The interventional pain management community saw the COVID-19 pandemic decimate elective interventional procedures and new patient visits across the United States until the reopening of America and the restarting of interventional procedures and elective surgical procedures began again. Health care providers, along with essential workers and patients, continue to be concerned about functioning in a safe and responsible manner. Consequently, a level of comfort is created by the testing health care workers with long exposure to new patients and patients undergoing interventions in high risk environments.

As the United States and the world suffers from an ongoing infodemic, there are substantial amounts of misinformation, and some appropriate information being produced on molecular, antigen and antibody testing. Consequently, this manuscript is undertaken to describe the value and validity of coronavirus antibody testing.

Methods: Literature review.

Results: Antibody tests detect antibodies or immunoglobulins that are produced as the human immune response to SARS-CoV-2 infection. A positive result suggests that the individual has potentially been exposed to SARS-CoV-2. When immunoglobulins M (IgM) antibodies are present, they can indicate an active or recent infection, whereas immunoglobulin G (IgG) antibodies show up later in the infection process and can often indicate a past infection, but does not exclude recently infected patients who can still be contagious, especially when IgM antibodies are also concurrently detected. While past knowledge indicates that for viral infections, IgG antibodies usually persist longer than IgM antibodies and provide immunity from re-infection, it is not clearly known if that is true for COVID-19.

Limitations: A narrative review with paucity of literature.

Conclusion: Antibody tests have been developed to detect IgG only, both IgG and IgM, or total antibodies. At present, multiple antibody tests are available for use in the United States. In a review of 54 available studies through the end of April, mostly from China, the accuracy of pooled results for combination IgG/IgM tests was 91.4% (95% CI, 87.0 - 96.6) for 15 to 21 days post-symptom onset. Thus, antibody tests provide a promise and a peril in the ongoing Covid-19 pandemic.

Key words: Corona, COVID-19, antigen testing, antibody testing, IgM antibodies, IgG antibodies
with 98% of the practicing physicians being affected, 52% with new burnout secondary to COVID-19 and 66% with a negative outlook. The survey also showed that risk factors were not only the COVID-19 scare, but also on the economic side, with coding and billing issues; 67% attributing it to in-house billing and 73% to electronic medical records (EMRs). These developments led to the formation of multiple task forces and publications of risk stratification (3), guidance for elective procedures (4), changes in education and communication (5), and the development of safe modalities or techniques with increased surveillance on infection and avoidance of immunosuppressive drugs (6-8). Now, without significant practice volumes for almost 3 months, followed by a slow start, and returning to near normal on an extremely slow basis, interventional techniques, which even before the pandemic had been flattening or declining, except for a few procedures, are expected to decline even further (9-21). This will, in all probability, lead to an increased use of opioids (19-22), despite evidence for the effectiveness of interventional techniques (6-8,16,23-32).

As America continues to reopen, including health care services and elective surgeries, despite warnings and occurrences of peaks and valleys and overall resurgence, the health care workforce and patients, rightfully are concerned with the consequences of long exposure in health care settings, specifically undergoing interventional techniques or elective surgeries (33-35). It has been proposed to screen all staff and testing all preoperative elective patients for the presence of the coronavirus through molecular testing on the basis that it would not only provide a safety value, but also may assist in preventing a second spike in the disease (33-35). However, testing for the presence of the virus is impossible as one may have to test on a daily basis over 150 million Americans going to work each day. It is also not practical to test all patients who are not undergoing interventional procedures, not having long exposures, and considered as low risk or even medium risk. Thus, support is emerging for testing for the presence of antibodies on a widespread scale, which could help drive evidence-based decision making, both on an individual and societal scale (36-46). Further, with the decline of confidence in evidence-based medicine, the numerous conflicts and confluences of interest at play, the current infodemic during COVID-19 that has inundated us with misinformation, some appropriate but with significant amounts which are misinformation, produced on all aspects of COVID-19, including molecular and antibody testing (6-8,47-54), that this focused review is undertaken to explore the value and validity of antibody testing.

