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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The impact of COVID-19 pandemic on technologic and process innovation in point-of-care diagnostics for sexually transmitted infections

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ABSTRACT

The STI diagnostic landscape of FDA cleared tests for use at point-of-care (POC), as well as those emergency use authorized for COVID-19 are reviewed; some of these COVID-19 diagnostics may have platform potential as STI diagnostics. Finally, process innovation is described with self-collection and hub-and-spoke mail-in to reference lab models. Movement of Clinical Laboratory Improvement Amendments (CLIA)-waived POC tests to over-the-counter formats will make tests more accessible to consumers. Together with public health messaging, these measures could accelerate STI and COVID-19 syndemic diagnostic solutions.

1. Introduction

Among 15–49-year-old men and women, modeled estimates of the global totals of curable urogenital infections in 2016 was 376.4 million: 127.2 million cases of chlamydia, 86.9 million cases of gonorrhea, 156 million cases of trichomoniasis, and 6.3 million cases of syphilis [1]. Global access to sexually transmitted infection (STI) diagnostics other than HIV is poor and results in empiric algorithmic care for symptomatic patients only. These data informed a World Health Organization (WHO) strategy for STI's to ensure universal access to sexual and reproductive health-care services [2]. In the US, there were more than 2.5 million cases of chlamydia, gonorrhea, and syphilis reported in 2019, which is the 6th consecutive year of STI rise [3]. STI's are not only responsible for infant morbidity and mortality, but also long-term health consequences such as infertility and chronic pelvic pain in women, and also facilitate HIV transmission [4]. Social inequity and health disparities limit access to prevention and treatment in the populations most at risk; racial and ethnic minorities and youth aged 15–24 proportionally bearing a larger burden than other groups. The STI National Strategic Plan was developed to address these alarming increases in STI rates [5]. Key goal 3.3 of the report was to "Support the development and uptake of innovative STI diagnostic technologies, therapeutic agents, and other interventions for the identification and treatment of STIs, including new and emerging disease threats".

In the US, the molecular diagnosis of STI's generally occurs in central reference labs with turnaround times that necessitate empiric algorithmic treatment in symptomatic patients. Rapid turnaround time and accessible POC diagnostics could enable diagnostic certainty at the point of need and decrease the risk of exacerbating antimicrobial resistance (AMR) in these symptomatic patients. The ominous emergence and acceleration of drug-resistant *N. gonorrhoeae* (NG) portends the emergence and spread of untreatable superbugs [6–8]. For asymptomatic patients, particularly women under 25 years, diagnosing and treating the reservoirs of infection could interrupt transmission and prevent sequelae. POC diagnostics facilitate rapid sexual health screening for asymptomatic women, which could be accomplished within the clinical encounter.

Despite disruptions to STI diagnoses and treatment services as a result of the coronavirus disease 2019 (COVID-19) pandemic, preliminary US 2020 STI surveillance data suggest further increases in STI's 2019 trends [9]. Reports of congenital syphilis, a robust measure of community syphilis burden, have dramatically increased during 2020 suggesting rates of STIs have continued, unabated, during the COVID-19 pandemic despite social distancing [10]. However, reports of less routine laboratory testing, diagnoses and reporting may also result in an overall underestimate of the true burden of STIs in 2020 [11,12].

The COVID-19 pandemic also uncovered the limitations to public health testing for emerging infectious diseases through federal and state labs. By May 2020, the private sector was performing the majority of

Abbreviations: AMR, antimicrobial resistance; CLIA, Clinical Laboratory Improvement Amendments; COVID-19, coronavirus disease 2019; CT, *Chlamydia trachomatis*; EUA, emergency use authorization; FDA, Food and Drug Administration; HIV, Human Immunodeficiency Virus; LMIC, low- and middle-income countries; NG, *Neisseria gonorrhoeae*; OTC, over-the-counter; PCR, polymerase chain reaction; POC, point-of-care; RADx, Rapid Acceleration of Diagnostics; STI, sexually transmitted infection; WHO, World Health Organization.

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COVID-19 testing in the US. The National Academies of Sciences, Engineering, and Medicine consensus report highlights that the "COVID-19 pandemic has exposed weaknesses in public health preparedness due to weak infrastructure, an under-capacitated and under-resourced workforce, and limited surge capacity." [13] Multiple parallel efforts to bring more diagnostic tests and innovation to the market occurred; the Rapid Acceleration of Diagnostics (RADx) Tech program [14,15] was funded by Congress to the National Institutes of Health to accelerate diagnostic test development, Food and Drug Administration (FDA) emergency use authorization (EUA), and commercialization.

