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Italian guidelines for cervical cancer screening. Multisocietal recommendations on the use of biomarkers in HPV screening with risk-based approach and GRADE methodology

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The European Council recommends adopting risk-based screening when relevant. In triaging HPV-positive women, it can be an effective strategy to reduce overtreatment and referral to colposcopy. HPV genotyping and p16/ki67 expression may allow a better risk stratification than cytology. In Italy, recommendations on their use (alone or combined) in screening were developed by a multi-professional (nine scientific societies) and multidisciplinary working group (including patients and decision makers). Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision frameworks were used. Data from large clinical trials on screening populations with long follow-up instructed the biomarkers' evaluation. The working group defined the CIN3+ risk thresholds (a surrogate marker of cancer risk) to guide decisions on management: immediate colposcopy, referral to 1-year and 3-year retesting. The risk-based approach allowed to reduce the number of possible strategies to be compared to five specific healthcare questions framed as PICOs. The prioritised outcomes were risk of cancer and of CIN3+ in HPV+/trriage-negative women, number of colposcopies, number of samples to be taken, and number of unneeded treatments. The combination of morphological markers (cytology or p16/ki67) and extended HPV genotyping was the only strategy with a conditional recommendation in favour when compared with cytology.

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BACKGROUND

Italian screening programmes introduced HPV (human papilloma-virus) DNA as the primary test for cervical cancer screening following an HTA report [1] based on the results of the European trials [2] and the first local piloting experiences [3–9]. The transition was slow to let the possibility of rescheduling invitations from 3 to 5-year intervals without introducing a discontinuity in the workload of sampling clinics, molecular and cytology laboratories and colposcopy clinics [10]. The algorithm adopted by the Italian screening programmes [1] follows the most intensive option among those recommended by the European guidelines [11]. HPV-positive women undergo cytology triage. Those with cytology ASC-US (atypical squamous cells of undetermined significance) or more severe are referred to immediate colposcopy, while women with negative cytology are referred to 1-year HPV retesting. If the HPV test is still positive after one year, the woman is referred to colposcopy, independently of cytology results; if the HPV test is negative, the woman is referred to the normal screening interval [1]. Genotyping is not considered.

The algorithm adopted by Italian guidelines in 2012 has very high sensitivity, but it implies an increase in colposcopy referral, at least in the first round of HPV screening [4–7, 9]. Furthermore, this algorithm also refers a group of women to colposcopy, i.e., those persistently positive after one year, who have a prevalence of CIN2+ (cervical intraepithelial neoplasia grade 2 or higher) that is below the threshold considered desirable for colposcopy by the Italian recommendations for cytology screening [4–7, 9, 12, 13], i.e., 15% [14]. This high colposcopy referral is concerning for both the sustainability of the programme and the possible over-treatment induced [15].

The Scientific Committee of the Italian Multisocietal Guideline for Cervical Cancer Prevention [16, 17] decided to prioritise clinical questions to define the best strategies to triage HPV-positive women, including the use of new biomarkers.

To increase the efficiency and reduce possible overtreatment of HPV screening, new biomarkers [18, 19], such as the E6/E7 mRNA overexpression [20], the dual staining for p16/ki67 (DS) [21], the partial or extended genotyping [19], and the methylation status of

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cellular/viral genes [22], alone or in combination with each other, are being evaluated as possible triage tests.

All these proposed biomarkers have a strong rationale for being able to distinguish women with an immediate need for colposcopy and those who can be safely referred to retesting [18]. Nevertheless, there is no consensus about the best combination of tests and the best algorithm in which the tests should be used.

Several studies on triage tests [12, 13, 23–25] showed that the accuracy of the triage test scarcely influences the efficiency of the screening algorithm now in use in Italy [1] and the USA [26]. The overall burden of colposcopy, including immediate and 1-year referral, is almost independent from the specificity of the triage test, with more specific triage referring fewer women to immediate colposcopy and more to 1-year colposcopy and less specific tests obtaining the opposite [12, 23, 25]. Only a major change in the screening algorithm can reduce the overall burden of colposcopies [24]. To change the screening algorithms while maintaining the high safety of those currently recommended by the guidelines adopted in Italy [1] and the USA [26], it is necessary to identify, among HPV-positive women, a group of women with a low enough risk of CIN3+, allowing them to be referred to screening after 3 years.