**Background**

Ever since its introduction into human populations in November 2019 (COVID -19), from Wuhan, China, the causative virus SARS-CoV-2 has rapidly spread around the world, and has created great social and economic havoc. The virus has created immense societal and individual lifestyle changes. With the introduction of physical and social distancing since then in varying degrees around the globe, the virus is on the decline in a number of states and countries. However, its ravages are still being felt around the globe. The major challenge at present appear to be to get communities and societies back to work while still maintaining safety and preventing a surge of infections.

Various strategies have been employed to get people back to work safely. These have included techniques like phased openings of various businesses, physical distancing at work and use of masks and other PPE, but challenges remain (42). Another strategy that is being employed is to check for viral serologies in persons returning to work or receiving health care. However, recently the Equal Employment Opportunity Commission (EEOC) has opined that while molecular testing is appropriate (55) and an employer can mandate it, antibody testing must not be mandated (56).

**Context**

When the epidemic initially started, crude methods of detection like temperature measurement were employed. This was followed by Nasal/nasopharyngeal and oropharyngeal swabs, which was initially marred by poor sensitivity; however, now it is considered the gold standard for a definitive diagnosis of COVID infection. With 10 million people worldwide that have been diagnosed with COVID-19 infection, there is still a concern for undiagnosed asymptomatic infections. Of the 20% of the 4,800 sailors who tested positive on the USS Theodore Roosevelt, 60% were asymptomatic (57,58). The Centers for Disease Control and Prevention (CDC) estimates that 35% of transmission happens in the asymptomatic stage (58).

This has enhanced already existing fears among health care work force and created a demand for strategies to instill confidence in people returning to work.
Testing for COVID-19

COVID-19 testing is crucial in managing the pandemic at present and into the future. It involves analyzing samples that indicate the presence or past presence of SARS-CoV-2 (59). The presence of the virus or acute infection is detected by detecting viral ribonucleic acid (RNA) using molecular methods such as polymerase chain reaction (PCR), which amplifies or replicates a small, well-defined segment of DNA many hundreds of thousands of times, creating enough of it for analysis (59,60). These can be measured with further testing such as reverse transcription polymerase chain reaction (RT-PCR) (60), real-time PCR (61-63) and quantitative polymerase chain reaction (qPCR) (59-62). A second test, which is also used to test present infection is the antigen test, which shows the presence of the viral antigens within the test samples. Multiple disadvantages of viral testing include the lack of availability, cumbersomeness, and low sensitivity. Consequently, alternate methods including antibody testing have been explored.

Antibody or serology testing is used to detect an immune response in the patient. Antibody tests include both traditional enzyme immunoassays and rapid lateral flow immunoassays (44,45,66,67). Most patients who have COVID-19 infection will mount an antibody response within 10-15 days (68). All the patients in a study of 285 patients tested positive for IgG within 19 days after symptom onset (69). Seroconversion for immunoglobulin G (IgG) and immunoglobulin M (IgM) occurred sequentially (70) or simultaneously, which is considered unusual by the CDC.

Clinical Significance

The clinical significance of the presence of antibodies is to identify prior exposure to the virus or response to vaccination (71). Whether the antibodies will provide adequate protection from a future infection, is an important question which remains to be answered.

Cases of reinfection/reactivation have been reported based upon return of PCR positivity after an initial negative test in approximately 21% of cases (72) but not definitively proven to be related to a new infection (73). These have been attributed to poor sampling and delayed clearance of the virus; however, occasional cases of asymptomatic patients have also been reported in the lay press.

Immunity to most viral infections is cell mediated i.e., based upon Helper and Cytotoxic T cells. Antibodies are also produced during the course of viral infections, however they are more an indicator of prior infection and may prevent initial infection but are not effective by themselves for controlling widespread infection. That is the role of the Helper and Cytotoxic T cells which are needed to get rid of the infected cells which contain intracellular virus. Also, since the initial mode of entry is usually the respiratory tract, mucosal immunity may be of importance to prevent initial attachment to the mucosal surface of the respiratory epithelium, although this remains unproven.

