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Point-by-point progress: gonorrhea point of care tests

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Abstract

Introduction: Point-of-care (POC) tests for Neisseria gonorrhoeae (Ng) are urgently needed to control the gonorrhea epidemic, so patients can receive immediate diagnoses and treatment. While the advent of nucleic acid amplification tests (NAATs) have improved the accuracy of Ng identification, very few POC assays are able to provide results of such tests at the clinical visit. Additionally, antimicrobial resistance (AMR) presents a unique treatment challenge for NG.

Areas covered: This review notes that older POC tests have lower sensitivity for Ng, compared to the currently-available NAATs, are not adequate for the current demand for high sensitivity. Promising newer assays, which can be used at the POC are covered. This review also includes data about clinicians' and patients' acceptability and expectations of POC tests for Ng, testing of extragenital specimens, pooling studies, as well as their impact clinically and use in low-resource settings.

Expert opinion: The ability to use POC tests to identify and immediately treat Ng infections at the patient encounter offers many benefits and opportunities. POC tests for Ng are currently available, but not widely used especially in low-resource settings. Further development of POC test with AMR testing capacity is needed to help guide antimicrobial stewardship.

Keywords

Neisseria gonorrhoeae; point-of-care tests; antimicrobial resistance; sexually transmitted infections; diagnostics

1. Introduction

Gonorrhea is the second most prevalent bacterial sexually transmitted infection (STI) with an estimated 87 million infections in 2016, the majority reported in low-resource settings [1]. In the United States, the rate of reported gonorrhea cases increased 5.0% from 2017–2018, with total of 583,405 cases reported, and increased 82.6% since the historic low in

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Declaration of Interest

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2009 [2]. Gonorrhea is associated with significant morbidity as well as increased rates of HIV transmission [3,4]. The threat of untreatable gonorrhea has become a global public health concern as *Neisseria gonorrhoeae* (Ng) has developed resistance to all commonly-prescribed antimicrobials, including the recommended treatment of ceftriaxone and azithromycin [5]. NG has been identified as one of the top three urgent threats among antibiotic-resistant bacteria requiring immediate public health attention to identify infections and limit transmission of 'untreatable' infections [6].

Nucleic acid amplification tests (NAATs) have been shown to provide enhanced diagnosis of gonorrhea, but the majority cannot be used at the point-of-care (POC) and are cost prohibitive in developing countries [7]. Two Federal Drug Administration (FDA)-cleared NAATs can be used at the POC, but are not widely used for POC testing, except in research venues, due to various issues. These barriers include expense, longer time to result than some patients will wait, and lack of FDA clearance as being CLIA (Clinical Laboratory Improvement Amendments)-waived for performance by personnel, who are not laboratorians. None of the commercially-available, FDA-cleared NAATs, which can be used at the POC include antimicrobial susceptibility testing (AST). As a result, patients may be treated with inappropriate antimicrobials, which can lead to the development and spread of antimicrobial resistant Ng [8]. The World Health Organization (WHO) has identified several strategies to control the spread of antimicrobial resistance (AMR) in Ng, including improved methods for diagnosis and characterization/monitoring of resistance [9]. If a POC test could provide a result for not only Ng, but also for a resistance marker(s), such a test would be invaluable for providing an immediate therapeutic option and for potentially sparing cephalosporins [10]. Unfortunately, no such POC diagnostic options currently exist. However, molecular genotyping of the *gyrA* gene has been shown to be highly sensitive and specific for predicting susceptibility to ciprofloxacin, [11–15] highlighting the feasibility of using this molecular marker for the development of a POC test for the rapid characterization of AMR.

Sensitivity and specificity are important parameters of the ideal POC test and very important in screening situations. Additionally, in settings where disease prevalence is low, the positive predictive value (PPV) can be very low; this may be the case when vaginal discharge is used as an indicator for treatment as part of syndromic clinical management. These factors, as well as overall performance vary in real-world conditions, and can be affected by staff training and their ability to interpret test results. POC tests may have the ability to circumvent timeliness of traditional diagnostics and permit patients to receive results and treatment before leaving the clinic or doctor's office. A diagnosis on the first day of presentation will reduce widespread and empirical administration of broad-spectrum antibiotics, drastically decrease the use of unnecessary treatment when the test is negative, and contribute to antibiotic stewardship. The main issues regarding POC endorsement include whether they are sensitive, specific, inexpensive, and simple enough to affect time to treatment, as well as if they are cost-effective. A modeling study has demonstrated that less sensitive POC tests can result in more patients being treated [16]. Another important issue in the implementation of POC tests is whether clinicians desire to use these rapid tests [17].

