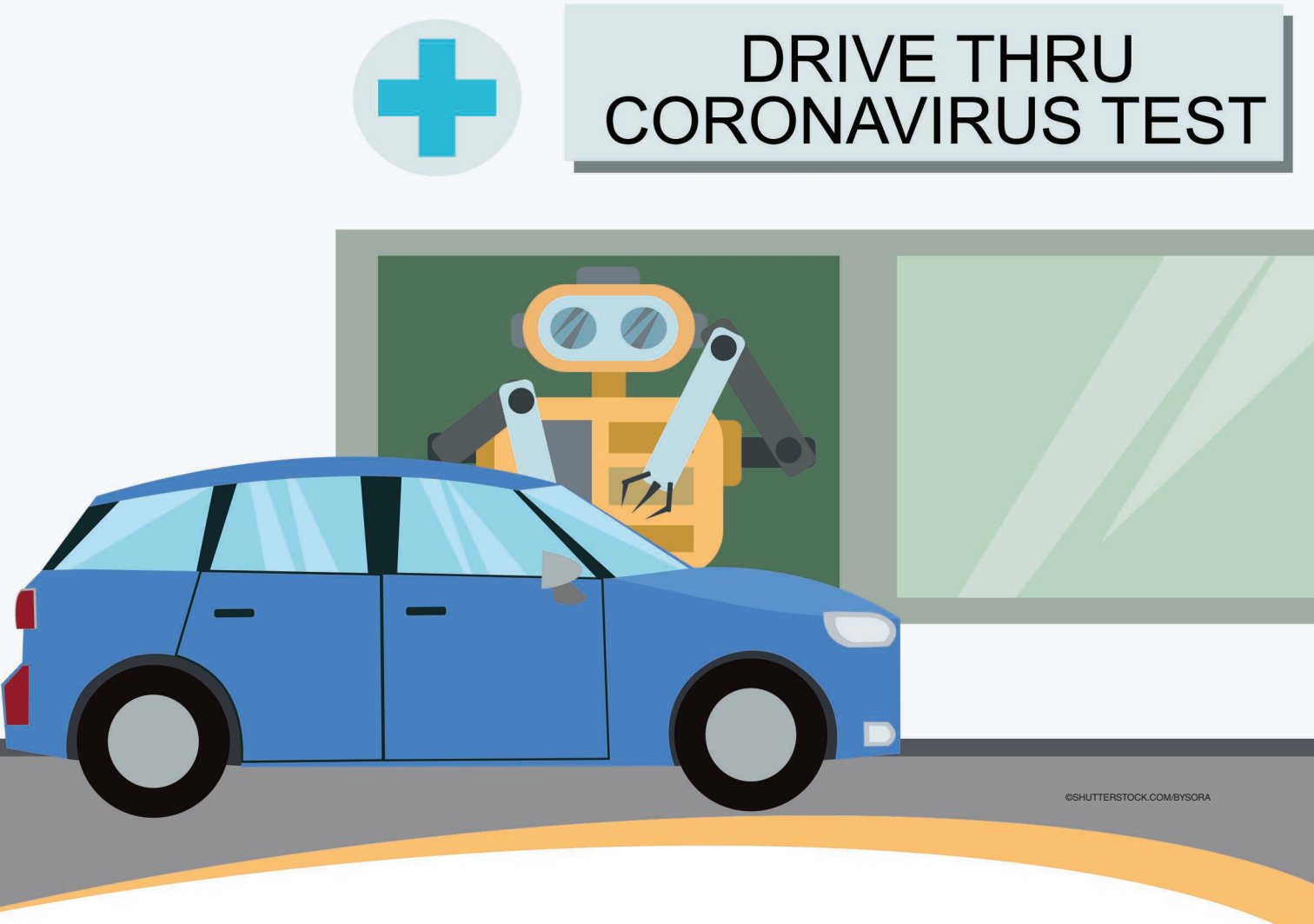

Using Robotics in Laboratories During the COVID-19 Outbreak

A Review

By Patrick Courtney and Paul G. Royall

The clinical and analytical laboratory has been at the forefront of the fight against the COVID-19 pandemic. This is where testing is carried out, guiding hospitalization and providing information on the spread of the disease. It is also central to the development of new medicines and the vaccines that are still being tested. Laboratories make extensive use of robotics and automation to safely improve quality and productivity at an acceptable cost.

However, laboratories are often hidden from view, and the specific needs and applications are not widely known within the robotics research community. In this special issue on the robotics response to the COVID-19 outbreak, we present a

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review of the current state of the use of robotics in the laboratory and some new ideas that have emerged during the pandemic. We focus on four main areas, existing diagnostics, new diagnostics, new medicines, and vaccines, and we summarize the impact of robotics on the lab and vice versa.

The Hidden Role of Robotics in the Lab

Daily news stories have presented laboratory work for diagnostics and progress in the development of vaccines. However, these have mostly focused on lab technicians carrying out such tasks as transferring materials using manual pipettes and have not shown the range of robotic systems available in the laboratory (Figure 1).

In reality, most labs are equipped with robotic systems able to carry out such work more quickly, reliably, and safely than would otherwise be possible (Figure 1). The use of robots has increased greatly in recent years and has been further accelerated by the pandemic. However, there are still many challenges, some of which have been highlighted in the current crisis, and many opportunities for future improvements. The scale of the pandemic has set new expectations in terms of such factors as the speed of the response, number of vaccine doses, and need to limit contamination, many of which robotics is well placed to help address.

Commercial activity in laboratory automation dates from at least the 1940s, and the first flexible robot may be the Zymark in 1985 [1], [2]. Since this time, a deep knowledge of the automated handling of liquids, from biological fluids to solutions and solvents, has been developed. (The handling of solid forms remains a challenge.)

