A proposal for the return to routine endoscopy during the COVID-19 pandemic

Short Title: Endoscopy during the COVID-19 pandemic

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Abstract

In response to the COVID-19 pandemic, many jurisdictions and gastroenterological societies around the world have suspended nonurgent endoscopy. Subject to country-specific variability, it is projected that with current mitigation measures in place, the peak incidence of active COVID-19 infections may be delayed by over 6 months. Although this aims to prevent the overburdening of healthcare systems, prolonged deferral of elective endoscopy will become unsustainable. Herein, we propose that by incorporating readily available point-of-care tests and conducting accurate clinical risk assessments, a safe and timely return to elective endoscopy is feasible. Our algorithm not only focuses on the safety of patients and healthcare workers, but also assists in rationalizing the use of invaluable resources such as personal protective equipment.

Introduction: COVID-19 and Endoscopy

In December 2019, a novel coronavirus termed SARS-CoV-2 emerged from a suspected zoonotic source in Wuhan, China. Driven by its ability to spread through respiratory droplets, including by asymptomatic individuals, SARS-CoV-2 has rapidly traversed international borders to infect over 1.5 million people in over 200 countries.[1] Now termed as coronavirus disease-19 (COVID-19) by the World Health Organization (WHO), it is the first coronavirus to be declared a global pandemic and carries a mortality rate of 1% to 10%.[1,2] In order to curtail the spread of COVID-19, restrictive measures have been implemented worldwide. This has included the closure of international borders, country-wide lockdowns, limitations on gatherings, social distancing and the quarantining of any suspected or confirmed COVID-19 cases.[3] The overarching intention of these measures is to “flatten the curve,” ie, reduce the peak incidence of active COVID-19 infections and hospitalizations so that healthcare systems are not overburdened. Unfortunately, healthcare workers (HCWs) remain up to 3 times more likely to contract COVID-19 than the general population,[4] with up to 20% having contracted the disease within certain geographical regions.[5]

Accordingly, jurisdictions and gastroenterological societies around the world have recommended the suspension of non-urgent endoscopy.[6-9] In this article, we discuss the risk of COVID-19 transmission associated with endoscopy and the implications of a reduced endoscopy service. We propose that by incorporating readily available point-of-care (POC) tests and conducting accurate clinical risk assessments, a safe and timely return to elective endoscopy is feasible. Our algorithm not only focuses on the safety of patients and HCWs, but also assists in rationalizing the use of invaluable resources such as personal protective equipment (PPE).

The Risk of COVID-19 Transmission during Endoscopy

Endoscopy is currently limited to emergency or urgent procedures including the treatment of GI bleeding, foreign body removal, acute luminal obstruction, and cholangitis. Furthermore, the endoscopic diagnosis, staging, or resection of advanced lesions and malignancy may be performed on a case-by-case basis. However, as peak SARS-CoV-2 viral loads are reached in the presymptomatic phase of disease, there are concerns that upper GI procedures including gastroscopy, ERCP, and EUS may aerosolize virus particles that are shed from the nasopharynx of infected individuals.[10] This risk may be further enhanced if a patient dry retches, sneezes, coughs, or requires endotracheal intubation. Although data on SARS-CoV-2 transmission via aerosol-generating procedures are lacking, prior studies on SARS-CoV revealed that HCWs exposed to such procedures were 4.66 times (95% CI, 3.13-6.94) more likely to become infected than nonexposed HCWs.[11] With the detection of live SARS-CoV-2 virus in stool surpassing that of respiratory samples in up to 23% of patients,[12-19] the risk of fecal-oral transmission during colonoscopy is also plausible. This concern is not unfounded, with tissue samples from the oesophagus, stomach, duodenum and rectum of COVID-19 patients all demonstrating the presence of SARS-CoV-2 RNA.[16] Additionally, as microbial dissemination can occur up to 6 feet away from a patient undergoing endoscopy[20] and bodily fluids may splatter when manipulating devices in and out of the working channel of an endoscope; there is also a risk of fomite and environmental transmission. This risk is extended to clerical and cleaning staff because SARS-CoV-2 has been demonstrated to easily contaminate a patient's surroundings, including sinks, light switches, and doors,[21] and is viable on plastics and stainless steel for hours.[22]

Thus, because endoscopy is viewed as a high-risk procedure for COVID-19 transmission, current guidelines recommend the use of PPE for all emergency and urgent procedures, including a full-sleeve gown, eye protection, hairnet, gloves, and respirator mask.[23] Although there was an initial concern over a potential shortage of PPE in the United States, with over 500,000 cases by mid-April 2020, this is looking less likely due to a smaller than projected case-load and increased PPE procurement,[1, 24, 25] Another byproduct of current mitigation measures is the delay of the projected peak by a further 6 months.[24,25] It should also be noted that the active case-load will take time to subside and the eventual relaxation of mitigation measures may also result in disease resurgence.[26] These additional challenges may result in a further delay to the re-institution of elective endoscopy.

