Utilising Point of Care Diagnostics to Minimise Nosocomial Infection in the 2019 Novel Coronavirus (SARS-CoV-2) Pandemic

McDermott JH[1,2†], Stoddard D[3], Ellingford JM[1,2], Gokhale D[1,2], Reynard C[4,5], Black G[1,2], Body R[4,5], Newman WG[1,2]

1. Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester, M13 9WL, UK
2. Division of Evolution and Genomic Sciences, School of Biological Sciences, University of Manchester, Manchester, UK
3. DS Analytics and Machine Learning Ltd, 12 Hammersmith Grove, Hammersmith, London, M6 7AP
4. Emergency Department, Manchester University NHS Foundation Trust, Manchester, M13 9WL, UK
5. Division of Cardiovascular Sciences, University of Manchester, Manchester, UK

†Correspondence to Dr John Henry McDermott, Manchester Centre for Genomic Medicine, Manchester University Hospitals NHS Foundation Trust, Manchester M13 9WL, UK

Tel: 0161 276 6506
e-mail: william.newman@manchester.ac.uk & john.mcdermott2@mft.nhs.uk

Word Count (Including References): 984

© The Author(s) 2020. Published by Oxford University Press on behalf of the Association of Physicians.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

During the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak, governments have strived to maximize their daily testing capacity in order to facilitate the diagnosis and isolation of cases (1). Although important, this metric alone is not sufficient to gauge the ongoing effectiveness of a nation's response. A healthcare system may have access to many tests, but unless these are used and distributed as part of a coherent testing strategy, their value is limited. Here we make the case that high-throughput testing should be combined with more nuanced, context specific, testing approaches using validated rapid point of care diagnostics.

The SARS-COV-2-associated respiratory disease (COVID-19) is highly variable and symptoms range from a mild coryza through to severe life threatening respiratory compromise (2). Furthermore, an unascertained proportion of individuals develop an asymptomatic viraemia (2, 3). This disease spectrum can lead to diagnostic and management challenges, including the reliable distinction of patients with COVID-19 from those without. This is a concern when considering how best to cohort patients within a healthcare system. A lack of accurate cohorting, with subsequent nosocomial spread, could lead to a persistent reservoir of infectivity within hospitals.

Detection of SARS-CoV-2, typically via real-time polymerase chain reaction (RT-PCR), is gold standard for the diagnosis of COVID-19. However, using standard testing approaches, the time from swab to clinically actionable result could be well over 24 hours, especially in Hospitals without their own laboratory facilities (4). Therefore it is unlikely that any molecular result would be available whilst the patient is in the Emergency Department (ED), a setting where this information could be of greatest value. The global biotechnology industry has been quick to recognise this gap in the testing paradigm and an increasing number of rapid point-of-care tests (POCTs) for SARS-CoV-2 are entering the market. These POCTs will most likely be a relatively limited resource, therefore strategies should be developed to guide their implementation.

Currently, without a molecular result in the ED, clinicians must assess whether a patient might have COVID-19 based on their clinical presentation. Early case series suggest that the most frequently

observed symptoms are fever (98%) and cough (76%), however dyspnoea (55%), myalgia (44%) and headache (8%) are also frequently reported (5). Additionally, radiographic imaging appears to be of value in reaching a diagnosis; in a study assessing over 1000 cases, CT scanning had a diagnostic sensitivity of 97% with a positive predictive value of 65% (6). The role of the clinician is to consider the available variables and, alongside generating a differential diagnosis, determine the probability that a given patient has COVID-19. It is this probabilistic assessment that could be used to guide the deployment of POCTs.

If a previously well patient presets with fever, cough and has bilateral infiltrates on CT chest, there is a high index of suspicion for COVID-19. In this scenario rapid molecular confirmation, negative or positive, adds little. There is a high pre-test probability and therefore a strong rationale for cohorting this patient alongside patients with COVID-19. Furthermore, even if a rapid molecular result were available and returned negative, the *a priori* odds are such that the post-test probability would still indicate a likely COVID diagnosis (Figure 1). Given a pre-test probability of 0.95, assuming a relatively conservative assay sensitivity of 70% and a specificity of 98%, positive and negative results would alter the post-test probabilities to 0.99 and 0.85, respectively. Both outcomes are still indicative of a likely COVID-19 diagnosis, therefore a rapid molecular result in this context has limited clinical value.

Frequently however patients cannot be clearly differentiated at presentation. The symptomatology may be equivocal, and imaging may be inconclusive. In a clinical scenario where there is equipoise, the pre-test probability is 0.5. In this situation there is an inherent difficulty in knowing how best to cohort the patient. If a POCT were available this could be of considerable benefit. Either outcome, positive or negative, notably alters the post-test probability in one direction or the other, allowing the clinician to make a more informed decision regarding cohorting and management (Figure 1). Assuming the same assay sensitivity and specificity as above, positive and negative results in this scenario adjusts the post-test probabilities to 0.97 and 0.23 respectively. This divergence in post-test probabilities may

empower clinicians to accordingly adjust their management strategies indicating that, in this context, a rapid assay represents a clinically more useful test.

