DETECTION OF NEISSERIA GONORRHOEAE USING MOLECULAR METHODS

QSOP 62

Issued by Standards Unit, Department for Evaluations, Standards and Training
Centre for Infections
STATUS OF NATIONAL STANDARD METHODS

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The reader is informed that all taxonomy in this document was correct at time of issue.

Suggested citation for this document:

Please note the references are now formatted using Reference Manager software. If you alter or delete text without Reference Manager installed on your computer, the references will not be updated automatically.
AMENDMENT PROCEDURE

<table>
<thead>
<tr>
<th>Controlled document reference</th>
<th>QSOP 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled document title</td>
<td>Detection of <em>Neisseria gonorrhoeae</em> using Molecular Methods</td>
</tr>
</tbody>
</table>

Each National Standard Method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@hpa.org.uk.

On issue of revised or new pages each controlled document should be updated by the copyholder in the laboratory.

<table>
<thead>
<tr>
<th>Amendment Number/ Date</th>
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<th>Section(s) involved</th>
<th>Amendment</th>
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</thead>
</table>

DETECTION OF NEISSERIA GONORRHOEAE USING MOLECULAR METHODS

INTRODUCTION

The isolation of the causative organism, *N. gonorrhoeae*, has been the ‘gold standard’ for the diagnosis of gonorrhoea for many years, and can have a high sensitivity and specificity, but the organism is intolerant of problems with transportation or isolation methods. Consequently, the sensitivity of culture can be reduced and also requires an invasively taken specimen. Increasing pressure both on GUM clinic time and for screening for sexually transmitted infections in non-GUM settings, has encouraged the use of nucleic acid amplification tests (NAATs) for the detection of *N. gonorrhoeae*.

Technologies such as NAATs have an advantage over conventional methods in that they offer accurate diagnosis (high sensitivity and specificity), and produce a result within a working day which results in shorter turnaround times. They can be used with non-invasive specimens without the need for an invasive examination or for chaperoning, which facilitates testing both in genitourinary medicine (GUM) clinics, and primary care such as GP surgeries.

The detection of *Chlamydia trachomatis* has been revolutionised by the use of NAATs, which are now considered the ‘gold standard’ and are in widespread use in the United Kingdom (*VSOP 37 - Chlamydia trachomatis Infection - Testing by Nucleic Acid Amplification Test (NAATs)*). The National Chlamydia Screening Programme (NCSP) recommends the use of NAATs in their core requirement document, and following the national roll-out of the NCSP in England NAATs are used in the majority of laboratories. The commercial kits for *C. trachomatis* produced in recent years have the ability to detect *Neisseria gonorrhoeae*, offering dual diagnosis for either little or no extra direct cost.

There has been some controversy over the use of NAATs for the detection of gonorrhoea and national guidance has been produced.
1 POPULATION TO BE ScreenED

Gonorrhoea is an infection predominantly of high-risk individuals attending GUM clinics. Symptoms are present in the majority of male patients but at least 50% of women may be asymptomatic and therefore it is essential to test all patients at risk. There is no evidence base to support widespread unselected screening for gonorrhoea and evidence for selective screening in community settings is limited57.

2 SPECIMENS TO BE TESTED

A range of specimen types are approved for use with GC NAATs including the following:

- All of the commercially available NAATs for *N. gonorrhoeae* have a reported high sensitivity and specificity with urethral swabs from men and cervical specimens from women (Table 1 shows the manufacturer’s claims)
- All GC NAATs are approved (CE marked and FDA approved) for use with male urine specimens. These tests have comparable sensitivity to paired urethral swabs (Table 2 and 3)
- Some GC NAATs are also approved for use with female urine specimens (Table 1). However, urine is sub-optimal specimen in women8, displaying a significant decrease in sensitivity when compared with paired cervical swabs (Table 2 and 3)

At the time of issue the Aptima Combo 2 [Genprobe], the ProbeTec *Neisseria gonorrhoeae* (GC) Q Amplified DNA Assay [Becton Dickinson] and the RealTime CT/NG [Abbott] are FDA approved and CE Marked for use with vaginal swabs.

Note: None of the commercially available NAATs are approved to test rectal or pharyngeal specimens.

3 EFFECT OF PREVALENCE

The prevalence of gonorrhoea, either as the number of individuals in the population or as positive tests, will affect the number of true/false positives and negatives obtained. The following should be noted:

- The sensitivity of a test determines the number of actual positives correctly identified
- The specificity determines the number of actual negatives correctly identified

Sensitivity and specificity is a balance, it is unusual for both to be 100%.

