Clinical Presentation: The initial symptoms of COVID-19 infection are generally mild and characterized most commonly by fever (43-98%), cough (68-82%), and shortness of breath (19-55%). A recent report of >4700 cases in healthcare workers had at least one of the symptoms of fever, cough, or shortness of breath. Other symptoms may also be present early in the illness such as headache (10-65%), myalgias (11-66%), sore throat (5-38%), loss of sense of smell or taste (up to 15-60%) and GI upset (nausea, vomiting, diarrhea 1-20%). Rhinorrhea (4-10%) and nasal congestion alone are relatively uncommon as opposed to many other respiratory viruses and seasonal allergies. Most persons infected with COVID-19 who are young and healthy will recover without problems. Those who are older or immunocompromised are more likely to progress to pneumonia which can be severe.

Testing Recommendations: Testing is widely available and all patients with symptoms suspicious for COVID-19 should undergo testing. Testing should be performed in patients who present with symptoms typical of COVID-19 (cough, fever, shortness of breath), those with severe symptoms, and those with a combination of the less typical symptoms listed above. Asymptomatic persons should not routinely be tested, although there are certain situations where screening for COVID-19 may be appropriate. We recommend testing be utilized in the following way:

1. **TEST** ➔ Patients who have symptoms which could be compatible with COVID-19. This includes both inpatient and outpatients.
   - Differentiating pneumonia due to COVID-19 from other forms of pneumonia can be difficult. See information below on differentiating types of pneumonia. Other respiratory testing (respiratory panels, culture, etc.) could also be obtained if appropriate.
   - Patients with respiratory symptoms who do not undergo testing should be presumed to have been infected with SARS CoV-2 and should self-isolate per available guidelines.

2. **TEST** ➔ Those working in a healthcare environment who have symptoms which could be compatible with COVID-19.
   - Because of their extensive and close contact with vulnerable patients in healthcare settings, even mild signs and symptoms of COVID-19 should be evaluated among potentially exposed healthcare personnel.
   - Testing directed by Employee Health or Student Health should be performed as directed. Employee Health is open 7AM – 4:30PM, Monday to Friday and can be reached at 402-552-3563. After hours and weekends, call the OUCH pager (888-OUCH).

Respiratory Pathogen Panel Use: The new RPP includes SARS-CoV-2 RPP and has utility in diagnosing a variety of viral and bacterial pathogens, but it is expensive and may not impact clinical management. Generally, it should be reserved for use in populations where knowledge of specific viral pathogens beyond SARS-CoV-2 will have clinical impact (i.e. RSV or Parainfluenza in stem cell transplant patient) or there is significant diagnostic uncertainty (i.e. atypical pneumonia not responding to antibiotics).

Current recommendations on use are outlined below.

- Patients with symptoms concerning for COVID-19 should be tested for SARS-CoV-2 using our current COVID-19 only tests and the RPP should generally be avoided.
- For patients where there is strong suspicion for other respiratory pathogens or where COVID testing is negative the RPP may be considered.
• The RPP is adequately sensitive for SARS-CoV-2 and can be used in the process of ruling out COVID if needed, although testing using the current SARS-CoV-2 only is preferred. The determination of the need for 1 or 2 tests should follow current protocols.
• Patients who have been tested with the RPP should not be retested for at least 7 days.
• Asymptomatic patients should **NOT** be tested using the RPP including pre-procedural and admission-based screening. Screening for COVID-19 should be done using the current SARS-CoV-2 only tests.

**Directing COVID-19 Testing in Patients with Pneumonia:** Differentiation of patients with COVID-19 infection from those with bacterial pneumonia can be difficult. The guidance below is provided to assist in deciding if a patient management. Patients with syndromes highly consistent with bacterial infection should still have COVID-19 ruled out with at least 1 test, while those presenting with an “atypical pneumonia” with features concerning for COVID-19 should always be placed in appropriate isolation and tested.

<table>
<thead>
<tr>
<th>COVID-19</th>
<th>Bacterial Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Fever, Cough, Shortness of Breath, Viral prodrome (headache, myalgias, nausea/vomiting/diarrhea)</td>
<td>Fever, Cough, Shortness of Breath, Purulent sputum</td>
</tr>
<tr>
<td><strong>Lab Abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Normal/low WBC, Lymphopenia common Mild hepatitis</td>
<td>Leukocytosis, bandemia</td>
</tr>
<tr>
<td><strong>Procalcitonin</strong></td>
<td></td>
</tr>
<tr>
<td>Usually low</td>
<td>Elevated</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td></td>
</tr>
<tr>
<td>Close contact with confirmed or suspected case of COVID-19 Work or live in high risk environment</td>
<td>None</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
</tr>
<tr>
<td>Bilateral infiltrates, “atypical pneumonia” Multifocal ground-glass opacities</td>
<td>Lobar Infiltrate</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Supportive Care, consider remdesivir Airborne, contact, droplet Isolation</td>
<td>Antibiotic Therapy Precautions per etiology</td>
</tr>
</tbody>
</table>