Determining pre-test probability is traditionally based upon clinical gestalt. However, to formalize this strategy, risk stratification tools could be developed using data from prospective observational cohort studies (7). The diagnostic utility of specific symptoms or findings at presentation could be combined via a Bayesian framework, generating reliable pre-test probabilities. For indeterminate cases, where there is greatest value from a molecular result, a rapid POCT could be deployed. Similar dynamic risk stratification strategies are already widely used in ED when triaging patients with cardiac chest pain and, as such, the workforce is accustomed to this approach (8).

If dynamic risk stratification approaches are to be adopted, the analytical sensitivity and specificity of any incorporated diagnostic test must first be established. Given the unprecedented demand for SARS-CoV-2 diagnostics, many new assays are receiving emergency regulatory approval with relatively limited analytical validation (9, 10). As an assay's sensitivity increases, so does its ability to differentiate indeterminate cases (Figure 2). Poorly validated assays could lead to inappropriate cohorting, increased nosocomial spread and avoidable patient deaths. It is therefore critical that any assay proposed for implementation is properly validated in the clinical setting.

At the time of writing many countries are beginning to slow their rates of infection and governments are cautiously relaxing social distancing measures. As caseloads begin to fall, efforts must be made to develop assessment and testing strategies to minimise hospital acquired infections. This should include evidenced based cohorting approaches, beginning in the ED. Ensuring that there is a formal and scientifically guided approach to triaging patients could improve outcomes, control disease spread and ultimately reduce the scale of the pandemic.

Contributors and Source: GB is the director of the North West Genomic Laboratory Hub. BN is chair of the NHS England clinical reference group for genomic medicine. DG is the principal scientist at the MCGM and leads the SARS-CoV-2 testing program. JME is a post-doctoral research fellow with an interest in genomic testing strategies. RB is a Professor of Emergency Medicine with an interest in analytical modelling. JHM is an NIHR Academic Clinical Fellow with expertise in the application of genetics in the acute setting. CR is an NIHR Clinical Doctoral Research fellow whose work explores dynamic risk stratification. DS is a data scientist at DS Analytics who has previously worked on modelling the value of acute genetic testing. WN, GB and JM developed the concept. JM and CR wrote the manuscript. RB, DG and JE provided advice around statistics. DS produced the figures. All authors debated and agreed the argument and contributed to the text of the paper.

Conflicts of Interest: None Declared

Funding: WGN is supported by the Manchester NIHR BRC (ISBRC-1215-20007). JME is funded by a postdoctoral research fellowship from the Health Education England Genomics Education Programme (HEE GEP). The views expressed in this publication are those of the authors and not necessarily those of the HEE GEP.

References

1. Black JRM, Bailey C, Swanton C. COVID-19: the case for health-care worker screening to prevent hospital transmission. Lancet. 2020.
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.
3. Zhang J, Tian S, Lou J, Chen Y. Familial cluster of COVID-19 infection from an asymptomatic. Crit Care. 2020;24(1):119.
4. Lippi G, Simundic AM, Plebani M. Potential preanalytical and analytical vulnerabilities in the laboratory diagnosis of coronavirus disease 2019 (COVID-19). Clin Chem Lab Med. 2020.
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
6. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020:200642.
7. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. medRxiv. 2020:2020.04.23.20076042.
8. Body R, Carley S, Wibberley C, McDowell G, Ferguson J, Mackway-Jones K. The value of symptoms and signs in the emergent diagnosis of acute coronary syndromes. Resuscitation. 2010;81(3):281-6.
9. Word Health Organisation. Laboratory testing strategy recommendations for COVID-19. March 2020.
10. European Centre for Disease Prevention and Control. An overview of the rapid test situation for COVID-19 diagnosis in the EU/EEA. April 2020.

