Modern approaches to cervical cancer screening (a review)

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article;
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The aim – systematization of data from modern scientific sources and own knowledge and experience regarding the problems, advantages and prospects of the development of various methods of diagnosing pathological conditions of the cervix.

The relevance of the problem of cervical cancer is beyond doubt, which is confirmed by the annual data of the official statistics and recommendations of WHO, European experts and relevant national recommendations. The analysis and generalization of information from the specialized literature regarding the assessment of problems and prospects for the development of leading methods of cervical screening in order to reduce the number of cervical cancer cases in the world is a priority task of the expert society.

Currently, the most recommended approach to cervical screening is to combine HPV testing with cytology but separate testing for HPV is the most promising. Colposcopy remains the only confirmatory method of diagnosing cervical pathology, subject to mandatory cervical biopsy and histopathological examination of the biopsy. Standardization of classifications and terminology in the assessment of cytological, histopathological and colposcopic conclusions will allow to reach an understanding in the issues of optimal management tactics for patients with cervical pathology.

Conclusions. Diagnosis of high-risk carcinogenic types of human papillomavirus is the most promising method of cervical screening in the near future. At the same time, at the moment, we consider it appropriate to use the cytology together with HPV testing, at least as a sorting method. Standardization of cytological/histopathological terminology should be done in accordance with the Bethesda 2014 system update.

Сучасні підходи до скринінгу раку шийки матки (огляд літератури)

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Мета роботи – систематизація відомостей сучасних наукових джерел, власних знань і досвіду щодо проблем, переваг і перспектив розвитку різних методів діагностики патологічних станів шийки матки.

Актуальність проблеми раку шийки матки не викликає сумнівів, що підтверджується щорічними даними офіційної статистики та рекомендаціями ВООЗ, європейських експертів і відповідними національними рекомендаціями. Пріоритетне завдання експертного товариства – аналіз та узагальнення відомостей фахової літератури щодо проблем і перспектив розвитку провідних методів цервікального скринінгу для зниження кількості випадків раку шийки матки у світі.

Нині під час цервікального скринінгу найчастіше рекомендують поєднання тестування на вірус папіломи людини (ВПЛ) із цитологічним методом дослідження, а найбільш перспективним вважають окреме тестування на ВПЛ. Єдиний вірогідний метод діагностики патології шийки матки – кольпоскопія за умови обов'язкового виконання цервікальної біопсії та патогістологічного дослідження біоптата. Стандартизація класифікацій, термінології під час оцінювання цитологічних, патогістологічних й кольпоскопічних висновків дасть змогу досягти консенсусу щодо оптимальної тактики ведення пацієнток із патологією шийки матки.

Висновки. Діагностика висококанцерогенних типів ВПЛ – найбільш перспективний метод цервікального скринінгу в найближчому майбутньому. Втім, доцільним вважають використання цитологічного дослідження разом із тестуванням на ВПЛ, принаймні як метод сортування. Стандартизацію цитологічної / гістопатологічної термінології слід здійснювати відповідно до рекомендацій термінологічної системи Бетесда (2014).

In 2020, the WHO approved the Global Strategy to accelerate the elimination of cervical cancer, which sets the ambitious goal of achieving 3 targets – "90–70–90". They are:

1) a 90 % rate of vaccination against the human papilloma virus (HPV) in girls under the age of 15 (before the onset of sexual activity);

2) the availability of at least 70 % of women of reproductive age to highly effective methods of screening (diagnosis) of cervical cancer, and finally;

3) the provision of treatment for at least 90 % of women diagnosed with cervical cancer [1].

However, despite all the efforts of the expert community, strategies for the prevention of cervical cancer, from our point of view, have acquired a tendency to become complicated in recent years, and some provisions are sometimes contradictory. The last most important breakthrough in the direction of prevention and diagnosis of cervical pathology occurred back in the early 1980s after the discovery of HPV [2]. The vast majority of cases of cervical cancer are associated with high-risk carcinogenic HPV types. And a clear trend towards an increase in confirmed cases of HPV-positive cervical cancer from 85.9 % in 1990 to 92.9 % in 2010 [3] is associated primarily with

the improvement of HPV detection methods. [4]. However, it should be noted that even now 3–8 % of cases of cervical cancer are classified as HPV-negative, that is, they refer to clinical cases where the relationship with HPV has not been proven. [5]. At the same time, a study with 371 biopsy-proven cases of primary cervical cancer found that 68 % of HPV-negative cervical cancers were in fact non-cervical cancers. These data imply that the number of HPV-negative cervical cancers may be overestimated due to false-negative HPV tests and histological diagnosis [6].