Interest from the robotics research community resulted in some promising ideas [3], [4] and continues at the cutting edge [5], [6]. However, this area does not receive the same attention as others. This is, in part, because a lab is not as visible as a factory or a farm, while materials can be hard to understand and procedures demanding. Moreover, recent progress in robotics, interest in artificial intelligence (AI) and the connected lab, and the demands of the pandemic make it worthwhile to re-establish the interaction [7], [8].

Specific needs in the laboratory impose requirements that differ from those in classic robotics applications (Table 1). As we discuss in this article, these needs have led to certain technological choices: adaption of industrial robots or custom designs. The pandemic and the speed with which it has progressed have resulted in considerable innovation and new concepts to which modern robotics is able to contribute.

In this review, we distinguish among current practice, new concepts, and open issues. In most cases, the new ideas are not yet fully validated or widely deployed, and the current status is reported from the available information.

Existing Diagnostics

In this section, we cover the steps from sample acquisition to reporting results, including in-clinic swabbing, in-field sampling, sample storage, novel in-field lab concepts, and new diagnostics and protocols that exploit the strength of robotics.

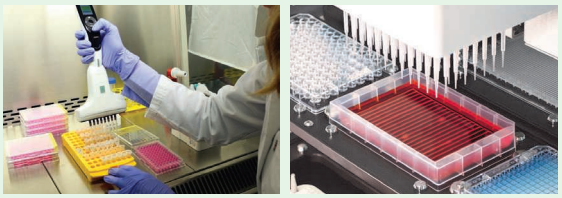


Figure 1. The (a) manual and (b) robotic manipulation of liquids in the laboratory. [Sources: (a) Integra Biosystems and (b) Analytic Jena; used with permission.]

Conventional Diagnostic Testing and Automation

The diagnosis of disease is an everyday task in clinics and hospitals. By some estimates, approximately 70%–80% of medical decisions are based on the results of such tests, with some 1.1 billion tests carried out in the United Kingdom each year [9]. Each hospital has access to a range of highly effective automated test systems for common tasks such as blood analysis (Figure 2). These comprise sophisticated sample-handling mechanisms and are, effectively, closed robotic systems. They act as platforms that can be updated as new medical conditions emerge [10]–[14]. In parallel, many labs also have access to general-purpose tools that are used for less common tests with more human intervention. All of these meet relevant U.S. Food and Drug Administration (FDA)/European Medicines Agency clinical test regulations [15], [16].

As the pandemic has progressed, suppliers have developed kits that run on existing automated platforms to

Table 1. The demands of laboratory robotics.

Characteristics	Requirements and Implications
Sample size	The small volume means there is no need for large robots.
Sample form	The sample is typically liquid; it does not bear high acceleration.
Sample carrier	The 5- to 100-g container means there is no need for large robots.
Sample number	The number varies from a few to many millions.
Sample value	The value is high when each is a unique patient sample.
Reliability	There is an expectation of 100%, as each sample is a human life.
Throughput	The time to results is more important than the capacity.
Safety	The sample can be dangerous; staff safety is essential.

detect the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. These have been based on the polymerase chain reaction (PCR) technique. This is a highly specific and sensitive method able to detect the presence of the virus. It requires a preparative step to extract the DNA (actually, the RNA) from the sample.

There has also been innovation in the tools. Danish company Flow Robotics has adapted its smart liquid-handling robot to perform automated screening and so provide additional testing capability to 400 samples/day in hospitals as well at field locations, such as sporting facilities [10]. The biggest success has been in removing the bottleneck of manual labor in tedious repetitive tasks. Established suppliers have also created new partnerships such as the Corona-Testsystem, which integrates robotic arms to run 6,000 tests/day. As integrated sample-preparation stations combine multiple devices, such systems raise new technical challenges regarding the interoperability of robotics to achieve a smooth handoff [7], [8], [17].

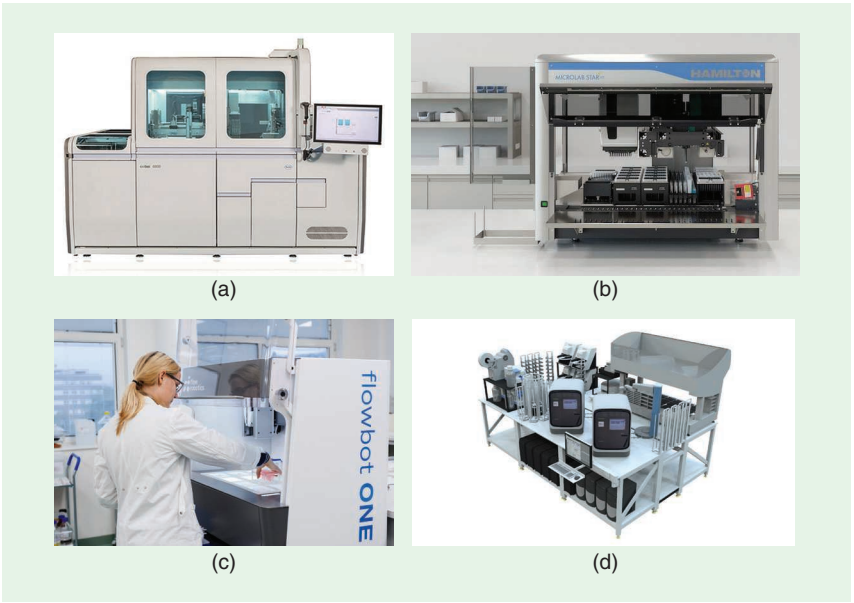


Figure 2. (a) A Roche clinical analyzer, (b) the Hamilton liquid-handling robot, (c) the Flow Robotics Flowbot ONE, and (d) the Tecan/Thermo Corona-Testsystem. [Sources: (a) Roche, (b) Hamilton, (c) Flow Robotics, and (d) Thermo; used with permission.]