In this paper, the STI diagnostic landscape of POC FDA cleared tests, as well as POC FDA emergency use authorized COVID-19 diagnostics are reviewed. In addition, process innovation with self-collection and hub-and-spoke reference lab models are described as well as movement of POC tests to more accessible over-the-counter (OTC) formats. Together with public health messaging, these measures could accelerate STI and COVID-19 syndemic diagnostic solutions.

2. Regulatory pathways for Point-of care (POC) tests

Regulatory pathways for in vitro diagnostics vary by the technical skill of the user which is reflected in the stated complexity of the test. For most POC in vitro diagnostics, having a Clinical Laboratory Improvements Amendment (CLIA)-waived test allows health care workers to perform tests within clinical spaces under a CLIA waiver certificate. Such tests must be easy enough for personnel to follow the instructions for use and accurately perform the test without additional training. If the test is available for purchase by lay users, it must receive an OTC designation by the FDA and must be able to be performed simply by following the instructions for use. Some tests receive a prescription designation where a provider would prescribe the test at a pharmacy, it would be released to the lay user who would perform the test, and the provider would interpret the results. Finally, FDA clearance also delineates the sample types that have been cleared to be used with a particular device and how they are to be collected. For example, for POC CLIA-waived devices, whether the sample will be clinician- or self-collected must also be part of the clinical studies to obtain approval for each sample type.

With molecular innovation, miniaturization, and microfluidics, POC tests that are CLIA-waived and offer a small device footprint or single-use disposable assays are being rapidly developed. Some have achieved FDA clearance. In the past, developers have concentrated on performance which is important for FDA clearance. However, access to innovation and adoption of innovation is dependent on many factors including turnaround time, cost, device footprint and need for electricity, connectivity and reporting (lab information systems), and workflow; all of these together determine the use case and the potential market which should be considered before design freeze [16]. A WHO technical panel considering POC assays wrote, "We suggest that the technology as such does not define a POC test nor determine its use at the POC. Rather, it is the successful use at the POC that defines a diagnostic process as POC testing. So, it may be best to think of POC testing programs, rather than POC tests. It is how the tests are deployed or implemented in a health system that defines a POC testing program" [17]. Pai and colleagues enumerated the diverse users and settings in low- and middle-income countries (LMIC) where POC tests could be impactful, but also detailed barriers that would need to be considered at the development stage to ensure adoption [18]. The ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment-free, Delivered) criteria have emphasized accuracy, accessibility and affordability; recently, the REASSURED diagnostic systems have added consideration of rapid advances in digital technology. Rapid reporting should also be incorporated whenever possible, to allow real-time disease surveillance to inform control efforts [19,20]. In high-income countries, adoption barriers occur when decision makers (at clinics, hospitals or health systems) do not understand the 'value proposition' of POC tests that is based in a clinical-needs driven approach [21]. For example, in an emergency department, keeping patients flowing through a limited clinical space may be more important than insurance reimbursement for an individual test. In public STI clinics, knowing the exact diagnosis and resistance profile influences treatment and subsequent follow-up and contact tracing.

3. POC STI Assays: Lateral flow antigen and molecular assays

The POC STI tests that have obtained FDA clearance or are under consideration are shown in Table 1.

Antigen testing has been largely insensitive for most reportable and treatable STI's even though rapid, lateral flow formats that are not dependent on electricity are attractive. However, the Osom® Trichomonas test, (Sekisui Diagnostics LLC, Burlington, MA, USA) detects *Trichomonas vaginalis* in under 15 min. Lateral flow immunoassays have also been leveraged for syphilis screening; two assays have been FDA cleared: Syphilis Health Check (Trinity Biotech, Plc, Bray, County Wicklow, Ireland), and the DPP® HIV-Syphilis (Chembio Diagnostics, Inc, Medford, NY USA). Anti-treponemal antibody is detectable weeks after primary infection and will remain positive regardless of treatment. Therefore, two-step confirmatory lab-based testing is required before treatment can be initiated.

