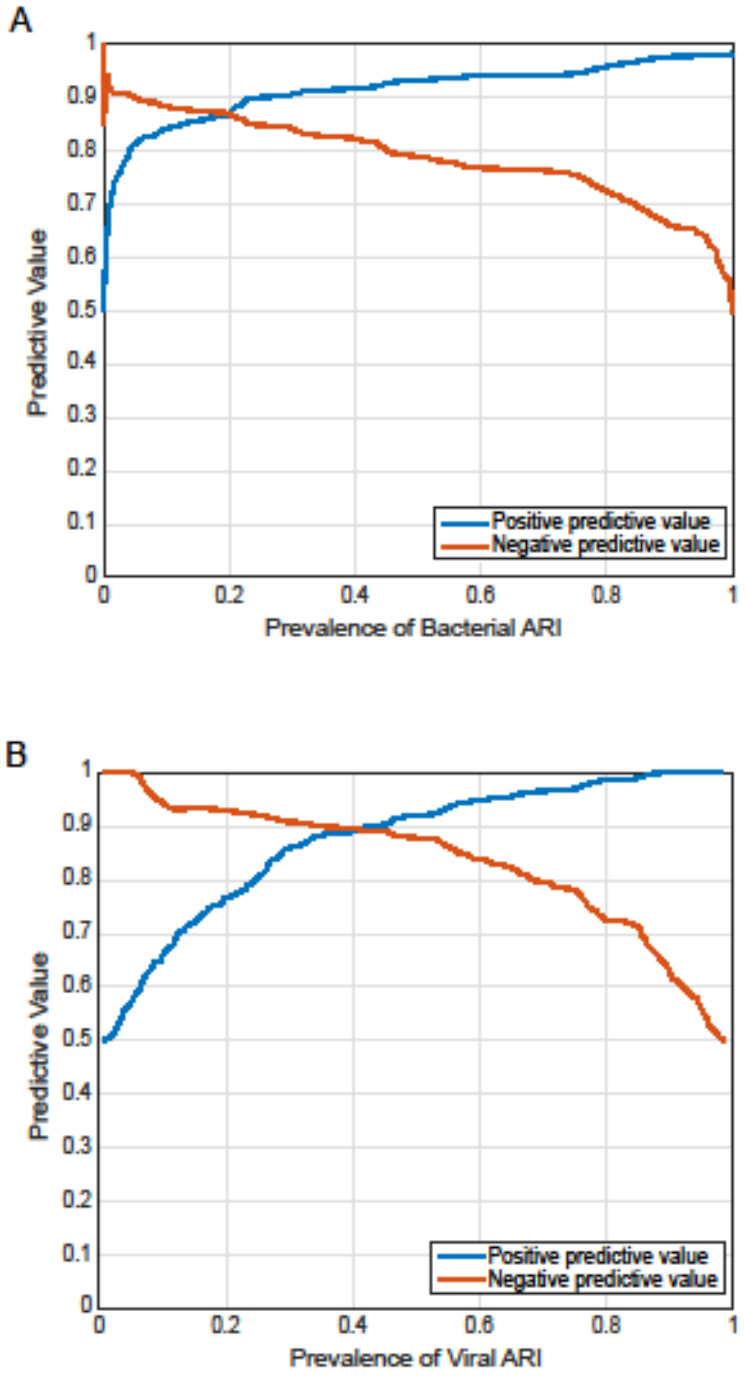

Figure S1: Positive and negative predictive values for A) Bacterial and B) Viral ARI classification as a function of prevalence.

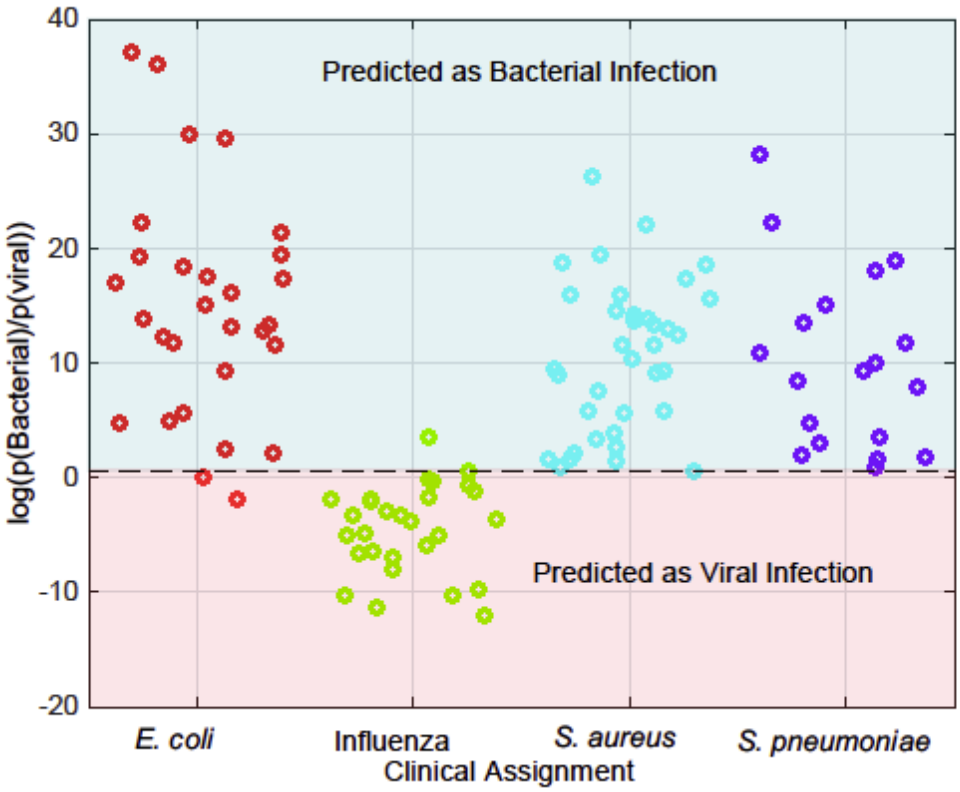

Figure S2: Validation of Bacterial and Viral ARI Classifiers in GSE6269. This dataset includes pediatric patients with acute infections caused by Influenza A virus (green circles), *Escherichia coli* (red circles), *Staphylococcus aureus* (light blue circles), or *Streptococcus pneumoniae* (purple circles). The vertical axis represents the log probability of classifier-assigned bacterial infection relative to classifier-assigned viral infection. Subjects falling in the top, blue section were classified as bacterial infection whereas those in the bottom, pink section were classified as viral infection.