Therefore most scientific research has been, and still is, focused on HPV-positive cervical cancer. First, on the issues of vaccination against high-risk carcinogenic types of HPV infection, as a key method of primary prevention of cervical cancer. And, secondly, on the implementation of sensitive for HPV testing in women from risk group of developing cervical cancer [7]. Despite the proven effectiveness of both vaccination [8,9] and HPV tests, the introduction of these methods into practical medicine remains relatively slow in most countries of the world, and vaccination rates today vary significantly [10]. Thus, the level of vaccination against HPV in the USA, despite being one of the highest in the world, does not reach the target values of the WHO and remains below 80 % [11].

Undoubtedly, at the moment, vaccination is the most obvious and vitally important long-term priority in the prevention of cervical cancer. Thus, according to published data, by 2070, vaccination of girls alone will lead to a reduction in mortality by 61.7 %, preventing 4.8 million deaths, and double screening and treatment in addition to vaccination will lead to a corresponding reduction in the number of deaths from cervical cancer by 92.3 %, preventing 14.6 million of deaths [12]. Nevertheless, according to the opinion of the expert community, generally accepted screening diagnostic methods will also remain important in the coming decades.

Aim

Systematization of data from modern scientific sources and own knowledge and experience regarding the problems, advantages and prospects of the development of various methods of diagnosing pathological conditions of the cervix.

From our point of view, there are several unambiguous and undeniable provisions regarding cervical screening. First, the definition of cervical screening. In our opinion, this definition can be formulated as follows. Cervical screening is a process of regular assessment of the condition of the cervix in the target group, the purpose of which is to reduce the total number of cases of cervical cancer through the early diagnostics of precancerous pathology by officially recommended methods [13]. Secondly, there is no doubt that cervical screening, along with HPV vaccination, is currently the most effective approach in reduction of cervical cancer incidence [14]. Thirdly, and this is also a fact, most national guidelines suggest using 3 methods as cervical screening: cytology, cytology in combination with HPV testing (cotest) or separate HPV testing [15–17]. It should be noted, however, that to our knowledge, only the Netherlands and Turkey are the only European countries that have fully implemented

national HPV-based cervical cancer screening. Australia has demonstrated its willingness to be the first country to eliminate cervical cancer (by 2028–2035), but has not yet reached the WHO target for participation in HPV screening (current target – 52 %). It is interesting to note that, for example, in the USA, separate HPV testing is approved for only one specific HPV test [17–19], but FDA approval for other tests is likely to follow. Little prospective comparative data available indicate that the most highly validated tests that have received or are under FDA approval are approximately comparable in terms of analytical sensitivity and predictive risk of subsequent cancer / precancer in a negative result [20].

This is all that is not disputed. In all other issues, related to cervical screening, there is some confusion in the expert community and permanent disputes continue [21–23]. We believe that a discussion of the relevant scientific data is a good starting point for solving existing problems, and accordingly, the following discussion will help to simplify their solution. Let's try to figure it out.

Many important practical factors influence the organization of cervical screening. We list the main ones – the attitude of society to this problem, and, accordingly, the cost, frequency and availability of cervical screening; accepted models of laboratory screening (with the predominant use of cytology) and, finally, the lack of clear standards in the use of various cytological, colposcopic and histological terms.

Thus, the factor of attention of the society / country to the problem of cervical cancer and the attitude of women themselves to this problem correlate with the incidence of cervical cancer in these countries [24–26].

