Opinion Paper

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COVID-19: making the right diagnosis

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Abstract: The commentary below was written by Dr. Gordon Schiff and Maria Mirica for the PRIDE (Primary Care Research in Diagnostic Errors) project, an initiative of the Betsy Lehman Center for Patient Safety and Brigham and Women's Hospital Center for Patient Safety Research and Practice with support from the Gordon and Betty Moore Foundation. It highlights some of the key issues related to diagnostic accuracy issues for COVID-19 and beyond.

Keywords: diagnostic error; differential diagnosis.

Test results: consequential false negatives and false positives

Health care providers and patients need to keep in mind that there are potentially serious issues and consequences related to diagnosing the COVID-19 infection. One of these issues is the potential for false negative test results for the infection. There are already more than 50 polymerase chain reaction (PCR) and serologic tests on the market. While the public has been clamoring for more and wider test availability, getting access to the test is only the first step in ensuring diagnostic testing accuracy. There are important concerns about imperfect ability of PCR viral testing, particularly its ability to rule out infection owing to its false negative rate, initially reported to be as high as 5–30% [1]. These rates of false negatives are reported to be higher in the highly desirable "rapid tests" being rolled out [2, 3]. Early reports of sensitivity of only 70%, meaning a 30% false negative rate, are due to the combined intrinsic laboratory limitations of the PCR test to detect the virus (the so called "*analytic*" sensitivity, which labs have been working to minimize and is generally quite good), but more importantly *clinical* factors such as collection technique and timing. Proper swab technique is quite technical [4] but has been considered essential for reducing false negative rates, especially when the specimens are collected during early stages of the infection and the concentration of the virus is lower.

Currently little is known about the characteristics of a myriad of emerging serologic tests which look for antibodies to provide evidence of prior infection and potential immunity. It will be especially important to know more about variations in lab techniques and products as they emerge, the optimal timing, and interpretation of the results, such as which detectable antibody levels confer immunity or ability to carry and spread infection. Consider the consequences of false positive results – telling a patient it is not necessary to isolate or protect themselves, when in fact they are still at risk for this potentially fatal infection.

Differential diagnoses

We need to remind ourselves that not every patient with malaise, pneumonia, cough, shortness of breath, or fever has COVID-19 infection. Currently there may be a high pretest likelihood we are dealing with coronavirus when a patient presents with these symptoms. But we can't forget about, for example, bacterial pneumonia, tuberculosis, endocarditis, HIV, or polymyalgia/temporal arteritis, all of which are serious conditions that require specific, urgent therapy. Such alternative "don't miss" diagnoses [5] need to be included in our differential diagnoses of presumptive COVID-19 infections, especially if there are atypical features or "red flags" [6] suggestive of alternate diagnoses warranting a different treatment. As the epidemic continues and our knowledge and experience with the varying typical and atypical ways COVID-19 infection presents grow, it is incumbent on us to become increasingly sophisticated in the way we diagnose this disease and avoid overlooking other diagnoses. Finally, there is the concern about the potential for co-infection [7] with more than one virus. We would not want to be distracted by our focus on the COVID-19 diagnosis and

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lack of specific treatment to the extent that we drop our guard and miss the opportunity to help patients in other major ways.

Remote diagnosis

As most of non-critical care has shifted to telemedicine, diagnosis over the telephone and video calls is becoming the new norm. We are learning a lot about how much we can do for patients, especially those we know well, in the virtual setting, rather than requiring them to come in for visits in person. And patients welcome the convenience of not having to leave home, miss work or school (especially once these reopen), pay for transportation and parking, and to avoid long waits and even be exposed to other potentially contagious patients. However, virtual diagnosis, in the absence of the hands-on physical exam, can be fraught with danger, as many things can be overlooked. For example, simple vital signs (how do we accurately measure pulse or respiratory rate?), subtle signs of respiratory distress (what is the sensitivity and specificity of "being able to talk in complete sentences"?), blood oxygenation (something we can routinely measure in clinic, but is challenging to do if a patient does not have a pulse oximeter at home) or air flow (does the patient have and know how to use a peak flow meter?) – these "vital sign" elements of physical exam can be challenging to implement in virtual care, but are critical for correct diagnosis. Other components of the physical exam, such as information from abdominal palpation and detection of abdominal masses, exam of lymph nodes, lung and cardiac auscultation, checking neurologic reflexes, sensory exams, and ENT examination, are all now being foregone in a virtual care visit and can contribute to missed diagnoses.

Secondary complications

Complications of COVID-19 and its treatment can be overlooked amid the pandemic frenzy, when we are all focused on diagnosing the disease itself. We should be mindful of some complications, such as QT prolongation [8] and cardiac arrhythmias [9, 10] from drug-drug interactions with widely used, though of doubtful efficacy, Hydroxychloroquine as well as pneumothorax from ventilator complications [11], and even suicide risk from depression from family loss. Social diagnoses that are generally on the rise will need to be diagnosed: depression, increases in domestic violence, and obesity from lack of exercise.

