Analysis of the Management of Patients with Altered Results in the HPV Self-test: Systematic Review of the Literature

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Análise do Manejo de Pacientes com Resultado Alterado no Autoteste de HPV: Revisão Sistemática da Literatura

Análisis del Manejo de Pacientes con Resultado Alterado en la Autoprueba de VPH: Revisión Sistemática de la Literatura

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ABSTRACT

Introduction: Human papillomavirus (HPV) self-testing has been increasingly adopted as a strategy for cervical cancer screening. However, the lack of consensus regarding clinical management after a positive result may lead to both undertreatment, with delayed diagnosis of precursor lesions or invasive cancer, and overdiagnosis with unnecessary interventions, negatively affecting quality of care and screening adherence. **Objective:** To compare different clinical management recommendations described in the literature for women with positive HPV self-test results in the context of cervical cancer screening. **Method:** A systematic review of the literature was conducted using the MEDLINE, Embase, and LILACS databases (2019–2024) to identify studies describing clinical management strategies following a positive DNA-HPV self-test. Two reviewers performed study selection independently, and the findings were synthesized narratively. **Results:** Seven studies were included, comprising a total of 56,580 participants. The publications were analyzed regarding management strategies adopted after positive HPV self-test results, including complementary screening methods, indications for additional diagnostic investigation, and follow-up intervals. A predominance of direct referral to colposcopy was observed for HPV 16 and 18 positive results, whereas for other high-risk genotypes, cervical cytology was frequently used as a complementary triage strategy to guide subsequent management. **Conclusion:** Management strategies based on HPV self-test results may contribute to optimizing cervical cancer screening and guiding care pathways across different healthcare settings.

Key words: Self-Testing; Human Papillomavirus Viruses; Mass Screening; Uterine Cervical Dysplasia; Uterine Cervical Neoplasms.

RESUMO

Introdução: O autoteste para o papilomavírus humano (HPV) tem se consolidado como estratégia de rastreamento do câncer do colo uterino. Entretanto, a ausência de consenso quanto ao manejo clínico após um resultado positivo pode resultar tanto em subtratamento, com atraso no diagnóstico de lesões precursoras ou câncer invasivo, quanto em sobrediagnóstico e intervenções desnecessárias, impactando negativamente a qualidade da assistência e a adesão ao rastreamento. **Objetivo:** Comparar diferentes recomendações de manejo clínico descritas na literatura para mulheres com resultado positivo no autoteste de HPV, no contexto do rastreamento do câncer do colo uterino. **Método:** Revisão sistemática de bibliografia pesquisada nas bases MEDLINE, Embase e LILACS (2019–2024) para identificar estudos que descrevessem estratégias de manejo clínico após resultado positivo no autoteste de DNA-HPV. A seleção foi realizada por dois revisores independentes e a síntese dos achados foi narrativa. **Resultados:** Sete estudos foram incluídos, totalizando 56.580 participantes. As publicações foram analisadas quanto às estratégias de manejo adotadas após resultados positivos no autoteste de HPV, contemplando métodos complementares de rastreio, indicação de investigação diagnóstica adicional e intervalos de seguimento. Observou-se predominância da indicação direta de colposcopia para resultados positivos para HPV 16 e 18, enquanto, para outros genótipos de alto risco, o teste de citologia oncótica foi frequentemente utilizado como estratégia de triagem complementar para definição da conduta subsequente. **Conclusão:** Estratégias de manejo baseadas no resultado do autoteste de HPV podem contribuir para otimizar o rastreamento e orientar o fluxo em diferentes contextos assistenciais.

Palavras-chave: Autoteste; Papilomavírus Humano; Programas de Rastreamento; Displasia do Colo do Útero; Neoplasias do Colo do Útero.