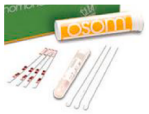
For reportable STI's such as CT and NG, there are several molecular POC platforms that have achieved FDA clearance. The Cepheid GeneXpert® System (Cepheid, Sunnyvale, CA, USA) is a flexible platform that is CLIA-waived; the system integrates and automates sample preparation, extraction, amplification, and detection into single-use cartridges. The instrument has a single moving piston part. It has a human gene internal positive control. For self-collected specimens, having a human gene control can be helpful as a sample adequacy control; human gene controls not only show that the assay chemistry worked (a valid test), but also ensures that a self-collected swab has human DNA. STI assays include standalone CT (Xpert® CT) and TV (Xpert® TV) assays, as well as a combined CT and NG (Xpert® CT/NG) assay. Xpert has been used extensively in LMIC for the detection of *Mycobacterium tuberculosis,* though the need for yearly calibration and reports of module failures and sensitivity to high temperature and humidity have been implementation challenges. Cost has been largely subsidized by donors in LMIC as the instruments are relatively expensive in high-income countries. More portable and robust systems such as Xpert® Omni are being developed, though final design freeze and roll-out has been delayed. Turnaround time is relatively long at 90 min, but the large install base globally, ease of use, and excellent performance makes this an attractive platform.

The Binx *io*® platform (Binx health, Trowbridge, UK and Boston, MA), previously Atlas Genetics) is a nucleic acid amplification POC test with a novel electrochemical DNA probe detection system. The *io*® CT/NG assay has a rapid turnaround time of 30 min with excellent performance and offers clinic-based use cases where a result could be returned to the patient during the clinical encounter. Self-collected vaginal swabs and urine samples for men received FDA clearance (August 2019) and then CLIA-waived status in March 2021.

The Solana Trichomonas Assay (Quidel, San Diego, CA, USA) is an isothermal nucleic acid amplification test (NAAT) (helicase-dependent amplification, HDA) with a 40-minute turnaround time; the platform requires separate specimen preparation, and then amplification and detection using a target-specific fluorescent probe. The moderate level of complexity placed the instrument in reference labs, the turnaround time, the cost, as well as the target, TV, make it unlikely that there will be wide adoption of this assay. However, there is platform potential if an assay for CT NG can be developed and deployed in places where lab technicians can be trained. The use case would be strongest at STI clinics with an attached reference lab where returning a clinical result during the clinical encounter may be important for public health.

The Visby Medical Sexual Health Test (Visby Medical, San Jose, CA, USA) is a deviceless, self-contained, single-use NAAT with integrated

Table 1
Sexually transmitted infection point-of-care tests (adapted from Gaydos et al. [52].

Company Product	Cepheid Xpert 	Binx *io*® 	Visby 	Osom 	Quidel Solana 	Diagnostics Direct Syphilis Health Check 	Chembio DPP HIV Syphilis 
Description	NG, CT, TV NAAT with molecular beacon detection in device [53–58]	NG, CT NAAT with electrochemical detection in device [59]	NG, CT, TV Single-use deviceless NAAT [60–61]	TV immunochromatographic lateral flow assay [62–63]	TV helicase-dependent amplification (previously AmpliVue)	IgG and IgM anti-treponemal antibody Lateral flow assay [64–65]	HIV, *Treponema pallidum* immunochromatographic lateral flow assay for detection of antibody with electronic reader [66–68]
Sensitivity	(vaginal) [53–54,69] 98.7% CT 100% NG (male urine) 97.5% CT 98.0% NG	(vaginal) 96.1% CT [59] 100% NG (male urine) 92.5% CT 97.3% NG	97.6% CT [61] 97.4% NG 99.2% TV	83–90% [70–71]	89.7% (vaginal swab) [54] 100% (urine)	71.4% (post licensure compared to Trep-Sure)	94.7% (syphilis) [67] 100% (HIV) (with reader in lab)
Specificity	(vaginal) [69] 99.4% CT 99.9% NG (male urine) 99.9% CT 99.9% NG	(vaginal) 99.1% CT 99.9% NG (Male urine) 99.3% CT 100% NG	98.3% CT 99.4 NG 96.9% TV	100%	99% (vaginal swab) 98.9% (urine)	91.5%	99.7% (syphilis) 98.7% (HIV)
Turnaround time	42 (TV)-90 min (CT/NG)	30 min	30 min	15 min	40 min	15 min	15 min
FDA cleared, CLIA waived	Yes, No	Yes, Yes	No, No (FDA pending)	Yes, Yes	Yes, No (moderate complexity)	Yes, Yes	Yes, Yes
Use Cases	Symptomatic, asymptomatic	Symptomatic, asymptomatic	Symptomatic, asymptomatic	Symptomatic, asymptomatic	Symptomatic, asymptomatic	Screening (needs confirmation)	Screening (needs confirmation)
Specimen types	Vaginal (self); Cervical (clinician); Urine; Rectal (self); Pharyngeal (self)	Vaginal (self); Urine	Vaginal (self)	Vaginal (self)	Vaginal (self); Urine	NA	NA
Blood types						Capillary fingerstick, serum, plasma, whole blood	Capillary fingerstick, serum, plasma, whole blood

