Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Innovations in infectious disease testing: Leveraging COVID-19 pandemic technologies for the future

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ABSTRACT

Innovations in infectious disease testing have improved our abilities to detect and understand the microbial world. The 2019 novel coronavirus infectious disease (COVID-19) pandemic introduced new innovations including non-prescription "over the counter" infectious disease tests, mass spectrometry-based detection of COVID-19 host response, and the implementation of artificial intelligence (AI) and machine learning (ML) to identify individuals infected by the severe acute respiratory syndrome - coronavirus – 2 (SARS-CoV-2). As the world recovers from the COVID-19 pandemic; these innovative solutions will give rise to a new era of infectious disease tests extending beyond the detection of SARS-CoV-2. To this end, the purpose of this review is to summarize current trends in infectious disease testing and discuss innovative applications specifically in the areas of POC testing, MS, molecular diagnostics, sample types, and AI/ML.

1. Introduction

The field of infectious diseases has benefited from numerous testing innovations – beginning with the first light microscope in 1716, followed by Koch's Postulates in 1890, and in modern times, discovery of polymerase chain reaction (PCR) in 1983 [1–3]. Many of these innovations have focused on detecting and understanding the microbial world with later discoveries aimed at improving the speed, efficiency, and portability of pathogen detection technologies. Today, infectious disease testing has evolved well beyond simple laboratory-based microscopy, microbiological culture, and PCR. Rapid immunoassays (*e.g.,* direct pathogen detection, serology), mass spectrometry (MS), and a broad range of molecular techniques (*e.g.,* sequencing, point-of-care [POC] PCR) have become commonplace and transformed the management of infectious disease (Fig. 1) [4].

Innovation is the practical implementation of ideas that result in the introduction/improvement of new goods or services [5]. The 2019 novel coronavirus infectious disease (COVID-19) pandemic has fueled a new wave of innovations such as expanded implementation of POC pathogen detection, use of artificial intelligence (AI) and machine learning (ML) for identifying individuals with COVID-19, and novel detection/sampling methods to overcome the many testing challenges faced during this COVID-19 pandemic [6–8]. As the world recovers from the COVID-19 pandemic and moves toward COVID-19 as an endemic disease; these innovative solutions will catalyze a new era of infectious disease testing that extends beyond the detection of the severe acute respiratory syndrome – coronavirus – 2 (SARS-CoV-2). However, this surge of new innovations must be tempered with real world evidence when adopting new devices. To this end, the purpose of this review is to summarize current trends in infectious disease testing, discuss innovative applications specifically in the areas of POC testing, MS, molecular diagnostics, sample types, and AI/ML, as well as highlight current barriers and concerns with these technologies.

2. Point-of-care testing

Point-of-care (POC) testing is defined as medical testing at or near the site of patient care [9]. Fig. 2 summarizes common POC testing formats. Traditionally, formats included handheld, portable, transportable, and bench top devices. Since early the 1980′s, POC testing has observed dramatic changes related to infectious disease testing over the last ten years including the development of bedside rapid molecular tests, proliferation of wearable health monitoring devices, and the growth direct to consumer (DTC) and over the counter (OTC) testing.

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2.1. Rapid molecular testing

Both automation and miniaturization have accelerated the speed and increased the portability of molecular infectious disease testing. Tests that would previously take days to complete could now be resulted in a matter of hours or minutes. In fact, rapid (<30 min) molecular testing has become the norm for many emergency departments [7]. This notion is underscored by the COVID-19 pandemic where POC reverse transcription (RT) real time PCR and isothermal nucleic amplification methods have received United States (US) Food and Drug Administration (FDA) emergency use authorization (EUA) for both home and hospital testing, with some platforms having sensitivity and specificity comparable to laboratory-based methods [6–10].

Clustered regularly interspaced short palindromic repeats (CRISPR) gene editing technology has also created new testing opportunities for COVID-19 [11]. This molecular technology enables low-cost rapid amplification free detection of SARS-CoV-2 that shows comparable performance to RT-PCR. In the study by Fozouni *et al.*, a CRISPR-based SARS-CoV-2 assay was coupled to a smart phone that yielded a limit of detection of ~100 viral copies/μL with an analytical turnaround time of less than 30 min [12]. Future CRISPR-based infectious testing may have other applications including integration with flow-based assays to provide low-cost high throughput testing at the point of care [13].

