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ABSTRACT

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THE ROLE OF NEXT-GENERATION SEQUENCING IN LUNG CANCER DIAGNOSIS

Among all malignant neoplasms, lung cancer is the cause of death in approximately every fifth patient. Next-generation sequencing can solve the issue of not only diagnosis but also the further treatment of lung cancer.

Aim. The work aims to search, process, generalize and bibliometrically analyze the scientific literature to study the main trends in next-generation sequencing in diagnosing non-small cell lung cancer.

Materials and methods. One thousand nine hundred thirty-one literature sources, including information about next-generation sequencing, were published between 2010 and 2023. The data search was carried out in electronic databases Scopus, PubMed, Web of Science, and Google Scholar using keywords: "lung cancer," "next-generation sequencing," "targeted therapy," "genetic mutations," "circulating tumor DNA," and "liquid biopsy." The authors used the bibliometric tools of the Scopus and SciVal databases to analyze the year, source, type of study, subject area, and country of publication.

Results and discussion. Next-generation sequencing is gradually becoming the new diagnostic standard. This technology allows to detect biological markers with high accuracy and specificity. Many studies have confirmed the effectiveness of next-generation sequencing for diagnosing lung cancer, assessing response to treatment and sensitivity to drug therapy, and predicting the prognosis of the disease. Lung cancer is one of the most common tumors with a high mutational load. Unique diagnostic panels allow for a short period to examine tumor tissue for a wide range of biological markers. The article aims to investigate the main areas of application of next-generation sequencing in patients with lung cancer and current clinical trials in this field. The bibliometric analysis of the scientific literature consisted of the study of publication activity from 2010 to 2023, the geography of publications, and the identification of scientific journals

where the articles about the role of next-generation sequencing were publicized.

Conclusions. Next-generation sequencing is widely used in medicine. This method can become one of the leading methods for diagnosing lung cancer because it can accurately identify specific biological markers. Tumor tissue embedded in paraffin blocks and various biological fluids can be used for diagnosis. Next-generation sequencing is effective even in cases where the amount of tumor tissue is limited and other methods cannot identify it. The advantages of the method are confirmed in clinical trials and described in many scientific publications of the leading countries of the world. As a result, next-generation sequencing appears to be an effective method for diagnosing lung cancer and selecting the most appropriate regimen of targeted or immunotherapy. Disadvantages of the method include the high cost in developing countries and the need for appropriate software.

Keywords: lung cancer, next-generation sequencing, targeted therapy, genetic mutations, circulating tumor DNA, liquid biopsy.

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РОЛЬ СЕКВЕНУВАННЯ НАСТУПНОГО ПОКОЛІННЯ ДЛЯ ДІАГНОСТИКИ РАКУ ЛЕГЕНЬ

Серед усіх злоякісних новоутворень рак легень є причиною смерті приблизно кожного п'ятого пацієнта. Єдиним методом, здатним вирішити питання не лише діагностики, але і подальшого лікування раку легень є генетичне тестування з використанням секвенування наступного покоління.

Мета. Метою роботи є пошук, обробка, узагальнення та бібліометричний аналіз наукової літератури для вивчення основних тенденцій застосування секвенування наступного покоління у діагностиці недрібноклітинного раку легень.

Матеріали та методи. Було досліджено 1931 літературне джерело, опубліковане за період з 2010 по 2023 роки, що містило інформацію про використання секвенування наступного покоління. Пошук даних проводився у електронних базах даних Scopus, PubMed, Web of Science та Google Scholar за ключовими термінами: «рак легень», «секвенування наступного покоління», «таргетна терапія», «генетичні мутації», «циркулююча пухлинна ДНК», «рідинна біопсія». Автори використовували бібліометричні інструменти бази даних Scopus та SciVal для аналізу року, джерела, типу дослідження, предметної галузі та країни видання.

