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Prognostic value of biohybrid screening results for assessing cancer risk using the example of lung cancer

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Introduction. One of the leading places in the structure of socially significant diseases in the Russian Federation is occupied by malignant neoplasms, among which cancer of the trachea, bronchi and lung occupies the first place in terms of prevalence. Screening for lung cancer is not carried out at the federal level in Russia; recommended screening measures include questionnaires to identify risk factors for the development of the disease (including occupational) and the formation of dispensary observation groups.

The study aims to assess the prognostic value of a new method of biohybrid screening of lung cancer by exhaled air.

Materials and methods. Scientists conducted a study at the National Medical Research Center of Oncology of the Ministry of Health, Russian Federation, with the participation of 24 conditionally healthy volunteers and 5 patients diagnosed with lung cancer in the early stages of the disease. The design of the study is simultaneous (on-line) with blinding; experts estimated the risk of systematic errors at 10 points on the QUADAS scale. The authors examined exhaled air samples on a gas analyzer (biohybrid detector) of the BGS-APK 02SZZ model, in which the sensor were animals — gray domesticated rats (Rattus norvegicus) with microelectrode matrices implanted into the olfactory bulb, and which were in the internal (ventilated) space of the analyzer in a state of drug anesthesia. The conclusion about the presence or absence of a risk of lung cancer was formed by an artificial neural network of the analyzer, at the input of which bioelectric signals from each microelectrode were received, which were preprocessed using a system for recording the focal activity of the olfactory analyzer. The specialists confirmed the presence or absence of a risk of lung cancer by a reference method, according to computed tomography of the chest in accordance with the Lung Imaging Reporting and Data System (LungRADS™).

Results. During the study, experts determined the effectiveness indicators of the method of biohybrid lung cancer screening by exhaled air: sensitivity (64%), specificity (87%), prognosticality of negative and positive conclusions about the presence/absence of disease risk (82% and 72%, respectively).

Conclusion. *The safety, efficiency and throughput of the investigated method, together with the reproducibility of the analyzer's conclusions, meet the criteria of practicability to ensure the first (population-based) stage of lung cancer screening.*

Keywords: *lung cancer; screening; exhaled air; animal sensor; biohybrid method; artificial neural network; occupational risk*

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Matukhno A.E. — data collection and processing;
Medvedev D.S. — data collection and processing, text writing;
Kiroy V.N. — the concept and design of the study, text editing;
Kovtun A.L. — the concept and design of the study, text editing;
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Introduction. According to statistics, one of the leading places in the structure of socially significant diseases in Russian Federation [1] is occupied by malignant neoplasms, among which cancer of the trachea, bronchi and lung occupies the first place [2, 3] in terms of prevalence. Of the patients with newly diagnosed oncopathology of these localizations, ~25% of patients have stage I–II, ~34% — stage III and ~35% — stage IV of the disease; patients with unspecified stage make up ~6%. The mortality rate in the first year after diagnosis is more than 55%, and the active detection rate does not exceed 20% [4]. Approximately 50% of all lung cancer cases occur in the working-age population [5].

Environmental factors (air pollution with carcinogens, including tobacco products) play an essential role in the pathogenesis of lung cancer. Occupational hazards include contact with coal dust, asbestos, beryllium, uranium and radon. In relation to lung cancer, smoking, asbestos and radon have synergism. There is evidence of an increased risk of lung cancer with burdened heredity (mutations of the RB1 and TP53 genes), chronic lung diseases (COPD, pneumoconiosis) and immunodeficiency conditions [6, 7].

Early detection of lung cancer is based on the active collection of complaints, among which attention is paid to prolonged cough (including a change in the nature of cough in smokers), hemoptysis, shortness of breath, chest pain, unreasonable increase in body temperature, general weakness and weight loss. The tactics of managing patients with suspected lung cancer involves consulting an oncologist to clarify the diagnosis and (according to indications) prescribing computed tomography of the chest organs [8]. Screening for lung cancer is not carried out at the federal level in Russia; recommended screening measures include questionnaires to identify risk factors for the development of the disease and the formation of dispensary observation groups [9].

The study aims to assess the prognostic value of a new method of biohybrid screening of lung cancer by exhaled air.

