The Daily COVID-19 Literature Surveillance Summary

July 14, 2020

DISCLAIMER

This free and open source document represents a good faith effort to provide real time, distilled information for guiding best practices during the COVID-19 pandemic. This document is not intended to and cannot replace the original source documents and clinical decision making. These sources are explicitly cited for purposes of reference but do not imply endorsement, approval or validation.

This is not an official product or endorsement from the institutions affiliated with the authors, nor do the ideas and opinions described within this document represent the authors' or their affiliated institutions' values, opinions, ideas or beliefs. This is a good faith effort to share and disseminate accurate summaries of the current literature.

NOW LIVE!

Daily audio summaries of the literature in 10 minutes or less.
https://www.covid19lst.org/podcast/

COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

CLIMATE:

- An opinion article by Swiss physicians titled "Is Clinical Effectiveness in the Eye of the Beholder?" warns against the implementation of treatments with unsound and incomplete evidence, arguing they may violate the principle of non-maleficence, or 'do no harm'. Hydroxychloroquine as an example of a drug that was widely adopted based off minimal in-vitro studies and unscientific promotion in the media. There is now a consensus that it does not offer therapeutic benefit and may have caused unnecessary harm through dangerous QT prolongation and diminished supply for patients with autoimmune diseases. The authors suggest that until effective treatments are proven, we should rely on social distancing and ensuring scientific journals and researchers are held to a high standard.

EPIDEMIOLOGY:

- A simulation model estimating the possible effect widespread use of remdesivir in South Africa - where the death rate is estimated at 85%-100% among patients who cannot obtain intensive care due to the lack of available ICU beds – predicted a reduction in COVID-19 mortality by 635 to 6,862 deaths (out of a projected 36,383 to 47,820 ICU patients as estimated by the South African National COVID-19 Epidemiology model (NCEM). These results suggest that remdesivir may reduce mortality indirectly by reducing the duration of illness and freeing up ICU beds.

UNDERSTANDING THE PATHOLOGY:

- This study investigates possible resistance to fibrinolysis as an additional underlying mechanism of the hypercoagulability in COVID-19. Investigators analyzed thromboelastometry profiles from five COVID-19 patients in France both before and after recombinant plasminogen activator administration (r-tPA), compared to 5 control samples. Results revealed a longer time to fibrinolysis in the COVID-19 samples, and acute pulmonary embolism in three out of the five COVID-19 patients despite thromboprophylaxis. The authors recommend larger prospective studies to further evaluate the fibrinolytic pathways involved in COVID-19 and to identify successful treatments for coagulopathy in this setting.
- Dermatologists review a possible underlying mechanism between severe COVID-19 and obesity, particularly focusing on ACE2 downregulation in SARS-CoV-2 infection leading to increased angiotensin II (Ang II) and angiotensin II type 1 receptor axis (AT1R) activation. The authors hypothesize that increased adipose tissue, which is known to produce angiotensinogen, also increases Ang II, thus contributing to renin-angiotensin-system dysregulation. Based on this hypothesis, they suggest ACE inhibitors, ARBs, Mas receptor agonists (antagonists of angiotensin I), and recombinant ACE2 may benefit patients with COVID-19; particularly those with obesity or metabolic disease.

MANAGEMENT:

- A case series of nine COVID-19 patients presenting with neurological symptoms discovered a common MRI finding of microbleeds in an unusual distribution (most notably the corpus callosum) suggesting a mechanism of damage to the endothelium of brain vessels (thrombotic microangiopathy) by SARS-CoV-2.
- Authors from Icahn School of Medicine at Mount Sinai performed a retrospective, single-center case series of seven COVID-19 stroke patients monitored for malignant cerebral edema (MCE). They found that of the 3/7 patients who underwent decompressive hemicraniectomy (DHC), 2 had favorable outcomes, suggesting that COVID-19 patients suffering from severe stroke may benefit from DHC and should not be excluded solely due to a positive COVID-19 test.

ADUSTING PRACTCE DURING COVID-19:

- A review from the Department of Ophthalmology at Harvard Medical School outlines the benefits of tele-ophthalmology and Artificial Intelligence (AI) for patients, physicians, and payors. Although barriers do exist (mistrust in technology, infrastructure costs, medical liability), the authors suggest that further developments in tele-ophthalmology may lead to better detection and earlier management of ocular diseases. Additional benefits include increased accessibility of care for rural patients and underserved communities, successful remote care for eye emergencies with an ophthalmologist, and improved remote screening of chronic eye diseases such as diabetic retinopathy and glaucoma.

R&D DIAGNOSIS AND TREATMENT:

- An interdisciplinary group from across the United States details the key factors that influence the Positive Predictive Value (PPV) and the Negative Predictive Value (NPV) of diagnostic testing for COVID-19, with the goal of enabling healthcare providers to better understand the implications of a positive or negative COVID-19 test result in the context of an unknown true prevalence of the disease in the population. Three key points include:

- For low disease prevalence, the sensitivity doesn't play a large role in the PPV or NPV; instead, the focus must be on having a very high specificity in order to achieve a clinically usable PPV.
- For high disease prevalence, neither the sensitivity nor the specificity has a major impact on the PPV; however, high sensitivity is needed to obtain a clinically relevant NPV, so the focus here must be identification of a test with very high sensitivity.
- In the situation where prevalence is neither low nor high, the sensitivity tends to influence the PPV and the specificity tends to influence the NPV, so increasing utility of a test in this situation can focus on improving either the sensitivity or specificity, or both.

CLIMATE

IS CLINICAL EFFECTIVENESS IN THE EYE OF THE BEHOLDER DURING THE COVID-19 PANDEMIC?

Sandoval JL, Friedlaender A, Addeo A.. BMJ Evid Based Med. 2020 Jul 9:bmjebm-2020-111423. doi: 10.1136/bmjebm-2020-111423. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

An opinion article by providers in Switzerland warns against the implementation of treatments with unsound and incomplete evidence, arguing that it may violate the principle of non-maleficence, or 'do no harm'. The authors suggest that until effective treatments are proven, we should rely on social distancing and ensuring scientific journals and researchers are held to a high standard.

