

Development of evidence-based guidelines for follow up of women treated for cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) in Italian screening programmes

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Background: The Italian Group for Cervical Cancer Screening (GISCi) promoted the update of recommendations for post Cervical Intraepithelial Neoplasia grade 2 or 3 (CIN2/3) treatment follow up. **Methods:** A multidisciplinary panel including all the professionals involved in cervical cancer screening and CIN treatment was set up. Systematic reviews have been conducted searching in PubMed. The GRADEpro online tool was used for: defining and prioritizing clinical questions framed in PICO (Population Intervention Comparator Outcomes); defining and scoring outcomes as critical, important or not important; synthesizing results of the systematic reviews in Evidence to Decision tables and to grade recommendations. **Results:** A systematic review identified the main prognostic factors, but these have almost no impact in HPV-negative women. Six questions were prioritized for the first phase: 3 about the test (Pap, HPV-DNA or Pap + HPV co-testing or co-testing + colposcopy); 1 about the number of episodes before returning to screening; 2 about the timing of episodes. For the test accuracy direct evidence was available, while for other questions mostly indirect evidence was retrieved in systematic reviews. **Conclusions:** The panel recommends HPV test or co-testing (conditional either the two), but not Pap test as follow up test (strong). Colposcopy can be added to assess surgical outcomes (conditional either yes or not). Two episodes instead of one, before referring women to regular screening, should be preferred (conditional). The first episode should be 6 months (vs. 12) after treatment (strong), in order to avoid progression of undiagnosed prevalent invasive cancers; the interval between first and second episode may be either 6 or 12 months (conditional).

Keywords

Cervical cancer; Cervical intraepithelial neoplasia (CIN) grade 2 or grade 3; Post-treatment follow up; Test of cure; Human papillomavirus; Guidelines; Evidence-based medicine

1. Background

Cervical screening aims to prevent cervical cancer through the identification and treatment of pre-invasive lesions, cervical intraepithelial neoplasia grade 2 and grade 3 (CIN2 and CIN3), and adenocarcinoma in situ (AIS) [1, 2]. The treatment of CIN2 and CIN3 by conization, Loop Electrosurgical Excision Procedure (LEEP), a Large Loop Excision of the Transformation Zone (LLETZ), or ablative treatment is a conservative treatment of the uterine cervix and organ function [2], although adverse obstetric outcomes (preterm birth, abortion and still birth) have been reported in the literature in treated women [3].

Screening programs reduced the incidence of cervical cancer in most industrialized countries. In Italy, in 2018 it has been estimated that about 3100 cancers have been diagnosed for an estimated crude incidence rate of 10.2/100,000 [4], while it is estimated that the annual number of CIN2+ treated is between 7000 and 15,000 [5]. The post-treatment relapse rate reported in the literature ranges from 5% to 20% [6], with Italian studies reporting mostly 10% [7–9]. Furthermore, these women remain at higher risk for developing CIN and cancer for a long time [10–12]. The purpose of the follow-up of women treated for CIN2 and CIN3 is the identification of relapses or new lesions possibly still in a pre-invasive phase to prevent the onset of invasive cancers.

Cervical cancer screening guidelines are provided by the European Commission [13] through general recommendations and the more specific recommendations are then reported by the European guidelines for quality assurance in cervical cancer screening [14, 15] and by national documents [16, 17]. Nevertheless, these documents do not give any de-