Hence, the presence of positive serology is proposed to be used as a surrogate for immunity as a consequence of prior infection or prior vaccination (in the future) and to be used in the public health setting to assess patients who may be immune and hence safe to go into society into various work settings with the expectation of safety for themselves and the people they come into contact with. The clinical validity of this approach, however, remains to be validated in large clinical trials.

Serologic Tests Approved

Earlier in April, 2020, more than 70 companies had been allowed to sell COVID-19 antibody tests without authorization (43). After meeting other requirements, the manufacturers of these tests must state that they’ve clinically validated their tests using specimens from patients with PCR-confirmed infections. The test reports must note that the Food and Drug Administration (FDA) has not reviewed the assays and that they should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform patients of infection status.

The FDA now requires commercially marketed serologic tests to receive Emergency Use Authorization (EUA). Tests that are not commercially marketed do not require FDA authorization but developers may voluntarily request authorization. Around 12 serological tests have been approved in the United States under an EUA as of May 25th 2020 (Table 1). The tests may test for specific IgG or IgM antibodies or total antibodies (including IgA as well) in a patient’s serum. All currently authorized tests are qualitative (the result may be positive, negative, or indeterminate) rather than quantitative (in the form of antibody titer levels).

The EUA provided to Chembio Diagnostic Systems for their DPP Covid-19 IgM/IgG system was revoked on June 16, 2020, based upon an NIH/NCI independent evaluation, raising concerns about its accuracy.

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Viral Antigens for Serologic Tests

The tests may be directed against 2 major viral target antigens:

- Spike Protein (S) – Full length(S1+S2), or partial (S1 domain or receptor binding domain [RBD] of S1 protein).

