Imaging. 2012; Vol. 30(9): 1234–1248. Doi: 10.1016/j.mri.2012.06.010.

30. Robust prostate segmentation using intrinsic properties of TRUS images / Wu P., Liu Y., Li Y., et al. / *IEEE Trans Med Imaging*. 2015; 34(6): 1321–1335. Doi: 10.1109/TMI.2015.2388699

31. Rutman, A.M., Kuo M.D. Radiogenomics: creating a link between molecular diagnostics and diagnostic imaging / Eur J Radiol. 2009; 70(2): 232–241. Doi: 10.1016/j.ejrad.2009.01.050.

32. Spatial genomic heterogeneity within localized, multifocal prostate cancer / PC Boutros, M Fraser, NJ Harding, et al. / Nat Genet. 2015; 47(7): 736–745. Doi: 10.1038/ng.3315.

33. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands / Goldgar D.E., Easton D.F., Cannon-Albright L.A., et al / J Natl Cancer Inst. 1994; 86: 1600–1608. Doi: 10.1093/jnci/86.21.1600.

34. The genetic epidemiology of prostate cancer and its clinical implications / R Eeles, C Goh, E Castro, et al / Nat Rev Urol. 2014; 11: 18–31. Doi: 10.1038/nrurol.2013.266.

35. The Cancer Genome Atlas Research Network, 2015, https://www.genome.gov/Funded-Programs-Projects/Cancer-Genome-Atlas.

36. U.S. Cancer Statistics Working Group. US cancer statistics: 1999–2009 incidence and mortality webbased report. Atlanta GA: USDHHS, CDC; 2013. http://www.cdc.gov/uscs.

37. World Health Organization. Global Health Observatory data repository. http://apps.who.int/gho/data/ view.main.SDG2016LEXREGv?lang=en, accessed [1st July 2017].

38. Zonal segmentation of prostate using multispectral magnetic resonance images / N Makni, A Iancu, O Colot, et al. / Med Phys. 2011; 38(11): 6093–6105. Doi: 10.1118/1.3651610.

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MICROARRAYS IN CLINICAL DIAGNOSTICS AND PROSPECTS FOR THEIR APPLICATION AS A SCREENING TOOL

Abstract. In this paper diagnostic microarrays and its application in various fields of clinical medicine are reviewed. The use of DNA microarray based diagnostics for carrying out the genetic carrier screening has been proposed.

Keywords: hereditary diseases, molecular genetic screening, biological microchips, practical medicine

Introduction. A series of outstanding discoveries: DNA and the genetic code gave a big impact to the development of genetics and methods in molecular biology. In 1977, Frederick Sanger developed the first in the modern sense of the method of DNA sequencing, which at that time was called the "chain termination method". Soon in 2001Human genome project were completed. In parallel with sequencing, after the discovery of the polymerase chain reaction in 1983, another method rapidly began to gain popularity and develop, which combines the developments of several areas from biology to electronics - microarray technology. Biological microchips are microarrays with various kinds of biopolymers deposited on a solid substrate as probes, and the biological material under investigation as targets.

There are two types of microchips, high and low density, which are widely used in basic research and in various fields of clinical medicine. High density microarray fabrication is characterized by the synthesis of probes directly on the substrate. For example, the GeneChip microchip photolithography technology developed by Affimetrix is designed to analyze large DNA fragments and the entire genome of an organism. Such types of microchips require expensive equipment and specially trained bioinformatics specialists to interpret a huge amount of information [21].

A slightly different approach is used in the manufacture of low-density microchips, in which the probes are applied to the prepared substrate surfaces. In clinical medicine, low-density microarrays are gaining more and more popularity due to their low cost and specificity of the studied DNA fragments.

Application of biological microchips in practical medicine. A significant part of ongoing genetic medical research is currently aimed at diagnose monogenic and multifactorial diseases caused by point mutations in the genome - single nucleotide polymorphisms. DNA microarrays are used to identify mutations and genetic polymorphisms to detect hereditary diseases, hereditary predisposition to various widespread diseases, for example, diabetes, cardiovascular diseases, oncology, ophthalmology, as well as for the diagnosis of infectious diseases. Table 1 presents a list of diagnostic microchips developed for use in clinical medicine.