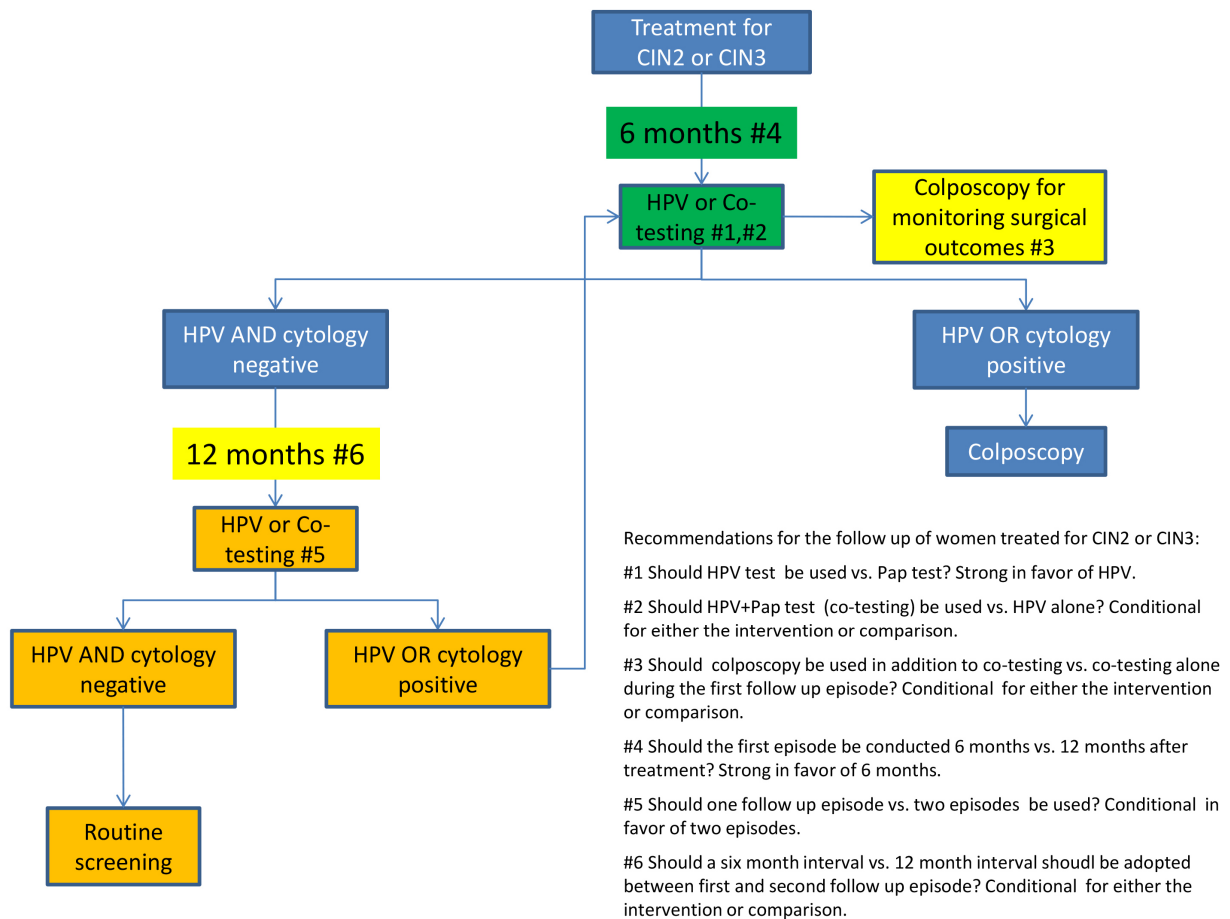


Fig. 1. Flowchart for management of women treated for CIN2 or CIN3. Green boxes represent strong recommendations; orange conditional recommendation in favor; yellow conditional recommendations for either the two; blue boxes are steps and/or decisions that are not topic of the present recommendations.

tail on how to follow up women after treatment for CIN2-CIN3. It is worth noting that in Italy about one third of the colposcopy activity in screening programmes is dedicated to the post treatment follow up [18].

The main questions that should be addressed to define the best management for following up women treated for CIN2 and CIN3 are: which test or combination of tests should be used, how many follow up episodes and at which interval should a woman undergo before she should return to a regular screening program.

Based on previous guidelines [19–23], the tests that can be used are HPV testing for high-risk types, Pap smear and colposcopy, combined or stand alone. While the number of follow up episodes proposed by the most recent guidelines is two [21], some pilots using only one episode are ongoing [24, 25]. Finally, for the interval from treatment to the first follow up episode, as well between first and second episodes, 6 or 12 months have been proposed [20].

The clinical questions about which and how many tests and when should be done have been combined to depict a potential management flow chart (Fig. 1) and to frame six PICO

(population, intervention, comparison, outcome) questions (Table 1).

In this paper we present the methodology adopted to frame and answer these six questions and the recommendations given by a multidisciplinary working group promoted by the Italian Group on cervical cancer screening (GISCi).

2. Methods

2.1 Population and setting

The clinical questions focus on women treated for CIN2 and CIN3. Follow up of women treated for AIS is out of the scope of these recommendations.

The recommendations are developed from an organized screening point of view, but they are applicable to an opportunistic screening setting as well.

Given the organized screening setting, recommendations are mostly focused on women aged 25 to over 70. In fact, although organized screening programs do not invite women over 64, treatment of CIN2 and CIN3 and post treatment follow up can last beyond this age.

2.2 Panel constitution and conflict of interest management

In 21 May 2015, the GISCi assembly decided to develop new guidelines on post treatment follow up of CIN2 and CIN3. A call for experts willing to participate to the panel and evidence review was launched. The GISCi Coordinating committee assessed the curricula and conflict of interests of the applicants, assuring that all the professionals involved were represented and managed conflict of interests according the following criteria: disclosure of all the possible conflicts, if the conflict was considered relevant and potentially impacting the participant was excluded from voting but not from discussion, if the conflict was considered serious the participant was excluded from discussion, finally if the conflict was not manageable the application was refused; the first three levels of conflict were evaluated specifically for each question, while the last type of conflict implied the exclusion from the whole project.

The panel included gynecologists, pathologists and cytopathologists, molecular biologists, midwives, epidemiologists, public health professionals and decision makers.

2.3 Systematic reviews

2.3.1 Search strategies and data sources

A first systematic review has been conducted to clarify the role of prognostic factors and inform eventual subgroup considerations. We adopted a Population Exposure Comparison Outcome (PECO) [26] frame to guide the search (Table 1). Other six systematic reviews have been conducted to inform the six clinical questions. Population Intervention Comparison and Outcomes are reported together with search string in Table 1. The systematic reviews were conducted uniquely on PubMed and were all based on a wide search string that provided the pool of relevant papers. Within this pool the question on specific inclusion and exclusion criteria were then applied. The search strategy was based on a previous systematic review by Kocken *et al.* [27] published in 2012 and including papers from 2003 to 2011, but inclusion criteria were adapted to the six PICO's and the prognostic question; the search update covered from 1 January 2011 to 31 August 2016, while the complete search included papers published from 1 January 2003 to 31 August 2016.

