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 in a recent report of >4700 cases in healthcare workers 92% 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%) 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 (see below).

2. **TEST →** Those residing or working in high-risk environments such as:
   - Healthcare workers and those who work in healthcare environments. 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 – 430PM, Monday to Friday and can be reached at 402-552-3563. After hours and weekends, call the OUCH pager (888-OUCH).
   - Older adults and those who are immunocompromised or have chronic medical conditions.
   - Residents and workers in long-term care facilities or other group settings (homeless shelters, groups, homes, etc.)
   - Public safety workers and first responders.

Testing Protocol: The decision to perform a Respiratory Pathogen Panel (RPP) should be individualized. An RPP does not need to be obtained before COVID-19 testing but may be useful in those presenting with atypical pneumonia.

- Testing will be performed using a single nasopharyngeal specimen. Oropharyngeal specimen collection is not recommended. An RPP can be run on the same swab as the COVID-19 test. Instruction on specimen collection are available on the Nebraska COVID website.
- Patients with pneumonia should undergo testing of sputum or of other lower respiratory tract specimens if available. Sputum induction and other aerosol generating procedures should be avoided.
Outpatients who were tested early in their illness and then present with worsening of symptoms should be retested as false negatives have occurred early in illness.

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

Ordering COVID-19 Testing:

- 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:
  - Roche Cobas 6800 (Turn around time (TAT) <24 hours)
  - NM Developed COVID Test (TAT <24 hours)
  - Hologic Aptima TMA SARS CoV2 (TAT <24 hours)
  - 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.
  - 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 is 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:
  o Not Detected - SARS CoV2 RNA NOT DETECTED by RT-PCR.
  o 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- nor 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.
  o If the new test is positive or inconclusive, the patient should be considered positive for COVID-19.
  o 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 were initially screened while asymptomatic (surgical screening, etc.) and subsequently develop symptoms concerning for COVID-19 should undergo repeat testing.
- Inpatients who have tested positive for COVID-19 should generally remain in isolation for 21 days unless they meet the test-based criteria for leaving isolation. Test-based criteria for exiting isolation are having two negative tests at least 24 hours apart. Testing to remove isolation should only be performed in those who are at least 10 days from symptom onset and who have been improving for at least 5 days (5 days of fever free without antipyretics and improving respiratory symptoms). Patients with positive tests can be discharged to home isolation. If discharged, COVID-19 positive patients should follow the outpatient guidance on when they can exit home isolation.
- Removing patients from COVID-19 isolation should be individualized and always based on discussion with Infection Control (888-4646) and/or COVID ID physician. The Infection Control Department is ultimately responsible for removing the isolation flag.

**Screening for COVID-19 in Asymptomatic Patients:**

- Screening for infection in asymptomatic patients is NOT generally recommended:
  - This includes patients without symptoms who have traveled, been exposed to someone with COVID-19, or who requires 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 validated 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.