extraction and multiplex PCR for CT, NG and TV. The initial trial showed excellent performance with self-collected vaginal swabs and the assay is currently under regulatory review at the FDA. A relatively high invalid rate (7%) in the trial was noted on initial testing which may be problematic if the cost of the test is high. The platform was also leveraged for a COVID-19 diagnostic (see #5 below) and was emergency use authorized as a CLIA-waived test, so the device is in use.

4. Clinical use case gaps for adoption of POC STI assays

Despite the recent progress in POC FDA-cleared STI assays, there are still clinical use case gaps to be filled. POC assays have the potential to allow for test and treat models that alleviate issues around tracing asymptomatic patients who test positive, but are no longer in clinic. Getting these patients traced and treated is time-consuming and expensive as is partner treatment. Furthermore, for NG, rapid information on antibiotic resistance mutations could allow tailored antibiotic regimens [22]. In a dynamic modeling study which included transmission among sexual partners, a hypothetical test with sensitivity ~ 10% lower than currently available reference tests could still have substantial impact on chlamydia prevalence and pelvic inflammatory disease incidence if, over 60% of the screened individuals received immediate treatment, and baseline lost-to-follow up was 20% in the current care delivery model [23]. Therefore, even a slightly lower test sensitivity could still have impact on diagnosis and treatment of STIs and avert complications of chronic infection.

Molecular assays that have a < 20-minute turnaround time would allow results is to be returned during a clinical encounter. Patient willingness to wait varied by setting. In China, 99% (1484/1497) of patients were willing to wait up to 2 h for a test result [24]. In the US, despite an average clinical encounter duration of 1–2 h, only 61% were willing to wait 20 min, and 26% up to 40 min for results (if they could be treated before leaving the clinic) [25]. For the adoption of a 30-minute test, 89.4% of patients were willing to wait up to 20 min after the clinical encounter was finished [26]. In a self-collected, sample-first workflow evaluation of a 90-minute assay, only 21.4% of the patients received their CT/NG result; among those who left, having a rapid result led to a 5-fold reduction in time to treatment (10–2 days) [27]

Amongst professionals engaged in STI care where 78% of the respondents practiced in the US, timeframe to perform the test was the most significant barrier, although number of steps, interruption of work flow, perceived wait time for patients were also commonly cited [28]. After sensitivity greater than 90%, cost less than $20 was the next most important criteria. Ability to detect resistance mutations especially for NG was considered an added advantage.

5. Impact of COVID-19 on POC diagnostics

The unprecedented emphasis on rapidly increasing the number of COVID-19 diagnostic tests available for testing in multiple user contexts has led to an acceleration of diagnostic innovation. Tables 2 and 3 show SARS-CoV-2 direct detection devices and assays that have been FDA emergency use authorized and CLIA-waived. There are 8 molecular platforms that are CLIA waived with turnaround times that range from 11 to 45 min (Table 2; 3 are multiplexed with other respiratory pathogens (BioFire Respiratory Panel 2.1-EZ, Cepheid SARS-CoV-2/

Table 2
Emergency Use Authorized, CLIA-Waived, Molecular Diagnostic Tests for SARS-CoV-2 (through September 23, 2021).