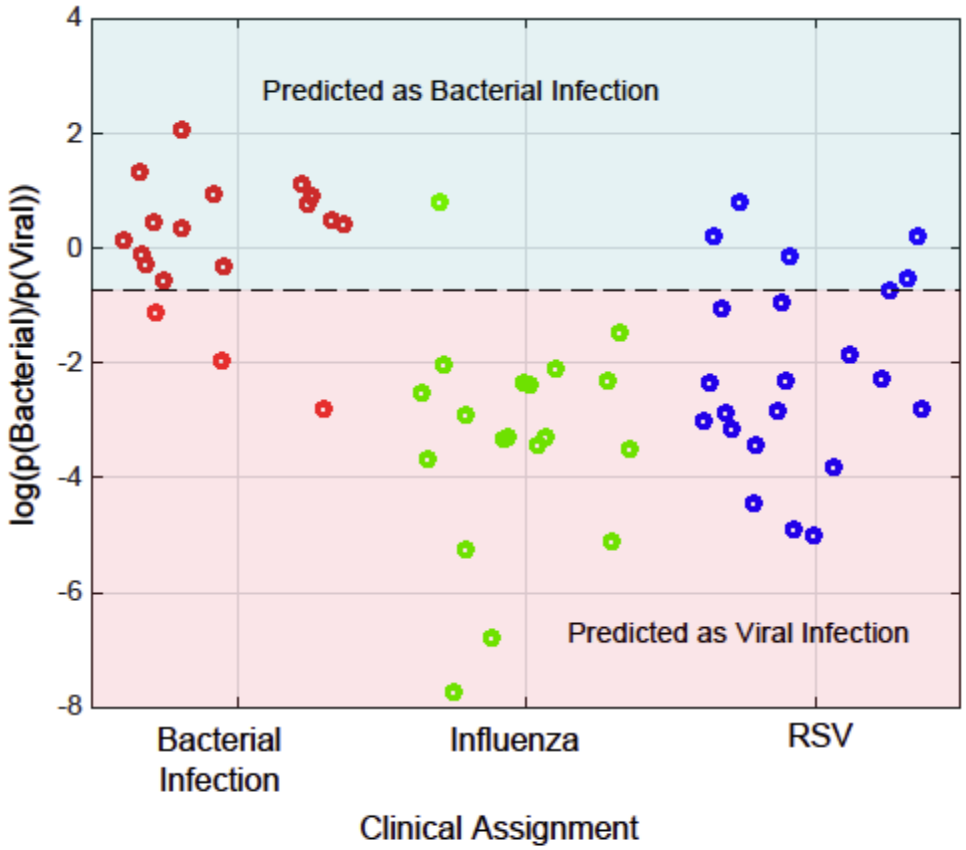

Figure S3: Validation of Bacterial and Viral ARI Classifiers in GSE42026. This dataset includes pediatric patients hospitalized with bacterial infection (red circles), Influenza H1N1/09 infection (green circles), or RSV infection (blue circles). The vertical axis represents the log probability of classifier-assigned bacterial infection relative to classifier-assigned viral infection. Subjects falling in the top, blue section were classified as bacterial infection whereas those in the bottom, pink section were classified as viral infection.

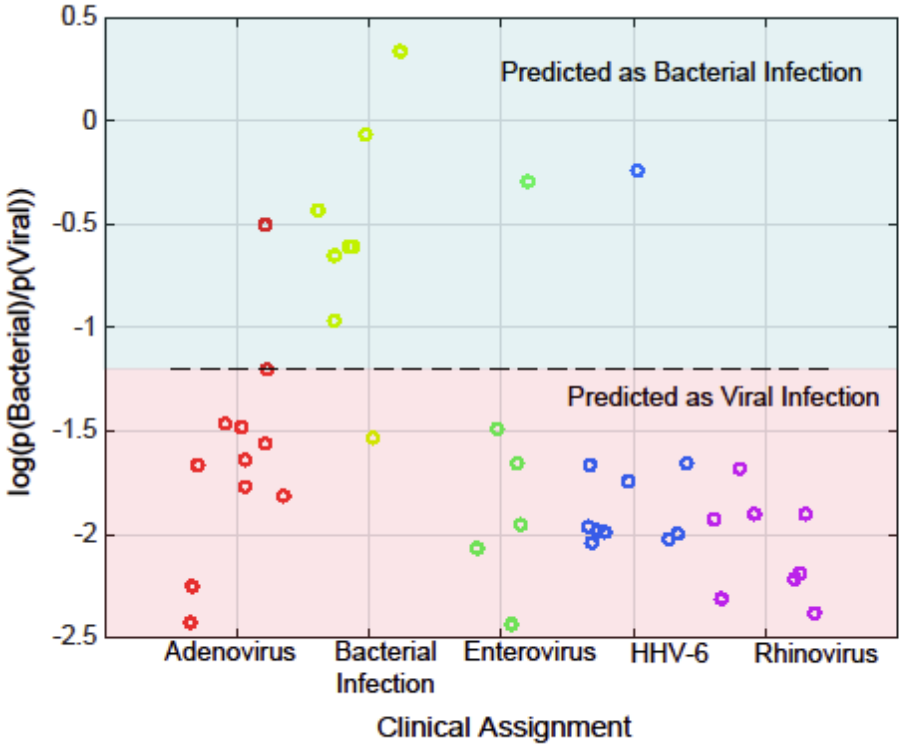

Figure S4: Validation of Bacterial and Viral ARI Classifiers in GSE40396. This dataset includes pediatric patients with infections due to adenovirus (red circles), bacteria (yellow circles), enterovirus (green circles), HHV-6 (blue circles), or rhinovirus (purple circles). The vertical axis represents the log probability of classifier-assigned bacterial infection relative to classifier-assigned viral infection. Subjects falling in the top, blue section were classified as bacterial infection whereas those in the bottom, pink section were classified as viral infection.

