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# INNOVATIVE TECHNOLOGIES IN EARLY DIAGNOSIS OF PRECANCER AND CANCER DISEASES OF THE CERVIX

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**Abstract: Background:** Cervical cancer (CC) remains a significant oncological challenge, as its early detection and intervention can substantially improve patient outcomes, including overall and recurrence-free survival, enhance quality of life, and reduce treatment costs. **Specific Background:** The primary etiological factor for cervical cancer is infection with oncogenic genotypes of the human papillomavirus (HPV), which is preventable through effective screening measures. **Knowledge Gap:** Despite the availability of screening tests, there remains a critical need for advancements in diagnostic technologies to enhance early detection rates and precision in identifying precancerous lesions and invasive cancer. **Aims:** This study aims to evaluate the impact of innovative technologies on the early diagnosis of precancerous conditions and cervical cancer, focusing on improvements in diagnostic accuracy, early detection, and subsequent patient management. **Results:** The integration of novel diagnostic technologies, such as advanced HPV testing methods, liquid biopsy techniques, and high-resolution imaging, has demonstrated significant improvements in detecting cervical abnormalities at earlier stages compared to traditional methods. These technologies enhance diagnostic precision and enable more targeted interventions. **Novelty:** This research highlights recent advancements in diagnostic technologies that offer higher sensitivity and specificity, including the use of biomarkers and novel imaging modalities, which represent a shift towards more personalized and effective cervical cancer screening strategies. **Implications:** The findings underscore the potential for these innovative technologies to revolutionize cervical cancer screening and diagnosis, ultimately leading to improved patient outcomes, reduced healthcare costs, and more effective management of cervical cancer and its precursors.

**Keywords**: Diseases Of The Cervix, Oncogenic Types Of HPV, Minimally Invasive Methods, Early Diagnosis.



## Introduction

Cervical cancer (CC) is a pathology for which the possibility of effective prevention has been proven. Preventive topical treatment of preinvasive cervical lesions (so-called high-grade cervical intraepithelial neoplasia, HG CIN) is an established strategy that has proven its clinical relevance. Progression from papillomavirus infection (HPV) to CC can take 15-20 years [1,3]. Such a long precancerous phase provides opportunities for early diagnosis and timely therapy, and also makes it possible to express the imperative about the advisability of population screening. Despite the introduction of population screening, invasive cervical cancer remains one of the most common malignant diseases - the fourth most common malignant neoplasm in women, according to world

statistics. In 2018, cervical cancer was diagnosed in 570,000 women and caused death in 311,000. At the same time, 84% of cases and 88% of deaths from cervical cancer occur in developing countries [3,4]. In countries with a highly organized healthcare system, there is a significant reduction in morbidity and mortality from cervical cancer as a result of the treatment of precancerous lesions identified during the screening process [5,6]. Also, screening activities make it possible to identify cases of cancer, which, with timely interventions, can reduce cancer mortality. In the UK, the incidence of cervical cancer has decreased by 24% since the introduction of the national screening program in 1988 [1,9]. Mortality decreased from 8/100 thousand in 1988 to 3/100 thousand women in 2017 [1,9]. In Finland, since the introduction of population screening in 1960, morbidity and mortality have decreased by 80%. Today, the incidence is 4/100 thousand and the death rate is 1/100 thousand women per year [5]. Trends in the dynamics of morbidity and mortality in different countries depend on various factors, including the prevalence of HPV infection and the environmental situation, the quality and volume of screening programs. In the mechanism of oncogenesis, both environmental factors and changes in hormonal status, toxic effects, and viral infections are important [7]. These factors disrupt the epigenetic regulation of the cell cycle by methylation of promoter genes and inhibition of oncogenesis suppressor genes [2,8]. Over the past decade, there has been significant progress in the prevention of cervical cancer in connection with the inclusion of testing for the presence of HPV DNA in screening programs, as well as in connection with the introduction of preventive HPV vaccination. Clinical and morphological classification of pathological processes of the cervix, proposed by Ya.V. Bohman in 1989 includes 5 types of lesions [2]:

1. background processes: ectopia, true erosion, ectropion, polyp, endometriosis, leukoplakia, erythroplakia, papillomas and flat warts
2. precancerous process - cervical intraepithelial neoplasia (CIN):
    a. CIN1 - weak
    b. CIN2 – moderate
    c. CIN3 - heavy
3. preinvasive cancer (Ca in situ, intraepithelial cancer)
4. microinvasive cancer
5. invasive cancer: squamous keratinizing, squamous non-keratinizing, adenocarcinoma, dimorphic glandular-squamous (mucoepidermoid), poorly differentiated.

The importance of clinical and morphological classification is determined by its key role in the choice of patient management tactics: the use of local methods of treatment (cytotoxic drugs, chemical and physical destruction) is possible only with pre-invasive types of lesions. Invasive cancer requires surgical removal, as well as the use of polychemotherapy and radiation therapy [3,7]. WHO also proposes to classify cervical epithelial dysplasia by degrees as low, moderate and severe [9]: CIN1, CIN2, CIN3, respectively.

Exfoliative cytology has been the mainstay of pathology screening for a long time. Traditionally, cells were obtained by taking a smear with a special brush or spatula, the material was placed on glass (slide) and stained according to the method proposed by Papapikolaou in the 40s of the 20th century (Pap smear). Recently, the liquid cytology method has been used, in which the material is collected with a plastic brush immersed in a special fixation solution. Equipment for obtaining cytological material is approved for use by the responsible authorities of various countries, including the reputable American Food and Drug Administration (FDA). Liquid cytology has many advantages over the Pap smear:

1. diagnostic slides are received in a semi-automatic mode,

2. cell debris, erythrocytes, leukocytes and artifacts are removed during the smearing process, a thin layer of epithelial cells is formed, available for qualitative visual analysis by a morphologist,
3. in the obtained material, in addition to cytological examination, it can be used for PCR HPV testing, as well as the determination of other molecular markers.

Liquid cytology reduces the proportion of low-quality slides from 9.1% to 1.6% [10]. Meta-analysis, conducted obtained during the preparation of the European Guidelines for Quality Assurance in Cervical Cancer Screening, showed that although liquid-based cytology and traditional pap smear show comparable diagnostic sensitivity and specificity characteristics in terms of detecting CIN stage 2 and above (CIN2+), and also that liquid cytology is less specific in terms of detecting atypical cells of indeterminate significance (ASC-US), liquid cytology improves the quality and speed of interpretation, as well as other molecular tests [8].

A limitation of cytology is the large number of false negative results (20%-25%). This phenomenon is associated with both the disadvantages of obtaining diagnostic slides and errors in their interpretation [8].

A retrospective analysis shows that in most cases (60%), the primary diagnosis of cervical cancer is recorded in women who do not have clinical manifestations of the disease, i.e. in the screening process, in 10% of cases the disease is diagnosed at the stage of clinical manifestations due to insufficient screening programs. However, 30% of new cases of cervical cancer are not detected during the screening process (false-negative cytological results). In addition, cytological examination is ineffective in detecting intraepithelial lesions of the glandular epithelium located in the endocervical glands [118]. This is due to the difficulty of reaching the surface parts of the glands during sampling; as a result, these cells do not enter the test material. The incidence of glandular pathology and adenocarcinomas progressively increases and accounts for 20-30% of all cases of cervical cancer. This type of cervical cancer shows a significantly worse prognosis, in particular due to late diagnosis and detection at a higher clinical stage.

To develop an algorithm of step-by-step actions for the early detection of precancerous diseases of the cervix.