The WHO has provided developers and users of POC diagnostics guidelines, known as ASSURED, to aid in the development and use of POC diagnostics for STIs that have true utility, both in developed and developing countries. **ASSURED** stands for: **A**ffordable by those at risk for infection, **S**ensitive, very few false negatives; **S**pecific, very few false positives; **U**ser-friendly, very simple to perform (minimal steps required with minimal training); **R**apid and Robust, to enable treatment at first visit (rapid) and does not require refrigerated storage (robust), **E**quipment-free, easily collected non-invasive specimens (e.g., saliva and urine) and not requiring complex equipment and **D**eliverable to end-users [18]. While the ASSURED criteria provides recommendations for the ideal POC test, many of the currently-available and under-development tests may not meet the criteria, especially those developed for under-developed countries. However, a test that can provide diagnosis, followed by treatment during the same clinic visit would be ideal.[19, 20] End users (patients) of POC tests prefer diagnostics that are rapid, easy to read and simple to use. While home POC testing is acceptable because of confidentiality, privacy, and convenience, patients prefer clinic-based POC tests because they offer definitive results and ensure immediate treatment [21]. The WHO has continued to support the development of POC tests for STIs and in collaboration with the Foundation for Innovative New Diagnostics (FIND) is working to assist and enhance this effort [22,23]. This development of new POC tests by WHO/FIND is largely focused in resource-limited settings, where laboratory infrastructure is lacking, and testing at the POC is the way forward, especially by providing improved disease surveillance. The focus of this review is to address shortcomings and advances of some POC tests and offer future perspectives for POC diagnostics for Ng. The authors performed a Pub Medicine (PubMed), U.S. National Library of Medicine, National Center for Biotechnology Information Search for ‘Point of Care Tests Gonorrhea’, which returned 119 papers published in the previous 10 years. Selection of articles was based on articles evaluating POC tests with comparison to a gold standard NAAT assay or using a FDA-cleared POC assay in clinical assessments. Several other PubMed searches on POC tests acceptability, cost effectiveness, and use in low-resource settings were conducted. Articles were included that measured the attributes and desirable characteristics of POC tests. While some clinical assays do not technically meet the best and ideal time-to-results that are most desirable for POC tests, they can be used in near-patient clinical encounters and are included in this review.

2. Older available POC tests for NG.

Older available Ng POC tests, suffer from poor sensitivity of about 70%; specificity has generally been better at above 95% [24]. Some of these published assays have been removed from the market or are of such low sensitivity that they would not meet inclusion criteria in today’s climate [25–26]. A review of the performance and operational characteristics of POC tests demonstrated that tests based on antigen detection lacked sufficient sensitivity (12.5% - 70%) to be used for screening, required 5 – 7 steps, and that results were available in 25 – 40 minutes [27].

Availability of poorly performing POC tests for gonorrhea has also been described in other review articles [28–31]. All of these non-NAAT assay publications, demonstrated that much

improved POC tests with better sensitivity for the detection of Ng were hugely needed [28–31].

2. Current near-patient and rapid POC tests

Newer assays have moved to molecular NAAT and have achieved commercial status and regulatory clearance, including FDA clearance and/or European Conformity (CE) In Vitro Diagnostic (IVD) (CE-IVD) certification for NG (Table 1). Other POC assays for Ng that are in development have been mentioned in the literature, but for which peer –reviewed publications do not yet exist, include: the ID NOW (CT/NG) and the Truenat (Molbio). For more details on these assays, please see Unemo et al. 2019 [31].

2.1. GeneXpert®

The first commercial assay to employ NAAT technology and receive FDA clearance is the GeneXpert® assay (Cepheid, Sunnyvale, CA). This assay has offered near-patient tests, combining microfluidic technology with real-time PCR. The cartridge-based assay extracts and amplifies the DNA, and detects the PCR amplicon in 90 minutes [32]. Sensitivities and specificities ranged from 95.6 to 100% and 99.9 to 100%, respectively for both female (vaginal, cervical, and urine) and male (urine) specimens. Additionally, research indicates there were no false-positive results with other *Neisseria* spp. or other genital near neighbors [33]. The WHO has also confirmed the sensitivity and specificity of this assay with a global selection of Ng isolates, finding high performance [34]. Although the assay requires 90 minutes which is a bit longer than ideal for some situations, it has been successfully used at some clinical encounters, especially when samples could be obtained before seeing the clinician. This has been shown in the widely-cited Dean Street Express (DSE) Clinic [35]. The DSE Clinic in London has used the rapid Xpert® assay extensively and has demonstrated that the rapid testing express visits resulted in a reduced mean time to notification of results from 8.68 days at the Dean Street clinic compared to 0.27 days for the DSE.

