

Developing evidence-based Multisociety Italian Guidelines for cervical cancer prevention: rationale, methods, and development process

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Objective: Cervical cancer prevention shows a variability across Italian Regions unjustified by available evidence, increasing the health, economic and organizational burden. Evidence-based recommendations on topics not covered by international guidelines are needed to tackle existing inequalities. This article describes the rationale, methods, and process for development of the Multisociety Italian Guidelines for cervical cancer prevention. **Methods:** The Italian legislative framework requires guidelines to be consistent with methodological standards set by the National System for Guidelines (SNLG) of the National Institute of Health. **Results:** The nine scientific societies involved in cervical cancer prevention participated to the project, including clinicians, policy makers, methodologists, and researchers. Patients were involved as full voting panel members. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was adopted to assess the certainty of evidence collected by systematic reviews. The GRADE Evidence-to-Decision framework (EtD) was used to structure the appraisal of evidence and to formulate final recommendations. The EtD and a conflict-of-interests management policy were adopted to minimize the influence of competing interests. **Discussion:** Full transparency guided the reporting of each step of the process, to support the implementation of recommendations in each context and the future updating process. Considerations for subgroups, monitoring and evaluation of the implementation of recommendations and research priorities were also provided. A two-step review process by external experts and SNLG reviewers, prior to online publication, ensured the methodological robustness underlying final recommendations. Finally, to increase publication timeliness, guidelines are organised in chapters that group sets of related recommendations to be published independently.

Keywords

Cervical cancer; Screening; Recommendations; Evidence-based medicine

1. Introduction

The European framework for colorectal, breast and cervical cancer screening was set up by the European Council 2003 recommending to all member countries to implement screening programs for these three cancers according to European

guidelines for quality assurance [1]. In 2001, the Italian National Health Service included cervical cancer screening in the core benefit package (Essential Levels of Care-LEA) to ensure uniform level of preventive services across the country [2].

The European guidelines on cervical cancer screening were published in 2008 and updated in 2015, with the introduction of Human Papillomavirus (HPV) test for primary screening [3, 4]. They provided recommendations on the age of screening, the test to be adopted and the screening intervals for women with negative tests. The guidelines also included recommendations for the management of women with positive primary tests, including the triage, providing a large spectrum of options, to be adapted to national contexts. The European guidelines have been adopted in Italy [5, 6] and Italian screening programs are currently inviting women 25 to 30 (or 35) every three years for Pap test and women 30 to 64 every five years for HPV test. HPV-positive women undergo cytology triage and if cytology is positive (atypical squamous cell of undermined significance or more) they are referred to immediate colposcopy. Cytology negative women repeat HPV testing after 12 months and are referred to colposcopy if still HPV-positive. Conversely, the European guidelines did not consider new biomarkers for triage of HPV-positive women, follow-up of women treated for lesions identified by screening, and the introduction of the adjuvant HPV vaccine for cervical lesions.

To date, the few national guidelines on these topics were produced by individual scientific societies, and women management is very heterogeneous and inconsistent across Italian regions. For post treatment follow up, the different managements range from colposcopic surveillance up to five years to only two HPV and cytology tests in 18 months. Also adjuvant vaccination became a routine practice covered by the public health system in some regions [7, 8], while in other regions there are no indications at all. Furthermore, new scientific evidence, useful to support specific recommendations in the topic, has recently emerged [9, 10].

Table 1. Scientific societies involved in the Guidelines Development Group, sorted alphabetically.

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- AIO Italian Association of Obstetrics (Associazione Italiana Ostetricia);
 - AOGOI Italian Association of Hospital Obstetricians and Gynaecologists (Associazione Italiana Ostetrici e Ginecologi Ospedalieri);
 - GISCi Italian group for cervical cancer screening (Gruppo Italiano per lo Screening del Cervicocarcinoma);
 - SIAPEC-IAP Italian Society for Pathological Anatomy and Diagnostic Cytology. Italian Division of the International Academy of Pathology (Società Italiana Anatomia Patologica e Citologia Diagnostica. Divisione Italiana dell'International Academy of Pathology);
 - SICi Italian Society of Cytology (Società Italiana di Citologia);
 - SICPCV Italian Society for Colposcopy and Cervico-Vaginal Pathology (Società Italiana di Colposcopia e Patologia Cervico-Vaginale);
 - SIGO Italian Society of Gynecology and Obstetrics (Società Italiana Ginecologia e Ostetricia);
 - SItI Italian Society of Hygiene, Preventive Medicine and Public Health (Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica);
 - SIV-ISV Italian Society for Virology (Società Italiana di Virologia).
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It was therefore necessary to produce updated evidence-based recommendations on these topics to be implemented in the Italian screening programs.