Результати та їх обговорення. Секвенування наступного покоління поступово стає новим діагностичним стандартом. Дана технологія дозволяє з високою точністю та специфічністю виявляти біологічні маркери. У багатьох дослідженнях була підтверджена ефективність секвенування наступного покоління для діагностики раку легень, оцінці відповіді на лікування та чутливості до медикаментозної терапії, прогнозуванні перебігу захворювання. Рак легень є однією із найбільш поширених пухлин з

високим мутаційним навантаженням. Спеціальні діагностичні панелі дозволяють за короткий проміжок часу дослідити пухлинну тканину на широкий спектр біологічних маркерів. Стаття спрямована на ознайомлення з основними напрямками застосування секвенування наступного покоління у пацієнтів з раком легень та актуальними клінічними дослідженнями у цій галузі. Бібліометричний аналіз наукової літератури полягав у дослідженні публікаційної активності за період з 2010 по 2023 роки, вивченні географії публікацій та встановленні наукових журналів, у яких найчастіше зустрічаються статті про роль секвенування наступного покоління для діагностики раку легень.

Висновки. Секвенування наступного покоління все ширше використовують у медицині. Цей метод може стати одним із провідних для діагностики раку легень, адже здатен з високою точністю ідентифікувати специфічні біологічні маркери. Для дослідження може використовуватися не лише пухлинна тканина залита у парафінові блоки, але і різноманітні біологічні рідини. Секвенування наступного покоління ефективне навіть у випадках, коли кількість пухлинної тканини обмежена і інші методи не здатні її ідентифікувати. Переваги методу підтверджені у клінічних дослідженнях та описані у багатьох наукових публікаціях провідних країн світу. Як наслідок, секвенування наступного покоління виглядає як особливо привабливий метод для діагностики раку легень і вибору найбільш відповідної схеми таргетної чи імунотерапії. Недоліками методу можна вважати високу ціну в країнах, що розвиваються та необхідність обробки великої кількості даних з використанням відповідного програмного забезпечення.

Ключові слова: рак легень, секвенування наступного покоління, таргетна терапія, генетичні мутації, циркулююча пухлинна ДНК, рідинна біопсія.

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INTRODUCTION / ВСТУП

Among all malignant neoplasms, lung cancer is the cause of death in approximately every fifth patient. According to Global cancer statistics, 1796144 people died from this disease in 2020 [1]. One of the essential factors in the low survival rate of patients is the diagnosis of the disease in the advanced stages. Lung cancer does not have specific symptoms in the early stages. Only persistent cough, chest pain, shortness of breath, and hemoptysis prompt patients to seek medical attention. That is why great efforts of scientists are directed at developing new diagnostic methods that would allow lung cancer to be detected as early as possible.

Low-dose computed tomography (LDCT) was one of the promising areas that allowed for a 20% reduction in mortality rates. However, the National Comprehensive Cancer Network (NCCN) recommends this method for patients over 50 who are current or former smokers. Another significant limitation is the difficulty in determining the origin of pulmonary nodules [2, 3].

In recent years, combining radiomic and qualitative semantic variable imaging with molecular blood biomarkers has become a popular direction of lung cancer screening [4]. This set of measures is promising. However, next-generation sequencing (NGS) can solve the issue of not only diagnosis but also the further treatment of lung cancer.

Targeted and immune checkpoint inhibitor therapies are widely used to treat locally advanced and metastatic lung cancer. NCCN guidelines recommend mandatory testing for the most common genetic mutations, such as EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET, RET, and PD-L1

expression [5]. Therefore, NGS may be the key to early diagnosis and effective lung cancer treatment.

NGS is a complex technology used to analyze the sequence (DNA) and gene expression (RNA species) [6]. The advantages of this method are low cost, quick results, wide application both for research purposes and in the clinic, and many commercially available laboratory panels. Disadvantages include the need for special computer programs, the lack of standardization for clinical use, and the high cost of diagnosis in developing countries [7]. The data obtained by the NGS method are used to improve diagnosis, prognosis, and effective treatment of many diseases, including lung cancer [8, 9].

Aim. The work aims to search, process, generalize and bibliometrically analyze the scientific literature to study the main trends in next-generation sequencing in diagnosing non-small cell lung cancer.