2.2. OTC and DTC infectious disease tests

Prior to the COVID-19 pandemic, infectious disease testing was limited to Clinical Laboratory Improvement Amendment (CLIA) certified or accredited facilities in the US. In brief, both the US FDA and Centers for Medicare and Medicaid Services exercise enforcement of CLIA. The FDA is responsible for formally approving devices and determining the level of testing complexity for the device (*i.e.,* waived vs. non-waived), while CMS defines how each testing site must perform and support the test (*e.g.,* testing personnel qualifications, training, performance validation/verification, etc). The COVID-19 pandemic prompted activation of the FDA EUA pathway to review and approve new *in vitro* diagnostic tests [10]. Emergency use authorization pathways are defined for COVID-19 molecular, antigen, and serology tests. Each pathway also provides criteria for waived, OTC, and DTC status. Although waived infectious diseases testing is not new [7], OTC and DTC tests represent a significant paradigm shift [10]. Effectively, under the EUA, OTC COVID-19 tests can now be performed without prescription. Likewise, online retailers can now sell DTC collection kits as a mail-in DTC PCR test and provide results within 24 h upon receipt to the central testing laboratory [10]. It will be interesting to see how the regulatory landscape will evolve post-COVID-19 pandemic and if these EUA technologies catalyze other OTC and DTC infectious disease testing applications in the future where patients become more directly involved in the selection and operation of testing.

2.3. Wearable POC devices

Wearable POC devices (*e.g.,* pulse oximetry, continuous glucose monitoring systems) have existed over the last 20 years. Today, a new generation of wearable devices include smart watches and rings that measure parameters such as oxygen saturation, one-lead electrocardiogram (ECG), and heart rate [14–15]. However, the use of wearable devices for infectious disease testing is relatively new. During the COVID-19 pandemic, FDA EUA was conferred to the Tiger Tech COVID Plus Monitor [10–16]. This optical detection device is not intended for the diagnosis or exclusion of SARS-CoV-2 infection, but instead, used for monitoring of COVID-19 in an asymptomatic population as part of an infection control plan [16]. In brief, the device uses two embedded photoplethysmography sensors worn as an armband around an

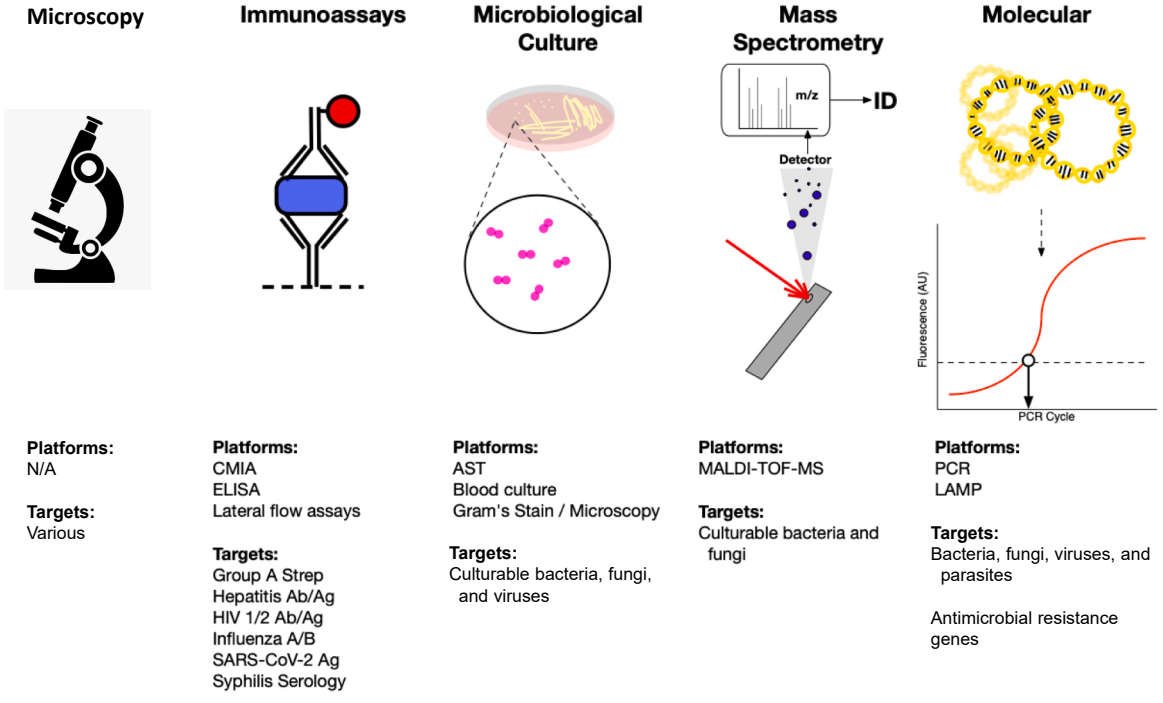

Fig. 1. Examples of Current Infectious Disease Testing Methods. From left to right, the figure illustrates current day infectious disease testing methods including microscopy, immunoassays, microbiological culture, mass spectrometry, and molecular techniques. Below each category are respective platforms, and example of infectious disease targets. Abbreviations: AST, antimicrobial susceptibility testing; CMIA, chemiluminescent microparticle immunoassay; ELISA, enzyme-linked immunosorbent assay; LAMP, loop-mediated isothermal amplification; MALDI-TOF-MS, matrix assisted laser desorption ionization – time-of-flight – mass spectrometry; PCR, polymerase chain reaction.