To introduce these algorithms in evidence-based guidelines, undesirable effects, i.e., increase in cancer risk, and desirable effects, i.e., reduction of colposcopies and overtreatment, linked to longer intervals must be quantified. Quantifying the risk of cancer with empirical studies is unethical, given that cervical cancer screening gives the opportunity to prevent the vast majority of invasive cancers. Thus, there is a large consensus in using the risk of CIN3+ in the subsequent 3 or 5 years as a proxy of cervical cancer risk [27–29]. Therefore, in defining recommendations on the best triage strategies, the Italian multisocietal guidelines adopted an equal risk equal management approach [30, 31]. With this approach, recently introduced by the US multisocietal guidelines [27], women with a similar risk of CIN3+ should receive similar management. This strategy requires that the guideline development panel defines the lower- and upper-risk thresholds of each group with similar risk.

In this paper, we present the methodology adopted to define the risk thresholds, the prioritisation of the clinical questions and how they were framed into PICO (Population, Intervention, Comparator, Outcome) questions, the methodology to systematically collect, grade and summarise the evidence from the literature, and the final recommendations given by the multi-disciplinary panel of the Italian Multisocietal Guidelines for Cervical Cancer Prevention.

METHODS

Setting and framework

These Multisocietal guidelines are promoted by 9 scientific societies involved in cervical cancer (see Supplementary Information). The project was promoted by the Italian group for cervical cancer screening (Gruppo Italiano per lo Screening del Cervicocarcinoma, GISCI), which invited the other societies to participate.

The process followed the guidance of the Italian National System of Guidelines (SNLG) and the dedicated “Methodological manual for the production of clinical practice guidelines” (SNLG – ISS v. 1.3.3 March 2023) [32], and adopts the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology [33], as described in the publications reporting the methodology and the first two chapters on post treatment follow-up and adjuvant HPV vaccination [16, 17]. Briefly, the Technical Scientific Committee (CTS, whose members include representatives of all the involved scientific societies) started the process according to the SNLG guidelines [32], by establishing the guidelines development group (GDG) and the evidence review

team (ERT), and formulating the clinical questions. The CTS selected also the panel members by consulting the list of panelists who already participated to the formulation of the previous guidelines promoted by GISCI, as well as additional lists of Italian independent experts; the final panel included healthcare professionals of different disciplines (i.e., epidemiologists, evidence-based medicine methodologists, public health and hygiene experts, virologists, molecular biologists, gynaecologists, pathologists, oncologists, cytologists, cytotechnologists, midwives), patients, and local and regional decision makers. The participation in the process was subordinated to the acceptance of the roles and rules set by the SNLG, and the timely submission of specific forms on Conflict-of-Interest (Col) disclosure and on commitment to confidentiality. The Col policy requested by CNEC (Centro Nazionale per l'Eccellenza Clinica, la qualità e la sicurezza delle cure), consistent with international recommendations, was implemented by the CTS. Within the panel, a Chair and a methodological Co-Chair were elected, in accordance with the guideline development methods required by CNEC [32].

The threshold definition

A dedicated working group searched for the implicit risk thresholds currently accepted for each management in the Italian cervical cancer screening programme. The thresholds were defined by translating some of the existing recommendations about colposcopy referral and intervals for cytology-negative and HPV-negative women. These findings were then used to propose explicit definitions of acceptable and desirable thresholds for a given management. If the 5-year risk was not available or the estimate came from studies giving low certainty, the 3-year risk has been used, without applying any correction for the shorter follow-up. The proposal was then discussed, modified, and voted on in a plenary session by the panel and CTS members. The final thresholds are reported in Fig. 1 and Supplementary Information – Table 1 (the table includes both the newly defined and the existing thresholds used as reference).

The prioritised questions

The process was started in 2019, but was interrupted for two years (after the first plenary session held in January 2020), due to the COVID-19 pandemic. The activities were resumed in 2022. As summarised in Supplementary Information – Table 2, the prioritisation of the biomarkers initially decided in 2020 was re-evaluated, and the clinical questions were updated in 2022 and 2023. In particular, HPV mRNA testing, and the combination of distinct cytological classes with p16/ki67 dual stain were deemed no longer appropriate (hrHPV E6/E7 mRNA testing because new studies showed that its accuracy characteristics make it suitable as primary but not as a triage test [23]; the combination of p16/ki67 with distinct cytological categories requiring two different cytological exams on different slides, was considered not feasible). Cellular and viral methylation status determination was postponed, waiting for more literature to define the technology and its possible use. Moreover, the use of self-collected samples in cervical screening will be the object of a new dedicated recommendation. On the other hand, two new questions were added: the use of a cytological triage vs. immediate referral to colposcopy in women with an hrHPV-positive test at 12-month repeat, and the combination of extended HPV genotyping with p16/ki67 dual stain vs. p16/ki67. The clinical questions evaluated in 2022/2023 represent the first chapter of the recommendations on the use of biomarkers in clinician-collected samples within HPV-based cervical cancer screening; the second chapter is forecasted in the next two years.