Materials and methods. The scientists conducted a study at the National Center of Oncology of the Ministry of Health, Russian Federation, (Rostov-on-Don), with the participation of 24 conditionally healthy volunteers and 5 patients diagnosed with lung cancer in the early stages of the disease (average age 59.4±8.1 and 60.8±4.0 years, respectively) after they issued informed voluntary consents to participate in the examination. The design of the study is simultaneous (on-line) with dazzle.

The authors took exhaled air samples from volunteers using disposable PPE-type sampling bags with a volume of 5 liters, which were examined within 1.5 hours after filling on a gas analyzer (biohybrid detector) model BGS-APK 02SZZ (BGS-APK, ***Fig. 1***) [10, 11]. The BGS-APK sensor were animals — gray domesticated rats (Rattus norvegicus), which were in the internal (ventilated) space of the BGS-APK in a state of deep drug-induced zolethyl-xylazine anesthesia, and in whose olfactory bulb (OB) a matrix of 8 microelectrodes [12] was implanted in advance. Before starting the study of air samples, BGS-APK underwent automatic self-calibration and additional calibration using chemical compounds-biomarkers of lung cancer (2-butanone and 2-propanol). The conclusion about the presence or absence of a risk of lung cancer was formed using an artificial neural network (ANN) BGS-APC [13], the input of which received signals from each implanted microelectrode, which were pre-processed using the Plexon data acquisition system [14] focal activity registration system. The scheme of the experimental setup for the formation of a training sample of artificial neural networks (ANN) is shown in ***Figure 2***.

The researchers report two implemented analyses: in real time (on-line) using ANN No. 1 installed on a laptop from the BGS-APK (the conclusion format is "There is or no risk of cancer"), and using ANN No. 2 of the computing cluster on the SFU server (in this case, the result was given after 1 day in the format "There is or no risk of lung cancer"). The training sample of INS No. 2 was formed on the basis of an array of bioelectric OB signals registered in 2018–2020. upon presentation to animals under anesthesia (*n*=164), exhaled air samples obtained from both healthy volunteers (*n*=3,416) and patients with: lung cancer (*n*=1,393), benign lung tumors (*n*=231), malignant neoplasms of other localizations (*n*=1,152), pulmonary tuberculosis, MBT"–" (*n*=72) and pneumonia (*n*=392, except in cases with confirmed COVID-19). 3–10 days after the analysis of exhaled air samples, conditionally healthy volunteers were examined using spiral computed tomography of the chest organs (CT), while until the completion of all examinations they were not aware of the results of assigning them to groups with a positive or negative risk of disease. The presence of a risk of lung cancer was confirmed by the results of computed tomography in accordance with the recommendations of the Fleischner Society [15] and the Lung Imaging Reporting and Data System (LungRADSTM) [16]. The risk of developing lung cancer was considered confirmed at levels of LR=2 and above. For statistical processing of the results, the scientists used the IBM SPSS STATISTICA v.21.0 software package.

Results. At the stage of preparation of the animal for inclusion in the composition of BGS-APC, an optically transparent cranial window was formed over the olfactory bulb (OB) of rats under anesthesia. The olfactory bulb was stained with microinjections of the fluorescent dye Oregon Green 488 VARTA-1, after which it was injected into the paranasal space: a) chemical compounds — biomarkers of lung cancer (volatile organic and inorganic substances) and b) exhaled air samples obtained from healthy people and from patients with established diagnosis of lung cancer before the start of a course of chemotherapeutic/surgical treatment.