<table>
<thead>
<tr>
<th>Approved Date</th>
<th>Company</th>
<th>Test Description</th>
<th>Antibody detected</th>
<th>Technology</th>
<th>Antigen</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/30/2020 Inbios</td>
<td>SCoV-2 Detect IgM ELISA</td>
<td>IgM</td>
<td>ELISA</td>
<td>Spike</td>
<td>None</td>
<td>92.5</td>
<td>98.95</td>
</tr>
<tr>
<td>6/26/2020 Beckman-Coulter</td>
<td>Access SARS COV-2 IgG</td>
<td>IgG</td>
<td>CLIA</td>
<td>RBD of S1</td>
<td>None</td>
<td>100</td>
<td>99.6</td>
</tr>
<tr>
<td>6/23/2020 Babson Diagnostics</td>
<td>Babson Diagnostics IgG1</td>
<td>IgG</td>
<td>High throughput CLIA</td>
<td>Spike</td>
<td>None</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6/19/2020 Hangzhou Laite</td>
<td>IgM/IgG Antibody Combo Test Kit (Colloidal Gold)</td>
<td>IgG/IgM</td>
<td>Lateral Flow</td>
<td>Spike</td>
<td>IgM – 96.7 IgG – 100</td>
<td>IgM – 100 IgG – 98.8</td>
<td></td>
</tr>
<tr>
<td>6/15/2020 Emory Medical laboratories</td>
<td>SARS-CoV-2 RBD IgG test</td>
<td>RBD IgG</td>
<td>ELISA</td>
<td>Spike</td>
<td>None</td>
<td>100</td>
<td>96.4</td>
</tr>
<tr>
<td>6/18/2020 Biohit Healthcare</td>
<td>Biohit SARS-CoV-2 IgM/ IgG Antibody Test Kit</td>
<td>IgM/IgG</td>
<td>Lateral Flow</td>
<td>Nucleocapsid</td>
<td>None</td>
<td>96.7</td>
<td>95</td>
</tr>
<tr>
<td>6/10/2020 Inbios</td>
<td>SCoV-2 Detect IgG ELISA</td>
<td>IgG</td>
<td>ELISA</td>
<td>Spike</td>
<td>None</td>
<td>97.8</td>
<td>99</td>
</tr>
<tr>
<td>6/8/2020 Siemens</td>
<td>Dimension Vista SARS-CoV-2 Total (COV2T)</td>
<td>Total antibody</td>
<td>High Throughput CMIA</td>
<td>Spike</td>
<td>None</td>
<td>100</td>
<td>99.8</td>
</tr>
<tr>
<td>6/8/2020 Siemens</td>
<td>Dimension EXS SARS-CoV-2 Total (COV2T)</td>
<td>Total antibody</td>
<td>High Throughput ELISA</td>
<td>Spike</td>
<td>None</td>
<td>100</td>
<td>99.8-99.9</td>
</tr>
<tr>
<td>6/4/2020 Vibrant</td>
<td>Vibrant COVID-19 Ab Assay</td>
<td>IgG/IgM</td>
<td>High Throughput CLIA</td>
<td>Spike and Nucleocapsid protein</td>
<td>None</td>
<td>98.1</td>
<td>98.6</td>
</tr>
<tr>
<td>6/4/2020 Hangzhou Biotest</td>
<td>RightSign COVID-19 IgG/ IgM Rapid Test Cassette</td>
<td>IgG/IgM</td>
<td>Lateral Flow</td>
<td>Spike</td>
<td>IgM – 100 IgG – 93.3</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>5/29/2020 Siemens</td>
<td>ADVIA Centaur SARS-CoV-2 Total (COV2T)</td>
<td>Total antibody</td>
<td>High Throughput CMIA</td>
<td>Spike</td>
<td>None</td>
<td>100</td>
<td>99.8</td>
</tr>
<tr>
<td>5/29/2020 Siemens</td>
<td>ADVIA Centaur SARS-CoV-2 Total (COV2T)</td>
<td>Total antibody</td>
<td>High Throughput CMIA</td>
<td>Spike</td>
<td>None</td>
<td>100</td>
<td>99.8</td>
</tr>
<tr>
<td>5/29/2020 Healgen</td>
<td>COVID-19 IgG/IgM Rapid Test Cassette</td>
<td>IgG/IgM</td>
<td>Lateral Flow</td>
<td>Spike</td>
<td>IgM – 100 IgG – 96.7 IgM – 100 IgG – 97.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/4/20 EUROMMUN US Inc.</td>
<td>Anti-SARS-CoV-2 ELISA (IgG)</td>
<td>IgG</td>
<td>ELISA</td>
<td>S1 Protein</td>
<td>None</td>
<td>90% (100% &gt; 21 days)</td>
<td>100</td>
</tr>
<tr>
<td>5/2/20 Roche Diagnostics</td>
<td>Elecsys Anti-SARS-CoV-2 assay</td>
<td>IgM/IgG</td>
<td>ECLIAs (electro-chemiluminescence assay)</td>
<td>Nucleocapsid</td>
<td>None</td>
<td>&gt; 14 days - 100 %</td>
<td>99.81</td>
</tr>
<tr>
<td>4/30/20 Wadsworth Center, New York State Department of Health</td>
<td>New York SARS-CoV Microsphere Immunoassay for Antibody Detection</td>
<td>Total antibody</td>
<td>MIA(Microsphere Immunoassay)</td>
<td>Full length recombinant nucleocapsid protein</td>
<td>None</td>
<td>88</td>
<td>98</td>
</tr>
<tr>
<td>4/29/2022 Bio-Rad Laboratories, Inc.</td>
<td>Platelia SARS-CoV-2 Total Ab assay</td>
<td>Total antibody - IgG, IgM, IgA</td>
<td>Modified ELISA</td>
<td>Recombinant nucleocapsid protein</td>
<td>None</td>
<td>92.2</td>
<td>99.6</td>
</tr>
<tr>
<td>4/26/20 Abbott Laboratories Inc.</td>
<td>Architect SARS-CoV-2 IgG assay</td>
<td>IgG</td>
<td>Chemiluminescent microparticle immunoassay (CMIA)</td>
<td>Nucleocapsid protein</td>
<td>None</td>
<td>100</td>
<td>99.6</td>
</tr>
<tr>
<td>4/26/20 Abbott Laboratories Inc.</td>
<td>Alinity SARS-CoV-2 IgG assay</td>
<td>IgG</td>
<td>Chemiluminescent microparticle immunoassay (CMIA)</td>
<td>Nucleocapsid protein</td>
<td>None</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>4/24/20 DiaSorin Inc.</td>
<td>Liaison SARS-CoV-2 S1/S2 IgG</td>
<td>IgG</td>
<td>High throughput CMIA</td>
<td>None</td>
<td>S1-S2</td>
<td>97.6</td>
<td>99.3%</td>
</tr>
</tbody>
</table>
tein): RBD is more conserved than S1 or Full length S protein