Use of the GeneXpert® assay in a busy Emergency Department (ED) in a clinical trial comparing the rapid test to the standard laboratory NAAT assay demonstrated that the rapid test resulted in a significant reduction in overtreatment for women without infections compared with the standard-of-care control group [36]. Undertreatment for both *Chlamydia trachomatis* (CT) and Ng in the ED was 0% for the rapid test group (Xpert® assay) and 43.8% for the control standard-of-care group. Specifically, clinicians overtreated 46.5% of uninfected standard-of-care control patients for CT compared with 23.1% of uninfected rapid test patients. For Ng-uninfected patients, clinicians overtreated 46.7% of standard-of-care control patients compared with 25.4% of rapid test patients. The length of stay did not differ significantly between groups.

2.1.1. Rectal and oropharyngeal samples—Until recently there have been no FDA-cleared NAATs for the detection of Ng from rectal and oropharyngeal samples. As of May 23, 2019, the FDA cleared two NAATs through the premarket notification (510(k)) pathway for detection of gonorrhea as well as chlamydia, one of which was the Xpert® CT/NG assay [37]. Previously, laboratories were required to perform self-validation studies to use such

assays clinically [38, 39]. A comparison analysis of 448 self-collected swabs revealed that the GeneXpert® was 100% sensitive and specific, in comparison to the Aptima Combo2, for detection of Ng from rectal swabs [38]. Similarly, a prospective evaluation of rectal swabs in Papua New Guinea showed that the positive, negative predictive values, and overall agreements of the GeneXpert® for detection of Ng were 93%, 100%, and 97.8%, respectively, when compared to the Cobas 4800 CT/Ng test [40]. An earlier comparison of the Xpert® assay with the Aptima AC2 assay in 409 residual Aptima rectal samples in the U.K. demonstrated high sensitivity, specificity, and positive and negative predictive values for Ng, despite the use of residual, diluted samples [41]. A systematic review of extragenital infections was conducted and data from five studies were combined to better assess positive percent agreement between Ng detection by the Xpert® CT/Ng with the Aptima Combo2 as the comparison assay [42]. The analysis demonstrated that for Ng detection in rectal specimens, the overall positive and negative percent agreement was 92.75% (95% CI: 87.91%, 96.46%) and 99.75% (95% CI: 99.46%, 99.93%), respectively, and in pharyngeal specimens, they were 92.51% (95% CI: 85.84%, 97.18%) and 98.56% (95% CI: 97.69%, 99.23%), respectively.

2.1.2. Pooling of specimens—

The GeneXpert CT/Ng assay has been used by some researchers for pooling of samples from several patients in order to save money since most samples are typically negative and positive pools can be “de-constructed” to determine which sample(s) in the pool are positive [43]. Detection of Ng and CT from pooled rectal, pharyngeal, and urine specimens from MSM found 100% agreement for Ng, when compared with individual specimen testing by the Cobas NAAT Assay [44]. However, another study found reduced sensitivity when pooling samples for STI testing on the Xpert® Assay [45]. Of the 388 participants who provided three individual anatomical specimens, 76 (19.6%) were found to be positive for CT and/or Ng at one or more sites. The pooling approach failed to detect four Ng pharyngeal infections. Cohen’s κ was 0.89 for Ng. Specimen pooling appears to save time potentially and costs when screening at-risk populations for Ng.

2.2. Binx *io*® Platform

The *io*® platform (Binx Health, Limited, Trowbridge, UK and Boston, MA, formerly Atlas Genetics) is the latest assay (August 2019) to receive FDA clearance as a molecular POC test for Ng [46, 47]. The assay also detects CT in the same test. A pilot study for detection of CT using this assay found high sensitivity and specificity, high patient acceptability, and that the majority of women (70%) preferred to collect vaginal self-swab if a POC test were available [48].

The *io®* CT/NG assay is the first molecular assay to provide sample to result, including DNA extraction and identification in 30 minutes, fitting the requirements for a short turn-around-time, so that results can be used to provide treatment to patients before they leave the clinical encounter. The test is approved for vaginal swabs and urine samples for men. . The assay was CE marked in Europe in April 2019.

In a recently-completed, multi-center clinical study with 1,523 participants, 96% of patient's vaginal swab samples were processed on the Binx *io*® platform by non-laboratorians in a POC setting. Clinical study performance for women demonstrated a 96.1% sensitivity and 99.1% specificity for chlamydia and 100% sensitivity and 99.9% specificity for gonorrhea [46]. For male urine, sensitivity and specificity for chlamydia were 92.5% and 99.3%, respectively. For gonorrhea the sensitivity and specificity were 97.3% and 100%, respectively.