**Ordering COVID-19 Testing to Detect SARS-CoV-2:**

• COVID-19 testing is available in EPIC using the COVID testing order panel. Clinicians should answer any necessary questions when ordering the assay to accurately reflect their reason for testing.
• Testing may be performed on a variety of molecular panels but only a single order is used to order all COVID testing. Tests currently in use include:
  o Roche Cobas 6800 (Turn around time (TAT) <24 hours)
  o NM Developed COVID Test (TAT <24 hours)
  o Hologic Aptima TMA SARS CoV2 (TAT <24 hours)
  o Cepheid SARS-CoV-2 (TAT <3 hours), limited supply
• In most cases, testing will be performed on the Roche Cobas 6800 platform. However, in certain circumstances, testing will be performed using our laboratory developed test, the Hologic Panther. Rapid testing will be performed using the Cepheid platform. The agreement between these assays is excellent.
  o Rapid testing is reserved for pre-solid organ transplant, laboring mothers, and very urgent surgical cases. Use outside of these parameters should be discussed with microbiology
• When ordering the test clinicians must designate if the patient has symptoms concerning for COVID-19 or if they are asymptomatic.
If symptomatic a patient flag for “COVID Rule Out” will be automatically added to the patient’s chart. The appropriate isolation should also be ordered (airborne, contact/droplet).

- Patients who are asymptomatic and being screened upon admission or pre-procedurally will not be flagged in any way.
- If the test is positive an infection flag for “COVID-19” will be automatically added to the patient’s chart.
- If the test is negative the “COVID Rule Out” flag will be automatically removed. Some patients will need additional testing to rule out COVID-19 (see below).

**Interpreting COVID Testing Results:** Two assays are currently being used to test for COVID-19 which may provide slightly different results.

**Roche Cobas 6800 (COV19) interpretation**
- This assay is designed to detect RNA from two genes within SARS CoV 2, the E-gene and the ORF1a-gene.
- If both the E- and ORF1a-genes RNA are not detected, the following will be resulted: **Not Detected - SARS CoV2 RNA NOT DETECTED by RT-PCR.**
- If both the E- and ORF1a-genes RNA are detected, or ORF1a- alone, the following will be resulted: **Detected - SARS CoV2 RNA DETECTED by RT-PCR.**
- If only the E-gene is detected, per the FDA EUA document, the following will be resulted: **Presumptive Positive – Sarbecovirus RNA DETECTED by RT-PCR.** Note that the E-gene is conserved with SARS-CoV and other coronaviruses found in bats. However, SARS CoV-1 has not been isolated since 2003 and infection from bats in highly unlikely. Thus, detection of the E-gene alone should be interpreted as positive for SARS-CoV-2.
- In rare cases, the sample will fail internal controls and the result will be Invalid. In this situation, we suggest recollection of the sample if clinically indicated.

**Hologic Aptima TMA SARS CoV2 interpretation**
- This assay is designed to detect RNA from two regions within the SARS-CoV-2 ORF1ab gene.
- Will be resulted as the following:
  - **Not Detected - SARS CoV2 RNA NOT DETECTED by RT-PCR.**
  - **Detected - SARS CoV2 RNA DETECTED by RT-PCR.**
- In rare cases, the sample will fail internal controls and the result will be Invalid. In this situation, we suggest recollection of the sample if clinically indicated.

**Laboratory developed test (NECoV19) interpretation**
- This assay is designed to detect RNA from two genes within SARS CoV 2, the E gene and the N-gene.
- If the E-gene RNA is not detected, the following will be resulted: **Not Detected - SARS CoV2 E gene RNA NOT DETECTED by RT-PCR.**
- If the E-gene RNA is detected, the same sample will be re-tested on the next run for both the E-gene RNA plus a separate N-gene target to confirm if it is positive. If either or both the E- or N- target RNA is detected upon retesting, the following will be resulted: **Detected - SARS CoV2 E gene RNA DETECTED by RT-PCR.**
- However, if neither the E- or N-gene RNA is detected upon retesting, a result of inconclusive is reported as follows: **Inconclusive result - Please contact Microbiology director for further consultation at 402-888-5626**

**Rapid Test Results (Cepheid)**
- Results are reported as either detected or not detected

**How to Manage Inconclusive Results:** Inconclusive result most probably reflect low levels of virus in the sample but may also represent a false positive result. We recommend the following:
- For inpatients who have an initial inconclusive result on a NP swab, we recommended a new respiratory tract sample be obtained 24 hours after the first sample. If possible, a lower respiratory tract specimen (sputum, tracheal aspirate, etc.) should be obtained, particularly in those with evidence of pneumonia.
  - If the new test is positive or inconclusive, the patient should be considered positive for COVID-19.
If the new test is negative, the need for additional testing depends on the suspicion of disease.