The positive predictive value (PPV) of a test is a function of the sensitivity and specificity but will vary with the prevalence of the infection.

The PPV will be <90%, when the prevalence is low (1% or below), even with tests that have a sensitivity and specificity of over 95% or higher (Table 1). However, the same tests in a high prevalence population will give a PPV of over >90%.

In low prevalence populations the combination of a screening test to determine the initial positives and a supplementary or confirmatory test for the initial positives achieves an acceptable PPV of >90%9.

For example, in a population with a 1% prevalence using a test with sensitivity of 98% and specificity of 99% the PPV is 50% and the NPV is 100%.
If the positives are tested using a supplementary test of equal sensitivity and specificity (98% and 99% respectively) then the prevalence becomes 50% and the PPV is 99% and the NPV is 98%.

In the laboratory the ‘prevalence’ will be the number of positive tests from the population tested.

The population tested will vary and may include symptomatic or asymptomatic patients from GUM clinics or non GUM settings.

4 TESTING METHODS

At the present time the main commercially available NAAT platforms for the detection of N. gonorrhoeae include: Gen-Probe APTIMA Combo 2 (AC2), Becton Dickinson ProbeTec Strand Displacement Assay (SDA), Roche Cobas Amplicor and the Abbott M2000. All of these commercial assays target different regions on the gonococcal genome and employ different amplification technologies. As such the sensitivity and specificities of each of the tests vary significantly. The key features of each of the assays are summarised in Table 1.

5 CONFIRMATORY TESTING

The application of confirmatory assays is to increase the PPV to an acceptable level (>90%) and this is considered best practice9. Confirmatory testing in most diagnostic laboratories is hampered by the lack of commercially available confirmatory assays for this application and the issue of transferability of clinical specimens between the different GC NAAT platforms. This situation has resulted in the publication of a large number of in-house confirmatory assays with a range of targets of which two are particularly useful10,11. However, such assays can be difficult to introduce and quality control in a routine primary diagnostic laboratory. In order to overcome this issue the Sexually Transmitted Bacteria Reference Laboratory (STBRL) has launched a GC NAAT confirmation service for this purpose, whereby the residual material from a GC reactive clinical specimen can be referred for confirmation. Further details can be found at Neisseria gonorrhoeae Reference Work.

There are some additional CE marked N. gonorrhoeae diagnostic real-time PCR kits including: Neisseria gonorrhoeae Real-TM kit [sacace biotechnologies], Neisseria gonorrhoeae PCR Detection Kit [Geneproof], DuplicaReal Time Neisseria gonorrhoeae [Euroclone] and the Cobas 4800 CT/GC assay [Roche]. Such kits may have a role in either primary or confirmatory GC testing; but would need independent validation. Laboratories who intend to use these kits should perform their own internal validation prior to use (see QSOP 23 – Commercial and in-house diagnostic tests: Evaluations and Validations).

Turnaround times

The turnaround time for a test includes the time taken for the specimen to reach the laboratory, for performing (and confirming where appropriate) and reporting the test result and delivery of the result report to the clinician.

The turnaround time in the laboratory from receiving the sample to issuing a report should be:

- Primary test: 2 working days
- Confirmed positive: 3-5 working days

If delay is envisaged an interim report should be issued.

The overall turnaround time from taking the sample from the patient to the clinician receiving the results should be no more than 7 working days. This is consistent with recommended standards12.
6 QUALITY ASSURANCE

Thorough quality assurance is essential for all diagnostic laboratories. It is especially important when carrying out molecular amplification tests as these procedures are technically complex and have multiple stages where errors can occur. In addition all NAATs are highly sensitive and the specificity of the tests can be drastically reduced if contamination occurs. Consequently internal and external quality assessment must be performed regularly and internal quality controls should be included in every run.

External quality assessment programmes are currently available for the molecular testing for Neisseria gonorrhoeae from either QCMD (www.qcmd.org) or Labquality (http://www.labquality.fi/in_english/).

Further information can be found in QSOP 27 - Quality assurance in the diagnostic virology and serology laboratory.

7 MEDICO-LEGAL SPECIMENS

The use of molecular methods for investigating cases of child or sexual abuse is a complex and often difficult area. Molecular methods offer the opportunity to test samples which may have been stored and where the infecting organism is no longer viable. However, their use has not been tested in a court of law and, particularly in children, commensal neisseriae may be present. It is therefore advisable to use a number of tests, with different DNA targets, to establish the presence of N. gonorrhoeae and DNA sequencing of some genes may be necessary for confirmation. Specimens from these patients are best tested in collaboration with the Sexually Transmitted Bacteria Reference Laboratory.