Company/ Supplier	Device	Set-Up	Sample type	Turnaround time	CLIA status	Target/Capacity/Comments
Abbott/ID NOW COVID-19	ID NOW (previously Alere i)	Modular, integrated system, isothermal amplification, molecular beacons	NP, throat, nasal swab directly	13 min	CLIA-waived (also for influenza)	Within the first 7 days of symptom onset; RdRp gene; single gene target; Limit of Detection 125 copies/mL (very limited clinical data in the IFU)
BioFire Defense, LLC BioFire COVID-19 Test	FilmArray 2.0, FilmAray Torch, RP2.1-EZ	Modular, integrated system	NP swabs (300 μL), pools of up to 8 samples	45 min	CLIA-waived	ORF1ab (2 regions) & ORF 8 gene targets; RNA process control (yeast Schizosacchoaromyces probe); Limit of Detection 330 copies/mL stand-alone assay; 500 copies/mL; multiplex*
Cepheid/Xpert® Xpress SARS-CoV-2	GeneXpert Xpress, Omni	Modular, integrated system	NP, nasal swab, NP aspirate, OP, mid-turbinate (600 μL of VTM)	45 min (30-minute positive early call)	CLIA-waived	N2 and E-gene targets; Limit of detection 250 copies/ml; Sample processing human RNase P gene control, probe check control; Multiplexed with Influenza A/B and RSV as well as SARS-CoV-2 only assays
Cue COVID-19 test	Cue cartridge reader, smart phone app	Integrated, isothermal	Nasal (direct or VTM)	20 min	CLIA-waived, OTC	N gene, RNaseP human gene control; Limit of Detection 1300 copies/ml, 20 copies/wand; 1.3 copies/uL
Lucira CHECK-IT COVID-19 test	Test unit pouch, and sample vial pouch	Integrated, isothermal RT-LAMP with halochromic reagents with pH change	Nasal, greater than14 self-collection or ≥ 2 years with adult collection	11 min positive, 30 min for negatives	CLIA-waived, OTC (home and prescription)	N gene 2 targets; Limit of detection 2700 copies/swab or 900 copies/mL of VTM; Resulting web portal
Thermo Fisher Scientific Accula SARS-CoV-2 Test**	Accula Dock, Silaris Dock	Modular, integrated system, RT-PCR	Mid-turbinate, nasal	30 min	CLIA-waived (also for influenza)	N gene; single gene target; Limit of detection 150 copies/ml Lateral flow assay requiring visual interpretation (internal negative and positive process controls)
Roche Cobas SARS-CoV-2 & influenza A/B NA test	Roche Liat	Integrated, RT-PCR	NP & nasal HCP, self-collected nasal (200ul)	20 min	CLIA-waived	SARS-CoV-2 (ORF1 a/b, N gene) and influenza A (matrix gene)/B (non-structural protein), Internal process control; Limit of Detection 12 copies/ml. Multiplexed with Influenza A/B.
Visby COVID-19	No device	Single-use disposable Integrated, RT-PCR	Nasal, mid-turbinate, nasal HCP or self-collected	30 min	CLIA-waived	N1 gene target; 18 s ribosomal RNA human gene control; Limit of Detection 435 copies/swab or 1112 genomic copies/ml

* BioFire Diagnostics LLC BioFire Respiratory Panel 2.1-EZ with de novo authorization includes Adenovirus, Coronavirus 229E, HKU1, NL63, OC43, Metapneumovirus, Rhinovirus/Enterovirus, Influenza A, B, Parainfluenza, RSV, *Bordetella parapertussis, Bordetella pertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae*
**Previously Mesa Biotech Inc.
NP = nasopharyngeal; OP = oropharyngeal; VTM = viral transport medium; OTC = over-the-counter CLIA = Clinical Laboratory Improvement Amendments;

Table 3
Emergency use authorized, CLIA-waived, antigen diagnostic tests for SARS-CoV-2 (through September 23, 2021).

