

1 **Scalable and robust SARS-CoV-2 testing in an academic centre**

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29  
30 **To the editor:**

31

32           The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)<sup>1-3</sup>  
33 has led to a pandemic infecting more than four million people worldwide in less than five  
34 months, posing a major threat to healthcare systems. This is compounded by the shortage of  
35 available tests causing numerous healthcare workers to unnecessarily self-isolate. Here, we  
36 provide a roadmap to show how a European research institute can be repurposed in the midst of  
37 this crisis, in collaboration with partner hospitals and an established diagnostic laboratory,  
38 harnessing existing expertise in virus handling, robotics, molecular testing and informatics to  
39 derive a rapid, high-throughput diagnostic testing pipeline for detecting SARS-CoV-2 in  
40 individuals with suspected COVID-19.

41           Comprehensive and reliable testing is essential to identify the virus in individuals  
42 presenting with COVID-19 symptoms in hospital, to guide community interventions that contain  
43 the spread, and to perform enhanced surveillance programs of healthcare workers to maintain a  
44 workforce to safely deliver care. These requirements have placed an unprecedented demand on  
45 the testing capability of all countries. This demand on diagnostic laboratories, coupled with a  
46 global shortage of commercial kits and reagents, reduced commercial flights and cargo capacity  
47 and international competition for testing resource, has rendered the testing capacity of many  
48 countries inadequate to deal with the outbreak effectively.

49           The pipeline we created is used to detect SARS-CoV-2 from combined nose-throat swabs  
50 and endotracheal secretions/bronchoalveolar lavage fluid. Notably, it relies on a series of in-  
51 house buffers for virus inactivation and the extraction of viral RNA, thereby reducing the  
52 dependency on commercial suppliers at times of global shortage. We use a commercial RT-PCR  
53 assay, from Shenzhen-headquartered BGI, and report the results using a bespoke online web  
54 application that integrates with the national healthcare digital system. This strategy allows the  
55 remote reporting of thousands of samples a day in around 24 hours, universally applicable to  
56 laboratories worldwide.

57           The Francis Crick Institute (the Crick) is a biomedical research institute dedicated to the  
58 discovery of biology underlying human health. Situated in central London, an epicenter of the  
59 UK pandemic, the Crick elected to repurpose its scientific and technical resource to support the  
60 immediate healthcare needs of its partner hospital, University College London Hospital, during  
61 the outbreak. Providing an end-to-end pipeline for clinical diagnostic testing of COVID-19,

62 would result in increased testing capacity that could meet local demand, and allow new  
63 surveillance programs of healthcare workers, to be implemented.

64 Key to finding a solution was the partnership created between the Crick, a major London  
65 healthcare provider together with its clinical virology expertise (University College London  
66 Hospitals (UCLH) National Health Services Trust) and a UK Accreditation Service (UKAS)-  
67 recognized clinical diagnostic laboratory (Health Services Laboratories; HSL), forming the  
68 CRICK COVID-19 Consortium (CCC). This partnership effectively removed the barriers of  
69 clinical translation and facilitated rapid implementation of robust end-to-end testing within 10  
70 days under the oversight of an accredited laboratory. Importantly, it also allowed resources and  
71 expertise to be mobilised to meet local healthcare needs.

72 A notable strength of the CCC pipeline is that it allows the testing of a wide variety of  
73 swabs that can be either dry or in any proprietary virus transport media (VTM). These are taken  
74 at hospital sites or local drive-through stations and submitted to HSL before being transferred to  
75 the Crick. Upon arrival, specimens are barcode tracked, then proceed immediately to viral  
76 inactivation, automated extraction of viral RNA and RT-PCR to quantify SARS-CoV-2 RNA.  
77 Results are accessed through a custom-made online web portal facilitating data to be analysed  
78 remotely by a panel of trained reporters, and are returned to the reference laboratory. The speed  
79 and precision of the pipeline permits the reporting of thousands of samples/day, adopts processes  
80 that are widely used by many research laboratories worldwide, and is free from dependence on  
81 supply-chain constraints.