Materials and methods

We examined 1,931 literature sources published between 2010 and 2023 that contained information on using NGS for lung cancer diagnosis and treatment selection. The data search was carried out in electronic databases Scopus, PubMed, Web of Science, and Google Scholar using key terms: "lung cancer," "next-generation sequencing," "targeted therapy," "genetic mutations," "circulating tumor DNA," and "liquid biopsy."

The authors used Scopus database bibliometric tools and SciVal to analyze the year, source, type of study, subject area, and country of the publication. The VOSviewer system from the University of Leiden (http://www.vosviewer.com/) was used to generate and visualize the bibliometric network.

A bibliometric analysis was performed using online platforms for monitoring and analyzing international scientific research, visualization tools, and modern citation metrics SciVal (Scopus). Bibliometric networks were constructed and visualized using the VOSviewer program.

Results and discussion

NGS for lung cancer diagnosis

NGS has high specificity and sensitivity, which allows to perform a wide range of studies even with a small amount of material. This method has a low rate of false negative results. It can identify specific mutations in paraffin-embedded tumor tissue samples [10] and in circulating tumor DNA obtained by liquid biopsy [11, 12, 13].

The promise of the NGS method for diagnosing lung cancer led to the appearance of specific commercial kits and panels. Representatives of panels based on RNA fusion are AccuFusion, OmniFusion, Ion AmpliSeq™ RNA Fusion Lung Cancer Panel, and QuantideX® NGS RNA Lung Cancer Kit. TruSight RNA fusion panel or Archer fusion plex Comprehensive Thyroid and Lung are recommended if the method is based on RNA sequencing. DNA sequencing requires using Lung Cancer-Targeted Gene Panel, Ion AmpliSeq™ Colon and Lung Research Panel v2, or AmpliSeq for Illumina Colon and Lung Research Panel [7].

One of the most common is the NextDaySeq-Lung panel, which contains primers for amplification of exons 18, 19, 20, 21 of EGFR, exons 9, 20 and PIK3CA, exons 2, 3 of KRAS, and exons 11, 15 of BRAF. The identification of a specific genetic mutation allows the use of targeted therapy drugs. For example, lung cancer associated with a BRAF mutation usually responds well to treatment with BRAF/MEK inhibitors [14]. Patients with a PIK3CA mutation can use alpelisib, which is usually effective in treating breast cancer [15, 16].

Another variant of the gene panel used to diagnose lung cancer is the Ion Ampliseq RNA fusion. The method focused on the identification of splicing changes based on RNA sequencing. This panel from ThermoFisher Scientific can evaluate translocations, interstitial deletions, and chromosomal inversions. It can examine 70 known ALK, RET, ROS1, and NTRK fusion transcripts. This panel can be used parallel with DNA sequencing, although the RNA fusion method is considered more sensitive [17, 18].

The ability of cells to avoid apoptosis and excessive proliferation is considered the primary pathogenetic mechanism of the development of malignant tumors. The number of somatic mutations is constantly increasing [19]. One of the most common tumors with a high mutational load is lung cancer. Therefore, NGS can be an extremely effective method with numerous advantages, allowing to evaluate of changes in genes involved in the development of lung cancer (EGFR, BRAF, KRAS, HER2, ROS, ALK, PIK3CA, NTRK, RET, and MET) [20].

An example of the practical application of NGS compared to standard mutation testing is the work of Judd et al. [21]. Scientists conducted DNA sequencing of tumor tissue samples of 17,095 non-small cell lung cancer patients. It was found that 37.2% of people with adenocarcinomas and 4.4% with squamous cell carcinomas had a KRAS mutation. As a result, such patients are candidates for targeted therapy. Clinical studies on the efficacy and safety of sotorasib [22] and adagrasib [23] are

ongoing so that effective targeted drugs may soon appear on the pharmaceutical market.

DNA methylation method is used for early lung cancer diagnosis using NGS based on liquid biopsy. Liang et al. [24] found that its sensitivity is 75% for stage 1A and 85.7% for stage 1B non-small cell lung cancer. Compared with FISH or IHC, NGS is more sensitive and specific when analyzing fusion changes in lung cancer.