individual's left arm. Measurements are taken over 3–5 min evaluating pulsatile signals that are then fed into an ML model. Positive percent agreement and negative percent agreement is reported to be 98.6% and 94.5% respectively when compared against PCR.

2.4. Smart device-based microscopy

High resolution imaging is no longer the unique domain of clinical laboratories. The imaging capabilities of smart devices now rival the performance of consumer grade cameras, and when coupled to magnifiers, could be used as a low-cost alternative for microscopy [17]. These innovations can be further enhanced by AI/ML which could aid in the detection of pathogens from biological specimens. The detection of malaria, for example, remains challenging due to the unique nature of *Plasmodium* species and the need for personnel experienced to evaluate thick/thin blood smears [18]. Machine learning, which will be discussed in greater detail later in this article, has been proposed to analyze microscopic images captured by point of care smart phone-based applications. In the study by Fuhad *et al.*, using neural network, support vector machine, and *k*-nearest neighbor ML approaches, the investigators were able to produce models that achieved a sensitivity and specificity as high as 99.5 and 99.1% with an accuracy of 99.2% when compared against microscopy [19].

3. Mass spectrometry

3.1. Antimicrobial resistance testing

Mass spectrometry (MS) entered the domain of clinical microbiology around 2014. Matrix-assisted laser desorption ionization (MALDI) – time of flight (TOF) – MS is now used at many institutions to accelerate the detection of bacteria and fungi direct from microbiological culture [5]. These MALDI-TOF-MS techniques produce a proteomic spectrum representing ionizable proteins specific for various bacterial and fungal species. More recent innovations in this space have included the use of MALDI-TOF-MS to rapidly detect antimicrobial resistance [20]. Beta-lactamase activity has been observed by MALDI-TOF-MS, with protocols developed for evaluating ertapenem resistance in *Bacteroides fragilis* strains [21–22].

3.2. Pathogen identification

Mass spectrometry-based detection of pathogens is not limited to MALDI-TOF-MS for testing pure culture isolates. The use of liquid chromatography (LC) – MS using electron spray ionization (ESI) has also shown promise in this space. This has now expanded to using hybrid MS and molecular techniques. In this approach, molecular methods such as PCR can rapidly amplify pathogen genetic targets [23]. These amplicons are then tested by ESI-MS where the mass spectra are unique for specific microorganisms. This approach is useful for detecting pathogens that are difficult to culture and have also been applied to for SARS-CoV-2 testing under EUA [10].

3.3. Novel 2019 coronavirus infectious disease (COVID-19)

The COVID-19 pandemic resulted in a significant global demand for molecular testing [24]. Molecular capacity remains restrained despite substantial investment by manufacturers. Alternative testing approaches using MALDI-TOF-MS has been proposed as a low-cost, rapid, and high-throughput solution to alleviate demand on molecular testing [8]. For COVID-19, anterior nares swab samples could be tested by MALDI-TOF-MS to produce spectra representing ionizable proteins consistent with the host-response to infection. Due to the complex spectra produced by these patient samples, AI/ML is used to analyze the data and predict COVID-19 status. In recent studies, a neural network approach was used to analyze MALDI-TOF-MS spectra and achieved a sensitivity and specificity of 100% and 96% respectively when compared against PCR, with an area under the ROC curve of 0.99 when using 487 peaks that span 1993.91 to 19,9590.89 *m/z* [8]. Subsequent studies reported sensitivities and specificities of 100% and 93% respectively with additional ML training using a more heterogeneous population that included asymptomatic individuals, those with COVID-19 vaccination, and a range of SARS-CoV-2 variants (*i.e.,* Alpha, Delta, etc) [25].