Nine scientific societies accredited to the Ministry of Health agreed to develop shared guidelines and to establish the Technical Scientific Committee (CTS). The purpose of the “Multisociety Italian Guidelines for cervical cancer prevention” working group was to define recommendations on cervical cancer screening, endorsed by all scientific societies involved in tackling cervical cancer.

The CTS decided to adopt a methodology compliant with the National Institute of Health (Istituto Superiore di Sanità ISS) guidance on the production of guidelines to be included in the Italian National System of Guidelines (SNLG) [11], including the adoption of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [12–17]. According to the recent law on legal responsibility of health professionals, guidelines included in the SNLG are the reference to define appropriate or non-appropriate clinical behaviours of healthcare professionals, particularly if called in legal trials [18].

The objective of this article describes the methods and process adopted to develop the “Multisociety Italian Guidelines for cervical cancer prevention” in the context of existing international and national recommendations for cervical cancer screening [4–6].

2. Guideline methodology and development

The process of guideline development follows the phases provided for by the “Methodological manual for the production of clinical practice guidelines” edited by the National Centre for Clinical Excellence, Quality and Safety of Care (CNEC), in charge by the Italian National Institute of Health [19].

As mentioned before, the process was started by the Italian group for cervical cancer screening (GISCi) with the sponsorship of the National Centre for Screening Monitoring (ONS). The first action was to invite all other involved scientific societies to join the project (Table 1). The representatives of the scientific societies constituted the CTS.

2.1 Roles

2.1.1 Technical scientific committee

The CTS has the following tasks:

- Definition of the structure of the guidelines development group (GDG) and the roles, tasks and relationships between the teams involved in accordance with the CNEC methodology;

- Outline of the budget and expected costs of the process;

- Definition of the scope that guides the Population, Intervention, Comparison, Outcomes (PICO) definition by the GDG, for each topic and chapter, including the identification of existing recommendations suitable for adoption or adaptation;

- Selection and recruitment of the members of the Panel of Experts, of the Evidence Review Team (ERT) and of the independent external reviewers;

- Definition, identification and management policy of specific Conflicts-of-Interest (COI);

- Participation in all the plenary sessions, with contribution to the discussion, but without right to vote.

The GDG members were selected by the CTS in collaboration with the participating scientific societies, with the purpose to include representatives with the necessary background, expertise, and knowledge.

The GDG included women who underwent Cervical Intraepithelial Neoplasia (CIN) treatment as end users of the recommendations, health care professionals, epidemiologists, and guideline methodologists with previous experience of GRADE approach.

The participation was voluntary, and these individuals were assigned to the Panel of Experts and the Evidence Review Team (ERT).

2.1.2 Panel of experts

Panel members were selected by the CTS starting from the list of panellists who already participated in the last guidelines produced by GISCi [20] and from lists of Italian independent experts. All the experts who accepted to participate and timely sent the Conflict-of-Interest disclosure were considered part of the panel.

The panel included experts from all the medical fields that could be interested in cervical cancer prevention (gynaecologists, pathologists, oncologists, cytologists, cytotechnologists, midwives, epidemiologists, evidence-base medicine methodologists, public health and hygiene experts, virologists), patients, local and regional decision makers.

Patients and other lay members of the panel were full voting members.

For each minimum set of recommendations to be developed, the panellists had to confirm the participation and to sign a PICO specific Conflict-of-Interest form.

The CTS checked that participants covered all the needed expertise and, if necessary, solicited the participation of relevant professionals.

Within the Panel, a Chair was elected to neutrally lead the Panel of Experts in the guidelines development process. The Chair had to be qualified, authoritative, and with experience in group coordination, in optimizing teamwork and in techniques of reaching consensus. In addition, a Methodological Co-Chair was elected considering the expertise in the application of guideline development methods required by CNEC.