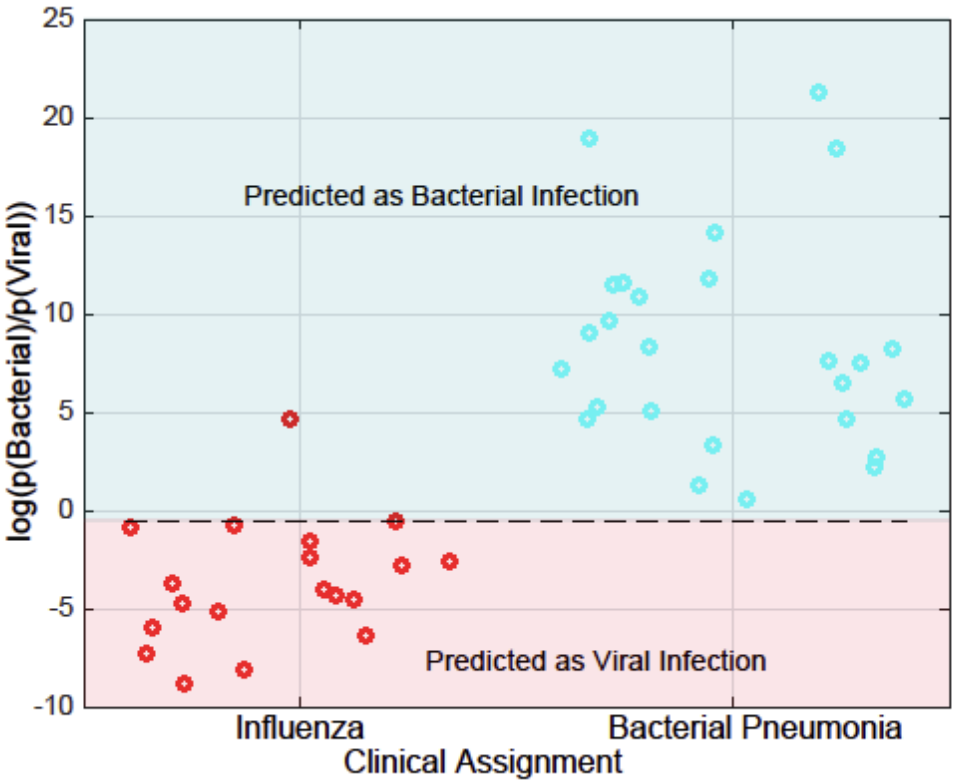

Figure S5: Validation of Bacterial and Viral ARI Classifiers in GSE20346. This dataset includes adult patients with influenza (red circles) or bacterial pneumonia (blue circles). The data represent subjects with serial samples whereby each sample was treated independently. The vertical axis represents the log probability of classifier-assigned bacterial infection relative to classifier-assigned viral infection. Subjects falling in the top, blue section were classified as bacterial infection whereas those in the bottom, pink section were classified as viral infection.

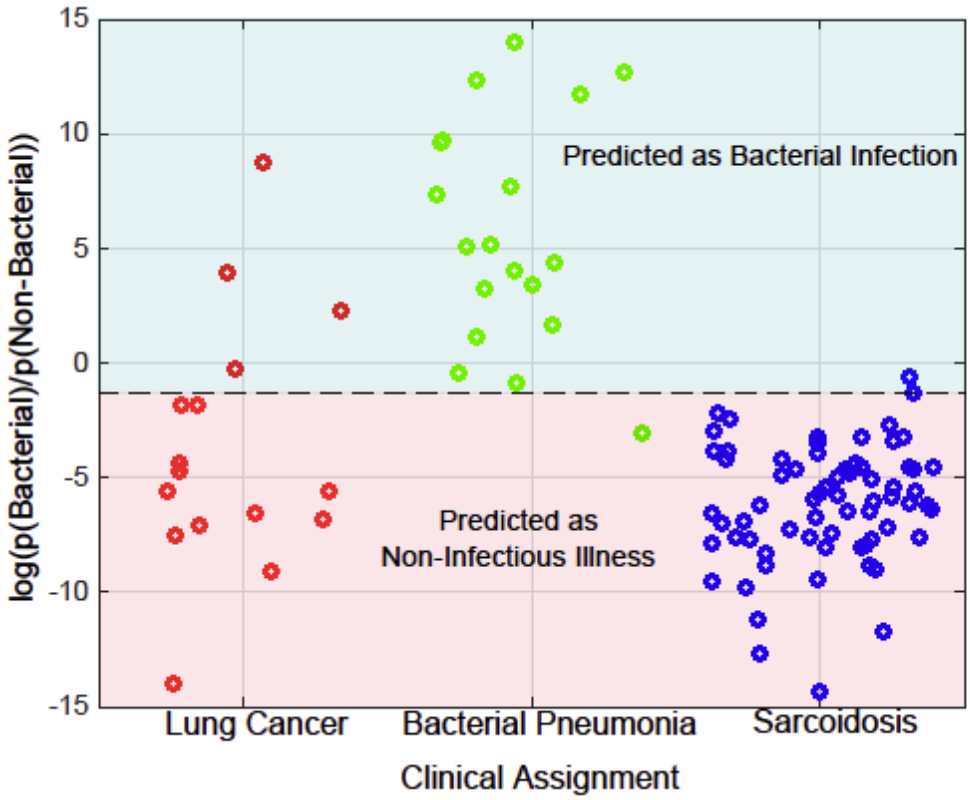

Figure S6: Validation of Bacterial ARI and Non-Infectious Illness Classifiers in GSE42834. This dataset includes adult patients with lung cancer (red circles), bacterial pneumonia (green circles), or sarcoidosis (blue circles). The vertical axis represents the log probability of classifier-assigned bacterial infection relative to classifier-assigned non-infectious illness. Subjects falling in the top, blue section were classified as bacterial infection whereas those in the bottom, pink section were classified as non-infectious illness.

