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## ABSTRACT

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## THE ROLE OF LIQUID BIOPSY IN THE DIAGNOSIS OF ENDOMETRIAL CANCER: A BIBLIOMETRIC ANALYSIS

**Background.** Liquid biopsy has emerged as one of the most promising approaches in modern oncological diagnostics, enabling the detection of tumor-derived components in biological fluids using minimally invasive methods. In recent years, this technique has attracted increasing attention in gynecologic oncology, particularly in the study of endometrial cancer.

**Aim.** Perform a bibliometric analysis of scientific publications dedicated to the application of liquid biopsy in endometrial cancer research.

**Materials and methods.** The analysis was conducted using the Scopus database and covered publications from 1956 to January 30, 2026.

**Results.** In total, 736 relevant documents were identified and analyzed. Bibliometric visualization and network analysis were performed using the software VOSviewer. The results demonstrated a significant increase in publications after 2016, indicating growing scientific interest in the clinical potential of liquid biopsy for cancer diagnostics and monitoring. Geographic analysis revealed that the largest contributions to this field come from China and the United States, followed by several European countries. Subject-area analysis showed a strong interdisciplinary nature to the research, with medicine, biochemistry, chemistry, computer science, and chemical engineering being the most represented disciplines. Cluster analysis identified four major research directions: oncology, gynecologic oncology, molecular biology, and diagnostic technologies. Chronological analysis revealed a gradual shift in research focus from traditional clinical diagnostic approaches to molecular and integrative technologies involving circulating tumor DNA, microRNA, and exosomes. gies involving circulating tumor DNA, microRNA, and exosomes.

**Conclusions.** The results confirm the growing scientific and clinical importance of liquid biopsy as a promising tool for early detection, monitoring, and personalized management of endometrial cancer.

**Keywords:** liquid biopsy, endometrial cancer, bibliometric analysis, ctDNA, biomarkers, oncogynecology.

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## РЕЗЮМЕ

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## РОЛЬ РІДИННОЇ БІОПСІЇ В ДІАГНОСТИЦІ РАКУ ЕНДОМЕТРІЮ: БІБЛІОМЕТРИЧНИЙ АНАЛІЗ

**Вступ.** Рідинна біопсія стала одним із найперспективніших підходів у сучасній онкологічній діагностиці, що дозволяє виявляти компоненти пухлинного походження в біологічних рідинах за допомогою малоінвазивних методів. В останні роки ця методика привертає все більшу увагу в гінекологічній онкології, зокрема у вивченні раку ендометрія.

**Мета.** Провести бібліометричний аналіз наукових публікацій, присвячених застосуванню рідкої біопсії в дослідженнях раку ендометрія. **Матеріали та методи.** Аналіз проводився з використанням бази даних Scopus та охоплював публікації з 1956 року по 30 січня 2026 року.

**Результати.** Загалом було виявлено та проаналізовано 736 відповідних документів. Бібліометричну візуалізацію та мережевий аналіз було виконано за допомогою програмного забезпечення VOSviewer. Результати продемонстрували значне збільшення кількості публікацій після 2016 року, що свідчить про зростаючий науковий інтерес до клінічного потенціалу рідкої біопсії для діагностики та моніторингу раку. Географічний аналіз показав, що найбільший внесок у цю галузь роблять Китай та Сполучені Штати, а також кілька європейських країн. Аналіз предметної області показав сильний міждисциплінарний характер дослідження, де найбільш представленими дисциплінами є медицина, біохімія, хімія, інформатика та хімічна інженерія. Кластерний аналіз визначив чотири основні напрямки досліджень: онкологія, гінекологічна онкологія, молекулярна біологія та діагностичні технології. Хронологічний аналіз виявив поступове зміщення фокусу досліджень від традиційних клінічних діагностичних підходів до молекулярних та інтегративних технологій, що включають циркулюючу пухлинну ДНК, мікроРНК та екзосоми.

**Висновки.** Результати підтверджують зростаючу наукову та клінічну важливість рідинної біопсії як перспективного інструменту для раннього виявлення, моніторингу та персоналізованого лікування раку ендометрія.