4. Machine learning applications for infectious disease testing

Artificial intelligence is the field of computer science that strives to develop technologies that can replicate human behavior [26]. Machine learning is a subset of AI that developing systems that can improve performance when trained with new data. At one time, AI/ML would have been seen as science fiction, but today, it has transformed our

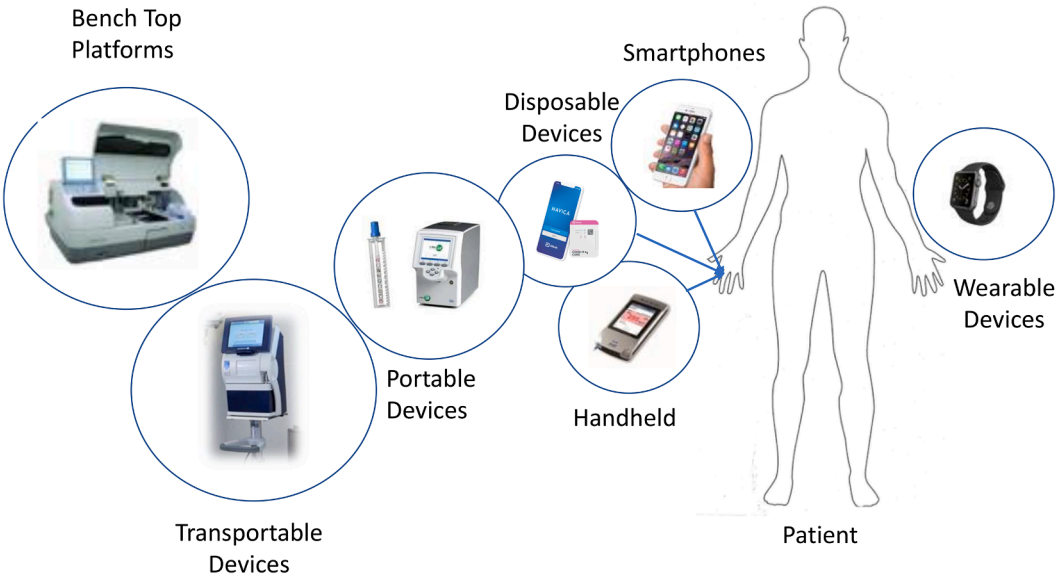

Fig. 2. Point of Care Testing Formats. Point-of-care testing formats range from wearable devices to larger bench top platforms. The figure provides examples of these platforms based on their portability. More portable testing formats are illustrated in closer proximity to the patient.

world and is expected to rapidly grow and perhaps grow in unpredictable ways. Examples of current AI/ML uses include allowing businesses to predict customer needs, autonomous vehicles to replicate human driving behavior, and help individuals search for information on the internet. In this same fashion, and already shown in this article, there are many applications that can disrupt healthcare, including field of infectious disease testing.

4.1. Lyme disease

Borrelia burgdorferi is the causative agent for Lyme disease [27]. Timely diagnosis is necessary to prevent disease progression. Unfortunately, early recognition remains challenging due to subtle signs that may be missed by both patients and healthcare professionals. Among early presenters, current Lyme disease testing exhibit poor sensitivity (<50%) and may lead to both underdiagnosis and overdiagnosis in some cases. In the study by Joung *et al.* AI/ML was proposed to augment performance when combined with a POC sero-diagnostic test that targeted bacterial antigens: OspC, BmpA, P41, ErpD, Crasp1, OspA, DbpB, VlsE, P35 and Mod-C6 [28]. The ML algorithm was able to achieve a sensitivity of 90.5% and specificity of 87.0% with conventional serology.

4.2. Meningitis

Meningitis remains a significant healthcare burden with 36,000 hospitalizations reported in the United States annually [29]. Rapid detection of pathogens causing meningitis has been augmented by molecular diagnostics, however, the primary specimen type remains cerebrospinal fluid (CSF). Likewise, rapid screening for meningitis via Gram Stain also requires a CSF sample combined with measuring white blood cells, glucose, and protein levels. To overcome these limitations, AI/ML has been applied to non-CSF parameters in hopes of predicting meningitis [30–31]. The study by Revett *et al.* described a neural network-based model using six features (*e.g.,* lymphocyte count, blood glucose, and age) that achieved a testing accuracy of 86.3% [31]. In another study, ML techniques were able to use age, race, sex, WBC, blood glucose, CSF glucose/protein/leukocytes (if available) features to produce a model that exhibited sensitivity and specificity of 99% and 100% respectively when compared against traditional microbiological techniques [30].