Information about the relevance of the problem of cervical cancer and the possibility of its successful prevention should be conveyed to the target audience by all available and effective means. Every woman from prepubertal age or living in the most remote area should have access to information about cancer and know what simple but regular steps she must take to avoid this disease [27,28]. At the same time, at all levels, there should be an understanding of the presence of a low, but non-zero level of cancer risk, even with regular participation in screening programs. This is the understanding that screening cannot provide complete (100 %) protection against cervical cancer, even with frequent unscheduled co-testing (HPV testing and cytology), even from adolescence, even at the cost of massive overtreatment [16]. The explanation for this is very simple: it is, for example, the presence of cases of rapidly progressive tumors in very young women [29] or deep lesions in the cervical canal that elude screening diagnostics.

Discussions are also ongoing regarding the frequency of screening after both negative and positive results. For example, there is currently a debate about when the next scheduled visit after a negative screening should be done [16,21]. Thus, in the expert community, there is significant resistance to the 5-year screening interval recommended for a negative co-test [21]. At the same time, the American Cancer Society (ACS) recommends starting cervical cancer screening at the age of 25 and having primary human papillomavirus testing every 5 years until the age of 65; and if primary HPV testing is not available, then those aged 25 to 65 should be screened with co-testing (HPV

testing combined with cytology) every 5 years or cytology alone every 3 years [30]. There is an understanding that the choice of an "ideal" interval between screening visits in the event of a negative result would lead to a significantly larger number of identified true precancerous diseases and, accordingly, to almost no cases of cervical cancer. However, the reality is that the existing intervals are either unreasonably short and lead to the detection of very few true precancerous conditions at screening, or vice versa, the detection of too many invasive cancers means that the screening interval is too long [31].

The management of positive screening results is also unresolved. Although it is widely accepted that positive HPV testing require triage rather than a universal, immediate referral for colposcopy with targeted biopsy, optimal triage methods are not defined and are highly variable. Theoretically, the ideal response to the presence of HPV infection without a cytologically confirmed precancer would be to repeat testing at an interval that takes into account the possibility of self-elimination of the most infections, for example, after 2 years. However, in practice, it is difficult for a woman and her doctor/health care provider to endure this period, primarily because of the risk of losing the possibility of observation, and therefore, at present, retesting after about 1 year is most often recommended [16,32]. In this case, possible sorting methods can include both cytology [17,23,33,34], and immunocytochemical dual stain cytology, which can assess as positive or negative (p16 / Ki-67 dual staining) [35], and HPV genotyping in various configurations [16,17,36], and other promising new technologies, including an automated cytological method that be programmed to provide a severity score (presented by Schiffman et al. at the 30th International HPV Conference in 2015). Studies of the methylation methods that would not require the preparation of a cytology slide are also of interest [37]. Thus, the exact balance has yet to be discussed and determined.

There is another problem. It is generally accepted that the main goal of cervical cancer screening programs is not to detect invasive cancer, but to perform its secondary prevention by detecting and treating precancerous conditions. It is, therefore, important to understand how objective the laboratory data are that we receive as a result of cervical screening. Taking this aspect in consideration, it is important to use common terminology when obtaining survey results. We advocate the definition that precancer is a subset of high-grade intraepithelial lesions of HSIL which describe pathological conditions capable of progressing to invasive cancer if left untreated [38,39].

Until now, when assessing the pathology of the cervix, various terms and categories have been used, which do not always fully correspond to the currently established stages of cervical carcinogenesis. According to the most of the experts, and we fully share this point of view, that the key stages of cervical carcinogenesis can be considered simply as a normal cervix, HPV infection of high-risk carcinogenic types, precancer and cancer. From our point of view, the simplification and standardization of terms could contribute to the creation of a unified approach to the management of patients at the post-screening stage: the need for re-screening, the timing of the next screening in case of a negative result, accelerated re-testing for

high-risk HPV infection, colposcopic targeted biopsy, as well as the need and amount of treatment. As an example, one can cite the LAST nomenclature, which recommends p16 staining to rule out dubious precancerous conditions (including CIN2) while completely abandoning CIN terms and older nomenclatures [40,41] or the Bethesda system [42,43] including terms that are in line to the norm (NILM), infection (LSIL), precancer (HSIL/AIS), and cancer [43]. As being strong proponents of the Bethesda system, we can't help but note that the most of high-risk infections are often described as NILM, while the most of histopathological precancerous conditions are found in women with LSIL or questionable LSIL (i. e. ASC-US) and not with HSIL.