The clinical questions were structured following the Population, Intervention, Comparison and Outcomes (PICO) frame as reported in Supplementary Information – Table 3.

The GDG prioritised the outcomes using a nine-point scale (7–9 critical = to be included immediately; 4–6 important = to be

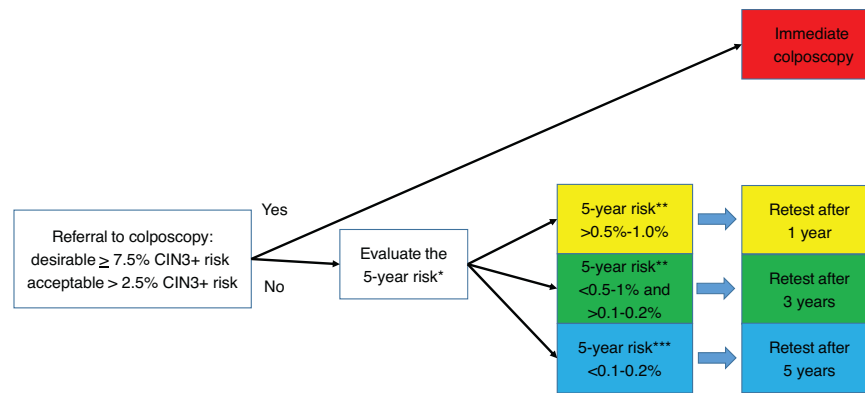


Fig. 1 CIN3+ risk groups and linked management adopted by the Italian Multisocietal Guidelines for Cervical Cancer Prevention. The acceptable and desirable risks are reported for referral to colposcopy, for 1-year, 3-year, and 5-year retesting. * If the 5-year risk is not available or the estimate comes from studies giving low certainty, the 3-year risk has been used, without applying any correction for the shorter follow-up. ** The desirable level of risk for referring a woman to HPV retesting after 3 years is <0.5, but <1% is acceptable. *** The desirable level of risk for referring a woman to HPV retesting after 5 years is ≤0.1%, but <0.2% is acceptable.

included later; 1–3 of limited importance = not to be included), according to the GRADE approach [33].

These guidelines apply the “equal risk, equal management” principle [27]. According to this principle, women with the same risk of developing cervical carcinoma should be equally managed. This approach makes it possible to give consistent recommendations among the different clinical questions. Moreover, as shown in Fig. 2, the process of coupling the risk stratification with the possible management should overcome the issue of combining the biomarkers by AND/OR Boolean operators: each cell is coupled with the management determined by the “equal risk, equal management” strategy. Additional considerations were provided for the few exceptions in which the recommendation cannot be directly applied, i.e., groups with risk very close to the threshold or small groups that, if managed separately, would increase the complexity of the screening algorithm with a small impact on patient-relevant outcomes.

Systematic reviews, context-specific evidence, and modelling

Systematic reviews and (published and preliminary) analyses of the Italian trials NTCC and NTCC2 (The New Technologies for Cervical Cancer screening, funded by the Ministry of Health) were used [12, 34]. Moreover, to obtain the data necessary for the production of recommendations on the use of biomarkers, the ERT and the panel members agreed upon the use of the systematic reviews produced within the COHEAR (COMparing HEALth services interventions for the Prevention of HPV-Related Cancer) project (funded by the European Commission) [35]. Additional reviews have been performed for parameters not specifically addressed therein. The reviews included cohort prospective or retrospective studies, favouring evidence collected in an epidemiological context close to the one where the recommendations will have to be applied. In addition, as the data on the viral clearance in women HPV-positive/triage-negative beyond the twelfth month were absent or not reported in a suitable way, the clearance curve over time has been modelled, using as baseline HPV-positivity rates those observed in the Italian screening programme routine indicators [36]. Furthermore, the number of preterm birth attributable to CIN2 and CIN3 treatments induced by screening were estimated using the probability of having a pregnancy after a CIN2+ diagnosis [37], the prevalence of preterm birth [37], and the relative risk of preterm birth in women treated for CIN2+ as estimated in a previous systematic review [38]. A specific protocol describing these methodological choices was prepared in 2021 and subjected to external review by two independent epidemiologists (the English version of the protocol is provided as Supplementary Information; see Appendix).