**Ключові слова:** рідинна біопсія, рак ендометрія, бібліометричний аналіз, ctDNA, біомаркери, онкогінекологія.

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## INTRODUCTION

Endometrial cancer (EC) is one of the most common gynecological cancers worldwide, with an increasing incidence [1]. Early diagnosis of the disease remains a pressing problem in modern oncology. Currently, no validated screening methods can be recommended for use in the general population. Although advanced EC has a poor prognosis, timely diagnosis can improve long-term treatment outcomes and increase patients' survival [2]. Effective early diagnosis is key to improving prognosis and reducing mortality, but existing methods, particularly invasive endometrial biopsies, have limitations: they can be uncomfortable for patients, technically difficult, and, in some cases, impossible to perform or yield insufficient tissue for analysis [3]. The last decade has brought advances in molecular classification, which reveal more accurate prognostic factors and the possibility of personalized adjuvant treatment. There is currently no consensus on early detection strategies for endometrial cancer, and current diagnostic methods, such as hysteroscopy and endometrial biopsy, are invasive, expensive, and have low specificity [4]. Endometrial sampling is associated with the risk of discomfort, bleeding, infection, and uterine perforation. In addition, in many cases, biopsy does not provide sufficient diagnostic information and yields only a partial picture of the tumor's molecular and morphological heterogeneity [5]. Liquid biopsy is a key element of the personalized oncology of the future, as it combines high informativeness, minimal invasiveness, and the potential for comprehensive molecular profiling of the tumor, opening new opportunities for early diagnosis and disease prognosis [6]. This method allows real-time observation of molecular changes in the tumor without surgical intervention, opening the door to monitoring the treatment of cancer patients [7]. The possibility of multiple sampling makes liquid biopsy particularly valuable for dynamic monitoring of tumor progression, especially when a traditional biopsy is not possible, and for in-depth study of tumor evolution, invasion, and metastasis. [8]. Liquid biopsy has demonstrated clinical utility across many cancer types and is already integrated into practice [9,10]. Its use in EC may now gain greater recognition, making liquid biopsy an attractive concept in gynecological oncology [11].

The **aim** of this work is to perform a bibliometric analysis and data systematization on the use of liquid biopsy in the diagnosis of endometrial cancer.

## MATERIALS AND METHODS

A search for studies on the use of liquid biopsy in the diagnosis of endometrial cancer was conducted in the Scopus database using the keywords “endometrial carcinoma”, “endometrial adenocarcinoma”, “uterine

neoplasms”, “endometrial fluid”, and “liquid biopsy” from 1956 to 2026. A total of 736 scientific publications were analyzed. The selected studies were systematized by year of publication, study type, subject area, and country of publication using the Scopus bibliometric tools and VOSviewer software (Leiden University, <https://www.vosviewer.com/>). VOSviewer was used to analyze co-authorship among countries/regions, authors, institutions, and authors' keywords. Filtering and selection of publications were carried out according to the specified inclusion/exclusion criteria (presence of keywords, semantic relevance to the topic).

## RESULTS

The term liquid biopsy was introduced into the scientific literature around 2010, when researchers began to describe the detection of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) in the blood of patients with various types of cancer as an alternative to traditional tissue biopsy [12]. However, the scientific basis for this direction dates back much further. Free nucleic acids in human blood were first described in 1948, which laid the foundation for further study of circulating DNA [13]. In 1977, publications showed that circulating DNA levels were significantly elevated in patients with cancer, providing the first empirical evidence for the diagnostic use of circulating DNA [14]. In 1989, researchers identified that part of this circulating DNA is of tumor origin, and in 1994, specific RAS mutations in circulating DNA were discovered, characteristic of tumor cells [15]. In the history of liquid biopsy as a diagnostic method, the 1950s are considered the period of the emergence of molecular biology and the understanding of the genetic mechanisms of tumor processes, which later formed the basis for the development of modern technologies for ctDNA analysis. Today, liquid biopsy is defined as a non-invasive diagnostic method that allows the detection and analysis of tumor markers in biological fluids, most often in blood, including CTCs, ctDNA, cfRNA, exosomes, and other components secreted by tumor cells [7].

