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***YE.ZH. BEKMUKHAMBETOV[1], S.K. BALMAGAMBETOVA[1], A.ZH. ZHYLKAIDAROVA[2], ZH.B. YELEUBAYEVA[2], A.K. KOYSHYBAYEV[1], O.N. URAZAYEV[1], B.K. KARIMSAKOVA[1], S.N. RYZHKOVA[1], O.V. ZAVALENNAYA[1], S.K. SAKHANOVA[1], ZH.ZH. URAZAYEVA[1], S.YE. KOKTOVA[3], K.K. SARKULOVA[4], L.M. YAKUPOVA[5]***

[1]West Kazakhstan State Medical University named after Marat Ospanov, Aktobe, the Republic of Kazakhstan
[2]Kazakh Research Institute of Oncology and Radiology (KazRIOR), Almaty, the Republic of Kazakhstan
[3]Consultative Diagnostic Department of the Aktobe Regional Perinatal Center, the Republic of Kazakhstan
[4]Cytological Laboratory of the Aktobe Regional Pathomorphological Bureau, Aktobe, the Republic of Kazakhstan
[5]Cytological Laboratoryof the West Kazakhstan Regional Oncological Dispensary, Uralsk, the Republic of Kazakhstan

# Current trends in cervical cancer screening

*The article provides a brief analysis of the current situation in diagnostics and prevention of cervical cancer worldwide, and the detection of cervical cancer in Kazakhstan during the implementation of the national screening program launched in 2008. The authors highlight the main features of Human papillomavirus as the causative factor of cervical cancer. The latest trends in the development of diagnostic tools in different countries are indicated along with various schemes of screening implemented in the neighbouring and other Asian countries.*

***Keywords:*** *cervical cancer, human papillomavirus, screening, modern technologies, Kazakhstan.*

In the annual report of the Barcelona Working Group of the Information Center on HPV and Cancer (ICO) for 2016, cervical cancer (CC) ranks third among female cancers in Asia with the incidence of 12.7 and the mortality rate of 6.4 per 100,000 of female population [1]. Cancer Today (former Globocan) cites the International Agency for Research on Cancer (IARC) reporting that in 2012 the highest frequency of CC among the neighbouring countries was registered in the Republic of Kazakhstan – the age-standardized indicator for 100,000 was 29.4, while the corresponding indicator was 15.3 in the Russian Federation, 13.5 in Uzbekistan, and 7.5 in China [2]. The global situation with CC is far from stabilizing. In November 2016, the American Cancer Society (ACS) and a group of researchers from the Lancet Center predicted an increase in the incidence by at least 25% globally by 2030. In general, the death rate from cancers of the female genital organs is expected to increase by 60%, mainly, in low- and middle-income countries [3]. However, CC is a real object for early detection due to its visual nature and can be largely prevented by both effective screening and vaccination [4]. Without secondary prevention (screening), CC can occur in about 3-5% of women with high-risk of human papillomavirus (HPV) infection which is the causative factor of the disease [5].

***Brief characteristics of HPV groups.*** Almost all cases of cervical cancer are caused by a persistent infection caused by a limited number of HPVs. In 2009, IARC has declared 12 types of HPVs as highly carcinogenic against CC (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and assigned them to Group 1 (high carcinogenic risk, HCR) [6]. In general, HPV is a large and diverse group of viruses, included 189 fully characterized types. HPV has 4 other groups except HCR: probably carcinogenic – like type 68 (group 2a), possibly carcinogenic – types 26, 53, 66, 67, 70, 73, and 82 considered as potential carcinogens, with inconsistent and not completely defined role in carcinogenesis (group 2b), not classified (group 3), and possibly not carcinogenic (group 4). Carcinogenicity of various types is determined by their potential to cause malignant process as a monoinfection, as well as the frequency (incidence) of such processes [7]. "Accumulative" damage to papillomaviruses is estimated in about 5% of all cancers in the human body [8]. Researchers are inclined to investigate the super group Alphapapillomavirus, which localizes in the genital epithelium, taking into account that the human papillomavirus is prone to constant evolution [9-11]. Some scientists believe that types 68, 73 and 82 should also be considered as carcinogenic in addition to types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59; and types 26, 53, and 66 should be considered as potential / probable carcinogens. As a proof of the constantly growing number of evidences of the constant evolution of HPV, recently Khalek et al. [14] have provided a clear molecular and biological evidence for the unique carcinogenicity of types that are currently classified as probably / possibly carcinogenic [12].