4.3. Sepsis

Sepsis is defined as life-threatening dysregulated host response to an infection [32]. Early recognition of severe sepsis is critical to survival and every hour delayed in initiating appropriate therapy significantly increases mortality odds [33]. Unfortunately, parameters for recognizing sepsis are not always sensitive nor specific, and applicable to every population. Being a repository of data, electronic medical records (EMR) are uniquely poised to leverage AI/ML to facilitate early sepsis recognition. Machine learning studies have been conducted in the general intensive care unit (ICU) population and reporting sensitivity/specificity of 87% using age, gender, blood pressure, HR, temperature, oxygen saturation, RR, WBC count, microbiological culture results, lactate, high sensitivity C-reactive protein, procalcitonin, arterial blood gas, use of vasopressors, and use of antibiotics as features [34]. However, such an ML model would perform poorly for special sepsis populations such as burns patients who are at high risk for sepsis. This limitation highlights a strength of AI/ML whereby algorithms could be trained for these special populations when new data is available. In a study by Tran *et al.*, an AI/ML model was developed for predicting burn sepsis with sensitivity and specificity of 95.8% and 87.8% respectively using HR, body temperature, hemoglobin, blood urea nitrogen, and total CO2 as features using a *k*-NN approach [35].

4.4. Molecular host-response analysis

Another AI/ML infectious disease application is molecular host response testing. Expanding from traditional indicators of sepsis, a multi-RNA host response profiles augmented by AI/ML has been shown to predict bacterial and viral infections. The study by Ducharme *et al.* evaluated a 29-host-mRNA 30-minute POC test that utilized AI/ML to identify patients with bacterial or viral infections [36]. This platform utilized a neural network ML algorithm which achieved an area under the ROC curve of 0.92 [37].

5. Alternative sample types

Infectious disease testing has often relied on collection of fluids and tissue specimens. For common respiratory infections, the nasopharyngeal (NP) swab sample has served as the accepted “gold standard” for testing. Unfortunately, the COVID-19 pandemic created a need for alternative sample types due to swab shortages early in the pandemic, and challenges in obtaining NP samples.

5.1. Saliva specimens

Saliva samples are now used by several facilities for mass COVID-19 screening. Rutgers University was the first institution to receive EUA for a saliva-based collection kit [10]. Saliva performance has been suggested comparable to NP swab based on recent studies and highlighted by the Infectious Disease Society of America (IDSA) [38]. However, widespread adoption of saliva remains limited due to no standardized approach for testing, and not all EUA SARS-CoV-2 PCR assays being compatible with this sample type. Saliva specimens may also have pre-analytic factors that could result in erroneous performance including patient food intake before testing, medications, hydration status, among other confounding factors [39]. Due to these limitations, swab-based samples remain the most common specimen type for COVID-19 testing, however, saliva’s comparability to NP provides hope that future infectious disease tests may consider this to be a less invasive sample type.

5.2. Breath specimens

The use of breath samples for infectious disease testing is most familiar with *Helicobacter pylori* testing. Like saliva samples, interest in breath testing was from challenges faced during the COVID-19 pandemic. In the study by Ruszkiewicz *et al.*, volatile organic compounds (VOC) were measured in breath samples by gas chromatography ion mobility spectrometry (GC-IMS) [40]. These VOC’s were determined to be aldehydes, ketones, and methanol that discriminated COVID-19 from other conditions and producing a sensitivity and specificity of 82.4% and 75% respectively. In addition to VOCs, breath samples have been shown to also contain virions including Influenza A [41]. Limitations of breath analysis, however, is the dependence on expensive analytical methods such as GC-IMS or other MS-based techniques, as well as the complexity of data which may require the use of ML methods.

6. Challenges and barriers

Advances in infectious disease testing discussed in this review must be tempered with caution. Evidence cited in early studies or in more controlled conditions may not fully reflect real-world performance [42]. Antimicrobial susceptibility testing by MS, for example, remains promising technology, but the shear complexity of the bacterial proteome and the impact of proteomics to *in vitro* antimicrobial resistance in clinical care remains unproven [43]. Likewise, during the COVID-19 pandemic, the US FDA EUA pathway greatly accelerate deployment of numerous molecular, antigen, and serological tests. Unfortunately, the real-world evidence for several tests did not match performance described on the

submitted EUA – exhibiting less sensitivity and specificity [44–45]. In the area of ML, the data used to train these algorithms is key to success [25]. Despite, promising performance of the cited ML-enhanced COVID-19 MALDI-TOF-MS, it was still based on a smaller sample size and requires large multicenter studies to be completed for regulatory consideration [8–25]. The authors reiterated this same notion that secondary and even tertiary dataset are further needed. At the time of this review, these multicenter studies are ongoing. Likewise, for novel COVID-19 sample types such as saliva and breath. More work is required given matrix effects which have not been fully vetted due to the urgent nature of the pandemic [46].