2.3.2 Inclusion criteria

For all studies it was necessary that follow up tests were at least cytology and HPV test for high risk virus types, the first episode was 12 months or less since treatment. Exclusion criteria were: population exclusively or selected to be at high risk of HIV infection, women treated for micro-invasive cancers or adenocarcinoma in situ, VAIN; women prevalently younger than 25; ablative treatment, non-surgical treatments for CIN (i.e., chemo or radiotherapy).

For the diagnostic questions (1, 2 and 3): studies were included if the outcome was assessed with colposcopy-guided or random biopsy in all women or at least in all women testing positive to one of the two tests.

Search results were screened for relevance by one re-

viewer and then full text were analyzed by two independent reviewers to assess the question of specific inclusion and exclusion criteria. Discordant judgements were resolved by consensus examining the papers with a third reviewer.

The process of identification, screening, and inclusion is summarized in Fig. 2.

2.3.3 Data extraction

For each study, participants, type of treatment, setting, mean age, follow up duration and timing, characteristics of the tests, colposcopy use and type of assessment, CIN2 or worse (CIN2+), CIN3 or worse (CIN3+), and cancers, test results of women with and without outcomes were extracted; also ascertainment bias adjusted sensitivity and specificity estimates were extracted if provided by the authors. Any subgroup analysis proposed by the authors was extracted.

2.3.4 Risk of bias and grading the certainty of evidence

To assess the risk of bias of each single study, we adopted the QUADAS2 (Quality Assessment of Diagnostic Accuracy Studies) tool for all the diagnostic studies [28]. For studies reporting long term outcomes (not cross-sectional diagnostic accuracy only) we used the ROBINS-I for non-randomized studies [29].

For each outcome, descriptive statistics of the studies and included women were summarized in the summary of finding tables. Meta-analytic estimates of sensitivity and specificity were computed; using the observed average prevalence of disease, we estimated the expected number of false positives and true positives, false negatives and true negatives; estimates and relative confidence intervals were computed using the "midas" package in STATA 13.0. Cumulative incidence and relative risks were also computed for long term outcomes.

According to GRADE criteria, evidence can be downgraded from high to moderate, low or very low considering the study design (here we considered double testing and cohort studies adequate as randomized studies for the included questions), risk of bias, indirectness, reproducibility/heterogeneity of results, precision of the estimates, presence of publication bias. On the contrary, it can be upgraded if the association is particularly strong, in the presence of dose response effect or of known biases going in the direction of underestimating the effect [30].

2.4 Evidence to decision framework

The GRADE framework for diagnostic has been adopted for questions 1, 2, and 3, while management framework has been adopted for the 4, 5, and 6 questions [31].

Briefly the evidence to decision framework guides the panel in the judgement about evidences on desirable and undesirable effects, certainty of the evidence, values given to the outcome by women, costs, equity, feasibility and acceptability of the intervention compared to the standard test or management.