However even after obtaining a unified terminological classification, we are forced to admit that at this stage, not a single screening or diagnostic test is perfect. For example, even histological examination, which is considered to be the reference standard of diagnostics, tends to overdiagnose precancerous conditions, due to the lack of clear criteria for determining which intraepithelial microscopic anomalies indicate that the lesion will spread, and which indicate the possibility of regression / self-elimination or persistence. The impact of replacing the CIN score with LAST criteria, including p16 testing, to clarify precancer still needs to be analyzed in detail [44,45]. Similarly, cytological categories tend to misclassify HPV status and the ability of the infection to progress to precancer / cancer. In this regard, for HPV testing is most effective, as it confirms the absence of HPV infection, which automatically implies an extremely low risk of cervical precancer/cancer. At the same time, positive test results cannot differentiate benign conditions from precancerous ones, and even more – from cervical cancer.

That is why we need to understand the strengths and weaknesses of each method of cervical examination (cytology, HPV testing, colposcopy, histopathology after colposcopic biopsy) in order to answer the most important question: what is the true state of the cervix: normal, HPV infected, precancerous, or cancer?

Let's try to evaluate, from the point of view of the objective data that we have, the key advantages and disadvantages of each of the main screening methods and confirmatory methods for diagnosing cervical pathology.

The advantages of cytology are well known, starting from the period of introduction into practical medicine of the original Papanicolaou classification. For more than a hundred years, cytology has transformed from a method for assessing the likelihood of cervical cancer to one of the main screening methods for diagnosing all cervical pathology [46]. The active implementation in recent decades of the methodology of liquid cytology and the Bethesda system [43] has led to a significant increase in the level of objectivity of this diagnostic method and simplification / standardization of the interpretation of cytological findings. However, the accuracy of cytology at the "lower level" for detecting high-risk carcinogenic HPV infection remains very low. Most high-risk infections have concurrent normal cytologic findings, and many minor cytological abnormalities are caused by low-risk carcinogenic HPV types or are unrelated to HPV [7].

At the same time, even evaluating the cytological image as characteristic of the presence of HPV, cytology

does not allow one to objectively predict the possibility of progression of the infection to precancer / cancer.

Large randomized controlled trials and observational studies have shown that HPV-based screening is significantly more sensitive for detecting cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and CIN3+ compared to cytological screening. A single negative HPV test provides more confidence in CIN2+ and CIN3+ than a single normal fluid cytology result, safely allowing longer screening test intervals. In addition, HPV-based screening is superior to liquid-based cytology (LBC) for detecting columnar epithelial lesions (eg, adenocarcinoma in situ) and for screening older women. Taken together, these results show that HPV-based screening can prevent more cervical cancer cases and deaths compared to cytology-based screening [47,48].

However, a disadvantage of HPV-based screening, noted by some authors, is its low specificity for detecting CIN2+, which results in more false positive screenings compared to cytology-based screening. The main reason for the lower specificity is that many HPV infections are transient and these short-term findings are associated with a low risk of CIN2+ over 5–10 years.

To increase the specificity of HPV screening and reduce unnecessary colposcopy, various triage strategies have been explored. One of the most commonly used sorting strategies is again cytology, with atypical squamous cells of uncertain significance (ASC-US) being the typical threshold for referral. Other triage strategies include the use of partial or full HPV genotyping of cervical specimens, as several studies have demonstrated a significant difference in CIN2+ risk between genotypes, with HPV type 16 being associated with the highest risk of CIN2+ [49].