RESUMEN

Introducción: La autoprueba para el virus del papiloma humano (VPH) se ha consolidado como una estrategia de detección del cáncer de cuello uterino. No obstante, la falta de consenso sobre el manejo clínico tras un resultado positivo puede dar lugar tanto a un subtratamiento, con retraso en el diagnóstico de lesiones precursoras o cáncer invasivo, como a un sobrediagnóstico y a intervenciones innecesarias, lo que impacta negativamente en la calidad de la atención y en el compromiso con la detección. **Objetivo:** Comparar las diferentes recomendaciones de manejo clínico descritas en la literatura para mujeres con resultado positivo en la autoprueba de VPH, en el contexto de la detección del cáncer de cuello uterino. **Método:** Se realizó una revisión sistemática de la literatura en las bases de datos MEDLINE, Embase y LILACS (2019–2024) para identificar estudios que describiesen estrategias de manejo clínico tras un resultado positivo en la autoprueba de ADN-VPH. La selección fue realizada por dos revisores independientes y la síntesis de los hallazgos fue narrativa. **Resultados:** Se incluyeron siete estudios, con un total de 56 580 participantes. Las publicaciones fueron analizadas en relación con las estrategias de manejo adoptadas tras resultados positivos en la autoprueba de VPH, incluyendo métodos complementarios de detección, indicación de estudios diagnósticos adicionales e intervalos de seguimiento. Se observó un predominio de la indicación directa de colposcopía para resultados positivos de VPH 16 y 18, mientras que, para otros genotipos de alto riesgo, la prueba de citología cervical fue utilizada con mayor frecuencia como estrategia de selección complementaria para definir la intervención posterior. **Conclusión:** Las estrategias de manejo basadas en el resultado de la autoprueba de VPH pueden contribuir para optimizar la detección y para orientar el flujo en distintos contextos de atención sanitaria.

Palabras clave: Autoevaluación; Virus del Papiloma Humano; Tamizaje Masivo; Displasia del Cuello del Útero; Neoplasias del Cuello Uterino.

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INTRODUCTION

Cervical cancer remains an important public health problem in Brazil and around the world, accounting for one of the main causes of female morbidity and mortality[1]. The most prevalent histological types are squamous cell carcinoma and adenocarcinoma[1]. In Brazil, in 2026, this neoplasm presented the third highest incidence rate among women, excluding non-melanoma skin tumors, with an estimated risk of 17.59 cases for every 100 thousand women in the country[2]. On a global scale, over 660,000 new cases and approximately 348,000 deaths by cervical cancer were estimated in 2022[3].

Human papillomavirus (HPV) persistent infection is recognized as a relevant etiological factor for the development of cervical cancer, being present in up to 99% of cases, with more relevance of the 16 and 18 oncogenic subtypes[4]. Clinically, the illness may vary from asymptomatic phases to abnormal uterine bleeding, including post-coital bleeding, especially in more advanced stages[5].

Screening is a fundamental strategy to reduce cervical cancer incidence and mortality, being traditionally done through oncotic cytology (Pap smear test) or, more recently, the DNA-HPV test, which presents more sensitivity to detect precursor lesions[6]. National and international guidelines have progressively incorporated HPV testing as a primary screening method[6].

In this context, self-collection of cervicovaginal material for DNA-HPV testing has emerged as a promising alternative, especially for women who present access barriers to healthcare services, like refusal to undergo gynecological examination, geographic limitations, or social vulnerability[7]. Recent studies demonstrate comparable sensitivity between self-collection and collection performed by a healthcare professional to detect high-risk HPV[8].

However, despite the expansion of self-collection, significant heterogeneity has been observed in the clinical management recommendations after a positive HPV result, especially regarding follow-up, need for reflex cytology, colposcopy, or repeat testing. The lack of consensus may lead to both undertreatment, with delayed diagnosis of precursor lesions or invasive cancer, and overdiagnosis with unnecessary interventions, negatively affecting quality of care and screening adherence.

This article aims to compare different clinical management recommendations described in the literature for women with positive HPV self-test results in the context of cervical cancer screening.

METHOD

Systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)[9] guidelines, whose protocol was previously recorded in the International Prospective Register of Systematic Reviews (PROSPERO)[10] database under number CRD420251036733.

The research question was to investigate the different clinical management strategies recommended in the literature for women with positive HPV self-test results in the context of cervical cancer screening.

The PICO strategy was adopted to formulate the question, considering the population of interest (women with a positive HPV self-test) and comparison between different strategies for clinical management proposed in the literature, with a focus on follow-up recommendations after a positive test.

The bibliographical search was conducted on April 21, 2025, on the MEDLINE (through PubMed), Embase, and LILACS databases, including publications from January 2019 through December 2024. Controlled descriptors from Medical Subject Headings (MeSH) and *Descritores em Ciências da Saúde (DeCS)* were used, as well as keywords related to the theme, including "self-sampling", "Human Papillomavirus", and "uterine cervical neoplasms", combined using the Boolean operator AND. The complete search strategies used in each base are described in Chart 1. The search was limited to articles published in Portuguese and English.