Gene expression profiling using DNA microarrays provides information on the relative differences in gene expression between two different cell populations, for example, in a comparative analysis of certain drugs tested on cultured cells, or a comparison of gene expression in cancer cells with normal cells. The human genome is made up of 3.2 billion nucleotides. According to some estimates, it contains about 10 million nucleotide substitutions - the so-called single nucleotide polymorphisms (SNPs). SNPs are distributed throughout the genome and can be used as genomic markers to find links between genes and diseases. SNP is essentially the replacement of one nitrogenous base in DNA with another. For example, guanine is replaced by cytosine, while all other bases located nearby remain unchanged. Since SNP can be located within one gene, or in several at once, therefore, the probe for the microchip must be designed in such a way that the entire genome is covered. This can be a serious obstacle to genome-wide analysis [34]

Microchips for the biomarker detection in multifactorial disease diagnostics. The discovery of new specific biomarkers associated with a specific disease is very important for making an accurate diagnosis and drug development. The search for a biomarker using a DNA microarray is carried out by analyzing a large amount of data on expression levels under various genotypic, phenomical, and environmental conditions, which makes it possible to identify a larger number of candidates. It allows the simultaneous identification of candidate biomarkers by analyzing differentially expressed genes in comparison with normal and pathological conditions. By carefully applying clinical specimens at different stages or conditions to the DNA microarray, it is possible to identify those

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Microarrays in clinical diagnostics

Classification / name	Disease /causative agent	references
Microarray for biomarker detection in multifactorial disease diagnostics	Crohn's disease	[11]
	Type 1 diabetes mellitus	[26]
	Oncological diseases, SNPs in the genes of the biotransformation, SNPs in the genes of the renin-angiotensin system	[3]
	Sporadic Alzheimer's Disease	[4]
	Breast cancer	[12]
	Chemotherapy resistance for uterine cancer	[36]
Microarray for infectious disease diagnostics	Tuberculosis and its drug-resistant forms; pathogens of HIV, hepatitis B and C, smallpox, 2 types of herpes simplex, anthrax, influenza A virus	[12]
	Oncogenic variants of human papillomavirus type 18 (HPV-18).	[33]
	Adenoviruses, bocavirus, Chlamydia trachomatis, coronaviruses types 229E, OC43, NL63, HKU1, human metapneumovirus (hMPV) types A and B, influenza A, influenza B viruses, influenza C - Mycoplasmae. 4, respiratory syncytial virus (RSV) types A and B, and rhinoviruses	[13]
	Neutropenia	[18]
	Resistance to the anti-tuberculosis drug Ethambutol	[25]
	Pathogens in Bacterial and Fungal Brain Infections	[9]
	AIV, NDV, IBV and IBDV for use in routine mass epidemiological monitoring.	[31]
Microarray for genetic disease diagnostics	Chromosomal disorders associated with developmental delay and congenital malformations (Down's syndrome, Patau's syndrome, Edward's syndrome, Turner syndrome, Klinefelter's syndrome, alpha-thalassemia syndrome, Charcot-Marie-Tooth neuropathy 1A, cri-du-chât syndrome, hereditary neuropathy with a tendency to paralysis from compression (HNPP), Prader-Willi syndrome, Rubinstein-Tybee syndrome, Williams syndrome, and Wolf-Hirschhorn syndrome)	[16]
	Gemoglobinopatiya	[30]
	Primary immunodeficiency	[32]
	Cystic fibrosis	[3,4]
	Tay-Sachs disease, Bloom syndrome, Canavan disease, Niemann-Pick disease, familial dysautonomia, torsion dystonia, mucolipidosis type IV, Fanconi anemia, Gaucher disease, glycogen storage disease type 1A, maple syrup urine disease, nonsyndromic hearing loss, familial Mediterranean hearing loss and type III glycogen storage disease	[15]
	Wilson's syndrome	[22]

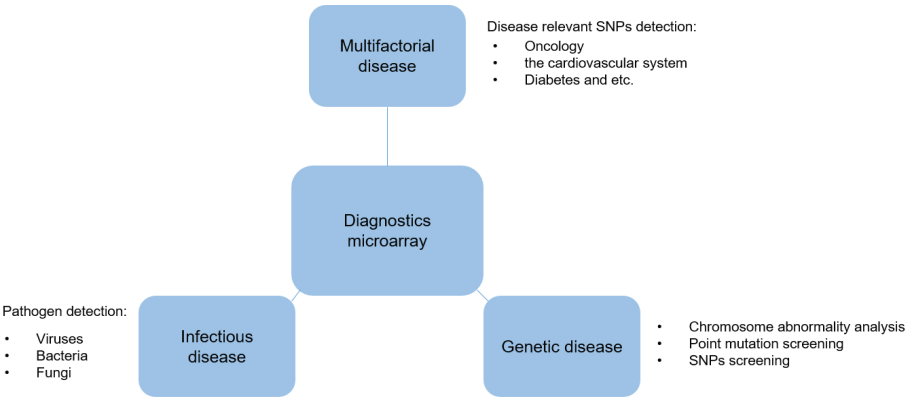

Fig. Application of diagnostic microchips in clinical medicine.