SUMMARY

The current COVID-19 pandemic has caused a rapid spread of false and inaccurate information, mainly due to the internet. In medicine, this has led to untested therapies being used to treat COVID-19 patients. This rapid implementation of treatments with unsound and incomplete evidence violates the principle of non-maleficence, or 'do no harm'. One example offered in this article is the use of chloroquine based on in-vitro evidence. This may lead to QT prolongation for many patients as well as drug shortages for patients who use chloroquine for other illnesses.

Until trials prove a therapy or a vaccine effective, we should rely on public health interventions such as social distancing, disinfecting surfaces, and improved hand hygiene. Additionally, efforts should be made to assure that scientific journals are held to a high standard and are publishing the most clinically-relevant studies.

HYDROXYCHLOROQUINE AND COVID-19: CRITIQUING THE IMPACT OF DISEASE PUBLIC PROFILE ON POLICY AND CLINICAL DECISION-MAKING

Aquino YSJ, Cabrera N.. J Med Ethics. 2020 Jul 9:medethics-2020-106306. doi: 10.1136/medethics-2020-106306. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

An opinion piece by experts from academic centers in Australia and Texas argues that non-clinical factors contributing to the the public profile of COVID-19 has become "a prominent, if not the sole" determinant in decision-making across various healthcare responses. The authors use the controversy surrounding the use of hydroxychloroquine (HCQ) to demonstrate how the COVID-19's public profile may undermine ethical concepts of evidence-based clinical practice, drive unsustainable resource allocation, and authorize structural forms of coercive consent.

SUMMARY

Insufficient Evidence

- The authors highlight the ethical impact of COVID-19's public profile on the unapproved or emergency use of HCQ to treat COVID-19, without sufficient clinical evidence. The authors point to the common agreement in the current literature that while there is uncertainty surrounding the effectiveness of HCQ to treat COVID-19, HCQ has sufficient potential to warrant randomized control trial (RCT) investigation. While awaiting the results of the HCQ RCT, the authors believe that there will be two main positions regarding HCQ: one that supports the HCQ off-label use, and one that does not consider the HCQ use and urges clinicians to provide supportive care alone to avoid possible adverse events from unproven therapy. The authors call to attention that supporting either position is by nature subjective and requires continued ethical scrutiny while awaiting results from RCT.

Unsustainable allocation:

- They argue that COVID-19's public profile has caused issues regarding resource allocation. The authors believe the government and hospital policies as well as public figure endorsement in HCQ to treat COVID-19 have created an issue surrounding the fair distribution of HCQ among its indicated use (i.e., malaria and lupus) and off-label use for COVID-19. The

authors highlight how one patient with lupus has been unable to receive HCQ prescription and was issued letters by her healthcare network stating that HCQ supply was being conserved for critical COVID-19 patients.

Coercive consent

- The authors argue that COVID-19's public profile influences patient consent to participate in research trials. When the US Food and Drug Administration (FDA) granted emergency authorization for HCQ, there was a shared concern that if off-label therapy of HCQ was offered outside the context of RCT, potential participants may be less motivated to enroll in a trial. Withholding an off-label HCQ may provide incentives for participants to enroll in RCT. However, the authors warn clinicians and administrators that withholding an off-label agent such as HCQ in the course of care functions as an inducement to consent to enroll in the RCT. Moreover, the authors call to attention that participants who may be randomized to the placebo arm may not have initially agreed to receive supportive care alone.

ABSTRACT

The controversy surrounding the use of hydroxychloroquine (HCQ), an antimalarial drug, for COVID-19 has raised numerous ethical and policy problems. Since the suggestion that HCQ has potential for COVID-19, there have been varying responses from clinicians and healthcare institutions, ranging from adoption of protocols using HCQ for routine care to the conduct of randomised controlled trials to an effective system-wide prohibition on its use for COVID-19. In this article, we argue that the concept of 'disease public profile' has become a prominent, if not the sole, determinant in decision-making across various healthcare responses to the pandemic. In the case of COVID-19, the disease's public profile is based on clinical and non-clinical factors that include contagiousness, clinical presentation and media coverage. In particular, we briefly examine the dangers of a heightened public profile in magnifying the inequality of diseases and undermining three key ethical concepts, namely (1) evidence-based practice, (2) sustainable allocation and (3) meaningful consent.

GLOBAL

SOLIDARITY IS FOR OTHER PEOPLE: IDENTIFYING DERELICTIONS OF SOLIDARITY IN RESPONSES TO COVID-19

West-Oram P.. J Med Ethics. 2020 Jul 9:medethics-2020-106522. doi: 10.1136/medethics-2020-106522. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A professor of bioethics at Brighton and Sussex Medical School (UK) states that universal solidarity (defined as a commitment to accept costs to help others due to a collective respect) was lacking in both individual, and to a greater extent, government response to the COVID-19 pandemic in the UK. Based on the observed failures (listed below), the author emphasizes the importance of governments supporting solidarity in their citizenry during times of crisis.

SUMMARY

The author discusses several ways in which the government failed to promote solidarity, including:
1) Defunding the British National Health Service (NHS) and limiting NHS's use of public funds to aid in the pandemic response.
2) Failing to properly inform the public of reasons why engaging in solidarity is necessary.
3) Failing to remove physical barriers to solidarity engagement (i.e. providing funds so people could stay at home from work).

ABSTRACT

The role and importance of solidarity for effective health provision is the subject of lengthy and heated debate which has been thrown into even sharper relief by the COVID-19 pandemic. In various ways, and by various authorities we have all been asked, even instructed, to engage in solidarity with one another in order to collectively respond to the current crisis. Under normal circumstances, individuals can engage in solidarity with their compatriots in the context of public health provision in a number of ways, including paying taxes which fund welfare state initiatives, and avoiding others when ill. While there has been significant engagement in solidarity worldwide, there have also been high profile examples of refusals and failures to engage in solidarity, both by individual agents, and governments. In this paper I examine the consequence of these failures with reference to the actions of the current British government, which has failed to deliver an effective response to the crisis. This failure has effectively devolved responsibility for responding to the crisis to people who are simultaneously more vulnerable to infection, and less able to do anything about it. I argue that such responses represent mismanagement of a public health crisis, and a rejection of important democratic and egalitarian norms and values.