The scope included randomized clinical trials and observational studies that contained clinical management protocols for women with a positive result on the DNA-HPV self-test from cervicovaginal samples, with a description of the recommended follow-up. The scope excluded studies with no defined management protocol, those that used exclusively vaginal or urinary samples, studies conducted exclusively in populations living with the human immunodeficiency virus (HIV)/Aids, and studies that used mRNA-HPV tests.

The study selection was conducted independently by two reviewers, by screening titles and abstracts using the Rayyan®[11] software. Disagreements were solved by consensus. After reading the texts in full, the eligibility criteria were confirmed and the reasons for exclusion documented. Additionally, the reference lists of the included studies were manually analyzed to identify additional relevant publications.

Data extraction was done through a standardized form that contemplated the following variables: author, publication year, study design, number of participants, type of HPV self-test (for example, Cobas® 4800, careHPV®, seqHPV™), clinical follow-up protocol, main assessed outcomes, and authors' conclusions. The highlighted information can be found in Chart 2, containing the summary of the articles used in

this systematic review and the chosen criteria for comparison.

No validated instruments were used to assess the risk of bias in the included studies, with each study's results being presented descriptively.

Additionally, the estimated prevalence of high-grade cervical intraepithelial lesions (CIN2+) per thousand women was described. For this calculation, the proportion of CIN2+ cases in relation to the total number of women screened (n) was multiplied by one thousand. Confidence intervals (CI) of 95% were estimated using the Wilson score interval method, recommended for presenting adequate coverage even for extreme proportions. The calculations were performed on R[12] software (version 4.4.1), using the *binom* pack (method = "wilson"). The estimated prevalences and their respective 95% CI were presented with two decimal places (Table 1).

Due to the heterogeneity of the studies' designs, self-test types, and clinical management protocols, the synthesis of results was done narratively, with studies grouped by self-test type and subsequent clinical algorithm.

RESULTS

A total of 715 records were identified in the electronic databases MEDLINE, Embase, and LILACS (Figure 1). The removal of 13 duplicated records was done using the Rayyan®[11] software, resulting in 702 titles and abstracts submitted to initial screening. Of those, 647 were excluded for not meeting the eligibility criteria regarding the publication period (2019–2024), type of study, or language.

Of the 55 articles assessed in the abstract reading step, 34 were excluded for not presenting clinical management protocols after a positive result in the DNA-HPV self-test. Thus, 21 studies were selected for full reading. After assessing the complete texts, 14 publications were excluded. Nine studies used HPV tests different from the DNA-HPV self-test or inappropriate collection methods, including mRNA-HPV tests or urinary samples. Three studies were excluded for including exclusively women living with HIV/Aids. Two studies presented outcomes incompatible with the objective of the review, characterized by qualitative approaches or a lack of a defined clinical management protocol. The studies' selection process is detailed in the flowchart presented in Figure 1, elaborated according to the PRISMA 2020[9] guidelines. At the end, seven studies were included in the present systematic review.

The seven studies comprised a total of 56,580 participants. Regarding methodological design, one study consisted of a cost-effectiveness analysis based on a randomized clinical trial; two were randomized clinical trials; one was an implementation interventionist study with a quasi-experimental design; one corresponded to the follow-up of a previously conducted randomized clinical trial; and two presented observational design, of which one was a prospective cohort and one a cross-sectional study.

Regarding geographic distribution, three studies were conducted in Europe (Sweden, Norway, and Greece), one in the United States, two in Asia (India and China), and one in Australia. Regarding the type of HPV self-test employed, four studies used the Cobas® 4800 HPV test, one assessed the hpVIR® test based on real-time polymerase chain reaction (PCR), one employed the careHPV® Test Kit, and one used the seqHPV™ Genotyping Test.