***HPV epidemiology by country.*** According to the meta-analysis of the IARC Working Group of 2007, the prevalence of HPV even in women with normal cytology differs by almost 20 times between populations: from 1.4% (95% CI 0.5-2.2) in Spain to 25.6% (22.428.8) in Nigeria [13]. In Denmark, where screening and immunization coverage is at a high within European level, nevertheless the prevalence of HPV is 20.5% and the leading genotype remains HPV 16 [14]. In Italy, where advanced screening schemes and universal vaccination of adolescent girls are also introduced, the prevalence of HPV remains high - 29.7%, according to N 9720 [15]. In countries bordering with our country, the statistics prevalence for HPV vary widely. For example, in China, the prevalence of HPV is generally 13.5-15.5% with the most common genotypes HPV16, HPV52, HPV58, HPV33 and HPV18 [16, 17]. According to a meta-analysis of current publications on the topic, significant data on cervical cancer (≥8 publications) were available in 10 most populous countries across China, the US, Japan, India, Brazil, and very limited data (0-2 publications) in Indonesia, Pakistan , Nigeria, Bangladesh, Russia and the post-Soviet period countries [18]. So far, there are only limited data on the epidemiology of HPV and virus-associated diseases in the Russian Federation, the Caucasus, the Baltic and Central Asia, including Kazakhstan [19]. For example,

in Uzbekistan, the total prevalence of HPV, without indicating the dominant genotypes, is 15.4% [20]. In Russia, data on the prevalence of HPV are very contradictory, on the whole, various sources indicate 24-28%, and the leading genotypes are 16, 18 and 45, with the prevalence of HPV 16 reaching 65.9% [21]. According to the pilot project of the West Kazakhstan Medical University, the prevalence of HCR HPV in the Western region of Kazakhstan in 2014 was 26.04%. The leading genotypes were 16 (10.7%), 39, 51, 31 and 56 [22]. Researchers of KazIOR, dealing with the problem, also revealed a high prevalence of HPV among Kazakh women on material N 2408 - 28.3%, and 25.1% were referred to the high risk group (HCR HPV) [23].

***The recent research in HPV diagnostics.*** Currently, the study of the immunogenesis of HPV infection gives way to other topical areas, like the role of molecular RNA (m-RNA) in the infection induction and predicting the rapidity of neoplastic transformation in patients with cervical intraepithelial neoplasia (CIN) [24]. m-RNA was found to be a marker for the process activity and the progression of CIN. According to the study conducted in Vito Fazzi hospital, Lecce (Italy) in 2015, either all the mRNA HPV-positive patients were at risk of progression of CIN1 and CIN 2/3 in about 12 months, or the mRNA-HPV test had a higher specificity than PAP tests (SurePath, Cobas) in post-surgery assessment of patients. The study has confirmed a strong association between the presence of HCR HPV mRNA and the risk of tumour progression.

Epithelial-mesenchymal transformation (EMT) is a current subject of study as an allaxis of epithelial cells into mesenchymal cells with a critical impact on embryonic development, wound healing, tissue regeneration, organ fibrosis, and cancer progression, including CC [25].