2.3. ResistancePlus® GC Assay

The ResistancePlus® GC (beta) assay (SpeeDX Pty Ltd, Sydney, Australia) is the first commercially-available, licensed molecular test for the simultaneous detection of Ng and susceptibility to ciprofloxacin. The assay utilizes the PlexPrime® and PlexZyme® technologies [49] to enable high-level multiplexing of two targets (*opa* and *porA*) for detection of Ng and the *gyrA* gene for characterization of ciprofloxacin susceptibility. An evaluation of the assay with 822 Ng isolates and 110 non-gonococcal isolates showed 100% sensitivity and 99.1% specificity for detection of Ng [50]. For a discussion on the performance of the assay for prediction of ciprofloxacin susceptibility, see section 7.2. Further evaluation of the ResistancePlus® GC assay with 402 Ng-positive clinical samples and 290 Ng-negative samples showed 96% sensitivity for detection of Ng and 100% specificity [50]. The plate-based format of this assay limits its use to the laboratory setting, where multiple samples can be simultaneously processed. However, the development of the ResistancePlus® *Mycoplasma genitalium* assay as a cartridge test using the Cepheid GeneXpert® platform [51,52], offers the potential for the ResistancePlus® GC assay to be developed into a cartridge-based test for near-POC testing.

3. POC assays for NG under development

The MobiNAAT platform is a standalone, rapid, portable, sample-to-answer NAAT system. The test is carried out in an inexpensive, disposable cartridge, which contains all of the necessary reagents for nucleic acid extraction and amplification [53, 54]. In the cartridge, a fluidic process based on droplet magnetofluidics, transports the nucleic acid-carrying particles through a multi-step process culminating with nucleic acid amplification and detection. The MobiNAAT platform has been previously evaluated for detection of CT and quantification of hepatitis C viral load and showed excellent concordance with gold standard tests [53, 54]. A 15-minute multiplex assay for the detection of Ng and determination of ciprofloxacin susceptibility has been recently developed and is currently undergoing clinical validation. A pilot study conducted at two public STD clinics in Baltimore, MD using prospectively collected penile-meatal swabs found 100% concordance between the MobiNAAT and the gold-standard NAAT results [55].

A prototype recombinase polymerase amplification (RPA) (Twist Diagnostics, Cambridge, UK) assay has been evaluated as a POC test for gonorrhea in a prospective, multicentre study of symptomatic and asymptomatic patients at three English sexual health clinics using vaginal swabs and urine samples. Using male urine, the prevalence of gonorrhea was 3.1% (12/392) and the sensitivity and specificity were 100%; for females only 3 samples were

positive from urine and vaginal swabs. Although the detection assay can be performed in 15 minutes, a processing step of desalting using a chromatography device was required for urines, thus increasing the time of the whole assay [56].

Another prototype assay in clinical evaluation is the Novel Microdevices LLC, (Baltimore, MD) Novel Dx platform [57]. The Novel Dx technology comprises a rapid, ultraportable, and inexpensive microfluidic molecular diagnostic assay automation instrument, and a single-use, self-contained test-specific cartridge. The Novel Dx assay for CT and NG takes ~ 25 minutes to complete and is intended for use at the POC. Analytical sensitivity of the CT/NG assay was evaluated using real-time LAMP at amplification and detection of 5 cells/test for CT and 25 cells/test for NG. Preliminary evaluation of the Novel Dx sample-to-answer system with clinical samples was performed with 15 archived urine samples and 46 vaginal swabs from CT-infected and uninfected individuals. For NG, 17 urine samples and 7 vaginal swabs were spiked with various concentrations of NG. The Novel NDx sample-to-answer assay demonstrated 100% concordance with NAAT results for both CT and NG [57].

4. Clinical implementation of POC testing

4.1. Benefits and Impact

A modelling study from Australia has suggested that molecular POC tests of high sensitivity have great promise as a public health strategy for controlling gonorrhea [58]. The introduction of a POC test with 95% sensitivity could theoretically reduce the prevalence of gonorrhea from 7.1% to 5.7% under baseline screening coverage of 44% per year. If screening coverage were increased to 60% per year, prevalence could be reduced to 3.6%, under conventional testing, and further reduced to 1.8% with the introduction of POC testing. Increasing screening coverage to 80% per year could result in a reduction in the prevalence of gonorrhea to 0.6% [58]. As an example of the applicability and power of models, a recent U.S. model for chlamydia predicted that POC tests could improve chlamydia prevention efforts if test performance characteristics could be significantly improved, which may also have broad applicability for gonorrhea [59]. In that model several different scenarios were modeled. In one case, POC test sensitivity of 90%, reductions from the baseline burden only occurred in scenarios in which over 60% of the screened individuals would get immediate treatment and the baseline loss to follow-up (LTFU) proportion was 20%. Use of a POC test with 99% sensitivity would be estimated to avert up to 12,700 cases of PID cases/year, if 100% were treated immediately with a baseline LTFU 20% and 3-week treatment delay. Multiple analyses were performed in this manuscript [59]. Similar models in the future would be needed to study gonorrhea separately or as in a mixed model using both organisms.