In the course of neuropathic research, experts have found that:

- when chemically pure biomarkers are presented in the projection of the target glomeruli of the olfactory bulb, there are specific areas of luminescence in the projection of the target glomeruli OB and these zones do not differ in their anatomical (stereotactic) coordinates in different rats of the same species;
- relatively large areas of the OB glow fields of rats differ from each other when presenting exhaled air samples

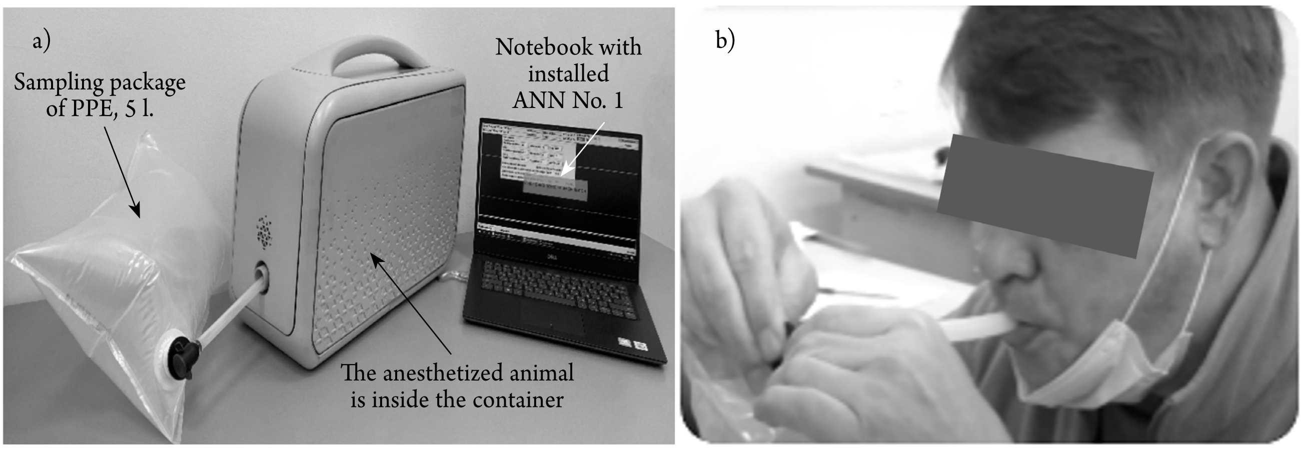

Fig. 1. a) Appearance of the gas analyzer (biohybrid detector) model «BGS-APC 02CSD» and b) procedure for sampling exhaled air from a volunteer

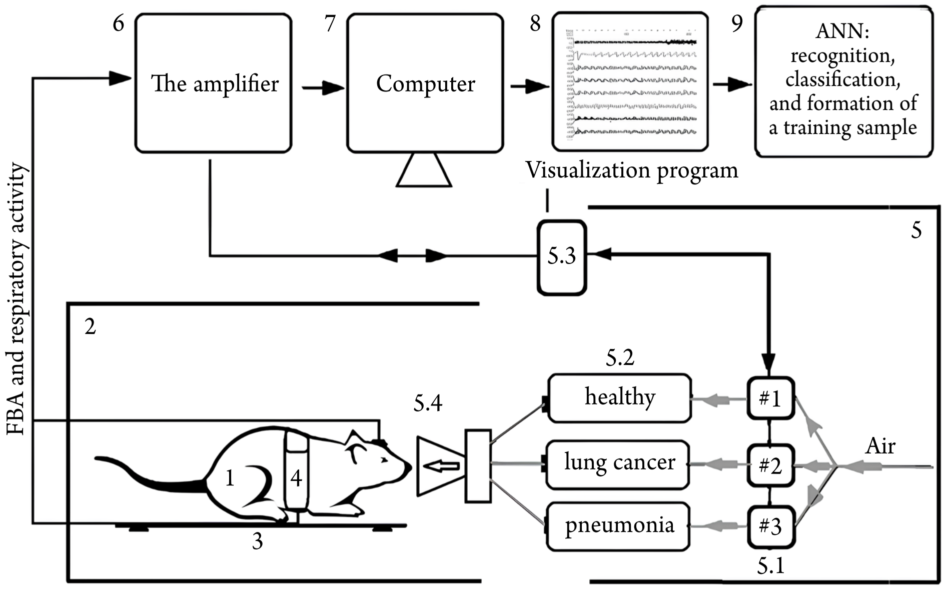

Fig. 2. Scheme of the experimental setup for forming a training sample of an ANN
Notes: 1 — anesthetized rat with microelectrodes implanted in the OB; 2 — experimental chamber (box); 3 — system for automatic maintenance of animal body temperature; 4 — respiratory control system; 5 — odorizer of original design; 5.1 — valves; 5.2 — PPE sampling packages; 5.3 — valve control board; 5.4 — mask for supplying a gas-air mixture; 6 — 32-channel Plexon Multichannel Acquisition Processor (MAP) system (Plexon Corp., Dallas, Texas, USA); 7 — computer; 8 — Plexon software; 9 — training sample of an artificial neural network (ANN); FBA — focal bioelectric activity of the animal's olfactory bulb.

from sick and healthy individuals, while there are "non-overlapping" glow fields (Fig. 3).