Namely, predicting the immediate risk and subsequent outcome of infection is currently a serious problem in cervical screening. Three principles should be emphasized: the group of carcinogenic HPV types that require mandatory treatment should be defined as those that cause invasive cancer, not precancerous conditions (which can be caused by a much larger group of types). Thus, there is no clinical reason to test for HPV infections other than high-risk carcenogenic types [34,50,51]. Secondly, 13 (according to some sources 15) carcinogenic HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68), which highly differ in the strength of the carcinogenic effect: from uniquely strong (HPV 16) to marginal (for example, HPV 51) [50,52]. And thirdly, different types of HPV infection act independently of each other, and one type can remain in the cell while the other has already been eliminated [7]. It is well known that high-risk types are genetically related and limited to a few species groups within the HPV alpha genus. The first acquaintance with HPV occurs at a very young age with the onset of sexual activity. Therefore, the emerging HPV infection of the cervix or the process of reinfection is likely to end in self-elimination. At the same time, the longer HPV infection persists (remains detectable using one of the standard DNA/RNA tests), the greater the likelihood of a high long-term risk of precancer [7,53]. Lastly, we found no evidence that individual tracking of carcinogenic types is clinically useful. The exception is the individual identi-

fication of the HPV types with the highest carcerogenic risk, such as HPV 16 and/or HPV 18.

Nevertheless, the definition of HPV infection, even related to the infection of the highest risk of cervical precancer, is not the final point of diagnosis. Therefore, it is colposcopy with targeted biopsy of doubtful / aceto-white areas that is currently the best diagnostic / confirmatory method for cervical pathology [54].

We cannot but repeat that this recommendation applies specifically to colposcopy with targeted biopsy. At the same time, the issue of using an isolated, exclusively visual assessment of the cervix as a confirmatory diagnostic method remains one of the most controversial in cervical diagnostics. This is mainly due to two problems of colposcopy. Firstly, colposcopy remains an extremely subjective diagnostic method, in which the frequency of false negative results (missed cases of even squamous intraepithelial pathology / invasive cancer) ranges from 13 % to 69 % [55,56] and directly depends on the competence of a specialist. Secondly, and we have already talked about this, in a certain percentage of cases, cervical pathology is difficult to visualize during colposcopy due to its small size or localization into the cervical canal.

So, to obtain a clinical diagnosis, we primarily rely on the histopathological diagnosis obtained after a colposcopically controlled biopsy. Histopathology remains our reference diagnostic method, yet it is often misclassified at several levels. The histopathological definition of precancer is particularly prone to false positive "high grade lesions" (CIN2 and even CIN3/AIS) [7]. In addition, the biopsy itself, even obtained under colposcopic targeting, often leads to underdiagnosis and underestimation of the prevalence of precancerous cervical lesions [55]. Moreover, the majority of histopathological precancerous conditions are found in women with LSIL or questionable LSIL (i. e., ASC-US) and not in women with HSIL.

In any case, histology cannot accurately distinguish a cervix which is infected by HPV infection from a normal one.

Now let's try, after everything controversial and contradictory in cervical screening, to state all the most interesting positions in the interpretation of diagnostic methods, considering the possibility of their maximum simplified (for accessibility) standardization.