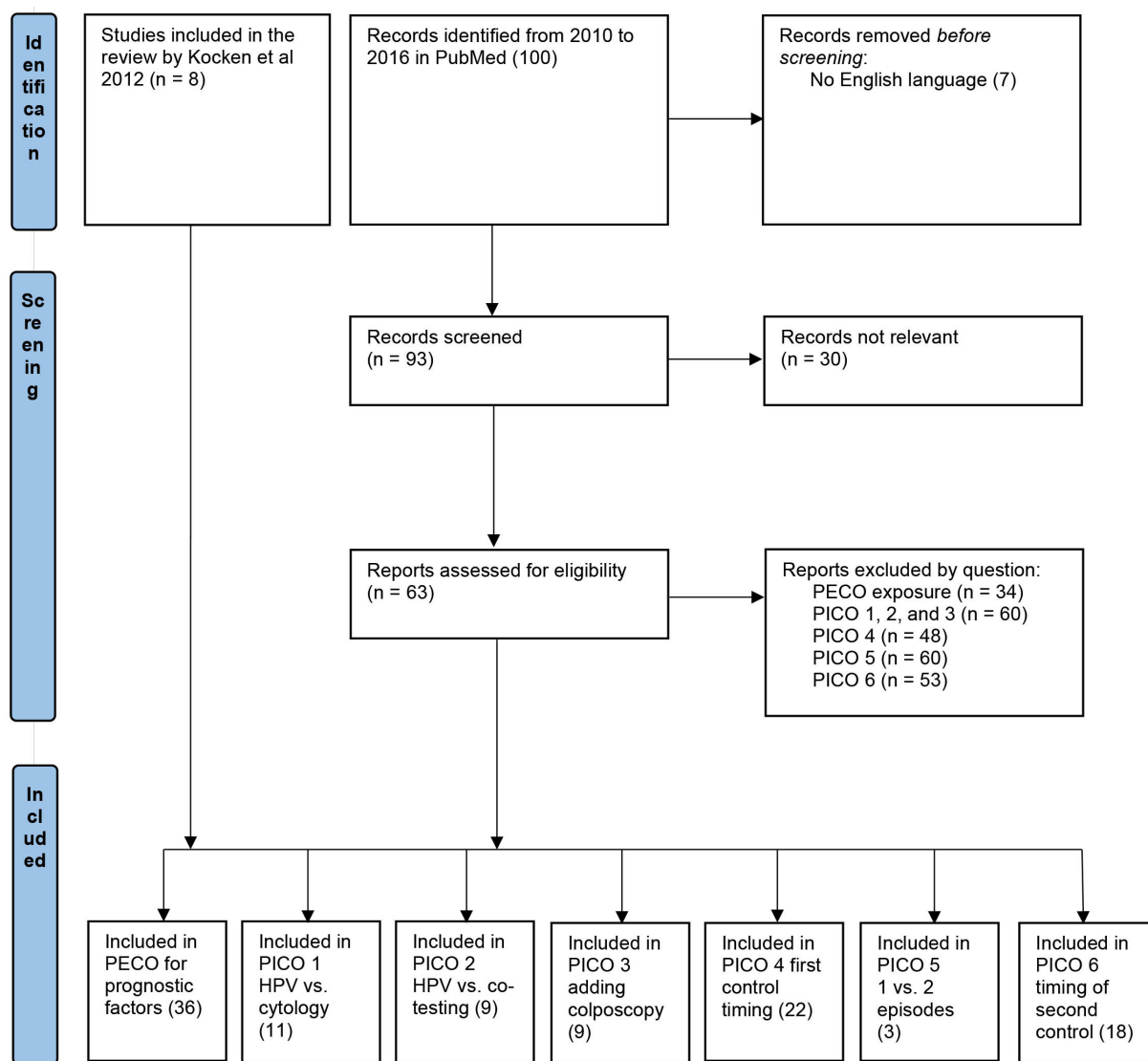


Fig. 2. PRISMA flow diagram for literature identification, screening and inclusion in the 6 PICOs and one PECO used for the guidelines for follow up of women treated for cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) in Italian screening programmes.

3. Results

3.1 Prognostic factors

Sixteen primary studies [9, 32–46] and 4 systematic reviews [47–50] were included for the role of surgical margins, including one systematic review (summarizing 14 primary works) focusing on the stratified analyses by HPV status that was considered particularly relevant by the panel. Thirteen papers were included for women’s age [9, 32, 33, 37, 40, 42, 45, 51–56], five for the underlying cytology [34, 41, 45, 55, 57] four for viral load [34, 45, 54, 58], seven for grade of CIN [8, 9, 33, 36, 37, 57, 59], and nine for HPV type [8, 9, 34, 41, 51, 59–62].

The risk of CIN2+ resulted 4 to 11 times lower in women with clean margins compared to positive margins. The difference was appreciable mostly in women HPV-positive at first follow up episode, while in HPV-negative women it was low independently from margin status.

CIN2+ were two times more frequent in women over 50. Results regarding the grade of lesion are not consistent with some studies reporting similar risk [8, 36] and other reporting higher risk in CIN3 [8, 9, 33, 37, 57]. Risk is also higher for HPV 16 persistent infection, high viral load and women with high grade cytology before treatment.

In general, all prognostic factors were important in HPV-positive women, while the risk was low independently from the other factors in HPV-negative women. This finding implies that, if HPV test is used in first follow up episode, the management of HPV-negative women should not be influenced by the presence of other prognostic factors. This applies to all the following health questions, except question 4, i.e., the interval between treatment and first follow up episode, because this decision is made before the assessment of HPV infection status.

Table 1. PICO (Population, Intervention/Exposure, Comparison, Outcomes) framing of health question and string search.

Question	Population	Intervention/exposure	Comparison	Outcomes	Search string
Prognostic factors	Women treated for CIN2 or CIN3	Affected margins in HPV-positive Affected margins in HPV-negative Age >50 High viral load Cytology low grade HPV type 16 Treated for CIN3	Clean margins in HPV-positive Clean margins in HPV-negative Age ≥50 Low viral load Cytology high grade HPV type non-16 Treated for CIN2	Cumulative risk of CIN2+ (at least 24 months follow up)	
#1 and #2 which test	Women treated for CIN2 or CIN3	HPV test	Pap test	End point CIN2+ (or CIN3+) reference test histology: false positives, false negatives, true positives, true negatives; number of ascertainment; invasive cancers	("Cervical Intraepithelial Neoplasia" [Mesh] AND ("Neoplasm Recurrence, Local"[Mesh] OR "Neoplasm, Residual" [Mesh]) AND ("follow up" [Text Word] OR "prediction" [Mesh] OR "Neoplasm Recurrence, Local/prevention and control" [Mesh])) AND (english [Filter])
#3 add colposcopy		Co-testing (HPV + Pap test) Add colposcopy to co-testing	HPV test Co-testing (HPV + Pap test)		
#4 first interval	Women treated for CIN2 or CIN3	First episode of follow up 6 months after intervention	First episode of follow up 12 months after intervention	Cancer detected at first episode or diagnosed between treatment and first episode Positivity at first episode Cumulative incidence of cancer;	
#5 number of episodes	Women treated for CIN2 or CIN3 and negative at first follow up episode	One negative follow up episode before returning to screening	Two negative follow up episodes before returning to screening	Cumulative incidence of CIN2+; cumulative incidence of CIN3+; Number of follow up episodes; Number of colposcopies	
#6 second interval		6 month interval between first and second follow up episode	12 month interval between first and second follow up episode	Invasive cancer detection rate; Number of colposcopies	

Table 2. Summary of finding table for questions on diagnostics.