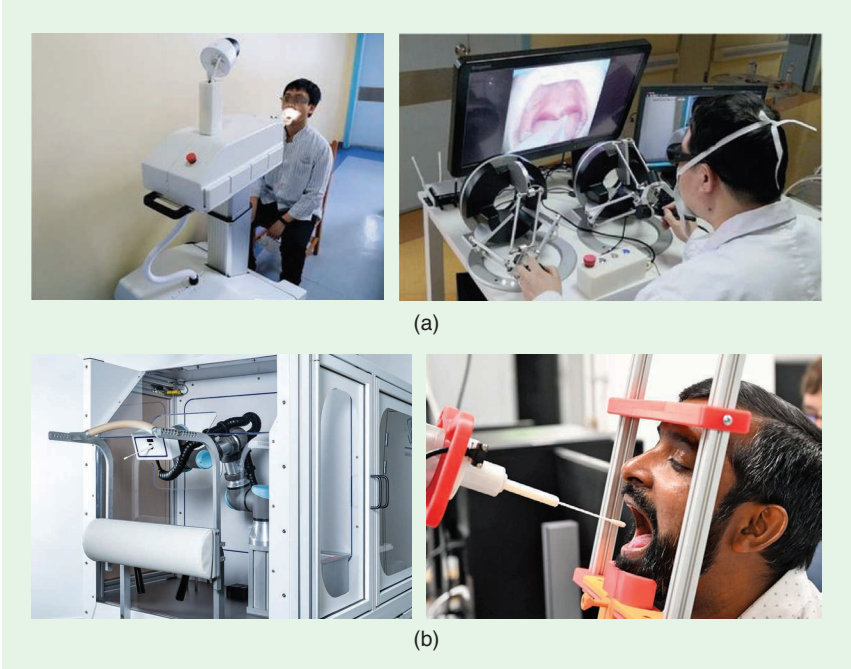


Figure 3. Semiautomated swabbing using robotics in (a) China and (b) Denmark. [(a) Reproduced with permission of the ©ERS 2020 [25]. (b) Source: Syddansk Universitet/Lifeline Robotics; used with permission.]

From Sample Acquisition to Processing

Studies show that laboratory error rates vary widely, with a relative burden that can span a wide range (0.1%–9.3%) [18]. Poor sample handling and tracking account for up to 93% of the errors encountered within the diagnostic chain [19]. In short, the measurement step is highly reliable, but sample handling is weak. Hence, we address the potential value of improved robotics and automation for sample handling in the following section.

Automated In-Clinic Swabbing

Although sample preparation and processing benefit from these automated tools, the other steps have only recently received due attention. The default test for the presence of SARS-CoV-2 requires the use of a nasopharyngeal or oropharyngeal swab. This is a tricky procedure even for health-care staff. It is error prone and has low throughput. In addition, it exposes staff to the risk of contamination, and it is unpleasant for test subjects. Several groups have taken up the challenge to try to automate the process.

In China, a robot comprising a snake-shaped mechanical arm, binocular endoscope, wireless transmission equipment, and human–computer interaction terminal was developed [Figure 3(a)] at the Guangzhou Institute of Respiratory Health and Shenyang Institute of Automation under the Chinese Academy of Sciences [20].

The robot has collected 80 throat swab samples since it was put into operation in the Guangzhou Institute of Respiratory Health on 28 February 2020 and showed improved speed (9 versus 14 s) and comfort for comparable data quality [25].

In Denmark, researchers from Syddansk Universitet developed a throat-swabbing robot [Figure 3(b)], which led them to set up a commercialization company [21], [24]. In South Korea, researchers at the South Korean Institute of Machinery and Materials and the Daegu Convergence Technology Research Center created a swabbing robot [20]–[24], [71]. Similar devices were reported by a Taiwanese company [27] and researchers in China [26] without further data.

Automated Drive-In Sampling

As testing volumes have increased, discussion has moved to establishing drive-in testing facilities for population sampling (although these are, strictly speaking, sample-collection rather than testing stations). Two further projects, both in Germany, have targeted the automation of drive-in testing: one in the Hamburg area by Freise Automation [Figure 4(a)] and the other by BoKa Automatisierung in Bavaria [Figure 4(b)]. These add a booth, swab stock, and sample management [22], [23].

These act as automated sample handlers for swabbing by health-care workers or test subjects, with the main goal of increasing test capacity (12/h) while preventing cross-contamination. Considerable care has been paid to subject identification and the transfer of results—important matters that have been a weakness in conventional systems as well as for the economic case. However, the designs are prototypes awaiting clinical validation and certification. In parallel, there have been efforts to develop alternative sampling approaches that make use of, e.g., saliva. As often happens in the history of robotics, efforts to automate one procedure risk being displaced by changes in the process. Close coordination between users and technologists is required to address this.

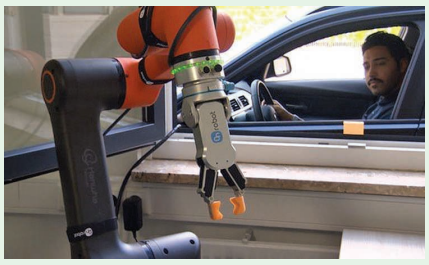
Sample Storage and Biobanking

Once a sample has been analyzed and the diagnostic result obtained, it is normal to archive the sample in a cold-storage facility. This is demanded in case reanalysis is required. With the rise of genomic techniques, access to such samples has become an invaluable resource for gaining new insight into the relationships among the disease, genetics, and other factors, often within collaborations between clinical and scientific teams. Being able to track and recover large numbers of such samples has led to the burgeoning field of biobanking and the development of a range of robotic tools to meet this need [7], [8], [28]. Thanks to such biobanks, it has been possible to create detailed maps of the spread of SARS-CoV-2 that exploit small changes in the virus genome over time, detect entry points, and assess mitigation [29].