Thus, there is strong evidence supporting the combination of LSIL and HPV-positive ASC-US in the aspect of "cytological evidence of HPV infection" [47]. In general, ASC-US represents abnormal cytological findings, in most cases expressing diagnostic uncertainty between NILM and LSIL. However, this uncertainty can be eliminated by HPV testing for – NILM with a negative result for the presence of high carcinogenic risk HPV [58]. If HPV testing is used instead of cytology to determine infection, the most useful cytological features are those that allow suggesting the presence of a true precancer, namely HSIL or the ambiguous ASC-H [58]. Another complication to keep in mind is that less than 1 % of women receive a HSIL cytology result, and, for example, in screening programs in the United States, it is extremely rare that a cytology result is classified as invasive cancer [7,58]. Likewise, Atypical glandular cells (AGC) and Adenocarcinoma in situ (AIS) results are rarely reported, while remaining clinically useful.
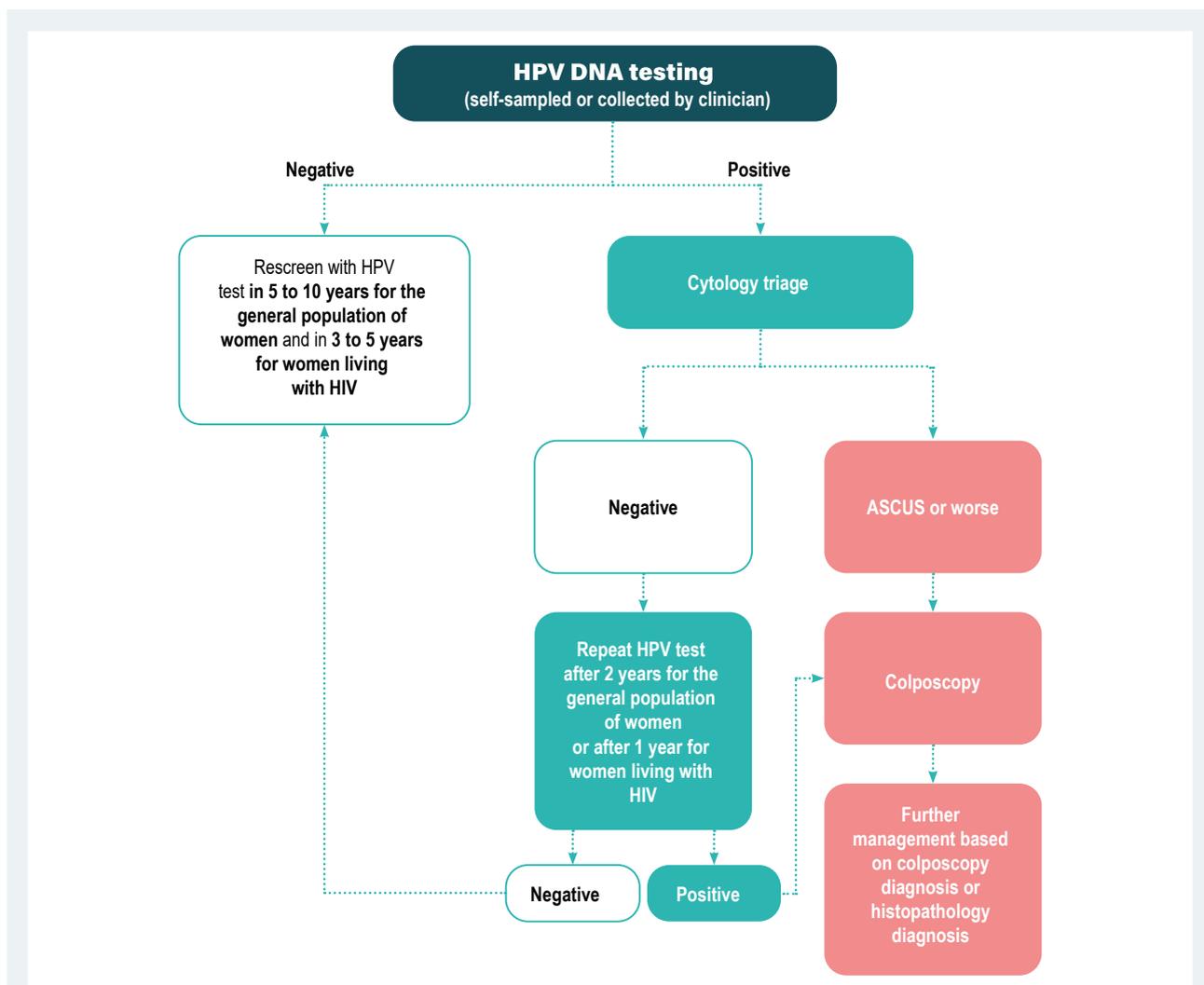
Fig. 1. Primary HPV screening and cytology triage followed by colposcopy (Screen, triage and treat approach) [69].

We cannot but recall that, in accordance with current recommendations, women with HSIL need urgent treatment, subject to the obligatory condition of a positive result for the current infection with high-risk carcinogenic HPV types [16].