2.1.3 Evidence review team

For each guideline chapter and topic, the CTS selected individuals from the GDG to be part of the ERT, including Evidence-based Medicine (EBM) specialists and panellists with clinical background.

The ERT produced systematic reviews of existing evidence following the Cochrane Collaboration standards, assessed the quality and certainty of evidence, and presented the results using the Summary of Findings (SoF) tables, according to the GRADE approach [12, 21, 22].

The SoF tables were sent to the Panellists at least one week before plenary sessions and presented during each meeting to collect feedback and to provide the necessary information to support evidence-based recommendations.

Synthesised evidence and plenary discussion guided the appraisal of Evidence-to-Decision (EtD) framework criteria by the Panel of Experts and the formulation of each recommendation [13].

2.1.4 Independent external reviewers

For each chapter and topic, the CTS invited three experts in the field, with complementary expertise, to make a peer review of the recommendations' development process. Experts were identified for their expertise and were asked to sign a Conflict-of-Interest form, assessed by the CTS according to the COI policy.

2.2 Operational steps

The operational steps in the development of recommendations were executed as follows (Fig. 1).

2.2.1 Conflict-of-interest management

The CTS applied the COI policy included in the CNEC methodology, which is consistent with international recommendations [12, 19, 23].

The COI disclosure was used to assess the eligibility of each member of the GDG by the CTS and it was PICO specific for Panel members.

Moreover, the COI declared by each panellist was classified in 3 degrees of relevance. COIs classified as of "minimal or insignificant relevance" posed no limitation to participation in all phases of the recommendation development process. Panellists whose COI was classified as "potentially relevant" were admitted to all the process phases but required a public disclosure in the final document or in the SNLG website. Finally, COIs classified as "relevant" led to a partial exclusion from the participation to discussion and voting of the criteria potentially influenced by the specific COI, up to the complete exclusion from the Guidelines Development process [19].

Moreover, the use of the GRADE Evidence-to-Decision framework minimized the influence of COI on recommendations' formulations, leading the experts to make informed choices based on predefined and transparent criteria [13, 19].

Finally, panellists refusing to fulfil and sign the COI disclosure form or not participating to the plenary session were excluded from the authors' list of each specific recommendation.

2.2.2 Scoping of guidelines

The CTS agreed on a wide scope of the guidelines covering all the aspects of primary and secondary prevention of cervical cancer. The CTS recognized that for public health interventions, national recommendations produced by scientific societies had to respect European Commission guidelines and to follow the National recommendations for country specific implementation of the European guidelines.

The CTS agreed on a gradual development of the Guidelines through chapters' prioritization.

Within each chapter, a more specific scoping phase was conducted to identify the relevant and important clinical questions.

In the first scoping phase, the topics included in the guideline's chapters were:

- Human Papillomavirus (HPV) Vaccination in women treated for Cervical Intraepithelial Neoplasia (CIN) grade 2 or 3;
- Follow-up of women treated for CIN2/CIN3 within organized screening programs;
- Use of biomarkers in HPV based cervical cancer screening programs;
- Management of low risk CIN2: treatment versus follow up.

According to the CNEC methodology [19], the criteria used for topic prioritization were:

- National variability in healthcare professional practices not justified by available evidence;
- Inequalities of care processes and outcomes;
- Availability and quality of evidence;

