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Short Communication

The Art of Unlearning: *Chlamydia Trachomatis* and the Limits of Light Microscopy

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Abstract

Objective: To evaluate the historical shift from cytological diagnosis to molecular detection of *Chlamydia trachomatis*, outlining the precise current role of cervical cytology in clinical practice.

Methods: Historical perspectives, updated international clinical guidelines, and recent technological literature were analyzed.

Results: Papanicolaou smear examination for *C. trachomatis* demonstrates poor sensitivity (<30%) and high false-positive rates caused by degenerative vacuoles and cellular artifacts. Nucleic Acid Amplification Tests (NAATs) represent the current diagnostic standard. Recent advancements in 2025–2026, including multiplex PCR platforms and point-of-care (POC) testing, have further solidified molecular diagnostics.

Conclusions: Cytology should not be used for direct diagnosis or screening of *C. trachomatis*. However, it remains a valuable tool for neoplastic screening and an indirect indicator of cervical inflammation, prompting targeted molecular testing.

Abbreviations

NAAT: Nucleic Acid Amplification Test; PCR: Polymerase Chain Reaction; POC: Point-of-Care; LBC: Liquid-Based Cytology; STI: Sexually Transmitted Infection; PID: Pelvic Inflammatory Disease

Introduction

The history of gynecological cytology reflects a continuous evolution in diagnostic methodologies. Ever since George Papanicolaou demonstrated the utility of cellular exfoliation for early cervical cancer detection, diagnostic pathology has sought to identify both neoplastic transformations and pathogen-associated morphological changes. However, scientific progress demands continuous critical evaluation of diagnostic techniques and their methodological limitations.

For decades, cytological examination was presumed to be a fertile ground for the identification of specific pathogens. During the late 1970s and early 1980s—marked by pioneering publications such as those by Gupta et al. [1] the description of specific cytoplasmic abnormalities became closely linked to the presence of *Chlamydia trachomatis*. Minute eosinophilic vacuoles and perinuclear vacuolated basophilic inclusions (the classic inclusion bodies) were described as diagnostic indicators. Such was the initial conviction that the 1988 Bethesda System formally established chlamydial infection as a diagnostic category within reactive cellular changes associated with pathogens [2].

Historical re-evaluation and diagnostic limits

However, daily clinical practice and the advent of validated reference methods unveiled a significant limitation: reliance

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on cellular morphology alone proved prone to diagnostic error. A substantial proportion of what was cataloged as "chlamydial inclusions" actually represented fixation artifacts, cellular degeneration vacuoles, phagocytosed mucus, or immature metaplasia [3]. With poor sensitivity (often dropping below 30%) [4] and an alarming lack of specificity, the Papanicolaou smear generated an unacceptably high rate of diagnostic inaccuracies. The 1991 revision of The Bethesda System modified its criteria, formally removing *Chlamydia* from its infectious categories [5] a stance categorically reaffirmed in the 2001 edition [6].

This paradigm shift highlighted the necessity of aligning diagnostic methods with technological developments, recognizing the physical limitations of light microscopy when applied to sub-microscopic intracellular pathogens. Today, Nucleic Acid Amplification Tests (NAATs) constitute the current diagnostic standard, offering sensitivity and specificity exceeding 95–98% using vaginal, endocervical, or urine specimens [7]. Recent innovations in 2025–2026, such as rapid point-of-care (POC) NAATs and multiplex PCR platforms targeting coinfections, have further enhanced diagnostic accessibility and turnaround times without sacrificing accuracy [8].

Epidemiology and prevalence: The impact of unseen infection

This change of direction in diagnostic strategy carries critical significance when analyzing the epidemiological magnitude of the problem. *Chlamydia trachomatis* remains the most prevalent bacterial sexually transmitted infection (STI) worldwide, accounting for more than 120 million annual cases according to estimates by the World Health Organization [9].

- **The clinical challenge:** Its primary impact stems from its asymptomatic nature—occurring in up to 70–80% of infected women and 50% of men [7].
- **Long-term consequences:** Lacking overt clinical symptoms or reliable cytological markers, untreated infections can progress silently toward Pelvic Inflammatory Disease (PID), carrying a substantial risk of tubal factor infertility, chronic pelvic pain, and ectopic pregnancy [7].
- **High-risk population:** Peak prevalence consistently concentrates among young adults and adolescents aged 15 to 24 [7,9].

The contemporary role of cytology in clinical management

Faced with this scenario, one must evaluate the actual remaining role of cytology in managing *Chlamydia* in the molecular era.

The response is clear according to current clinical guidelines: liquid-based or conventional cervical cytology should not be utilized as a primary tool for the direct diagnosis or screening of C. trachomatis [7].

Nevertheless, cytology retains an indirect yet valuable function within comprehensive gynecological health management:

1. **Indicator of inflammation and clinical alert:** A smear displaying a dense neutrophilic exudate (reflecting mucopurulent cervicitis) or severe reactive cellular changes, in the absence of cytologically visible pathogens (such as *Trichomonas* or *Candida*), provides clinical rationale to order specific molecular testing (NAAT) for C. trachomatis and Neisseria gonorrhoeae [7].
2. **Co-screening in the Liquid-Based Cytology (LBC) Era:** LBC has established an efficient technical workflow. Although morphology in the smear preparation remains non-diagnostic, the residual LBC fluid serves as an ideal substrate for opportunistic NAAT processing. Consequently, a single sampling procedure enables cervical cancer screening alongside molecular STI detection in high-risk populations [7,9].

Conclusion

In conclusion, the trajectory of *Chlamydia* diagnosis in cytology underscores an essential principle in pathology: diagnostic practice must reflect a clear understanding of the scope and limitations of visual microscopy. Accepting that cellular morphology alone cannot reliably identify *C. trachomatis* has reinforced the necessity of molecular precision, while focusing the primary value of cervical cytology on neoplastic screening and the evaluation of inflammatory tissue responses.

Authors' contributions

FJ T-G conceived the study, conducted the literature search, and drafted the manuscript. R S de M-G participated in critical revisions and literature verification. All authors read and approved the final manuscript.

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