New Laboratory Concepts—OpenCell

The traditional approach to clinical testing has involved a central hub laboratory that can afford to install the most modern high-capacity machines, which are run with a high load by a critical mass of skilled staff. Although this is efficient, it can lead to some challenges in the sample logistics, tracking, and reporting of results. During the pandemic, where geographically dispersed populations are to be screened, there is some advantage in bringing the laboratory closer to the sampling site.

One innovative approach proposed has been for the use of modular labs in containers, an idea pioneered by OpenCell.



(a)

(b)

Figure 4. Robotized drive-in sampling stations developed by (a) Freise and (b) BoKa. [Sources: (a) W. Kazemi, Freise Automation and (b) C. Hartung, BoKa Automatisierung; used with permission.]

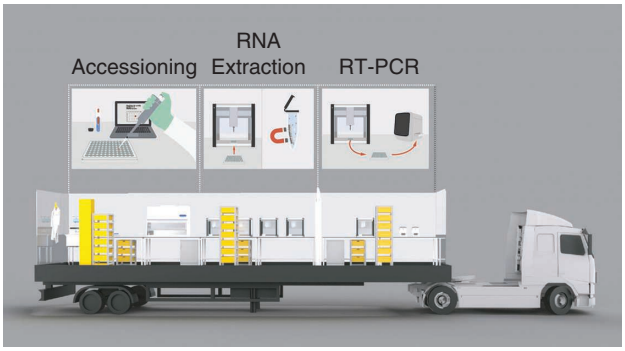


Figure 5. The OpenCell lab in a container. (Source: OpenCell Biomedical; used with permission.)

These are fully equipped SARS-CoV-2 testing laboratories, with appropriate biosafety mechanisms (BSL2/3) and multiple robotic stations capable of 2,400 tests/day when staffed by one technician (Figure 5) [30], [31]. A unit is deployed by the airport on the Channel Island of Jersey, where its throughput fits well with capacity needs and visitor numbers. It avoids long delays required by the use of mainland labs, reducing the time to results from 30 to 4 h. Such a system would not be possible without the new generation of low-cost lab robots (open source OpenTrons).

New Laboratory Concepts—Sample Pooling

As the demand for testing has increased, more capability has come online, with new instruments ordered and entire facilities built. For example, the U.K. Lighthouse Labs at Milton Keynes uses some 45 robots [32] as part of a set of three labs to provide 100,000 tests/day.

At the time of writing, 800,000 tests are carried out in the United States each day, and strategies to end the lockdown call for 5–20 million or more [33]. In addition to being costly, this places extreme demands on the supply of reagents—the chemicals needed to run the tests.

Some new ideas have developed based on the pooling of samples: when most findings are expected to be negative, combining many samples and testing them as a group can be helpful. If the result is negative, the whole group can be given the all-clear. If the group shows a positive result, a further round of testing can reveal which sample or samples are positive, saving tests and time [34]. Such an approach relies on the measurement process being sufficiently sensitive to detect the virus in a diluted sample.

The PCR process used is highly sensitive since it involves a temperature-dependent chemical amplification process (25–35 heat–cool cycles, equivalent to 10^9-fold at 30 doubling cycles). Thus, detection in a diluted sample would not appear to be a barrier. Indeed, the use of pooling received FDA approval on 18 July 2020, and four-way pooling is being used by the large-scale testing program in Luxembourg [35]. Several variants have been proposed to achieve more efficient use of equipment and reagents and make tradeoffs in time and test savings. However, these add complexity beyond what can be carried out manually and so require the use of automation to pool and decode the results [36].

Development of New Diagnostics

RNA-Based Diagnostics

At the emergence of SARS-CoV-2 and the publication of the viral genome, diagnostic tests quickly became available from vendors. These must be tested, validated, and produced in volume. At the time of writing, more than 300 million tests have been carried out, and this is increasing rapidly [37], [38].

However, many tests have suffered from challenges in terms of throughput (in Europe), quality (in the United States), and access to reagents. The time to results extends to several days. Testing would be improved by diagnostics that address these issues.

New tests have been proposed that reduce the time to results by running on more compact point-of-care instruments that can be placed in the field and run by less-skilled staff. Alternative test protocols have also been developed, using different reagents that are easier to obtain. For example, the loop-mediated isothermal amplification (LAMP) assay avoids the time and complexity of temperature cycling in classical PCR and can yield results in 20 min. One such system has been deployed by Optigene, working with lab automation supplier PAA, in a pilot in Hampshire, United Kingdom [39].

Swabs are awkward and require a health-care professional. Alternatives have been sought, and several tests now work with saliva and other samples that can be collected in the home. If these tests prove to be unreliable, the benefits of faster results will be lost, trust will be eroded, and the disease will spread further. There is, therefore, a strong need for robust testing.

Validating a test is a substantial task [15], [16], [37], [38]. It requires an extensive set of standard positive and negative samples (the test panel) as well as rigorous testing processes, with robotics and automation playing an important role in meeting regulations.

As an illustration, to provide a reliable estimate of a sensitivity of, e.g., 99%, sufficient testing is required to obtain a good estimate of the 1% failure rate. For this, several failures must be seen, which means several hundred tests. When the disease is rare in the population (say, 1%), a test sensitivity of 99% gives a false-positive result one time in 100 for healthy subjects. If the disease is present at 1% and testing 100 subjects returns one positive result, there is a 50% chance that this result is due to a true case and a 50% chance that it is an artifact of the test. This, again, requires many hundreds of test samples (and many more if a sensitivity of better than 99% is required and claimed). This is clearly more than can be reasonably performed by hand, so automation is required, and the robotic systems mentioned earlier (Figure 2) are often used.

Antibody-Based Diagnostics

Early diagnostic testing relied on laboratory tests to determine the prevalence of the virus. As the pandemic progressed, the attention given to testing grew to determine exposure to the disease. This relies on a different test that detects molecules in the blood that remain after the body has been exposed. These molecules can be detected using a matching antibody along with a suitable readout signal.

