>Arcanobacterium</td>
<td>3996.12</td>
<td>91.09</td>
</tr>
</tbody>
</table>

**Microbial Taxa by DNAseq (Top 20)**

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dechloromonas</td>
<td>19173.73</td>
<td>190.31</td>
</tr>
<tr>
<td>Prevotella</td>
<td>959.3043</td>
<td>50.73</td>
</tr>
<tr>
<td>Castellaniella</td>
<td>664.3317</td>
<td>63.33</td>
</tr>
<tr>
<td>Rothia</td>
<td>474.939</td>
<td>84.06</td>
</tr>
<tr>
<td>Alicyciphilus</td>
<td>460.3326</td>
<td>168.62</td>
</tr>
<tr>
<td>Azospira</td>
<td>199.6302</td>
<td>66.99</td>
</tr>
<tr>
<td>Aeromonas</td>
<td>182.0592</td>
<td>32.28</td>
</tr>
<tr>
<td>Tolumonas</td>
<td>123.5655</td>
<td>4.05</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>122.2832</td>
<td>235.16</td>
</tr>
<tr>
<td>Verminephrobacter</td>
<td>85.4793</td>
<td>49.41</td>
</tr>
<tr>
<td>Erysipelotrich</td>
<td>82.9808</td>
<td>1.24</td>
</tr>
<tr>
<td>Thauera</td>
<td>53.1648</td>
<td>63.85</td>
</tr>
<tr>
<td>Methylbacillus</td>
<td>49.312</td>
<td>9.2</td>
</tr>
<tr>
<td>Pseudopedobacter</td>
<td>45.2172</td>
<td>15.38</td>
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<tr>
<td>Roseolovirus</td>
<td>44</td>
<td>0.22</td>
</tr>
<tr>
<td>Novosphingobium</td>
<td>30.926</td>
<td>16.45</td>
</tr>
<tr>
<td>Laribacter</td>
<td>30.5185</td>
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<tr>
<td>Azaracmus</td>
<td>29.951</td>
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</tr>
<tr>
<td>Riemerella</td>
<td>29.4448</td>
<td>26.29</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>29.312</td>
<td>36.64</td>
</tr>
</tbody>
</table>

**Significant Microbe List**

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus</td>
<td>Human rhinovirus A</td>
<td>New Pathogen</td>
<td>1.00</td>
</tr>
<tr>
<td>Rothia</td>
<td>R. mucilaginosa</td>
<td>Unlikely Pathogen³a</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Inclusion/Exclusion Criteria for Significant Microbe List**
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

**Microbe Classification:**

1. **Confirmed pathogens**
   (known pathogens identified on conventional and mNGS)

2. **New potential pathogens**
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)

3. **Unlikely pathogens**
   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

**Final Patient Classification:**
- [ ] Confirmed LRT Infection
- [x] Likely LRT Infection
- [ ] No LRT Infection
**Patient 19**

**Total RNAseq Reads:** 27,041,426  
**Total RNAseq Non-Human Reads:** 1,242,751 (4.60%)  
**Total DNAseq Reads:** 34,263,734  
**Total DNAseq Non-Human Reads:** 192,160 (0.56%)  

### Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus</td>
<td>940718.3</td>
<td>19680.3</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>294385</td>
<td>953.71</td>
</tr>
<tr>
<td>Actinomyces</td>
<td>253354.7</td>
<td>1760.63</td>
</tr>
<tr>
<td>Rothia</td>
<td>38236.78</td>
<td>1892.91</td>
</tr>
<tr>
<td>Tobamovirus</td>
<td>22025.52</td>
<td>111.24</td>
</tr>
<tr>
<td>Beutengeria</td>
<td>21347.37</td>
<td>215.63</td>
</tr>
<tr>
<td>Carnobacterium</td>
<td>17579.77</td>
<td>260.75</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>16000.76</td>
<td>418.43</td>
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<tr>
<td>Kineococcus</td>
<td>13086.75</td>
<td>153.25</td>
</tr>
<tr>
<td>Thermomonospora</td>
<td>11640.67</td>
<td>173.25</td>
</tr>
<tr>
<td>Actinobaculum</td>
<td>10931.58</td>
<td>110.42</td>
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<tr>
<td>Veillonella</td>
<td>4127.563</td>
<td>277.39</td>
</tr>
<tr>
<td>Saccharomonospora</td>
<td>4075.92</td>
<td>48.96</td>
</tr>
<tr>
<td>Atoxiaxeres</td>
<td>4011.898</td>
<td>39.46</td>
</tr>
<tr>
<td>Arcanobacterium</td>
<td>3784.042</td>
<td>88.64</td>
</tr>
<tr>
<td>Lactococcus</td>
<td>3075.259</td>
<td>210.49</td>
</tr>
<tr>
<td>Vibrio</td>
<td>3009.162</td>
<td>82.24</td>
</tr>
<tr>
<td>Solibacillus</td>
<td>2573.109</td>
<td>25.85</td>
</tr>
<tr>
<td>Macrococcus</td>
<td>2369.878</td>
<td>31.06</td>
</tr>
<tr>
<td>Gemella</td>
<td>1918.62</td>
<td>9.69</td>
</tr>
</tbody>
</table>

### Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus</td>
<td>S. mitis</td>
<td>New Pathogen</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>E. faecalis</td>
<td>Unlikely Pathogen&lt;sup&gt;3b&lt;/sup&gt;</td>
<td>0.31</td>
</tr>
<tr>
<td>Actinomyces</td>
<td>A. odontolyticus</td>
<td>Unlikely Pathogen&lt;sup&gt;3b&lt;/sup&gt;</td>
<td>0.27</td>
</tr>
<tr>
<td>Rothia</td>
<td>R. mucilaginosa</td>
<td>Unlikely Pathogen&lt;sup&gt;3b&lt;/sup&gt;</td>
<td>0.02</td>
</tr>
<tr>
<td>Beutengeria</td>
<td>B. cavernae</td>
<td>Unlikely Pathogen&lt;sup&gt;3b&lt;/sup&gt;</td>
<td>0.02</td>
</tr>
<tr>
<td>Carnobacterium</td>
<td>C. maltaromaticum</td>
<td>Unlikely Pathogen&lt;sup&gt;3b&lt;/sup&gt;</td>
<td>0.02</td>
</tr>
<tr>
<td>Kineococcus</td>
<td>K. radiotolerans</td>
<td>Unlikely Pathogen&lt;sup&gt;3b&lt;/sup&gt;</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Microbe Classification:

1. **Confirmed pathogens**  
   (known pathogens identified on conventional and mNGS)

2. **New potential pathogens**  
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)

3. **Unlikely pathogens**  
   a) limited/no literature evidence of pulmonary pathogenicity  
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample  
   c) determined to be clinically insignificant by treatment team  
   d) low-abundance DNA virus (<5 rpM)

### Inclusion/Exclusion Criteria for Significant Microbe List

1. Genus identified by alignment against NCBI nt and nr databases  
2. Genus Znt and Znr > 0  
3. Bacteria and Fungi detected by both RNAseq and DNAseq  
4. DNA viruses may be detected only by DNAseq  
5. RNA viruses may be detected only by RNAseq

---

### Final Patient Classification:

- ☐ Confirmed LRT Infection  
- ☒ Likely LRT Infection  
- ☐ No LRT Infection
Patient 22

**Total RNAseq Reads:** 53,764,899  
**Total RNAseq Non-Human Reads:** 2,578 (0.00%)

**Total DNAseq Reads:** 35,765,259  
**Total DNAseq Non-Human Reads:** 2,005 (0.01%)

**Microbial Taxa by RNAseq (Top 20)**

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphatorquevirus</td>
<td>476.091</td>
<td>3.85</td>
<td>23.66</td>
</tr>
</tbody>
</table>

**Microbial Taxa by DNAseq (Top 20)**

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphatorquevirus</td>
<td>933.3714</td>
<td>6.63</td>
<td>40.78</td>
</tr>
</tbody>
</table>

**Significant Microbe List**

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphatorquevirus</td>
<td>Torque teno virus 5</td>
<td>Unlikely Pathogen&lt;sup&gt;2a&lt;/sup&gt;</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Inclusion/Exclusion Criteria for Significant Microbe List**

1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

**Microbe Classification:**

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   (known pathogens identified on conventional and mNGS)
2. **New potential pathogens**  
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)
3. **Unlikely pathogens**  
   a) limited/no literature evidence of pulmonary pathogenicity  
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample  
   c) determined to be clinically insignificant by treatment team  
   d) low-abundance DNA virus (<5 rpM)

**Final Patient Classification:**

- [ ] Confirmed LRT Infection
- [ ] Likely LRT Infection
- [x] No LRT Infection
**Patient 23**