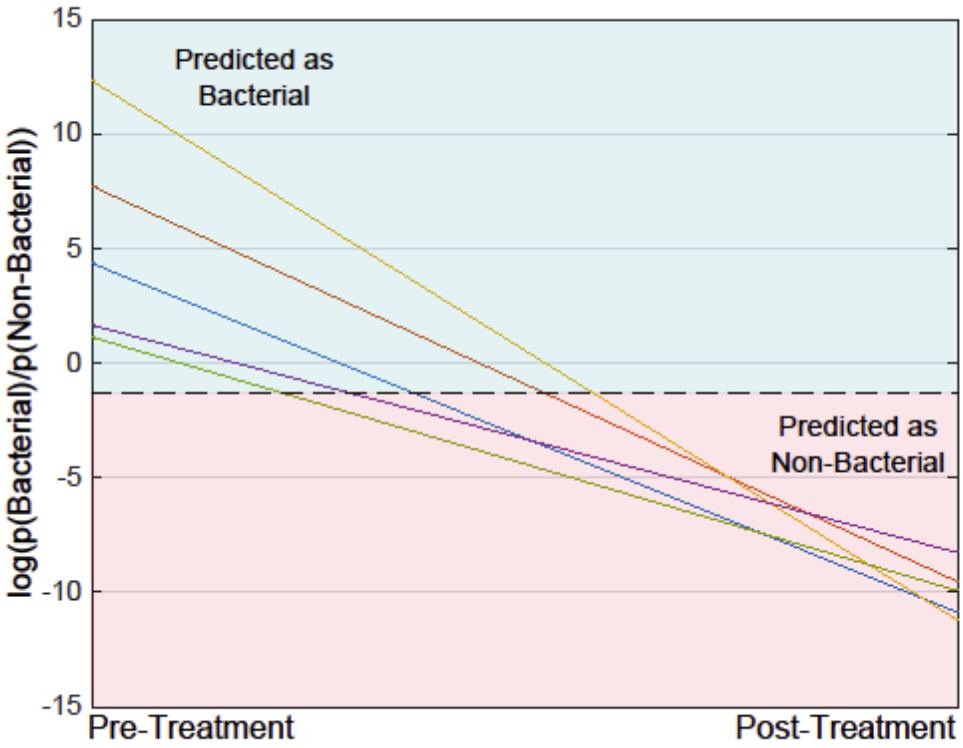

Figure S7: Treatment effect on bacterial ARI classification. Among the subjects included in GSE42834 (Figure S6) were five individuals with bacterial pneumonia, sampled prior to treatment as well as after treatment (at least 6 weeks after discharge). The vertical axis represents the log probability of classifier-assigned bacterial infection relative to classifier-assigned non-infectious illness. Subjects falling in the top, blue section were classified as bacterial infection whereas those in the bottom, pink section were classified as non-infectious illness. All five subjects were correctly classified as bacterial ARI prior to treatment, which resolved after treatment.

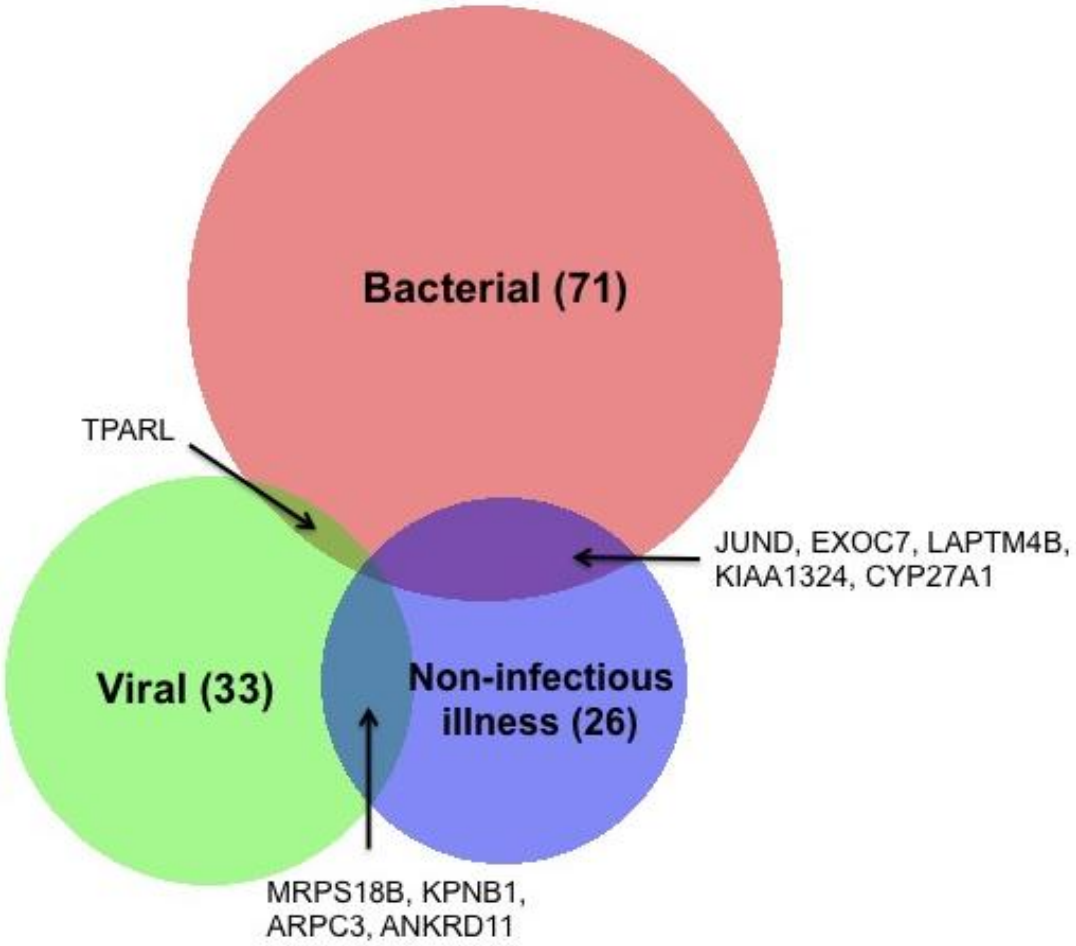

Figure S8. Venn diagram representing overlap in the Bacterial ARI, Viral ARI, and Non-infectious Illness Classifiers. There are 71 genes in the Bacterial ARI Classifier, 33 in the Viral ARI Classifier, and 26 in the Non-infectious Illness Classifier. One gene overlaps between the Bacterial and Viral ARI Classifiers. Five genes overlap between the Bacterial ARI and Non-infectious Illness Classifiers. Four genes overlap between the Viral ARI and Non-infectious Illness Classifiers.

Table S1. Etiological causes of illness for subjects with viral ARI, bacterial ARI, and non-infectious illness. For subjects with infection, the source of positive microbiology is presented.

