Health Alert

Benton-Franklin Health District

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Serologic Testing for SARS-CoV2

Requested Actions

- Be aware of and educate patients about both the promises and the limitations of serologic testing for SARS-CoV2.
- When serologic testing is pursued, exercise caution in selection of the testing platform and interpretation of results.
- Stay tuned for updated guidance on respiratory PCR testing.

Recommendations & Summary

- BFHD makes no systematic recommendation for serologic testing at this time and urges cautious and judicious use of these new products.
- Although some products have had limited review for emergency use authorization from FDA, most have had no review whatsoever, and few of these assays have been independently assessed for accuracy.
- For some assays, cross reactions with antibodies to circulating seasonal coronaviruses may cause a false positive result.
- Relevance of SARS-CoV2 antibody detection to diagnosis of COVID-19 illness and to individual patient management is not clear at this time and, in general, serology does not have a role in the diagnosis of COVID-19 illness.
- Correlation of antibody detection with durable immunity remains to be demonstrated and at the current time great caution should be exercised with respect to making any infection control or occupational placement decisions based on serologic results alone. However, this remains a valuable *potential* use of serology going forward *if* evidence emerges to support that application.
- The chief benefits of an accurate test in the present moment are for the monitoring of population prevalence of prior infection, not for the evaluation and management of individuals. The value and precision of that information, and by extension its relevance to individual patient care, will increase with rising prevalence and with independent validation of tests' performance.

Background

The recent emergence of assays for detection of antibodies to SARS-CoV2 (the virus that causes COVID-19) has been met with high hopes among health care providers, patients, and the media. Testing platforms being offered include laboratory-based ELISA or chemiluminescent immunoassays as well as point-of-care lateral flow assays similar to pregnancy tests in concept. IgM antibodies typically appear within about seven days of onset

of COVID-19 and IgG antibodies within four weeks. Aspirations for this technology hinge upon the supposition that recovery from COVID-19 affords at least short-term immunity and protection against re-infection. *Potential* applications include:

- increasing the sensitivity of the diagnostic evaluation by detection of IgM antibodies in acutely ill patients with falsely negative respiratory tract PCR results;
- identification of potential convalescent plasma donors for use in therapeutic clinical trials;
- detection of prior resolved infection and *presumed* immunity for clinical, infection control, and occupational purposes;
- monitoring of population prevalence of prior infection to inform implementation or modification of social distancing and other mitigation measures;
- identification of antibody correlates of protection for vaccine research; and
- confirmation of vaccine response when an effective vaccine is developed.

While these are some of the benefits we seek from serologic testing, they may not have arrived yet. Key concerns about widespread implementation or over-interpretation of results include:

- It remains to be determined which viral epitopes elicit protective antibodies and the quantitative level of those antibodies necessary for protection.
- Qualitatively positive results without quantitation may be of uncertain meaning.
- Duration of immunity afforded by prior infection remains to be determined.
- False-negative results may be obtained early in the disease course.
- False-positive results may occur in due to technical difficulties inherent in IgM detection.
- False-positive results may occur due to cross reaction with circulating human coronaviruses that can account for up to 10-20% of viral respiratory infections (e.g., HKU1, NL63, OC43, 229E).

Furthermore, this is a relatively unregulated and unvalidated market of products—albeit due to the nature of the emergency we are in. Like the multitude of PCR diagnostics for SARS-CoV2, eight serology market entrants have received limited Food and Drug Administration (FDA) review and emergency use authorization for clinical use (Cellex, Vitro [Ortho Diagnostics], Mount Sinai Laboratory, Autobio, Abbott, DiaSorin and ChemBio). The rest of the products on the market have utilized an additional pathway afforded by FDA policy that permits marketing and use of tests *without prior FDA review*, albeit with some provisions for internal manufacturer validation, notification, and labeling (including that the tests are not to be used as a sole basis for diagnosis). Consequently, sensitivity and specificity of these tests

remain largely unvetted; we are left to rely on manufacturer and vendor reports. In some cases, no information is available at all on a test's performance.