It is in relation to the HPV positive patient management tactics that it is assumed that there is a general uncertainty that needs to be discussed and resolved. For example, according to the recommendation of the ASCCP, not all HPV-positive women need to do a colposcopically controled biopsy [16,59]. Findings from worldwide studies of invasive species of the cervical cancer, including adenocarcinoma, allow to propose that positive HPV16 and HPV18 (and possibly HPV45) genotyping results are the most often indicators for colposcopy and targeted biopsy for difinition subsequent management tactic [50,52]. At the same time, the value of ditection of other HPV types, even from the carcinogenic group, requires further study. Thus, according to current recommendations in the United States, women with identified genotypes of the highest risk (HPV16 and HPV18) directly sent for colposcopy, and the rest are retested after a year [16], as a rule, using the method of partial genotyping [60–62].

Thus, there is an urgent need to standardize the conduct of such a confirmatory diagnostic method as colposcopy. We are confident that clinical practice of colposcopy without targeted biopsy will continue to lead to missed cases of precancer / cancer. And this, from our point of view, is due to the lack of unified indications for referral for colposcopy. For example, patients with a persistent HPV-positive status or vice versa HPV-negative with an ASC-US cytological result. Of course, in these groups there is a risk of developing cervical precancer, but it is low and its colposcopic diagnostics can be difficult due to the inability to visualize it. Besides, to the best of our knowledge, there are currently no generally accepted recommendations (including the FDA) on what to do with women with questionable colposcopy results, including indications for HPV testing after colposcopy. To avoid creating an even larger group of women who are unreasonably referred for colposcopy, it is necessary to achieve an increase in colposcopic sensitivity, for example, standardization of colposcopic terminology and colposcopy techniques through multiple biopsies targeting areas of the acetowhite epithelium or the introduction of modern, using artificial intelligence models, methods for assessing the visual image [55,63,64].
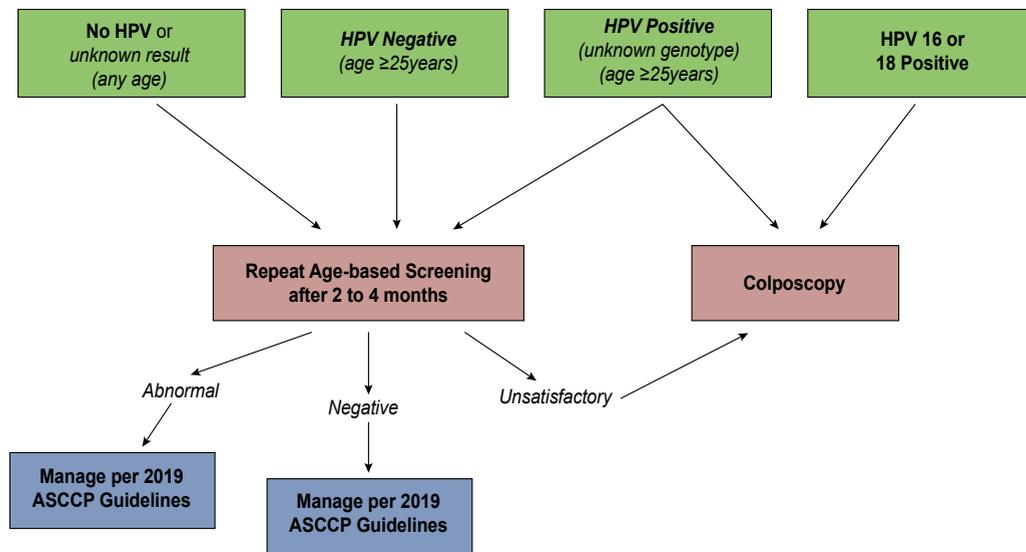
Fig. 2. Management patients with unsatisfactory result of cytology [74].

Nevertheless, there is evidence of the need to obtain a consistently negative HPV test to return women to the general screening group [65].

If only HPV-positive women were referred for colposcopy, pathologists could focus on identifying the histological evidence of squamous or glandular precancer without being distracted by the rather subjective histological features of HPV infection. So, according to the LAST criteria, it is CIN3 that should be accepted as a true precancer (as a practical compromise until a more specific biomarker is found) and p16 staining is recommended to differentiate from other precancerous conditions, primarily CIN2. However, there is a risk of overtreatment in CIN1 cases since many CIN1 lesions are p16 positive [7].

