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Review Article

Liquid-based cytology screening in Gynecologic oncology

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Abstract

Liquid-based cytology (LBC) is transforming the diagnostic landscape of gynecologic oncology, offering enhanced accuracy in the early detection and effective management of cancers like cervical, ovarian, and endometrial. This article provides an in-depth review of the principles underpinning LBC, elaborates on its application in modern gynecologic oncology, and discusses the distinctive advantages that it holds over traditional cytology methods. Furthermore, the article recognizes the potential limitations of LBC, including cost implications and residual challenges with sample interpretation. The discussion also highlights the ability of LBC to synergistically work with additional testing methods such as high-risk HPV DNA testing, which enriches the diagnostic information gathered from each sample. With this comprehensive analysis, the article illustrates the compelling role of LBC in revolutionizing the quality of diagnostic samples and its consequent potential for improving patient outcomes in gynecologic oncology. This exploration paves the way for future research to further harness and optimize the benefits of LBC in advancing gynecologic healthcare.

Keywords: Liquid-based cytology, Gynecology, Oncology

1. Introduction

The diagnostic approach to gynecologic oncology has significantly evolved over the past century, driven by advances in cellular and molecular biology [1]. A central focus of this development has been the study of individual cells, or cytology, which continues to be a critical element in diagnosing gynecologic cancers, including those of the cervix, ovary, and endometrium [2]. Despite its importance, conventional cytology methods, such as the Papanicolaou (Pap) smear, have exhibited limitations that may impact diagnostic accuracy and patient management [3]. Some of these limitations include high false-negative rates and issues with sample adequacy related to the uneven distribution or overlapping of cells [4].

Liquid-based cytology (LBC) has emerged as a powerful tool designed to address these challenges, offering an innovative approach that promises to enhance the quality and accuracy of cellular diagnosis [5]. The impetus for the development of LBC lies in its potential to mitigate issues of false negatives and insufficient sampling, which are prevalent with the conventional Pap smear [3]. LBC presents a technological leap forward, utilizing a special collection device to preserve and process cells in a manner that has the potential to significantly improve the diagnostic yield [6]. The shift from traditional smear cytology to LBC marks a pivotal moment in gynecologic oncology, redefining the way cytological samples are collected, prepared, and evaluated [7]. This has consequential implications for the early detection and management of gynecologic malignancies, where accurate cytologic interpretation is key [4,8,9].

In this article, we delve deeper into the transformative potential of LBC, discussing its principles, benefits, limitations, and applications. We provide an examination of how LBC is improving the quality of diagnostic samples and reflect its influence on patient management in gynecologic oncology, ultimately highlighting why this diagnostic methodology is now considered an essential tool in the field.

2. Liquid-Based Cytology - A Closer Look

Liquid-Based Cytology (LBC) is an innovative technique designed to improve sample quality and interpretive accuracy over the conventional smear [10]. The technique involves the collection of cells from the cervix, or other sites, using a specialized device which is then immersed in a vial containing a liquid preservative [7]. This approach offers a significant advantage by ensuring that all collected cells are preserved

immediately, which is not the case with conventional smear tests [11].

Following sample collection, the cell suspension is subjected to a process of centrifugation or filtration to separate cells from debris. This step eliminates non-diagnostic material such as blood, mucus, and inflammatory cells, that often obscure or complicate the interpretation of conventional smears [12].

Once the diagnostic cellular material is isolated, it is then transferred onto a glass slide to create a thin, monolayered spread of cells. This crucial step overcomes another limitation of the conventional smear, where cells are often unevenly distributed, overlapped, or obscured. The monolayer of cells in LBC provides an optimal visualization environment for cytological evaluation [13].

Additionally, the use of liquid media in LBC allows for more than one slide to be prepared from the same sample. The remaining cellular material, if any, can be stored and used for further testing. This has significant implications in diagnostic pathology, where additional tests such as molecular studies, immunocytochemistry or high-risk HPV DNA testing may be warranted based on initial findings [12,14].

Moreover, LBC has been recognized for its utility in automation. The process of slide preparation can be automated, reducing manual errors and standardizing the quality of slides. In addition, LBC is compatible with automated image analysis systems, facilitating screening and primary diagnosis [13].

