

Call for Expressions of Interest (EOI) from test developers for tests to identify susceptibility/resistance of gonorrhoea to antibiotics to facilitate antibiotic stewardship

BACKGROUND

Gonorrhoea infection — caused by *Neisseria gonorrhoeae* (NG) — is the second most common bacterial sexually transmitted infection worldwide, with substantial morbidity and economic cost.^{1,2} The World Health Organization (WHO) has identified NG as a high-priority pathogen because of widespread antimicrobial resistance (AMR) to penicillin, tetracyclines, macrolides (including azithromycin), sulphonamides, trimethoprim, and quinolones, including emergent resistance to the “last line” extended-spectrum cephalosporins (ESCs) cefixime and ceftriaxone.

Countries need diagnostic tools to guide treatment choices, ensure current therapies remain effective for as long as possible, and preserve new drugs from rapid development of resistance by overuse. Providing a drug stewardship approach through the use of appropriate diagnostic tools will allow for controlled introduction of a new drug, preserving its efficacy for as long as possible and ensuring that current therapies are preferentially prescribed in patients who remain treatable with these drugs.

FIND (finddx.org) is facilitating the development of new diagnostics tools for improved clinical management of NG, with a particular focus on low- and middle-income countries (LMICs). FIND has developed target product profiles (TPPs) and requests for proposals (RFPs) for the highest priority diagnostics to manage NG infections. To support a diagnostic stewardship plan for treatment of NG, FIND has identified the need for a reflex test to determine NG susceptibility (antimicrobial resistance) to currently used first line antibiotics for cases with confirmed NG infections or NG treatment failure, with an option for additional markers of resistance to other antimicrobials. (Appendix 2).

The purpose of this EOI is to solicit researchers or commercial companies who have, or are working on further development of, tests that can identify antibiotic susceptibility/resistance of gonorrhoea so that FIND can update its diagnostics landscape and inform a new call for partners to collaborate with us to develop and support new NG AMR diagnostics prior to the introduction of new NG treatments.

OBJECTIVES

The objectives of this call are to: 1) update the landscape of available tests identifying susceptibility/resistance of gonorrhoea to antibiotics to facilitate antibiotic stewardship; and 2) support the writing in the near future of an RFP for the development of a new NG AMR diagnostic test.

RESPONSE TIMELINES

Expressions of Interest should be submitted in English to the project manager, Cecilia Ferreyra, by email (cecilia.ferreyra@finddx.org), and formatted as described in Appendix 1. The EOI timeline can be found in the table below; the deadline for full proposal reception is **October 1, 2019** by 18h00 Central European Time (CET). Proposals received after the deadline shall be considered invalid.

Activity	Date
EOI published	09/08 2019
Deadline for EOI questions	30/08 2019
EOI Closing time [18h00 Geneva time]	01/10 2019

Questions should be submitted in writing to the project manager, Cecilia Ferreyra (cecilia.ferreyra@finddx.org) and team member Laura Mazzola (laura.mazzola@finddx.org), no later than 30 August 2019. Based on the submitted information, we will contact you for a more detailed review of the instrument and parameter characteristics. We will also inform you should your submitted solution not currently meet the requirements of an NG antibiotic resistance test for use at the point-of-care.

CONFIDENTIALITY

If required, FIND can sign a Confidentiality Disclosure Agreement (CDA) with interested developers prior to their EOI submission. FIND will not disclose the proposal to third parties without the prior written agreement of the proposal submitter. Review of EOIs will be carried out by FIND and FIND's independent Scientific Advisory Committee, whose members are also under confidentiality. Should a Committee member have a potential conflict of interest which he is obliged to disclose, he will recuse himself. Any specific questions concerning confidentiality should be addressed to the FIND contacts indicated above.

Appendix 1: EOI response template for developers*

Tests to identify susceptibility/resistance of gonorrhoea to antibiotics to facilitate antibiotic stewardship

General details	
Name of applicant	List the name of the main applicant and co-applicants. Can include name of company and/or principal investigator for lab-developed tests.
Contact details	Provide contact details of corresponding investigators for further communication with FIND.
Test details	
Name of test	Provide the product or trade name of test.
Test description	Briefly describe the assay. Should include information on: <ul style="list-style-type: none"> - Test type [e.g. NAT or ELISA kit, validated platforms, LFA etc.] - Sample analyte [e.g. RNA/DNA, IgG, IgM, or Ag with specificity] - Sample type [e.g. urine, swab, culture, etc.]
Analytical performance	Provide results from analytical performance studies and references to published papers. Should include data on limit of detection (LOD), cross reactivity, and accuracy (i.e. test sensitivity and specificity). Include reference assay. If unavailable at the time of submission, include a timeline of when analytical performance data will be available.
Clinical performance	Provide results from clinical performance studies and references to published papers, if available. Include reference assay.
Regulatory and commercialization plans	Looking for FDA and/or CE approval. Use for patients management or surveillance of resistance. Target LMIC.
Cost	Provide cost per kit/reagent and platform (as appropriate).
Organization details	
Type of organization	Describe type of organization (e.g. academic research laboratory, government laboratory, registered company, etc.)
Location	Provide the location where your organization/company is registered.
Website	Provide the web link to your organization/company's website, if available.
Test supply	Is research group/organization/company the manufacturer of the test presented to FIND? <input type="checkbox"/> Yes <input type="checkbox"/> No If YES: please detail the location of manufacturing site and production capacity. If NO: please describe how end-users can obtain tests.
Other products available	List here the names of other products available, if applicable.