	Number of subjects	**Sources**[a]
Total Cohort	273	
All Viral ARI	115	
Coronavirus	7	All identified from respiratory sample sources
Cytomegalovirus	1	
Enterovirus [b]	23	
Human Metapneumovirus	9	
Influenza, non-typed	7	
Influenza A, non-subtyped	6	
Influenza A, 2009 H1N1	37	
Parainfluenza	1	
Rhinovirus	19	
Respiratory Syncytial Virus	6	
Multiple viruses (Coronavirus, Rhinovirus, Enterovirus)	1	
All Bacterial ARI	70	
Bacillus species [c]	1	Bl
Bordetella bronchiseptica	1	Bl
Enterobacter aerogenes	1	Bl, BAL, and Sp
Escherichia coli	1	Bl
Haemophilus influenza	3	Sp(2), Pl(1)
Legionella sp.	3	Ag(3)
Mycoplasma pneumoniae	1	Ser
Pasteurella multocida	1	Bl
Proteus mirabilis	1	Sp

Pseudomonas aeruginosa	4	Sp(4)
Staphylococcus aureus	7	Bl(6), Sp(1)
Streptococcus pneumoniae	30	Ag(21), Bl(3), Bl and Ag (4), Pl(1), Sp(1)
Streptococcus pyogenes	4	Ph(3), Bl and Ph(1)
Viridans Group *Streptococcus*	1	Pl
Polymicrobial [c]	11	
Pantoea sp. / Coagulase negative *Staphylococcus*	1	Bl/Bl
Pseudomonas aeruginosa / Alcaligenes xylosoxidans	1	Sp/Sp
Pseudomonas aeruginosa / Serratia marcescens	1	BAL/BAL
Staphylococcus aureus / Haemophilus influenzae	2	Sp/Sp(2)
Staphylococcus aureus / Proteus mirabilis / Haemophilus influenza	1	Sp/Bl/Sp
Staphylococcus aureus / Viridans Group *Streptococcus / Escherichia coli / Streptococcus pneumoniae*	1	BAL/BAL /BAL/Ag
Streptococcus pneumoniae / Haemophilus sp.	1	Sp and Ag/Sp
Streptococcus pneumoniae / Staphylococcus aureus	3	Ag (3)/Sp(2), and Bl(1)
All Non-Infectious Illness	88	
Acute Renal Failure; Hypovolemia	1	
Alcohol intoxication; Spinal cord stenosis; Hyperglycemia	1	
Arrhythmia	2	
Asthma	1	
Atypical Chest Pain	2	
AV Graft Pseudoaneurysm and Thrombus	1	

Brain Metastases with Vasogenic Edema	1
Cerebrovascular Accident	1
Chronic Obstructive Pulmonary Disease	6
Cocaine Intoxication	1
Congestive Heart Failure	17
Congestive Heart Failure; Amiodarone Toxicity	1
Congestive Heart Failure; Arrhythmia	1
Congestive Heart Failure; Pulmonary Artery Hypertension	1
Constrictive Pericarditis	1
Cryptogenic Organizing Pneumonia	1
Gastrointestinal Hemorrhage	3
Hematoma in Leg	1
Hemochromatosis	1
Hemothorax	1
Heroin Overdose	1
Hyperglycemia	2
Hypertensive Emergency	3
Hypovolemia	1
Infarcted Uterine Fibroid	1
Lung Cancer; Coronary Artery Disease	1
Lung Cancer; Hemoptysis	1
Mitochondrial Disorder; Acidosis	1
Myocardial Infarction	2
Myocardial Infarction; Hypovolemia	1
Nephrolithiasis	2
Pancreatitis	4

Post-operative Vocal Cord Paralysis	1
Hyperemesis Gravidarum; Allergic Rhinitis	1
Pulmonary Embolism	5
Pulmonary Embolism; Myocardial Infarction	1
Pulmonary Embolism; Pulmonary Artery Hypertension	1
Pulmonary Fibrosis	2
Pulmonary Mass	1
Reactive Arthritis	1
Rhabdomyolysis	1
Ruptured Aneurysm; Hypovolemic Shock	1
Severe Aortic Stenosis	1
Small Bowel Obstruction	1
Stills Disease	1
Systemic Lupus Erythematosus	1
Tracheobronchomalacia	1
Transient Ischemic Attack	1
Ulcerative Colitis	1
Urethral Obstruction	1

[a] The number of times each pathogen was identified in the specified source is noted in parentheses. A given pathogen may be isolated from more than one source (e.g., blood and sputum), which are separated by a comma. For polymicrobial bacterial infections, the source of pathogen identification is listed for each organism, separated by a forward slash. Ag-Antigen Test, Bl-Blood Culture, BAL-Bronchoalveolar Lavage Culture, Pl-Pleural Fluid Culture, Ph-Pharyngeal Swab Culture, Ser-Serology, Sp-Sputum Culture

[b] Enterovirus indicates the identification of Echovirus or Coxsackievirus as in most cases the molecular assay did not differentiate.

[c] This patient was adjudicated as having a bacterial ARI with Bacillus species identified as the etiologic agent. We later recognized Bacillus species was not the correct microbiological etiology although the clinical history was otherwise consistent with bacterial pneumonia. As this error was identified after model derivation, we included the subject in all subsequent analyses.

Table S2. Summary of clinical features for the derivation cohort.

	Bacterial ARI	**Viral ARI**	**Non-Infectious Illness**
Total Cohort Size	70	115	88
Comorbidities			
Diabetes	17/70 (24%)	17/74 (23%)	35/88 (40%)
Congestive Heart Failure	4/63 (6%)	2/74 (3%)	15/75 (20%)
Chronic Kidney Disease	8/69 (12%)	2/74 (3%)	20/88 (23%)
Chronic Liver Disease	2/70 (3%)	0/74 (0%)	2/84 (2%)
Chronic Lung Disease	24/69 (35%)	24/74 (32%)	31/88 (35%)
Immunosuppression	3/69 (4%)	7/74 (9%)	13/84 (15%)
Corticosteroids[a]	3/3 (100%)	5/7 (71%)	11/13 (85%)
Chemotherapy	1/3 (33%)	1/7 (14%)	2/13 (15%)
Other	0/3 (0%)	3/7 (43%)	0/13 (0%)
Neoplastic Disease	6/70 (9%)	2/74 (3%)	9/86 (10%)
Smoker, Current	26/67 (39%)	16/108 (15%)	28/81 (35%)
WBC count $x10^9$/L, mean ± SD	14.0 ± 7.2 (N=68)	9.3 ± 4.6 (N=41)	12.5 ± 6.1 (N=73)
Neutrophil %, mean ± SD	84.2 ± 10.8 (N=65)	73.6 ± 14.9 (N=41)	75.9 ± 12.7 (N=70)
Abnormal chest imaging	62/69 (90%)	22/54 (41%)	40/63 (63%)
Temperature <36 or >38°C	36/70 (51%)	33/69 (48%)	37/87 (43%)

All values are presented as n/cohort size for whom data was available (%), unless otherwise specified.