The Consequences of Reduced Endoscopy

The importance of recommencing routine endoscopy is reflected by its economic and health impacts. In the United States, 17.7 million endoscopic procedures are performed annually, accounting for 5.6% of the population.[27] Furthermore, over $136 billion USD is spent on gastrointestinal disease annually, exceeding that of heart disease, trauma and mental health.[27] Similar trends exist in less-populous countries such as Australia, where over 850,000 endoscopic procedures are performed annually, accounting for 3.5% of the population, 13.0% of all same-day separations from healthcare facilities and 7.2% (or $5 billion AUD) of all public and private hospital expenditure.[29,29] In the United States alone, a hypothetical suspension of elective endoscopy for 6 months is predicted to result in the delayed diagnosis of over 2,800 colorectal cancers and 22,000 high-grade adenomatous polyps with malignant potential.[27] The 6 month mortality rate for those eventually diagnosed with colorectal cancer would increase by 6.5%.[30] Just as ominously, with over 600,000 cirrhotic patients in the United States, over 1,500 may have a terminal variceal bleed that may have been otherwise prevented by endoscopic surveillance .[31-34] Thus, it is clear that the long-term suspension of routine endoscopy is unsustainable, and therefore imperative that we resume elective endoscopy as early and safely as possible. A deeper understanding of available screening tools and the host-immune response to SARS-CoV-2 is valuable in working toward achieving this goal.

SARS-CoV-2: Immunity, Testing, and its Implications on the Return to Elective Endoscopy

Is Immunity to SARS-CoV-2 Possible?

An animal study using a COVID-19-recovered rhesus macaque model raised the possibility of immunity to SARS-CoV-2 after the virus remained undetected in nasopharyngeal and anal swabs after an intra-tracheal re-challenge with SARS-CoV-2.[35] Furthermore, a promising study on the plasma of recovered patients identified the presence of neutralizing antibodies, the activity of which was transferred to recipients after plasma infusion.[36] Contrastingly, epidemiological data from China suggests that COVID-19 re-infection or re-activation may be possible, with a minority of recovered HCWs who experienced symptom resolution and had 2 consecutive negative PCR results, subsequently yielded positive PCR results up to 13 days later.[37] Moreover, these recovered HCWs were only re-screened due to their need to recommence healthcare work. However, because the quality of the screening tests used is unclear, there is a possibility that the negative PCR results may have been false negatives. This is reflected in other studies that reveal that despite a median seroconversion time of 7 days and rising antibody titres, viral shedding and the clearance of SARS-CoV-2 RNA from sputum and stool could take up to 3 weeks, including in asymptomatic individuals.[15,38,39] Hence, given the limited body of knowledge pertaining to SARS-CoV-2 immunity, it would be prudent to currently assume that re-activation, re-infection, and viral shedding can occur despite seroconversion.

Testing for COVID-19

With the aforementioned concerns of aerosol-generation, spread by asymptomatic individuals and the possibility of re-infection, we believe that rapid point-of-care (POC) tests are a vital component of any algorithm proposing a return to routine endoscopy. Current testing methods for COVID-19 include reverse transcriptase-polymerase chain reaction (RT-PCR), isothermal nucleic acid amplification tests (iNAAT), clustered regularly interspaced short palindromic repeat (CRISPR) assays, enzyme-linked immunosorbent assays (ELISA) and lateral flow immunoassays (LFA).