The microelectrode matrices implanted in rat OB used in the BGS-APC were configured in such a way that mainly specific zones (fields) of activation of neuronal activity [17] were located under the electrodes (differing when presenting rats with air taken from sick and healthy people).

The primary results of the study of exhaled air samples using BGS-APC are shown in ***Table 1***.

Table 2 provides estimates reflecting the diagnostic significance of the study results. When calculating the indicator of the F-measure, experts used the coefficient β=1.

In this case, when assessing the statistical significance of the conclusions formed using BGS-APK, the F-index was equilibrium, and in the calculations there was no preference for either the completeness of the selection of persons at risk of developing cancer from the sample, or the accuracy of their selection from the sample.

Discussion. The development and introduction into practical medicine of new methods and tools designed for cancer screening is one of the most promising areas for improving the quality of life of a modern person [18]. However, there are currently no clear recommendations regarding quantitative indicators of screening effectiveness. It is believed that the screening method should have sufficient sensitivity and specificity, and with regard to the prognosticality of the conclusion, preference should be given to the value of a negative result [19]. Unlike diagnostic

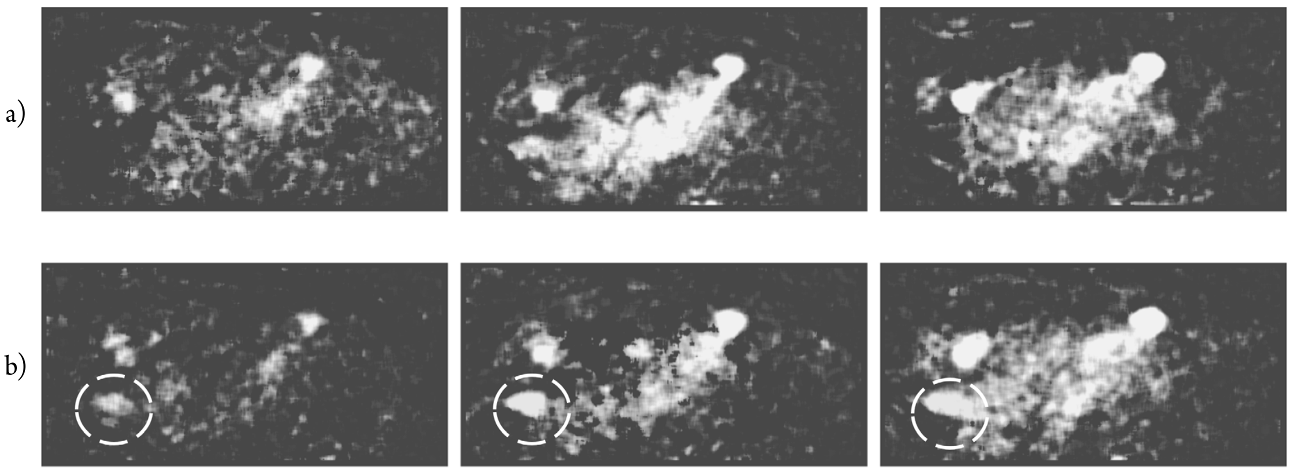

Fig. 3. Visualization of the activation zones of the glomerular layer of the rat upon presentation of exhaled air samples obtained from a) healthy volunteers and b) patients with lung cancer
Note: The dotted line highlights the OB zones, which are activated only upon presentation of air samples received from patients with an established diagnosis of lung cancer.