*NOTE: Up to three (3) pages maximum

Appendix 2: TPP for NG AMR Test

Target product profile for a test to identify antibiotic susceptibility/resistance of gonorrhoea and to facilitate antibiotic stewardship		
Characteristic	Minimal	Optimal
SCOPE		
1. Intended use	A test to confirm <i>Neisseria gonorrhoea</i> (NG) infection and to detect genetic markers of antibiotic susceptibility ¹ /resistance for NG to facilitate antibiotic stewardship ²	A rapid disposable test to detect NG only or and NG and <i>Chlamydia trachomatis</i> (CT) infection as previously defined, ³ plus detection of genetic markers of antibiotic susceptibility/resistance for NG to facilitate antibiotic stewardship
2. Target use setting	Level 2 ⁴ healthcare facility ⁵ (e.g. District hospital and peri-urban clinics) defined as having a functioning laboratory with trained personnel, water, electricity with intermittent surges and/or outages, limited climate control, dust, and medical staff onsite	Primary health care settings including health posts (Level 1 ¹)

¹ Genetic markers of antibiotic susceptibility/resistance refers to genetic resistance mutations, the absence of which are consistent with wild type genotype and antibiotic susceptibility. Detection of the presence or absence of resistance mutations does not provide confirmation of susceptibility, but rather predict the likelihood of resistance, since mechanisms of resistance other than those detected by specific genetic marker(s) may exist.

² Antibiotic stewardship refers to determining targeted therapy with antibiotics to preserve the use of second or third line antibiotics

³ See the target product profile for a rapid, low-cost diagnostic to distinguish gonorrhoea from *Chlamydia* infection at primary care

⁴ Ghani AC, Burgess DH, Reynolds A, Rousseau C (2015). Expanding the role of diagnostic and prognostic tools for infectious diseases in resource-poor settings. *Nature* 528: S50-52

⁵ The intended use for the minimal case in level 2 could serve both naïve cases as well as those referred from lower levels of the health system.

Characteristic	Minimal	Optimal
3. Test format	Fully integrated instrument ⁶ designed for use in level 2 facilities in combination with a self-contained, disposable assay cartridge containing all required reagents to execute a test from sample to result	Standalone, non-instrumented, single use, disposable diagnostic test for use in level 1 facilities preferred, reader ⁷ optional and only if required to achieve the intended use
4. Target users	Trained laboratory personnel (e.g., 1-2 year certificates) and any health worker with a similar or superior training level	Minimally skilled healthcare personnel (e.g. 3-6 months, able to operate an integrated test with minimal additional steps)
5. Training required	< 90 minutes	30 minutes
6. Target analytes	Detection of genetic markers of susceptibility/resistance ⁸ to any one of the following antibiotics ⁹ : <ul style="list-style-type: none"> • ciprofloxacin • ceftriaxone • cefixime • penicillin • gentamicin • azithromycin • zoliflodacin 	Detection of genetic markers of susceptibility/resistance to at least 2 of the following antibiotics: <ul style="list-style-type: none"> • ciprofloxacin • ceftriaxone • cefixime • penicillin • gentamicin • azithromycin • zoliflodacin

⁶ Instrument specific characteristics are defined in Appendix 1

⁷ Reader specific characteristics are defined in Appendix 2

⁸ Examples include: *gyrA* locus related to DNA *gyrA*se for ciprofloxacin, beta-lactamase and mosaic type of *penA* for penicillin, mosaic-like sequences within the *mtr* (multiple transferable resistance) efflux pump locus for azithromycin, and the mosaic type of *penA* for expanded spectrum cephalosporins (ceftriaxone and cefixime), etc.

⁹ There are considerable differences in geographical patterns of resistance between high and low- and middle-income countries; therefore, detection of resistance markets to particular antibiotics should be considered depending on intended markets for use.