Accuracy parameter	N studies N patients	Design	Factors downgrading the certainty	Other factors	Intervention	Comparison	Intervention	Comparison	Difference	Quality of evidence
PICO #1 HPV vs. Pap test										
Sensitivity	11 studies 2415 patients	Cross-sectional and cohort	None	Strong association	93% (89% to 96%)	79% (72% to 84%)	False Negatives: 5/1000 (3 to 9)	False Negatives: 17/1000 (13 to 22)	12 less per 1000	⊕⊕⊕⊕ high
Specificity			Lack of generalizability	Strong association	78% (76% to 79%)	81% (80% to 83%)	False Positives: 207/1000 (190 to 224)	False Positives: 173/1000 (158 to 189)	34 more per 1000	⊕⊕⊕⊕ high
PICO #2 Co-testing vs. HPV test										
Sensitivity	9 studies 2100 patients	Cross-sectional and cohort	None	Strong association	96% (92% to 98%)	93% (88% to 96%)	False Negatives: 3/1000 (1 to 7)	False Negatives: 6/1000 (3 to 10)	3 less per 1000	⊕⊕⊕⊕ high
Specificity			None	Strong association	70% (68% to 72%)	77% (75% to 79%)	False Positives: 278/1000 (259 to 297)	False Positives: 208/1000 (191 to 226)	70 more per 1000	⊕⊕⊕⊕ high
PICO #3 Co-testing + colposcopy vs. Co-testing										
Sensitivity	5 studies 546 patients	Cross-sectional and cohort	Imprecision		100%	98% (90% to 100%)	False Negatives: 0/1000	False Negatives: 2/1000 (0 to 10)	2 less per 1000	⊕⊕⊕ moderate
Specificity			None	Strong association	0%	71% (67% to 75%)	False Positives: 898/1000 (889 to 906)	False Positives: 260/1000 (224 to 298)	638 more per 1000	⊕⊕⊕⊕ high

False negatives and False positives are estimated based on pooled estimated sensitivity and specificity at the prevalence of 8% of CIN2+ for questions #1 and #2, and and 9.3% for question #3.

⊕⊕⊕⊕: high; ⊕⊕⊕: moderate; ⊕⊕: low; ⊕: very low.

3.2 Type of test (recommendations 1 and 2)

The update produced 93 papers; after screening for relevance, 63 were evaluated in full text. Three papers [34, 36, 42] were selected and added to the 8 included [8, 51, 63–68] in the Kocken review [27], for a total of 11 papers available for the comparison between HPV and Pap-test, and 9 papers available for the comparison between co-testing and HPV test alone [8, 42, 51, 63–68].

In the first comparison pooled sensitivity was 93% (95% CI 89–96) and 79% (95% CI 72–84) for HPV and Pap test, respectively, while specificity was 78% (95% CI 76–79) and 81% (95% CI 80–83) for HPV test and Pap test, respectively (Table 2). The panel considered that the desirable effects are moderate and the undesirable effects are small and the balance is in favor of HPV. The panel noted that specificity is strictly dependent from disease prevalence, so sensitivity estimated in a given setting should not be applied to another with different prevalence, to estimate false positives and positive predictive value. Evidence on accuracy was graded as high because it was direct, the single studies had moderate risk of bias, but overall the results were precise and no heterogeneity was observed and the effect was strong, i.e., the direction was very unlikely to be reverse both for sensitivity and specificity. Downstream consequences of the test were considered to be moderately certain since direct effects of the test are negligible, management (colposcopy if positive, follow up if negative) is moderately certain as well as the consequences of false positive and false negative in the long term (i.e., risk of developing a cancer for false negative and having unneeded colposcopy for false positive with small risk of unnecessary treatments if false positive histology). Despite a systematic review of cost effectiveness was not conducted, the panel judged that HPV test was probably more cost effective than cytology. In this the panel also considered that the high negative predictive value of the HPV could allow to less intensive and shorted follow up strategies. Including false positive tests among the critical outcomes, the possibility of an important uncertainty or variability in the values given to the outcome by women emerged. Finally, the intervention was considered feasible and with no impact on health, but probably not acceptable (Table 3a).

The second question compared co-testing with HPV test alone. Sensitivity was slightly increased adding cytology, i.e., 96% (95% CI 92–98) and 93% (95% CI 88–96) for co-testing and HPV test, respectively, while specificity substantially decreased from 77% (95% CI 75–79) to 70% (95% CI 68–72) (Table 2). At the prevalence of 8%, this corresponds to 3 less false negative and 70 more false positive adding cytology to HPV test. The panel considered that the desirable (reduction of false negative) and undesirable effect (increase in false positive) were both small and the balance was not in favor of either the two. The certainty of evidence on accuracy was considered high for the same reasons reported for the first question, and overall certainty of the effect moderate even if the panel noted that the potential for progression of HPV-

negative/cytology positive lesions is difficult to assess and it is known that they have higher proportion of histological false positive [69]. The panel reported that the intervention would cause moderate additional costs, but it was considered feasible and acceptable (Table 3a).

In the follow up of women treated for CIN2 or CIN3 the panel recommends to use HPV test instead of Pap test alone. Strong recommendation.