Grading of the certainty of the evidence

The certainty of the evidence (for each outcome and overall) was rated according to the GRADE approach. A Summary of Findings (SoF) table and a first draft of an Evidence to Decision (EtD) framework for each recommendation were provided in advance of the plenary sessions to the panel [33].

Evidence to decision-making process

Dedicated plenary sessions were conducted in person or remotely (due to the COVID-19 pandemic, the web-based meetings outnumbered those in person). The Chair and the methodological Co-Chair provided specific background information and illustrated the SoF table to the panel members. Each specific domain (Supplementary Information – Table 1) of the EtD framework was then judged by the panel; the final decision was the result of unanimous consent or a majority consensus after individually voting. The final recommendation on each question was then agreed upon. Additional considerations on specific subgroups, implementation aspects, monitoring/evaluation and research priorities were eventually formulated. Particular attention was paid to favouring the acquisition of the patients’ opinions; in case of non-attendance at a meeting, their comments were collected through the exchange of minutes via email.

Peer review process

The draft of the recommendations, together with all the methodological and supporting documents, has been submitted to external peer review. The same two epidemiologists who reviewed the protocol and two clinicians were involved in this phase.

The final document (including the reviewers’ comments and the GDG answers) then underwent a revision process by SNLG and was published on the SNLG website [17].

RESULTS

This chapter includes the recommendations relative to the clinical questions on the use of cytology, p16/ki67 dual stain, partial or extended hrHPV genotyping, performed on clinician-collected cervical specimens and used alone or in combination, as biomarkers for the triage of hrHPV-positive women, at baseline or at 1-year repeat (Supplementary Information – Table 3).

A preliminary PICO was included to compare the management options for women HPV-positive/triage-negative repeating HPV after one year and re-testing HPV-positive: should they be immediately referred to colposcopy, or should they undergo a further triage? The PICO has been informed with data coming

	HPV 16–18	HPV 31–33–35–45–52–58	HPV 39–51–56–59–66–68
HSIL	Colposcopy (CIN3+ risk 36%)	Colposcopy (CIN3+ risk 19%)	Colposcopy (CIN3+ risk 22%)
LSIL	Colposcopy (CIN3+ risk 5.5%)	Colposcopy (CIN3+ risk 3.1%)	Retesting after 1 year (CIN3+ risk 1.1%)
NILM	Colposcopy (CIN3+ risk 3.4%)	Retesting after 1 year (CIN3+ risk 1.5%)	Retesting after 3 years (CIN3+ risk 0.5%)

	HPV 16–18	HPV 31–33–35–45–52–58	HPV 39–51–56–59–66–68
p16/ki67-positive	Colposcopy (CIN3+ risk 17.3%)	Colposcopy (CIN3+ risk 6.7%)	Colposcopy (CIN3+ risk 4.2%)
p16/ki67-negative	Retesting after 1 year (CIN3+ risk 1.2%)	Retesting after 1 year (CIN3+ risk 1.1%)	Retesting after 3 years (CIN3+ risk 0.5%)

Fig. 2 Clinical management of hrHPV-positive women by combining extended genotyping and grouping of hrHPV types according to high (16–18), intermediate (31–33–35–45–52–58), low (39–51–56–59–66–68) oncogenic potential, with cytology (upper panel) or p16/ki67 dual stain (lower panel). Each cell reports the CIN3+ risk observed in the NTCC2 at 24-month follow-up [24], which guarantees that all women received at least one colposcopy if HPV-positive. For the values below the 5% risk for which retesting after 1 or 3 years was considered, the working group also evaluated the risk observed in NTCC at >3-year follow-up with similar, but not identical, grouping [39, 40].

from cytology triage, but it is applicable to any triage strategy referring to 1-year HPV-retesting according to the adopted thresholds. The panel, according to the judgements reported in Table 1, suggested that either management could be adopted (neutral conditional recommendation). Pros and cons of the two strategies and conditions favouring one or the other are explained in the justification and implementation considerations. Adopting a second triage led to a small decrease in the number of colposcopies and an increase in the number of other appointments and tests. Moreover, the time lasting from the first abnormality communicated to the woman and a definite diagnosis is longer for a quite large proportion of women. Second triage should be considered in case of a shortage of colposcopies.