Lin et al. [25] compared the efficiency of different methods for detecting ALK rearrangements. So, when using NGS, the detection rate was 92.7%, FISH - 82.4%, IHC - 94.5%. In addition, 87.3% of NGS results were concordant with IHC results. The researchers concluded that IHC fusion testing is better for screening, while NGS fusion testing is more appropriate for selecting targeted therapies, particularly crizotinib.

One of the following examples of the use of NGS is the study of circulating non-coding RNA, which allows the prediction of drug resistance and adverse reactions to immunotherapy, chemotherapy, targeted, and radiation therapy. Li et al. [26] believe that circulating non-coding RNA may be a promising biomarker for developing targeted drugs.

To solve the problem of the lack of tumor tissue samples available for testing, non-invasive methods of biomarker research are increasingly being implemented. In recent years, the idea that NGS based on liquid biopsy should be the diagnostic standard for patients with metastatic non-small cell lung cancer has become increasingly popular [27]. Leighl et al. indicate that this method is sensitive [28]. The similarity was observed when comparing NGS for circulating tumor DNA and tissue DNA in non-small cell lung cancer patients. Similar results were obtained by Mack et al. [29] while performing NGS on more than 8,000 patients with lung cancer.

Many conducted studies and obtained favorable results confirm the effectiveness of NGS for diagnosing lung cancer. As a result, ESMO and various groups of scientists recommend the broader use of this technique [30, 31]. A successful example is the NGS method analysis of circulating tumor DNA, which allows detecting the EGFR T790M mutation and establishing the feasibility of using osimertinib [32].

According to data from Clinical.Trials.gov, 149 clinical studies are associated with NGS [33]. Active patient recruitment is ongoing in 48 clinical trials, with ten more to begin soon. This indicates the growing interest of scientists in this topic. The results obtained in clinical studies, scientific and medical institutions are actively covered in publications. As a result, we decided to conduct a bibliometric analysis of scientific literature.

Bibliometric analysis of scientific literature

NGS is a very modern diagnostic field. The first publications devoted to this topic appeared only in 2010. Until 2014, interest in NGS grew slowly, but then a rapid rise in popularity began. The most significant number of scientific publications (almost 600) was in 2019. The COVID-19 pandemic has made adjustments and somewhat reduced interest in this topic. Already in 2021, the number of scientific sources grew again and peaked in 2022. The decline in publishing activity in 2023 is because the year is now in progress (Fig. 1).

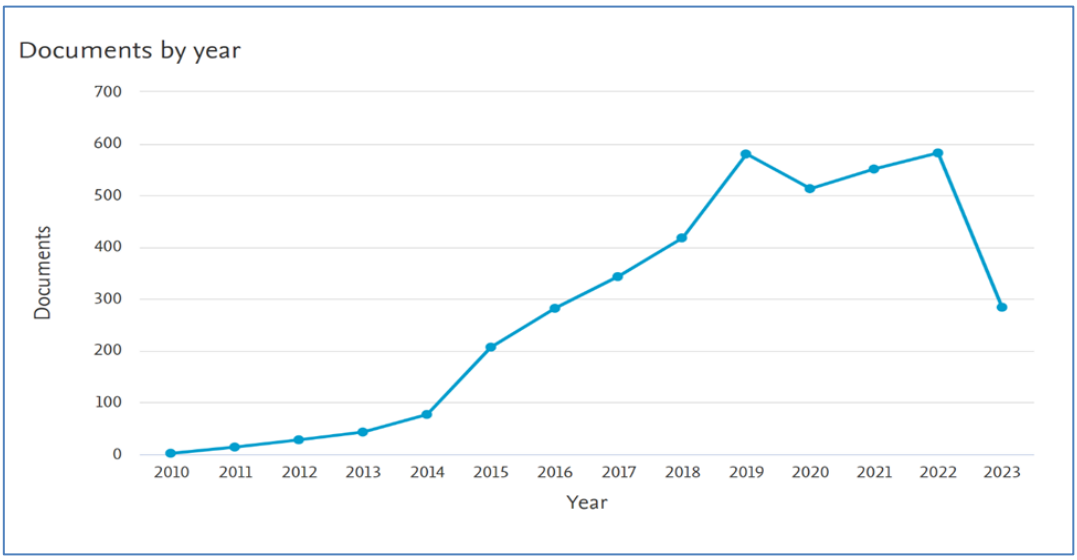

Figure 1 – Chronology of publications on NGS for lung cancer diagnosis from 2010 to 2023 according to the bibliometric analysis of the Scopus database