COVID-19: LESSONS IN RISK COMMUNICATION AND PUBLIC TRUST

Nutbeam D.. Public Health Res Pract. 2020 Jun 30;30(2):3022006. doi: 10.17061/phrp3022006.
Level of Evidence: Other - Expert Opinion

BLUF

In this editorial, an Australian public health researcher argues that the countries that have fared best during the COVID-19 pandemic are those where governmental leaders have communicated advice to the public with "clarity and consistency", based on the best available public health research. The author goes on to claim that as the pandemic progresses in to second and third waves, governments will need to adjust their communication strategies in more "nuanced and targeted" ways. He concludes by pointing readers toward four papers published in this same journal.

SUMMARY

The four recommended articles cover the following topics:
1. Leask & Hooker 2020 outlines challenges with communication about the risks of school attendance for children and offers practical suggestions moving forward.
2. Currie et al. 2020 models the potential impact of a smartphone app in limiting transmission during a second wave.
3. Smith & Lim 2020 investigates the impact of ongoing social distancing measures on mental health outcomes.
4. Ratzan et al. 2020 explores challenges faced by public health communicators and offers strategies as the pandemic shifts from an acute phase into the "next normal."

THE ROLE OF REMDESIVIR IN SOUTH AFRICA: PREVENTING COVID-19 DEATHS THROUGH INCREASING ICU CAPACITY

Nichols BE, Jamieson L, Zhang SRC, Rao GA, Silal S, Pulliam JRC, Sanne I, Meyer-Rath G.. Clin Infect Dis. 2020 Jul 6:ciaa937. doi: 10.1093/cid/ciaa937. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

A Monte-Carlo simulation modeling study conducted by an international group of researchers found that the use of remdesivir in ICU patients in South Africa - in a situation where the death rate is assumed to be 85%-100% among patients who need ICU care but cannot obtain it due to the lack of available ICU beds - would reduce the death count of COVID-19 patients by 635 to 6,862 deaths (out of a projected 36,383 to 47,820 ICU patients as estimated by the South African National COVID-19 Epidemiology model (NCEM); Figure 1). These results suggest that remdesivir saves lives partially through reducing the number of ICU days needed per patient, therefore allowing for quicker patient turnover and more ICU beds available for newer, sicker patients. As the findings rely on assumptions of preliminary mortality benefit based on early clinical trials, the authors note that additional research is needed to create more precise estimates of benefit.

ABSTRACT

Countries such as South Africa have limited intensive care unit (ICU) capacity to handle the expected number of COVID-19 patients requiring ICU care. Remdesivir can prevent deaths in countries such as South Africa by decreasing the number of days people spend in ICU, therefore freeing up ICU bed capacity.

FIGURES

Figure 1

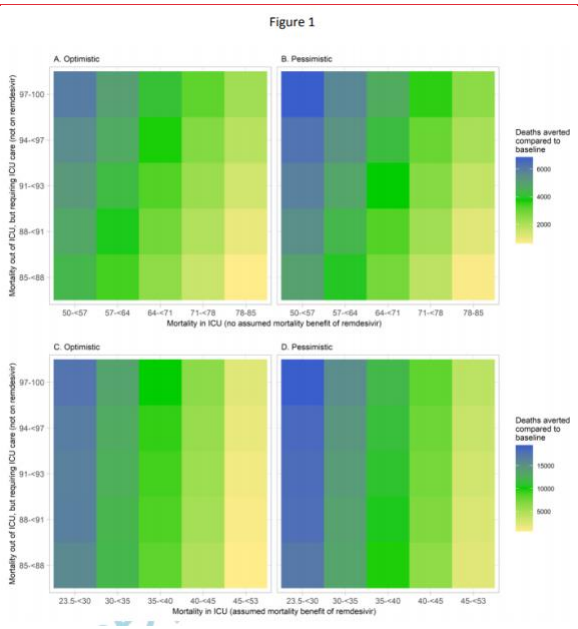

Figure 1. Mortality estimates for use of remdesivir (vs. no remdesivir) in COVID-19 ICU patients.

ADULTS

CHANGES IN RT-PCR TEST RESULTS AND SYMPTOMS DURING THE MENSTRUAL CYCLE OF FEMALE INDIVIDUALS INFECTED WITH SARS-COV-2: REPORT OF TWO CASES

Zheng H, Tan J, Ma K, Meng W.. J Med Virol. 2020 Jul 8. doi: 10.1002/jmv.26275. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

Authors affiliated with Tongji Medical College and University of Dundee present case reports on 2 women infected with SARS-CoV-2 in late January 2020 in China whose symptoms and COVID-19 test results varied with their menstrual cycles. Patient 1, who had a fever beginning on day 1 of menstrual cycle, had symptom remission following treatment yet developed fever again day 1 of her next cycle. Patient 1 also had a positive RT-PCR test during both menstrual cycles but a negative RT-PCR during hospitalization (Figure 1). Patient 2 had a similar progression with exception being that chest CT and history yielded a clinical COVID-19 diagnosis (despite a negative RT-PCR). Although further research is needed, these findings suggest that COVID-19 may affect women in a hormone-dependent manner and tracking of menstrual cycles in women with COVID-19 may be beneficial in practice.