[a] Corticosteroid ≥ 60mg/day of prednisone or equivalent for ≥ three days, or ≥ 10mg/day for > 30 days. A subject could be taking more than one type of immunosuppressant, hence the sums may exceed 100%.

Table S3. Probes selected for the Bacterial ARI, Viral ARI, and Non-infectious Illness Classifiers. Probe names are presented as Affymetrix probe IDs. Values for each probe represent the weight of each probe in the specified classifier.

Affymetrix Probe ID	Bacterial ARI Classifier	Viral ARI Classifier	Non-Infectious Illness Classifier
200042_at	0	0.0389975	0
200947_s_at	1.78944	0	0
201055_s_at	0	0	1.25363
201188_s_at	0.606326	0	0
201341_at	0.109677	0	0
202005_at	-0.680527	0	0
202145_at	0	0.166043	0
202284_s_at	-0.356457	0	0
202411_at	-0.0522361	0	0
202509_s_at	0	0	0.416714
202644_s_at	0.340624	0	0
202688_at	0	0.0050837	0
202709_at	0.427849	0	0
202720_at	0	0.0787402	0
202864_s_at	0	0.0293697	0
202973_x_at	-0.112081	0	0
203045_at	-0.850903	0	0
203153_at	-0.133743	0	0
203275_at	0	0.0745763	0
203313_s_at	-1.09463	0	0
203392_s_at	0	-0.0139199	0
203455_s_at	0	0	-0.0805395

203882_at	0	0.0345339	0
203979_at	-0.00999102	0	0.301178
204392_at	0	0.111394	0
204490_s_at	0.00732794	0	0
204545_at	0.342478	0	0
204750_s_at	0.537475	0	0
205001_s_at	0	-0.067117	0
205008_s_at	0	0.223868	0
205033_s_at	0	-0.0878603	0
205048_s_at	-0.0114514	0	0
205098_at	-0.116414	0	0
205153_s_at	0.132886	0	0
205164_at	0.46638	0	0
205200_at	0.87833	0	0
205312_at	0	0	-0.394304
206207_at	-0.0852924	0	0
206371_at	0.0439022	0	0
206647_at	0.0650386	0	0
206676_at	0	0	0.0774651
206896_s_at	0.482822	0	0
206918_s_at	1.00926	0	0
206934_at	0.151959	0	0
207075_at	-0.0627344	0	0
207194_s_at	0.3162	0	0
207244_x_at	1.30636	0	0
207436_x_at	0	0.243737	0

207606_s_at	0.299775	0	0
207718_x_at	0.0392962	0	0
207840_at	0	0.118889	0
207860_at	0.376517	0	0
208029_s_at	-0.020511	0	0.394049
208545_x_at	0.265408	0	0
208601_s_at	-0.270581	0	0
208702_x_at	0	0	0.0426262
208736_at	0	0.582264	-0.0862941
208886_at	0.149103	0	0
208974_x_at	0	0.742946	0
209031_at	0	0	0.237916
209360_s_at	0.303561	0	0
209396_s_at	0	0	0.0355749
209511_at	0	-0.031194	0
209605_at	-0.499338	0	0
209919_x_at	0.613197	0	0
210365_at	0.576935	0	0
210724_at	0	0	0.482166
210797_s_at	0	0.185097	0
212035_s_at	2.0241	0	-1.26034
212162_at	0	-0.0102331	0
212657_s_at	0	0	-0.254507
212697_at	0	0	-1.02451
212708_at	0.0325637	0	0
212914_at	0	0	0.0099678

212947_at	0.286979	0	0
213223_at	0.686657	0	0
213300_at	-0.578303	0	0
213573_at	0	0	-0.497655
213633_at	-1.01336	0	0
214085_x_at	-0.367611	0	0
214097_at	0.00914993	-0.576801	0
214175_x_at	0	0	-0.266628
214326_x_at	-0.698109	0	0.261075
214582_at	0	0	0.0377349
214617_at	-0.261957	0	0
214800_x_at	0	0.103261	0
214955_at	-0.100645	0	0
215184_at	0	-0.0650331	0
215268_at	0.0381782	0	0
215606_s_at	0.479765	0	0
215804_at	1.94364	0	0
215848_at	0	0.326241	0
216289_at	0	-0.000746072	0
216303_s_at	0.31126	0	0
216473_x_at	0	-0.0342987	0
216571_at	0.878426	0	0
216713_at	0.510039	0	0
216867_s_at	-0.0534745	0	0
216943_at	-0.916433	0	0
217143_s_at	-0.389097	0	0

217408_at	0	1.07798	-0.0690681
217593_at	-0.0747507	0	0
217717_s_at	0.638943	0	0
218095_s_at	0	-0.613773	0
218306_s_at	0	0	0.784894
218595_s_at	0	0	-0.411708
218812_s_at	-0.967987	0	0
219055_at	-0.0852367	0	0
219066_at	0	0.221446	0
219130_at	0	-0.150771	0
219382_at	0.866643	0	0
219437_s_at	0	-0.405445	0.198273
219523_s_at	0	0	-0.0236667
219777_at	0	0.25509	0
220059_at	-0.86817	0	0
220122_at	0.399475	0	0
220308_at	0	-0.0345586	0
221491_x_at	-0.651431	0	0
221874_at	-0.40581	0	0.017015
222059_at	0	-0.112261	0
44673_at	-0.0307987	0	0

Table S4. Subjects with discordant predictions compared to clinical assignments. Discordant cases are individually presented including the predicted probabilities of bacterial ARI, Viral ARI, or non-infectious illness. Demographic information, procalcitonin value when available, and clinical details accompany each case.