Nucleocapsid protein (N) – Most abundant viral protein, more conserved than S

The sensitivity and specificity of these tests, as described in the table are, what is reported to the FDA. They have not had enough clinical validation.

### Types of Antibody Responses

After COVID-19 infection – 2 types of antibodies are described: Binding and Neutralizing antibodies. Binding antibodies are those that can be detected in patient’s blood which may signify the presence of prior infection without a definite depiction of viral replication inhibition. Testing for the detection of binding antibodies can be performed in lower biosafety level laboratories. These tests can include point-of-care (POC) tests like the lateral flow tests and do not require cumbersome equipment for testing or the laboratory tests like ELISA (Enzyme-Linked Immunosorbent Assay) or CIA (chemiluminescent immunoassay) methods for antibody detection. These may detect IgG, IgM or IgA separately or as total antibody, depending on the reagents involved.

Detection of neutralizing antibodies (Nab) on the other hand is more specialized and is based upon detection of the functional ability of antibodies in serum/plasma to prevent infection by the virus in vitro. This involves incubation of serum or plasma with live virus followed by infection or incubation of cells. Such tests require BSL-2 or BSL-3 laboratories depending on what kind of virus is used. In a study of 175 patients (68), low Nab were described in 30% of patients, with 10 patients who recovered demonstrating antibodies below the limit of detection. The titers of Nab among these patients correlated with the spike-binding antibodies targeting S1, RBD, and S2 regions. Elderly and middle-age patients had significantly higher plasma Nab titers and spike-binding antibodies than young patients. A smaller study did not find a similar decrease in Nab, but found adequate cellular immunity in patients recovering from COVID-19 infection (74). In animal studies on rhesus macaques (75), reinfection was not possible after rechallenge, 28 days after initial infection, suggesting that some degree of immunity is obtained.

### Studies Using Serologic Tests

Based upon a sample of 3,324 samples from St. Clara County in California (76), a prevalence of 2.8% was estimated in early April using the Premier Biotech test kit. In LA county, out of 865 individuals tested (77), using the above test, a prevalence of 4.65% was estimated.

In a preliminary study of 8000 patients performed...
by the Northwell Health System in New York City churches, 27% of population tested positive, higher in the lower income communities (78).

A prior study from NY State had shown a prevalence of 12.3% statewide and 19.9% in NYC based on a random sample of 15000 people who were out shopping (79).