ABSTRACT

BACKGROUND: The implications of the menstrual cycle for disease susceptibility, development, and severity of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are largely unknown. CASE PRESENTATION: Here we describe two women infected with SARS-CoV-2 whose RT-PCR test results and symptoms changed during the menstrual cycle. The first patient developed a fever on the first day of her menstrual period, and again on the first day of her next menstrual period after hospital discharge. RT-PCR test results were positive during the first menstrual period before admission, but turned negative during hospitalization, and then were positive again during the second menstrual period after hospital discharge. Another one also developed a fever again on the first day of her menstrual period after hospital discharge. RT-PCR test results were negative before admission and during hospitalization, but turned positive during the first menstrual period after hospital discharge. CONCLUSIONS: The cases indicate sex hormones may play an important role in SARS-CoV-2 infection. For women with history of exposure to SARS-CoV-2, the management protocol should include assessment of the menstrual status. This article is protected by copyright. All rights reserved.

FIGURES

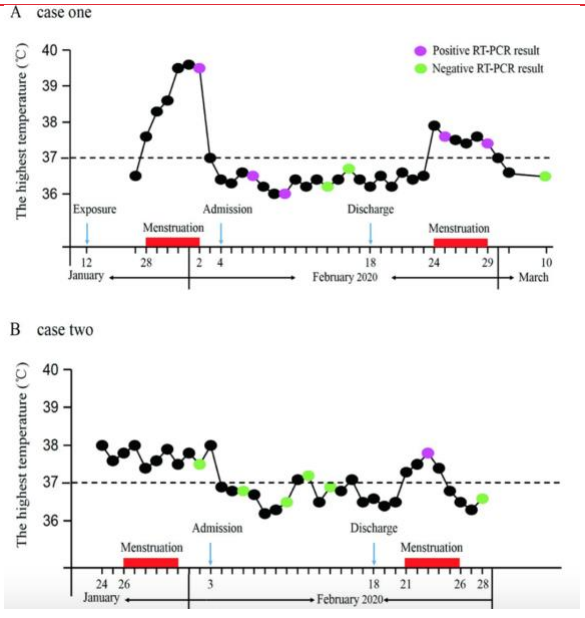

Figure 1. Timeline of changes of RT-PCR test results and symptoms during the menstrual cycle of cases infected with SARS-CoV-2. Case one (A). (A) Sixteen days after exposure to SARS-CoV-2, fever occurred on the first day of her menstrual period, and again on the first day of her next menstrual period after hospital discharge. RT-PCR test results were positive during the first menstrual period before admission, turned negative during hospitalization, and then positive again during the second menstrual period, which occurred after hospital discharge. Case two (B). (B) Fever occurred two days before her menstrual period, and again on the first day of her next menstrual period after hospital discharge. RT-PCR test results were negative before admission and during hospitalization, but turned positive during the first menstrual period after hospital discharge. RT-PCR indicates real time polymerase chain reaction test for the coronavirus disease 2019 (COVID-19) nucleic acid.

UNDERSTANDING THE PATHOLOGY

FIBRINOLYSIS RESISTANCE: A POTENTIAL MECHANISM UNDERLYING COVID-19 COAGULOPATHY

Weiss E, Roux O, Moyer JD, Paugam-Burtz C, Boudaoud L, Ajzenberg N, Faille D, de Raucourt E.. Thromb Haemost. 2020 Jul 9. doi: 10.1055/s-0040-1713637. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

This study investigates possible resistance to fibrinolysis as an additional underlying mechanism of the hypercogauability seen in COVID-19 patients. Investigators used thromboelastometry profiles from five COVID-19 patients who received care at Beaujon University Hospital, France between April 21st, 2020 and May 4th, 2020, both before and after recombinant plasminogen activator administration (r-tPA), and compared the profiles to 5 control samples from healthy individuals (Figure 1), with results revealing:
1. When adding r-tPA to the assays, all control samples induced fibrinolysis within 60 minutes, while a longer time to fibrinolysis was observed in the COVID-19 patient samples.
2. Three out of the five COVID-19 patients developed an acute pulmonary embolism during the follow-up period despite thromboprophalaxis.
The authors indicate that larger prospective studies are needed to better evaluate the fibrinolytic pathways involved in COVID-10 and to identify successful treatments for coagulopathy in this setting.

FIGURES

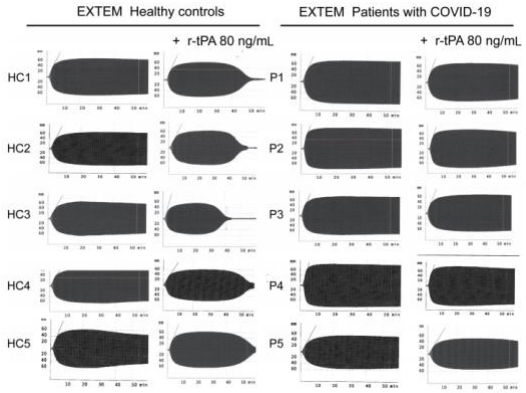

Figure 1. Thromboelastometry profiles of patients with COVID-19 and of healthy controls in the presence and absence of recombinant tissue plasminogen activator (r-tPA). HC, healthy control; P, patient.

MOLECULAR MECHANISMS OF SEX BIAS DIFFERENCES IN COVID-19 MORTALITY

Li Y, Jerkic M, Slutsky AS, Zhang H.. Crit Care. 2020 Jul 9;24(1):405. doi: 10.1186/s13054-020-03118-8.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

This article by medical institutions in China and Canada discusses potential mechanisms behind the reduced fatality rate of COVID-19 infection in females compared to that of males. Various genes including angiotensin converting enzyme 2 (ACE2) and toll-like receptor (TLR) genes are encoded on the X-chromosome, potentially providing greater protection from infection. Estrogen is also proposed to play a role in mounting a stronger and more effective immune response, compared to the immunosuppressive effect of androgens, suggesting the potential use of estrogen-related compounds along with androgen receptor antagonists to treat COVID-19 (Figure 1).

ABSTRACT

More men than women have died from COVID-19. Genes encoded on X chromosomes, and sex hormones may explain the decreased fatality of COVID-19 in women. The angiotensin-converting enzyme 2 gene is located on X chromosomes. Men, with a single X chromosome, may lack the alternative mechanism for cellular protection after exposure to SARS-CoV-2. Some Toll-like receptors encoded on the X chromosomes can sense SARS-CoV-2 nucleic acids, leading to a stronger innate immunity response in women. Both estrogen and estrogen receptor-alpha contribute to T cell activation. Interventional approaches including estrogen-related compounds and androgen receptor antagonists may be considered in patients with COVID-19.