82 Given the urgent, two-week timeframe set to implement SARS-CoV-2 testing, it was not  
83 possible to secure clinical laboratory accreditation for the Crick to an appropriate standard (The  
84 International Standards Organisation (ISO) 15189:2012; and the equivalent to College of  
85 American Pathologist (CAP) /Clinical Laboratory Improvement Amendments (CLIA)  
86 accreditation). As an alternative, the Crick took steps to ensure that the CCC test was evaluated,  
87 verified and performed for diagnostic use in an environment that adhered to equivalent  
88 international standards.

89 The Crick is partnering with HSL (Analytics) LLC to provide diagnostic PCR testing to  
90 UCLH and other NHS Trust customers of HSL. All HSL services are compliant with HTA and  
91 MHRA regulatory requirements, where appropriate. The Crick worked with HSL—which  
92 already had a clinically validated COVID-19 RT-PCR test against the SARS-CoV-2

93 nucleocapsid (N) gene —to ensure that the research institute’s RT-PCR test against the SARS-  
94 CoV-2 ORF1a gene was properly audited and validated. Samples have been regularly exchanged  
95 with HSL and the Crick laboratory is also expecting quality control samples from the QMCD  
96 EQA (reg. GB396) with whom the CCC is registered.

97 Advice and oversight was also sought from registered professionals from existing nearby  
98 UKAS-accredited medical laboratories; HSL (UKAS 10204); Royal Marsden Hospital and North  
99 Thames Genomic Laboratory Hub (UKAS 9839); Great Ormond Street Hospital, North East  
100 Thames Regional Genetics Lab and North Thames Genomic Lab Hub (UKAS 7883); Institute of  
101 Neurology (UKAS 8045) and an approved UKAS inspector. CCC protocols were either written  
102 on demand, or based on existing institutional protocols, to ensure clinical grade testing at the  
103 Crick. Guidance from these professionals assisted the compiling of clinical diagnostic Standard  
104 Operating Procedures (SOPs) for every stage of the pipeline, including implementing checklists  
105 and risk mitigation steps alongside the methods. Additional SOPs were followed for sample  
106 storage, disposal of materials, batch certification of reagents and incident reporting. Appropriate  
107 risk assessments, training and competency assessment procedures were established and  
108 documented. Record sheets were created to document the receipt, batch acceptance testing, and  
109 start/end of use dates for key reagents and consumables. An inventory of all key equipment was  
110 compiled which, where appropriate, included details of service and calibration records. Systems  
111 were established for the control of all key documents (version implementation, distribution and  
112 acknowledgement), audit trail (what samples were tested when, by whom, with what equipment  
113 and using which consumable/reagent batches), and a record of all incidents/issues (to facilitate  
114 appropriate investigation, rectification and recurrence prevention).

115 Assurance of the pipeline was performed in collaboration with quality assessment  
116 provider Genomic Quality Assessment (GenQA; <https://www.genqa.org/>), following their  
117 checklist for non-accredited laboratories, the lab and CCC workflow was inspected by a qualified  
118 UKAS assessor against the GenQA guidelines to verify compliance to ISO15189 equivalent  
119 standard.

120 To ensure full traceability, samples were barcoded and all processes were recorded using  
121 Clarity LIMS software (Illumina). UCLH provided access to barcoded swabs pre-booked onto  
122 the Crick’s laboratory information management system (LIMS) to enable tracking from sample  
123 receipt through to result reporting. In urgent response to the clinical need, formation of these

124 partnerships was vital to drive the speed of pipeline setup in the Crick’s central London research  
125 laboratory (all key documents are available at [https://www.crick.ac.uk/research/covid-  
126 19/covid19-consortium](https://www.crick.ac.uk/research/covid-19/covid19-consortium)).