Thus, before proceeding to the presentation of the general conclusions that can be drawn on the basis of the above review, we consider it appropriate to briefly formulate the main positions. First, HPV testing is the most sensitive method for diagnosing HPV infection with a high risk of progression to precancer / cancer and thus already differentiate from a "normal cervix". All of the data that we obtained, with the exception of studies with a serious stastistic error [22,23], showed that HPV is more sensitive and has advantages in determining the prognosis for longer periods [29,66–68]. Most likely, exactly HPV testing in the near future will become the main method of primary cervical screening. In accordance with the recommendations of the WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition [69] HPV DNA testing is already recommended as a primary screening method for both Screen-and-treat and Screen, triage and treat approaches (*Fig. 1*). In same time, HPV DNA testing still remains only one of the alternative methods of cervical screening.

In this context, it is interesting that, in accordance with the recommendations of this manual [69], the possibility of self-sampling for HPV DNA testing is confirmed. In support of this thesis, the results of a meta-analysis by M. Arbyn et al. [70] who showed that the sensitivity to self-obtained sample for HPV testing was similar to physician-collected detection but demonstrated lower sensitivity to cervical intraepithelial neoplasia (CIN) with hybrid capture technology [71].

At the same time, from our point of view, the most promising strategy for the transitional period is the strategy of joint for HPV testing and cytology [72]. However, it should be taken into account that cotesting is an expensive strategy [7], and it has been quite convincingly shown that among HPV-negative women, the additional use of cytology reduces the diagnostic risks of developing cancer within 5 years very slightly (by about 0.003 %) [29]. HPV-negative cancer is rare, and therefore, with HPV-negative results, cytological positive results of co-tests in most cases represent testing errors or such cytological abnormalities as ASC-US [73]. In this regard, the Recommendations of the American Society for Colposcopy and Cervical Pathology (ASCCP, 2019) Consensus Guidelines [74], for example, on the clinical management patients with unsatisfactory result of cytology according to their age and HPV status, are of particular interest (*Fig. 2*).

In addition, this Guideline (ASCCP, 2019) recommends the use of a personalized approach, in contrast to the recommendations of the US Preventive Services Task Force (USPSTF) (2012), which proposed compliance with the principles of "equal management of equal risk", "risk thresholds", and "benchmarking" [75]. Based on new knowledge about the course of HPV infection and cervical carcinogenesis, these recommendations suggest that when choosing a patient management strategy, it is necessary to take into account not only the current results of screening tests, but also the results of previous screening tests and biopsies, taking into account personal factors such as age and immunosuppression status [74,76,77].

In this regard, there is a need to discuss an impact of HPV vaccination on our approaches to cervical screening.

While we are not yet in a position to discuss the significance of vaccination in terms of the evidence obtained (the first group of vaccinated women continues to be at screening age), it is already clear that vaccination will accelerate the shift in screening priorities from cytology to HPV testing [7]. This is primarily due to the fact that, while objectively reducing the overall frequency of precancer / cancer, vaccination does not contribute to a significant reduction in the total number of abnormal cytological results. Vaccine-targeted types are a minority of the total pool of HPV infections, including the pool of types presenting with ASC-US or LSIL, which are much more common than HSIL / AIS (specific cytological signs of precancer). Thus, in the vaccinated group against the background of a significant decrease in the level of true precancer, there will be slight fluctuations in the total number of cytological anomalies, which casts serious doubt on the need for cytological screening, at least in this group. Given the extremely low risk of developing cancer at an early age, screening before the age of 25 among vaccinated cohorts may not be necessary at all [7,78].

Conclusions

1. Most likely, it is a separate testing for HPV that will become the main monomethod for primary screening of the cervical pathology in the near future.

2. For the period until there are convincing data on the possibility of separate testing for HPV as the optimal method of screening the cervix, the most correct strategy, in our opinion, is the combined use of both HPV testing and cytology, at least as a triage method.

3. When evaluating the results of a cytology / histopathology study, we consider standardization and simplification of terminology in accordance with the Bethesda 2014 system update to be optimal.

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