The trial by Aarnio et al.[13] used an HPV test capable of simultaneously detecting strains 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. In one branch of the study, a protocol was adopted in which positive HPV results indicated repeating the test after 3 to 6 months, with two consecutive positive results leading to colposcopy and oncotic colpocytology (CTO). Conversely, a negative

Chart 1. Search strategies utilized in the databases

Database	Utilized search strategy	Applied filters
MEDLINE (via PubMed)	("Self Sampling") AND ("Human Papillomavirus" OR HPV) AND ("Uterine Cervical Neoplasms" OR "cervical cancer")	Language: Portuguese and English; Period: 2019–2024
Embase	('self sampling') AND ('human papillomavirus' OR 'HPV') AND ('uterine cervical neoplasm')	Language: Portuguese and English; Period: 2019–2024
LILACS	("autocoleta" OR "self sampling") AND ("papilomavírus humano" OR "HPV") AND ("neoplasias do colo do útero" OR "uterine cervical neoplasm")	Language: Portuguese and English; Period: 2019–2024

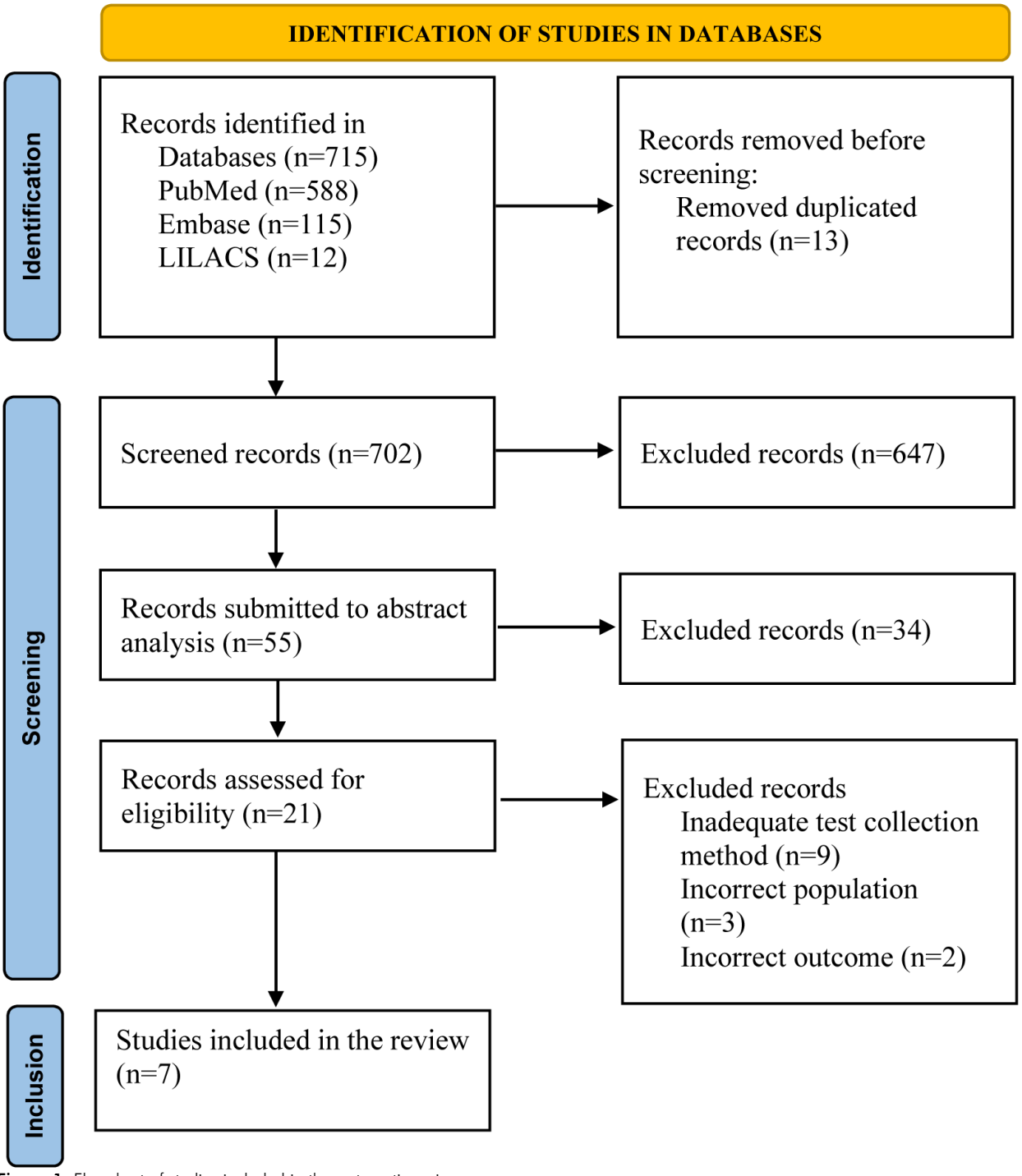

Figure 1. Flowchart of studies included in the systematic review
Source: Adapted from PRISMA[9].