genes that are specifically associated with different stages of the disease. DNA microarray approaches for searching for biomarkers have been used to study several chronic diseases, including diabetes, arthritis, cardiovascular and oncological diseases. For example, biomarkers for the diagnosis of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), which are chronic autoimmune and inflammatory diseases, can be tested by profiling expression in leukocytes, since differential gene expression in leukocytes is clearly related to SLE and RA. Osteoarthritis, a degenerative joint disease that can be confused with RA, can also

be diagnosed by leukocyte expression profiling. Based on these facts, Wohlgemuth et al. Developed a method for diagnosing and monitoring autoimmune or chronic inflammatory disease, especially SLE, based on differentially expressed genes. The selected genes were further studied by comparing them with clinical data. The nucleotide sequences of the selected genes were determined and used to diagnose these diseases [5]. Crohn's disease, ulcerative colitis, and inflammatory bowel disease (IBD) can also be diagnosed using biomarker genes selected from gene expression profiles using DNA microarrays. In particular, a diagnosis of high incidence and incidence of IBD is important for assessing prognosis and treatment. Mannick and his colleagues made a diagnostic chip for diseases based on sequences of overexpressed and underexpressed genes selected using high-density chips Affymetrix GeneChip.As a result, in patients with IBD, 25 sequences were identified as genes related to IBD, giving a sensitivity of 84% and specificity 100%. In Crohn's disease in patients with ulcerative colitis, 36 genes were identified as genes related to Crohn's disease with ulcerative colitis, giving a sensitivity of 89% and a specificity of 80% [11].

Scientists Natarajan and Myao have developed a DNA microarray to map histone modifications in the coding regions of genes involved in gene regulation and expression. They compared the patterns of histone modifications in the coding regions of disease-specific genes by analyzing the localization of the entire genome using chromatin immunoprecipitation coupled to cDNA microarrays. Were selected those genes that showed increased (more than 2-fold) and decreased (less than 0.5-fold) expression under certain conditions. This patent proposes a method for determining the risk of developing a disease by examining the presence or absence of histone modification (H3-K9 dimethylation) associated with type 1 diabetes, which is an autoimmune disease that can be accompanied by complications such as retinopathy, neuropathy and nephropathy [25]. In Russia, Institute of Molecular Biology. V.A. Engelhardt RAS microchips for the analysis of single nucleotide polymorphisms in humans with various diseases have been developed: a biochip for the diagnosis of lymphoproliferative diseases, microchips for detecting and diagnosing a genetic predisposition to the development of oncological diseases of various etiologies and for determining individual sensitivity to certain drugs, and others designed for the analysis of polymorphism in the genes of the biotransformation system, for the determination of polymorphism in the genes of the renin-angiotensin system and for hemostasis genes, and are used to analyze the genetic predisposition to the development of complications during pregnancy [1]. A biological microchip has been developed to study the hereditary predisposition to the sporadic form of Alzheimer's disease. The biochip is capable to detect 10 polymorphic markers in the *APOE, TOMM40, APOJ, EXOC3L2, GAB2, A2M, CR1, BIN1* and *PICALM* genes. The genotyping procedure includes the amplification of the nucleotide sequences of the selected genes and subsequent hybridization of the fluorescently labeled regions with allele specific DNA probes, immobilized on a biochip [2]. A low-density microchip was developed, which contains markers of 132 genes that are differentially expressed in breast cancer and also associated with signs of a malignant tumor (cell cycle disorders, hormonal sensitivity, proteolysis) and the developed system has shown itself as an alternative way to diagnose breast cancer at an early stage [12]. Scientists from China proposed a method based on a low-density microchip, which allows to identify 83 differentially expressing genes that indicate resistance to chemotherapy in uterine cancer [36]. An oligunocleotide biochip was created by a Mexican group of scientists to detect 19 point mutations in the 5th, 7th and 9th exon of the *TP53* gene, which is a known oncogene and mutations in which lead to malignancy and are observed in most patients with various types of cancer, and this approach has been proposed as a screening tool and early detection of malignant cancer for timely treatment [23]. An oligonucleotide biochip was developed to detect the carriage of 182 mutations in the *LDLR* and *APOB* genes that cause hypercholesterolemia, which in turn leads to early diseases of the cardiovascular system [10].