Adjudicated Phenotype	Predicted Prob. of Bacterial ARI	Predicted Prob. of Viral ARI	Predicted Prob. of Non-Infectious Illness	Adjudicated Clinical Disease/Pathogen	Age	Race	Sex	PCT	Clinical details
Bacterial	0.433679	0.464459	0.068001	Bacillus species	57	Black	Female	N/A	Presented with 1 day of dyspnea, 1 day after discharge for ankle fusion. Multilobar pneumonia on radiography. No cough, fever, hypoxia. All clinical cultures negative. Also with chronic HCV and SLE.
Non-infectious fever	0.582005	0.0149736	0.349332	Asthma	51	Unknown	Male	0.105	Respiratory distress, fever, cough, vomiting, diarrhea. Radiography normal. History of asthma requiring intubations.
Non-infectious fever	0.194149	0.576351	0.533146	Thrombus/AV Graft pseudoaneurysm	58	Black	Female	0.9545	Diarrhea, nausea, vomiting 3 days prior to enrollment. Also with pain at old fistula site, found to have pseudoaneurysm. Culture of excised tissue was negative. History of SLE.
Bacterial	0.344464	0.533779	0.0568271	Legionella sp.	71	Black	Female	0.5380	One week of fever, nausea, anorexia, malaise. No respiratory symptoms. Chest x-ray with infiltrate. Legionella urinary antigen positive.

Viral	0.453922	0.163974	0.7749	Coxsackievirus/Echovirus	19	White	Male	0.0647	3 days of dental pain, neck pain, sore throat, mild cough. Leukocytosis. Cultures negative including monospot, urinary Streptococcus antigen, CSF.
Viral	0.780981	0.49098	0.0443173	Cytomegalovirus	71	White	Male	0.1019	Orthotopic heart transplant with CMV+ donor but negative recipient. Two days fever, nausea, cough, malaise, new pulmonary infiltrate. CMV shell vial culture positive. Other cultures negative but treating team expressed concern that bacterial pneumonia led to CMV activation.
Viral	0.00145462	0.28323	0.640647	Human Metapneumovirus	50	Black	Male	0.063	Three weeks of dry cough, fever, nasal congestion, chills, myalgias, sore throat, rhinorrhea, nausea. Worsening 3 days prior to enrollment. Not responding to antibacterials prescribed elsewhere. Routine laboratory and radiography testing were normal.
Non-infectious fever	0.00128437	0.510543	0.365797	Congestive Heart Failure	50	Black	Male	3.75	Then had 2 days of dyspnea, nasal congestion, malaise, wheeze following recent treatment for bacteremia and DVT. Presented with hypertension, tachycardia, and hypoxia. Radiography with edema and superimposed infiltrate consistent with pneumonia. Microbiological testing was negative. Treated for hypertensive emergency and possible pneumonia.

Bacterial	0.00727129	0.301131	0.171867	*Mycoplasma pneumoniae*	43	White	Female	0.0805	Two months of cough, fever despite courses of amoxicillin and cefuroxime. Presented with new chest pain, nausea. Leukocytosis present. CT showed lobar pneumonia. Mycoplasma serologies sent 5 days later, notably positive for IgM and IgG.
Viral	0.314994	0.113423	0.228395	Influenza	52	Black	Female	0.1495	Two weeks of productive cough with one day of chest pain and chills. Chest x-ray with lobar infiltrate. Patient with SLE and rheumatoid arthritis on methotrexate.
Non-infectious fever	0.997491	0.00598759	0.200125	Congestive Heart Failure	87	Black	Male	42.08	Patient with CHF and multiple myeloma had weakness, cough for 1 week. Febrile on presentation with infiltrate on chest x-ray. Patient with evidence of CHF and myocardial infarction.
Non-infectious fever	0.00234552	0.896471	0.115316	Congestive Heart Failure	59	Black	Male	0.033	Patient with HIV and HCV viremia had 1 week of rhinorrhea, cough, headache, cough, chills. Also w/recent cocaine use and hypertension.
Non-infectious fever	0.960204	0.108072	0.188852	COPD	64	Black	Female	0.4678	Patient with COPD had several days of headache, sneezing, myalgias, postnasal drip and cough followed by dyspnea, purulent sputum, and wheeze.
Viral	0.314038	0.0788716	0.226326	Influenza	61	White	Male	0.1095	Symptoms included dyspnea, productive cough, chills, hypoxia, and

									bilateral heterogeneous opacities on chest x-ray.
Viral	0.00240081	0.177579	0.702856	Influenza	49	White	Female	0.051	Two weeks sinus congestion, rhinorrhea, sore throat, dry cough. Followed by 1 day of chest tightness, wheeze, fever, nausea prior to enrollment. Chest x-ray normal.
Bacterial	0.00910652	0.0858135	0.598645	*S. aureus* and *H. influenzae*	62	Black	Male	0.4349	Two days of fever, rigors, productive cough, dyspnea. Leukocytosis and chest x-ray with scattered reticular opacities. Heavy growth of *S. aureus* and *H. influenzae* in sputum culture.
Bacterial	0.000493681	0.663552	0.298311	*Pseudomonas aeruginosa*	31	White	Male	0.1652	Cystic fibrosis, discharged 1 week prior for flare. One day prior to enrollment developed dyspnea, abdominal cramping, diarrhea. Sick contact had "stomach virus". Cultures revealed known colonizers. No viral testing done.
Bacterial	0.12685	0.798854	0.0484662	*Streptococcus pneumoniae*	38	Black	Male	0.3085	HIV + patient developed 4 days of productive cough, dyspnea, diaphoresis, chills.
Bacterial	0.227432	0.650525	0.0179104	*Streptococcus pneumoniae*	50	Black	Female	0.0517	Patient with CHF and cocaine use had 4 days of productive cough, fever, nausea.
Bacterial	0.014179	0.35817	0.223517	*Streptococcus pneumoniae*	75	White	Male	1.02	Chest congestion, fever, nausea, chills developed on the day of enrollment. Normal chest x-ray. Sputum culture

									with *S. pneumoniae*. No other cause of symptoms identified.
Bacterial	0.0639225	0.270096	0.0969815	*Streptococcus pneumoniae*	46	Black	Female	0.4887	Patient with asthma developed fever, dyspnea. Found to have leukocytosis and normal chest radiography.
Bacterial	0.0410368	0.0109875	0.915803	*Streptococcus pneumoniae*	61	White	Male	0.7384	Patient with COPD and metastatic lung cancer. Was treated 3 weeks prior for post-obstructive pneumonia. Then had 3 days of dyspnea, productive cough, wheeze, pleuritic chest pain. Chest x-ray with worsening cancer-related opacities. *S. pneumoniae* bacteremia.
Non-infectious fever	0.444024	0.11632	0.388948	Pancreatitis	49	Black	Male	0.1334	Patient with recurrent pancreatitis. Developed abdominal pain, nausea, presyncope on the day of enrollment. Lipase elevated and CT showed uncomplicated pancreatitis. Febrile but with negative microbiological workup.
Non-infectious fever	0.84564	0.0381138	0.297308	Pulmonary Embolism	43	Black	Female	0.0754	One day of pleuritic chest pain, mild cold symptoms including clear phlegm. CT with bilateral pulmonary emboli.
Non-infectious fever	0.737696	0.339834	0.0247815	Pulmonary Embolism	33	Black	Female	86.2700	Patient with SLE and end-stage renal disease developed 6 days of cough, chest pain, hemoptysis. CT showed small pulmonary embolism and infiltrate, possibly pneumonia or infarcted lung.