**Total RNAseq Reads:** 28,416,370  
**Total RNAseq Non-Human Reads:** 75216 (0.26%)  

**Total DNAseq Reads:** 31,664,965  
**Total DNAseq Non-Human Reads:** 6,997 (0.02%)  

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Z_{nt}+Z_{nr})</th>
<th>rpM</th>
<th>Z_{nt}</th>
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</thead>
<tbody>
<tr>
<td>Porphyromonas</td>
<td>5468.246</td>
<td>123.8</td>
<td>21.43</td>
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<tr>
<td>Bacteroides</td>
<td>4358.192</td>
<td>196.05</td>
<td>16.54</td>
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<tr>
<td>Rhodotorula</td>
<td>4055.719</td>
<td>23.79</td>
<td>71.48</td>
</tr>
<tr>
<td>Helicobacterium</td>
<td>3605.58</td>
<td>36.42</td>
<td>99</td>
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<tr>
<td>Myrioides</td>
<td>781.6694</td>
<td>54.02</td>
<td>9.21</td>
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<tr>
<td>Roseburia</td>
<td>742.3074</td>
<td>16.43</td>
<td>19.15</td>
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<tr>
<td>Faecalibacterium</td>
<td>703.8066</td>
<td>108.78</td>
<td>6.27</td>
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<tr>
<td>Candidatus Competibacter</td>
<td>515.79</td>
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<td>Eubacterium</td>
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<tr>
<td>Magnaparthe</td>
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<td>35.89</td>
</tr>
<tr>
<td>Beggiatoa</td>
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<td>4.93</td>
<td>100</td>
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<tr>
<td>Serratia</td>
<td>402.5203</td>
<td>64.61</td>
<td>5.53</td>
</tr>
<tr>
<td>Ureaplasma</td>
<td>341.55</td>
<td>3.45</td>
<td>99</td>
</tr>
<tr>
<td>Prevotella</td>
<td>217.0746</td>
<td>16.47</td>
<td>2.05</td>
</tr>
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<td>Acholeplasma</td>
<td>208.0728</td>
<td>14.82</td>
<td>14.04</td>
</tr>
<tr>
<td>Blautia</td>
<td>127.1952</td>
<td>21.78</td>
<td>5.63</td>
</tr>
<tr>
<td>Finegodia</td>
<td>85.7681</td>
<td>11.33</td>
<td>1.74</td>
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<td>Idiomarina</td>
<td>60.1536</td>
<td>2.08</td>
<td>28.43</td>
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<tr>
<td>Lachnoclostridium</td>
<td>57.5667</td>
<td>2.43</td>
<td>0.59</td>
</tr>
<tr>
<td>Kangiella</td>
<td>53.8652</td>
<td>8.66</td>
<td>5.43</td>
</tr>
</tbody>
</table>

**Microbial Taxa by RNAseq (Top 20)**

**Microbial Taxa by DNAseq (Top 20)**

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Z_{nt}+Z_{nr})</th>
<th>rpM</th>
<th>Z_{nt}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphatorquevirus</td>
<td>35.7245</td>
<td>0.35</td>
<td>2.07</td>
</tr>
<tr>
<td>Lymphocryptovirus</td>
<td>21.2724</td>
<td>0.19</td>
<td>12.96</td>
</tr>
<tr>
<td>Meyerozyma</td>
<td>1.2231</td>
<td>0.09</td>
<td>13.54</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocryptovirus</td>
<td>Human herpes virus 4 (EBV)</td>
<td>Unlikely Pathogen³⁴</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Inclusion/Exclusion Criteria for Significant Microbe List**

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**Final Patient Classification:**

- [ ] Confirmed LRT Infection  
- [ ] Likely LRT Infection  
- [x] No LRT Infection
Patient 24

Total RNAseq Reads: 12,563,059
Total RNAseq Non-Human Reads: 306,620 (2.44%)

Total DNAseq Reads: 14,938,276
Total DNAseq Non-Human Reads: 26,381 (0.18%)

Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neofusicoccum</td>
<td>73224.21</td>
<td>712.09</td>
<td>99</td>
</tr>
<tr>
<td>Kytococcus</td>
<td>62114.82</td>
<td>577.49</td>
<td>99</td>
</tr>
<tr>
<td>Pyrenophora</td>
<td>59733.65</td>
<td>447.98</td>
<td>99</td>
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<tr>
<td>Salinispora</td>
<td>58455.07</td>
<td>571.52</td>
<td>99</td>
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<tr>
<td>Aspergillus</td>
<td>41228.92</td>
<td>409.22</td>
<td>99</td>
</tr>
<tr>
<td>Roseburia</td>
<td>38074.16</td>
<td>302.08</td>
<td>99</td>
</tr>
<tr>
<td>Aureobasidium</td>
<td>38061.54</td>
<td>192.23</td>
<td>99</td>
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<tr>
<td>Isoperlicola</td>
<td>24467.85</td>
<td>247.15</td>
<td>99</td>
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<tr>
<td>Bibersteinia</td>
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<td>90.91</td>
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<td>Cladosporium</td>
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<td>166.28</td>
<td>99</td>
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<td>Parastagonospora</td>
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<td>Talaromyces</td>
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<td>Methylcobacterium</td>
<td>15095.14</td>
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<td>5.55</td>
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<tr>
<td>Actinoplanes</td>
<td>12743.82</td>
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<td>31.16</td>
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<td>Setosphaeria</td>
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<td>Neurospora</td>
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<td>Baudoinia</td>
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<td>103.96</td>
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<tr>
<td>Alternaria</td>
<td>10314.81</td>
<td>104.19</td>
<td>99</td>
</tr>
<tr>
<td>Pseudocercospora</td>
<td>10175.39</td>
<td>101.49</td>
<td>99</td>
</tr>
<tr>
<td>Coniosporum</td>
<td>10084.31</td>
<td>89.79</td>
<td>99</td>
</tr>
</tbody>
</table>