Microchips for the infectious diseases diagnostics. DNA microarrays are widely used and improved in the field of diagnostics of various infectious diseases. So, developed at the Institute of Molecular Biology. V.A. Engelhardt RAS hydrogel microchips allow to determine the causative agent of tuberculosis and its drug-resistant forms; pathogenš HIV, hepatitis B and C (22 subtypes), smallpox, 2 types of herpes simplex, anthrax, infections of newborns, 30 subtypes of influenza A virus, including avian influenza H5N1 [24]. Scientists from the University of Mexico have developed a low-density oligonucleotide microchip for the rapid screening of oncogenic variants of the human papillomavirus type 18 (HPV-18) strain. The technology used in the development can be used to differentiate three possible phylogenetic branches of HPV-18 [33]. Scientists at University College Dublin described the development of a test system based on oligonucleotide microarrays for the simultaneous detection, differentiation and typing of 18 viral and bacterial respiratory pathogens, including 16 viruses and two atypical bacteria: adenoviruses, bocavirus, chlamydia (Chlamydophila) pneumoniae, coronaviruses of types 229 , NL63, HKU1, human metapneumovirus (hMPV) types A and B, influenza A, influenza B viruses, influenza C - Mycoplasmae. 4, respiratory syncytial virus (RSV) types A and B, and rhinoviruses [13]. A similar approach was used in the development of a microchip for the rapid diagnosis of bloodstream infections caused by bacterial pathogens in pediatrics and general therapy [27]. PCR amplification in combination with an oligonucleotide microchip was used to identify the bacterium Bacillus anthracis based on the ITS region in rRNA. Several studies have reported the use of microarrays to identify pathogenic yeasts and molds by targeting the ITS region in fungal rRNA genes [14]. In another study, a DNA microarray was created to detect and identify 14 common fungal pathogens in clinical specimens from neutropenic patients [18]. At the University of Barcelona, a method based on a DNA microchip was proposed for the simultaneous diagnosis of mutations in the embB gene, which indicates resistance to the anti-tuberculosis drug Ethambutol [25]. DNA microchip for the detection of 14 strains of bacteria (Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli, Haemophilus influenza, Stenotrophomonas maltophilia, Neisseria meningitidis, Enterobacter spp. Candida tropicalis, Candida glabrata, and Cryptococcus neoformans pathogens in bacterial and fungal infections of the brain [9].

Scientists from Kazakhstan have described a method for the rapid detection of viral diseases AIV, NDV, IBV and IBDV simultaneously for use in routine mass epidemiological monitoring [31].

Microchips for the genetic disease diagnostics. Foreign companies Affymetrix and Illumina present biochips for genotyping 2,800,000 and 1,000,000 SNPs, respectively. The technologies of these companies are based on the methods of allele-specific hybridization and allele-specific primer extension, respectively. In allele-specific hybridization,

probes are concentrated in the center of the mutation site so that the variable base is in the middle of the probe. This allows the formation of nonspecifically bound hybrids to be maximized, and the sensitivity of the probe to the target is significantly increased. Two probes are used to detect a specific SNP: one probe corresponds to one allelic variant, and the other probe is intended for the second allelic variant. The genotype is determined by analyzing the relative signal strength of the two probes. Despite this, Affymetrix uses about 20 probes for each SNP analyzed in order to obtain more accurate analysis results [20]. The same technology used for SNP analysis is used to genotype specific mutations that cause monogenic diseases. Biochip technology here effectively replaces labor-intensive and time-consuming sequencing technology. Considering the methods used in biochip technologies and sequencing methods, biochips have a number of advantages: they are cheaper, faster and less laborious. Diseases caused by chromosomal abnormalities include several types, such as Down syndrome (associated with chromosome 21), Edwards syndrome (chromosome 18), Patau syndrome (chromosome 13), Turner syndrome (XO) and Klinefelter syndrome (XXY), which leads to irreversible physical and mental abnormalities and even death. Microchips are widely used in cytogenetics to detect various chromosomal pathologies. For example, chromosomal microarray analysis (CMA) to detect variations in copy number, homozygosity, and triploidy, replacing karyotyping as a diagnostic tool for many cases where chromosomal is suspected. CMA is significantly more sensitive (from 10 to 100 kb) than traditional karyotyping (from 5 to 10 Mb). In addition, CMA does not require cell culture, which reduces processing time and is an excellent alternative tool when cell division is not available for analysis. This method can be used for various purposes, for example, to determine the cause of miscarriage or to identify aneuploidies such as Down's syndrome [7]. CMA uses comparative genomic hybridization (CGH) technology, a molecular cytogenetic technology that combines the standard cytogenetic karyotyping technique and the method of fluorescence in situ hybridization. CHG is based on a comparison of test and control DNA labeled with different fluorochromes, which mix in a 1: 1 ratio and hybridize on the metaphase chromosomes of a karyotypically healthy person. After chromosome isolation, the program automatically calculates the fluorescence ratio for each point of the chromosome and, based on the data obtained, builds a color-coded image. CGHs have been designed to cover the entire genome, for targeted analysis of known microdeletions / microduplications, and for known loci of inherited mutations [6]. Chip sensitivity depends on the size and type of probes used. The most common are oligonucleotide probes (~ 60 bp) or probes with single nucleotide polymorphism (SNP) (32-40 bp). Oligonucleotide probes can be used to cover the entire genome with an average resolution of about 35 kb. Modern SSG chips typically use a combination of copy number probes (oligonucleotides) to detect increases and decreases in copy numbers and single nucleotide polymorphism (SNP) probes to detect single nucleotide sequence similarity (homozygosity). The combination of probes detects a series of homozygosity between the maternal and paternal copies of each chromosome, which allows the diagnosis of triploidy, homogeneous disomy and consanguinity, and also improves the detection of low levels of mosaicism [8]. Several commercial CMA tests are available today, including GeneDx's GenomeDx CMA. GenomeDx can confirm clinical diagnoses, distinguish between de novo and familial cases, and assist in the prenatal diagnosis of high-risk pregnant women. This test takes three weeks to complete, and both blood and buccal scraping can be used as the test sample. GenomeDx is a full genome CMA containing 118,000 oligonucleotide probes that detect copy number variations [17]. LabCorp has developed the Reveal® microchip that detects chromosomal abnormalities associated with developmental delay and congenital malformations [29]. Scientists from South Korea have also developed a microchip for diagnosing chromosomal abnormalities that cause various diseases: Down's syndrome, Patau's syndrome, Edward's syndrome, Turner's syndrome, Klinefelter's syndrome, alpha-thalassemia, Charcot-Marie-Tooth disease, hereditary neuropathy with a tendency to paralysis from compression, Prader-Willi syndrome, Rubinstein-Tybee syndrome, Williams syndrome and Wolff-Hirschhorn syndrome [16].