For the other PICO, the systematic reviews and the NTCC and NTCC2 data were used to estimate the CIN3+ immediate risk and risk at more than three years associated with each result for the triage tests [2, 12, 24, 34, 39, 40]. The subsequent management was then identified for each outcome on the basis of the risk thresholds previously agreed upon (Fig. 1). Finally, the desirable (cancer risk reduction) and undesirable (number of screening episodes, of colposcopies, and of unnecessary treatments and associated obstetric adverse events) effects were quantified for each scenario.

Each triage test or combination of tests can distinguish two or three levels of risk (Fig. 2); the panel defined the woman's management (immediate referral to colposcopy or repeat HPV testing after one or three years), according to the results of different algorithms. Only combinations of tests, including cytology or p16/ki67 dual staining and extended genotyping, identified a group of women with a 3-year risk lower than the threshold identified for referring at new screening after 3 years. All the other combinations only defined groups of women deserving immediate colposcopy and 1-year retesting.

Table 1 summarises the judgements for each domain of the EtD for each PICO and the final recommendations. PICO Q1 through Q4 considered the cytology triage as a comparator; the PICO for Q5 considered the p16/ki67 triage as a comparator. The SoF tables are reported in Supplementary Information - Tables 4–8.

In summary, the panel produced a conditional recommendation of either of the two for p16/ki67 vs. cytology and partial genotyping (i.e., a genotyping distinguishing HPV16 and HPV18 from all the other high-risk HPV types, in addition to cytology or in addition to p16/ki67). In this last scenario, women with HPV16 and cytology (or p16/ki67) negative should be referred immediately to colposcopy; thus, the partial genotyping should be used only in cases the colposcopy is not a limited resource.

On the other hand, the panel suggests using extended genotyping in addition to cytology (or to p16/ki67) instead of cytology (or p16/ki67) alone. For the extended genotyping, high-risk HPV types are classified in three groups: 16–18 with the highest oncogenic potential group; 31, 33, 35, 45, 52, 58 with intermediate oncogenic potential; and 39, 51, 56, 59, 66, 68 with low oncogenic potential. This grouping is robust to some differences in the classification of some single genotypes; for example, HPV35 can be downgraded to low oncogenic potential, without substantially changing the risk level in each group. The combination of extended genotyping with cytology, classified as high grade, low grade (including ASC-US) and negative, produces 9 risk groups (Fig. 2). The management of each group was identified according to the risk; thus, women with high-grade cytology are referred to colposcopy independently from the HPV type, women with low-grade cytology are referred to colposcopy if infected with high or intermediate oncogenic HPV types (i.e., 16, 18, 31, 33, 35, 45, 52, 58). Cytology-negative women with low oncogenic HPV types are the only group that can be referred to 3-year retesting. All other groups are referred to 1-year retesting. Other slightly different managements were considered and judged to have less favourable balance between desirable and undesirable effects. With the combination of p16/ki67 and extended genotyping, women are classified into six groups. All women positive to p16/ki67 have a risk deserving immediate colposcopy regardless of the HPV type. p16/ki67-negative women with low oncogenic HPV types are the only group that can be referred to 3-year retesting. All the other groups are referred to 1-year retesting. The current Italian protocol based on triage cytology and the screening protocols, including the triage

Table 1. Judgements by the panel in the evidence to decision framework for the included questions (Q).