The current status of HPV-associated infections cannot be investigated without relying on the sequencing of HPV genes due to the proven high genetic variability of many types of HCR HPVs. The sequencing of genes described in the already mentioned work of Halek et al. [12] has evidenced the evolution of the so-called "weak", "possibly" and "probably" carcinogenic types, such as 26, 53, 66-68, 70, 73 and 82, that until 2005-2009 were believed to be virtually incapable of causing a progression of CIN to the stage of invasive cancer as a monoinfection.

***Modern methods of HPV diagnostics.*** PCR methods are most common for HPD diagnostics in the post-Soviet territory and aimed at the maximum sensitivity of detection of viral DNA but do not always lead to direct clinical correlations. Digene-test is the first diagnostic method for detecting HPV DNA officially approved by the FDA (Federal Office for Food and Drug Administration, approval date 31.03.2003) [26]. Digene-test is a molecular technology aimed at identifying specific fragments of human papillomavirus DNA ("hybrid capture", HC-II). Digene HPV test is widely used due to its reliability and ease of use. The sensitivity of the test in combination with the cytological test (PAP test) in detecting precancerous changes in the cervix and CC is much higher than the cytological examination alone. Currently, the Digene combination of HPV test and cytological PAP test has become the "gold standard" in this area of diagnostics and is offered for screening of women over 30 years. In addition to the hybrid capture method, a number of promising and highly sensitive methods for diagnosis of papillomavirus infection have been developed over the past decade, of which, three were approved by FDA: HR Cervista HPV test (CER, Hologic, Madison, WI), Cobas HPV test (Roche, Pleasanton, USA), and the test based on HPV APTIMA RNA analysis (Hologic, San Diego, CA). The Cobas HPV test, being one of the latest developments, was recently approved by FDA for primary CC screening [27]. The Cervista test demonstrated high efficacy in detecting HPV, but in trials it was revealed its propensity to false positive conclusions results also identified using DNA genome analysis. The diagnostic performance of the new methylation panel showed higher specificity. This will prevent unnecessary colposcopy in women with abnormal cytology. These newly discovered markers can be used as a sorting test in HPV-positive women in population screening [29].

The progress in nanomaterial research has significantly affected the development of diagnostics of infectious diseases. Although HPV diagnostics currently relies only on molecular tests, a method has been discovered for using fast and light quantum dots and superparamagnetic nanoparticles based on hybridization analysis that allows detecting 16 HPV types. It combines the advantages of superparamagnetic nanoparticles and quantum points and completely differs from the usual hybridization analysis because the reaction proceeds in a homogeneous solution, and the test takes NMT 1 hour [30].

***Colposcopy in diagnostics of cervical pathology.*** Colposcopy is one of the most costly diagnostic techniques and is included in later stages of measures for early detection of CC. Colposcopy requires an experienced specialist and expensive equipment, and it assumes subjectivity of clinical assessment. The literature provides ambiguous assessments of diagnostic value of this method. According to various estimates, its sensitivity varies in the range of 49-84% [31]. Nevertheless, colposcopy, as one of the final diagnostic tools used for targeted biopsy is a constant focus of attention of the researchers seeking to increase its effectiveness [32, 33].

***Modern screening of cervical cancer.*** The known diagnostic sensitivity of PAP test does not exceed 50-70% with a specificity of 95-98% [34]. It is now generally accepted that liquid-based cytology (LBC) methods eliminate many shortcomings of traditional cytology. The liquid method has twice more advantages than the number of its disadvantages compared to the traditional cytology (PAP-test). Its most significant disadvantages include: higher cost of consumables, longer time for preparation of samples and higher work load of screening, as well as possible difficulties in the interpretation of glandular pathology. However, the better preservation of cells, the improved visualization, the possibility of preparing up to 15 preparations from a single sample (which is important for the use of additional methods and automated analysis), minimization of artefacts and a 5-fold lower frequency of inaccuracy (only 1-2%) compared with traditional cytology, substantially outweigh the shortcomings, which are mainly resource, rather than diagnostic, [35]. In the most large-scale studies (N to 26782), the liquid method was highly appreciated and recommended for mass screening [36]. As is known, FDA-approved transport media for liquid cytology, such as SurePath, ThinPrep, EasyPrep, in 1990s allowed isolating the HPV DNA and the vaginal microbiota DNA from the residual liquid after cytological test; that is why they are also called "universal" media. This approach provides huge advantages for patients who simultaneously undergo all the tests necessary for an adequate diagnostics. It is also cost-effective as no additional supplies are needed.