A DNA microchip was developed for neonatal screening for hemoglobinopathy. The following approach to the manufacture of a microchip was used - a fragment of the human beta-globin gene was amplified and immobilized on a glass substrate, on which the solution was then applied with the test sample-labeled with a fluorescent dye oligonucleotide probes corresponding to either the wild-type or mutant alleles S, C, and E of the beta-gene. Globin [30].

Research team from the Netherlands, the United Kingdom and Thailand has developed a biochip for the diagnosis of primary immunodeficiency (PID), which is a group of heterogeneous diseases that includes more than 400 different monogenic hereditary diseases that affect the development and function of the immune system. Modern approaches to genetic diagnosis of PID are based on Sanger sequencing, next generation sequencing (NGS), and copy number variant (CNV) analysis. However, these methods are time-consuming, expensive and require complex data interpretation, which up to now limits the number of analyzes. For this development, the biochip platform of Illumina The Illumina Custom GSA was used, which includes 9,415 mutations in 277 genes associated with PID. The test system allows high-precision screening for known mutations in a short time and at a lower cost [32].

Also, the Alkor Bio group of companies (St. Petersburg) has developed a test system for detecting the 25 most common mutations in the CFTR gene “Cystic fibrosis-biochip” in the Russian Federation and Europe [3]. Every year biological microchips are being introduced more and more in various fields of clinical medicine. Many different types of microchips are being developed. Microarray technology continues to improve in terms of performance in terms of sensitivity and accuracy, and is becoming the most economical research method.

Prospects for the use of diagnostic DNA microarray in genetic carrier screening. Modern microchips can contain millions of markers for thousands of diseases, which makes it possible to significantly reduce the cost of screening diagnostics of the population. However, as noted earlier, due to the great complexity and laboriousness of the technology for printing microchips at the moment, they have not yet become widespread in clinical practice. In addition, since mass screening of people from various populations for thousands of genetic diseases (most of which are not common) is not an urgent task at this time. The most intensive introduction of microchips of medium and low print density, containing tens and hundreds of genetic markers. Such microchips have a relatively low cost and affordable printing technology, and also allow screening only for the most common mutations. In addition, the method of microchip DNA diagnostics has a high speed of analysis and high reliability of the results obtained, which, according to

scientists, ensures the future leadership of this method in the segment of DNA diagnostics.

In isolated populations, for example, in the Yakut ethnic group, there is an accumulation of certain forms of monogenic disorders caused by ethnospecific mutations, the frequency of heterozygous carriage of which significantly exceeds the global data [4]. In this regard, the development and implementation of new effective methods of DNA diagnostics is an integral task of medical genetic services. An excellent example is the research of scientists from Stanford University, who proposed the development of a microchip to identify ethnospecific mutations responsible for the occurrence of hereditary diseases common among the Ashkenazi Jewish population - Tay-Sachs disease, Bloom syndrome, Canavan disease, Niemann-Pick A, familial dysautonomia , torsion dystonia, mucolipidosis type IV, Fanconi anemia, Gaucher disease, glycogen storage disease type 1A, maple syrup urine disease, non-syndromic hearing loss, and glycogen storage disease type III [15]. Also, a research group of scientists from India developed a low-density oligonucleotide biochip to detect the carriage of 62 mutations of the *ATP7B* gene, characteristic of the Indian population, that are the cause of Wilson's syndrome. The frequency of heterozygous carriage of these mutations in India is 1: 90. In their development, the method of allele-specific primer extension was used. This development has already been introduced into the practice of clinical medicine in India for the diagnosis of Wilson's syndrome in the Indian population [22].