FIGURES

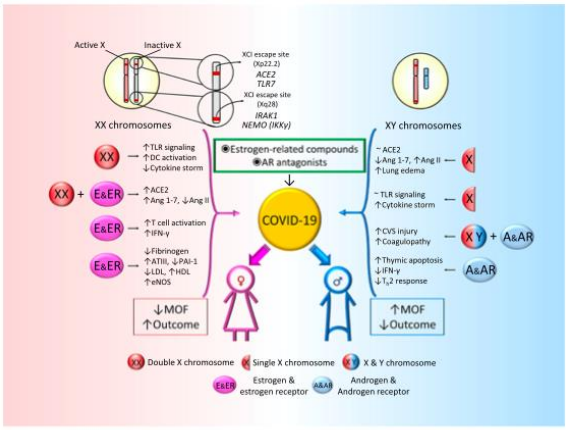

Fig. 1 Main mechanisms responsible for increased immune activity in females, providing a survival advantage in COVID-19. In females, the second X chromosome is randomly silenced during X chromosome inactivation (XCI) in order to minimize duplication of proteins encoded by X-linked genes. However, several genes bypass this inactivation. The ACE2 gene location on Xp22.2 is known to avoid X-inactivation, contributing to phenotypic differences between sexes. IRAK1 and IKKγ are also encoded on the XCI escaping sites, which may confer an advantage in responding to and resolving SARS-CoV-2 infections in females. The X chromosome has numerous genes involved in immunity. Naturally occurring variations in one gene copy might result in two distinct alleles with different regulatory and response capacities, suggesting that females, but nor males, may not only avoid the effects of deleterious gene mutations, but also benefit from added physiological diversity when facing new immune challenges, such as SARS-COV-2 infections. Estrogen and estrogen receptor signaling play a crucial role in both innate and adaptive immune responses as well as in tissue repairing processes during respiratory virus infection. Sex-based targeted therapeutic and interventional approaches such as estrogen-related compounds and androgen receptor antagonists may be considered in patients with COVID-19. ACE2: angiotensin-converting enzyme 2; TLR7: Toll-like receptor 7; IRAK1: Interleukin-1 receptor-associated kinase 1; NEMO (IKKγ): NF-kappa-B essential modulator (inhibitor of nuclear factor kappa-B kinase subunit gamma); DC: dendritic cell; TLR: Toll-like receptor; Ang 1–7: angiotensin 1-7; Ang II: angiotensin II; IFN-γ: interferon gamma; ATIII: antithrombin III; PAI-1: plasminogen activator inhibitor-1; LDL: low-density lipoprotein; HDL: low-density lipoprotein; eNOS: endothelial nitric oxide synthase; CVS: cardiovascular system; $T_{H}2$: Type 2 helper T cells; MOF: multiorgan failure

ANGIOTENSIN II RECEPTORS - IMPACT FOR COVID-19 SEVERITY

Aksoy H, Karadag AS, Wollina U.. Dermatol Ther. 2020 Jul 9:e13989. doi: 10.1111/dth.13989. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Dermatologists from Turkey and Germany review possible factors underlying the link between severe COVID-19 and obesity, particularly focusing on ACE2 downregulation in SARS-CoV-2 infection leading to increased angiotensin II (Ang II) and angiotensin II type 1 receptor axis (AT1R) activation (Figure 1). The authors hypothesize that increased adipose tissue, which is known to produce angiotensinogen, also increases Ang II and, thus, contributes to renin-angiotensin-system dysregulation in SARS-CoV-2 infection (Figure 2). Based on this hypothesis, they suggest ACE inhibitors, ARBs, Mas receptor agonists (antagonists of angiotensin I), and recombinant ACE2 may benefit patients with COVID-19; particularly those with obesity or metabolic disease.

ABSTRACT

COVID-19 is an outbreak of viral pneumonia which became a global health crisis, and the risk of morbidity and mortality of people with obesity are higher. SARS-CoV-2, the pathogen of COVID-19, enters into cells through binding to the Angiotensin Converting Enzyme (ACE) homolog-2 (ACE2). ACE2 is a regulator of two contrary pathways in renin angiotensin system (RAS): ACE-Ang-II-AT1R axis and ACE2-Ang 1-7-Mas axis. Viral entry process eventuate in downregulation of ACE2 and subsequent activation of ACE-Ang-II-AT1R axis. ACE-Ang II-AT1R axis increases lipid storage, reduces white-to-beige fat conversion and plays role in obesity. Conversely, adipose tissue is an important source of angiotensin, and obesity results in increased systemic RAS. ACE-Ang-II-AT1R axis, which has proinflammatory, profibrotic, prothrombotic and vasoconstrictive effects, is potential mechanism of more severe SARS-CoV-2 infection. The link between obesity and severe COVID-19 may be attributed to ACE2 consumption and subsequent ACE-Ang-II-AT1R axis activation. Therefore, patients with SARS-CoV-2 infection may benefit from therapeutic strategies that activate ACE2-Ang 1-7-Mas axis, such as Ang II reseptor blockers (ARBs), ACE inhibitors (ACEIs), Mas receptor agonists and ACE2.

FIGURES

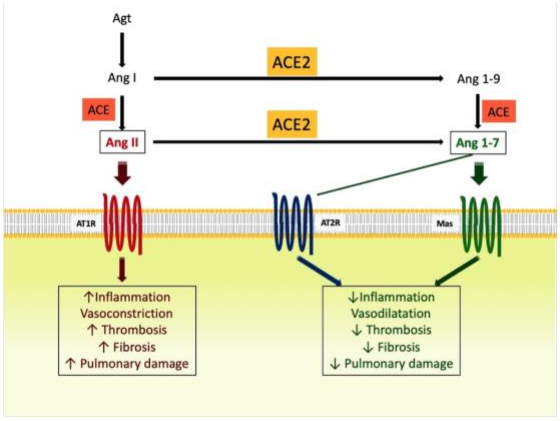

Fig. 1

Figure 1. Effects of Ang II and Ang 1-7 in the course of COVID-19.