There is no clear advantage in using HPV test alone or adding cytology to HPV (co-testing) and both strategies can be used in the follow up of women treated for CIN2 or CIN3. Conditional recommendation either the two test combinations.

3.3 Role of colposcopy in the first follow up episode (recommendation n. 3)

For this health question 9 papers were included [8, 42, 51, 63–68]. Sensitivity and specificity for the intervention were set by definition to 100% and 0% respectively, because in the intervention all women are managed as those positive to test, i.e., they undergo a colposcopy. Sensitivity and specificity for co-testing are those reported above (Table 2). Consequently, the intervention would cause 2 less false negatives and 638 more false positives. The Panel states that the contribution of adding colposcopy to sensitivity for neoplastic lesions is negligible, if any; on the other hand, colposcopy has a role on monitoring surgical outcomes on cervix anatomy, but how this role translates in changes in management is not clear.

The overall certainty of the effects was considered moderate for the same reasons reported above. The panel judged that the intervention requires moderate additional costs and that it is less cost-effective than co-testing. Finally, the panel judged the intervention feasible and acceptable, because it is the current practice in many programs (Table 3a).

There are no elements to suggest of not adding a colposcopy to the first follow up episode in women treated for CIN2 or CIN3. Conditional recommendation either the two test combinations.

3.4 Timing of first follow up episode (recommendation n. 4)

For the question comparing 6 with 12 month interval between intervention and the first follow up episode, 22 studies were included [8, 9, 24, 25, 34, 36, 43, 44, 46, 51, 63–68, 70–75], including 7497 women who received their first control at 6 months and 1285 at 12 months. Out of the 18 studies useful for this outcome, only 5 invasive cancers were found, all in the 6 month group (Table 3). Evidence was rated very low for this outcome because of the small number of women with test at 12 months. For the quantification of HPV positivity, 20 studies reporting 9939 and 1285 women with first control at 6 and 12 months, respectively, were considered; restricting the analysis to comparison between 6 and 12 months in the same population, five studies including 1819 women were included [43, 44, 63, 67, 72]. Both analyses suggest that HPV clearance is only slightly lower at 12 months compared to 6 months (about 2 percent points absolute difference) (Ta-

ble 3). Evidence was rated moderate for this outcome, but the overall certainty was downgraded to low, because the risk of prevalent cancers at six months was definitely demonstrated and non-negligible; the presence of prevalent cancers at 6 months makes the rationale for adopting the shortest interval very strong in order to avoid delay in diagnosis and progression of the disease. The panel estimated that intervention does not have impact on costs and equity and it is feasible and acceptable (Table 3b).

The panel recommend to call women for the first episode of follow up 6 months post treatment for CIN2 or CIN3, instead after 12 months. Strong recommendation.

3.5 Number of follow up episodes (recommendation n. 5)

Based on 3 studies and 283 women followed for more than 5 years, no cancers were identified with neither of the two managements [76–78]. Risk of CIN2+ was about 4.3% in women with one co-testing negative episode and 1.7% after two co-testing negative episodes [57, 76–78] (Table 3). Evidence for the two outcomes was rated as very low due to imprecision and heterogeneity of the results (for CIN2+), particularly if compared with the very large cohorts of women observed in Scotland [24] and Denmark [25]. Number of episodes was 1.3 per woman with only one episode and 2.4 if two episodes are adopted, while the proportion of women undergoing colposcopy is 35% vs. 49% (Table 3). Certainty of evidence was rates moderate for these two outcomes. Reducing the episodes from two to one would bring moderate savings, and probably the management would be more cost effective than two episodes. The intervention has been considered feasible but not acceptable by both women and professionals (Table 3b).

In the follow up of women treated for CIN2 or CIN3 the panel suggests to obtain two negative follow up episodes (instead of one) before referring the woman to routine screening. Conditional recommendation.

3.6 Timing of second follow up episode (recommendation n. 6)

Eighteen studies were included for estimating incidence between first and second episode (including those detected at second episode) reporting data for 8439 women with 6 month interval and 4831 with 12 months interval [8, 9, 34, 43, 44, 57, 63–68, 70–72, 75, 79, 80]. No cancer was detected in neither of the two managements. No study was included to compare the number of colposcopies needed (Table 3). The certainty of the evidence was rated as very low. The two managements have similar costs, no impact on equity and are both acceptable and feasible (Table 3b).

Both 6 or 12 month intervals between first and second follow up episodes may be used in women treated for CIN2 or CIN3 with negative results at the first episode. Conditional recommendation for either of the two intervals.

4. Discussion

4.1 Summary of the recommendations and implementation considerations

The six recommendations developed by the panel allow to depict a flowchart for the management of women during post CIN2 or CIN3 treatment follow up (Fig. 1).

While in the comparison between HPV alone vs. Pap test alone the balance between desirable and undesirable effect clearly favors HPV, the balance between desirable and undesirable effects of co-testing compared to HPV-alone did not favored either the two, given the small decrease in false negative and the small increase in false positive, furthermore the moderate additional costs of co-testing were balanced by higher acceptability. Consequently, the panel's recommendation was neutral suggesting that both the strategies can be adopted. Nevertheless, implementation considerations lead the group to consider, at least in the initial phase, co-testing as the usual care in screening programs. In fact, the management emerging from these six recommendations is definitely less intensive than the managements often adopted in the real practice, according to panelists' experience, where the introduction of HPV test is not yet complete, but colposcopy is used in most episodes, and controls are performed every six months for up to five years. However, excluding Pap test from controls at all and simultaneously reducing the number of episodes as well as the duration of follow up would be perceived as a too radical change by professionals and women.