Programs to prevent the spread of hereditary diseases have been introduced and are being practiced in several countries. For example, such measures have been shown to be effective in reducing the incidence of β-thalassemia, sickle cell anemia by 70% in Mediterranean populations, and by 90% the incidence of TSD (Tay-Sachs disease) in the Jewish population in the United States of America and Canada [35, 19]. Currently used classically diagnostic methods such as PCR-RFLP, real-time PCR, sequencing methods have a number of disadvantages that limit the number of analyzes performed due to the laboriousness and high cost of consumable reagents, which greatly complicate the conduct of DNA diagnostics on a large scale and, therefore, the introduction of such preventive measures. Also, as we mentioned earlier, ready-made high-resolution microchips from large companies "Illumina", "Affimetrix", "PerkinElmer" and others include simultaneous detection for thousands and millions of SNPs, which makes them very expensive and not in demand in clinical the practice of a geneticist and a doctor of another specialty. To process the huge information obtained from these microchips, it is necessary to use special programs and trained personnel. Commercially available off-the-shelf microchips often do not correspond to the interests of research in a specific area, for example, in the Republic of Sakha, due to the specificity of mutations characteristic of the Yakut ethnic group, which have a high frequency in the region, but are completely rare for other populations in the world. Thus, the independent production of microchips at the workplace is very important for regions burdened with hereditary diseases for the detection of heterozygous carriers and application in molecular genetic screening.

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References

1. Технология гидрогелевых биочипов и ее применение в медицинской лабораторной диагностике/ Д.А. Грядунов, Д.В. Зименков, В.М. Михайлович [и др.] // 2009. – *Лаборатория*. - Т.3 (11). – С.. 10-14. A. [Hydrogel biochip technology and its application in medical laboratory diagnostics / DA Gryadunov, D.V. Zimenkov, V.M. Mikhailovich [et al.] *Laboratory*. 2009; vol. 3 (11): 10-14. (In Russ.).]

2. Технология гидрогелевых биочипов ИМБ РАН: 30 лет спустя / Д. А. Грядунов, Б. Л. Шаскольский, Т. В. Наседкина [и др.] //2018. – *Actae Nature*, том 10 No 4 (39). [D. A. Gryadunov, B. L. Shaskolsky, T. V. Nasedkina, A. Yu. Rubina, A. S. Zasedatelev. Technology of hydrogel biochips from the Institute of Biology and Biology, Russian Academy of Sciences: 30 years later. 2018. - *Actae Nature*, Volume 10 No 4 (39). (In Russ.).]

3. Павлов А.Е. Молекулярно-генетическая диагностика муковисцидоза в формате микрочипа/ А.Е. Павлов, С.В. Апалько,Е.В. Воробьев// Лаборатория. 2012. – (4): 16-19 [A.E. Pavlov, S.V. Apalko, E.V. Vorobyev. Molecular genetic diagnostics of cystic fibrosis in microchip format (In Russ.).]

4. Пузырев В.П. Наследственные болезни у якутов / В.П. Пузырев, Н.Р. Максимова //Генетика. 2008. – (44): 1308–1314 [Puzyrev V.P., Maksimova N.R. Hereditary diseases in the Yakuts. (In Russ.).]

5. Adriana Lagraulet, Current Clinical and Pharmaceutical Applications of Microarrays: From Disease Biomarkers Discovery to Automated Diagnostics / *Journal of the Association for Laboratory Automation.* 2010; – 413JALA; Vol 15, issue 5: 405-, 405-413

6. Bejjani B.A., Theisen A.P., Ballif B.C., Shaffer L.G. Array-based comparative genomic hybridization in clinical diagnosis / *Expert Rev Mol Diagn* 2005. – 5(3):421–9.

7. Brynn Lev, Ronald Wapner. Prenatal diagnosis by chromosomal microarray analysis/ *Fertility and Sterility.* 2018. – Vol. 109, No. 2, 0015-0282

8. Cao J, Gao S, Chen J, Zhu B, Min R, Wang P. The preparation and clinical application of diagnostic DNA microarray for the detection of pathogens in intracranial bacterial and fungal infections/ *Exp Ther Med.* 2018; 16(2):1304-1310

9. Diego Tejedor. Reliable Low-Density DNA Array Based on Allele-Specific Probes for Detection of 118 Mutations Causing Familial Hypercholesterolemia/ Diego Tejedor, Sergio Castillo, Pilar Mozas, Elisa Jiménez, Mónica López, M Teresa Tejedor, Marta Artieda, Rodrigo Alonso, Pedro Mata, Laureano Simón, Antonio Martínez, Miguel Pocoví / *Clinical Chemistry*, 2005; Volume 51, Issue 7: 1137–1144

10. E. Mannick, Zhiun Liu, Diagnostic microarray for inflammatory bowel disease, crohn's disease and ulcerative colitis/ 2004; US20040077020A1

11. Francoise De Longueville, Marc Lacroix, Anna-Maria Barbuto, Vincent Bertholet, Dominique Gallo, Denis Larsimont, Laurence Marcq, Nathalie Zammatte, Sophie Boffe, Guy Leclercq. Molecular characterization of breast cancer cell lines by a low-density microarray/ *International journal of oncology*. 2005; Vol. 27 Issue 4: 881-892.