Although lab-based RT-PCR performed on nasopharyngeal swabs is limited by a complex and expensive protocol that can take up to 4 hours to yield a result, the Food and Drug Administration (FDA) in the United States has recently approved a POC test that can yield a result within 45 minutes.[40] Now commercially available, it carries a 95% sensitivity for diagnosing acute infection, although it is unreliable beyond week one of disease as nasopharyngeal viral loads may reach undetectable levels.[15,40] Although RT-PCRs can detect SARS-CoV 2 RNA in blood, this usually occurs in the setting of clinically severe disease[14] and thus unlikely to be useful in assessing asymptomatic patients presenting for endoscopy. Both iNAAT and CRISPR can also be performed on nasopharyngeal swabs and are highly specific (>95%) to SARS-CoV-2 (41-44). Unlike RT-PCR, iNAAT does not require multiple heating cycles and therefore can provide results within 15 minutes with a sensitivity of >95%.[45] A FDA-approved iNAAT POC test is readily available and has already been procured by clinics and hospitals across the United States. CRISPR relies on the Cas13a protein to form a complex with amplified RNA product, which then cleaves a fluorophore-quencher probe to produce a fluorescent light, signalling disease. Although it can yield a result in 60 minutes with a sensitivity of 90% and specificity of 100%, there is currently no POC test available.[43,44,46-48] ELISA is inadequate for detecting early infection, with a sensitivity of 38.3% at day 7 of the disease.[49] Contrastingly, LFA combines IgG and IgM within a single assay to yield a result within 15 minutes with a sensitivity of 88.7% and specificity of 90.6%.[50] A recent FDA-approved POC test only requires 2 drops of blood via a finger-prick.[51]

A Proposal for the Return to Routine Endoscopy: Important Components

Many units are to be commended for their work on COVID-19 risk stratification for patients presenting for endoscopy. Although Repici et al[52] prudently stratified risk based on clinical and epidemiological factors, there is potential for asymptomatic individuals to be overlooked. More recently, Han et al[53] introduced a laboratory-based RT-PCR test to assess risk, however this was time-consuming and it is unclear if it assisted in rationalizing the use of PPE. Interestingly, Lui et al[54] stratified risk based on the proposed endoscopic procedure, although recommend use of respirator masks in all cases. We believe that a safe return to routine endoscopy is possible by using a strict protocol that stratifies risk by combining an assessment of epidemiological and clinical risk-factors with the use of highly sensitive rapid POC tests (**Figure 1**).

Epidemiological and Clinical Factors

Clinicians should establish the pre-test probability of COVID-19 in asymptomatic patients based upon epidemiological and clinical risk factors. Although dependent on relevant locoregional factors, standard questioning can include:

1) Epidemiological: Have you had close contact with a suspected or confirmed case of COVID-19? Have you traveled overseas or on a cruise ship in the past 14 days? Have you been in contact with anyone who has traveled overseas in the past 14 days?
2) Clinical: In the last 14 days have you had fever (>37.5°C), cough, sore throat, or respiratory problems?

Point-of-Care Testing: Establishing a False Negative Threshold

Population-screening data from Iceland suggests that up to 43% of COVID-19 patients are asymptomatic at the time of diagnosis.[55] Hence, with over 500,000 cases in the United States and a current symptomatic prevalence of approximately 0.15%, the rate of asymptomatic disease can be estimated as 0.11% (or 370,000 persons). This information can be assessed against the sensitivity of available POC tests to determine the number of false negative results expected per 10,000 asymptomatic individuals tested (**Figure 2**). For example, in an endoscopy unit that serves 10,000 patients annually in the United States, a POC test with 95% sensitivity would result in only 1 false negative result. Comparatively, in a higher-prevalence population of 2%, there would be 10 false negative results per 10,000 patients. This, of course, would evolve with changes in disease prevalence and test sensitivity.

Precautionary Measures Required

If each endoscopy unit establishes a false negative threshold deemed acceptable to them, a 3-tiered system for the precautionary measures required during endoscopy can be used (**Table 1)**. For example, in a low-risk patient with no risk factors and a negative POC result, should the false negative threshold be satisfied, then standard precautions may be used over enhanced precautions. The key difference here is the use of a surgical mask over a respirator mask, and may help preserve valuable PPE. As transmission of the small SARS-CoV-2 virus (3 µm) is via larger respiratory droplets, both masks may offer adequate protection. This is reflected in a previous study on SARS-CoV, which revealed marginally better protection by respirator masks (odds ratio, 0.86).[56] However, studies on SARS-CoV-2 are lacking.