127 The CCC pipeline is illustrated in Figure 1. The specific reagents and requirements for  
128 each step of the entire pipeline—sample receipt, virus inactivation, RNA extraction, RT-PCR  
129 assay for the ORF1a gene, data quality assessment, online web reporting, barcode sample  
130 tracking—are available at protocols.io<sup>4</sup>.

131 In response to potential shortages of supplies, we forecasted demand, ordered reagents in  
132 large batches, used in-house buffers wherever possible, and an in-house N gene assay was  
133 established as a contingency plan.

134 Several amendments to procedures were implemented to ensure the CCC test performed  
135 robustly at the Crick. Although the Crick performed viral inactivation in a containment level 3  
136 suite with trained staff, other research laboratories with only containment level 2 (CL2) facilities  
137 may be able to adapt the CCC test model, provided that appropriate risk assessments are carried  
138 out or swabs are inactivated before transportation (a containment level 2 procedure is also  
139 provided with our protocols). Moreover, other protocols also exist for alternative viral-  
140 inactivation methods using heat, further demonstrating the potential for CCC pipeline  
141 applicability where availability of guanidinium may be limited.

142 Another adaptation made in the CCC test is to use a series of home-made buffers for  
143 automated RNA extraction which circumvents dependence on reagents that may be in short  
144 supply during a pandemic. At the time of writing, the most important bottleneck in performing  
145 PCR tests for COVID-19 detection is the shortage of kits for RNA extraction. We developed an  
146 in-house RNA extraction protocol using magnetic silica beads from G-Biosciences, and we have  
147 also validated our assay with SeraSil Mag 400 beads (GE Healthcare/Cytiva), which can serve as  
148 a reliable substitute. RNA extraction using silica is based on the protocol developed by Boom *et*  
149 *al.*<sup>5</sup> over 30 years ago. In the Boom method, concentrated guanidinium thiocyanate serves as  
150 virus and RNase inactivation agent and promotes binding of nucleic acids to silica. We have  
151 tested RNAClean XP SPRI magnetic beads (Beckman) and found them compatible with our virus  
152 inactivation solution; viral RNA could be purified following manufacturer’s recommendations.  
153 Moreover, protocols exist for the production of either type of magnetic beads from inexpensive  
154 and accessible starting materials<sup>6</sup>. Therefore, we designed a pipeline that uses common reagents

155 and is automatable on widely available liquid handling platforms allowing its implementation in  
156 a large number of biomedical laboratories with suitable robotic platforms that can be re-  
157 programmed for this use. The reagents can also be utilised for manual RNA extraction where  
158 liquid handling platforms are unavailable. The universal applicability of this approach could  
159 allow a resilient response to future critical events even in countries where particular resources  
160 may be limited.

161 Selection of an appropriate PCR assay for detection of SARS-CoV-2, the BGI kit, was  
162 based on (i) our accredited laboratory having a ready set of validation data and experience with  
163 the US Food and Drug Administration (FDA) emergency use authorised assay and (ii) a  
164 guaranteed supply chain for the assay kit in the face of falling demand in China, and growing  
165 demand in the United States (for US suppliers). The primers used in the CCC test target SARS-  
166 CoV-2 ORF1a, enabling detection of full-length genomic and antigenomic RNA, whereas the N  
167 gene assay also targets the abundant subgenomic RNAs. With many mutations having been  
168 reported in the ORF1 region of SARS-CoV-2, it was paramount to adequately assess false  
169 positive and false negative rates. The verification steps of the CCC pipeline allowed us to  
170 compare the BGI kit with the in-house developed N gene assay. Overall, the diagnostic  
171 sensitivity of the CCC test is 92.86% with a specificity of 100% and a high degree of accuracy in  
172 the detection of SARS-CoV-2. The N gene assay is slightly more sensitive than the CCC assay at  
173 the limits of detection. When performed in duplicate, we observed a discordant rate of 1.1% (95  
174 samples of 8433 samples). To improve the accuracy of true positive reporting (and reduce the  
175 chance of reporting false positive tests), the assay is performed in duplicate and discordant  
176 samples are recommended for re-testing at source. The full verification is documented on  
177 Figshare<sup>7</sup>.