Non-infectious fever	0.409134	0.504434	0.12448	Pulmonary Embolism	39	White	Female	0.0759	Had productive cough and dyspnea 6 days prior while hospitalized for elective procedure. Then 1 day prior to enrollment developed pleuritic chest pain. CT showed pulmonary embolism with infarct.
Bacterial	0.000329349	0.647979	0.241464	*Streptococcus pyogenes*	18	White	Female	0.0504	Two days subjective fever, chills, cough, sore throat. Culture of oropharynx revealed *S. pyogenes*.
Non-infectious fever	0.761944	0.0620277	0.354231	Severe Aortic Stenosis	76	White	Female	0.6965	Patient had abdominal pain, nausea and presented with situational syncope. CT showed small bowel wall thickening consistent with enteritis though hospitalization focused on concurrently identified severe aortic stenosis.
Non-infectious fever	0.752293	0.112757	0.276949	Stills Disease	23	White	Female	0.4844	Two weeks of fever, myalgia, and nausea despite outpatient empiric treatment with Tamiflu followed by azithromycin. Returned on the day of enrollment with pleural effusion, infiltrate, rash. No definitive diagnosis made at that time. After multiple recurrences, Still's Disease was diagnosed.
Viral	0.0126355	0.0957349	0.852353	Influenza A 2009 H1N1	60	Black	Male	0.114	Patient with congestive heart failure developed fever, headache, cough, nausea, myalgias with known exposure to others with influenza.

Bacterial	0.0864339	0.204116	0.338616	*Streptococcus pyogenes*	29	Black	Female	0.1631	Three days sore throat, anorexia, malaise, productive cough, slight fever. Sick contacts with similar symptoms.
Viral	0.0146315	0.171745	0.587374	Respiratory Syncytial Virus A	43	Black	Female	0.166	Five days before enrollment, the patient had fever, rhinorrea, and cough. One day prior to enrollment, the patient had dyspnea, nausea, wheeze, headache, earache. Patient with reactive airway disease.
Viral	0.862128	0.0530905	0.0680673	Rhinovirus	33	Black	Female	0.1443	Asthma flare for 1 day associated with nausea, vomiting, diarrhea, abdominal pain.
Viral	0.00252091	0.0911986	0.762412	Rhinovirus	64	Black	Female	0.0741	Four days of productive cough, dyspnea, nasal congestion, rhinorrhea, and wheezing. Chest x-ray normal.
Viral	0.00714781	0.41287	0.488051	Rhinovirus	28	White	Female	0.0661	Two days of cough, nasal congestion, chills, myalgias, wheeze, fever, rhinorrhea, nausea, vomiting, diarrhea. Chest x-ray with infiltrate vs. summation shadows.

Table S5. Genes in the Bacterial ARI, Viral ARI, and Non-infectious Illness Classifiers, grouped by biologic process.

Biologic process	Bacterial	Viral	Non-infectious Illness
Cell cycle regulation	JUND* (-), NINJ1, IFI27, CDKN1A, C7orf19, SERTAD3	ZNF291	JUND* (+)
Regulation of cell growth	YWHAB, PDGFA		APLP2
Development/ Differentiation	GLIPR1, RUNX1, ST14, TGIF , EPHA1	CTBP1	SP1, CEACAM8, ODZ3
RNA transcription, processing	FLJ10379, RPS21* (+), RPL28, TAF4, RPP25	DDX3Y, POLR2F, RPS21* (-), BTF3, MRPS18B* (+), HSPC117, FLJ10287	HEATR1, MRPS18B* (-)
Role in nuclear transport		KPNB1	KPNB1
Role in cell and membrane trafficking	RAB6IP2, SH3BP1, EXOC7* (+), LAPTM4B, CPNE1, GNG7, TPARL, KIAA1324	TPARL	EXOC7* (-), HERC1, LAPTM4B, KIAA1324, APLP2
Cell structure/ adhesion	TMPRSS6, TUBB1, ARHGAP12, ICAM4, DSC2, FMOD	TES, ARPC3* (+), KIDINS220	PDLIM4, IGSF4, PDE3B, ARPC3* (-), CHI3L1
Role in cell stress response	KIAA1324, KRIT1, ENC1		CBX7, APLP2, KIAA1324
Role in autophagy	LAPTM4B* (-), KIAA1324* (-)		KIAA1324* (+), LAPTM4B* (+)
Role in apoptosis	KRIT1, GLIPR1, CIAS1	DAPK2, TNFSF10	
General Inflammatory response	TNFA1P3, FMOD, ITPR3, CIAS1, GNG7, CLC, IFI27, CCR1	TNFSF10	HNRPA0, EMR3, IL1RN, TNFAIP2, CHI3L1
Interferon response	IFIT1	SP100, IRF2, OASL, ISGF3G	
Cytotoxic response	PRF1	DefA1/3	
Toxin response	P450 gene cluster, CYP2A6, ENC1, GGT1, TST		
T-cell signaling	TRA/D@, CD44	Ly6E, CAMK1, CD160	

B-cell signaling	BRDG1, HLA-DRB1/3/4, CD40		
NK-cell response	NCR1	CD160	
Phospholipid and calcium signaling	MTMR1, CPNE1, PSPH, ITPR3, CLC, MCTP1		
Fatty acid metabolism	PEX6, GLUD1		
Cholesterol metabolism	CYP27A1* (-)		CYP27A1* (+)
Amino acid metabolism	GLUD1, PSPH, GCAT		

* Genes listed in more than one classifier. For genes in multiple classifiers, increased expression is denoted by (+) and decreased expression is denoted by (-).