LBC, therefore, represents a significant technological shift in cytology, improving both the quality of samples and the workflow efficiency in the laboratory. By reducing the presence of non-diagnostic material and enabling a clear view of cellular morphology, LBC enhances diagnostic confidence and clinical decision-making [15]. While the technique was initially developed for cervical screening, its utility has expanded to other areas of gynaecological and non-gynaecological cytopathology, redefining the landscape of cytologic diagnosis [16]

3. Advantages of Liquid-Based Cytology

The shift from conventional smear cytology to Liquid-Based Cytology (LBC) has introduced several significant advantages to the practice of cytopathology, particularly in the realm of gynecologic oncology. The following are key benefits:

3.1 Improved Sensitivity and Specificity

Perhaps one of the most impactful advantages of LBC is the increase in sensitivity and specificity. By providing a cleaner, evenly distributed slide preparation, the visualization of cellular abnormalities is enhanced. The elimination of obscuring elements like blood, mucus, and inflammation ensures that cellular details are not missed, thus reducing false negatives, and increasing detection of precancerous lesions or malignancies [4,16].

3.2 Reduced Unsatisfactory Rates

The quality of samples prepared using LBC is significantly better compared to conventional cytology. This improvement largely stems from the collection and preservation method, which ensures that all collected cells are effectively utilized, resulting in fewer unsatisfactory samples due to air-drying artefacts or obscuring elements. With LBC, the percentage of samples that need to be recollected due to insufficient cellular material can be greatly reduced [14,17]. (Figure 1).

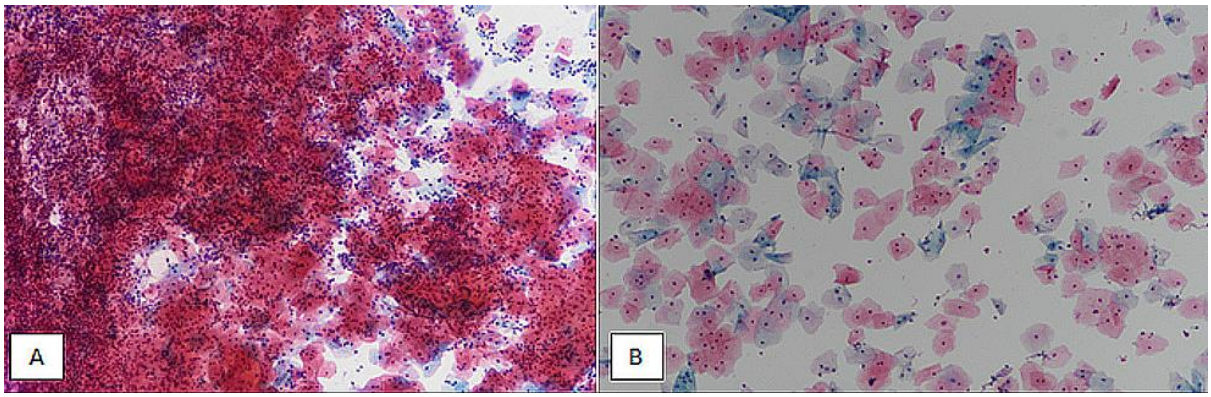

Figure 1: Difference between Conventional PAP Smear and LBC for Cervical Cytology. (A) Conventional PAP Smear Magnified at 100 times shows overlapping squamous cells with a lot of inflammatory and hemorrhagic background, making individual cellular details difficult to interpret. (B) Liquid-based cytology at 100 times magnification reveals widely dispersed squamous cells without any inflammation or haemorrhage in the background, resulting in clear individual cellular details [18].

Table 1: Comparison of cytoplasmic details [19].

Cytoplasm	Group	
	Conventional N (%)	**Uprep N (%)**
Not clear	12 (21.8)	3 (5.5)
Clear	30 (54.5)	0 (0)
Very Clear	13 (23.6)	52 (94.5)
Total	55 (100)	55 (100)

Table 2: Comparison of Nucleus Details [19].

Nucleus	Group	
	Conventional N (%)	**Uprep N (%)**
Not clear	13 (23.6)	3 (5.5)
Clear	28 (50.9)	4 (7.3)
Excellent Details	14 (25.5)	48 (87.3)
Total	55 (100)	55 (100)

3.3 Ancillary Testing: LBC offers a unique advantage in terms of ancillary testing. The remaining cell suspension, after slide preparation, can be used for additional tests like high-risk HPV DNA testing, molecular studies, or immunocytochemistry.

This capability not only enriches the diagnostic information obtained from a single sample collection but also minimizes patient discomfort and inconvenience associated with repeat sampling [20].