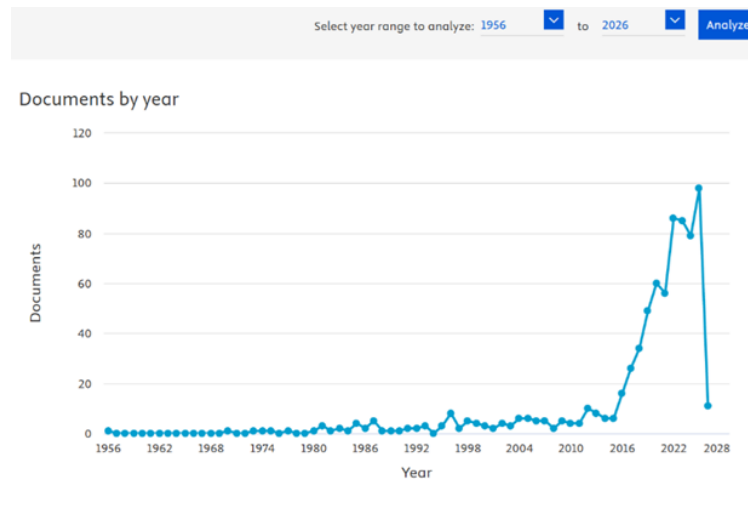
In parallel with the development of the concept of analyzing circulating tumor components in blood, a research direction on biological fluids obtained by aspiration from pathological foci emerged. Since the middle of the 20th century, fine-needle aspiration biopsy (FNA) has been actively used as a minimally invasive method of cytological diagnosis of tumors. Later, the development of molecular biology and the introduction of PCR, next-generation sequencing (NGS), and digital PCR allowed the use of aspirates not only for cytomorphological assessment, but also for molecular profiling of tumors [16]. Thus, along with the classical concept of liquid biopsy, based on the analysis

of peripheral blood, a separate direction was formed - liquid biopsy of aspirates, which involves the study of tumor markers in fluid obtained from cysts, pleural or peritoneal effusion, lymph nodes, thyroid nodes, breast tumors, and other pathological formations.

Therefore, due to the rapid growth in the number of scientific publications describing various markers, methods for their detection, and clinical applications, there is an urgent need to systematize this data through bibliometric analysis, which enables us to reflect the field's development trends and identify promising areas of research.

#### *Bibliometric analysis of scientific literature*

During the bibliometric analysis of the scientific literature, which we conducted using the Scopus database for the period from 1956 to 2026, 736 publications were identified using keywords related to uterine neoplasia, endometrial carcinoma, and liquid biopsy. The liquid biopsy method was first described in the 1950s, but rapid growth in interest in this topic began in 2016, with a peak in 2022-2025, confirming the relevance and prospects of research on using liquid biopsy for the diagnosis of uterine oncopathology (Fig. 1).



**Figure 1. Result of visualization of the chronology of publications on this topic using the tools of bibliometric analysis of the Scopus database**

The steady increase in publications on liquid biopsy in endometrial cancer over recent years indicates growing scientific interest in the field and its prospects in clinical practice.

Analysis of the geographical distribution of scientific publications on liquid biopsy shows that the leading positions in research are occupied by China and the USA, which are significantly ahead of other countries in the number of publications. European countries, in particular Spain, the United Kingdom, and Italy, demonstrate significant scientific activity, while Australia, Germany, Japan, Canada, and Poland have moderate indicators (Fig. 2). This geographical distribution of publications indicates the heterogeneity of the development of scientific activity, which determines priority areas for future international initiatives and cooperation in the field of liquid biopsy.