A Proposal for the Return to Routine Endoscopy: Workflow Considerations

Emergency and Urgent Endoscopy

By the very nature of emergency endoscopy, for life-threatening procedures, POC testing should not be performed. The decision regarding the level of precautionary measures required should be determined through a clinical and epidemiological risk assessment. However, for urgent procedures, which we defined as requiring endoscopy within 3 days, POC testing (RT-PCR or iNAAT) offers the ability to further stratify risk (**Table 1)**. For example, a patient with a low pre-test probability and positive POC result will require maximum precautions, whereas a patient with a high pre-test probability and negative POC result can proceed with enhanced precautions. To minimize unnecessary contact, all patients requiring maximum precautions should be kept isolated outside of the endoscopy unit and taken straight into their allocated procedure room, once endoscopy staff is ready. After the procedure, they should be moved into a dedicated COVID-19 recovery bay.

Elective Endoscopy: Booking Cases

For the safe and gradual re-introduction of elective endoscopy, cases should adhere to guidelines for the appropriate use of endoscopy and be triaged on their clinical merits.[57] Patients with a low pre-test probability should proceed to a serological IgG test to assess for previous COVID-19 exposure, whereas higher-risk patients should be isolated for further clinical assessment and only undergo serological testing once cleared. As viral shedding and viral RNA detection can occur up to 3 weeks postseroconversion, a positive serological result requires deferral of endoscopy for this time period.[15] In the future, with greater clarity of a patient's immune status, this delay may no longer be required. Although we acknowledge that false positive results may delay endoscopy by up to 3 weeks, the alternative would be no endoscopy.

Elective Endoscopy: Admission and Discharge

On the day of endoscopy, patients should present to an independent screening bay located outside of the endoscopy unit. Upon arrival, a dedicated staff member using enhanced precautions should re-assess patient risk factors and perform a POC test (RT-PCR or iNAAT) to rule out acute infection. Patients satisfying all criteria would be allowed to enter the unit, with accompanying individuals remaining outside. Those with newly identified risk factors or a positive result would be isolated and re-triaged. If still deemed necessary to proceed, maximum precautions would be required. If deemed nonurgent, the procedure would be deferred until the patient is well and exposure to the risk factor has passed. Upon discharge, patients would be met by their accompanying individual at a separate exit to the unit. Follow-up should be organised with the referring physician by telehealth consultation if possible.

Elective Endoscopy: Intra-Procedural Safety

To reduce the spread of COVID-19, staff should use correct hand hygiene[58] and follow local recommendations for the donning and doffing of PPE. In critical shortages, the re-use of respirator masks is possible after decontamination with ultraviolet light, hydrogen peroxide vapour or moist heat.[59-65] Although the effect of these methods on SARS-CoV-2 is yet to be established, prior studies demonstrate effective inactivation of coronaviruses.[59-65] To further conserve supplies, it is possible to conduct the donning of a respirator mask up to 5 times before fit factors consistently drop to unsafe levels.[4,66] In such cases, great care would need to be exercised to avoid accidental contact with the front of the mask. Anecdotally, the use of a surgical mask over a respirator mask may help preserve it for longer, although further studies are required.[67] However, these measures are unlikely to be required as the FDA has taken steps to increase procurement of PPE by providing clear guidelines for importers and manufacturers to follow .[68]

Elective Endoscopy: Staffing Considerations

Social distancing should be practiced by staff, with work conducted using designated chairs, computers and phones. As a contingency measure, endoscopy staff should be split into 2 teams, who work nonconcurrent shifts. Each endoscopy department should have a detailed plan addressing the systematic cleaning of all surfaces in the procedure room, including the chemical agents required to inactivate coronaviruse.[69,70] If it is deemed that seroconversion confers immunity to SARS-CoV-2, then HCWs within the endoscopy unit should also be tested for COVID-19 at set intervals with serology-based tests. This may enable seroconverted staff to perform endoscopy in high-risk patients or those with confirmed COVID-19. However, at present, the duration and protective antibody thresholds after SARS-CoV-2 exposure remain unclear. Furthermore, if it is deemed that fecal-oral transmission is not viable, then colonoscopies in patients with a negative POC result may be able to be performed with standard precautions, irrespective of the false negative threshold.

Conclusions

Amid the COVID-19 pandemic, in order to conserve resources and reduce the risk of transmission, jurisdictions across the world have suspended elective endoscopy. With mitigation measures projected to increase the duration of the pandemic, elective endoscopy may be delayed for an unsustainable period of time. Our algorithm proposes a return to elective endoscopy in a safe and timely manner through a multifaceted approach to risk-stratification. This requires an assessment of epidemiological and clinical risk factors, rapid POC testing, and evaluation of a predefined false negative threshold based upon the prevalence of asymptomatic disease in the community and the sensitivity of the POC test used. This maximizes safety for patients and HCWs, whereas rationalizing the use of valuable resources such as PPE. Ultimately, herd immunity or vaccination may be required to reduce risk of community transmission and enable endoscopy units to reach full capacity once again.

