Supplemental Online Content

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**eTable 1.** Comparator Algorithm, Tests for Pathogen Detection and Host Response

**eTable 2.** Bacterial and Viral Pathogens Detected

**eTable 3.** Performance Characteristics, Microbiologically Confirmed Infection

**eTable 4.** Pretest and Posttest Probability

**eFigure 1.** Comparator Algorithm

**eFigure 2.** Pretest and Posttest Probability

This supplemental material has been provided by the authors to give readers additional information about their work.
### eTable 1. Comparator Algorithm, Tests for Pathogen Detection and Host Response

| Bacterial | Viral                        | Host Response                          |
|-----------|------------------------------|----------------------------------------|
| Bacterial Culture | PCR                            | Complete Blood Cell Count (CBC)        |
| PCR       | Bacterial Culture             |                                        |
| Bordetella pertussis | PCR (Adenovirus)                     | B.R.A.H.M.S Procalcitonin (PCT)        |
| Chlamydia pneumonia | PCR (Coronavirus HKU1)            | Epstein Barre Virus (EBV) IgM          |
| Mycoplasma pneumonia | PCR (Coronavirus NL63)            |                                        |
| Fusobacterium necrophorum | PCR (Coronavirus 229E)          |                                        |
| Neisseria gonorrhoeae | PCR (Human Metapneumovirus (hMNV)) |                                        |
|          |                              | (Human Rhinovirus/Enterovirus (RV/EV)) |
|          |                              | Influenza A                            |
|          |                              | Influenza A/H1                         |
|          |                              | Influenza A/H3                         |
|          |                              | Influenza A/H1-2009                    |
|          |                              | Influenza B                            |
|          |                              | Parainfluenza Virus 1                  |
|          |                              | Parainfluenza Virus 2                  |
|          |                              | Parainfluenza Virus 3                  |
|          |                              | Parainfluenza Virus 4                  |
|          |                              | Respiratory Syncytial Virus (RSV)     |
|          |                              | Epstein Barre Virus (EBV) DNA         |
|          |                              | Herpes Simplex Virus (HSV) -1          |
|          |                              | Herpes Simplex Virus (HSV) -2          |
|          |                              | Cytomegalovirus (CMV)                  |
|          |                              | Bocavirus                              |
|          |                              | SARS-CoV-2                             |
### eTable 2. Bacterial and Viral Pathogens Detected

| Bacterial Pathogens | n  | Viral Pathogens                      | n  |
|---------------------|----|--------------------------------------|----|
| Methicillin-susceptible *Staphylococcus aureus* - MSSA | 138 | Influenza A                           | 117 |
| Methicillin-resistant *Staphylococcus aureus* - MRSA  | 23  | Influenza B                           | 63  |
| Group A Streptococcus - GAS                           | 37  | Undetermined Influenza (SOC Rapid Flu Test) | 3   |
| Group A Streptococcus - GCS                           | 14  | SARS-CoV-2                            | 45  |
| Group A Streptococcus - GGS                           | 5   | Coronavirus (non-SARS-CoV-2)          | 26  |
| *Fusobacterium necrophorum*                           | 12  | Adenovirus                            | 5   |
| *Klebsiella pneumoniae*                                | 6   | Herpes Simplex Virus - HSV            | 9   |
| *Haemophilus influenzae*                               | 5   | Parainfluenza Virus                   | 12  |
| *Mycoplasma pneumoniae*                                | 5   | Human Metapneumovirus - hMPV         | 17  |
| *Pseudomonas Aeruginosa*                               | 3   | Respiratory Syncytial Virus - RSV    | 15  |
| *Neisseria gonorrhoeae*                                | 3   | Human Rhinovirus/Enterovirus – RV/EV | 22  |
| *Moraxella catarrhalis*                                | 2   | Cytomegalovirus - CMV                | 1   |
| *Enterococcus faecalis*                                | 2   |                                       |     |
| *Legionella*                                           | 1   |                                       |     |
| *Escherichia coli*                                     | 1   |                                       |     |
**eTable 3. Performance Characteristics, Microbiologically Confirmed Infection**

|                          | Microbiologically Confirmed Bacterial Infection | Microbiologically Confirmed Viral Infection |
|--------------------------|-------------------------------------------------|---------------------------------------------|
|                          | n/n | Value (%) | 95% Confidence Interval | n/n | Value (%) | 95% Confidence Interval |
| Prevalence               | 33/496 | 7 | 5 - 9 | 289/496 | 58 | 95 - 99 |
| Sensitivity              | 33/33 | 100 | 90 - 100 | 202/289 | 70 | 63 - 75 |
| Specificity              | 368/416 | 88 | 85 – 90 | 136/160 | 85 | 79 – 90 |
| Positive Predictive Value| 33/81 | 41 | 30 – 52 | 202/226 | 89 | 85 – 93 |
| Negative Predictive Value| 368/368 | 100 | 99 – 100 | 136/223 | 61 | 54 – 67 |
| Likelihood Ratio (+)     | - | 9 | 6 – 11 | - | 12 | 8 – 17 |
| Likelihood Ratio (-)     | - | 0 | NA | - | 0.3 | 0.3 – 0.4 |