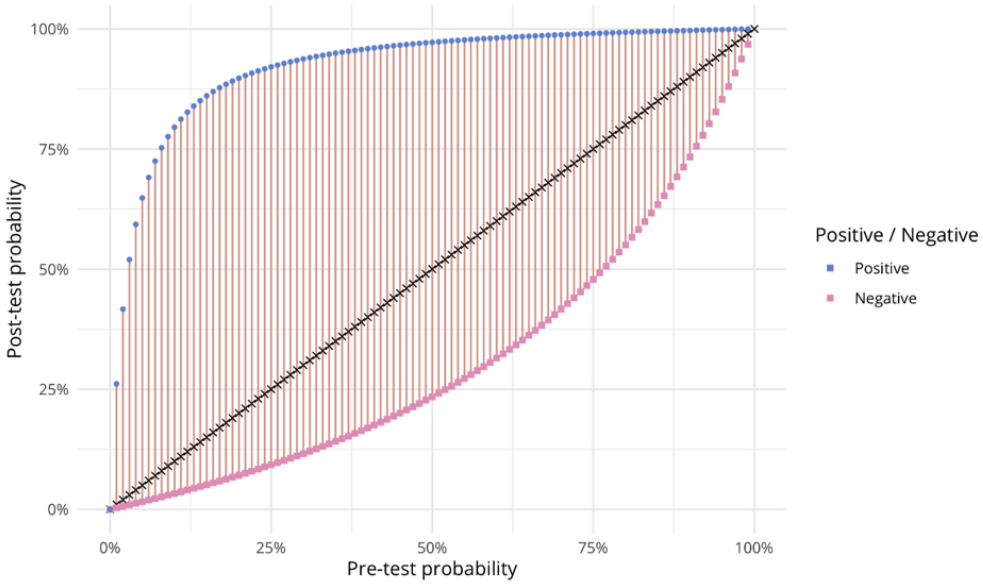

Figure 1. Impact of a Molecular Result. The impact of a rapid molecular result for SARS-CoV-2 on post-test probability. Likelihood calculated assuming a sensitivity of 70% and a specificity of 98%.

159x94mm (150 x 150 DPI)

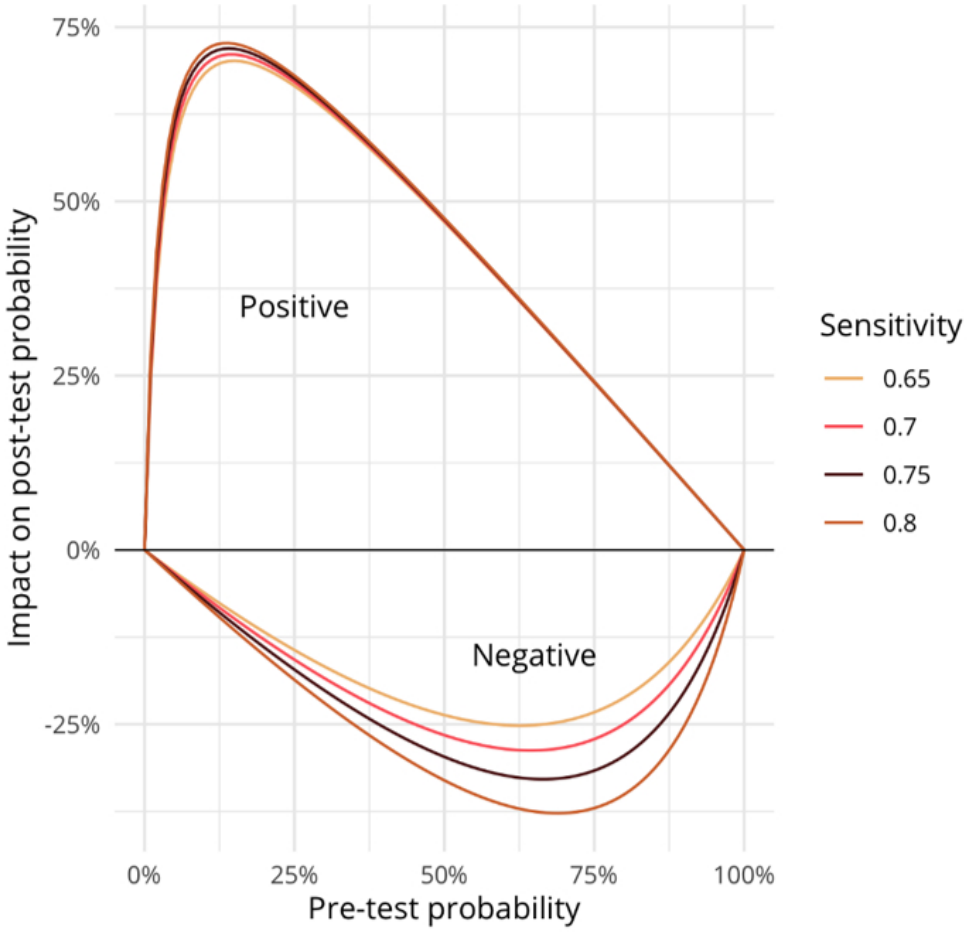

Figure 2. Impact of Analytical Sensitivity on the Value of an Assay. With increasing sensitivity, any point of care test for SARS-CoV-2 will become of increasing value in differentiating equivocal cases.

119x112mm (150 x 150 DPI)