The panel highlighted that the shift from Pap test to HPV test for primary screening is increasing feasibility and reducing costs of HPV testing in follow-up.

Including a colposcopy in the first follow up episode has been suggested on the basis of reasons that are not linked to cervical cancer prevention, but is used for monitoring the anatomic surgical outcomes. This colposcopy should not be included in the management if waiting time for colposcopy is already critical and, in any case, colposcopy is a bottle neck in screening workload.

A cancer detection rate of about 1/1000 at first follow up episode indicates that the risk of prevalent invasive cancers is not negligible. This prevalence should be also considered in the light of a relatively high proportion of cancers reported in the Kaiser Permanente cohort among the recurrences after CIN2 or CIN3 treatment where 15 cancers, 85 CIN2 and 105 CIN3 or AIS were identified [57]. In the absence of any advantage in delaying the first control, the opportunity to diagnose the cancer 6 months earlier convinced the panel to make a strong recommendation in favor of the 6 month interval option. The panel considered that presence of risk factors, as positive surgical margins, makes the need for an early follow up even more stringent [6, 50].

Despite the emerging evidences showing a quite low detection rate of CIN2+ in women who had only one negative co-testing [24, 25], the systematic review and data from the Kaiser Permanente [57] highlighted a reduction of risk in women with two negative co-testing episodes.

Table 3. Summary of finding table for questions on management questions.

Outcome	N studies	Design	Factors downgrading the certainty	Other factors	Intervention	Comparison	Relative risk	Risk difference for 1000 women	Quality of evidence	Importance
PICO #4 first episode at 6 vs. 12 months										
Invasive cancers detection*	18	Observational, cohort	Serious risk of bias; lack of reproducibility; very imprecise		5/7497 (0.1%)	0/1285 (0.0%)	Not estimated	Not applicable	⊕ very low	Critical
Positivity to follow up episode	20	Observational, cohort	Very serious risk of bias; lack of generalizability	Possible bias over-estimating positivity at 12 months	2309/9939 (23.2%)	282/1285 (21.9%)	1.06 (0.95–1.18)	13 more (from 11 less to 37 more)	⊕ very low	Important
Positivity to follow up episode (same studies)	5	Observational, cohort	Lack of generalizability	Strong association	319/1819 (17.5%)	178/1139 (15.6%)	1.12 (0.93–1.36)	19 more (from 11 less to 56 more)	⊕⊕⊕ moderate	Important
PICO #5 one episode vs. two episodes										
Invasive cancers**	3	Observational, cohort	Very imprecise		0/283	0/221	Not applicable	Not applicable	⊕ very low	Critical
CIN2+**	4	Observational, cohort	Lack of reproducibility; very imprecise	Possible ascertainment bias, over-estimating risk for intervention	14/325 (4.3%)	5/295 (1.7%)	2.5 (0.93–6.97)	Not applicable	⊕ very low	Important
CIN3+**	3	Observational, cohort	Lack of reproducibility and generalizability; very imprecise	Possible ascertainment bias, over-estimating risk for intervention	4/283 (1.4%)	0/221 (0.0%)	Not applicable	Not applicable	⊕ very low	Important
Number of episodes	3	Observational, cohort	Lack of reproducibility	Strong association	587/435 (134.9%)	1040/435 (239.1%)	Not applicable	1041 less (from 947 to 1097 less)	⊕⊕⊕ moderate	Important
Number of colposcopies	3	Observational, cohort	Lack of reproducibility	Strong association	152/435 (34.9%)	214/435 (49.2%)	0.71 (0.61–0.83)	140 less (from 947 to 78 less)	⊕⊕⊕ moderate	Important
PICO #6 6 vs. 12 month interval between 1st and 2nd episode										
Invasive cancers	17	Observational, cohort	Very imprecise		0/8439 (0.0%)	0/4831 (0.0%)	Not applicable	Not applicable	⊕ very low	Critical
Number of colposcopies	No included									Important

*Cancer detected at first episode or diagnosed between treatment and first episode. **Five year follow up since negative co-testing.

⊕⊕⊕⊕: high; ⊕⊕⊕: moderate; ⊕⊕: low; ⊕: very low.

Table 3a. Evidence to decision table for the diagnostic questions.

Judgement domain	HPV test vs. Pap test (question #1)	Co-testing (HPV + Pap test) vs. HPV test (question #2)	Co-testing and colposcopy vs. co-testing (question #3)
Problem	Yes	Yes	Yes
Accuracy of the test	Very accurate	Very accurate	Inaccurate
Desirable effects	Moderate	Small	Small
Undesirable effects	Small	Small	Moderate
Certainty of evidence for accuracy	High	High	Moderate
Certainty about direct effects	High	High	No included studies
Certainty about management effects	Moderate	High	No included studies
Certainty about link result and management	High	High	No included studies
Certainty about overall effects	Moderate	High	No included studies
Values	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability
Balance of effects	Favours the intervention	Does not favor either the intervention or the comparison	Does not favor either the intervention or the comparison
Resources required	Moderate savings	Moderate costs	Moderate costs
Certainty of evidence of required resources	No included studies	No included studies	High
Cost effectiveness	Probably favors the intervention	No included studies	Probably favors the comparison
Equity	Probably no Impact	Probably no Impact	Probably no Impact
Acceptability	Probably no	Yes	Yes
Feasibility	Yes	Yes	Yes
Final recommendation	Strong in favour of the intervention	Conditional for either the intervention or the comparison	Conditional for either the intervention or the comparison

Table 3b. Evidence to decision table for the management questions.