178 As sample timing and adequacy are likely to be more important determinants of false  
179 negatives than qPCR sensitivity<sup>8</sup>, we have chosen a test that also includes a control for cellular  
180 RNA (beta-actin), which serves as a partial proxy for sample adequacy. Although high  
181 sensitivity at the assays limits of detection could impact identification of low levels of viral  
182 shedding beyond the assay's limits of detection, these samples are unlikely to be producing  
183 infectious virus<sup>9</sup>. BGI PCR therefore exhibits adequate sensitivity for current clinical algorithms,  
184 in which testing for symptomatic healthcare workers is performed within a specific timeframe.

185           The high-throughput RT-PCR assay carried out at the Crick in 96-well plate format has  
186 the potential to screen thousands of samples per day and can be scaled up to 384-well format  
187 with further optimisation. Since conception of the CCC, we have performed over 14,000 tests;  
188 starting with one batch of 39 samples on the first day of live testing and scaling up to around  
189 500-1000 samples per day. 1000 samples/day is delivered on a pipeline operated by 44 members  
190 of Crick scientific staff working a 10 hour (staggered) shift. Competency training was conducted  
191 for staff to work on virus inactivation, RNA extraction, RT-PCR and result reporting. This is far  
192 less than our maximum capacity for CCC testing, and throughput is limited by logistic and  
193 operational limitations within the community and partner hospitals e.g. local swabbing capacity.  
194 Our partner laboratory HSL has capacity for 1000-1250 samples per day, but due to limitations  
195 on supply chain, their testing is reserved for hospital inpatients. Conversely, the CCC pipeline  
196 created capacity to test a new population that had hitherto been unable to access testing, namely  
197 asymptomatic and symptomatic healthcare workers, and self-isolating keyworkers. Indeed, we  
198 now provide the healthcare worker testing for UCLH NHS trust and North Central London  
199 Hospitals. We believe that this approach fulfilled a critical gap in the existing testing  
200 infrastructure, and one that has major impact on the safe delivery of healthcare during the  
201 COVID-19 pandemic.

202           To establish the CCC pipeline at the Crick, we made use of category 3 equipment, liquid  
203 handling platforms and RT-PCR instruments that were available within our institute and simply  
204 repurposed them for COVID-19 testing. The barcoding equipment and tool tracker were already  
205 used with our LIMS system. Only a limited amount of additional protective equipment was  
206 procured for buffer preparation and the pipeline can be potentially scaled up further with  
207 minimal additional equipment. A rate limiting step preventing the CCC pipeline to proceed at  
208 full capacity is the global availability of swabs. Additional testing regimens are being considered  
209 which would circumvent the dependency on viral swabs.

210           Medical laboratory accreditation is held to the standard of ISO 15189:2012 across the  
211 world, with the exception of the USA, which operates to CLIA certification/CAP accreditation.  
212 Laboratories are assessed for compliance to ISO or CLIA/CAP standard by a national awarding  
213 body; in the case of the United Kingdom this body is UKAS. While the process of acquiring  
214 accreditation, and the typical assessment time span and rules for extending existing ISO or  
215 CLIA/CAP scope to partnering institutions will vary between countries, any research institution

216 seeking to establish clinical testing should seek clinical accreditation wherever possible. While  
217 pursuing this process, our approach has been to implement processes in line with international  
218 accreditation standards, and those processes remain under the supervision of our partner  
219 accredited laboratory (HSL). We have also regularly sought advice from GenQA and are in the  
220 process of implementing their recommendations in an agreed timeframe to comply with the  
221 standards required to meet ISO151890.