3.4 Standardization and Automation: LBC enables standardization of slide preparation, which helps in achieving consistency in sample quality [21]. The steps involved in LBC are easily automated, making the process more efficient and less dependent on manual skills. This automation extends to screening, with several platforms allowing automated primary screening of LBC samples [22]. This dramatically increases the throughput of samples, essential in large-scale screening programs. For example, An LBC PAP Smear test kit called U-PREP was designed to be used with a standard swing-bucket centrifuge. By batch processing with different size rotor heads, low to high volumes can be achieved.

3.5 Storage and Record-Keeping: The leftover cell suspension after slide preparation can be stored for several years without significant degradation. This allows retrospective analysis if needed and helps maintain patient records. In an era where personalized medicine is becoming increasingly important, this ability to reanalyze samples with novel techniques can be highly beneficial [23]. Overall, the use of LBC significantly enhances the diagnostic process by improving sample quality, reducing unsatisfactory rates, facilitating ancillary testing, and increasing efficiency through automation [21,22]. The advent of LBC marks a crucial step forward in the field of gynaecological cytopathology, leading to improved patient care and management [24].

4. Limitations and Challenges

Despite its many advantages, LBC also comes with limitations. One of the main limitations is the cost of the procedure, which is higher than conventional cytology. Also, while LBC reduces unsatisfactory samples, it does not eliminate them [12].

5. Liquid-Based Cytology in Gynecologic Oncology

Liquid-based cytology (LBC) has reshaped the field of gynecologic oncology, offering significant advancements in diagnostic accuracy, improved patient management, and opportunities for integrated molecular testing [25].

5.1 Cervical Cancer Screening and Diagnosis

The most significant application of LBC has been in cervical cancer screening, where it has largely replaced conventional Pap smears [13]. The ability of LBC to provide a cleaner, clearer sample, free from obscuring material, enhances the detection of cervical intraepithelial neoplasia (CIN), thereby allowing for early intervention [26]. Furthermore, the preserved samples can be utilized for high-risk HPV DNA testing, providing a co-testing strategy for more accurate risk stratification and management of patients.

5.2 Endometrial and Ovarian Cancer

Although the use of LBC is not as established for endometrial and ovarian cancers as it is for cervical cancer, several studies have shown promising results. LBC can improve the sensitivity of endometrial cancer detection by reducing the number of inadequate samples [27]. As for ovarian cancer, the use of LBC for the assessment of pelvic washings or ascitic fluid samples can enhance the accuracy of cytologic diagnosis [28].

6. Opportunities for Integrated Testing

One of the unique advantages of LBC is the ability to perform additional tests on the same sample [29]. With advances in molecular biology, testing for genetic and molecular changes associated with gynecologic cancers can provide valuable diagnostic and prognostic information [30]. For instance, the preserved samples in LBC can be utilized for tests like p16 and Ki-67 immunostaining, which can further enhance the detection and risk stratification of cervical pre-cancerous lesions [31]. This aspect of integrated testing is particularly relevant in the era of personalized medicine, where treatment decisions are increasingly guided by molecular markers [23].

7. Implication for Patient Management

From a clinical perspective, the use of LBC can reduce the need for repeat testing due to unsatisfactory samples, leading to faster diagnosis and treatment initiation [32]. The possibility of performing HPV DNA testing and other molecular tests on the same sample can provide a comprehensive understanding of the disease, aiding in personalized patient management [33]. In conclusion, LBC has a significant role in gynecologic oncology, not only for the early detection of gynecologic malignancies but also for integrated molecular testing and patient management[34]. The continued evolution of LBC technology and further research into its application can further enhance its utility in this field.

8. Conclusion

Liquid-based cytology (LBC) has indeed brought a paradigm shift in the field of gynecologic oncology. From its inception as an innovative technique designed to improve sample quality and accuracy, it has demonstrated the capacity to enhance diagnostic outcomes and patient management. The impact of LBC is most evident in the domain of cervical cancer screening, where it has significantly improved the detection of pre-cancerous lesions and allowed for integrated HPV DNA testing. Yet, the utility of LBC is not restricted to cervical cytology.