Scientists from the USA and China were most actively studying NGS for the diagnosis of lung cancer. The publication activity of scientists from Italy, Japan, France, Germany, Great Britain, Spain, Canada, and South Korea was significantly lower (Fig. 2).

The most significant number of research results is covered in such scientific journals as the Journal of Thoracic Oncology, Lung Cancer, Frontiers in Oncology, Cancers, and Thoracic Cancer. It is worth noting that in the journal Frontiers in Oncology, about 60 articles were devoted to the value of NGS for diagnosing and treating lung cancer (Fig. 3).

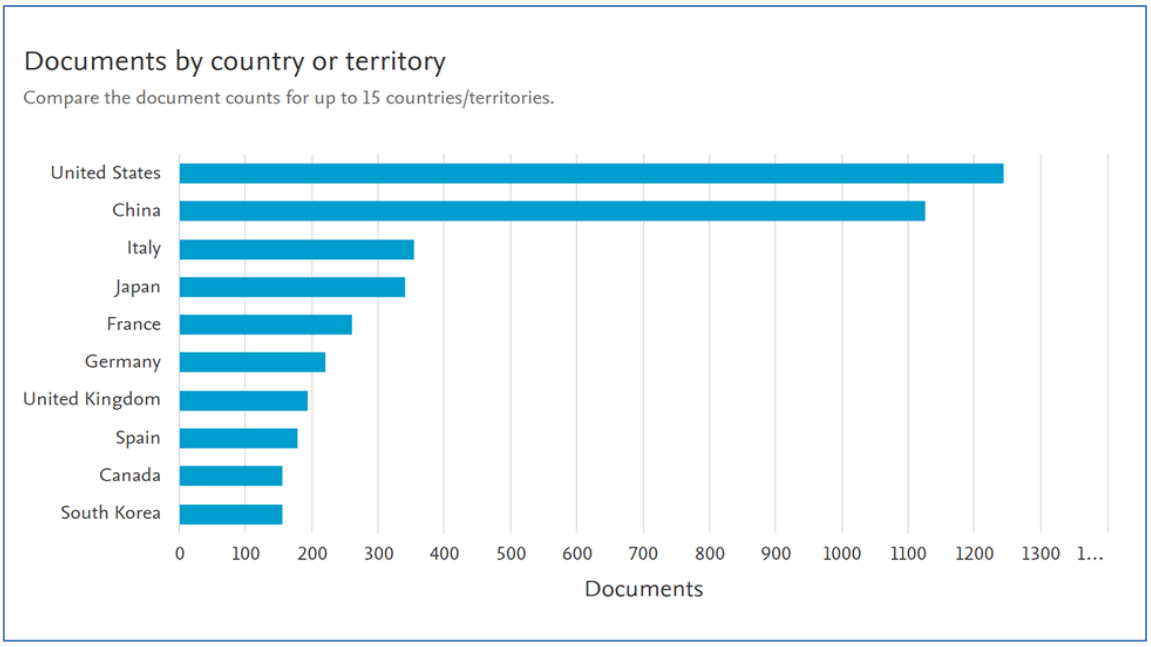

Figure 2 – The number of publications in different countries about NGS for lung cancer diagnosis from 2010 to 2023 according to the bibliometric analysis of the Scopus database