Table 1

The primary results of the study

No.	The group of examined ("UZ" / "RL")	Conclusion of the BGS-APK based on the results of the analysis of the exhaled air sample		Survey results at the Scientific Medical Research Center of Oncology		Assessment of the quality of the conclusion BGS-APK	
		On-line	A posteriori through one day	Chest CT scan results (for the "UZ" group) / Diagnosis (for the "RL" group)	Conclusion about the risk of lung cancer	On-line	A posteriori after one day
1	2	3	4	5	6	7	8
1.	RL	+	–	*Diagnosis: peripheral cancer of the upper lobe of the left lung (T2N1M0)*	Lung cancer has been diagnosed	TP	FN
2.	RL	+	+	*Diagnosis: atypical carcinoid of the lower lobe of the left lung (T1N0M0)*	Lung cancer has been diagnosed	TP	TP
3.	RL	+	+	*Diagnosis: peripheral cancer of the upper lobe of the left lung (T1N0M0)*	Lung cancer has been diagnosed	TP	TP
4.	RL	+	+	*Diagnosis: peripheral cancer of the upper lobe of the left lung (T1N0M0)*	Lung cancer has been diagnosed	TP	TP
5.	RL	+	+	*Diagnosis: malignant neoplasm of the lower lobe of the right lung (T2N0M0)*	Lung cancer has been diagnosed	TP	TP
6.	UZ	+	+	SRKT: in S4 of the middle lobe of the right lung, a focus of 0.8×0.4 cm (LR=3); in the upper lobe of the left lung, a focus of 0.5×0.4 cm (LR=2); in S9 of the lower lobe of the left lung, a focus of 0.4×0.3 cm (LR=2)	Risk of lung cancer	TP	TP
7.	UZ	–	+	SRKT: in S8 of the lower lobe of the right lung, a solid focus of 0.4×0.3 cm (LR=2), in S8 of the lower lobe of the left lung, a solid focus of 0.3×0.2 cm (LR=2)	Risk of lung cancer	FN	TP
8.	UZ	+	–	SPKT: in S10 of the lower lobe of the left lung, a subpleural solid focus of 0.5×0.4 cm (LR=2)	Risk of lung cancer	TP	FN
9.	UZ	+	+	SRKT: in S10 of the lower lobe of the right lung, the lesion is 0.4×0.4 cm (LR=2); in S9 of the lower lobe of the right lung, calcinate is 0.3 cm (LR=1)	Risk of lung cancer	TP	TP
10.	UZ	+	+	SRKT: in S1 of the upper lobe of the left lung calcinate 0.4 cm (LR=1); in S8 of the lower lobe of the right lung solid focus 0.4=0.3 cm (LR=2)	Risk of lung cancer	TP	TP
11.	UZ	+	+	SRKT: in S2 of the upper lobe of the right lung, a solid focus of 0.4×0.4 cm (LR=2)	Risk of lung cancer	TP	TP
12.	UZ	+	–	SRKT: on both sides there are infiltration sites of the "dry leaf" type (lesion volume up to 20%). Bilateral pneumonia in the reverse stage of development	The risk of lung cancer has not been identified	FP	TN
13.	UZ	–	–	SRKT: no signs of bulky formations. Post-inflammatory pneumosclerosis in the lower lobe of the left lung	The risk of lung cancer has not been identified	TN	TN

14.	UZ	+	–	SRKT: in S10 of the right lung, calcifications are 0.7 and 0.6 cm (LR=1). In the projection of the roots C3–C4, C7=–C8 on the right, C8–C10 on both sides there are multiple formations with smooth contours up to 1.8 cm. Hernia of the esophageal orifice of the diaphragm (contents – the cardiac department and the body of the stomach)	The risk of lung cancer has not been identified	FP	TN
15.	UZ	+	–	SRKT: multiple calcifications in the lower lobe of the left lung up to 0.7 cm (LR=1)	The risk of lung cancer has not been identified	FP	TN
16.	UZ	+	+	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	FP	FP
17.	UZ	+	+	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	FP	FP
18.	UZ	–	–	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	TN	TN
19.	UZ	+	+	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	FP	FP
20.	UZ	–	–	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	TN	TN
21.	UZ	–	–	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	TN	TN
22.	UZ	–	–	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	TN	TN
23.	UZ	+	–	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	TP*	TN
24.	UZ	+	–	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	FP	TN
25.	UZ	+	–	SRKT: no signs of bulky formations	The risk of lung cancer has not been identified	FP	TN
26.	UZ	+	–	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	FP	TN
27.	UZ	+	+	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	FP	FP