Another different type of mathematical modeling study, using Baltimore, MD and San Francisco, CA prevalence data, was performed for several screening strategy interventions to improve gonorrhea screening from current levels and were shown to be able to reduce infections [60]. For example, in this study annual screening of the population aged 15–24 was the most efficient of the five-year interventions with 17.9 additional screening tests being needed per infection averted. The authors also showed that twice annual screening of the same population averted the most infections (5.4%, 95% CrI 3.1–8.2%) overall, but

requiring 25.3 (95% CrI 19.4–33.4) tests per infection averted [60]. Use of a POC test in this type model in the future would yield interesting results. Overall, modelling studies on the capacity of POC tests to reduce the prevalence and incidence of STIs are an important tool in helping to design control efforts, both in the US and globally [61].

4.2. Cost analysis

Few studies have looked at the cost effectiveness of using POC assays for gonorrhea separately, but several studies have been conducted for chlamydia and gonorrhea together. Turner et al. estimated the cost and benefits of clinical use of these assays for both CT and Ng in genitourinary clinics compared with standard off-site laboratory testing [62]. The primary outcome of the simulation was the incremental cost-effectiveness ratio, while secondary outcomes were the number of inappropriate treatments, complications, and transmissions averted. Using a POC test for CT/Ng was both more effective and cheaper, demonstrating that replacing standard laboratory tests for CT/Ng with a POC test would be cost-saving. Also use of the POC test was associated with a small increase of 46 quality adjusted life years and potentially would effectively eliminate the need for presumptive treatment. The authors estimated that using POC tests could prevent 95,000 inappropriate treatments, prevent 189 cases of pelvic inflammatory disease (PID), and 17,561 forward transmissions, on an annual basis. When clinical pathways were mapped for using POC CT/NG NAATs versus standard laboratory NAATs, they were shorter and cheaper than most clinical pathways [63]. Clinician's time was reduced by 10 minutes per patient. Estimation of cost for sexual health screening per patient were reduced by as much as £16 for symptomatic patients and by £6 for standalone CT/NG testing. Such immediate test results and treatment would be expected to prevent forward transmission during the wait time for standard test results and treatment of patients' loss to follow-up.

4.3. Challenges and opportunities

Implementation of POC tests for detection of gonorrhea in clinical encounters presents many barriers. Not only are there financial issues needed to change clinic methods for ordering routine laboratory tests versus performing POC tests in the clinic, but funds for an instrument and consumables must be considered. If the assay is CLIA-waived, the clinical practice must obtain a CLIA certificate in order to provide the test; the test must be validated, and proficiency of the operator(s) should be demonstrated. Other countries besides the US face similar challenges regarding the implementation of POC tests into clinical care. For example, in Europe and Australia, the implementation of CE-marked or other approved assays requires the establishment of training protocol for staff, development of quality control protocols and proficiency testing for test operators, and incorporation into the clinical work flow. In all countries, quality control (QC) measures for the performance of POC tests will need to be carefully implemented to insure that recommendations regarding positive and negative controls are met and that both training and proficiency testing for test operator is required. QC will be necessary whether POC tests are performed in the laboratory or at the POC. QC for physician's office testing is especially important, especially with regard to amplicon contamination and the need for extensive operator training, adherence to of rigorous training principles, and observance of fastidious techniques. While resource-limited settings face the same challenges, concerns regarding the cost of the test is

another major challenge to the implementation of POC testing. The ability to load the results into an electronic database should be performed. Consideration of a new workflow algorithm in the clinic has to be studied if patients have to wait for their results, as well as attention to billing and reimbursement for testing services, which are ordinarily done by the laboratory. While these issues are not insurmountable, concern of the impact the changes will have on the clinic must be considered. Another challenge to the implementation of POC testing is how to report notifiable diseases from POC tests performed in places like colleges, pharmacies, emergency departments. In order to maintain surveillance systems, reporting via "cloud–linked" systems will need to be developed [36, 64]. Despite the previously described challenges and limitations, new POC tools are beginning to be developed and implemented to make an impact on the epidemic of gonorrhea and other STIs [58].

5. Acceptability of POC testing – patients and providers

Patients (89%) were willing to wait for Binx io® CT/NG test results up to 20 minutes beyond the conclusion of their visit in a university student health clinic study [65]. Similar results were reported for wait time in adolescent and STI clinics, where most women (61%) were willing to wait up to 20 minutes, and 26% were willing to wait up to 40 minutes for results, if they could be treated before leaving clinic [48].

When health care workers were surveyed about acceptability of using a prototype smartphone-based POC test platform for use in the Emergency Department, acceptance was uniformly high [66]. Although Obstetricians and Gynecologists in the U.S. would like to have the availability of POC tests, not many actually used them, citing complexity and lack of accuracy as barriers [67]. Additionally, primary care providers have indicated high acceptability of POC tests in remote settings [68].