Figure Legends

Figure 1: Algorithm for a return to endoscopy during the COVID-19 pandemic. FN, False Negative; iNAAT, isothermal nucleic acid amplification; PPE, personal protective equipment; POC, point-of-care; PCR, polymerase-chain reaction.

Figure 2: The rate of false negatives per 10,000 asymptomatic individuals as determined by test sensitivity and the prevalence of asymptomatic COVID-19.

Table 1: Three-tiered system for the precautionary measures required during endoscopy

	Maximum Precautions	Enhanced Precautions	Standard Precautions
Safety Measures			
Isolate Patient	Yes	No	No
Negative pressure room	Yes	No	No
Head and shoe covering	Yes	Yes	No
Full-sleeved gown	Yes	Yes	Yes
Face shield or goggles	Yes	Yes	Yes
Gloves	Yes	Yes	Yes
Mask	Respirator (N95+)	Respirator (N95+)	Surgical Mask
Timing of Procedure			
Emergency Endoscopy	High Clinical or Epidemiological Risk	Low Clinical and Epidemiological Risk	N/A
Urgent Endoscopy	High Clinical or Epidemiological Risk, with a Positive POCT (or no test) **OR** Low Clinical and Epidemiological Risk, with a Positive POCT	Low Clinical and Epidemiological Risk, with a Negative POCT (or no test) **OR** High Clinical or Epidemiological Risk, with a Negative POCT	N/A
Elective Endoscopy	High Clinical/Epidemiological Risk or Positive POCT and Procedure re-triaged as Urgent	Low Clinical and Epidemiological Risk with a Negative POCT and Unacceptable FN Threshold	Low Clinical and Epidemiological Risk with a Negative POCT and Acceptable FN Threshold

* FN, False negative; POCT, Point-of-care test.