The necessary antibodies can be obtained from a variety of sources: from cell cultures and also from animals. They can be quite variable and hard to create at high quality. Some early commercial antibody-based tests showed quite poor performance, and independent evaluation of

both specificity and sensitivity, with sufficient confidence, is essential.

Specificity measures response in the presence of other coronaviruses. Sensitivity can vary across individual patients with diverse immune systems and presenting differing amounts of the molecules to be detected. Testing, therefore, requires the use of a good representative test panel. Already, some 780 test kits (360 RNA and 390 antibody) are listed and have been evaluated [37] [38] following U.S./European Union regulations, and this will likely increase as more and improved tests are created.

Automated Blood Taking

Antibody-based testing relies on blood samples. Although this is one of the most common medical procedures, with some 1.4 billion per year in the United States, there are issues of pain, injury, or contamination in as many as one in five cases [40], [41]. Consequently, efforts have been made to automate this step, with Rutgers University/VascuLogic proposing one system (Figure 6) and Veebot (Mountain View, United States) offering another. The first clinical evaluations have been carried out [41]; however, it is not clear if they have yet been widely deployed.

Important ancillary tasks, such as blood-tube handling, have been manual and error prone. This has been improved with the introduction of automation by systems such as the Inpeco Protube Suite [42].

Use of Drones for the Logistics of Diagnostics

Improvements in automation and the secondary impacts of the pandemic have stressed the logistics associated with COVID-19 testing. Such challenges cover the 1) supply of consumables required for laboratory tests, 2) delivery of human samples for testing (swab/blood tests) from remote sampling locations to centralized analysis laboratories, and 3) the collection of COVID-19 testing kits from those who are self-isolating or who have difficulty getting to sampling locations/testing centers. Uncrewed aerial vehicles or drones have the potential to meet most of these logistical challenges presented by COVID-19.

One of the benefits but also disadvantages of robotic analytical equipment is the large number of assays that may be completed at any one time. During the pandemic, consumable supplies for these pieces of analytical equipment—for example, of mass spectroscopy-grade water—were limited. As drones are not physically crewed and are typically semiautonomous, there is potential for savings in human resource requirements if they are deployed in the supply chain. In addition, there is an increase in the speed of delivery, as they are not affected by traffic congestion or geographical barriers. Drones have already benefited the biopharmaceutical supply chain [43] and distributed COVID-19 supplies across hospital campuses and beyond [44], [45].

Among the existing medical drone services, there has been a reorientation to address logistical needs due to COVID-19. Zipline drones have been repurposed from their typical blood-product delivery missions to those involving the delivery of personal protective equipment (PPE) in Ghana [46]. Such missions of up to 70 mi allowed the delivery of this limited resource to where it was most needed within hours, compared to the equivalent trip by vernacular transport, which would take days. Collision avoidance systems, in combination with inertial measurement units and global positioning systems, facilitate such distant missions.

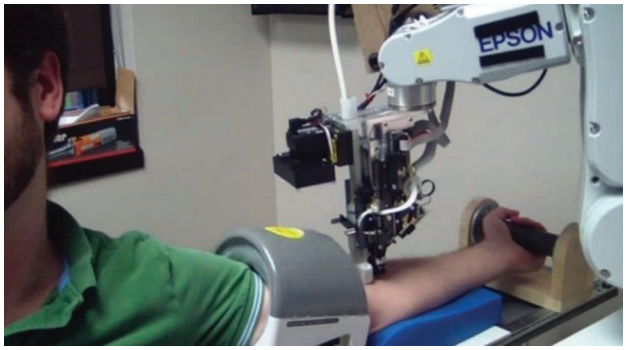


Figure 6. Automated blood taking using robotics. (Source: M. Yarmush, Rutgers University; used with permission.)

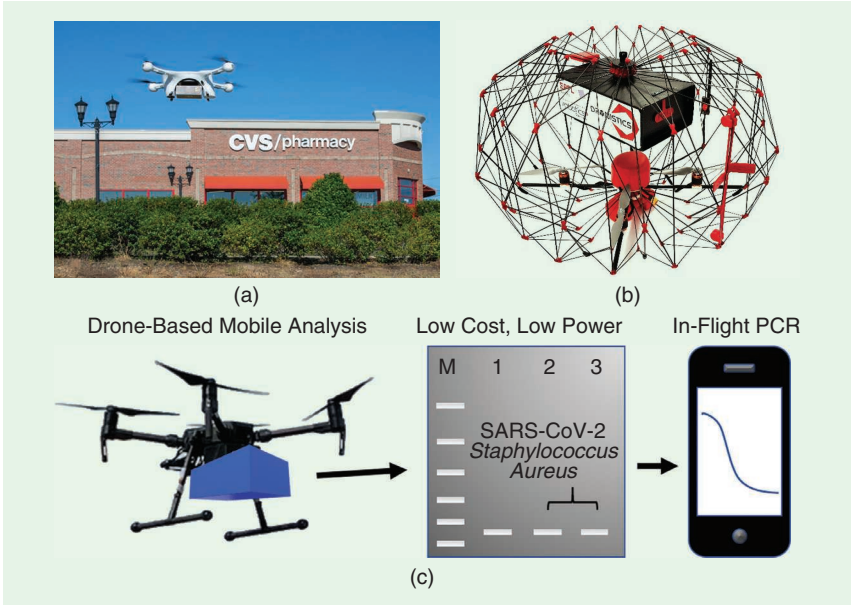
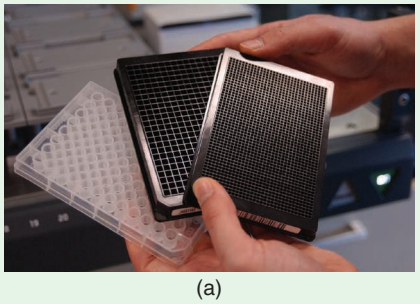


Figure 7. Drone support for diagnostics. (a) A drone delivery of medical products and test kits in the United States. (b) A drone safety cage to allow door-to-door delivery. (c) A lab on a drone with the potential for point-of-care COVID-19 testing. [Sources: (a) Matternet; (b) P. Kornatowski, Dronistics; and (c) adapted from Priye et al. [51]; used with permission.]