Needs assessments research is important to ascertain the requirements of clinicians who use POC tests, before they are implemented [69]. Focus group discussions with medical providers discussed topics included currently available POC tests, perceived barriers to use, and what were attributes of an ideal POC test. Clinicians would like a POC test with a rapid turnaround time of 20 minutes, ease of use, un-invasive sample type, and sensitivity, and specificity in the high 90 percent range [69].

To investigate the possible effects of different levels of attributes of a POC test on STI professionals' decisions regarding the ideal POC test for STI(s), an online survey of 256 subjects was conducted. The survey was designed based on the results of prior in-depth focus group discussions study among STI medical providers [69]. One section of the survey "build your own POC Test" was designed by employing the discrete choice experiment approach. Using choice modeling, the authors found that all participants who completed the survey selected sensitivity as their top priority issue for building a new STI POC test, followed by cost, specificity, and time. They preferred the new POC test to have a sensitivity of 90–99%, a cost of $20, specificity of 99%, and a turn-around-time of 5 minutes [70]. In subgroup analyses of different types of professional clinicians or on different geographical regions of the world, sensitivity was still reported as the top priority and time was the last priority for all subgroups. However, specificity was the second most important priority for

those who were medical directors, while cost was the second one for those who were not medical directors. In addition, subjects from the U.S. preferred cost as second priority issue over specificity, while cost and specificity were tied for the second priority issue.

When comparisons between frontline clinicians and professionals in industry were studied using an online survey, differences in the perceptions regarding barriers and ideal attributes for STI POC tests were identified. Clinician survey participants (n = 218) identified “the time frame required” (39.9%), “complexity” (31.2%), and “interruption of work flow” (30.3%) as the top 3 barriers to using STIs POC tests, whereas the industry survey participants (n = 107) identified “complexity” (65.4%), “unreliability” (53.3%), and “difficulty in reading results” (34.6%) as the top 3 barriers (all $P < 0.05$) [71]. Sensitivity was always the most important attribute to be considered for a new STI POC test by both groups of participants. Participants of the clinician group chose cost as the second-priority attribute, whereas those of the industry group chose specificity as the second priority [71].

Equally important for the future implementation of POC tests is to determine the qualities of the POC test that patients require. A qualitative study of five focus groups of attendees of STI and adolescent health centers in Maryland and Ohio found that participants were in favor or diagnostic tests that were rapid, easy to read, and simple to use [72].Home testing options for POC tests were acceptable and were thought to provide better confidentiality, privacy and convenience, but clinic-based POC tests were also acceptable, because they offered definitive results and ensured immediate treatment. Barriers to home-performed POC tests centered on cost and the ability to perform and read the test correctly at home. Patients attending STI and adolescent medical centers were in favor of STI POC tests if they were affordable, rapid, easy to read, and simple to use.

6. POC testing in remote and low-resource settings

POC tests can play an important role in resource-limited settings, where sophisticated laboratory facilities are not readily available. As a result, samples have to be sent to a regional laboratory and results are not returned in a timely fashion, often resulting in undertreatment and overtreatment due patients’ loss to follow-up and to syndromic treatment, respectively. As such, immediate treatment following diagnosis with a POC test is highly desirable. The GeneXpert® assay for detection of NG at the POC has been evaluated in resource-poor settings. A diagnostic accuracy study of the Xpert CT/NG assay in 247 women in South Africa showed that the rapid test had excellent sensitivity (100%) for detection of Ng in this setting and was a useful tool for the rapid diagnosis of STIs [73]. A study in antenatal clinics in Botswana, where women provided self-collected vaginal swabs, demonstrated that when women tested positive for STIs with the GeneXpert® CT/Ng assay, they were more likely to receive same-day treatment [74].Of 400 women enrolled, 13.5% tested positive for an STI. Those women who received same-day results were more likely to be treated (74%) than women receiving delayed results (67%) [74].

In Australia, the near-patient Xpert® assay has been used successfully in indigenous populations [75]. Retesting rates were too low to draw conclusions on the effect of the intervention on repeat infections. However, results indicated that time-to- treatment of CT or

Ng infections in primary care clinics in remote areas in Australia could be substantially reduced by the use of molecular POC tests. An additional study indicated high accuracy of the rapid test in 12 remote primary health settings where training was provided to 99 clinicians who performed the GeneXpert® assays themselves [76].

Although, rapid tests have shown promise for detection of Ng in low resource settings, additional cost-effectiveness and implementation studies are necessary to further evaluate the utility of implementing these tests in settings with limited resources [73]. Of concern in remote settings is the impact of specimen storage temperature and time of implementation of testing. These logistical challenges were found not likely to have an impact on the performance of routine STI diagnostics using the GeneXpert® platform implemented in these resource-constrained settings [77].