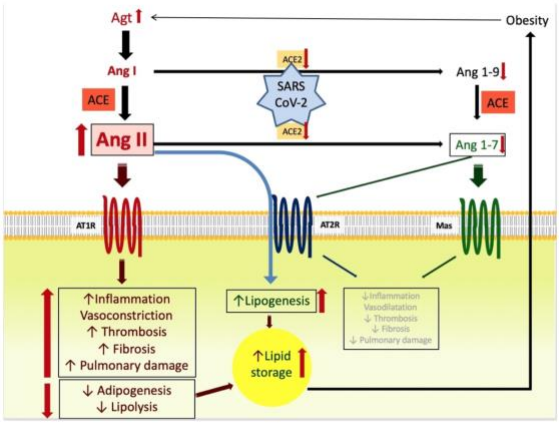

Fig. 2

Figure 2. Dysregulation of RAS in COVID-19 patients with obesity and potential link between obesity and more severe disease.

NEUROLOGY

UNUSUAL MICROBLEEDS IN BRAIN MRI OF COVID-19 PATIENTS

Fitsiori A, Pugin D, Thieffry C, Lalive P, Vargas MI.. J Neuroimaging. 2020 Jul 8. doi: 10.1111/jon.12755. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

In a case series by authors at University Hospitals of Geneva and Faculty of Medicine of Geneva, Switzerland enrolled 9 SARS-CoV-2 positive patients presenting with neurological symptoms and discovered a common MRI finding of microbleeds in an unusual distribution (most notably the corpus callosum; Figure 1, 2) suggesting a mechanism of damage to the endothelium of brain vessels (thrombotic microangiopathy) by SARS-CoV-2.

SUMMARY

This study enrolled 9 patients (2 women/7 men, mean age: 67.7 years) infected with SARS-CoV-2 (confirmed via polymerase chain reaction) and presenting with neurological symptoms (delayed recovery of consciousness or psychomotor agitation) who subsequently underwent brain MRI showing a common finding of microbleeds in atypical distribution. The most significant location was the corpus callosum, while other locations included the internal capsule, middle cerebellar peduncles, and subcortical white matter. Authors suggest a most likely mechanism of brain vessel endothelium injury by SARS-CoV-2, as previously proposed by Li and Huang et al. (2020) and Baig et al. (2020) but also discuss possible mechanisms such as SARS-CoV-2 induced hypercoagulability leading to microthrombi, and microbleeds resulting from diffuse axonal injury or fat embolism. Though further research is needed, the observations in this study highlight potential mechanisms of neurological manifestations and brain involvement in those with COVID-19.

ABSTRACT

BACKGROUND AND PURPOSE: Covid-19, initially described as a respiratory system's infection, is currently more and more recognized as a multiorganic disease, including neurological manifestations. There is growing evidence about a potential neuroinvasive role of SARS-CoV-2. The purpose of this study is to describe new findings, in the form of cerebral microbleeds affecting different brain structures, observed in MRIs of critically ill patients. METHODS: For this purpose, the MR images of 9 patients with a common pattern of abnormal findings (2 women/7 men; 55-79 years of age; mean age: 67.7 years) were depicted. All patients were tested positive for SARS-CoV-2 and presented with delayed recovery of consciousness or important agitation, requiring brain MRI. RESULTS: All patients had suffered from severe (5/9) or moderate (4/9) acute respiratory distress syndrome, requiring prolonged stay in the intensive care unit. Their common MRI finding was the presence of microbleeds in unusual distribution with a specific predilection for the corpus callosum. Other uncommon locations of microbleeds were the internal capsule (5/9), as well as middle cerebellar peduncles (5/9). Subcortical regions were also affected in the majority of patients. CONCLUSIONS: Brain MRI raised evidence that Covid-19 or its related treatment may involve the brain with an unusual pattern of microbleeds, predominantly affecting the corpus callosum. The mechanism of this finding is still unclear but the differential diagnosis should include thrombotic microangiopathy related to direct or indirect-through the cytokine cascade-damage by the SARS-CoV-2 on the endothelium of brain's vessels, as well as mechanisms similar to the hypoxemia brain-blood-barrier injury.

FIGURES

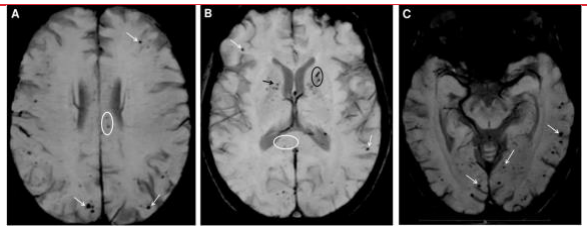

Figure 1: Multiple hypoattenuating foci involving the subcortical white matter (white arrows in A-C), as well as the corpus callosum (white ellipse in A and B), the anterior limb of the internal capsule (black arrow in B) and both middle cerebellar peduncles (not shown here), observed in susceptibility weighted imaging of the brain MRI of a 56-year-old woman. Interestingly, some of the lesions present a more linear shape, opening a differential diagnosis of microthrombi within vessels (black ellipse in B).

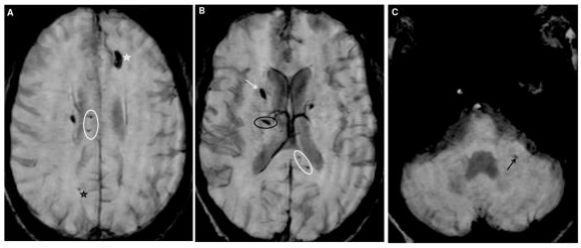

Figure 2: Brain MRI findings of a 66-year-old man include multiple microbleeds, involving the corpus callosum (white ellipse in A and B), the anterior limb of the right internal capsule (white arrow in B), the left middle cerebellar peduncle (black arrow in C), the basal ganglia (black ellipse in B), subcortical white matter (black star in A), as well as one left frontal macrobleed (white star in A). Similarly to the previous patient, some of the lesions appear linear (black ellipse in B).