28.	UZ	–	+	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	TN	FP
29.	UZ	–	–	SRKT: no signs of bulk formations	The risk of lung cancer has not been identified	TN	TN

Note: UZ is a conditionally healthy volunteer, RL is a patient with lung cancer, LR is the risk of lung cancer in accordance with the "Lung Imaging Reporting and Data System", TR is a truly positive conclusion, TR* is a truly positive conclusion (volunteer No. 23 was diagnosed with pancreatic cancer), TN is a truly negative conclusion, FP is a false positive conclusion, FN is a false negative conclusion.

Table 2

Diagnostic significance of the study results

Conclusion of the BGS-APK based on the results of the analysis of the exhaled air sample	Sensitivity	Specificity	The predictive value of a negative result	The predictive value of a positive result	Statistical indicator F1 is a measure (equilibrium). Coefficient β=1
On-line	52%	88%	92%	41%	0.67
A posteriori after one day	64%	87%	82%	72%	0.72

methods, the means used in screening should provide rapid treatment of many cases, but may not be as accurate, since screening tests are used to identify the likely presence or absence of a disease or condition in people who do not have symptoms, while diagnostic medical equipment is used for quantitative physiological measurements. confirmation and determination of the development of a suspected disease or condition [18]. It is important to note that the final indicator of the effectiveness of screening programs is the reduction of mortality from a particular disease in the region where such screening is carried out, compared with neighboring, similar demographic and socio-economic conditions, but without an ongoing screening program. However, this indicator can be quantified only in the course of long-term continuous prospective studies organized in accordance with the classical criteria of Wilson and Jungner [20]. Nevertheless, the importance of timely assessment of the safety and effectiveness of any new screening method is beyond doubt.

Given the asymptomatic course of lung cancer in the early stages, it is relevant not only to develop new tests-questionnaires to determine the risk factors of this disease, but also methods that allow relatively cheap and fast examination of large groups of the population and/or persons classified as at risk, including professional ones. Screening for lung cancer using chest X-ray computed tomography is associated with fairly high financial costs, the inaccessibility of the procedure for a part of the population, especially for those who live in remote regions of the country, and an additional population risk of stochastic effects during X-ray irradiation of conditionally healthy volunteers without obvious medical indications [21]. The use of other existing screening methods for this disease also imposes an additional financial burden on the healthcare system and often proves ineffective [19].

The study of early biomarkers of the development of the pathological process — volatile organic compounds (VOCs), in particular hydrocarbons, aldehydes, alcohols, ketones and a number of others [22] — became scientifically sound prerequisites for the development of a method of biohybrid screening of lung cancer by exhaled air. Currently, there are more than 3 thousand such biomarkers, and this list is constantly expanding. Despite the fact that the specificity of VOCs for various human diseases requires additional research, the authors found that just over 100 such compounds [22, 23] are associated with oncological diseases that may be present in exhaled air in various amounts and combinations. Currently, this approach has been tested on a number of pathological conditions, including diseases of the lungs, gastrointestinal tract and metabolic disorders. Researchers carry out the recognition of diseases by changes in VOCs of metabolic origin using gas chromatography/mass spectrometry [24] and "electronic noses" [25]. However, these methods have limitations that prevent their use as screening tests, such as the maximum resolution (up to 10–14 g/cm^3), low throughput and/or the need for pre–preparation of samples.

Despite the exceptionally high sensitivity of macroscopic mammals to odorous stimuli (concentration response threshold: $10^{-21...-23}$ g/cm^3 [26]) and the ability to work in real time, the use of trained animals to recognize the early stages of cancer [27] is limited by logistical and ethical difficulties they are used in the clinic. The process of interaction of VOCs with olfactory receptors, the activity of which is represented in the form of topographically ordered activation patterns of OB holomerules, has relatively recently become available for research and visualization using the method of optical functional calcium imaging [28, 29]. The results of these studies became the basis for the development of a method for biohybrid screening of lung cancer by exhaled air.