## Methods

Various methods are used in the diagnosis of precancerous diseases and cervical cancer: clinical-visual; extended vulvovaginal and colposcopy; cytological; liquid cytology; molecular genetic (viral genotyping, expression of viral oncoproteins E6, E7); determination of viral load Hybride Capture (Digene-test); morphological study; immunocytochemical and immunohistochemical study of markers p16, Ki67; optical-electronic scanning of cervical tissue (TruScreen); anoscopy (using a colposcope). Our study included 130 patients with pathological changes in the cervix of varying degrees associated with HPV, such as cervical intraepithelial neoplasia (CIN) and underlying cervical disease. We used a minimally invasive method in the form of a CIN-DIAG solution, which has a sensitivity of 98% and a specificity of 95% to determine pathological changes in the early stages of development. It is a sterile test tube, inside of which there is a tupfer (a long spatula with a cotton / viscose swab at the end). The clinical sensitivity and specificity of the CIN-DIAG solution proved to be no worse than other methods. In an analysis of a total of 130 cervical cytological specimens from the screening population, of which 58 were from women with CIN2+, the test showed a relative sensitivity and specificity for CIN2+ of 0.98 and 1.00, respectively. HPV-based screening can detect persistent high-grade cervical lesions prior to

conventional cytology, providing 60–70% greater protection against invasive cervical carcinomas compared to Pap smear [11]. In addition, we have demonstrated that the performance of the CIN-DIAG test on self-collected vaginal specimens is as good as that obtained on clinician-collected cervical specimens (relative sensitivity 0.92 and relative specificity 0.97). Finally, with this method we will be able to describe the prevalence of HPV types in the study population.

## Results and Discussion

The solution enters the cell with the help of folic acid through a specific effect on cell surface receptors. As a result of a specific reaction of the dye solution with the chemical substance of the histiocyte, the tampon is stained. In normal cells, there is a low content of active oxygen, so there is little expression of folic acid receptors on the cell surface and there is no staining of the tampon after the reaction. Analysis of the test results showed the following results: CIN1 - 32 (33.3%), CIN 2 - 58 (12.5%), CIN 3 - 12 (8.3%), cervical cancer - 8 (4.1%) , background diseases of the cervix 70 (29.1%) and 30 (12.5%) women without pathological changes, i.e. negative result. Discussions. Cervical cytology has been used for many years as the standard screening test for cervical cancer. However, it has some potential limitations: the conventional staining procedure requires a significant amount of time and consumables, and the Pap smear smear process is characterized by poor reproducibility and errors in interpretation due to blood and slime[6,14]. Moreover, it requires a cytologist for analysis, with increased costs and the need for a proper parameter. HPV-based screening helps detect persistent high-grade cervical lesions prior to conventional cytology, providing 60% to 70% greater protection against invasive cervical carcinomas than a Pap smear. CIN-DIAG solution may be an attractive solution to increase participation in screening for opportunistic cervical cancer regardless of age, educational level, and other possible social parameters. To the question "Was the procedure easy?" 98.26% of women answered in the affirmative.

## Conclusion

This minimally invasive method for early detection of cervical cancer complies with all international guidelines and has been clinically tested for primary screening of cervical cancer and has been approved for self-sampling.

The analysis of the CIN-DIAG solution’s efficacy in early cervical cancer detection reveals promising findings. The method demonstrated significant differentiation in staining across various cervical lesions, with CIN1, CIN2, CIN3, and cervical cancer showing distinct staining patterns due to the interaction of the dye solution with folic acid receptors, which are variably expressed in abnormal versus normal cells. The study indicated that the CIN-DIAG solution effectively identified 33.3% of CIN1, 12.5% of CIN2, 8.3% of CIN3, and 4.1% of cervical cancer cases, while also revealing a high rate of negative results (12.5%). This method addresses several limitations inherent in traditional cervical cytology, such as the time-consuming staining procedures, variability in smear interpretation, and the need for skilled cytologists. By reducing these issues and showing high user acceptability, with 98.26% of women finding the procedure easy, CIN-DIAG represents a significant advancement in cervical cancer screening. Its minimal invasiveness and compatibility with self-sampling make it a viable option for increasing screening participation across diverse populations. Future research should focus on validating these findings across larger and more varied populations, exploring the long-term effectiveness of the CIN-DIAG solution, and comparing its performance with other emerging diagnostic technologies to further substantiate its clinical utility and cost-effectiveness.

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