8 TESTING EXTRA-GENITAL SPECIMENS

The detection of gonorrhoea in both rectal and pharyngeal specimens sourced from men who have sex with men (MSM) is extremely important. The prevalence at both sites remains high and accurate detection is essential to reduce morbidity and prevent onward transmission.

There are two key issues that must be addressed when attempting to detect gonococcal infection at these sites:

- The sensitivity of N. gonorrhoeae culture (the traditional gold standard) is greatly reduced at rectal and pharyngeal sites. This makes culture an unacceptable first line diagnostic or confirmatory test for N. gonorrhoeae at extra-genital sites, as cases will be missed. Consequently the use of GC NAATs with a secondary confirmatory test is the most appropriate method for the detection of gonorrhoea in rectal and pharyngeal sites.

- The application of GC NAATs to test extra-genital swabs can be problematic as both the rectum and the pharynx contain higher levels of commensal Neisseria species which may cross-react with some tests. This is especially pronounced when using those GC NAATs where specificity has been shown to be low (Section 3) and the use of these tests to examine extra-genital samples either with or without confirmatory testing will result in large numbers of patients being either (i) unnecessarily recalled to provide additional specimens for confirmation or (ii) misdiagnosed with gonorrhoea (Figure One).

There is currently no substantial data on the performance of GC NAATs for the detection of either Disseminated Gonococcal Infection (DGI) (common specimen types: blood, knee fluid) or ophthalmia neonatorum (eye swabs). Given the possible serious clinical implications of
misdiagnosis if GC NAATs are used as a screening tool for these specimen types, confirmatory testing combined with timely culture is essential.

9 ANTIMICROBIAL SUSCEPTIBILITY TESTING

As *N. gonorrhoeae* has developed resistance to most therapeutic agents used, antimicrobial susceptibility testing both for patient management and surveillance purposes is essential to guide appropriate therapy. The Gonococcal Resistance to Antimicrobial Programme (GRASP) is a sentinel study which has monitored gonococcal resistance in England and Wales and informed a change in national guidelines. The sentinel sites were chosen for regional representation of patients with gonorrhoea attending GUM clinics, and for burden of disease (over 100 diagnoses per annum). A viable organism is essential to maintain surveillance programmes particularly to detect emerging resistance to new agents and to provide sufficient sample for surveillance purposes in order to detect the 5% resistance level. Molecular approaches can be used to detect mutations or plasmids known to be associated with resistance although this is difficult for resistance to quinolones in *N. gonorrhoeae* which is known to be linked to multiple mutations. There is a concern that if the detection of gonorrhoea is primarily performed using automated molecular methods that it will be difficult to maintain high quality culture methods to obtain a representative sample and it is recommended that a culture for susceptibility testing be taken before treatment is given, whenever possible.

It is recommended culture is undertaken in patients with signs and symptoms compatible with gonorrhoea and/or with a confirmed NAAT result so that susceptibility testing can be performed and resistant isolates identified.
10 ACKNOWLEDGEMENTS AND CONTACTS

This National Standard Method has been initiated and developed by Professor Catherine Ison and Dr. Sarah Alexander of the Sexually Transmitted Bacteria Reference Laboratory. The contributions of many individuals in clinical bacteriology laboratories and specialist organisations who have provided information and comment during the development of this document are acknowledged.

The National Standard Methods are issued by Standards Unit, Department for Evaluations, Standards and Training, Centre for Infections, Health Protection Agency, London.

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London
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E-mail: standards@hpa.org.uk
**TABLE ONE: SUMMARY OF THE COMMERCIAL AVAILABLE FDA APPROVED GC NAAT PLATFORMS (NOTE ALL INFORMATION HAS BEEN PROVIDED FROM THE KIT INSERTS)**