One of the central tenets for nearly every nation affected by COVID-19 was the need for its population to stay indoors and self-isolate during the peak of infection. This presented a contradictory challenge: isolate to avoid potential infection but travel to a testing center if infection is suspected. There are testing kits that may be delivered and collected by postal and courier services, but this presents a huge risk for those handling the packages, as any rupture of the packaging could potentially infect postal workers with the virus.

Robotic technologies, namely, drone delivery and collection services from remote sampling sites to centralized analysis labs, avoid human contact, making the test kit collection service much safer. Those evaluating the robotic innovations that have been applied to control COVID-19 have highlighted the potential for drones to act as the first step in the analysis and detection of the virus [47]. An additional benefit of the use of drones is their ability to record their geographical position, i.e., to map where the test was collected and where it is being delivered, in real time.

Health mapping using geographic information systems captures both the frequency of positive COVID-19 results and their locations, thus permitting local lockdowns in very specific areas and lowering the economic impact of subsequent waves of infection [48]. Furthermore, localized COVID-19 detection makes a compelling case for further direct delivery and collection of testing kits to the residents of these specific zones, thus preventing a local outbreak from transferring into disease-free areas, i.e., breaking the chain of infection.



(a)

(b)

Figure 8. A (a) Society for Biomedical Sciences (SBS) multiwell plate and (b) high-throughput screening system. [Sources: (a) Wikipedia/SBS/S.D. Hamilton and (b) HighRes Biosolutions; used with permission.]

Autonomous aerial drones are beginning to meet this need; for example, they have been deployed by Aerodeli, which was one of the first companies to receive permission from the Civil Aviation Administration of China to transport samples in connection with COVID-19 testing [49]. However, a number of safety issues must be addressed before personal drone delivery services become commonplace. The potential for the drones' propellers or rotor blades to come into contact with members of the public must be eliminated. A simple and elegant solution is placing the drone within a protective cage [50] [Figure 7(b)]. When these missions occur over a distance of 500 m, application to the local civil aviation authority and a robust safety case are required for such missions that run beyond the visual line of sight (BVLOS).

One intriguing possibility is the development of a "lab on a drone" [51], which has been shown in a proof of concept for the deployment of smartphone-enabled nucleic acid-based diagnostics for mobile health care, whereby the equipment required to conduct a PCR has been miniaturized to fit within the payload of a semiautonomous drone. Thus, the future of drone technologies in response to COVID-19 could be point-of-care testing.

Effective Medicines

Medicine Development

Despite early reports and some progress, there are still very few effective medicinal therapies for patients affected by COVID-19. Treatment options focus on the use of mechanical ventilators, and this places high demands on clinical resources. Intense efforts are underway to find new drugs. Public registers indicate that at least 315 treatments are in development, with some 1,700 clinical trials [52].

However, the development of new drugs is well known to be slow, expensive, and error prone. This results from the many tests that must be carried out to ensure efficacy and safety as well as the regulations requiring that these are performed correctly. Since most candidate drugs fail during this evaluation, the process has been estimated to take 10–12 years and cost US$2.6 billion [53].

Laboratory operations play a key role at many stages, and robots are already heavily used. The early steps involve defining a suitable test assay to assess potential drug molecules. A set of candidates is screened using large automated systems to search libraries of 100,000 or more compounds.

Screening makes heavy use of the multiwell plate (Figures 1 and 8), a sample container with a format standardized under the American National Standards Institute. These plates enable small-volume samples to be carried in groups of 96, 384, or 1,536. This seemingly minor component is important to highlight because it acts as a tool that permits the exchange of larger numbers of samples between instruments and the creation of complex and flexible sample processing chains: plate preparation, imaging, washing, and so on.

Screening typically examines the effect on cells that must be grown in a consistent manner. This requires the careful preparation, feeding, and monitoring of many cell cultures, in parallel, 24/7. Automated tools have made good progress, and robotic systems are widely used, with the added benefit that cells are protected from contamination by human operators.

Antiviral drugs have tended to be small molecules that may be created using chemical processes. For large-molecule drugs (proteins or antibodies), cells are used to generate the candidates via protein synthesis, and, again, cell culture automation provides quality and productivity [54].

Promising drug candidates are further adapted, submitted for more evaluation, optimized, and tested again in a number of iterations. The creation of multiple dose–response curves benefits from automated sample handling and robotics in terms of productivity and repeatability. Drug candidates with a suitable profile may then be moved to testing in animals—typically, rodents (hamsters or mice) and, later, primates—to obtain information about the effect of the drugs in a biological system [55]. The management of these animals is demanding work, and larger facilities are equipped with automation for care, feeding, and cleaning (Figure 9).

Traditional animal testing has many challenges, including the representativeness of the results for a broad human population as well as ethical and cost issues. Scientists have been developing models that can more faithfully replicate human biology by using tissue models, such lab-on-a-chip and organ-on-chip (OoC) technologies. These create multiple samples that can be studied using robotic and automation technologies already in the lab. The first reports of such OoC technologies applied to COVID-19 have begun to appear [56], [57].

Candidates remaining at this stage can be prepared for clinical trials in humans, initially to understand how the healthy body responds and then in carefully selected groups of patients. These steps are highly regulated and make extensive use of hospital labs to track changes and detect many problems. Still, seven out of eight candidates fail in these trials [53].