HPV result indicated repeating the test after 5 years. In the comparative branch, the protocol used cervical cytology as the primary screening method.

In the group that used the HPV test as primary screening, 1,633 more tests were conducted, with 107 additional diagnoses of CIN2+, at a lower cost in comparison with the group that used cytology. In the branch where HPV testing was the screening standard, 7,997 women were tested, of which 501 presented two consecutive positive results for HPV. Among those, 175 were diagnosed with CIN2+, corresponding to an estimated prevalence of 21.88 cases per thousand women (95% CI: 18.90–25.33).

Aasbø et al.[14] followed the clinical recommendation of performing CTO after positive HPV 16 or 18 results. In that context, patients with any alteration in results, such as

Chart 2. Summary of articles used for the systematic review, and the chosen criteria for comparison

Author	Country	HPV Test	N	Design	Objectives	Results	Management after positive HPV
Aarnio et al.[13]	Sweden	hpVIR® (real-time PCR)	17,997	Cost-effective analysis of a randomized clinical trial	Compare the cost-effectiveness of self-collection for the DNA-HPV test with CTO in the primary screening of cervical cancer, in addition to estimating the cost of treatment and follow-up of CIN2+ cases	The self-collection for the DNA-HPV test presented an 8% larger participation in screening and a lower cost in comparison with CTO. For the Pap smear test, the cost per patient was 4.2 times higher in screening and 45% higher in the treatment of CIN2+	The positive HPV result indicates repeating the test in 3 to 6 months. If the next result is positive, CTO and colposcopy are indicated. Any negative result leads to repeating the test in 5 years (screening interval)
Aasbø et al.[14]	Norway	Cobas® 4800 HPV	218	Randomized clinical trial	Compare different strategies to increase cervical cancer screening in women whose screening was delayed by more than 10 years	In comparison to the strategy of sending reminders asking women to show up for an HPV test collected by a healthcare professional (control group), the strategy of sending a self-collection kit for an unsolicited DNA-HPV test to patients increased participation in 22.9% (95% CI: 20.7-25.2) and the strategy to provide a platform for patients to request it increased participation in 12.3% (95% CI: 10.3-14.2)	Positive HPV 16/18 results indicate colposcopy if CTO is LSIL or HSIL+, or indicate repeating the self-test in 12 months if CTO is negative. Positive results for other high-risk strains indicate colposcopy if HSIL+, repeating the self-test in 12 months if LSIL, or repeating the self-test in 24 months if CTO is negative. A negative HPV result indicates repeating the test in 5 years
Agorastos et al.[15]	Greece	Cobas® 4800 HPV	12,843	Cross-sectional observational study	Analyze the implementation of cervical cancer screening with self-collection for high-risk DNA-HPV testing and genotyping for HPV 16/18 or other oncogenic strains, and compare it with the current screening strategy used in Greece	The detection of high-risk HPV strains through self-collection was a promising method for cervical cancer screening, with a positive predictive value of 9.7% for CIN2+ among women with a positive high-risk HPV result. In women living in remote areas, this strategy may be even more beneficial, contrary to the current CTO screening strategy	Women with at least one positive result for high-risk oncogenic strains of HPV, that is, HPV-16 or HPV-18 or 12 more selected strains (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), were directly referred to colposcopy. It was not recommended to wait before repeating the HPV test after an initial negative result
Oommen et al.[16]	India	Care HPV Test Kit	1,170	Implementation interventional study	Identify the barriers faced by healthcare professionals and vulnerable populations in locations with limited resources to implement a screening program with the use of self-collection for DNA-HPV testing	The challenges found were a reduced number of trained colposcopy professionals, a lack of adequate infrastructure for gynecological exams, limited logistic capacity, and women's embarrassment during gynecological exams	A positive HPV result would indicate colposcopy for women in pre-menopause and CTO for women in post-menopause. From the results of these exams, the patients would be referred to thermoablation or cryotherapy. Whereas a negative result would indicate repeating the HPV test in 5 years