Test follow up

Dozens of developers are now working on antibody tests and they could be available shortly [12]. With any such varied sources of tests, the question is how will the results be documented, tracked, and properly followed-up? Any test, but especially critical ones, require "closing the loop" [13], where the results are delivered to the clinicians and patients in a timely, reliable manner. It is even more important to do so during the current pandemic. Perhaps this is the time for a true interoperable secure national registry of test results? Clinicians, with their patients' consent, would be able to access the results anytime needed, and patients should also be able to access their own results and provide documentation for any needed requirements since as employment or family decision-making. Although logical and intuitively obvious that we need such a simple central registry, this is something the US has worked for decades to achieve for vaccinations and even medications, but has been unable to deliver [14–17].

Leaders in the field of diagnostic error have often referred to ensuring reliable follow-up as the "low hanging fruit" for improving diagnosis safety. Tackling the so called "cognitive" errors is said to be much more challenging, yet but ensuring that test results, especially abnormal lab and radiology tests, are acknowledged, followed up, and communicated to patients should be relatively easy. However, it turns out to be not so simple, and we collectively are far from "six sigma" test follow-up reliability [18]. Perhaps COVID-19 can provide the will and the ways to collectively implement much more reliable systems to ensure results do not fall through the cracks as they not infrequently do with other tests.

Lapses in routine diagnostic and preventive care

There is serious danger of lapses in regular primary and preventive care due to putting on hold routine care [19–21]. There is already evidence that this is occurring due to the distractions and closures related to the urgent COVID-19 situation. Tests and referrals for patients for weight loss work-ups, who have blood in their stool, have swollen lymph nodes, or suspicious skin lesions are being deferred and canceled. When staff are pulled away from their clinics to work on inpatient COVID-19 units to deal with the crisis, the challenge for us as healthcare providers is ensuring we don't drop the ball.

Further, deferred colonoscopies, mammograms, pap smears, and retinal exams will inevitably lead to diagnostic

errors and delays in cancer diagnosis and preventable morbidity. To minimize the impact of such delays, we will need to create an inventory of deferred diagnostic evaluations to be rescheduled once the COVID-19 pandemic is under control and it is safe to perform them.

Conservative diagnosis

One of the prior activities of the PRIDE project was development of a 10-point model for approaching diagnosis more conservatively [22]. Many of these 10 principles seem particulary relevant in the COVID-19 era. We touch on just a few here.

Principle #1: Patients with anxiety and multiple somatic symptoms pose a real diagnostic challenge in the best of times due to a high prevalence of signal to noise. In the times of COVID-19 we must not be overly dismissive of such patients and their symptoms, lest we miss important organic etiologies, but create more anxiety related to false positive or incidental findings from unnecessary testing.

Principle #2: Learn ways to better deal with and communicate diagnostic uncertainty to patients. There is a lot we don't know about this new disease and the uncertainties about the diagnosis in a given patient. This calls for modesty, better communication approaches, and reliable follow-up safety nets. Even more than with other diagnoses we deal with every day in primary care, COVID-19 challenges us to hone our skills in this regard, particularly given the high level of anxiety patients experience in the face of this scary disease.

Principle #5: Creating better systems to operationalize "watchful waiting" is another conservative diagnosis domain that, by necessity, COVID-19 has thrust upon us. We cannot and should not fill emergency departments and hospital beds with every person who we suspect could have the infection. The new reality is caring for patients without a definite diagnosis by monitoring at home, symptom tracking and using simple tools such as pulse oximeters – a $30 device that should be much more widely available and used to detect when a patient's oxygen saturation drops.

Principle #6: We need to closely examine the relationship between diagnosis and treatment, only pursing tests when they will affect how the patient is treated. If you are going to treat all patients with flu-like symptoms and fever by careful home monitoring, social distancing, and serologic follow-up, perhaps there is no need to subject the patients to the harms of a test with high false negative result rates.

Bipartisan support and the precautionary principle: making a timely diagnosis

Historically, when it came to the national emergencies [23] or the environmental crisis [24], there was sound bipartisan support for precautionary public health and science-based approaches [25, 26]. Earlier in the epidemic, there was an opportunity to diagnose and isolate the first cases and make a more timely diagnosis of the grave threat that this new virus posed. In large part due to this delayed diagnosis, the U.S. became the #1 COVID-19 country in the world [27].

Moving forward, we see the need for a strong bipartisan effort – the two parties being health care workers and institutions on the one hand, and the patients and general public on the other. It has never been clearer that good diagnosis must be co-produced by both parties working together to share information, follow advice, closely monitor symptoms, advocate for each other, and err on the side of being both conservative and cautious. Making the right diagnosis of the current status of the epidemic to determine our next moves means we can be neither complacent nor complicit in rationing needed diagnostic evaluation and testing. Each party needs to continue and expand advocacy for needed resources, vital epidemiologic information, and science-based decision-making to assess both individual patients and the current national (and global) status of the COVID-19 pandemic.