SURGICAL SUBSPECIALTIES

NEUROSURGERY

COVID-19 AND DECOMPRESSIVE HEMICRANIECTOMY FOR ACUTE ISCHEMIC STROKE

Liang JW, Reynolds AS, Reilly K, Lay C, Kellner CP, Shigematsu T, Gilligan J, Majidi S, Al-Mufti F, Bederson JB, Mocco J, Dhamoon MS, Dangayach NS; Mount Sinai Stroke Investigators.. Stroke. 2020 Jul 8:STROKEAHA120030804. doi: 10.1161/STROKEAHA.120.030804. Online ahead of print.
Level of Evidence: 4 - Case-series or case control studies, or poor quality prognostic cohort study

BLUF

Authors from Icahn School of Medicine at Mount Sinai and Westchester Medical Center performed a retrospective, single-center case series of 7 COVID-19 stroke patients monitored for malignant cerebral edema (MCE) between March 24 to April 30, 2020. They found that 4/7 patients died due to COVID-19-related complications and 3/7 patients underwent decompressive hemicraniectomy (DHC), from which 2 had favorable outcomes (Figure). Authors suggest that COVID-19 patients suffering from severe stroke can benefit from DHC and should not be excluded from this intervention solely due to a positive COVID-19 test.

ABSTRACT

BACKGROUND AND PURPOSE: Young patients with malignant cerebral edema have been shown to benefit from early decompressive hemicraniectomy. The impact of concomitant infection with coronavirus disease 2019 (COVID-19) and how this should weigh in on the decision for surgery is unclear. METHODS: We retrospectively reviewed all COVID-19-positive patients admitted to the neuroscience intensive care unit for malignant edema monitoring. Patients with >50% of middle cerebral artery involvement on computed tomography imaging were considered at risk for malignant edema. RESULTS: Seven patients were admitted for monitoring of whom 4 died. Cause of death was related to COVID-19 complications, and these were either seen both very early and several days into the intensive care unit course after the typical window of malignant cerebral swelling. Three cases underwent surgery, and 1 patient died postoperatively from cardiac failure. A good outcome was attained in the other 2 cases. CONCLUSIONS: COVID-19-positive patients with large hemispheric stroke can have a good outcome with decompressive hemicraniectomy. A positive test for COVID-19 should not be used in isolation to exclude patients from a potentially lifesaving procedure.

FIGURES

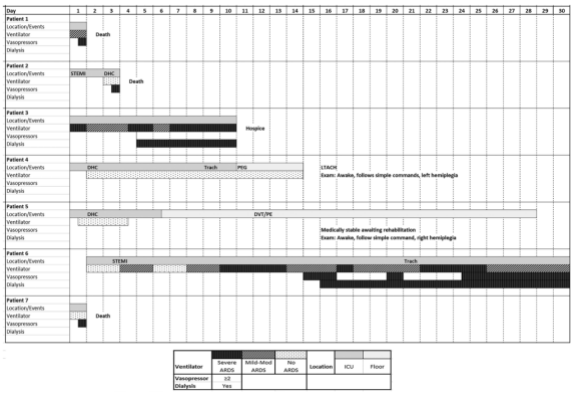

Figure. Hospital course of coronavirus disease 2019 (COVID-19) patients admitted for malignant cerebral edema monitoring. ARDS indicates acute respiratory distress syndrome; DHC, decompressive hemicraniectomy; DVT, deep vein thrombosis; ICU, intensive care
unit; LTACH, long-term acute care hospital; Mod, moderate; PE, pulmonary embolism; PEG, percutaneous endoscopic gastrostomy; and STEMI, ST-segment–elevation myocardial infarction.

ADVANCES IN TELEMEDICINE IN OPHTHALMOLOGY

Parikh D, Armstrong G, Liou V, Husain D.. Semin Ophthalmol. 2020 Jul 9:1-6. doi: 10.1080/08820538.2020.1789675. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review from the Department of Ophthalmology at Harvard Medical School outlines the benefits of tele-ophthalmology and Artificial Intelligence (AI) for patients, physicians, and payors (summarized below). Although barriers do exist (mistrust in technology, infrastructure costs, medical liability, etc.), the authors suggest that further developments in tele-ophthalmology and AI may lead to better detection and earlier management of ocular diseases.

SUMMARY

Benefits of tele-ophthalmology and AI include increased care accessibility (for rural patients, underserved communities, etc.), successful remote care for eye emergencies with an ophthalmologist who could also make appropriate triage decisions (versus emergency room care with non-ophthalmologist physician), decreased demand on emergency room providers, reduced costs, enhanced ability to serve a large patient population, and improved remote screening of multiple eye diseases (diabetic retinopathy, glaucoma, etc.).

ABSTRACT

Telemedicine is the provision of healthcare-related services from a distance and is poised to move healthcare from the physician's office back into the patient's home. The field of ophthalmology is often at the forefront of technological advances in medicine including telemedicine and the use of artificial intelligence. Multiple studies have demonstrated the reliability of tele-ophthalmology for use in screening and diagnostics and have demonstrated benefits to patients, physicians, as well as payors. There remain obstacles to widespread implementation, but recent legislation and regulation passed due to the devastating COVID-19 pandemic have helped to reduce some of these barriers. This review describes the current status of tele-ophthalmology in the United States including benefits, hurdles, current programs, technology, and developments in artificial intelligence. With ongoing advances patients may benefit from improved detection and earlier treatment of eye diseases, resulting in better care and improved visual outcomes.