	Triage biomarkers considered in the five clinical questions				
	Q1-Cytology triage at 12-months vs. colposcopy referral	Q2-p16/ki67 dual stain vs. cytology	Q3-Partial HPV16/18 genotyping vs. cytology	Q4-Extended HPV genotyping vs. cytology	Q5-Extended HPV genotyping vs. p16/ki67 dual stain
Problem	Yes	Yes	Yes	Yes	Yes
Desirable effects	Small	Trivial	Small	Moderate	Moderate
Undesirable effects	Trivial	Small	Small	Small	Small
Certainty of evidence	Low	Low	Low	Very low	Very low
Values	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Probably favours the intervention	Does not favour either the intervention or the comparison	Probably favours the intervention	Probably favours the intervention	Probably favours the intervention
Resources required	Moderate costs	Negligible costs and savings	Moderate costs	Moderate savings	Don't know
Certainty of evidence of required resources	Very low	No included studies	No included studies	No included studies	No included studies
Cost effectiveness	No included studies	No included studies	No included studies	Probably favours the intervention	No included studies
Equity	Probably no impact	Probably reduced	Varies	Probably reduced	Probably reduced
Acceptability	Varies	Varies	Varies	Varies	Varies
Feasibility	Probably yes	Yes	Yes	Varies	Varies
Final recommendation	Conditional for either the intervention or the comparison	Conditional for either the intervention or the comparison	Conditional for either the intervention or the comparison	Conditional for the intervention	Conditional for the intervention

HPV genotyping is considered in adjunct to cytology in Q3 and Q4, and in adjunct to p16/ki67 in Q5.

strategies for which a conditional recommendation in favour was developed (Q4 and Q5), are reported in Supplementary Information – Figs. 1–3.

DISCUSSION

Methodological remarks

In the design of the possible triage algorithms, each biomarker can be adopted in different ways, determining different management options for each result; furthermore, some biomarkers, as cytology or HPV genotyping, give non-dichotomous results. Thus, when combined together, each triage solution can classify HPV-positive women into several tens of different groups. With several candidate biomarkers, many more combinations of tests that can be used, and several choices of management that can be proposed for each group of women, the guideline process could theoretically need to evaluate hundreds of PICO questions to compare two strategies. Therefore, there is a need to reduce the comparisons without excluding any potentially useful option. Although the equal risk equal management approach does not suggest which is the most efficient strategy, this principle helped us to identify the meaningful scenarios for each triage test or combination of tests. Since each triage produces a risk stratification, the panel applied the equal risk equal management approach to reduce the output groups resulting from the application of the triage tests, by putting together those with similar CIN3+ risk and then identifying the appropriate management for each risk group. The thresholds adopted by the panel are derived from the existing management in the Italian screening programmes, such as the recommendation about appropriate referral to colposcopy in cytology screening, the average risk of women with Pap-negative for referring at three years and the

average risk of women with HPV-negative for the 5-year referral. The panel considered that these clear references to current practice could make the thresholds more acceptable. We acknowledge that these thresholds are lower than those adopted by other European countries [41] and discussed now within the European Commission Initiative on Cervical Cancer (EC-CvC; <https://cancer-screening-and-care.jrc.ec.europa.eu/en/ec-cvc>), and they will produce very aggressive protocols. Figure 3 summarises the process adopted by the panel to fit the dichotomous PICO questions in the equal risk equal management approach.

The process of outcome prioritisation needed several rounds to produce a list including all the main desirable and undesirable effects of the possible triage strategies. The panel recognised three main consequences of the triage that are relevant for the woman and for the health system:

- The cervical cancer risk in women referred to a new screening round, approximated with a 3 or 5-year risk of CIN3+. The efficacy in preventing cancers is inversely proportional to the risk in those referred to long intervals after triage. Of note, the panel considered negligible the risk of cancer in those referred at 1-year retesting.
- The proportion of HPV-positive women referred to colposcopy (immediately or at 1-year). This is, at the same time, a measure of the efficiency of the algorithm and of possible adverse effects. If two strategies have the same risk of missing cancers, then the one with the highest number of colposcopies will expose the woman to a higher risk of unnecessary biopsies [15] and treatment of histological false positives or regressive lesions [12, 24].
- The number of screening episodes, as a measure of the acceptability and sustainability of the algorithm and of the