The application of this technology is progressively expanding into the detection and management of other gynecologic cancers, like endometrial and ovarian cancer, though the efficacy in these areas still warrants further study. Additionally, the capacity of LBC to facilitate integrated

molecular testing on the same sample is an aspect of considerable significance in the era of personalized medicine. Despite the clear advantages of LBC, it is crucial to remember its inherent limitations and challenges, including increased costs, a need for training in slide preparation and interpretation, and dependency on specialized equipment. However, these challenges should not deter us from embracing LBC and working towards overcoming the obstacles.

The benefits, in terms of improved sensitivity and specificity, reduced unsatisfactory rates, and the potential for integrated testing, strongly support the continued use and development of LBC. In conclusion, LBC is a significant technological advancement in gynecologic oncology that holds promise for improving diagnostic accuracy and enhancing patient management. Its application in gynecologic oncology signifies a major step forward in the goal of early detection and effective management of gynecologic malignancies. The continual refinement of this technology, combined with further research in its application and strategies to overcome its limitations, is essential for harnessing the full potential of LBC in improving women's healthcare worldwide.

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References:

1) Olson AJ. Perspectives on structural molecular biology visualization: from past to present. Journal of molecular biology [Internet]. 2018 Oct 19;430(21):3997-4012. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6186497/ https://doi.org/10.1016/j.jmb.2018.07.009 PMid:30009769 PMCid:PMC6186497

2) Venkat PS, Parikh N, Beron P. Recent advances in gynecologic radiation oncology. Current Opinion in Obstetrics and Gynecology. 2019 Feb 1;31(1):38-42. https://doi.org/10.1097/GCO.0000000000000519 PMid:30531605

3) Haghighi F, Ghanbarzadeh N, Ataee M, Sharifzadeh G, Mojarrad JS, Najafi-Semnani F. A comparison of liquid-based cytology with conventional Papanicolaou smears in cervical dysplasia diagnosis. Advanced Biomedical Research [Internet]. 2016 Oct 26 [cited 2020 Sep 24];5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5137229/?fbclid=IwAR3Gcx0lilXKLr42ooC0j4zewrZ8AJsxC19e3oLSrgCga2aPDUhalsRlVDQ

4) Strander B, Andersson-Ellström A, Milsom I, Rådberg T, Ryd W. Liquid-based cytology versus conventional Papanicolaou smear in an organized screening program: a prospective randomized study. Cancer cytopathology. 2007 Oct 25;111(5):285-91. https://doi.org/10.1002/cncr.22953 PMid:17724676

5) Norimatsu Y, Yanoh K, Hirai Y, Kurokawa T, Kobayashi Tadao K, Fulciniti F. A Diagnostic Approach to Endometrial Cytology by Means of Liquid-Based Preparations. Acta Cytologica. 2019 Aug 30;64(3):195-207. https://doi.org/10.1159/000502108 PMid:31473735

6) Akira Mitoro, Nishikawa T, Yoshida M, Sawai M, Okada Y, Kitagawa K, et al. Diagnostic Efficacy of Liquid-Based Cytology in Endoscopic Ultrasound-Guided Fine Needle Aspiration for Pancreatic Mass Lesions During the Learning Curve. Pancreas. 2019 May 1;48(5):686-9. https://doi.org/10.1097/MPA.0000000000001304 PMid:31091216

7) Einstein A, Shukla S, Shukla A, Mishra D. Comparison of specimen adequacy and smear quality in oral smears prepared by manual liquid-based cytology and conventional methods. Journal of Oral and Maxillofacial Pathology. 2015;19(3):315. https://doi.org/10.4103/0973-029X.174611 PMid:26980958 PMCid:PMC4774283

8) Singh U, Qureshi S, Negi N, Singh N, Goel M, Srivastava K. Comparative study between liquid-based cytology & conventional Pap smear for cytological follow up of treated patients of cancer cervix. The Indian journal of medical research. 2018 Mar;147(3):263. https://doi.org/10.4103/ijmr.IJMR_854_16 PMid:29923515 PMCid:PMC6022377

9) Daoud T, Sardana S, Stanietzky N, Klekers AR, Bhosale P, Morani AC. Recent Imaging Updates and Advances in Gynecologic Malignancies. Cancers. 2022 Nov 10;14(22):5528. https://doi.org/10.3390/cancers14225528 PMid:36428624 PMCid:PMC9688526