12. Gemma A. Cannon, Michael J. Carr, Zoe Yandle, Kirsten Schaffer, Rachel Kidney, Ger Hosny, Allen Doyle, John Ryan, Rory Gunson, Terry Collins, William F. Carman,Jeff Connell, William W. A low density oligonucleotide microarray for the detection of viral and atypical bacterial respiratory pathogens / *Journal of Virological Methods*. 2010; 16: 17–24

13. He Z., Gentry, T., Schadt, C. GeoChip: a comprehensive microarray for investigating biogeochemical, ecological and environmental processes. 2007; ISME J 1: 67–77

14. Iris Schrijver, Comprehensive arrayed primer extension array for the detection of 59 sequence variants in 15 conditions prevalent among the (Ashkenazi) Jewish population/ Iris Schrijver, Maigi Kulm, Phyllis I, Gardner, Eugene P. Pergament, Morris B. Fiddler //Journal of Molecular Diagnostics. 2007. – (9): 229-236

15. Kang J.-J. Detection method for chromosome abnormality and microarray chip/ 2007: US20070048742A1

16. Genetic testing including targeted gene panel in a diverse clinical population of children with autism spectrum disorder: Findings and implications/ Kalsner L, Twachtman-Bassett J., Tokarski K., et al./*Mol Genet Genomic Med*. 2018. – 6(2):171-185.

17. Kevin S. McLoughlin, Microarrays for Pathogen Detection and Analysis, Briefings in Functional Genomics/ 2011; Volume 10, Issue 6, Pages 342–353

18. Langlois S., Wilson R.D. Genetics Committee et al. Carrier screening for genetic disorders in individuals of Ashkenazi Jewish descent / *J Obstet Gynaecol Can*. 2006; (4): 324-332.

19. Lei Jiang, Dana Willner, Patrick Danoy, Huji Xu, Matthew A. Brown Comparison of the Performance of Two Commercial Genome-Wide Association Study Genotyping Platforms in Han Chinese Samples */G3 Genes Genomes Genetics*, 2013; Volume 3, Issue 1: 23–29

20. Lockhart D.J., Winzeler E.A. Genomics, gene expression and DNA arrays / *Nature* 2000. – 405 (6788): 827–36.

21. Manjula Mathur, Ekta Singh. Development of low-density oligonucleotide microarrays for detecting mutations causing Wilson's disease/ *J Med Res*. 2015; 141(2): 175–186.

22. Meza-Menchaca, T., Williams, J., Rodrí-

guez-Estrada R.B., García-Bravo A.; Ramos-Ligonio Á., López-Monteon A., Zepeda, R.C. A Low-Density Microarray Method for the Identification of Human Papillomavirus Type 18 Variants/ *Sensors,* 2013; 13: 12975-12993.

23. Mikhailovich V.M., Gryadunov D.A., Kolchinsky A.M., Makarov A.A. DNA microarrays in the clinic: infectious diseases/ *Bioessays*, 2008; v. 30: 673-682.

24. Raquel Moure, Montserrat Español, Griselda Tudó, Eva Vicente, Pere Coll, Julian Gonzalez-Martin, Virginie Mick, Margarita Salvadó, Fernando Alcaide. Characterization of the embB gene in Mycobacterium tuberculosis isolates from Barcelona and rapid detection of main mutations related to ethambutol resistance using a low-density DNA array / *Journal of Antimicrobial Chemotherapy*, 2014; Volume 69, Issue 8: 2299–2300

25. R. Natarajan. Mapping histone modifications by DNA microarray/ R. Natarajan. /2007: US20070292857A

26. Shang, S., Chen, G., Wu, Y. Rapid Diagnosis of Bacterial Sepsis with PCR Amplification and Microarray Hybridization in 16S rRNA / *Gene. Pediatr Res*. 2005; 58: 143–148.

27. Shen Y, Wu BL. Microarray-based genomic DNA profiling technologies in clinical molecular diagnostics/ *Clin Chem*. 2009; 55(4):659–69.

28. SNP microarray-prenatal (Reveal) Labcorp URL: https://www.labcorp.com/tests/510100/snp-microarray-prenatal-reveal (date: 23.01.2021)

29. Steven F. Dobrwolski, Newborn screening for hemoglobinopathy by DNA microarray analysis. 2003: US20030124581A1

30. Sultankulova, K. New oligonucleotide microarray for rapid diagnosis of avian viral diseases/ Sultankulova, K., Kozhabergenov, N.S., Strochkov, V.M. et al. // Virol J. 2017. – 14, 69.