7. Summary

The complex and evolving nature of infectious diseases requires constant innovation to stay ahead of current and future pathogens. Advances in automation and miniaturization have fueled the expansion of molecular infectious disease testing into the POC testing space. The COVID-19 pandemic has required innovators to think well outside the box to keep up with the rapidly changing science behind SARS-CoV-2 infections. Disruptive technologies such as wearable devices, novel low-cost molecular approaches (*i.e.,* CRISPR), AI/ML, and MS are poised to transform infectious disease testing. These new technologies can be further enhanced with less invasive sampling techniques (*e.g.,* saliva, breath) via OTC/DTC tests and address challenges that limit patient access to care.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] P. Smit, J. Heniger, Antoni van Leeuwenhoek (1632–1723) and the discovery of bacteria, Antonie Van Leeuwenhoek 41 (1) (1975) 217–228.
[2] S. Falkow, Molecular Koch's postulates applied to bacterial pathogenicity – a personal recollection 15 years later, Nat. Rev. Micro 2 (1) (2004) 67–72.
[3] K. Mullis, F. Faloona, S. Scharf, R. Saiki, G. Horn, H. Erlich, Specific enzymatic amplification of DNA in vitro: the polymerase chain reaction, Cold Spring Harb. Symp. Quant. Biol. 51 (0) (1986) 263–273.
[4] P.-E. Fournier, M. Drancourt, P. Colson, J.-M. Rolain, B.L. Scola, D. Raoult, Modern clinical microbiology: new challenges and solutions, Nat. Rev. Microbiol. 11 (8) (2013) 574–585.
[5] Schumpeter, Joseph A., 1883–1950 (1983). *The theory of economic development: an inquiry into profits, capital, credit, interest, and the business cycle*. Opie, Redvers,, Elliott, John E. New Brunswick, New Jersey.
[6] A.O. Oyewole, L. Barrass, E.G. Robertson, J. Woltmann, H. O'Keefe, H. Sarpal, K. Dangova, C. Richmond, D. Craig, COVID-19 impact on diagnostic innovations: emerging trends and implications, Diagnostics. 11 (2) (2021) 182.
[7] G. Hansen, J. Marino, Z.-X. Wang, K.G. Beavis, J. Rodrigo, K. Labog, L. F. Westblade, R. Jin, N. Love, K. Ding, S. Garg, A. Huang, J. Sickler, N.K. Tran, A. J. McAdam, Clinical performance of the point-of-care cobas Liat for detection of SARS-CoV-2 in 20 minutes: a multicenter study, J. Clin. Microbiol. 59 (2) (2021), https://doi.org/10.1128/JCM.02811-20.
[8] N.K. Tran, T. Howard, R. Walsh, J. Pepper, J. Loegering, B. Phinney, M.R. Salemi, H.H. Rashidi, Novel application of automated machine learning with MALDI-TOF-MS for rapid high-throughput screening of COVID-19: A proof of concept, Sci. Rep. 11 (1) (2021), https://doi.org/10.1038/s41598-021-87463-w.
[9] G.J. Kost, N.K. Tran, Effects of point-of-care testing on time, process, decision making, treatment, and outcome, in: G.J. Kost (Ed.), Principles & Practice of Point-of-Care Testing, Lippincott Williams and Wilkins, Philadelphia, 2002.
[10] Food and Drug Administration website: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization, Accessed on September 9, 2021.
[11] X. Wang, X. Shang, X. Huang, Next-generation pathogen diagnosis with CRISPR/Cas-based detection methods, Emerg. Microbes Infect. 9 (1) (2020) 1682–1691.
[12] P. Fozouni, S. Son, M. Díaz de León Derby, G.J. Knott, C.N. Gray, M.V. D'Ambrosio, C. Zhao, N.A. Switz, G.R. Kumar, S.I. Stephens, D. Boehm, C.-L. Tsou, J. Shu, A. Bhuiya, M. Armstrong, A.R. Harris, P.-Y. Chen, J.M. Osterloh, A. Meyer-Franke, B. Joehnk, K. Walcott, A. Sil, C. Langelier, K.S. Pollard, E.D. Crawford, A. S. Puschnik, M. Phelps, A. Kistler, J.L. DeRisi, J.A. Doudna, D.A. Fletcher, M. Ott, Amplification-free detection of SARS-CoV-2 with CRISPR-Cas13a and mobile phone microscopy, Cell 184 (2) (2021) 323–333.e9.
[13] Q. He, D. Yu, M. Bao, G. Korensky, J. Chen, M. Shin, J. Kim, M. Park, P. Qin, K. Du, High-throughput and all-solution phase African swine fever virus (asfv) detection using crispr-cas12a and fluorescence based point-of-care system, Biosens. Bioelectron. 154 (2020) 112068, https://doi.org/10.1016/j.bios.2020.112068.
[14] B.L. Smarr, K. Aschbacher, S.M. Fisher, A. Chowdhary, S. Dilchert, K. Puldon, A. Rao, F.M. Hecht, A.E. Mason, Feasibility of continuous fever monitoring using wearable devices, Sci. Rep. 10 (1) (2020), https://doi.org/10.1038/s41598-020-78355-6.