Company/ Supplier	Antigen/ antibody	Set-Up	Sample type	Turnaround time	FDA EUA	PPA	NPA	Target/Capacity/ Comments
Abbott BinaxNOW COVID-19 Ag Card Home Test	Nucleocapsid antigen	Lateral flow visual read, serial screening	Dual nares	15 min after sample application	CLIA-waived, OTC	84.6%	98.5%	Within 7 days of symptoms; self-collected ≥ 15 years, adult collected ≥ 4 years Limit of Detection 140.6 $TCID_{50}$/mL
Access Bio Inc, CareStart COVID-19 antigen Home Test	Nucleocapsid antigen	Lateral flow visual read, serial screening (twice over 2–3 days)	Dual nares	10–15 min after sample application		70% (asymptomatic) 92.6%†	97.6% (asymptomatic) 97.3%	Within 5 days of symptoms; self-collected ≥ 13 years, adult-collected ≥ 2 years Limit of Detection 2800 $TCID_{50}$/mL
Becton Dickinson and Company BD Veritor System for Rapid detection of SARS-CoV-2	Nucleocapsid antigen	Chromatographic Digital Immunoassay, Instrument Read, Serial Screening (twice over 2–3 days)	Dual nares	15 min then put in device	CLIA-waived, also multiplexed with Flu A + B, OTC	84%	100%	Within 5 days of symptom onset; Limit of Detection 140 $TCID_{50}$/mL Analyze now and walk-away modes for reader
Celltrion USA Inc. Celltrian DiaTrust COVID-19 Ag Rapid Test	Nucleocapsid and spike receptor binding domain	Lateral flow, visual read, serial screening (twice over 2–3 days)	NP swabs	15 min	CLIA-waived	93.3%	99%	Within 7 days of symptom onset; Limit of Detection 140 $TCID_{50}$/mL (using beta-propiolactone inactivated virus)
Ellume Limited, Ellume COVID-19 Home Test	Nucleocapsid antigen	Lateral Flow, Fluorescence, Instrument Read, Screening	Mid-turbinate nasal	15 min	CLIA-waived, OTC	91% (Asymptomatic) 96%	96% (asymptomatic) 100%	Symptomatic and asymptomatic; self-collected ≥ 16 years, adult-collected ≥ 2 years Symptomatic PPA; NPA Limit of Detection $10^{3.80}$ $TCID_{50}$/mL
GenBody Inc GenBody COVID-19 Ag	Nucleocapsid antigen	Lateral flow, visual read	NP swab	15–20 min	CLIA-waived	91.1%	100%	Within 6 days of symptom onset; Limit of Detection 111 $TCID_{50}$/mL
InBios International Inc. SCoV-2 Ag Detect Rapid Test	Nucleocapsid antigen	Lateral flow, visual read, serial screening (twice over 2–3 days)	Dual nares	25 min	CLIA-waived	86.7%	100%	Within 5 days of symptom onset; Limit of Detection 6300 $TCID_{50}$/mL
Luminostics, Clip COVID	Nucleocapsid antigen	Lateral flow, immunoluminescent assay, instrument read	Dual nares	30 min	CLIA-waived	96.9%	100%	Within 5 days of symptom onset; Limit of Detection 88 $TCID_{50}$/mL
LumiraDx SARS-CoV-2 Ag	Nucleocapsid antigen	Antigen microfluidic immunofluorescence assay, instrument read	Direct dual nares swab, NP	12 min	CLIA-waived	97.6% (nasal) 97.5% (NP)	96.6% (nasal) 99.5% (NP)	Within 12 days of symptom onset; Limit of Detection 32 $TCID_{50}$/mL 280,000 TCID50/ml (BEI)
OraSure Technologies InteliSwab COVID-19 Rapid Test	Nucleocapsid antigen	Lateral Flow, Visual Read, serial screening (with at least 24 hrs, but not more than 36 hrs. between tests)	Blow nose first, then dual nares	30–40 min	CLIA-waived, OTC	84.3%	98%	Symptomatic up to 7 days or asymptomatic; self-collection ≥ 15 years; Limit of Detection 252 $TCID_{50}$/mL
PHASE Scientific International, Ltd INDICAID COVID-19 Rapid Antigen Test	Nucleocapsid antigen	Lateral flow, visual read	Dual anterior nares	20 min	CLIA-waived	84.4%	96.8%	Within 5 days of symptom onset; self-collection ≥ 18 years; Limit of Detection 2800 $TCID_{50}$/mL
			NP swab	15 min	CLIA-waived	93.9%	100%	

(continued on next page)

Table 3 (*continued*)