To be continued

Chart 2. Continuation

Author	Country	HPV Test	N	Design	Objectives	Results	Management after positive HPV
Song et al.[17]	China	*seqHPV™ Genotyping Test*	2,731	Prospective cohort	Based on self-collection for DNA-HPV testing, explore if genotype determination and p16 immunocytochemistry, in isolation or combined, can optimize the management of women with positive HPV and negative CTO	Genotyping for HPV subtypes 16 and 33 can optimize the management of women with HPV-positive and CTO-negative tests. Immunoassay with p16, in isolation or combined with genotyping, is more effective than isolated genotyping for optimizing the management of the same group of patients, detecting up to 83.1% of patients with CIN2+	Colposcopy was indicated for (1) patients with a positive HPV 16 or 18, (2) non-16 or 18 positive HPV results and positive inspection with acetic acid, and (3) positive HPV, negative acetic acid inspection and positive p16
Sultana et al.[18]	Australia	Cobas® 4800 HPV	1,769	Follow-up to a previous randomized clinical trial	Record the follow-up of cervical cancer screening in a previous randomized clinical trial. The study's objective was to determine if the self-collection for the DNA-HPV test would increase the participation of never-screened women or those with delayed screening (>5 years), in comparison with sending reminders to undergo CTO	After a 36-month follow-up, 19% of women who had never been screened and 9% of women with delayed screening (>5 years) returned the HPV test, revealing a higher participation rate in screening for the first group when compared to the second group	Women with a positive HPV 16 or 18 result were referred to colposcopy. For non-16/18 positive HPV results, CTO was recommended. A negative result or LSIL would indicate repeating the HPV test in 12 months, and an HSIL+ result would indicate colposcopy. In the second HPV test (after 12 months), one positive result associated with an altered CTO would indicate colposcopy. For initially negative HPV results, the recommendation was to repeat the test in 24 months
Winer et al.[19]	USA	Cobas® 4800 HPV	19,851	Randomized clinical trial	Compare the effectiveness of self-collection for the DNA-HPV test sent through the mail with the usual reminders for clinic screening to increase detection and treatment of CIN2+	The mailing of self-collection kits for DNA-HPV testing, in comparison with usual reminders, increased the detection of CIN2+ with a relative risk (RR) of 1.49 (95% CI; 0.61-3.64), and increased the treatment rate with a relative risk of 1.70 (95% CI; 0.67-4.32). Thus, there was no statistically significant difference among groups. However, the mailing of HPV self-tests increased adherence to screening in comparison to usual reminders (RR=1.51; 95% CI 1.43-1.60)	Negative or undefined HPV results recommended doing the Pap smear test. Patients with a positive non-16 or 18 HPV result were referred to do a co-test (Pap smear and HPV). Whereas positive HPV-16 or HPV-18 results were immediately referred to colposcopy

Captions: CTO = oncotic colpocytology; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; HPV = human papillomavirus; CIN2+ = cervical intraepithelial neoplasia grade 2 or higher; CI = confidence interval.

low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL+), would be referred to colposcopy, while those with a negative CTO would be advised to repeat the HPV test after 12 months.

The positive results for other high-risk strains (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) would also require CTO, whose result would guide management. Patients with HSIL+ would be directly referred to colposcopy, those with LSIL would be guided to repeat self-testing in 12 months, and those with a negative result should repeat the self-test in 24 months. Among the 933 screened women, 33 (3.5%) presented CIN2+ after a minimal follow-up of 15 months, with a prevalence estimated in 35.37 cases of CIN2+ per thousand women (95% CI: 25.29-49.26). This value is high and in line with the sample profile, composed of women with delayed screening for more than 10 years in Norway.

The observational study by Agorastos et al.[15] recommended direct follow-up to colposcopy for patients with a positive result for HPV 16 or 18, as well as for those with a positive result for other high risk strains (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Among the 12,843 patients screened using the HPV test, 75 CIN2+ cases were identified, which corresponds to CIN2+ prevalence of 5.84 per thousand women (95% CI: 4.66-7.31).

The pragmatic implementation trial (quasi-experimental) directed by Oommen et al.[15] used an HPV test capable of detecting 13 oncogenic strains (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The management of positive results was based on the World Health Organization guidelines[20], considering the pre- or post-menopausal state of patients. Women in pre-menopause were referred directly to colposcopy after a positive HPV result, whereas patients in post-menopause went through an initial screening with CTO. In case of atypical squamous cells of undetermined significance (ASC-US) or more advanced results, colposcopy was indicated, while negative cytologies led to repeating the HPV test after five years.

During the average 8-month follow-up, 1,170 women were screened, and 6 presented lesions detected by colposcopy. The estimated prevalence of detectable CIN2+ lesions in this group was 5.13 cases per thousand women (95% CI: 2.35-11.14).