[15] S. Shrivastava, T.Q. Trung, N.-E. Lee, Recent progress, challenges, and prospects of fully integrated mobile and wearable point-of-care testing systems for self-testing, Chem. Soc. Rev. 49 (6) (2020) 1812–1866.
[16] Food and Drug Administration website: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-machine-learning-based-screening-device-identify, Accessed on May 31, 2021.
[17] A. Naqvi, N. Manglik, E. Dudrey, C. Perry, Z.D. Mulla, J.L. Cervantes, Evaluating the performance of a low-cost mobile phone attachable microscope in cervical cytology, BMC Womens Health. 20 (1) (2020) 60.
[18] R.N. Bronzan, M.L. McMorrow, S. Patrick Kachur, Diagnosis of malaria: challenges for clinicians in endemic and non-endemic regions, Mol. Diagn. Ther. 12 (5) (2008) 299–306.
[19] K.M.F. Fuhad, J.F. Tuba, M.R.A. Sarker, S. Momen, N. Mohammed, T. Rahman, Deep learning based automatic malaria parasite detection from blood smear and its smartphone-based application, Diagnostics (Basel) 10 (5) (2020) 329.
[20] C.V. Weis, C.R. Jutzeler, K. Borgwardt, Machine learning for microbial identification and antimicrobial susceptibility testing on MALDI-TOF-mass spectra: A systematic review, Clin. Microbiol. Infect. 26 (10) (2020) 1310–1317.
[21] U.S. Justesen, Z. Acar, T.V. Sydenham, Å. Johansson, Antimicrobial susceptibility testing of Bacteroides fragilis using the MALDI biotyper antibiotic susceptibility test rapid assay (MBT-ASTRA), Anaerobe 54 (2018) 236–239.
[22] Å. Johansson, E. Nagy, J. Sóki, Detection of carbapenemase activities of *Bacteroides fragilis* strains with matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS), Anaerobe 26 (2014) 49–52.
[23] D.M. Wolk, E.J. Kaleta, V.H. Wysocki, PCR-electrospray ionization mass spectrometry: the potential to change infectious disease diagnostics in clinical and public health laboratories, J. Mol. Diagn. 14 (4) (2012) 295–304.
[24] O. Vandendberg, D. Martiny, O. Rochas, et al., Considerations for diagnostic COVID-19 tests, Nat. Rev. Microbiol. 14 (2020) 1–13.
[25] H.H. Rashidi, J. Pepper, T. Howard, et al. Comparative performance of two automated machine learning platforms for COVID-19 detection by MALDI-TOF-MS. Submitted 2021.
[26] H.H. Rashidi, N.K. Tran, E. Vali Betts, et al., Artificial intelligence and machine learning in pathology: the present landscape of supervised methods, Acad. Pathol. 6 (2019), 2374289519873088.
[27] P.S. Mead, Epidemiology of Lyme disease, Infect. Dis. Clin. North Am. 29 (2) (2015) 187–210.
[28] H.A. Joung, Z.S. Ballard, J. Wu, et al., Point-of-care serodiagnostic test for early-stage Lyme disease using a paper-based immunoassay and machine learning, ACS Nano (2020) 229–240.
[29] N. Khetsuriani, E.S. Quiroz, R.C. Holman, L.J. Anderson, Viral meningitis-associated hospitalizations in the United States, 1988–1999, Neuroepidemiology 22 (6) (2003) 345–352.
[30] G. D'Angelo, R. Pilla, C. Tascini, S. Rampone, A proposal for distinguishing between bacterial and viral meningitis using genetic programming and decision trees, Soft. Comput. 23 (22) (2019) 11775–11791.
[31] K. Revett, F. Gorunescu, M. Ene, A machine learning approach to differentiating bacterial from viral meningitis, IEEE (2006) 155–162.
[32] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, R. Bellomo, G.R. Bernard, J.-D. Chiche, C.M. Coopersmith, R. S. Hotchkiss, M.M. Levy, J.C. Marshall, G.S. Martin, S.M. Opal, G.D. Rubenfeld, T. van der Poll, J.-L. Vincent, D.C. Angus, The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (8) (2016) 801, https://doi.org/10.1001/jama.2016.0287.
[33] G. Husabø, R.M. Nilsen, H. Flaatten, E. Solligård, J.C. Frich, G.T. Bondevik, G. S. Braut, K. Walshe, S. Harthug, E. Hovlid, M. Crivellari, Early diagnosis of sepsis in emergency departments, time to treatment, and association with mortality: an observational study, PLoS ONE 15 (1) (2020) e0227652.
[34] K.H. Goh, L. Wang, A.Y.K. Yeow, H. Poh, K. Li, J.J.L. Yeow, G.Y.H. Tan, Artificial intelligence in sepsis early prediction and diagnosis using unstructured data in healthcare, Nat Commun. 12 (1) (2021), https://doi.org/10.1038/s41467-021-20910-4.