7. Antimicrobial susceptibility testing at the POC – Challenges and way forward

7.1. Benefits of susceptibility testing at the POC

Rapid diagnosis of gonorrhea and determination of antimicrobial susceptibility at the POC could lead to precision treatment, including reusing previously-recommended antimicrobials like ciprofloxacin [10]. This approach could ensure that patients are treated with appropriate antimicrobials on the day of diagnosis and reserve the use of currently recommended antimicrobials, such as ceftriaxone, for when it is truly necessary. A recent modeling study of gonorrhea transmission was used to investigate the impact of POC tests on antibiotic resistant Ng in MSM and heterosexual men and women (HMW) [78]. The study evaluated the effect of POC tests with and without resistance testing and concluded that the use of POC test with resistance testing would result in the lowest proportion of resistant infections in 30 years. Additionally, the continued use of POC tests for detection of gonorrhea without resistance testing would not be recommended as it could accelerate the spread of antibiotic-resistant gonorrhea. Using data collected in sexual health clinics in England, Turner et al, developed a mathematical model to investigate the treatment impact and economic implications of introducing antimicrobial resistance testing at the POC [79]. Their study concluded that the use of a POC test for ciprofloxacin or penicillin susceptibility could reduce ceftriaxone treatment by 66% and 79%, respectively. Additionally, the use of resistance testing could reduce time till treatment by 2 days. Another study evaluated the hypothetical effect of POC testing with antibiotic susceptibility determination on slowing the spread of AMR [80]. According to this model, continued empiric treatment without antimicrobial susceptibility testing at the POC was projected to result in >5% of NG isolates being resistant to both azithromycin and ceftriaxone within 15 years. Further, the use of a POC test for determination of susceptibility to either of these antimicrobials could delay the emergence of resistance by 5 years, but that a POC test for ciprofloxacin, azithromycin, and ceftriaxone susceptibility could have the greatest impact in delaying the emergence of triply-resistant strains [80]. Others have stressed that rapid, accurate POC tests for diagnosis of all STIs would be valuable, but that in order to be able to affect accurate treatment and management of Ng, as well as *Mycoplasma genitalium* infections, combinations of rapid POC diagnostic and POC AMR testing would be required [10].

7.2. Preliminary data and future assays for AMR testing

Given the increasing rates of multi-drug resistant (MDR) Ng worldwide and the threat of untreatable gonorrhea, increasing capacity for antimicrobial susceptibility testing, including at the POC, is rapidly becoming a necessity to help guide antimicrobial stewardship and prevent outbreaks of MDR Ng. Over the last few years, the re-use of ciprofloxacin for targeted precision treatment has been proposed as a suitable strategy to delay the emergence of ceftriaxone-resistant NG [10–15]. Given that the wildtype *gyrA* genotype is an excellent predictor of ciprofloxacin susceptibility [11, 13], a variety of assays have been developed for the rapid characterization of *gyrA* genotyping, including some which could be used at the POC. The ResistancePlus® NG assay (section 2.3) is the only commercially-available molecular test for characterization of ciprofloxacin susceptibility. In addition to detecting Ng, the multiplex assay is designed to detect both the *gyrA* S91F mutation and the *gyrA* wildtype 91 codon, which are highly predictive of ciprofloxacin resistance and susceptibility, respectively [50]. A diagnostic evaluation of the assay using Ng isolates demonstrated 99% sensitivity and >97% specificity when compared with phenotypic ciprofloxacin susceptibility. When tested with Ng-positive clinical samples (n=402), the assay showed 100% sensitivity/specificity for detection of the *gyrA* S91 mutation [50] Further development of this assay, including adaptation to POC platforms, such as the Cepheid GeneExpert® system, may allow for near POC testing [51,52].

Binx Health (Table 1) is developing a multiplex assay on the *io*® platform for detection of Ng and molecular characterization of ciprofloxacin susceptibility. This assay will soon be undergoing clinical validation. The previously-described MobiNAAT platform, which can detect Ng in 15 minutes, can simultaneously detect the wildtype *gyrA* genotype. Following a pilot study of this platform in the U.S. [55], this platform is currently undergoing clinical validation in Kampala Uganda.

The development of molecular POC tests for resistance testing to antimicrobials other than ciprofloxacin can be more changeling due to complex mechanisms of resistance [5, 31]. For example, while the *penA* mosaic allele is widely recognized as the primary mechanism associated with decreased susceptibility to extended spectrum cephalosporisns (ESC), clinical isolates with decreased susceptibility to ceftriaxone displaying various resistance markers have now been described [81–83]. Because of these complex, and still unknown, resistance mechanisms, a rapid test for determination of ceftriaxone resistance in Ng at the POC is still not available. Phenotypic susceptibility testing is still the best approach to identify and characterize resistant strains [5]. However, phenotypic characterization in Ng is hindered by the slow-growing nature of the organism, thus limiting the capacity for the development of rapid phenotypic tests. Recent studies, however, have suggested that RNA signatures could be promising as a tool in the development of future POC diagnostics for characterization of AMR in NG [84–87].