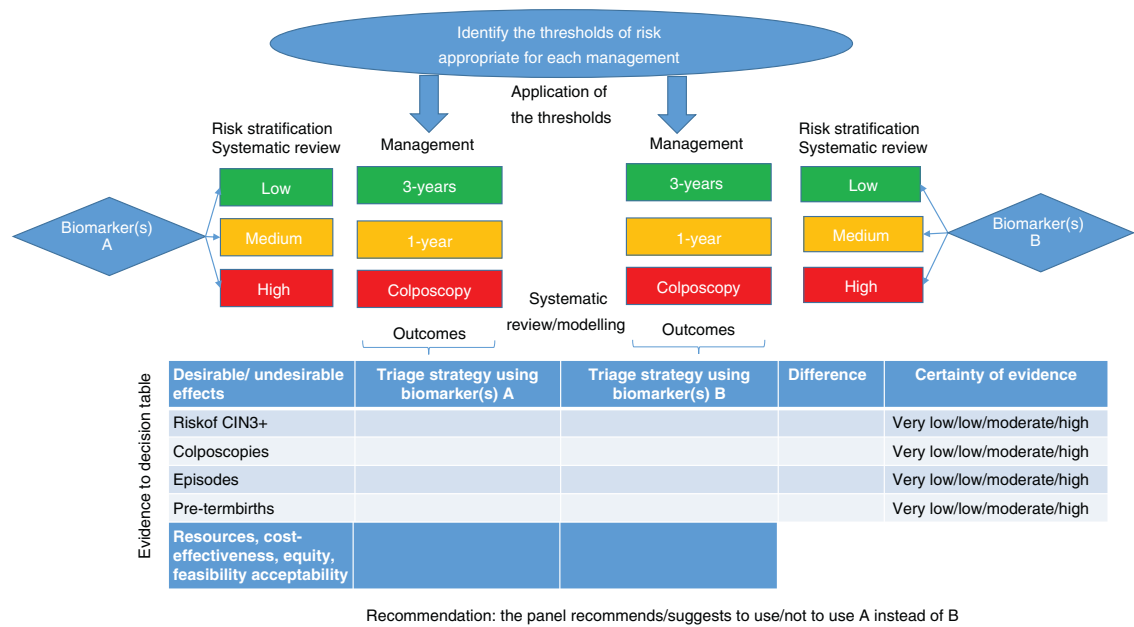


Fig. 3 Process adopted by the panel to fit dichotomous PICO questions in the equal-risk equal-management approach.

possible undesirable direct consequences of the cervical sampling, i.e., time loss, discomfort, pain, and bleeding.

Furthermore, in some cases, the panel considered the time needed to conclude the assessment phase for the HPV-positive women as a further criterion in the implementation considerations, i.e., the longer the time needed to conclude this phase, the longer the woman may live in a situation causing anxiety.

Concerning the first outcome prioritised, i.e., risk of cancer, and its surrogate measure (risk of CIN3), it is worth mentioning some considerations. Since CIN3 lesions can regress, particularly those with low-risk biomarkers, intensive follow-up overestimates the long-term risk.

Furthermore, other factors can modify the association between CIN3 risk and cancer risk. For example, CIN3 found at older ages may imply a higher risk of progression to cancer, and the genotypes associated with glandular lesions (i.e., HPV 16, 18 and 45) have shorter and less detectable sojourn times; thus, the underlying risk of cancer may be larger [42].

Limitations

In these recommendations, we also included data from the Italian NTCC2 trial, reporting the CIN3+ risk at 24 months instead of at 3 or 5 years [12, 23, 24]. Nevertheless, the 24-month estimates were also corroborated by similarly low risks at 5 years in comparable groups of women [43].

The use of systematic reviews was limited to cross-sectional accuracy. For prospective risk, we started from a selection of already known large cohort studies, present in the cross-sectional accuracy systematic review. This was justified by the long time needed from baseline to publication of the long-term risk and the very large sample size needed to assess these small absolute risks of CIN3+. These two characteristics made it very unlikely that unpublished cohorts would produce results for longitudinal risk. The advantage was that we could use the methodological evaluation, at least for the inclusion criteria, definition of biomarkers and laboratory methods, performed by the previous EC-funded systematic reviews.

For some parameters that the panel considered to be strongly context-specific, such as the prevalence of HPV infection and the proportion of cytology positivity among HPV-positive women, the

prioritised source of information came from routine indicators collected in the Italian screening programmes.

These two points, as well as the validity of the models used to compute the desirable and undesirable effects starting from the cross-sectional and longitudinal accuracy of triage strategies, were so critical that we decided to have an external peer review of the methodology protocol before developing the SoF and EtD tables.