A further aspect of drug development that has an important impact on efficacy and patient acceptability is the design of the drug-delivery systems, from tablets to an injectable form via nanomaterials [58]. These raise challenges in terms of performance and stability, for which automated testing is, again, very valuable.

One approach that has generated a lot of excitement in searching for new drugs effective against COVID-19 is the repurposing of existing drugs. Approved medicines with known safety profiles may be used for disorders other than their original targets with some success, a practice termed *off-label use*. AI tools have also been applied to search databases of potential compounds. The repurposing of such compounds against COVID-19 still requires lab tests to determine efficacy [55], [59] but avoids having to repeat the full set of safety and pharmacological tests, potentially getting drugs to the market and bedside faster.

Medicine Manufacturing

While production is generally undertaken with existing robotics and automation solutions dedicated to manufacturing (having much in common with the chemical and food/beverage industries, such as fermentation), pharmaceuticals manufacturing has very high quality standards and regulations in common with semiconductor manufacturing, and so it also makes use of laboratory facilities for quality control and troubleshooting. The very high volumes expected to treat COVID-19 will lead to stresses on existing processes. One important example is the quality control and sterility testing required for all product batches and performed manually [60].

Many process steps and tools were originally developed for laboratory technicians and are well adapted to manual manipulation. Robots replicating aspects of such methods have been deployed with some success (Figure 10).

Development of New Vaccines

As with medicines, effective vaccination against SARS-CoV-2 is still an active area. In fact, relatively few vaccines are available: the Centers for Disease Control and Prevention lists 59 against 26 diseases (United States), and there are vaccines against 40 diseases worldwide [61]–[63]. This reflects an underdeveloped and poorly funded area. There are four major suppliers with the capability to manufacture at scale, as others have withdrawn. The SARS, Zika, and Ebola outbreaks resulted in substantial interest from newer biotechnology firms and the formation of organizations to

(a)

(b)

Figure 9. An (a) Ambr cell culture robot and (b) animal cage-cleaning robot. [Sources: (a) Sartorius and (b) TecniplastUK; used with permission.]

reinvigorate this area, including the Global Alliance for Vaccines and Immunizations (GAVI) and the Coalition for Epidemic Preparedness Innovations (CEPI) [64], but they lack effective tools.

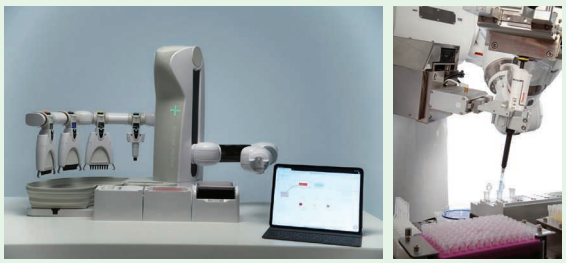


Figure 10. Tool-using robots: the (a) Andrew Alliance pipetting arm and (b) Yaskawa arm. [Sources: (a) Andrew Alliance and (b) Yaskawa Europe GmbH; used with permission.]

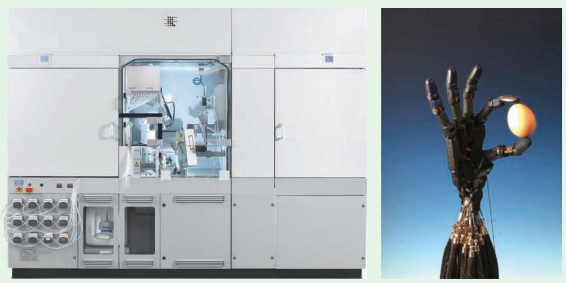


Figure 11. Vaccine production: (a) the CompacT by Sartorius and (b) a robot hand by Shadow. [Sources: (a) Sartorius and (b) Shadow Robot Company; used with permission.]

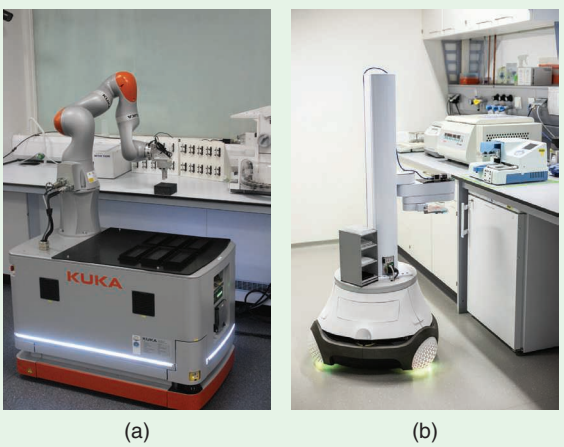


Figure 12. Mobile laboratory robots from (a) the University of Liverpool and (b) Fraunhofer IPA. [Sources: (a) University of Liverpool, United Kingdom and (b) Fraunhofer IPA, Germany; used with permission.]

Vaccine Development

Diverse vaccine models have been proposed, including live attenuated, inactivated, virus-like, subunit, and novel genetic forms. These involve similar tools to those used in drug development—cell culture, protein synthesis, and animal testing—with the same call for robotics and automation (Figure 11). As with the creation of new medicines, vaccine development from discovery to license can cost billions of dollars and take 4 to 10 or more years to complete, with an average 94% chance of failure [65]. Public registers indicate that there are at least 200 vaccines in development and some 50 entering early trials [61]–[63]. Given these figures, we can expect a number of vaccines to emerge, but only after substantial further work.

One important distinction between vaccines and medicines is that medicines are given to patients who are already suffering the effects of a disease, whereas vaccines are given to nominally healthy individuals who represent a much broader population: children, those with existing conditions, and so on. This means that the acceptable risk threshold for vaccines is stricter than for medicines and more rigorous evidence of safety is expected, and it imposes greater demands on laboratory testing capability and capacity, which robotics and automation are called upon to meet.