The World Health Organization (WHO) is conducting a multinational study of seroprevalence – SOLIDARITY II study by pooling antibody data from half a dozen countries (80). NIH has started a nationwide survey beginning May, 2020, to assess seroprevalence in 10000 individuals (81). Walker (44) described the value and validity of COVID-19 antibody tests. The article was based on a Cochrane review performed by Deeks et al (45). In this review of 54 available studies through the end of April, 2020, mostly from China, the accuracy of pooled results for combination IgG/IgM was 91.4% (95% CI, 87.0 - 96.6) for 15 to 21 days post-symptom onset. However, pooled sensitivity increased to 96% (95% CI, 90.6 – 98.3) for 21 to 35 days after symptoms, but, which involved smaller sample sizes. Further, they found insufficient studies to identify the sensitivity of tests beyond 35 days of symptom onset.

The National Institute of Allergy and Infectious Diseases (NIAID) published a review of a workshop conducted in May, 2020, which reiterated that serology testing should not be a stand-alone clinical decision-making tool, and that more research is needed about what a positive antibody test means in terms of risk for reinfection and immunity. In addition, on June 19, 2020, the FDA issued another letter to healthcare providers about serology tests through its MedWatch system, emphasizing that, “The FDA is not aware of an antibody test that has been validated for diagnosis of SARS-CoV-2 infection (46)”. However, the FDA continues its collaboration with the National Cancer Institute to validate commercially available antibody tests. Deeks et al (45) emphasized that while COVID-19 antibody tests show potential, specifically when used 2 or 3 weeks after the onset of symptoms, the data are nearly all from hospitalized patients. Consequently, the data does not show how accurately they can identify COVID-19 in people with mild or no symptoms, or tested more than 5 weeks after symptoms started. A significant amount of data in the review by Deeks et al was not yet peer-reviewed. Consequently, the design, execution, and reporting of studies of the accuracy of COVID-19 tests requires considerable improvement in avoiding the risk of bias and also with inclusion of high quality studies. Another finding from the Deeks’ review of pooled results from immunoglobulin A (IgA), IgG, and IgM tests found that sensitivity was less than 30% in the first week, rose up to 72.2% (95% CI, 63.5 - 79.5) for 8 to 14 days and reached 91% for 15 to 21 days. Deeks et al (45) also questioned the role of antibody testing in serosurveys for public health purposes because the high risk of bias and lack of applicability make it likely that the accuracy of tests when used in clinical care will be lower than reported in the included studies. In fact, researchers estimated that if 1,000 people were administered antibody tests 3 weeks after symptoms started, 5% of whom actually had COVID-19, as is typical in a national survey, 21% would be false-positives and 0.4% would be false-negatives. Thus, in a high-risk setting, like a health care facility, where 50% of symptomatic people had COVID-19, the false-positive rate would drop to 2% and the false-negative rate would rise to 8%.

Clinical Utility

The major clinical utility of the serological tests is to assess the history of prior infection. The CDC does not recommend the use of serologic tests to assess for immunity among individuals or for returning persons to the workplace (82).

The Infection Disease Society of America (IDSA) recommendations for potential utility of serology in SARS-CoV-2 (83) are as follows:

Epidemiologic studies of disease prevalence in the community

Detection of PCR-negative cases, especially in patients who present late with a very low viral load below the detection limit of RT-PCR assay or when lower respiratory tract sampling is not possible.

Identification of convalescent plasma donors: The FDA recommends using serologic tests to detect Nab in titers of at least 1:160 to SARS-CoV-2 to help identify persons exposed to or recovered from COVID-19 infection, who may qualify to donate blood.

Verification of Vaccine Response

The CDC also has recommended serologic testing as a method to help establish a diagnosis when patients present with late complications of COVID-19 illness, such as multisystem inflammatory syndrome in children.

Conclusion

Serologic tests for COVID-19 are useful to assess prior exposure to Covid-19 infection. While they are a
useful epidemiologic tool, their clinical use is restricted to specific clinical situations. With improved knowledge of viral immunity correlates, they may prove to be of more value in the future, to assess immunity or response to vaccination.

**AUTHOR CONTRIBUTIONS**

The study was designed by AM and LM.

All authors contributed to preparation to the manuscript, reviewed, and approved the content with final version.

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