Judgement domain	First episode after 6 vs. 12 months (question #4)	One vs. two episodes (question #5)	6 month vs. 12 month interval between first and second episode (question #6)
Problem	Yes	Yes	Probably yes
Desirable effects	Moderate	Small	Trivial
Undesirable effects	Trivial	Large	Trivial
Certainty of evidence	Low	Moderate	Very low
Values	Probably no important uncertainty or variability	No important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Probably favours the intervention	Probably favours the intervention	Does not favor either the intervention or the comparison
Resources required	Negligible costs and savings	Moderate savings	Negligible costs and savings
Certainty of evidence of required resources	Low	High	No included studies
Cost effectiveness	Probably favours the intervention	Probably favours the intervention	Does not favor either the intervention or the comparison
Equity	Probably no impact	Probably no impact	Probably no impact
Acceptability	Yes	No	Probably yes
Feasibility	Yes	Yes	Yes
Final recommendation	Strong in favour of the intervention	Conditional against the intervention	Conditional for either the intervention or the comparison

Finally, the interval between the first and second follow up episodes can be 6 or 12 months. In fact, if the rationale for a second follow up after one testing negative is to reduce the probability of false negative mostly due to sampling problems. Intervals shorter than 6 months do not allow sampling conditions to change, thus the added value of a second episode would be limited. On the other hand, longer intervals increase the probability of detecting new infections instead of persisting infections. Furthermore, implementation considerations highlight that the usual care in the actual context is a 12 month interval. In fact, adopting a 6 month interval would lead the entire follow up to last only 12 months, that is much shorter than what usually applied in the screening programmes before the present recommendations.

4.2 Research priorities

The panel identified the knowledge gaps that should be filled to get the evidences to sustain stronger recommendations, but also to implement and overcome acceptability issues. In fact, some recommendations were strongly influenced by lack of acceptability by professionals and women. The panel identified the issue of how to effectively communicate with the women during the follow up process as a field of research. In particular, it is critical how to explain the rationale of less intensive protocols when they are equally efficacious, avoiding that the women perceive it as cost reduction driven interventions.

The panel identified as a research priority an accurate study of the viral clearance during follow up, including the understanding of the role of new and persistent infections. This would be relevant to define the best intervals and the potential benefits of using tests able to genotype the HPV in order to distinguish persistent infections, that may be predictive of a recurrence, from new infections, that are associated to a risk similar to the infections found in the general population; this is relevant for the application of a risk-based management [81, 82].

The panel highlighted the importance to understand the reasons for inconsistency between the data from the Kaiser Permanente [57] retrospective study and the Scotland and Danish [24, 25] prospective pilots about the absolute risk of CIN2+ and CIN3+ after only one co-testing episode. In particular, it is important to accurately assess the risk to define the best number of episodes and the time to return to screening.

An accurate monitoring of the guidelines implementation in screening programs could generate the evidences to answer most of the identified research priorities.

4.3 Next steps: the multisocietal guidelines and adolopment

The present guidelines were among the first recommendations developed through an application of the GRADE process in Italy. They have been developed and disseminated [83] before the ISS adopted GRADE as the official method for national guidelines and before the law about the Italian national guideline system was approved [84]. Therefore, for

some aspects they did not follow the guidance issued by the ISS [85]. In particular, even if they were developed by a multidisciplinary panel, they did not officially involve all the relevant Scientific societies and stakeholders.

To overcome this limit, the present recommendations have been included in an adolopment process [86] to become, after adaptation or adoption, part of the “Multisocietal Italian guidelines for cervical cancer prevention” [87]. This project aims to develop Italian guidelines for cervical cancer prevention, starting from the framework given by the European [14, 15] and Italian recommendations [16, 17]. The first topic that has been afforded is follow up of treated women, including the use of HPV vaccine and the management of women with positive results in follow episodes. These recommendations together with the adolopment of the six recommendations here presented will give complete guidance on how to manage women treated for CIN2 or CIN3 until they return to routine screening.

Author contributions

PGR, AI, PG, together with some members of the GISCI working group on follow up after treatment, conceived the project. AI, CBV, FV conducted the systematic reviews and prepared the summary of finding tables. PGR and PG defined the guideline development methodology. PG, AI and PGR chaired the plenary sessions. All the working group members reviewed and amended the systematic review protocols, reviewed and eventually integrated the summary of finding tables, participated to the plenary discussion, voting step by step all the judgements and contributing to writing the additional considerations, the final recommendations and all other texts in the final Evidence to Decision tables; finally, approved the recommendations and the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

PGR declares that as PI of an independent study, funded by the Italian ministry of Health, conducted negotiations with Roche, Hologic and Becton Dickinson to obtain reagents at reduced price or for free; the other authors declare no conflict of interests.

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