The combined (optical-microelectrode) methodological approach made it possible to preserve the natural sensitivity of animal sensors for more than 6 months after microsurgical manipulations, and in combination with the speed of artificial intelligence methods and technical means of their implementation made it possible to achieve practically acceptable performance indicators in providing lung cancer screening by exhaled air.

Safety for the subject. This is ensured by the "rupture" of the exhaled air sampling sites and the place where the analysis is carried out using BGS-APK. This was confirmed by toxicological safety studies at the Federal State Budgetary

Scientific Research Center named after S.N. Golikov of the FMBA of Russia (test reports No. 7/21-13 dated 07/16/2021, No. 8/21-13 dated 07/23/2021 and No. 8/21-5 dated 07/27/2021) technology approval certificates approved by the Ministry of Health of the Novgorod Region and the Ministry of Health of the Republic of Tatarstan: "The risks of using BGS-APC in the examination of volunteers have not been identified. No complications were recorded during the tests. The experts rated the safety of the method at "2" points (there are no predicted complications) [30, 31].

Effectiveness. Scientists conducted tests to confirm the effectiveness under controlled conditions on the basis of the National Center of Oncology of the Ministry of Health of the Russian Federation, MBUZ "City Hospital No. 4 of Rostov-on-Don" and GBUZ "Clinical Tuberculosis Dispensary" of the Ministry of Health of the Krasnodar Territory. Test report dated 08/25/2021 [32]. The authors conducted technical tests in the ANO "Center for Quality, Efficiency and Safety of Medical Devices", accredited by Rosaccreditation (register of accredited persons No. RA.RU.21MD11 dated 30.04.2015, accreditation for compliance with the requirements of GOST ISO/IEC 17025-2019) [33]. Based on the results of testing the method in the Novgorod region and the Republic of Tatarstan, it was concluded that the use of BGS-APK in mass examinations to ensure screening of socially significant diseases has advantages over the recommended methods [9, 30, 31] and the method itself can potentially reduce the amount of financial costs for medical care. It should be noted that the approbation in the Novgorod region was organized with visits to enterprises: JSC Borovichi Refractory Plant, JSC Laktis, JSC Spectrum, JSC NPO Kvant, JSC Novgorod Metallurgical Plant, Municipal Unitary Enterprise Novgorod Vodokanal, JSC 261 Refueling and Transportation Repair Plant fuel"), whose employees are associated with occupational risk factors for lung cancer.

Bandwidth. Despite the fact that the recorded time of one analysis in this study was 72±7 seconds, the confirmed maximum throughput in real operation of the BGS-APK for its intended purpose with a mass flow of samples was 250 samples/8 hours or ~2 minutes per sample. The downtime is due to the need to calibrate the analyzer before starting work with each animal under anesthesia. If the depth of anesthesia of the rat did not correspond to the set one, the BGS-APK automatically issued the conclusion "Replace the animal" or "Suspend the analysis until it is ready to work". The researchers replaced the rats in the analyzer every 2–4 hours of operation, which also required additional time.

Reproducibility of conclusions obtained using BGS-APK. The approbation of the sample in the Republic of Tatarstan (2021, 365 examined volunteers for 2 days) did not reveal differences in the conclusions issued by two analyzers when analyzing the same samples using different animals; comparative reproducibility was 99.3%.

It is predicted that the method of biohybrid lung cancer screening can be used at the first (population) screening stage together or after interviewing target populations in the age category "50+" to form risk groups and reduce by ~10 times the number of subjects examined at the second (diagnostic) stage.

Conclusion. *For the INS BGS-APC training sample, formed on the basis of 6656 observations, within the framework of a controlled one-stage (with blinding) direct assessment study, scientists calculated the following indicators: sensitivity (64%), specificity (87%), prognosticality of negative and positive conclusions about the presence/absence of disease risk (82% and 72% accordingly). According to forecasts, as the training sample increases, the effectiveness of the proposed selection method will increase. The limit of such an increase can be determined in the course of further research.*

The safety, efficiency and throughput of the method, as well as the reproducibility of the BGA APK findings, meet the criteria of practicality to ensure the first (population-based) stage of lung cancer screening.

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