LABORATORY ASSAY EVALUATION DEMYSTIFIED: A REVIEW OF KEY FACTORS INFLUENCING INTERPRETATION OF TEST RESULTS USING DIFFERENT ASSAYS FOR SARS-COV-2 INFECTION DIAGNOSIS

Pham HP, Staley EM, Raju D, Marin MJ, Kim CH.. Lab Med. 2020 Jul 7:lmaa045. doi: 10.1093/labmed/lmaa045. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

An article written by a group of researchers from across the United States sought to explain the key factors that influence the Positive Predictive Value (PPV) and the Negative Predictive Value (NPV) of any given diagnostic test for COVID-19, with the goal of enabling healthcare providers to better understand the implications of a positive or negative COVID-19 test result in the context of an unknown true prevalence of the disease in the population. Three key points include:

1. For low disease prevalence, the sensitivity doesn't play a large role in the PPV or NPV; instead, the focus must be on having a very high specificity in order to achieve a clinically usable PPV (Figure 1).
2. For high disease prevalence, neither the sensitivity nor the specificity have a major impact on the PPV; however, high sensitivity is needed to obtain a clinically relevant NPV, so the focus here must be identification of a test with very high sensitivity (Figure 2).
3. In the situation where prevalence is neither low nor high, the sensitivity tends to influence the PPV and the specificity tends to influence the NPV (Figure 3), so increasing utility of a test in this situation can focus on improving either the sensitivity or specificity, or both.

ABSTRACT

Laboratory tests are an integral part of the diagnosis and management of patients; however, these tests are far from perfect. Their imperfections can be due to patient health condition, specimen collection, and/or technological difficulty with performing the assay and/or interpretation. To be useful clinically, testing requires calculation of positive predictive values (PPVs) and negative predictive values (NPVs). During the current global pandemic of COVID-19 (coronavirus disease 2019), multiple assays with unknown clinical sensitivity and specificity have been rapidly developed to aid in the diagnosis of the disease. Due to a lack of surveillance testing, the prevalence of COVID-19 remains unknown. Hence, using this situation as an clinical example, the goal of this article is to clarify the key factors that influence the PPV and NPV yielded by diagnostic testing, By doing so, we hope to offer health-care providers information that will help them better understand the potential implications of utilizing these test results in clinical patient management.

FIGURES

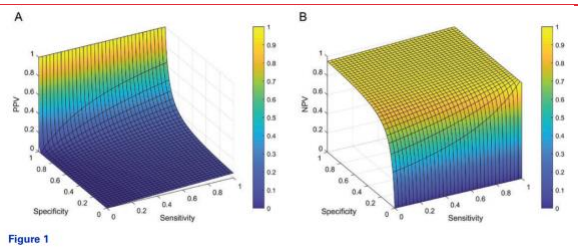

Figure 1

Figure 1. Positive predictive value (PPV) and negative predictive value (NPV) as a function of sensitivity and specificity when the prevalence of the disease is 5%. A, As seen in this graph, specificity is the most important factor in the PPV when the disease prevalence is low. The PPV almost does not change significantly across the range of sensitivities of the assay. Nevertheless, the specificity must be close to 100% to obtain good PPV, and its effect on PPV is exponential (i.e., small decrease in specificity leads to very large decrease in PPV). B, When the disease prevalence is low (5% in this example), sensitivity and specificity (as long as specificity is approximately less than 0.4) do not have a major effect on NPV.

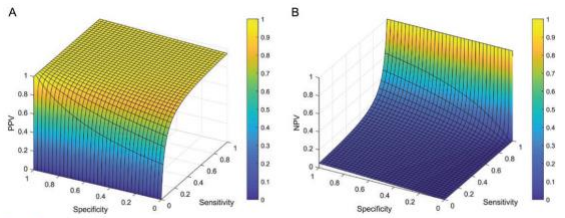

Figure 2

Figure 2. Positive predictive value (PPV) and negative predictive value (NPV) as a function of sensitivity and specificity when the prevalence of the disease is 95%. A, When the disease prevalence is high, sensitivity (as long sensitivity is approximately >0.4) and specificity do not have a major effect on PPV. B, As seen in this graph, sensitivity is the most important factor in the NPV when the disease prevalence is high (95% in this example). The NPV almost does not change significantly across the range of specificities of the assay. Nevertheless, the sensitivity must be close to 100% to obtain good NPV, and its effect on NPV is exponential (ie, small decrease in sensitivity leads to large decrease in NPV).

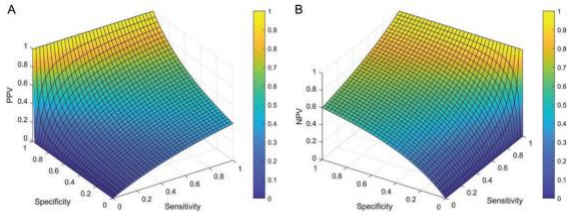

Figure 3

Figure 2. Positive predictive value (PPV) and negative predictive value (NPV) as a function of sensitivity and specificity when the prevalence of the disease is 95%. A, When the disease prevalence is high, sensitivity (as long sensitivity is approximately >0.4) and specificity do not have a major effect on PPV. B, As seen in this graph, sensitivity is the most important factor in the NPV when the disease prevalence is high (95% in this example). The NPV almost does not change significantly across the range of specificities of the assay. Nevertheless, the sensitivity must be close to 100% to obtain good NPV, and its effect on NPV is exponential (ie, small decrease in sensitivity leads to large decrease in NPV).

ACKNOWLEDGEMENTS

CONTRIBUTORS

Carter Butuk
Colin Bartz-Overman
Jesse Abelson
Maryam Naushab
Priscilla Natcher
Renate Meckl
Shayan Ebrahimian
Simran Mand
Tina Samsamshariat
Tyler Gallagher
Veronica Graham

EDITORS

Alvin Rafou
Cameron Richards
Julie Tran
Maggie Donovan
Marjorie Thompson
Michelle Arnold

SENIOR EDITORS

Allison Hansen
Ann Staudinger Knoll
Charlotte Archuleta
Kyle Ellingsen
Sangeetha Thevuthasan

EXECUTIVE SENIOR EDITOR

Stephen Ferraro

CHIEF EDITOR

Jasmine Rah

ADVISOR

Will Smith