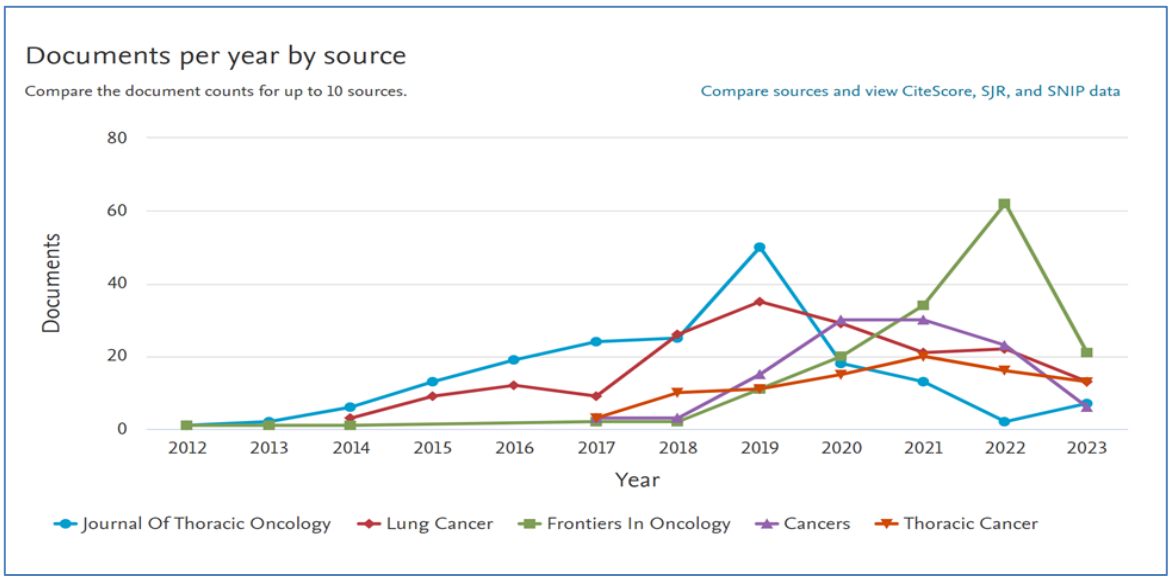

Figure 3 – The number of publications on NGS for lung cancer diagnosis in scientific journals from 2012 to 2023 according to the bibliometric analysis of the Scopus database

With the help of the VOSviewer program, which allows the visualization of bibliometric networks, the publication activity from 2010 to 2023 was investigated and graphically depicted. Keywords "lung cancer," "next generation sequencing," "targeted therapy," "genetic mutations," "circulating tumor DNA," and "liquid biopsy" were used. With the help of the SciVal service and the bibliometric

analysis tool VOSviewer, it was possible to highlight and display 612 keywords that appear most often in articles about NGS. All of them were divided into five thematic clusters (Fig. 4).

The first thematic cluster (in red) is represented by 256 keywords that reflect the value of NGS for selecting targeted therapy in patients with lung cancer.

The second thematic cluster (in green), with 177 words, reflects research on NGS's role in predicting complications of chemotherapy, immunotherapy, and targeted therapy.

The third cluster (in blue) is devoted to biomarkers used for diagnosing lung cancer by the NGS method. A total of 94 keywords are focused on this topic.

The fourth cluster (in yellow) reflects publications comparing the performance of NGS with other diagnostic methods, such as immunohistochemistry and polymerase chain reaction. Fifty-three keywords indicate this direction.

The fifth (purple) thematic cluster is represented by 32 keywords and is devoted to NGS analysis by the liquid biopsy method.