Still, not all authors are happy about liquid cytology. In a study of efficiency of ThinPrep transport media from N to 5652 [37], fluid (LBC) and normal cytology were statistically equivalent, although the sensitivity of conventional cytology was at least 5 per cent higher at all pathology levels.

In recent years, it has been clinically proven that HPV typing is necessary to detect severe cervical pathology, since the sensitivity of the DNA test is 75-95% compared to 70-90% of the PAP test, and the predictive value of the negative HPV DNA test is 99% [38]. A large-scale study in Mexico involving women aged 30 to 80 on the cost of a single PAP test compared to a combined PAP + HPV DNA test showed that in the end a combined study was always more cost-effective than just PAP since it prevented many negative outcomes that was paid by the state [39]. HPV screening tests in combination with traditional PAP tests provided an unprecedented opportunity to significantly reduce the prevalence of CC in the United States [40].

In general, a lot of evidence was gathered around the world to prove higher efficiency of HPV testing in diagnostics of severe cervical lesions which ultimately led to radical changes in the methods of screening, or to a conceptual transition. Cervical screening based on HPV DNA has been clinically confirmed as the primary screening instrument. When following the appropriate protocol, it is more effective than screening based on cytology to prevent invasive CC. Screening with HPV testing can reduce the invasive CC incidence by 60-70% compared to screening based only on PAP tests [41]. In 2007, the IARC research group carried out large-scale population studies on screening techniques and has developed the "10 Key Recommendations". One of them is the transition to HPV tests as the main screening instrument [42]. HPV tests were also recommended by WHO in order to sort out minor cytological abnormalities and then follow-up of women after treatment of severe cervical lesions [43, 44]. HPV testing as the main tool is also recommended for low-income countries. A demonstration project N 44110 in India showed the possibility to implement HPV-based screening using the existing primary health care infrastructure [45].

Figure 1 depicts a new CC screening scheme generally adopted in Italy since 2016 under MIDDIR project [46] developed by a group of Italian specialists based on pan-European (British, Dutch) techniques.