The prospective cohort study conducted by Song et al.[17] assessed the management of patients based on HPV genotyping results, visual inspection with acetic acid (VIA), and immunoassay of protein p16. The direct follow-up to colposcopy was indicated to three groups of patients: (1) women with a positive result for HPV 16 or 18 subtypes; (2) patients with a positive non 16/18 HPV associated with a positive VIA; and (3) patients with positive HPV, negative VIA, and positive p16 test.

Initially, the patients were submitted to cervical cytology, but the cases with altered results were excluded from the analysis. The CIN analysis scope was restricted to patients with positive HPV and negative cytology, totaling 2,731 women in this category. Among those, 136 presented CIN2+. Considering the total of 73,537 women screened with valid HPV results, the prevalence of CIN2+ associated with positive HPV and negative cytology was estimated in 1.85 cases per thousand women (95% CI: 1.56-2.19).

The study conducted by Sultana et al.[18] recommended direct referral to colposcopy for positive HPV-16 or 18 results. Among the assessed women, 27 presented this condition and accepted undergoing colposcopy with biopsy. Of those, 9 (33.3%) were diagnosed with high-grade lesions (CIN2+).

For positive HPV results for non-16/18 oncogenic strains (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), the suggested protocol was to perform CTO, whose result should guide clinical management. Women with negative cytology or LSIL were recommended to repeat the HPV test after 12 months, while those with HSIL+ were referred to colposcopy.

Among the 103 women who tested positive to non-16/18 HPV oncogenic strains, 93 patients accepted undergoing CTO. Of those, 5 (4.58%) presented HSIL results and 1 (0.97%) had cytology suggestive of squamous cell carcinoma. The five women with HSIL were submitted to colposcopy with biopsy, which identified 3 CIN2+ cases and 1 CIN-NOS (not otherwise specified cervical intraepithelial neoplasia) case. In total, the study detected 15 CIN2+ lesions across a 36-month follow-up. Based on 1,769 screened women, the prevalence of CIN2+ lesions was estimated in 8.48 cases per thousand women (95% CI: 5.15-13.94).

The clinical trial by Winer et al.[19] followed the recommendations by the American Society for Colposcopy and Cervical Pathology (ASCCP)[21] to manage cervical alterations. These guidelines ground direct referral to colposcopy for positive HPV 16 or 18 results, a conduct with a BII[21] level recommendation.

For patients with positive results for oncogenic non-16/18 strains, the study recommended a CTO or HPV co-test (CTO and HPV test simultaneously conducted by healthcare professionals). In cases of negative cytology, it was indicated to repeat co-testing after 1 year. Conversely, results classified as HSIL, as well as ASC-US or LSIL associated with positive HPV, indicated immediate referral to colposcopy. In total, 19,851 patients were screened across 12 months, with 20 CIN2+ cases detected, of which 19 were properly treated up to 12 months after detection. From this data, it is possible to estimate a

prevalence of 1.01 CIN2+ cases per thousand women (95% CI: 0.65-1.56).

DISCUSSION

The present systematic review identified and analyzed seven studies published between 2019 and 2024 that addressed clinical management strategies after positive HPV self-test results. The selection reflects the utilized methodological criteria, centered specifically in post-test clinical management protocols, and with presentation of data related to detecting high-grade cervical lesions. Despite this standardization, a relevant heterogeneity was observed in the studies' design, epidemiological profile of assessed populations, and healthcare contexts, which limits direct comparisons and universal extrapolation of the findings.

Generally, the analyzed studies converge to a predominant pattern of management stratified by genotype, especially regarding HPV-16 and HPV-18 infection. In four of the seven publications, positive results for those subtypes led to direct referral to colposcopy, with no need for reflex cytology. This conduct is supported by the high association of these genotypes with CIN2+ lesions and invasive cervical cancer, as demonstrated in evidence consolidated in the literature[22–24]. The adoption of immediate colposcopy, in these cases, aims to reduce diagnostic delays and minimize the risk of progression of precursor lesions.

Conversely, CTO demonstrated having a relevant complementary role in the management of patients with positive non-16/18 HPV, especially in five of the studies included in this review. Although isolated cytology can, in certain scenarios, delay colposcopy investigation, its utilization as a risk stratification tool allowed to differentiate conducts, avoiding unnecessary colposcopies in women with lower risk and directing early interventions to those with significant cytological alterations (persistent ASC-US, LSIL, or HSIL). Thus, when employed in a reflex and integrated way to the HPV test result, CTO contributes to optimizing the diagnosis flow and rational use of resources.