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Abbreviations

COVID-19, Covid-disease-19

CRISPR, Clustered regularly interspaced short palindromic repeat

ELISA, Enzyme-linked immunosorbent assay

ERCP, Endoscopic retrograde cholangiopancreatography

EUS, Endoscopic

FDA, Food and Drug Administration

GI, Gastrointestinal

HCW, Healthcare worker

iNAAT, isothermal nucleic acid amplification test

LFA, Lateral flow immunoassay

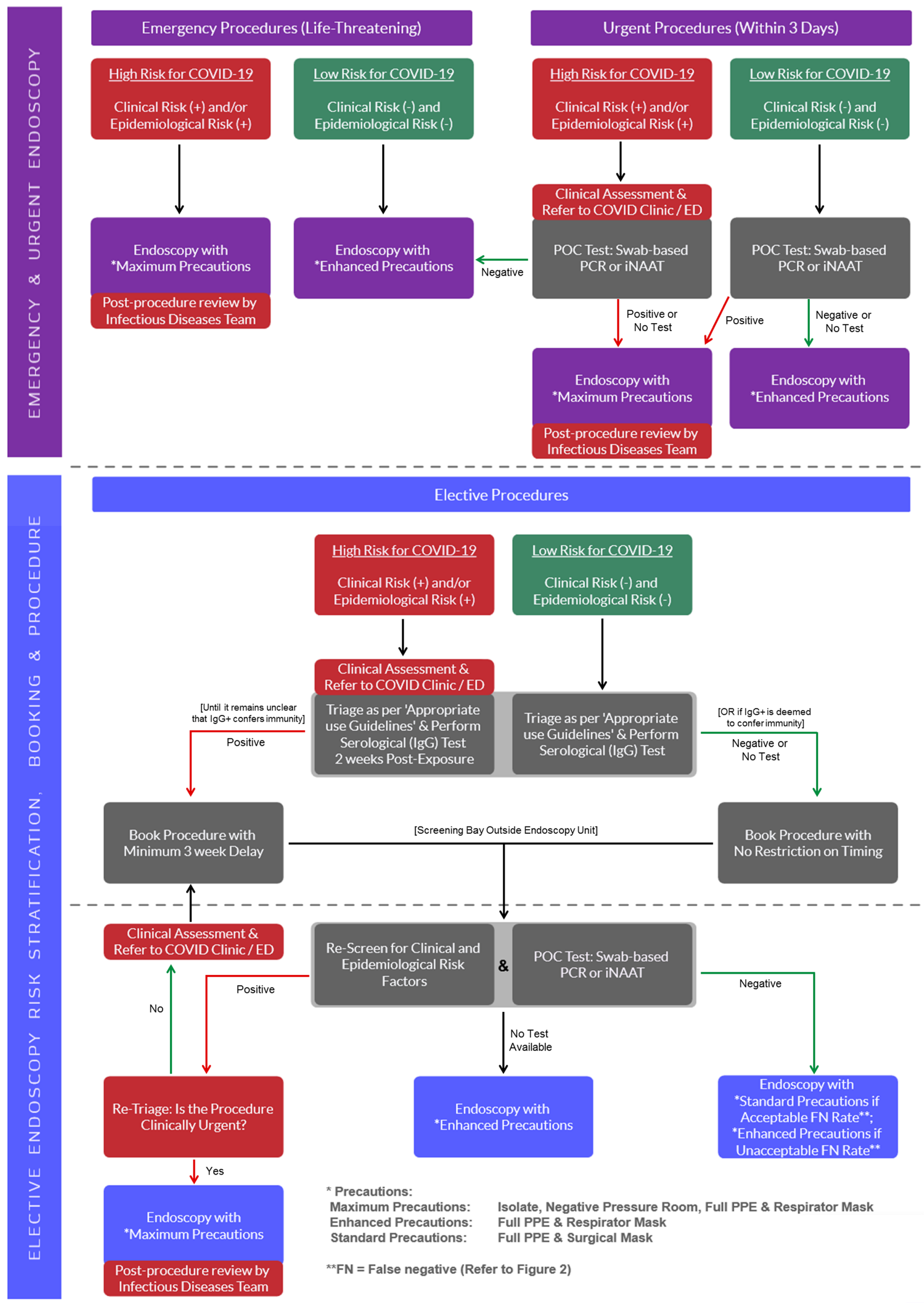
POC, Point-of-care

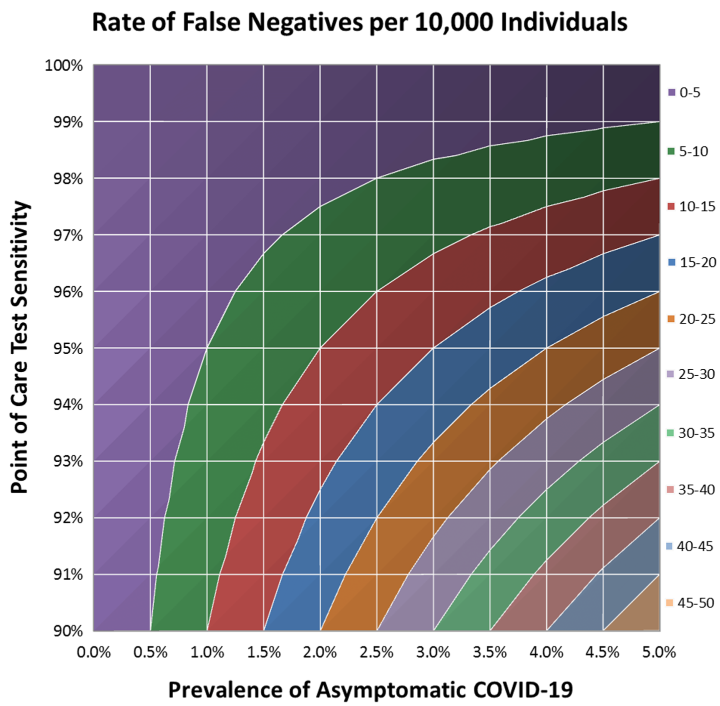
PPE, Personal protective equipment

RT-PCR, Reverse transcriptase-polymerase chain reaction

WHO, World Health Organisation

ENDOSCOPY DURING THE COVID-19 PANDEMIC





Rate of False Negatives per 10,000 Individuals
Point of Care Test Sensitivity
100%
99%
98%
97%
96%
95%
94%
93%
92%
91%
90%
0.0%
0.5%
1.0%
1.5%
2.0%
2.5%
3.0%
3.5%
4.0%
4.5%
5.0%
Prevalence of Asymptomatic COVID-19
0-5
5-10
10-15
15-20
20-25
25-30
30-35
35-40
40-45
45-50