10) Priscilla, Rutger Quispel, Cahen DL, Snijders-Kruisbergen MC, Petri van Loenen, Erler NS, et al. Diagnostic yield and agreement on fine-needle specimens from solid pancreatic lesions: comparing the smear technique to liquid-based cytology. Endoscopy International Open. 2020 Jan 22;08(02):E155-62 https://doi.org/10.1055/a-1038-4103 PMid:32010748 PMCid:PMC6976322

11) Celik C, Gezginc K, Toy H, Findik S, Yilmaz O. A comparison of liquid-based cytology with conventional cytology. International Journal of Gynecology & Obstetrics. 2008 Feb 1;100(2):163-6. https://doi.org/10.1016/j.ijgo.2007.07.023 PMid:17920599

12) Arbyn M, Herbert A, Schenck U, Nieminen P, Jordan J, McGoogan E, Patnick J, Bergeron C, Baldauf JJ, Klinkhamer P, Bulten J. European guidelines for quality assurance in cervical cancer screening: recommendations for collecting samples for conventional and liquid-based cytology. Cytopathology. 2007 Jun;18(3):133-9. https://doi.org/10.1111/j.1365-2303.2007.00464.x PMid:17573762

13) Pankaj S, Nazneen S, Kumari S, Kumari A, Kumari A, Kumari J, et al. Comparison of conventional Pap smear and liquid-based cytology: A study of cervical cancer screening at a tertiary care center in Bihar. Indian Journal of Cancer. 2018;55(1):80. https://doi.org/10.4103/ijc.IJC_352_17 PMid:30147099

14) Pankaj S, Kumari A, Kumari S, Choudhary V, Kumari J, Kumari A, Nazneen S. Evaluation of sensitivity and specificity of pap smear, LBC and HPV in screening of cervical cancer. Indian Journal of Gynecologic Oncology. 2018 Sep;16:1-5. https://doi.org/10.1007/s40944-018-0186-9

15) Klug SJ, Neis KJ, Harlfinger W, Malter A, König J, Spieth S, Brinkmann-Smetanay F, Kommoss F, Weyer V, Ikenberg H. A randomized trial comparing conventional cytology to liquid-based cytology and computer assistance. International journal of cancer.

2013 Jun 15;132(12):2849-57. https://doi.org/10.1002/ijc.27955 PMid:23175270

16) Sherwani RK, Khan T, Akhtar K, Zeba A, Siddiqui FA, Rahman K, Afsan N. Conventional Pap smear and liquid based cytology for cervical cancer screening-A comparative study. Journal of cytology. 2007 Oct 1;24(4):167-72. https://doi.org/10.4103/0970-9371.41888

17) Abulafia O, Pezzullo JC, Sherer DM. Performance of ThinPrep liquid-based cervical cytology in comparison with conventionally prepared Papanicolaou smears: a quantitative survey. Gynecologic oncology. 2003 Jul 1;90(1):137-44. https://doi.org/10.1016/S0090-8258(03)00176-8 PMid:12821354

18) Hashmi AA, Naz S, Ahmed O, Yaqeen SR, Irfan M, Asif MG, et al. Comparison of Liquid-Based Cytology and Conventional Papanicolaou Smear for Cervical Cancer Screening: An Experience From Pakistan. Cureus [Internet]. 2020 Dec 26;12(12). Available from: https://www.cureus.com/articles/48210-comparison-of-liquid-based-cytology-and-conventional-papanicolaou-smear-for-cervical-cancer-screening-an-experience-from-pakistan https://doi.org/10.7759/cureus.12293

19) Bindhuja J, Aswathy Jeyachadran. Validity of UPREP liquid based cytology in FNAC examination for palpable lesions type of article - original article. Tropical Journal of Pathology and Microbiology. 2019 May 31;5(5):300-8. https://doi.org/10.17511/jopm.2019.i05.08

20) Martini M, Capodimonti S, Cenci T, Bilotta M, Guido Fadda, Luigi Maria Larocca, et al. To Obtain More With Less: Cytologic Samples With Ancillary Molecular Techniques-The Useful Role of Liquid-Based Cytology. Archives of Pathology & Laboratory Medicine. 2018 Mar 1;142(3):299-307. https://doi.org/10.5858/arpa.2017-0148-RA PMid:29494225

21) Makde MM, Sathawane P. Liquid-based cytology: Technical aspects. Cytojournal [Internet]. 2022 Jun 14;19(41):41. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9345114/ https://doi.org/10.25259/CMAS_03_16_2021 PMid:35928530 PMCid:PMC9345114