*Microbiologically Confirmed Infection was defined as the pathogen detected and determined to be the causative agent of the host-immune response.*
**eTable 4. Pretest and Posttest Probability**

| Pre-test Probability Bacterial Infection | Post-test Probability Bacterial Infection |
|----------------------------------------|------------------------------------------|
| 10%                                    | 47%                                      |
| 20%                                    | 67%                                      |
| 30%                                    | 77%                                      |
| 40%                                    | 84%                                      |
| 50%                                    | 89%                                      |
| 60%                                    | 92%                                      |
| 70%                                    | 95%                                      |
| 80%                                    | 97%                                      |
| 90%                                    | 99%                                      |

| Pre-test Probability Viral Infection | Post-test Probability Viral Infection |
|-------------------------------------|--------------------------------------|
| 10%                                 | 3%                                   |
| 20%                                 | 7%                                   |
| 30%                                 | 11%                                  |
| 40%                                 | 17%                                  |
| 50%                                 | 23%                                  |
| 60%                                 | 31%                                  |
| 70%                                 | 41%                                  |
| 80%                                 | 55%                                  |
| 90%                                 | 73%                                  |

**e5b. FebriDx positive for Viral Infection**

| Pre-test Probability Bacterial Infection | Post-test Probability Bacterial Infection |
|----------------------------------------|------------------------------------------|
| 10%                                    | 40%                                      |
| 20%                                    | 60%                                      |
| 30%                                    | 72%                                      |
| 40%                                    | 80%                                      |
| 50%                                    | 86%                                      |
| 60%                                    | 90%                                      |
| 70%                                    | 93%                                      |
| 80%                                    | 96%                                      |
| 90%                                    | 98%                                      |

**e5c. FebriDx Negative for Bacterial Infection**

| Pre-test Probability Bacterial Infection | Post-test Probability Bacterial Infection |
|----------------------------------------|------------------------------------------|
| 10%                                    | 1%                                       |
| 20%                                    | 2%                                       |
| 30%                                    | 3%                                       |
| 40%                                    | 5%                                       |
| 50%                                    | 7%                                       |
| 60%                                    | 11%                                      |
| 70%                                    | 16%                                      |
| 80%                                    | 24%                                      |
| 90%                                    | 42%                                      |

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eFigure 1. Comparator Algorithm

Patient With Acute Respiratory Infection - Chief complaint: sore throat, cough, or sinusitis

Is There a Pathogen?
- + Bacterial Culture + Bacterial PCR
  - Always Bacterial Pathogen
  - Common Bacterial Pathogen
  - Common Bacterial Colonizer
  - Common Viral Pathogen
  - Common Viral DNA Shedder/Colonizer

Is There a Systemic Host Response?
- PCT < 0.1 or WBC ≤ 12,000 + PCT < 0.15 or PCT = 0.24
- PCT ≥ 0.25 or WBC > 12,000 + PCT ≥ 0.15 or PCT = 15–24
- PCT < 2
- PCT = 2
- PCT < 0.1–2 or WBC > 10,000 + Lymphocytes > 4,000 Bands + EBV DNA/Mg
- PCT < 0.1–2 or WBC > 10,000 + Lymphocytes > 4,000 Bands + EBV DNA/Mg

Final Diagnosis
- Bacterial
- Bacterial
- Negative
- Negative
- Bacterial
- Bacterial
- Viral
- Viral
- Negative
- Negative
- Viral
- Viral
- Bacterial
- Bacterial
- Viral
- Viral
- Bacterial

What if Both Bacterial and Viral Pathogens Are Identified?

- Common Bacterial Pathogens or Common Bacterial Colonizer + Common Viral Pathogen
  - PCT < 0.75
  - Viral

- Common Bacterial Colonizer + Common Viral Pathogen
  - PCT < 0.75
  - Viral

- Common Bacterial Pathogens or Common Bacterial Colonizer + Common Viral Pathogen
  - PCT ≥ 0.75
  - Bacterial

- Common Bacterial Pathogens + Common Viral Pathogen
  - PCT ≥ 0.25
  - WBC < 15,000
  - Viral

- Common Bacterial Pathogens + Common Viral Pathogen
  - PCT ≥ 0.25
  - WBC ≥ 15,000
  - Bacterial

- Common Bacterial Pathogens + Common Viral Pathogen Shedder/Colonizer
  - PCT ≥ 0.25
  - Bacterial

Procalcitonin (PCT) measurement (ng/mL); White Blood Cell Count (WBC); Epstein-Barr Virus (EBV).

* The combination was classified as a host response to both a bacterial and viral infection (co-infection), however Final Diagnosis classification was deemed to be "bacterial".

Always bacterial pathogen: Pharyngitis (H. gordonii, A. hominis/cutanum)
Common bacterial pathogen: Pharyngitis (Streptococcus, M. pneumoniae, C. pneumoniae, F. necrophorum); cough or sinusitis (S. pneumoniae, H. influenzae, M. catarrhalis, AB (M. pneumoniae, C. pneumoniae, B. pertussis))
Common bacterial colonizer: Cough, pharyngitis, sinusitis (any rare bacteria and common isolated outside the common pathogens - site for the chief complaint)
Common viral pathogen: Cough, pharyngitis, sinusitis (Influenza, Parainfluenza, Respiratory Syncytial Virus, Human Metapneumovirus); cough, pharyngitis (Adenovirus); cough, shortness of breath, pharyngitis (SARS-CoV-2)
Rarely viral pathogen/Common viral DNA shedder/colonizer: Pharyngitis (EBV, Cytomegalovirus (CMV), Herpes Simplex Virus (HSV)); cough (CMV); Amy (Bocanitas, Rhinovirus/ Enterovirus, Coronavirus)

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Pre, Post Test Probability (Bacterial Infection) 

Pre-test odds = \( \frac{p}{1-p} = \frac{0.5}{1-0.5} = 1 \)

Pre-test odds were multiplied by the LR (8 for bacterial infection as an example) = \( 1 \times LR = 1 \times 8 = 8 \) (post-test odds)

Pre-test odds was then converted to post-test probability = \( \frac{O}{O+1} = \frac{8}{8+1} = 89\% \)