- If suspicion is low, consider negative for COVID-19.
- If suspicion is high (atypical pneumonia, high risk exposure, etc.), consider third test, again preferentially of lower tract secretions if possible.
- Discussions with infection control are appropriate to decide if additional testing is needed in cases where results are difficult to interpret. Please contact 888-4646 to discuss.

- For outpatients who have an inconclusive result, a second swab should be collected 24 hours after the first swab was obtained and re-tested.
  - If the second test is negative, the patient will be considered as negative for COVID.
  - If the second test is positive, the patient will be considered positive for COVID and a public health investigation will be opened.
  - If the second test remains inconclusive, interpretation is difficult. This may indicate presence of low-level viral RNA or be falsely positive. Out of an abundance of caution, the patient should be advised to continue home isolation similar to a patient with a positive result (10 days from symptom onset and at least 5 days of fever free without antipyretics and improving respiratory symptoms). If symptoms were to progress or worsen, obtaining additional specimens for repeat testing may be considered.

Ruling Out COVID-19:

- The currently utilized assays are very sensitive, particularly early in illness. Patients who have recently (within last 7 days) developed symptoms (either outpatient or inpatient) can usually be adequately ruled out with a single appropriately obtained NP swab. As viral levels in the nasopharynx begin to decline around a week into the illness a second test could be considered in patients who are 7 or more days into illness, especially if they have evidence of pneumonia. In these situations, a specimen from the lower respiratory tract would be preferred. Those with inconclusive results should have a second test obtained. Patients who need 2 tests to rule out COVID-19 should generally have a minimum of 18 hours between specimen acquisition.
- Patients who were initially screened while asymptomatic (surgical screening, etc.) and subsequently develop symptoms concerning for COVID-19 should undergo repeat testing
- Patients who have tested positive for COVID-19 should follow published isolation duration guidance available on our website based on their setting of care (inpatient vs. outpatient).

Screening for COVID-19 in Asymptomatic Patients:

- Screening for infection in asymptomatic patients is **NOT** generally recommended:
  - This includes persons who have traveled or been exposed to someone with COVID-19.
  - Some locations require testing before or after travel and some employers require testing before returning to work. While we do not generally recommend this practice if it is required for patients to undergo testing for these purposes, it is reasonable to obtain testing.
- Testing asymptomatic patient is appropriate in the following situations:
  - Before immunologically high-risk procedures such as bone marrow or organ transplant.
  - Pre-procedural testing meeting risk criteria
    - Not all procedures require testing and current institutional guidance should be followed
    - Testing should be arranged in the outpatient setting 48-72 before the procedure
  - Admission screening of all inpatients even if asymptomatic is required
  - Outbreak investigation as directed by infection control, employee health, or public health
Role of Serology in COVID-19 Diagnosis:

- Infection with COVID-19 produces a rapid serologic response with 95% of persons with symptomatic infection demonstrating detectable IgG antibodies by day 14.
- Numerous serologic assays are available in the US. Many of these have not been well validated and may produce both false positive and negative results. Outside serologic testing is difficult to interpret.
- A serologic assay is available at Nebraska Medicine (DiaSorin SARS CoV2 IgG) which detects COVID-19 IgG antibodies. This is a qualitative assay which yields a positive or negative result only. It has been validated and is highly sensitive. Furthermore, this assay will not detect antibodies directed against seasonal coronaviruses.
  - IgM testing is not currently available nor are quantitative IgG levels. These may become available in the future.
- The current role of serologic testing is unknown. Possible use cases are noted below.
  - Patients who previously had a syndrome compatible with COVID-19 and were not tested
  - High risk exposure patients who did not develop symptoms
  - Conflicting test results in an asymptomatic patient
  - Serology is NOT recommended to diagnose COVID-19 infection in patients with symptoms. Current molecular testing should be used in these situations.
- The duration of immunity in patients with positive serology is unknown and a positive serology does not mean that PPE recommendations can be disregarded.

Testing for Recurrent COVID-19 Infection:

Currently there is no data to indicate persons can become re-infected but there is concern that this may be possible. The CDC states the following “Patients previously infected with SARS-CoV-2 who have clinically recovered but later develop symptoms c/w COVID19, should be isolated and retested.” This means patients who had COVID-19 and recovered, and then develop symptoms suggestive of COVID-19 at a later date (typically at least 3 months later) should be considered for repeat COVID-19 testing. Unfortunately, for patients who test positive it is unknown if reinfection is actually occurring or if this represents prolonged test positivity (viral shedding). RT-PCR assays can remain positive for weeks or months and in do not correlate with recovery of viable virus or transmissibility of disease.

We recommend patients with a history of COVID who have recovered and subsequently present with symptoms suggestive of COVID-19 be placed in isolation and testing and isolation be discussed with the COVID ID MD.