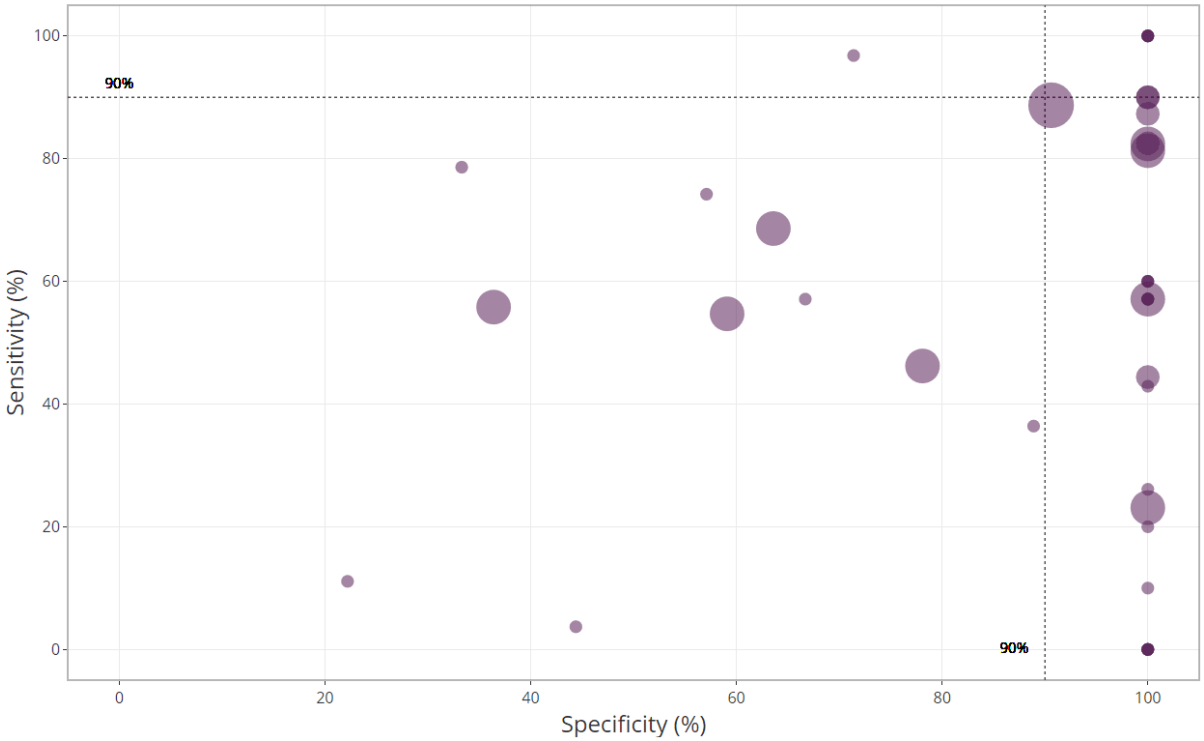
Locally, the University of Washington Department of Virology's validation of the Abbott Laboratories' IgG assay showed that it offers about 50% sensitivity at two weeks after onset and "almost 100%" at 25 days. Specificity is reported at 99.67%. LabCorp is also scheduled to offer SARS-CoV-2 IgG testing for asymptomatic patients, but test performance has not yet been reported in its marketing literature.

To demonstrate the impact of even small declines in specificity upon the predictive value of a positive test result when population prevalence is low, see the following table.

PREVALENCE	SENSITIVITY	SPECIFICITY	PPV	NPV
2%	99	99	66	100
	95	99	66	99.9
	95	96	**33**	99.9
5%	99	99	84	99.9
	95	99	83	99.9
	95	96	**56**	99.7
20%	99	99	96	99.7
	95	99	96	99.7
	95	96	86	98.7

With 853 COVID-19 cases reported to date in Benton and Franklin Counties and assuming that only 1 in 10 total cases are actually diagnosed and reported, then a rough estimate of prevalence of antibodies to SARS-CoV2 is 8500 (~3%) countywide. If population prevalence of COVID-19 antibodies is in the 2-5% range, even small decrements in specificity can result in the majority of positive results being falsely so. Not only should this prompt cautious use and interpretation of SARS-CoV2 serology, but it also explains why we also discourage respiratory PCR testing of patients who are asymptomatic—especially among those who have not had an exposure; false positive results may equal or exceed true positive results.

FDA is working with the National Institutes of Health and the Centers for Disease Control and Prevention to develop a system for validation of these serologic tests. Meanwhile, the Foundation for Innovative New Diagnostics is conducting independent evaluations of both molecular tests and immunoassays, in collaboration with the World Health Organization, the University Hospitals of Geneva, and others. Data from these evaluations are made publicly available as they emerge. A current plot of its findings in SARS-CoV2 serologic test sensitivity and specificity are as follows:



Source: FIND https://finddx.shinyapps.io/COVID19DxData/

Additional Resources

- Infectious Diseases Society of America. COVID-19 Antibody Testing Primer. https://www.idsociety.org/globalassets/idsa/public-health/covid-19/idsa-covid-19-antibody-testing-primer.pdf
- Center for Health Security. Serology-based Tests for COVID-19. https://www.centerforhealthsecurity.org/resources/COVID-19/serology/Serology-based-tests-for-COVID-19.html
- FDA. Serological Test Validation and Education Efforts. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-serological-test-validation-and-education-efforts
- Vogel G. Science 2020; 368: 350-351. DOI: 10.1126/science.368.6489.350. https://science.sciencemag.org/content/368/6489/350?utm_campaign=toc_sci-mag_2020-04-23&et_rid=321322875&et_cid=3300228

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