Thematic analysis of 736 articles divides them into 10 main subject areas, among which medicine, biochemistry, chemistry, computer science and chemical engineering predominate, which indicates the interdisciplinary nature of research on liquid biopsy in

the diagnosis of endometrial cancer (Fig. 3). The dominance of medical and biochemical research indicates the clinical focus of this topic and its importance for oncological practice. A significant proportion of publications in chemistry and chemical engineering reflects the active development of analytical methods and technologies for biomarker detection. The involvement of computer science underscores the growing role of bioinformatics, machine learning, and the analysis of large datasets in improving the accuracy and efficiency of diagnostic approaches. Overall, the results obtained emphasize the complex nature of research and confirm the prospects of integrating diverse scientific areas to further develop liquid biopsy in oncology and gynecology.

According to the results of bibliometric network visualization using VOSviewer, all publications can be grouped into four main thematic clusters: oncology, oncogynecology, molecular biology, and diagnostics, reflecting the key areas of scientific effort in this field (Fig. 4).

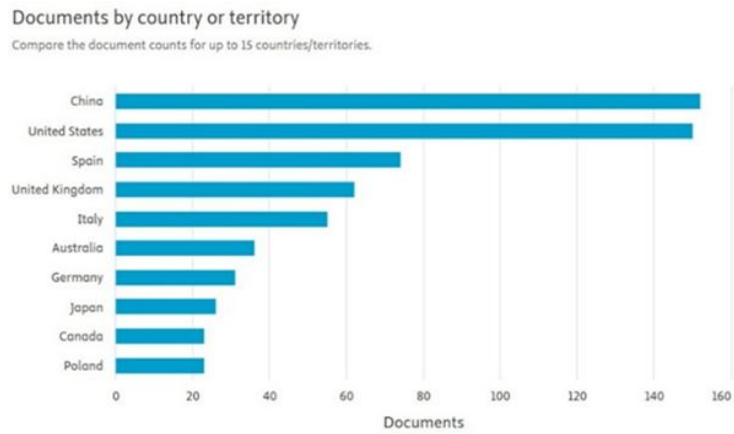


Figure 2. Result of visualization of the distribution of publications on a given topic by geographical distribution using the bibliometric analysis tools of the Scopus database

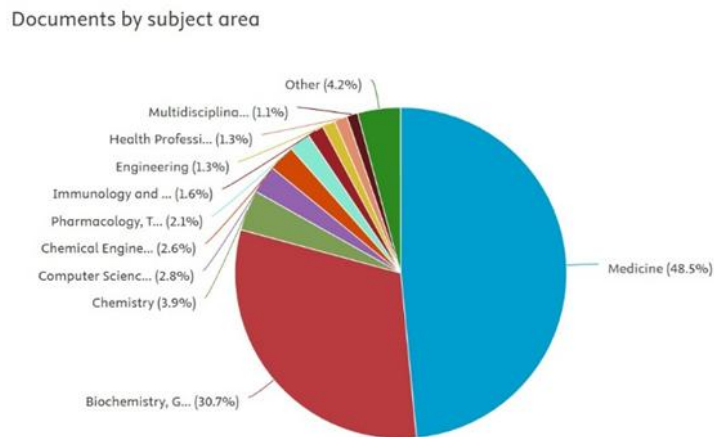


Figure 3. Result of visualization of the distribution of publications on this topic by subject areas using the bibliometric analysis tools of the Scopus database