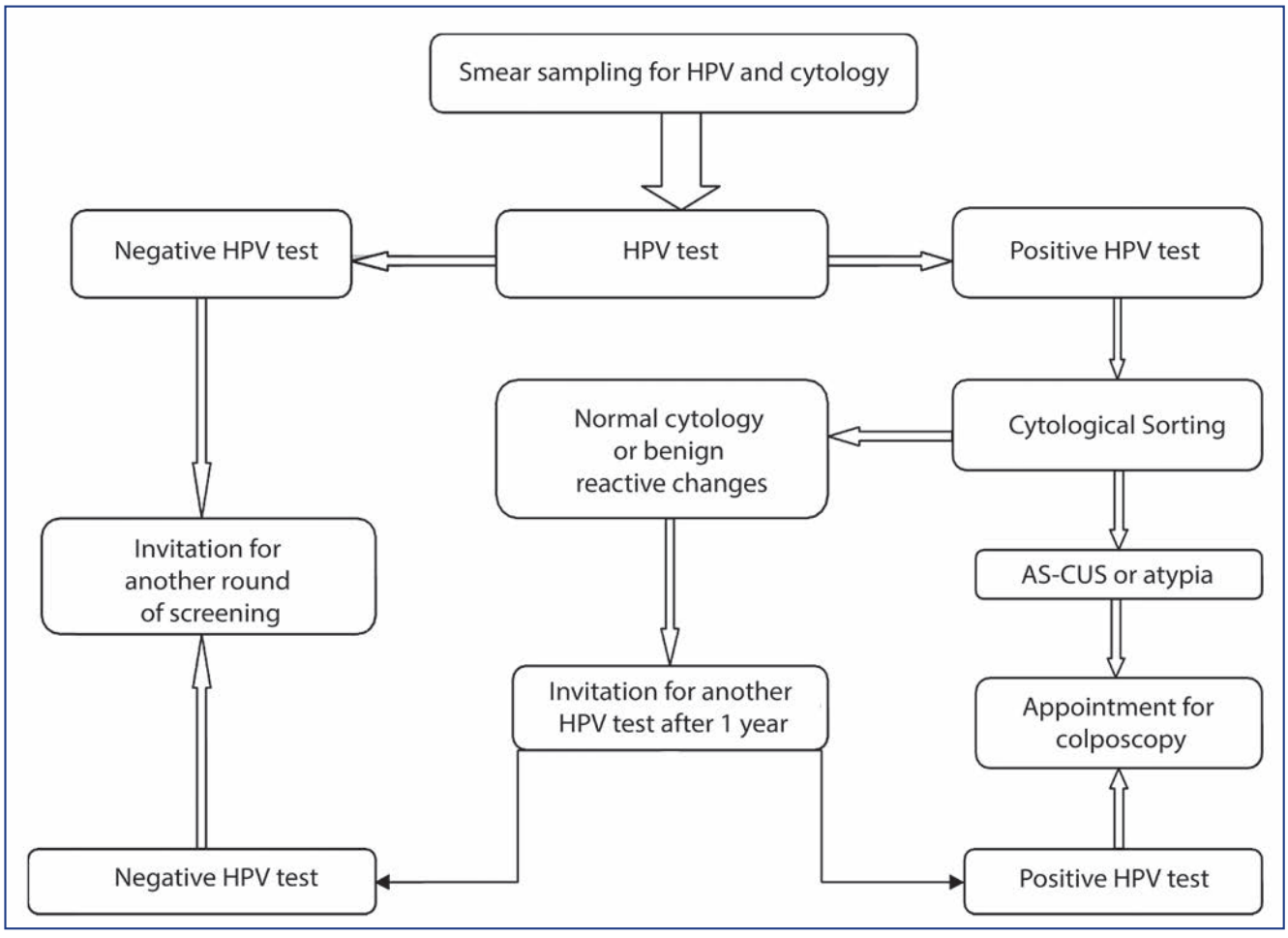


**Figure 1** – Scheme of HPV-oriented screening used in all regions of Italy. Source: MIDDIR Project text

The scheme shows that HPV test is the main tool for determination of further tactics, and cytology is used as a sorting tool. This approach allows timely identification of women at risk of CC development and a significant reduction of massive labour-consuming cytological studies in women with a negative HPV test.

Today different countries apply a wide variety of screening techniques. The mentioned scheme of HPV-oriented screening introduced in 2016 in Italy is affordable only for high-income countries of Western Europe. As is known, a high frequency of CC is observed in the developing countries. However, some countries (China, India) have

introduced HPV testing as a pilot or demonstration project. Table 1 provides information on the state of screening in general, and the use of various screening techniques in some countries in Asia and in the countries neighbouring with Kazakhstan.

***Current situation with CC in Kazakhstan.*** Kazakhstani scientists report on the growth of CC incidence in the country from 14.5 per 100,000 of female population in 2004 to 20.2 in 2014. They associate the increase in the incidence of CC with a growth of detection of malignant cervical pathology after the introduction of the screening program. The red flag is the fact that "the analysis of age-specific incidence rates has revealed a significant risk of the disease in the young age and its marked increase by the age of 40-44. The peak incidence has shifted to a younger age over the past 6 years, with an overall increase in the incidence due to the women aged 35 to 55" [47]. This data is consistent with the results of independent experts from the ICO Barcelona working group. According to their annual report for 2015, CC in Kazakhstan is the second most common among women and ranks first in frequency in the age group of 15-44, with the incidence rate increase up to 32.8 [48].