Characteristic	Minimal	Optimal
TEST OPERATIONAL CHARACTERISTICS		
7. Test kit	All materials required for test procedure are integrated on the test cartridge except for consumables required to diagnose one individual, included in packaged, self-contained kit	
8. Specimen¹⁰	Women: self-collected and provider collected high vaginal swabs, urine preferred Men: urethral swab acceptable, urine preferred Same test format able to accept multiple specimen types in order to achieve results for men and women	Women: same as minimal Men: urine, and rectal and pharyngeal swabs Same test format able to accept multiple specimen types in order to achieve results for men and women
9. Specimen preparation	Minimal sample processing; no more than one operator step	Integrated, no sample preparation required by user
10. Ease of use	No more than three operator steps none of which is timed or labour intensive	One operator step (none of which has a timed interval), excluding waste disposal
11. Duration of sample stability	Immediate testing of the sample once collected	
12. Additional consumables required but not provided within the test kit	None, except for specimen collection	

¹⁰ Sensitivity and specificity for rectal and pharyngeal swabs is not yet determined

Characteristic	Minimal	Optimal
TEST PERFORMANCE CHARACTERISTICS		
13. Clinical sensitivity to predict resistance	≥98% sensitivity for predicting gonococcal resistance to the antibiotics listed in target analytes	>98% sensitivity for predicting gonococcal resistance to the antibiotics listed in target analytes
14. Clinical specificity to predict resistance	≥95% specificity for predicting gonococcal resistance to the antibiotics listed in target analytes	>98% specificity for predicting gonococcal resistance to the antibiotics listed in target analytes
15. Time to result	≤60 minutes	≤20 minutes
16. Internal process control	A full internal process control must be integrated into the assay cartridge and the instrument	
17. Positive / Negative controls	External positive and negative controls are not required for each test but are performed daily; Control for sample adequacy is required for self-collected swabs	External positive and negative controls are not required for each test and do not need to be run daily; Control for sample adequacy is required for self-collected swabs
STORAGE AND OPERATION		
18. Operating conditions	Operation between 15°C and 40°C at an altitude up to 2000 meters Extremely low relative humidity to condensing humidity Result interpretation in low light settings	Same, plus operation between 10°C and 45°C at an altitude up to 3000 meters preferred
19. Cold chain	None required at any point	

Characteristic	Minimal	Optimal
20. Test kit stability and storage conditions	12 months, stable between 2-35°C, 70% humidity, 3000 meters altitude Indicator of instability or expiration	18 months, stable between 0-50°C, 90% humidity, 3000 meters altitude Indicator of instability or expiration
21. Environmental tolerance of packaged test kit	Transport stress (48 hours with fluctuations up to 45°C and down to 0°C); Tolerate exposures between 2°C and 45°C at an altitude up to 2000 meters, up to and including condensing humidity	Transport stress (48 hours with fluctuations up to 50°C and down to 0°C); Tolerate exposures between 2°C and 45°C at an altitude up to 3000 meters, up to and including condensing humidity
22. Safety precautions (bio-safety requirements)	Closed, self-contained system; unprocessed sample transfer only; no open handling of biohazardous material	
23. Waste/disposal requirements	Standard biohazardous waste disposal or incineration of consumables, no high temperature incineration required	Small environmental footprint; compostable plastics for test cartridges and other materials after decontamination
24. Result display; result interpretation	Result lists each antibiotic tested and report whether a resistant marker(s) was detected	Same as minimal and the result can be read with the naked eye with minimal instructions for interpretation required by user, or with an integrated reader if addition of the reader supports enhanced test performance (See Appendix 4 for reader requirements)
25. Connectivity and data export	Connectivity required to support surveillance, See Appendix 3 for instrument requirements	Connectivity required to support surveillance, See Appendix 2 for reader requirements

Characteristic	Minimal	Optimal
PRICING AND ACCESSIBILITY		
26. Regulatory requirements	WHO PQ or other stringent regulatory body (e.g. FDA or CE mark)	
27. Target list price¹¹ per test (excluding the cost of a reader or instrument)	< \$25 USD at volume production	< \$15 USD at volume production

¹¹ List price – the price the manufacturer has arrived at for the product, taking into account the cost of goods and other factors (e.g., margin); the list price does not include any volume or other discounts or potential markup for distribution or other costs, including freight, taxes, etc. This cost is assumed a volume production and the prices listed in the TPP are considered for public health preferential pricing in low and middle income countries only.