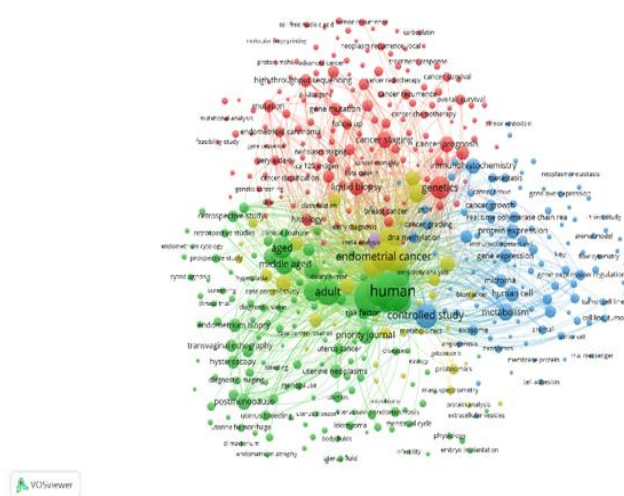


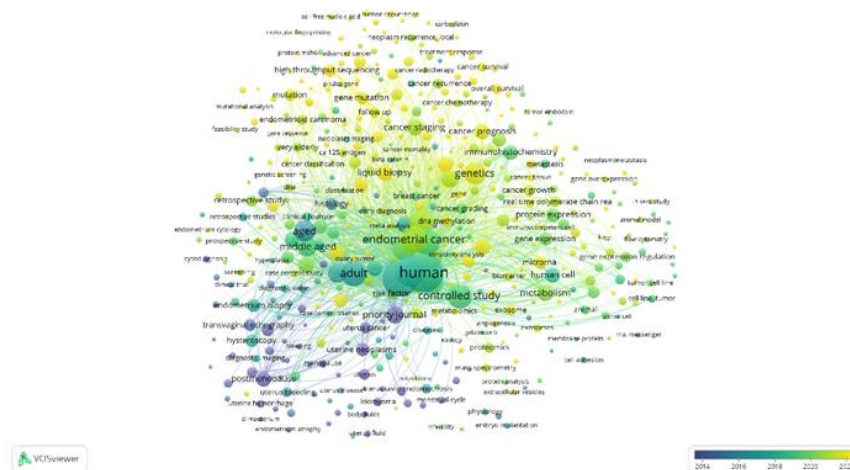
Fig. 4 The result of the visualization of the regularities of the thematic distribution of a given topic using VOSviewer bibliometric analysis tools

This clustering reflects the structural organization of modern research on liquid biopsy in endometrial cancer and underscores the complex nature of this scientific problem. The oncology cluster includes works devoted to the general mechanisms of carcinogenesis, tumor molecular heterogeneity, and the clinical aspects of the course of oncological diseases. Its dominance underscores the fundamental role of liquid biopsy in understanding tumor biology and assessing disease prognosis. The oncogynecological cluster focuses on the specific features of endometrial cancer, including early diagnosis, risk stratification, and a personalized approach to patient treatment. The presence of a separate cluster confirms the growing interest in adapting liquid biopsy methods specifically to the needs of clinical oncogynecology. The molecular biology cluster comprises studies aimed at identifying and characterizing biomarkers, particularly circulating tumor DNA, microRNA, and other molecular components for non-invasive diagnostics. This indicates an active search for molecular targets and a desire to increase the sensitivity and specificity of diagnostic methods. The diagnostic cluster unites works devoted to

the development, optimization, and clinical validation of liquid biopsy methods, as well as the integration of the latest analytical and digital technologies into the diagnostic process. Its formation indicates a gradual transition from experimental research to the practical application of the obtained results.

In summary, the results of the cluster analysis confirm the interdisciplinary nature of the research and demonstrate the evolution of scientific approaches – from fundamental molecular research to clinically oriented diagnostic solutions. This emphasizes the prospects of liquid biopsy as a key tool in modern oncogynecology and justifies the feasibility of further comprehensive research in this area.

A chronological analysis of scientific publications, based on overlay visualization of bibliometric networks in the VOSviewer program, identified three main stages in the evolution of research on the use of liquid biopsy in the diagnosis of endometrial cancer. The color gradation of key terms reflects the sequential transition from clinical and descriptive approaches to molecularly oriented and technologically complex research (Fig. 5).



**Figure 5. Result of the visualization of the patterns of chronological development of this topic using VOSviewer bibliometric analysis tools**