***Modern problems of CC screening in Kazakhstan.*** Since 2008, our country has adopted a three-stage system of preventive measures in the fight against CC in accordance with the State Program for Health Development of the Republic of Kazakhstan "Salamatty Kazakhstan" approved by the Decree of the President of the Republic of Kazakhstan dated November 29, 2010 No. 1113, by order of the President; Order of the Minister of Health of the Republic of Kazakhstan of November 10, 2009, No. 685 "On the Approval of the Rules for Conducting Preventive Medical Examinations of Target Populations" with additions and amendments as of December 29, 2014 No. 361 and other legislative documents [49].

**Table 1** – Screening technologies implemented in some Asian countries

| Country | Availability of a screening program | Structures ensuring qulity and authorized to monitor the screening process | Active invitation for screening | Main test for primary screening | Demo projects | Decreed groups | Screening frequency or interval |
|---|---|---|---|---|---|---|---|
| Afganistan | yes | No | No | cytology | VIA | 15-49 | 5 лет |
| Azerbaijan | No | - | - | - | - | - | - |
| China | yes | No | No | cytology/ VIA | HPV test | 30-59 | 3 year cytology (35-59 years); VIA for rural women 30-54 years |
| India | yes | No | No | cytology | VIA/HPV test | 35-64 cytology | 3 years |
| Indonesia | yes | Yes | No | VIA | - | 30-50 | 5 years |
| Israel | yes | No | No | cytology | - | 35-54 | 3 years |
| Japan | yes | yes | Yes | cytology | - | 20+ | 2 years |
| Kazakhstan | yes | No | No | cytology | - | 30-60 | 5 years |
| Turkey** | yes | yes | Yes | HPV test/ cytology | - | 30-65 | 5 years - cytology, 5 to 10 years – HPV-test |
| Uzbekistan | yes | No | No | cytology | - | 25-49 | - |

*Notes: * - data taken from the report of the ICO - the Barcelona group monitoring the cituation with cervical cancer [1]. The data was evaluated as of 15.10.2015.*

*** - HPV-based screening was introduced in Turkey since 2014. Data from the International Workshop on Cancer Screening and Monitoring, 13-15 October2015,Ankara, Turkey*

In spite of a certain success of the national screening program implemented in Kazakhstan for 8 years, some problems still prevent a significant reduction in CC incidence in the country. Undoubtedly, the reduction of the share of advanced stages of CC can be attributed to achievements. According to the local data, "in 2007, the share of advanced stages was 26.7%. It means that every 4th woman had advanced cancer. Since 2008, after the introduction of the state screening program for CC, the share of advanced stages has reduced by more than 2 times" [50].

Problems of Kazakhstani screening can be divided into several groups:

- Organizational problems, namely, the attendance of screening activities (coverage);
- Verification of tools used for screening;
- Relevance of the technique used;
- Availability of qualified personnel.

It is well known that to make a CC screening program efficient, the coverage of women from the decreed groups shall approach 100%. In Kazakhstan, the attendance rises is about 70% [19], since 2015 – about 50%. The reasons for insufficient popularity of screening among women shall be explored.

Concerning the verification of the basic screening instrument: in 2013, Kazakhstan has adopted the BD technology (SurePath®, BD diagnostics, Tripath, Burlington, North Carolina, USA) which provides for simultaneous extraction of HPV DNA from the liquid transport media for molecular biological study, then has changed to the Cell Scan technology (Tech Bio Co. LTD, South Korea) that has not yet been evaluated in the scientific literature (in " Core Collection "publications). This might be explained by the relatively short lifespan of this technology - Cell Scan was developed by IMSTAR laboratory, France in 2010.