22) Barbieri D, Venturoli S, Costa S, Landini MP. Improving Laboratory Efficiency by Automation of Preanalytic Processing of ThinPrep Specimens for Real-Time PCR High-Risk HPV Testing. Journal of Laboratory Automation. 2016 Jun;21(3):432-8. https://doi.org/10.1177/2211068215569347 PMid:25673634

23) Plönes T, Engel-Riedel W, Stoelben E, Limmroth C, Schildgen O, Schildgen V. Molecular Pathology and Personalized Medicine: The Dawn of a New Era in Companion Diagnostics-Practical Considerations about Companion Diagnostics for Non-Small-Cell-Lung-Cancer. Journal of Personalized Medicine. 2016 Jan 15;6(1):3. https://doi.org/10.3390/jpm6010003 PMid:26784235 PMCid:PMC4810382

24) Bhardwaj N, Gupta N, Gupta P, Malhotra P. Flow cytometric immunophenotyping in Liquid-based Cytology Sample of Pleural Fluid: Connecting the dots. Cytopathology. 2021 Dec 8; https://doi.org/10.1111/cyt.13086 PMid:34878677

25) Sharma R, Zaheer S, Ahluwalia C. Diagnostic utility of conventional and liquid-based cytology in the management of thyroid lesions; an institutional experience. Cytojournal. 2022 Jun 7;19:36. https://doi.org/10.25259/Cytojournal_34_2021 PMid:35928535 PMCid:PMC9345136

26) Traynor D, Shiyamala Duraipandian, Bhatia R, Cuschieri K, Martin C, O'Leary J, et al. The potential of biobanked liquid based cytology samples for cervical cancer screening using Raman spectroscopy. Journal of Biophotonics. 2019 Mar 25;12(7). https://doi.org/10.1002/jbio.201800377 PMid:30653819

27) Zhang H, Wen J, Xu PL, Chen R, Yang X, Zhou LE, et al. Role of Liquid-based Cytology and Cell Block in the Diagnosis of Endometrial Lesions. Chinese Medical Journal. 2016 Jun 20;129(12):1459-63. https://doi.org/10.4103/0366-6999.183431 PMid:27270542 PMCid:PMC4910370

28) Hodgson A, Kim V, Murali R. Cytologic features of gynecologic germ cell tumors and carcinomas exhibiting germ cell tumor differentiation. Cancer Cytopathology. 2022 Dec 27; https://doi.org/10.1002/cncy.22673 PMid:36574209

29) Michael CW, Bedrossian C. The Implementation of Liquid-Based Cytology for Lung and Pleural-Based Diseases. Acta Cytologica. 2014 Jan 1;58(6):563-73. https://doi.org/10.1159/000369198 PMid:25427721

30) Prendergast EN, Elvin JA. Genomic profiling of gynecologic cancers and implications for clinical practice. Current Opinion in Obstetrics & Gynecology. 2017 Feb 1;29(1):18-25. https://doi.org/10.1097/GCO.0000000000000335 PMid:27984344

31) Gothwal M, Nalwa A, Singh P, Yadav G, Bhati M, Samriya N. Role of Cervical Cancer Biomarkers p16 and Ki67 in Abnormal Cervical Cytological Smear. The Journal of Obstetrics and Gynecology of India. 2020 Nov 18;71(1):72-7. https://doi.org/10.1007/s13224-020-01380-y PMid:33814802 PMCid:PMC7960869

32) Patel NM, Rupali Bavikar, Buch A, Kulkarni M, Arpana Dharwadkar, Viswanathan V. A Comparison of Conventional Pap Smear and Liquid-Based Cytology for Cervical Cancer Screening. Gynecology and Minimally Invasive Therapy. 2023 Jan 1;12(2):77-82. https://doi.org/10.4103/gmit.gmit_118_22 PMid:37416097 PMCid:PMC10321340

33) ŞAHİNER F. Current Problems and Recent Advances in the Molecular Diagnosis of Genital Human Papillomavirus Infections. Mikrobiyoloji Bulteni. 2014 Oct 28;48(4):689-706. https://doi.org/10.5578/mb.7631 PMid:25492665

34) Barodawala SM, Chadha K, Kavishwar V, Murthy A, Shetye S. Cervical cancer screening by molecular Pap-transformation of gynecologic cytology. Diagnostic Cytopathology. 2018 Nov 23;47(5):374-81. https://doi.org/10.1002/dc.24116 PMid:30468313