The first stage ( $\approx$  2014–2016) is clinical and diagnostic. At the initial stage, studies were focused mainly on traditional clinical and instrumental methods of endometrial cancer diagnosis. During this period, terms related to clinical practice and patient population characteristics predominate, in particular postmenopause, uterine bleeding, transvaginal echography, hysteroscopy, endometrial biopsy, retrospective study, and case-control study. The main focus was on assessing the diagnostic value of standard methods, analyzing risk factors, and examining the clinical manifestations of the disease. Liquid biopsy at this stage was considered fragmentary and mainly as an auxiliary or promising approach,

without clearly established methodological standards. The second stage ( $\approx$  2017–2019) is molecular biology. The second stage is characterized by increased interest in the molecular mechanisms of carcinogenesis and the active introduction of molecular biology methods. In bibliometric networks, the keywords genetics, gene mutation, DNA methylation, microRNA, protein expression, immunohistochemistry, and high-throughput sequencing appear and gain importance. During this period, liquid biopsy began to be recognized as a source of molecular biomarkers reflecting the tumor's genetic and epigenetic heterogeneity. Research focuses on identifying prognostic and diagnostic markers and on

comparing liquid biopsy results with tissue sample data. The third stage ( $\approx$  2020–2022) is integrative and technological. At this stage, the focus shifts towards integrating liquid biopsy into personalized medicine and clinical patient management algorithms. The terms liquid biopsy, circulating tumor DNA, exosome, metabolomics, proteomics, real-time polymerase chain reaction, cancer prognosis, survival, and treatment response are dominant in the network. Research in this period aims to assess the clinical efficacy of liquid biopsy for early diagnosis, disease monitoring, minimal residual disease detection, and prediction of treatment response. Interdisciplinary approaches that combine molecular data with bioinformatic analysis and digital technologies are increasingly playing an important role.

Thus, the chronological analysis demonstrates a consistent evolution of scientific research – from traditional clinical methods through in-depth molecular studies to modern integrative and technology-driven approaches. This confirms the growing role of liquid biopsy as a key tool in modern diagnostics and personalized treatment of endometrial cancer.

#### DISCUSSION

The results of the bibliometric analysis confirm that liquid biopsy has gradually transformed from an experimental concept into a promising tool of modern oncogynecology. The revealed dynamics of publications are consistent with the historical development of this direction: from the fundamental discoveries of circulating nucleic acids in the middle of the 20th century to the active introduction of highly sensitive molecular genetic technologies into clinical practice over the past decade. As shown in the classic review by Thierry et al. (2016), advances in molecular biology, genomics, and analytical methods laid the foundation for the emergence of liquid biopsy as a diagnostic modality [15].

The rapid increase in publications observed in our analysis after 2016 correlates with the spread of high-throughput sequencing technologies, digital PCR, and methods for analyzing circulating tumor DNA [17, 18]. These technologies have overcome key limitations of early studies, such as low tumor material concentrations in blood and insufficient analytical sensitivity. This is of particular importance for endometrial cancer, as the disease is characterized by significant molecular heterogeneity, which limits the capabilities of traditional tissue biopsy.

Thematic analysis demonstrated a clearly expressed interdisciplinary nature of the research, with medicine and biochemistry dominating, while chemistry, chemical engineering, and computer science also play significant roles. This is consistent with modern ideas of liquid biopsy as an integrative technology that combines clinical oncology, molecular diagnostics, and bioinformatics. The

growing share of research in computer science reflects the need to process large molecular datasets and the use of machine learning methods to interpret results and improve diagnostic accuracy.

Cluster analysis using VOSviewer identified four main areas of research that reflect the logic of this field's development. Oncology and oncogynecology clusters emphasize the clinical significance of liquid biopsy not only for early diagnosis but also for predicting disease course and assessing treatment response. In this context, the results are consistent with those of Łukasiewicz et al. (2021), who demonstrated the promise of liquid biopsy for increasing diagnostic accuracy in endometrial cancer, particularly when combined with biomarker approaches [7].

The identification of a molecular biology cluster supports the intensive search for specific biomarkers. Considerable attention is paid to ctDNA, the most studied component of liquid biopsy, which can reflect the tumor's mutational profile, DNA methylation levels, and genetic instability [18,19]. Studies show that ctDNA can be used to detect relapse early, often before clinical or radiological signs of disease progression [20]. In addition to ctDNA, microRNA, exosomes, and circulating tumor cells are of increasing interest. In particular, exosomes are considered stable carriers of molecular information that reflect the functional state of tumor cells and their interactions with the microenvironment [21]. In the context of endometrial cancer, these components have the potential to increase diagnostic sensitivity when combined with other biomarkers, as confirmed by systematic reviews [7, 22]. These components are considered potential indicators of minimal residual disease and early recurrence, which is particularly relevant for postoperative monitoring of patients with endometrial cancer.