Microbial Taxa by DNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dechloromonas</td>
<td>2215208</td>
<td>65.87</td>
<td>14.72</td>
</tr>
<tr>
<td>Pneumocystis</td>
<td>426512</td>
<td>3.68</td>
<td>99</td>
</tr>
<tr>
<td>Castellaniella</td>
<td>4989111</td>
<td>18.41</td>
<td>1.55</td>
</tr>
<tr>
<td>Brugia</td>
<td>36722</td>
<td>3.01</td>
<td>-0.04</td>
</tr>
<tr>
<td>Alicyciphilus</td>
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<tr>
<td>Prevotella</td>
<td>19669</td>
<td>8.9</td>
<td>1.07</td>
</tr>
<tr>
<td>Riemerella</td>
<td>129672</td>
<td>18.01</td>
<td>0.16</td>
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<tr>
<td>Tolumonas</td>
<td>124352</td>
<td>1.34</td>
<td>6.8</td>
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<td>Azospira</td>
<td>111746</td>
<td>18.94</td>
<td>0.43</td>
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<tr>
<td>Chryseobacterium</td>
<td>109286</td>
<td>20.62</td>
<td>0.17</td>
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<tr>
<td>Pseudopseudobacter</td>
<td>10496</td>
<td>6.56</td>
<td>0.51</td>
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<tr>
<td>Plasmodium</td>
<td>100298</td>
<td>0.94</td>
<td>4.24</td>
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<tr>
<td>Aeromonas</td>
<td>97234</td>
<td>7.97</td>
<td>0.83</td>
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<tr>
<td>Geodermatophilus</td>
<td>92732</td>
<td>3.88</td>
<td>1.18</td>
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<td>Pantoea</td>
<td>89096</td>
<td>6.02</td>
<td>1.3</td>
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<td>8701</td>
<td>1.54</td>
<td>1.41</td>
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<tr>
<td>Pyrenophora</td>
<td>85827</td>
<td>2.01</td>
<td>2.62</td>
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<tr>
<td>Blastococcus</td>
<td>83538</td>
<td>4.42</td>
<td>0.39</td>
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<tr>
<td>Fusarium</td>
<td>76824</td>
<td>3.88</td>
<td>0.45</td>
</tr>
<tr>
<td>Erysipelothrix</td>
<td>65424</td>
<td>0.47</td>
<td>1.42</td>
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</table>

Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrenophora</td>
<td>P. tritici-repentis</td>
<td>Unlikely Pathogen</td>
<td>1</td>
</tr>
<tr>
<td>Parastagonospora</td>
<td>P. nodorum</td>
<td>Unlikely Pathogen</td>
<td>0.272039</td>
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<tr>
<td>Setosphaeria</td>
<td>Setosphaeria turcica</td>
<td>Unlikely Pathogen</td>
<td>0.198998</td>
</tr>
<tr>
<td>Alternaria</td>
<td>Alternaria alternata</td>
<td>Unlikely Pathogen</td>
<td>0.17268</td>
</tr>
<tr>
<td>Chryseobacterium</td>
<td>C. sp. SHR8126</td>
<td>Unlikely Pathogen</td>
<td>0.135712</td>
</tr>
<tr>
<td>Fusarium</td>
<td>Fusarium graminearum</td>
<td>Unlikely Pathogen</td>
<td>0.037864</td>
</tr>
<tr>
<td>Bipolaris</td>
<td>Bipolaris zeicola</td>
<td>Unlikely Pathogen</td>
<td>0.032942</td>
</tr>
<tr>
<td>Neisseria</td>
<td>N. meningitidis</td>
<td>Unlikely Pathogen</td>
<td>0.02066</td>
</tr>
</tbody>
</table>

Microbe Classification:

1. **Confirmed pathogens**
   (known pathogens identified on conventional and mNGS)

2. **New potential pathogens**
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)

3. **Unlikely pathogens**
   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

Inclusion/Exclusion Criteria for Significant Microbe List

1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

Final Patient Classification:

☐ Confirmed LRT Infection
☐ Likely LRT Infection
☒ No LRT Infection
Patient 25

Total RNAseq Reads: 16,427,393
Total RNAseq Non-Human Reads: 272,913 (1.66%)

Total DNAseq Reads: 12,423,425
Total DNAseq Non-Human Reads: 407 (0.00%)

Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
<th>RpM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachybacterium</td>
<td>19859.17</td>
<td>434.46</td>
<td>45.71</td>
</tr>
<tr>
<td>Oceanobacillus</td>
<td>15475.68</td>
<td>78.16</td>
<td>99</td>
</tr>
<tr>
<td>Rhodotorula</td>
<td>15065.82</td>
<td>76.09</td>
<td>99</td>
</tr>
<tr>
<td>Halomonas</td>
<td>9641.081</td>
<td>159.12</td>
<td>39.5</td>
</tr>
<tr>
<td>Sneathia</td>
<td>6576.943</td>
<td>38.05</td>
<td>99</td>
</tr>
<tr>
<td>Vanderwaltozyma</td>
<td>6544.129</td>
<td>51.13</td>
<td>99</td>
</tr>
<tr>
<td>Neisseria</td>
<td>5001.555</td>
<td>118.83</td>
<td>29.05</td>
</tr>
<tr>
<td>Naumovozyma</td>
<td>4211.028</td>
<td>39.26</td>
<td>8.26</td>
</tr>
<tr>
<td>Bacillus</td>
<td>2666.153</td>
<td>140.25</td>
<td>10.43</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>2174.554</td>
<td>2338.23</td>
<td>0.49</td>
</tr>
<tr>
<td>Winogradskyella</td>
<td>1863.021</td>
<td>30.01</td>
<td>28.88</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>1722.867</td>
<td>745.83</td>
<td>1.23</td>
</tr>
<tr>
<td>Sarocladium</td>
<td>1615.68</td>
<td>8.16</td>
<td>99</td>
</tr>
<tr>
<td>Streptosporangium</td>
<td>1583.539</td>
<td>37.92</td>
<td>14.97</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>1564.315</td>
<td>724.22</td>
<td>0.82</td>
</tr>
<tr>
<td>Natranaerobius</td>
<td>1073.16</td>
<td>10.84</td>
<td>99</td>
</tr>
<tr>
<td>Chromohalobacter</td>
<td>1050.306</td>
<td>45.35</td>
<td>23.16</td>
</tr>
<tr>
<td>Saprospira</td>
<td>935.0016</td>
<td>12.48</td>
<td>74.92</td>
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<tr>
<td>Beauveria</td>
<td>921.3156</td>
<td>24.84</td>
<td>37.15</td>
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</table>

Microbial Taxa by DNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
<th>RpM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyomavirus</td>
<td>95.52</td>
<td>0.48</td>
<td>99</td>
</tr>
<tr>
<td>Alphatorquevirus</td>
<td>49.3968</td>
<td>0.48</td>
<td>2.91</td>
</tr>
<tr>
<td>Betatorquevirus</td>
<td>48</td>
<td>0.24</td>
<td>100</td>
</tr>
</tbody>
</table>

Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyomavirus</td>
<td>WU Polyomavirus</td>
<td>Unlikely Pathogen3a</td>
<td>n/a</td>
</tr>
<tr>
<td>Alphatorquevirus</td>
<td>n/a</td>
<td>Unlikely Pathogen3a</td>
<td>n/a</td>
</tr>
<tr>
<td>Betatorquevirus</td>
<td>n/a</td>
<td>Unlikely Pathogen3a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Inclusion/Exclusion Criteria for Significant Microbe List
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

Microbe Classification:
1. **Confirmed pathogens**
   (known pathogens identified on conventional and mNGS)
2. **New potential pathogens**
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)
3. **Unlikely pathogens**
   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

Final Patient Classification:
☐ Confirmed LRT Infection
☐ Likely LRT Infection
☒ No LRT Infection
Patient 31

Total RNAseq Reads: 37,692,471
Total RNAseq Non-Human Reads: 282,897 (0.75%)

Total DNAseq Reads: 44,268,231
Total DNAseq Non-Human Reads: 55,354 (0.13%)

Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevotella</td>
<td>4268.835</td>
<td>139.55</td>
</tr>
<tr>
<td>Rhodotorula</td>
<td>3879.81</td>
<td>39.19</td>
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<tr>
<td>Staphylococcus</td>
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<tr>
<td>Acidithiobacillus</td>
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<td>89.83</td>
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<tr>
<td>Streptococcus</td>
<td>2339.802</td>
<td>1175.78</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>755.7882</td>
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<tr>
<td>Pasteurella</td>
<td>607.7022</td>
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<tr>
<td>Truepera</td>
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<td>Tannerella</td>
<td>365.8916</td>
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<tr>
<td>Actinobacillus</td>
<td>252.996</td>
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<tr>
<td>Planococcus</td>
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<tr>
<td>Microbacterium</td>
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<td>Nostoc</td>
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<tr>
<td>Croceibacter</td>
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<td>Gramella</td>
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<td>5.92</td>
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<td>Acinetobacter</td>
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<td>Actinomyces</td>
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<td>Rhodopirellula</td>
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<td>Psychrobacter</td>
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<tr>
<td>Aspergillus</td>
<td>24.9888</td>
<td>6.08</td>
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Microbial Taxa by DNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevotella</td>
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<tr>
<td>Veillonella</td>
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<td>Campylobacter</td>
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<td>Dechloromonas</td>
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<td>23.88</td>
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<tr>
<td>Selenomonas</td>
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</tr>
<tr>
<td>Leptotrichia</td>
<td>55.814</td>
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<tr>
<td>Neisseria</td>
<td>32.208</td>
<td>9.76</td>
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<tr>
<td>Capnocytophaga</td>
<td>27.975</td>
<td>7.5</td>
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<tr>
<td>Fusobacterium</td>
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<td>Castellaniella</td>
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<td>11.88</td>
</tr>
<tr>
<td>Granulicatella</td>
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<tr>
<td>Alphatorquevirus</td>
<td>14.1078</td>
<td>0.14</td>
</tr>
<tr>
<td>Rothia</td>
<td>13.518</td>
<td>15.02</td>
</tr>
<tr>
<td>Parivononas</td>
<td>8.777</td>
<td>1.31</td>
</tr>
<tr>
<td>Bacteroides</td>
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<td>8.9</td>
</tr>
<tr>
<td>Odoribacter</td>
<td>4.6374</td>
<td>0.59</td>
</tr>
<tr>
<td>Actinobaculum</td>
<td>4.401</td>
<td>0.18</td>
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<tr>
<td>Atopobium</td>
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<td>0.88</td>
</tr>
<tr>
<td>Porphyromonas</td>
<td>3.444</td>
<td>2.8</td>
</tr>
<tr>
<td>Scardovia</td>
<td>2.9974</td>
<td>0.07</td>
</tr>
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</table>

Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevotella</td>
<td>P. melaninogenica</td>
<td>Unlikely Pathogen(^{2a})</td>
<td>1.00</td>
</tr>
<tr>
<td>Tannerella</td>
<td>T. forsythia</td>
<td>Unlikely Pathogen(^{2a})</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Microbe Classification:
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   (known pathogens identified on conventional and mNGS)
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2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

Final Patient Classification:
☐ Confirmed LRT Infection
☐ Likely LRT Infection
☒ No LRT Infection
Total RNAseq Reads: 7,189,791
Total RNAseq Non-Human Reads: 201,139 (2.80%)

Total DNAseq Reads: 28,755,549
Total DNAseq Non-Human Reads: 738 (0.00%)

Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trueperella</td>
<td>207084.5</td>
<td>2848.48</td>
<td>72.7</td>
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<tr>
<td>Pseudomonas</td>
<td>138199.3</td>
<td>6024.38</td>
<td>10.66</td>
</tr>
<tr>
<td>Clostridium</td>
<td>47595.91</td>
<td>1204.35</td>
<td>23.49</td>
</tr>
<tr>
<td>Roccella</td>
<td>36503.28</td>
<td>368.72</td>
<td>99</td>
</tr>
<tr>
<td>Alishewanella</td>
<td>26864.64</td>
<td>271.36</td>
<td>99</td>
</tr>
<tr>
<td>Exiguobacterium</td>
<td>22760.95</td>
<td>308.08</td>
<td>73.34</td>
</tr>
<tr>
<td>Alkalimomas</td>
<td>14760.9</td>
<td>149.1</td>
<td>99</td>
</tr>
<tr>
<td>Rhodotorula</td>
<td>13384.8</td>
<td>67.6</td>
<td>99</td>
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<tr>
<td>Glaciozyma</td>
<td>7816</td>
<td>39.08</td>
<td>100</td>
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<tr>
<td>Acinetobacter</td>
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<td>0.97</td>
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<td>Cercospora</td>
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<td>40.61</td>
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<td>Jonesia</td>
<td>3952.08</td>
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<td>99</td>
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<td>Nectria</td>
<td>3910.5</td>
<td>39.5</td>
<td>99</td>
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<td>Rhodosporidium</td>
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<td>31.99</td>
<td>99</td>
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<td>Rosellinia</td>
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<td>Arcanobacterium</td>
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<td>Actinobaculum</td>
<td>2960.1</td>
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<td>99</td>
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<tr>
<td>Enterobacter</td>
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</tr>
<tr>
<td>Trichoderma</td>
<td>2035.605</td>
<td>35.75</td>
<td>56.97</td>
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</tbody>
</table>