Company/ Supplier	Antigen/ antibody	Set-Up	Sample type	Turnaround time	FDA EUA	PPA	NPA	Target/Capacity/ Comments
Princeton BioMeditech Corp Status COVID-19/Flu	Nucleocapsid antigen	Lateral flow, visual read, multi-analyte						Multiplexed with influenza A, and influenza B Within 5 days of symptom onset; Previous influenza (PPA 85.5–90.8%; NPA 75.9–90.1%); Limit of Detection 2700 $TCID_{50}$/mL
Quidel QuickVue At-Home/OTC COVID-19/ SARS Antigen Test	Nucleocapsid antigen	Lateral flow visual read for OTC, serial screening (twice over 2–3 days with at least 24 hrs., and no more than 36 hrs between tests)	Dual anterior nares	5 min prep, 10 min read	CLIA-waived, OTC	84.8%	99.1%	Within 6 days of symptom onset; self-collection ≥ 14 years; adult-collected ≥ 8 years; Limit of Detection 1910 $TCID_{50}$/mL
Quidel Sofia SARS Antigen FIA	Nucleocapsid antigen	Lateral flow with reader, serial screening	Direct NP or nasal	5 min prep, 15 min read	CLIA-waived	96.7%;	100%;	Within 5 days of symptom onset; Limit of Detection 340 $TCID_{50}$/mL Walk-away or read now modes
Salofa Oy Sienna-Clarity COVID-19 Antigen Rapid Test Cassette	Nucleocapsid antigen	Lateral flow, visual read	NP swab	10 min		87.5%	98.9%	Within 6 days of symptom onset; Limit of Detection 1250 $TCID_{50}$/mL

Turnaround time after sample is applied. NPA and PPA for symptomatic patients unless specified.
† 93.75% PPA[a] and 99.32% NPA[b] when used with nasopharyngeal swab; 87.18% PPA[a] and 100% NPA[b] when used with anterior nasal swab (https://accessbiodiagnostics.net/carestart-covid-19-antigen/).
NP = nasopharyngeal; VTM = viral transport medium; OTC = over-the-counter CLIA = Clinical Laboratory Improvement Amendments; PPA = positive percent agreement; NPA = negative percent agreement; $TCID_{50}$ = median tissue culture infectious dose.

influenza/RSV, Roche Liat). Two isothermal tests (Cue COVID-19 test, Lucira CHECK-IT COVID-19 test) are available as over-the-counter (OTC) tests. In general, the RT-PCR tests with integrated extraction followed by RT-PCR have superior sensitivity to isothermal platforms but are more expensive. Interestingly, Binx leverages novel CRISPR technology for SARS-CoV-2 detection.

In Table 3, the 15 CLIA-waived SARS-CoV-2 antigen tests are listed. All are lateral flow assays some with a reader (which generally increases sensitivity) and some with visual detection. All have reasonably high sensitivity in symptomatic patients. Only 5 tests are available as OTC. Four of these are approved for use in asymptomatic patients with serial screening, where a user is expected to test at least twice in a short period of time to increase the likelihood of detection (Abbott BinaxNOW Ag Card Home Test, OraSure InteliSwab COVIS-19 Rapid Test, Quidel QuickVue At-Home SARS Antigen Test, BD Veritor At-Home COVID-19 Test). The Ellume COVID-19 Home Test is the only one authorized for asymptomatic, single-use screening.

6. COVID-19 innovation with applicability to STIs

Many of the molecular platforms could be engineered for other pathogen targets and could easily be pivoted toward STI detection. (Interestingly, Binx, Visby, and Cepheid started in the sexual health space and diversified to SARS-CoV-2 detection.) Many more molecular assays are in the pipeline and could add to the STI diagnostic platforms available for consumers with faster turnaround times with comparable sensitivity. Platforms with multiplex capability are attractive as additional AMR genetic determinants can be added particularly for NG. Targeting the *gyrA* or *parC* genes for ciprofloxacin resistance may have clinical treatment implications in the US as only a proportion of isolates are resistant to ciprofloxacin currently [29], allowing recycling of this antibiotic in an individualized medicine approach. Internationally, ciprofloxacin resistance is more complete and may preclude use [30]. Similarly, high level azithromycin resistance is found with 23S rRNA gene mutations which could allow molecular detection [31–33]. Genomic sequencing approaches still need to be optimized to be clinically useful, but have become small and inexpensive enough to be considered at point of need (MinION, Oxford Nanopore Technologies) [34,35].For other antibiotics like extended-spectrum cephalosporins where resistance is emerging [36], multiple genetic mutations can mediate this resistance and precludes molecular genotypic diagnosis [37]. Agar dilution phenotypic characterization is often necessary, but novel hybrid systems using quantitative PCR as a tool to assess bacterial growth after only 4–8 h in the presence or absence of antibiotics to identify resistant isolates have passed the proof-of-concept stage [38,39].