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References

1. West CP, Montori VM, Sampathkumar P. COVID-19 testing: the threat of false-negative results. Mayo Clin Proc 2020;S0025-6196:30365–7.
2. Stein R. Study raises questions about false negatives from quick COVID-19 test; 2020. Available from: https://www.npr.org/sections/health-shots/2020/04/21/838794281/study-raises-questions-about-false-negatives-from-quick-covid-19-test.
3. Yang Y, Yang M, Shen C, Wang F, Yuan J, Li J, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. medRxiv 2020;20021493. https://doi.org/10.1101/2020.02.11.20021493.
4. Marty FM, Chen K, Verrill KA. How to obtain a nasopharyngeal swab specimen. N Engl J Med 2020;382:e76.
5. Bordi L, Nicastri E, Scorzolini L, Di Caro A, Capobianchi MR, Castilletti C, et al. Differential diagnosis of illness in patients under investigation for the novel coronavirus (SARS-CoV-2), Italy, February 2020. Euro Surveill 2020;25:2000170.
6. Ramanayake R, Basnayake B. Evaluation of red flags minimizes missing serious diseases in primary care. J Fam Med Prim Care 2018;7:315–8.
7. Xiaojing W, Ying C, Xu H, Xin Y, Li Z, Fan W, et al. Co-infection with SARS-CoV-2 and Influenza A virus in patient with pneumonia, China. Emerging Infect Dis J 2020;26:1324–6.
8. Borba MGS, Val FdA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). medRxiv 2020:20056424. https://doi.org/10.1101/2020.04.07.20056424.
9. Bessière F, Roccia H, Delinière A, Charrière R, Chevalier P, Argaud L, et al. Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with Hydroxychloroquine alone or in combination with Azithromycin in an intensive care unit. JAMA Cardiol 2020;e201787. https://doi.org/10.1001/jamacardio.2020.1787.
10. Simpson Timithy KR, Eric S. Ventricular arrhythmia risk due to Hydroxychloroquine-azithromycin treatment for COVID-19: cardiology magazine; 2020. Available from: https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19.
11. Hsu C-W, Sun S-F. Iatrogenic pneumothorax related to mechanical ventilation. World J Crit Care Med 2014;3:8–14.
12. Simon Malory YG. What are antibody tests and what do they mean for the coronavirus pandemic?. CNN Health 2020. Available from: https://www.cnn.com/2020/04/14/health/antibody-test-explainer/index.html.
13. Closing the loop: using health IT to mitigate delayed, missed, and incorrect diagnoses related to diagnostic testing and medication changes. ECRI Institute; 2018. https://www.ecri.org/Resources/HIT/Closing_Loop/Closing_the_Loop_Toolkit.pdf.
14. CDC. Keeping your vaccine record up to date; 2020. Available from: https://www.cdc.gov/vaccines/adults/vaccination-records.html.
15. CDC. About immunization information systems. Available from: https://www.cdc.gov/vaccines/programs/iis/about.html.
16. Schiff G, Mirica M, Dhavle A, Galanter W, Lambert B, Wright A. A prescription for enhancing electronic prescribing safety. Health Aff 2018;37:1877–83.
17. Myth busters: health information and the Law; 2015 [Available from: http://www.healthinfolaw.org/lb/download-document/6040/field_article_file.
18. Schiff GD. Eight questions for getting beyond "getting results". Jt Comm J Qual Patient Saf 2010;36:224–5.
19. Hoffman J. Vaccine rates drop dangerously as parents avoid doctor's visits; 2020. Available from: https://www.nytimes.com/2020/04/23/health/coronavirus-measles-vaccines.html.
20. Krumholz H. Where have ALl the heart attacks gone? 2020. Available from: https://www.nytimes.com/2020/04/06/well/live/coronavirus-doctors-hospitals-emergency-care-heart-attack-stroke.html.
21. Davenport L. Cancer diagnosis and treatment upended by COVID-19, says CRUK; 2020. Available from: https://www.medscape.com/viewarticle/929575.
22. Schiff G, Martin S, Eidelman D, Volk AL, Ruan E, Cassel C, et al. Ten principles for more conservative, care-full diagnosis. Ann Intern Med 2018;169:643–5.
23. Nelson C, Lurie N, Wasserman J, Zakowski S. Conceptualizing and defining public health emergency preparedness. Am J Public Health 2007;97:S9–11.
24. Curwood S, Parenteau P. Living on earth [internet]; 2020. Podcast. Available from: https://www.loe.org/shows/segments.html?programID=20-P13-00017&segmentID=4.
25. Read R, O'Riordan T. The precautionary principle under fire. Environment 2017;59:4–15.
26. Rose DA, Murthy S, Brooks J, Bryant J. The evolution of public health emergency management as a field of practice. Am J Public Health 2017;107:S126–33.
27. Sachs J. Why the US has the World's highest number of COVID-19 deaths? 2020. Available from: https://www.cnn.com/2020/04/12/opinions/coronavirus-us-death-toll-trump-sachs-opinion/index.html.