Microbial Taxa by DNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphatorquevirus</td>
<td>65.3877</td>
<td>0.63</td>
<td>3.79</td>
</tr>
</tbody>
</table>

Inclusion/Exclusion Criteria for Significant Microbe List
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphatorquevirus</td>
<td>n/a</td>
<td>Unlikely Pathogen³a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Microbe Classification:
1. Confirmed pathogens
   (known pathogens identified on conventional and mNGS)
2. New potential pathogens
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)
3. Unlikely pathogens
   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

Final Patient Classification:
☐ Confirmed LRT Infection
☐ Likely LRT Infection
☒ No LRT Infection
Patient 35

**Total RNAseq Reads:** 15,795,575  
**Total RNAseq Non-Human Reads:** 103,977 (0.66%)  
**Total DNAseq Reads:** 9,574,097  
**Total DNAseq Non-Human Reads:** 5,902 (0.06%)

### Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
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### Microbial Taxa by DNAseq (Top 20)

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<td>0.31</td>
<td>3.71</td>
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<td>Hydrogenobacter</td>
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<td>4.65</td>
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<td>Castellaniella</td>
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<td>Tolumonas</td>
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### Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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</tbody>
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**Inclusion/Exclusion Criteria for Significant Microbe List**
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq

**Microbe Classification:**

1. **Confirmed pathogens**  
   (known pathogens identified on conventional and mNGS)

2. **New potential pathogens**  
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)

3. **Unlikely pathogens**
   a) limited/no literature evidence of pulmonary pathogenicity
   b) scored 2-fold less than the top-ranking microbe, suggesting a polymicrobial sample
   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

**Final Patient Classification:**
- ☐ Confirmed LRT Infection
- ☐ Likely LRT Infection
- ☒ No LRT Infection
Total RNAseq Reads: 33,938,836
Total RNAseq Non-Human Reads: 156,227 (0.46%)

Total DNAseq Reads: 18,149,216
Total DNAseq Non-Human Reads: 9,321 (0.05%)

Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>Znt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopobium</td>
<td>83094.66</td>
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</tr>
<tr>
<td>Actinomyces</td>
<td>75550.55</td>
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<tr>
<td>Arcanobacterium</td>
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<td>Beutenbergia</td>
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<td>Kineococcus</td>
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<td>Mobiluncus</td>
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<td>Saccharomonospora</td>
<td>3545.819</td>
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</tr>
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<td>Actinobaculum</td>
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<td>Microbispore</td>
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</tr>
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<td>Dactylellina</td>
<td>2018.61</td>
<td>20.39</td>
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<tr>
<td>Isoptericola</td>
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<tr>
<td>Scardovia</td>
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</tr>
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<td>Bifidobacterium</td>
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<td>Cellulomonas</td>
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<td>Jonesia</td>
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<td>Nonomuraea</td>
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<td>Frankia</td>
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<td>Exiguobacterium</td>
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<td>Amycoliciicoccus</td>
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<td>Veillonella</td>
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</table>

Microbial Taxa by DNAseq (Top 20)

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<th>Znt</th>
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<tbody>
<tr>
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<td>Roseolovirus</td>
<td>1984</td>
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<td>Veillonella</td>
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<td>Lactobacillus</td>
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<td>Mageebacillus</td>
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Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopobium</td>
<td>A. parvulum</td>
<td>Unlikely Pathogen&lt;sup&gt;3a&lt;/sup&gt;</td>
<td>1.00</td>
</tr>
<tr>
<td>Veillonella</td>
<td>V. parvula</td>
<td>Unlikely Pathogen&lt;sup&gt;3a&lt;/sup&gt;</td>
<td>0.01</td>
</tr>
<tr>
<td>Roseolovirus</td>
<td>Human herpes virus</td>
<td>Confirmed Pathogen</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Microbe Classification:
1. **Confirmed pathogens**
   (known pathogens identified on conventional and mNGS)
2. **New potential pathogens**
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)
3. **Unlikely pathogens**
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   c) determined to be clinically insignificant by treatment team
   d) low-abundance DNA virus (<5 rpM)

**Final Patient Classification:**
☒ Confirmed LRT Infection
☐ Likely LRT Infection
☐ No LRT Infection

---

**Inclusion/Exclusion Criteria for Significant Microbe List**
1. Genus identified by alignment against NCBI nt and nr databases
2. Genus Znt and Znr > 0
3. Bacteria and Fungi detected by both RNAseq and DNAseq
4. DNA viruses may be detected only by DNAseq
5. RNA viruses may be detected only by RNAseq
**Total RNAseq Reads:** 5,277,784  
**Total DNAseq Reads:** 3,913,906