Although flocked swabs have superior collection and organism/nucleic acid release characteristics, supply chain disruptions have catalyzed innovation in this space as well. Injection molded plastic swabs have been developed (Yukon ClearTip™ swabs) that are comfortable for users (as opposed to 3-D printed swabs with sharp edges), cheap to produce, and have very low carrying capacity; these swabs absorb negligible buffer compared to flocked swabs (that absorb ~ 150 μL) and make them potentially suitable for more accurate pooling studies. Concentration capture has also been a way to increase the sensitivity of isothermal or lower sensitivity assays using nanotraps [40] or magnetic beads, streamline sample processing, and ameliorate the effect of inhibitors that can lead to invalid results. Importantly, cross-cutting, cloud-based lab information systems and reporting innovation translate into improved ways to accomplish both public health reporting and individual test results that can be shared with treating physicians. Paper microfluidics [41] and silicon chip microfluidics offer inexpensive

scaling options that could significantly reduce cost and complexity offering solutions that may be affordable enough for LMIC.

7. Diagnostic process innovation and impactful use

In order to fully realize the impact potential of POC diagnostics, users and patients must be able to perform the test without interruption and also have access to test reagents and devices. Ease of sample collection should also be taken into consideration. During the COVID-19 era, waiting for long periods of time in a crowded clinic may increase likelihood of transmission. In addition, regardless of COVID-19, travel to and from testing venues costs money and has an opportunity cost because of time spent away from work. COVID-19 has focused attention on validating self-collection of specimens in all settings (high-income countries and LMIC) and also on self-testing. OTC testing decreases population movement and occupational exposure risks, and improves resource utilization, and, allows rapid self-diagnosis and isolation [42]. For STIs, only the OraQuick In-Home HIV Test kit (OraSure Technologies, Bethlehem, PA, USA) has been approved for OTC screening use (2012, for age 17 and older).

Another model is mail-in testing for both STIs and COVID-19 testing. In this model, self-collection kits are mailed to users and then mailed back to central reference labs for testing. To validate mail-in testing, self-collection and mailing to the reference lab has to be validated against clinician-collected reference lab testing. Test validation must also include the mailing process, where dry swabs have to be subjected to a wide range of temperatures over time to ensure that there is no significant degradation of results (under such conditions that may be found in a mailbox) [43,44]. Iwantthekit (IWTK) was established in 2004 as an on-line platform to provide free, home-based specimen collection for STI testing [45–51] for Maryland, Alaska, and for parts of Arizona. Users receive specimen collection supplies and a pre-paid return envelope. Returned specimens are tested and then results are verified and posted to the HIPAA compliant website for viewing. To date >20,000 user samples have been tested for chlamydia, and gonorrhea. During the COVID-19 pandemic, when STI public health clinics were closed, IWTK offered testing to Baltimore City residents with a 645% increase in order volumes, an increase in priority populations, high positivity rates of reportable STIs, and 96% treatment completion. Takemehome.org offers similar services for 18 other jurisdictions with CT/NG/TV as well as hepatitis C antibody testing. Many health departments are mailing OraQuick self-tests as part of efforts to end the HIV epidemic. Taken together, self-collection with mail-in or OTC testing are important additional testing options to increase the proportion of at-risk patients who can get tested and know their status.

A plethora of commercial on-line testing for both STIs and COVID-19 have emerged where users' self-collect specimens at home or in static lab locations. Regulation and quality assurance will be needed to verify the testing platforms and lab quality certification which are rarely transparently reported on websites. Most commercial programs can be costly for users, although some accept insurance.

8. Conclusions

STI control both in the US and globally will require access to more POC testing options within clinical settings that are rapid enough for results to be returned within the clinical encounter. The COVID-19 pandemic has accelerated diagnostic development and catalyzed a paradigm shift for self-collection, OTC and mail-in testing. These process innovations will increase the proportion of patients who 'know their status' for STIs and COVID-19. Further technologic innovation already in the pipeline should decrease cost and turnaround time that will, in turn, accelerate adoption of new tests. Even more rapid direct detection technology without PCR amplification would allow very rapid diagnostic certainty and is the next exciting frontier for POC assays.

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