Order No. 926 of the Minister of Health of the Republic of Kazakhstan dated 30.11.2015 is has established the Joint Commission on the Quality of Medical Services engaged in the evaluation of medical technology at the review stage. The Cell Scan technology was introduced before the establishment of the evaluation system in Kazakhstan. Nevertheless, the quality of the main CC screening tool shall be assessed because of low efficiency of screening.

The concept of using only liquid cytology is also relatively outdated since the leading role of molecular-biological HPV tests in early detection of precancerous cervical conditions has been proven by the experts. Our country has not yet accepted the WHO recommendations concerning primary HPV testing. The appropriate specialists shall consider the possibility of implementing such testing.

Unfortunately, the public institutions in some regions of the country experience a deficit of specialists on cervical pathologies. Through the state screening program is accessible for all segments of population what is a significant achievement of the public health system in itself, and though almost 100% of regional outpatient clinics have got colposcopies, many patients cannot undergo colposcopy with targeted cervical biopsy in time.

***Conclusion.*** Despite the screening activities, the incidence and mortality from CC in Kazakhstan are still increasing, especially among young women. Insufficient efficiency of the existing program is due to the low coverage of the female population and the lack of a clear validation of the diagnostic tools of population screening, as well as a poor connection between the screening stages, possibly, due to lack of qualification of relevant specialists.

The prevalence of HCR HPV in Kazakhstan induces the urgent need to renew the state program of primary prevention of the infection, i.e. universal compulsory vaccination of adolescents. The vaccination program successfully launched in Kazakhstan was stopped primarily because of the negative attitude of parents not ready for the challenges of the modern world. Nevertheless, further efforts are needed to overcome prejudices in primary prevention of CC. According to the press release of the Center for Disease Control (CDC), in the US after 7 years of implementation of vaccination against CC of teenage girls (2006-2013) the prevalence of vaccine types of HPV in the age group of 14-19 years has decreased by 56% [51]. Recommendations for vaccination have been developed by the world's leading cancer institutes (ACS, IARC) not only for girls, but also for 11-12 years boys. The efficiency of vaccination has been proven convincingly and is no doubt [52].

Thus, in order to receive problems of preventing and early detection of CC, Kazakhstan has to increase the effectiveness of screening and renew the state immunization programs. These problems require further comprehensive study for finding the optimal solutions.

The following recommendations were developed taking into account the urgency of the problem and the experience gained by Kazakhstani experts:

1) to review methodological approaches to the screening strategy implemented in the country. To organize the transition to HPV-oriented screening which efficiency has been proven globally, that is, to use only the combined HPV test + PAP screening tools.

2) to approve a mechanism of validation of screening methods and conduct all tests of population screening using such mechanism. To develop an appropriate Application to the Committee of the MoH of the RK on Assessment of Medical Technologies according to the generally accepted international assessment procedure.

3) To increase the coverage of female population, also through raising the awareness by launching an Internet awareness campaign regarding screening and vaccination against CC. According to the Committee for Statistics of the Republic of Kazakhstan, 94.6% of women aged 15-24 use the Internet (social networks, messengers) vs. only 16.1% of women aged 15-49 who use mass-media (newspapers, magazines, radio, TV) at least once a week [53].

4) To increase the responsibility of specialists in cervical pathology (colposcopy) rooms for the final results of screening in the relevant PHC institution; to strengthen the connection between the screening stages: PHC screening – general practitioner – gynaecologist – colposcopy room, i.e. to debug the direct communication

and feedback in the system of rehabilitation of women with the revealed pre-tumour pathology.

5) To teach the cytologists to use Bethesda's terminology (TBS, 2001) when issuing screening conclusions and to ensure free interpretation of molecular-biological tests.

6) To adjust the state system of training of laboratory doctors for state PCR laboratories, to improve quality of training and the number of trained molecular biologists.

7) To recommence the state immunization program against CC by including a mandatory vaccination of girls aged 10-13 years in the school vaccination card.

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