<table>
<thead>
<tr>
<th></th>
<th>Aptima Combo 2 [AC2] (Genprobe)</th>
<th>Cobas Amplicor (Roche)</th>
<th>Probetec GC Qx Amplified DNA Assay (Becton Dickinson)</th>
<th>Probetec ET GC Amplified DNA Assay (Becton Dickinson)</th>
<th>RealTime CT/NG (Abbott)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>16S rRNA</td>
<td>Cytosine DNA methyltransferase</td>
<td>Pillin (Different region to the Probetec ET test)</td>
<td>Pillin</td>
<td>Opa gene</td>
</tr>
<tr>
<td>**Amplification **</td>
<td>Transcription Mediated Amplification (TMA)</td>
<td>Polymerase Chain Reaction (PCR)</td>
<td>Strand Displacement Amplification (SDA)</td>
<td>Strand Displacement Amplification (SDA)</td>
<td>Real-time PCR</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>97.8%*</td>
<td>97.1%</td>
<td>99.3%</td>
<td>96.2%</td>
<td>98.0%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>99.2%*</td>
<td>98.1%</td>
<td>99.4%</td>
<td>98.6%</td>
<td>99.7%</td>
</tr>
<tr>
<td><strong>Positive predictive value</strong></td>
<td>1% Prevalence</td>
<td>55%</td>
<td>35%</td>
<td>63%</td>
<td>41% 77%</td>
</tr>
<tr>
<td></td>
<td>5% Prevalence</td>
<td>87%</td>
<td>73%</td>
<td>90%</td>
<td>78% 95%</td>
</tr>
<tr>
<td></td>
<td>10% Prevalence</td>
<td>93%</td>
<td>85%</td>
<td>95%</td>
<td>88% 97.0%</td>
</tr>
<tr>
<td><strong>Alternative GC Assay and Assay Target</strong></td>
<td>GC 16S rRNA (different region to the AC2)</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Reported Cross reaction with other Neisseria specie</strong></td>
<td>None Reported</td>
<td>N. cinera, N. flavescens N. lactamica, N. sicca, N. subflava*</td>
<td>Potential cross reaction with N. cinera and N. lactamica*</td>
<td>Potential cross reaction with N. cinera, N. flavescens N. lactamica, N. subflava*</td>
<td>None Reported</td>
</tr>
<tr>
<td><strong>Manufacturer approved Specimen types</strong></td>
<td>PreservCyt liquid Pap specimens, Vaginal swabs Cervical swabs Urethral Swabs (male) Urine (Male and female)</td>
<td>Cervical swabs Urethral Swabs (men) Urine (Male)</td>
<td>PreservCyt liquid Pap specimens Surepath liquid Pap specimens Cervical swabs Urethral Swabs (men) Urine (Male and female) Vaginal swabs</td>
<td>Cervical swabs Urethral Swabs Urine (Male and female)</td>
<td>Cervical swabs Urethral Swabs (men) Urine (Male and female) Vaginal swabs</td>
</tr>
</tbody>
</table>

*As defined by the product insert: A combined figure for all validated specimen sites. Note that definition of patient infected status differs between inserts. See individual inserts for details.

*The Aptima Combo Two data is based on the figure for a combined figure for all validated specimens with the exception of vaginal swabs and pap specimens.

#: Note that the cross reactivity of these tests with closely related Neisseria specie has only been demonstrated in analytical studies when presented with bacterial isolates.

*All PPVs are calculated from the sensitivity and specificity values presented in the package inserts. Note this data was NOT generated in a head to head evaluation of the different testing platforms and is consequently not intended to be used to compare the performance of the different platforms but merely to illustrate the influence of using each of the tests in low prevalence settings.

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**DETECTION OF NEISSERIA GONORRHOEAE USING MOLECULAR METHODS**

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This NSM should be used in conjunction with the series of other NSMs from the Health Protection Agency  www.evaluations-standards.org.uk  Email: standards@hpa.org.uk
### TABLE TWO: SENSITIVITY AND SPECIFICITY OF THE GC NAAT PLATFORMS IN SYMPTOMATIC PATIENTS BY SPECIMEN TYPE (NOTE ALL INFORMATION HAS BEEN PROVIDED FROM THE KIT INSERTS)