31. Suratannon N., van Wijck R.T.A., Broer L., Xue L., van Meurs J.B.J., Barendregt B.H., van der Burg M., Dik W.A., Chatchatee P., Langerak A.W., Swagemakers S.M.A., Goos J.A.C., Mathijssen I.M.J., Dalm VASH, Suphapeetiporn K., Heezen K.C., Drabwell J., Uitterlinden A.G., van der Spek P.J., van Hagen P.M. Rapid Low-Cost Microarray-Based Genotyping for Genetic Screening in Primary Immunodeficiency / *Front. Immunol*. 2020; 11:614.

32. Thuluz Meza-Menchaca, John Williams, Rocío B. Rodríguez-Estrada, Aracely García-Bravo, Ángel Ramos-Ligonio, Aracely López-Monteon and Rossana C. Zepeda. A Low-Density Microarray Method for the Identification of Human Papillomavirus Type 18 Variants/ *Sensors*; 2013: 13, 12975-12993. (29)

33. Varela M.A., Amos W. Heterogeneous distribution of SNPs in the human genome: microsatellites as predictors of nucleotide diversity and divergence / *Genomics*. 2010; 95 (3): 151–9.

34. Opinion for Reproductive Genetic Carrier Screening: An Update for All Canadian Providers of Maternity and Reproductive Healthcare in the Era of Direct-to-Consumer Testing/ Wilson R., De Bie I., Armour C. M. et al. Joint SOGC-CCMG //*J Obstet Gynaecol Can.* 2016. –38(8):742-762.e3.

35. Zhu H.L., Zeng H.X., Liang X.D., Chang X.H., Wang J.L., Cui H., Wei L.H. Prediction of chemotherapeutic resistance in serous ovarian cancer with low-density custom microarray/ *Chin Med J* 2020. – 133:871–873.

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SURGICAL TREATMENT OF POST-OPERATIVE STERNOMEDIASTINITIS (LITERATURE REVIEW)

Postoperative sternomediastinitis is an infectious complication occurring after sternotomy with the sternal bone tissue and mediastinal tissues being involved into the infectious process, with the involvement or noninvolvement of superficial soft tissues and with the stable or unstable sternum. According to domestic authors [3], up to 8,000 reconstructive surgical operations for postoperative sternomediastinitis are performed annually in the developed countries. According to various sources, infectious complications occur up to 6.9% of cases [8]. Due to the rapid development of cardiac surgery in the late 20th century, the number of studies on postoperative sternomediastinitis has increased significantly. At present cardiosurgical patients are people of older age with multiple comorbid diseases determining a great number of risk factors, which lead to the complicated healing of surgically operated tissues. Postoperative sternomediastinitis morbidity increases the early in-hospital mortality to 7% as compared to patients having no inflammatory changes in the sternum with mortality rate of 1.8% [30], and the risk ratio of decreased long-term survival of patients after a deep sternal infection is 1.91 [30]. Postoperative sternomediastinitis aggravates the clinical status of the patient and increases the duration of the treatment, and the long-term expensive treatment of post-operative complications caused by cardiac surgery interventions makes us consider the economic dimension [15]. The cost of treatment of deep postoperative sternum infection doubles the cost of overall treatment of cardiac patients [15]. Thus in the US specialized centers this cost is about 500,000 dollars which even with an infection rate of less than 1% presents impressively high expenses for a country.

Keywords: thoracic surgery, postoperative sternomediastinitis, purulent complications of cardiac surgery

Historical stages of treatment of postoperative sternomediastinitis. First, sternomediastinitis was treated by an open method which included re-exploration and surgical revision of the wound with dressings of the wound applied constantly, and the expectation of spontaneous closure of the wound with granulations followed by epithelization. The treatment took a long time. The mortality reached 50%, with the death usually being caused by the development of sepsis, bleeding or the direct damage to the heart inflicted by the sharp bone fragments or the edges of the sternum [31].

Later a surgical treatment of the wound was proposed in combination with the system of continuous flow irrigation of the wound with antibiotics or antiseptics, among which 0.5% povidone-iodine solution was most often used. According to the data of foreign authors [34], treatment with the system of continuous flow irrigation of the wound lasted 12.7 days on the average, with 87% of such cases recognized as being treated effectively, 13% of cases characterized by sternal instability, and 13% of lethal cases due to deep infection.

Another technique suggested an open management after surgical treatment with further using a variant of musculoplasty, or with the preservation of the wound until complete granulation. In this case, the mortality rate reached 50%, and the development of a new technology for surgical treatment of the pathology in question was required.

In 1975, a radical surgical d-bridement of sternotomy wounds with myoplasty or omentoplasty but without continuous flow irrigation of the wound or open treatment were proposed, which decreased the mortality to 10% [14].

By the end of the XX-th century foreign researchers [22] offered a more active use of the surgical treatment technique applying reconstructive methods of

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