Appendix 3: Instrument requirements

INSTRUMENT CHARACTERISTICS	Minimal	Optimal
1. Size	Small, table-top instrument (50 cm x 75 cm by 50 cm, or smaller)	
2. Weight	≤25 kg	≤10 kg
3. Power requirements	Local 110-220 AC mains power, plus uninterruptable power supply (UPS) to complete current cycle. Includes rechargeable battery back-up (8-hour operation). External UPS and circuit protector included with the system	Same, plus UPS and circuit protector must be integrated within the system
4. Throughput	Throughput of 16 or more sample runs per instrument per 8-hour day	
5. Service, maintenance and calibration	Routine preventive maintenance no more than 30 minutes 1x per week (with hands on time <10 minutes). Mean time between failures of at least 36 months or 30,000 tests, whichever occurs first. Self-check alerts operator to instrument errors or warnings; and ability to be calibrated remotely, or no calibration needed	
6. Patient identification capability	Manual entry of alphanumeric patient identifier keypad or touchscreen compatible with protective gloves	Same, plus bar code, RFID or other reader
7. Result display; result interpretation	Qualitative result reported	
8. Data acquisition and display	On-instrument visual readout with ability to function in various lighting conditions ranging from direct sunlight to low ambient light conditions. Able to add information (patient ID, operator ID, date, location, etc.)	

INSTRUMENT CHARACTERISTICS	Minimal	Optimal
9. Connectivity	<ul style="list-style-type: none"> • Integrated Local Area Network (LAN) port • Integrated Wi-Fi 802.11b/g/n • USB 3.0 • Internally designatable static IP address • Support for DHCP issued IP addresses • Support for HTTPS and SFTP protocols • Integrated global positioning system (GPS) <p>Ability to update connectivity software stack via USB or LAN</p>	<p>Same as minimal, plus:</p> <ul style="list-style-type: none"> • Multi-band GSM chipset 2G, 3G, LTE • Integrated Bluetooth 5.0 • Integrated Wi-Fi 802.11ac <p>Bi-directional communication – ability to update connectivity software stack</p>
10. Data export	<p>Export of all instrument and test data over integrated hardware. Secured data export with end-to-end encryption. Data export in .CSV file format. Configurable destination IP and DNS address. User initiated data export. Connectivity to external printer.</p>	<p>Same as minimal, plus scheduled/automatic data export using interoperable standards via the Global System for Mobile Communications SMS.</p>
11. Regulatory requirements	<p>GMP compliant, ISO 13485:2016 certified and authorized for use by a stringent regulatory authority (i.e. FDA or CE mark)</p>	
12. List price of Instrument	<p><\$5000 USD at volume production</p>	<p><\$1000 USD at volume production</p>

Appendix 4: Requirements for RDT reader (if required)

Adapted from RDT reader TPP prepared by the Murtagh Group, LLC (2014)

READER CHARACTERISTICS (if reader is required)	Minimal	Optimal
1. Ease of Use	No more than 3 operator steps (position RDT (cassette/strip) as required by the reader; take image or scan; read result); simple test menu; integrated LCD screen; simple key pad or touchscreen with icons	
2. Size	Small, portable table-top or hand-held device; or disposable reader	
3. Power requirements	Standard AA/AAA batteries or rechargeable battery with 8-hour operation between charges. Rechargeable battery lifetime > 2 years	
4. Service, maintenance and calibration	Routine preventive maintenance no more than 30 minutes 1x per week (with hands on time <10 minutes). Mean time between failures of at least 36 months or 30,000 tests, whichever occurs first. Self-check alerts operator to reader errors or warnings; and ability to be calibrated remotely, or no calibration needed	
5. Patient identification capability	Manual entry of alphanumeric patient identifier keypad or touchscreen compatible with protective gloves	Same, plus bar code, RFID or other reader
6. Result display; result interpretation	Easy pictorial display: susceptible, not susceptible, no gonorrhoea detected, or invalid for each assay; no instructions for interpretation required.	
7. Data acquisition and display	Able to add information (patient ID, operator ID, date, location, etc.); able to store patient results; able to print out results utilizing commoditized paper products (i.e. standard paper specifications and sizes)	

INSTRUMENT CHARACTERISTICS	Minimal	Optimal
8. Connectivity	Reader has integrated global positioning system (GPS) module	If combined with a reader, internally integrated GPS/ general packet radio service (GPRS) module and conformity with HL7 messaging standards
9. Data export	Full data export over mobile phone network	<p>Full data export over mobile phone network (data transmission can automatically select between GPRS or more advanced networks and global system for mobile communication (GSM), based on available coverage)</p> <p>GPRS should be able to utilize the internet file transfer protocol to transmit data: data transfer should be initiated every 6–12 hours automatically by the reader; data can be exported in a format compatible with HL7 standards, where appropriate; instrument tracks and transmits quality assurance data over time (e.g. identify shifts or trends)</p>
10. Regulatory requirements	GMP compliant, ISO 13485:2016 certified and authorized for use by a stringent regulatory authority	
11. Cost of reader	Reader cost included in the list price of the test	