8. Conclusion

In conclusion, as the technological field continues to evolve, tests become faster, and more sensitive POC tests are developed, as well as their ability to detect AMR genotypes and/or phenotypes, there is reason to believe in a bright future for POC tests to be able to effect the

epidemic of STIs. Additional implementation studies involving end-users, clinicians, and public health experts will be warranted.

9. Expert opinion

Although NAATs have revolutionized the diagnosis of STIs, the use of POC molecular tests for detection of Ng is still in its infancy. In order for POC test for Ng to be truly useful, resulting in treatment of infected persons at a clinical encounter, it will be necessary for the assay to have a CLIA waiver. Adoption of such assays have barriers both from the clinic directors' and the clinicians' perspectives. There has been a recent and strong movement for broad stakeholder input and comprehensive evaluation of device performance beyond just cost and clinical performance, leading to value-based decision making [88]. Such input from all the stakeholders in a clinical situation could lead to a multi-dimensional checklist to guide the evaluation of POC tests, which incorporate the validity, utility, usability, and cost effectiveness of the assay, as well as the patient experience. Such an approach may lead to expert stakeholder workshops to help guide the evaluation and implementation of POC tests into clinical care [89]. Additional studies, including needs assessments of clinicians and patients, especially in low-resource settings, will be required. For example, a recent report indicates that some patients are happy to wait longer periods of time for results, if they can be treated the same day [65].

In terms of low and middle-income countries (LMIC), POC tests, meeting WHO's ASSURED criteria, need to be developed and evaluated. As cost might be the most important factor in the decision-making process of implementing POC testing in LMIC, cheaper, but tests with lower sensitivity might be acceptable in this setting, as long as high specificity is maintained. In addition to cost, others barriers, such as clinic flow and antimicrobial stewardship need to be considered before the implementation of POC testing in LMIC.

In addition to rapid diagnosis, POC tests could also be useful in helping to guide antimicrobial treatment. The current efforts to develop rapid tests for characterization of ciprofloxacin susceptibility at the POC could be an effective strategy to delay the emergence of ceftriaxone resistance, but only in regions where ciprofloxacin treatment could still be effective such as in the US and Europe [90–92]. In other regions, such as the Asia Pacific and Africa [93–95], where the documented rates of ciprofloxacin-resistant Ng are close to 100%, tests for other antimicrobials need to be developed. However, a major drawback to the use of molecular assays for prediction of AMR is that genotype does not always predict phenotype [30]. Furthermore, the complex mechanism of AMR in antimicrobials, such as cephalosporins, has so far prevented the development of reliable molecular assays for AMR prediction [5, 30]. Recent studies suggest that RNA signatures could be promising as a tool in the development of future POC diagnostics [84–87].

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Article Highlights

- Sensitivity, specificity, and positive and negative predictive values are important parameters of the ideal POC test for gonorrhea and very important in screening situations, especially in low prevalence settings.
- Using POC tests to identify and immediately treat Ng infections at the patient encounter may result in opportunities to prevent forward transmission.
- POC tests for diagnosis of gonorrhea are acceptable to both clinicians and patients.
- There are optimistic newer POC assays, which can be used at the clinical encounter that are FDA cleared and others that are showing promising results.
- Currently, there are two FDA-cleared assays that have been recognized for use at the point of the clinical encounter, which can provide results in either 30 or 90 minutes. Other promising assays are in the pipeline.
- Genotypic antimicrobial testing for gonorrhea for ciprofloxin by PCR is possible by research assays, but there is not yet a test that is available as a commercial POC assay.
- POC assays for other antibiotics could help antimicrobial stewardship.
- Quality control issues concerning the use of proper controls and user's training will require careful adherence for widespread adoption of POC assays outside of the laboratory.

Table 1

Point-of Care tests available and in development for *Neisseria gonorrhoeae*

Assay	Io® CT/NG	GenXpert® CT/NG	ResistancePlus® GC
Company	Binx Health	Cepheid	SpeeDX
Platform	Table Top Integrated	Table Top Integrated	Table Top PCR machine
Technology	NAAT Small molecule chemistry	Real-time PCR	Real-time PCR Ciprofloxin Resistance
Sample Type	Self- & clinician- collected vaginal swabs, male urines	Cervical swabs, Self-collected vaginal swabs, male & female urines	Cervical, vaginal, male & female urines, urethral, pharyngeal ocular swabs
Procedure	~4 steps	~4 steps	~4 steps
Result Time	30 min.	90 min.	50 min.
Regulatory	FDA, CE-IVD	FDA, CE-IVD	CE-IVD FDA pending

Table legend: Integrated, DNA extraction contained in platform; PCR, polymerase chain reaction; FDA, Federal Drug Administration; CE-IVD, European Conformity, Investigational device