The diagnostic cluster, in turn, demonstrates a gradual transition from laboratory studies to clinical validation of methods, a necessary condition for their implementation in medical care standards. This is consistent with current recommendations, which consider liquid biopsy a promising addition to standard diagnostic methods rather than a complete replacement [12, 23, 24]. For endometrial cancer, this is especially important, since traditional tissue biopsy does not always reflect intratumoral heterogeneity and dynamic molecular changes.

Chronological analysis confirmed the evolution of scientific approaches from clinical-descriptive to integrative-technological. Early works were focused on traditional diagnostic methods, while modern research is oriented towards personalized medicine, where liquid biopsy is considered a tool for dynamic monitoring of the tumor process. This shift aligns with global trends in

oncology and the concept of precision medicine, which prioritizes non-invasive, repeatable, and highly accurate diagnostic methods [7, 25]. However, despite significant scientific progress, the results of the bibliometric analysis suggest that certain limitations persist. These include the lack of standardized protocols for sample collection and analysis, variability in results across laboratories, and the limited number of large-scale, prospective clinical trials. This emphasizes the need for further multicenter studies and the development of unified methodological approaches.

Overall, the analysis confirms that liquid biopsy is one of the most dynamic and promising areas of modern gynecological oncology. Its further development, integrating interdisciplinary approaches and clinical validation, has the potential to significantly change the diagnosis, prognosis, and personalized treatment of endometrial cancer.

### **CONCLUSIONS**

Bibliometric analysis showed that liquid biopsy has transformed from an experimental approach into a promising tool in modern oncogynecology. Since

2016, there has been a rapid increase in scientific publications, reflecting interest in its clinical application for the diagnosis and monitoring of endometrial cancer. The studies are interdisciplinary, combining medicine, molecular biology, analytical chemistry, and bioinformatics. Chronological and cluster analyses indicate an evolution from clinical-descriptive methods to integrative, technology-oriented approaches that use ctDNA, microRNA, and exosomes as promising biomarkers.

Along with the classical concept of liquid biopsy, based on the analysis of peripheral blood, a separate direction has emerged: liquid biopsy of aspirates, which involves the study of tumor markers in fluid obtained from various pathological formations.

Despite significant progress, the implementation of liquid biopsy is limited by the lack of standardized protocols and large-scale clinical trials. All this highlights the high potential of liquid biopsy for the diagnosis, prognosis, and personalized treatment of endometrial cancer, with further methodological integration and clinical validation.

### **PROSPECTS FOR FUTURE RESEARCH**

Despite significant progress in the application of liquid biopsy and the analysis of circulating tumor DNA (ctDNA) in clinical oncology, several aspects remain poorly understood. First, there is an urgent need to standardize sample collection, processing, and analysis methods, as different technologies and laboratories exhibit significant variability in results, limiting their comparability. Second, increasing the sensitivity and specificity of ctDNA detection, especially in early stages of the disease or in patients with minimal residual tumor, opens the door to the development of new platforms and sequencing strategies. Third, integrating ctDNA with other biomarkers, such as circulating tumor cells, exosomes, and protein markers, may provide more comprehensive and reliable diagnostics, prognosis, and monitoring of therapeutic response. Large prospective clinical trials are needed to determine optimal sampling time points, correlate ctDNA levels with clinical outcomes, and assess the impact of liquid biopsy on treatment choices. Finally, the cost-effectiveness and accessibility of ctDNA technologies are critical for their widespread implementation into routine practice, opening up the prospect of personalized oncology.

### **AUTHOR CONTRIBUTIONS**

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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### **CONFLICT OF INTEREST**

The authors have no conflict of interest to declare.

### **ETHICAL CONSIDERATIONS**

The study was conducted without involving human subjects.

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