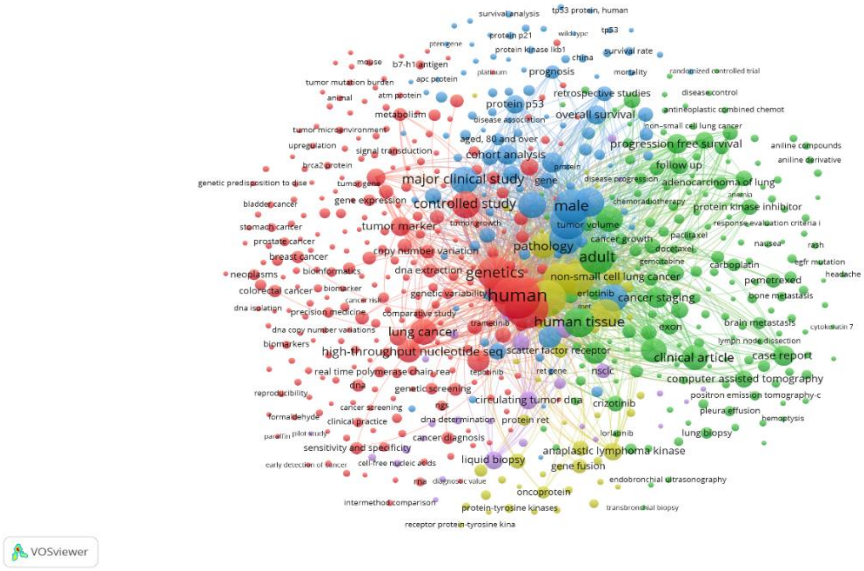

Figure 4 – Distribution of thematic clusters related to NGS for lung cancer diagnosis and treatment

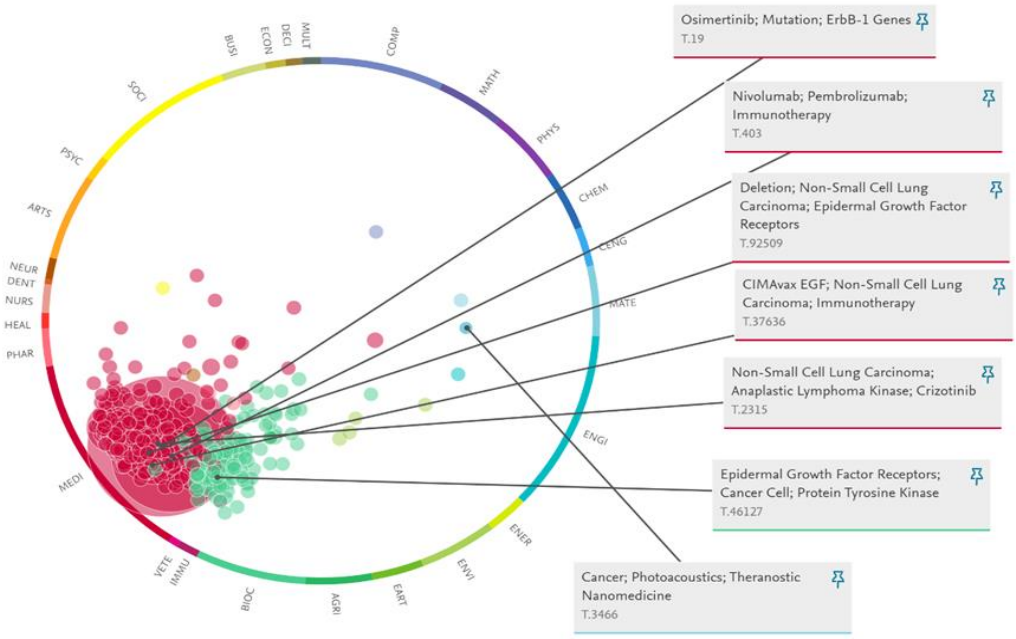

Figure 5 – Interdisciplinary interaction of scientific fields using NGS

It is worth noting that NGS is used not only in medicine. With the help of the SciVal service, an interdisciplinary interaction between scientific fields in which this method is actively used was discovered: pharmacology, biochemistry, immunology, and veterinary medicine (Fig. 5).

Limitations. This research includes publications only in the Scopus database from 2010 to 01.08.2023.

CONCLUSIONS / ВИСНОВКИ

NGS is increasingly used in medicine. This method can become one of the leading methods for diagnosing lung cancer because it can accurately identify specific biological markers. Tumor tissue embedded in paraffin blocks and various biological fluids can be used for diagnosis. NGS is effective even in cases where the amount of tumor tissue is limited, and other methods cannot identify it. The technique's advantages are confirmed in clinical trials and described in many leading countries' scientific publications. As a result, NGS appears to be an effective method for diagnosing lung cancer and selecting the most appropriate regimen of targeted or immunotherapy. Disadvantages of the method include the high cost in developing countries and the need to appropriate software.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

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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