Implication for practice

Despite the adoption of very low thresholds, comparable to those adopted by the US guidelines [26], the protocols combining extended genotyping and cytology or p16/ki67 that have recommendations in favour would reduce the colposcopy workload. Indeed, these protocols are much less aggressive than the Italian current one and probably represent the maximum acceptable change in the direction of de-intensification of surveillance in HPV-positive/triage-negative women. The use of p16/ki67 expression instead of cytology has a small, if any, impact on any of the outcomes identified. The choice should be made on feasibility and cost analyses. In particular, p16/ki67 is more expensive but can require a shorter learning period and expertise than cytology. Partial genotyping has a small impact on outcomes except for a slight increase in immediate and, to a lesser extent, in overall colposcopy referral. On the other hand, partial genotyping has the advantage of reducing the time to complete the assessment phase for some women. Finally, extended genotyping has the potential, when used in combination with both cytology or p16/ki67, to identify a group of women (representing about 40% of those hrHPV-positive) that have a sufficiently low CIN3+ risk to be referred to 3-year retesting, which can be considered a referral to a new screening round. In the absence of this conservative management, the introduction of extended genotyping has no practical advantage.

CONCLUSIONS

The Multisocietal guidelines suggest that extended genotyping, combined with cytology or p16/ki67 dual staining, is the only strategy with a conditional recommendation in favour when compared to cytology; providing a better risk stratification, these biomarkers should be used in triaging HPV-positive women to

identify those with sufficiently low risk to be referred to 3-year retesting.

DATA AVAILABILITY

The guideline development project and final recommendations were published on the database of the Italian National System of Guidelines (SNLG) of the National Institute of Health (ISS) (Sistema Nazionale Linee Guida, Istituto Superiore di Sanità). <https://www.iss.it/-/snlg-prevenzione-carcinoma-cervice-uterina>. It includes the complete Evidence-to-Decision and Summary of Findings tables (and relative references), and is available upon request to the corresponding author; simplified copies are included in the Supplementary material.

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AUTHOR CONTRIBUTIONS

TM, RG, PC, GN, AP, MB, FM, ET, FMB, PM, AI, PG (as Technical Scientific Committee members or additional collaborators at the start of the guidelines project) conceived the guidelines, defined the scope, and prioritised the Health Questions in each chapter. ADM, PGR, FC (as chair or co-chairs) defined the protocol for literature reviews and modelling. SG, FV (as Evidence Review Team members) conducted the research, extracted the data, and filled the Sof and EtD for plenary sessions. ADM, PGR, SG, FV, FC edited the draft recommendations after plenary sessions and made changes to take into account the reviewers' comments. ADM cured the contacts with the Italian National guideline system, submitted and got approved the recommendations. EA, BA, KLA, PA, MB, SB, AB, SB, EB, FC, EC, LC, CC, LDM, PF, HF, CF, PG, DG, VM, LM, MM, SM, VN, BP, TR, CS, PSdB, MLT, EV, CBV (as panel members) participated in prioritisation of outcome and framing of PICOs, took an active part in the plenary sessions, voted or agreed to each criteria, reviewed the draft recommendations and approved the final version after review. LDM also conceived the reported chapter of the guidelines. IB, MZ (as external reviewers) revised the review and modelling protocol. IB, MZ, ADI, and EPP (as external reviewers) reviewed the draft of the

recommendations, asking for integrations and clarifications. PGR, FV, ADM, and SG drafted and edited the manuscript; FC edited the manuscript. All contributed to the final version of the guidelines and fulfilled the criteria for contributors according to the ICMJE criteria. All the authors and contributors read and approved the final version of the manuscript and agreed with its submission to the journal. ADM, as corresponding author, confirms to have read the *Nature* journal policies on author responsibilities and is submitting the manuscript in accordance with those policies.

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COMPETING INTERESTS

SG, FV, FC, and ADM have disclosed no conflicts of interest; PGR participated in the preparation of the IARC Handbook 18 on cervical screening. COIs were collected from all the Contributor Group members. Overall, seven members disclosed potential conflicts of interest and these COIs are included in the final document published on the database of the Italian National System of Guidelines (SNLG) of the National Institute of Health (ISS) (Sistema Nazionale Linee Guida, Istituto Superiore di Sanità): https://www.iss.it/documents/20126/8403884/LG_197_GISCI_Biomarcatori-screening-cervicale_29ago24.pdf/40999ebc-246c-fe99-d483-4da375d9f76a?t=1724836991806. The Technical Scientific Committee members judged as "potentially relevant" those of three members; they were allowed full participation in the vote, with COI public disclosure.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. The guideline development project has been submitted to and approved by the Italian National System of Guidelines (SNLG) of the National Institute of Health (ISS) (Sistema Nazionale Linee Guida, Istituto Superiore di Sanità) <https://snlg.iss.it/>.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41416-025-03161-8>.

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