222 Health information systems, such as the EPIC electronic medical record used at UCLH,  
223 interface with LIMS, such as WinPath, to enable sample barcodes to be associated with patient  
224 hospital numbers. The pipeline set up at the Crick uses a custom-made reporting web application  
225 compatible with remote reporting. This allows multiple trained reporter personnel to access  
226 anonymised data through a portal from home, which is particularly advantageous in a pandemic.  
227 As a result, the CCC pipeline is capable of an accelerated turn-around for results of 2500-3000  
228 samples in approximately 24 hours.

229 The potential advantages of implementing a clinical diagnostic pipeline in research  
230 laboratories are clear: a substantial increase in capacity for testing, and the ability to adopt  
231 flexible and agile approaches to testing in the face of global constraints. Our experience at the  
232 Crick in implementing mass-scale testing within the CCC has taught us invaluable lessons for the  
233 wider academic community: first, diagnostic testing to clinical standards can be successfully  
234 achieved through partnership and guidance from a clinical diagnostic laboratory; second, the  
235 choice of techniques and approaches should be adapted to the local resource, and staff expertise,  
236 already existing within a research laboratory; and third, the scale and implementation of testing  
237 should be aligned with the healthcare needs and demands of the local population.

238

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247 **Competing Interests statement**

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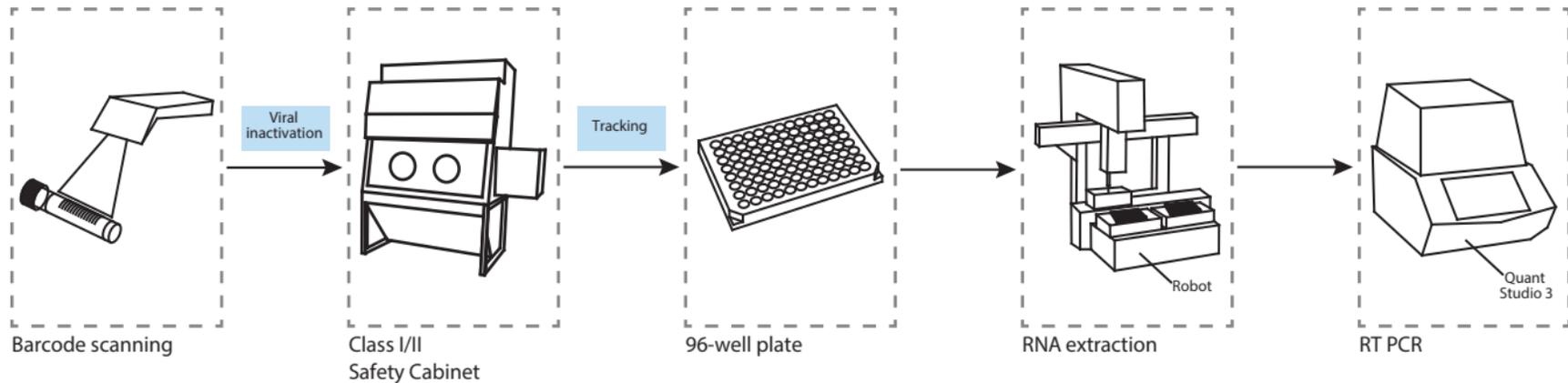
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283 **Figure 1. Schematic of the CCC test and reporting pipelines.** (a) Specimen barcodes are  
284 scanned at sample reception, before viral inactivation in a Class I or II safety cabinet, processing  
285 through RNA extraction using an in-house protocol and RT-PCR testing using a commercial kit  
286 (BGI). The number of samples processed through the pipeline per day has ranged from 39 (one  
287 plate) to a maximum of 1270 (14 plates). (b) CCC reporting pipeline. Test results are reported  
288 continuously through a custom-made remote web application, allowing remote clinical scientists  
289 and pathologists working outside of the institute to authorise reports, in line with the established  
290 SOP.

291

292 **Table 1.** Major issues encountered while setting up the CCC pipeline and information on how  
293 these issues were dealt with.

a



b