[35] N.K. Tran, S. Albahra, T.N. Pham, J.H. Holmes, D. Greenhalgh, T.L. Palmieri, J. Wajda, H.H. Rashidi, Novel application of an automated-machine learning development tool for predicting burn sepsis: proof of concept, Sci. Rep. 10 (1) (2020), https://doi.org/10.1038/s41598-020-69433-w.

[36] J. Ducharme, W.H. Self, T.M. Osborn, N.A. Ledeboer, J. Romanowsky, T. E. Sweeney, O. Liesenfeld, R.E. Rothman, A multi-mRNA host-response molecular blood test for the diagnosis and prognosis of acute infections and sepsis: proceedings from a clinical advisory panel, J Pers Med 10 (4) (2020) 266, https://doi.org/10.3390/jpm10040266.

[37] M.B. Mayhew, L. Buturovic, R. Luethy, U. Midic, A.R. Moore, J.A. Roque, B. D. Shaller, T. Asuni, D. Rawling, M. Remmel, K. Choi, J. Wacker, P. Khatri, A. J. Rogers, T.E. Sweeney, A generalizable 29-mRNA neural-network classifier for acute bacterial and viral infections, Nat. Commun. 11 (1) (2020), https://doi.org/10.1038/s41467-020-14975-w.

[38] IDSA Guidelines on the Diagnosis of COVID-19: Molecular Diagnostic Testing (Published 12/23/2020): https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/, Accessed on August 24, 2021.

[39] M.L. Landry, J. Criscuolo, D.R. Peaper, Challenges in the use of saliva for detection of SARS-CoV-2 RNA in symptomatic outpatients, J. Clin. Virol. 130 (2020), 104567.

[40] D.M. Ruszkiewicz, D. Sanders, R. O'Brien, F. Hempel, M.J. Reed, A.C. Riepe, K. Bailie, E. Brodrick, K. Darnley, R. Ellerkmann, O. Mueller, A. Skarysz, M. Truss, T. Wortelmann, S. Yordanov, C.L.P. Thomas, B. Schaaf, M. Eddleston, Diagnosis of COVID-19 by analysis of breath with gas chromatography-ion mobility spectrometry – a feasibility study, EClinicalMedicine 29-30 (2020) 100609, https://doi.org/10.1016/j.eclinm.2020.100609.

[41] P. Fabian, J.J. McDevitt, W.H. DeHaan, R.O.P. Fung, B.J. Cowling, K.H. Chan, G. M. Leung, D.K. Milton, R.A.M. Fouchier, Influenza virus in human exhaled breath: an observational study, PLoS ONE 3 (7) (2008) e2691.

[42] Food and Drug Administration website: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence, Accessed on October 16, 2021.

[43] E.A. Idelevich, K. Becker, How to accelerate antimicrobial susceptibility testing, Clin. Microbiol. Infect. 25 (11) (2019) 1347–1355.

[44] J. Shuren, T. Stenzel, The FDA's experience with COVID-19 antibody testing, N. Engl. J. Med. 384 (2021) 592–594.

[45] A. Basu, T. Zinger, K. Inglima, et al., Performance of Abbott ID Now COVID-19 rapid nucleic acid amplification test using nasopharyngeal swabs transported in viral transport media nad dry nasal swabs in a New York City academic institution, J. Clin. Microbiol. 58 (2020) e01136–20.

[46] D. Beale, O. Jones, A. Karpe, S. Dayalan, D. Oh, K. Kouremenos, W. Ahmed, E. Palombo, A review of analytical techniques and their application in disease diagnosis in breathomics and salivaomics research, Int. J. Mol. Sci. 18 (1) (2017) 24, https://doi.org/10.3390/ijms18010024.