Regarding follow-up after negative results in the HPV self-test, variability was observed in the recommended intervals, ranging from 24 months to five years. These guidelines are consistent with the low probability of CIN2+ development in women with no detectable infection of oncogenic HPV, as demonstrated by previous longitudinal studies[23]. However, the lack of standardization reinforces the need for clearer guidelines that are adapted to the local context, considering factors like screening coverage and access to the healthcare system.

The findings of this review are in line with classical recommendations, as the ones described by Wentzensen et al.[24] and Castle et al.[25], who support direct colposcopy for HPV-16/18 and reflex cytology for other high-risk genotypes. The present study strengthens this evidence by incorporating more recent data and by specifically focusing on the HPV self-test scenario, a strategy still in consolidation in many countries.

However, substantial differences between the analyzed protocols have been observed. Less interventionist strategies, like repeating the test in 3 to 6 months after a positive result, as described by Aarnio et al.[13], contrast with more aggressive approaches like the direct indication of colposcopy after a positive HPV result proposed by Agorastos et al.[15]. These discrepancies seem to reflect not only differences in the prevalence of CIN2+ among the studied populations but also variations in access to healthcare services, installed facilities for colposcopy, and

Table 1. Estimated prevalence of CIN2+ per thousand women in the included studies

Author (Year)	Number of participants included (n)	CIN2+ cases	Prevalence/thousand (95% CI)
Aarnio et al.[13]	7,997	175	21.88 (18.90 – 25.33)
Aasbø et al.[14]	933	33	35.37 (25.29 – 49.26)
Agorastos et al.[15]	12,843	75	5.84 (4.66 – 7.31)
Oommen et al.[16]	1,170	6	5.13 (2.35 – 11.14)
Song et al. [17]	73,537	136	1.85 (1.56 – 2.19)
Sultana et al.[18]	1,769	15	8.48 (5.15 – 13.94)
Winer et al.[19]	19,851	20	1.01 (0.65 – 1.56)

Captions: n = number of screened patients in each study; CIN2+ = cervical intraepithelial neoplasia grade 2 or higher; CI = 95% confidence interval calculated by Wilson score interval.

priorities of screening systems. In contexts with limited access to colposcopy, phased strategies can be more viable, while scenarios with greater availability of resources favor more immediate approaches.

In the Brazilian context, these findings are particularly relevant. Brazil faces historical challenges related to the irregular coverage of cervical cancer screening, to the reliance on cytopathologic tests as the primary method, and access barriers to specialized services. The incorporation of the HPV self-test, associated with clear protocols for post-test management, can represent a promising strategy to amplify screening, especially in unassisted populations. However, the lack of international consensus on management after positive results reinforces the need for adaptations based on the epidemiological reality and local infrastructure.

Among the limitations of this review, we highlight the reduced number of eligible studies, methodological heterogeneity, and the need for indirect calculation of CIN2+ prevalence in some publications, due to the lack of explicitly presented data. Furthermore, the variability in the utilized HPV tests and follow-up criteria impairs direct comparisons between the studies.

Despite these limitations, the main potential of the present review is its critical synthesis of contemporary strategies for post-HPV self-test management, highlighting emerging patterns and relevant knowledge gaps. The results have implications for clinical practice by making the management models based on risk stratification explicit, and for further research, by indicating the need for prospective studies that assess clinical outcomes, cost-effectiveness, and patient adherence in different care contexts.

CONCLUSION

The analyzed studies indicate that the management of patients with positive HPV-16 or HPV-18 results tends to benefit from direct referral to colposcopy. In contrast, positive results for other HPV oncogenic strains may be adequately managed through complementary strategies, such as reflex oncotic colpocytology, with risk stratification and definition of clinical follow-up.

These findings contribute to clinical practice by reinforcing management models based on risk in the context of HPV self-testing, favoring opportune interventions in women at greater risk and avoiding unnecessary procedures in lower risk populations. Furthermore, the results from this review support the organization of cervical cancer screening flows, especially in scenarios with access restrictions to specialized services, such as colposcopy, enabling adaptations to local realities without compromising the effectiveness of the screening.

CONTRIBUTIONS

Both authors have substantially contributed to the study design, data acquisition, analysis, interpretation, wording, and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All the contents associated with the article are included in the manuscript.

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