**Total RNAseq Non-Human Reads:** 160,651 (3.04%)  
**Total DNAseq Non-Human Reads:** 1,312 (0.03%)

### Microbial Taxa by RNAseq (Top 20)

<table>
<thead>
<tr>
<th>Genus</th>
<th>rpM (Znt+Znr)</th>
<th>rpM</th>
<th>Znt</th>
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<tr>
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### Significant Microbe List

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Microbe Classification</th>
<th>Relative Score</th>
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<tr>
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<td>Pseudomonas</td>
<td>P. fluorescens</td>
<td>Unlikely Pathogen$^{3a}$</td>
<td>n/a</td>
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**Microbe Classification:**

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   (known pathogens identified on conventional and mNGS)

2. **New potential pathogens**  
   (known pathogens identified on mNGS testing only and with a score 2-fold greater than any other microbe)

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2. Genus Znt and Znr > 0  
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4. DNA viruses may be detected only by DNAseq  
5. RNA viruses may be detected only by RNAseq

**Final Patient Classification:**

☐ Confirmed LRT Infection  
☐ Likely LRT Infection  
☒ No LRT Infection
<table>
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<td><strong>Microbes of Uncertain Pathogenicity</strong></td>
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## Table S5. Expression Values for Composite Host Immune Response Gene Metric

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<th>IFN-β</th>
<th>IFN-γ</th>
<th>IL-6/JAK/STAT5</th>
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<th>Composite</th>
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<tr>
<td>Median (IQR)</td>
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<td>25.2 (17.2-53.4)</td>
<td><strong>37.4 (26.8-46.1)</strong></td>
<td>60.4 (51.7-63.1)</td>
<td>28.5 (25.1-34.4)</td>
<td><strong>10.9 (4.6-13.1)</strong></td>
<td>94.9 (93.8-105.6)</td>
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|     |           |         |         |         |                |                   |           |
| 6   | 33.57704  | 42.37076| 47.06333| 87.08615| 30.18206       | 18.8665         | 107.5283  |
| 7   | 33.01413  | 53.36764| 38.96304| 63.14905| 25.13806       | 4.610494        | 93.82128  |
| 13  | 24.68779  | 25.85632| 36.09369| 62.48182| 33.42504       | 1.224408        | 105.2205  |
| 14  | 33.30571  | 50.60248| 50.20039| 75.77266| 19.50819       | 4.368497        | 51.01284  |
| 18  | 4.361665  | 8.816133| 4.460994| 4.454467| 11.325         | 0               | 11.325    |
| 19  | --        | --       | --       | --       | --             | --              | --        |
| Median (IQR) | 33.3 (24.7-33.6) | 28.0 (25.9-42.4) | 36.1 (27.2-47.1) | 62.5 (51.8-75.8) | 19.5 (12.4-30.2) | 4.4 (1.2-5.8) | 69.6 (51.0-105.2) |

|     |           |         |         |         |                |                   |           |
| 3   | 4.358969  | 4.358969| 16.85848| 4.36821 | 15.22575       | 0                | 32.09347  |
| 11  | 0.039604  | 14.3336 | 17.10211| 33.19125| 16.16125       | 1.20448         | 53.56116  |
| 22  | 23.1373   | 31.35812| 30.48124| 81.13062| 39.30469       | 6.476112        | 112.8556  |
| 23  | 38.87041  | 39.30542| 29.28327| 97.53923| 38.42794       | 9.271892        | 75.08393  |
| 24  | --        | --       | --       | --       | --             | --              | --        |
| 25  | 8.215386  | 8.724272| 16.17955| 33.27414| 5.944689       | 0               | 33.08655  |
| 31  | 4.307147  | 3.176816| 9.758044| 15.61494| 1.240927       | 0               | 15.02851  |
| 34  | --        | --       | --       | --       | --             | --              | --        |
| 35  | 10.92091  | 13.95849| 14.36115| 29.84377| 4.922826       | 0.018651        | 20.69227  |
| 37  | --        | --       | --       | --       | --             | --              | --        |
| Median (IQR) | 8.2 (4.3-23.1) | 14.0 (4.4-31.4) | **16.9 (14.4-29.3)** | 33.2 (15.6-81.1) | 15.2 (4.9-38.4) | **0.1 (0.6-5.4)** | 33.1 (20.7-75.1) |

| Significance | p=0.063 | p=0.116 | p=0.015 | p=0.116 | p=0.116 | p=0.116 | p=0.022 | p=0.022 |