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Aptima Combo 2 [AC2] (Genprobe)</th>
<th>Cobas Amplicor (Roche)</th>
<th>Probetec GC Qx Amplified DNA Assay (Becton Dickinson)</th>
<th>BD ProbeTec ET GC (Becton Dickinson)</th>
<th>M2000 (Abbott)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Urine</td>
<td>Sensitivity: 98.4%</td>
<td>96.0%</td>
<td>100%</td>
<td>97.9%</td>
<td>98.8%</td>
</tr>
<tr>
<td></td>
<td>Specificity: 99.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethral Swabs</td>
<td>Sensitivity: 99.0%</td>
<td>99.4%</td>
<td>100%</td>
<td>98.4%</td>
<td>99.2%</td>
</tr>
<tr>
<td></td>
<td>Specificity: 98.8%</td>
<td>96.2%</td>
<td></td>
<td></td>
<td>99.3%</td>
</tr>
<tr>
<td>Female Urines</td>
<td>Sensitivity: 92.6%</td>
<td>Not approved for this specimen type</td>
<td>97.4%</td>
<td>83.7%</td>
<td>93.8%</td>
</tr>
<tr>
<td></td>
<td>Specificity: 99.1%</td>
<td></td>
<td></td>
<td></td>
<td>99.7%</td>
</tr>
<tr>
<td>Cervical Swabs</td>
<td>Sensitivity: 100%</td>
<td>94.5%</td>
<td>100.0%</td>
<td>96.1%</td>
<td>INP</td>
</tr>
<tr>
<td></td>
<td>Specificity: 98.1%</td>
<td>98.7%</td>
<td></td>
<td></td>
<td>99.3%</td>
</tr>
<tr>
<td>Vaginal Swabs</td>
<td>Sensitivity: 96.2% (CC)</td>
<td>Not approved for this specimen type</td>
<td>100%</td>
<td>Not approved for this specimen type</td>
<td>96.8% (CC)</td>
</tr>
<tr>
<td></td>
<td>Specificity: 99.1% (CC)</td>
<td></td>
<td></td>
<td></td>
<td>99.7% (CC)</td>
</tr>
</tbody>
</table>

INP = Information not provided in Kit insert
CC = Clinician collected
* Data represents urine specimens which are in Q+ urine preservative transport
### APPENDIX - TABLE THREE: SENSITIVITY AND SPECIFICITY OF THE COMMERCIALY AVAILABLE GC NAAT PLATFORMS IN ASYMPTOMATIC PATIENTS BY SPECIMEN TYPE (NOTE ALL INFORMATION HAS BEEN PROVIDED FROM THE KIT INSERTS)

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<th>Probetec GC Qx Amplified DNA Assay (Becton Dickinson)</th>
<th>BD ProbeTec ET GC (Becton Dickinson)</th>
<th>M2000 (Abbott)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Specimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td>75.0%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.5%</td>
<td>99.6%</td>
<td>99.5%</td>
<td>99.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Male Urethral Swabs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td></td>
<td>100%</td>
<td>95.5%</td>
<td>INP</td>
</tr>
<tr>
<td>Specificity</td>
<td>96.7%</td>
<td></td>
<td>99.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Specimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Urines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87.5%</td>
<td></td>
<td>100%</td>
<td>86.5%</td>
<td>87.0%</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.5%</td>
<td></td>
<td>99.3%</td>
<td>99.6%</td>
<td></td>
</tr>
<tr>
<td>Cervical Swabs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>96.9%</td>
<td>98.0%</td>
<td>96.3%</td>
<td>97.4%</td>
<td>INP</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.6%</td>
<td>98.7%</td>
<td>99.5%</td>
<td>99.6%</td>
<td>INP</td>
</tr>
<tr>
<td>Vaginal Swabs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100% (PC) 95.5 % (CC)</td>
<td></td>
<td>100%</td>
<td>Not an approved specimen type for this test</td>
<td>INP</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.5% (PC) 99.3%(CC)</td>
<td></td>
<td>98.6%</td>
<td>Not an approved specimen type for this test</td>
<td>INP</td>
</tr>
</tbody>
</table>

INP = Information not provided in Kit insert  
PC = Patient collected  
CC = Clinician collected  
* Data represents urine specimens which are in Qx urine preservative transport
Detection of Neisseria gonorrhoeae using molecular methods

**FIGURE ONE: TESTING ALGORITHM**

- **GC NAAT Test**
  - Negative: No Evidence of *Neisseria gonorrhoeae* DNA
  - Positive: Confirm same specimen with second GC NAAT target
    - Negative: Inconclusive. Possible non-specific cross reactivity or possible *Neisseria gonorrhoeae* DNA. Advise a repeat specimen to confirm.
    - Positive: Evidence of *Neisseria gonorrhoeae* specific DNA. Advice that either:
      - (i) A culture specimen be obtained for *N. gonorrhoeae* sensitivity testing.
      - (ii) A test of cure be performed post treatment.

*Some GC NAAT tests have a low specificity and are known to cross react with some non-pathogenic Neisseria. These are commensal organisms, which are generally not present in high levels in the genital tract. Therefore by obtaining a second specimen from a patient with an unconfirmed GC NAAT result and testing it with two targets, should resolve this issue.

$ Only necessary if PPV is <90% If PPV >90% on initial test a reproducibility check with same target is recommended.

DETECTION OF NEISSERIA GONORRHOEAUS USING MOLECULAR METHODS
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