Vaccine Manufacturing

Many existing vaccines are legacy products with older processes, for example, grown in eggs. Robotics has been used in some of the more recent vaccines, such as chicken pox in the United States [66]. As with medicine manufacturing, the quality procedures to be followed are very stringent (Good Manufacturing Practice) and involve many manual steps using gloveboxes and clean rooms.

Some development projects are attempting to introduce modern robotics into vaccine manufacture, but these are at early stages. It is not clear how billions of doses will be produced without additional progress in this area.

Other Applications and Benefits

The Public Health and Surveillance Roles of Lab Robotics

While diagnostics and new medicines focus on the treatment of individuals, it is important not to neglect the role in the analysis of trends and transmission at the population level. The analysis and collection of samples as diverse as air and waste water have provided valuable insights [67] but require the processing of large numbers of samples, with a rapid time to results and high reliability. Robotic autosamplers are essential to support such campaigns with so many samples.

New Materials and Processes

It is also worth noting that new medical concepts need validation and optimization. For example, new face mask

designs and materials have been proposed, and users expect some evidence that they work. The pandemic has led to many new studies on materials, contamination, transmission by aerosols [68], [69], testing of new ventilator designs [55], and so forth. While these would normally be carried out in existing lab facilities with traditional equipment, the urgency and speed as well as the number of samples to be processed in a repeatable manner make robotics and automation very attractive.

Laboratory Robotics as a Means to Continue Lab Work

After a period when lab users were skeptical of technologies such as automated guided vehicles and unconvinced by point solutions that leave scientists to complete the workflow, they are again receptive to new solutions. Advanced concepts, such as dual-arm robots [5], mobile robots (Figure 12) [6], and in-lab flying drones [70] are being evaluated to considerable interest.

A further benefit in the current context is that such automation enables social distancing in the lab, facilitating a safe and productive return to work. Connected and cloud-enabled robots, such as the Andrew Alliance arm (Figure 10), have permitted experiment design and execution from home.

Discussion, Prospects, and Conclusions

This brief review brings together the current state of practice and use of robotics and automation in the service of addressing the current coronavirus (and any future) pandemic. The laboratory is already a heavy user of robotic technologies; however, their use in labs has been hidden from view, at least until the current crisis. (There may be as many as 1,350 robots deployed per 1 million of daily test capacity, an estimate based on [32]).

The number of clinical samples to be processed was increasing even before COVID-19 due to the growth of health care and to clinical lab staff retiring faster than new technicians are being trained. The pandemic has created the impetus to look again at these needs, as has been shown in the examples presented earlier. Returning to the requirements presented in Table 1, it should be apparent that the new smaller and collaborative robots, drives, and algorithms are a good fit, especially when combined with flexible and easy-to-use interfaces suitable for nonroboticists.

As shown in Table 1, the lab has specific requirements that are different from those of industry. Some developers have adapted industrial robots, and agile repurposing has indeed been one of the themes of the crisis (Table 2). At the same time, specialists in drug development, cell culture, blood taking, and so on have been rethinking what is accepted as conventional in robotics, and several other models have emerged as strong alternatives. Returning to the list of needs in Table 1, it is possible to identify several topics that remain open (Table 3).

The fine details of lab needs and applications can appear somewhat esoteric to those outside the field, and there has been limited interaction between researchers and industrial

Table 2. The robotic models applied in the laboratory.

Robotic Model	Example Applications Relating to the Laboratory
Gantry robot	High-throughput liquid handling (Figures 1, 2, and 8)
Repurposed industrial robot	Patient sample collection, automation of testing, and the development of vaccines (Figures 3, 4, 9, and 12)
Re-engineered industrial robot	Drug screening and cell culture (Figures 8 and 11)
Custom robotics	Swabbing, blood taking, cell culture, and logistics (Figures 3, 6, 9, and 12)
Open source	Stand-alone field laboratory, demonstrated by OpenCell (Figure 5)
Adapted drones	Logistics and sample collection, demonstrated by Matternet and Dronistics (Figure 7)
Humanoid robot	Liquid handling and tool use: Yasgawa arm, Andrew Alliance arm, and Shadow hand (Figures 10 and 11)
Cloud robots	Tool handling, demonstrated by Andrew Alliance arm (Figure 10)

Table 3. Some open issues in laboratory robotics.

Characteristics	Status (State of the Art, Open Issues)
Sample size and form	
Liquid samples (1 μL–10 mL)	Liquid-handling robots and some tool use
Liquid sampling (blood)	Prototypes in evaluation
Solid (swab/tube)	Prototype swab handling in evaluation
Solid (generic sample tube)	*Open issue*—no general solution
Solid (lab supply logistics)	Prototype mobile robots—*open issue*
Solid (drug delivery materials)	General lab tools but *little automation*
Aerosol (test PPE/surfaces)	General lab tools but *little automation*
Cell culture (drug/vaccine)	Products but not fully automated—*open issue*
Animal cage cleaning	Products exist
Animal handling (drug/vaccine)	*Open issue*
Reliability	
Expectation of 100%/no loss	Reduce loss from current 0.1–10% by automated sample handling—*open issue*
Throughput	
1,000–1,000,000+ per day	2,400/day: OpenCell; 6,000/day: Thermo 100,000+ semiautomated—*open issue*
Time to result	
20 min	Point-of-care/BVLOS drone—*open issue*
2 h	Prototypes in evaluation
24 h	State of the art with robotics
Under five days	Current laboratory practice
Safety of staff	
Physical distancing (BSL2/3)	Critical feature—to be proven
Self-cleaning robots (to 10^6)	Critical capability—to be proven

practitioners. However, as this discussion has shown, there are major and urgent opportunities for collaboration between robotic and domain experts, especially in areas beyond diagnostics, such as medicines and vaccines. It is hoped that this overview encourages more interaction between the two.

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