Guidelines development process

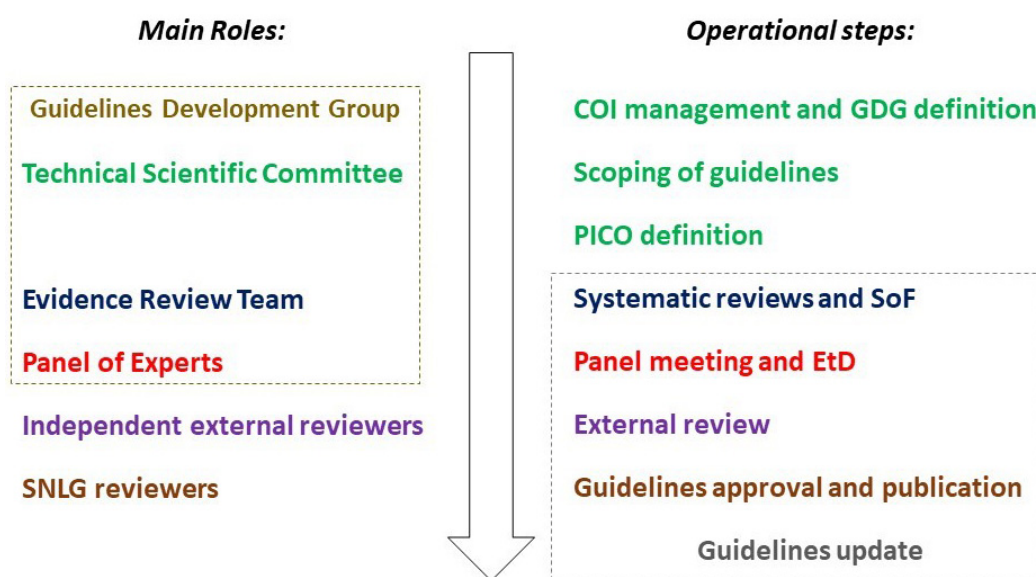


Fig. 1. Guidelines development process. Guidelines development process including operational steps and main roles, leading each step. COI, Conflict of Interest; EtD, Evidence-to-Decision framework; GDG Guidelines Development Group; PICO, population, intervention, comparison, outcomes; SNLG, Italian National System of Guidelines; SoF, Summary of Findings.

- Health practices with high costs for the NHS and high organizational or technological burden;
- Social demands and needs perceived by the population;
- Lack of up-to-date guidelines of high methodological quality, directly implementable in the Italian context.

The first chapter, including only one recommendation on HPV vaccination in women treated for CIN2/3, has been concluded and published on the SNLG website in July 2020 [11]. The chapter on the follow up of women treated for CIN2/CIN3 ended the voting phases and it is currently under review by external reviewers, while the chapter on the use of biomarkers is in the scoping phase.

2.2.3 PICO definition

Each clinical question prioritized was framed in PICOs by the panel. According to the GRADE approach to guideline development, the panellists listed and prioritised the PICOs according to the indications given by the CTS, using the GRADEpro online platform [24]. For each PICO or group of similar PICOs included in the chapter, the panel identified the possible patient relevant outcomes through an online brainstorming process. Then the proposed outcomes were grouped by the underlying clinical condition that they intended to measure and were prioritized as critical, important, and non-important, through a voting and consensus process [24, 25].

2.2.4 Systematic review of evidence

For each PICO or group of PICOs, the ERT conducted systematic reviews and summarised the findings for each critical and important outcome, grading the certainty of evidence

and quantifying the effects in relative and absolute differences through the SoF table proposed by the GRADEpro [24].

Evidence was graded according to the risk of bias, the indirectness, the reproducibility/heterogeneity of results, the precision of the estimates, the presence of publication bias, the strength of association, and eventually the presence of dose response effect or of known biases going in the direction of underestimating the effect [25].

2.2.5 Panel meeting and Evidence-To-Decision framework

During panel meetings, the SoF was reviewed and the evidence on health outcomes was integrated with context specific evidence provided by panellists on how women valued outcomes, costs/resources, eventually cost effectiveness, equity, feasibility, and acceptability. These integrations could be simply included as additional consideration during the plenary session, or could require an integration of systematic review outputs.

In some cases, the panel or the external reviewers could ask for a specific systematic review on some of the aspects if they thought it was worthwhile. This was the case of cost effectiveness for the PICO on vaccine after CIN2 and CIN3 treatment, where the external reviewers asked for such a systematic review, but no studies were found.

All the evidence was then integrated and reported to panellists in a systematic way using the EtD Table proposed by the GRADEpro [13, 24, 25]. Two kinds of EtD were used: the intervention framework and the diagnostic framework (Table 2, Ref. [21]). The first one compared the desired and undesired effects of two interventions (or intervention versus no intervention). In the diagnostic framework, we com-

pared the accuracy of two tests or combinations of tests and then, according to estimates of true positives, true negatives, false positives, and false negatives, the panel compared the estimated downstream consequences of each tests [13, 24, 25].

The panel judged each of the specific domains of the EtD framework: priority of the question, magnitude of the desirable and undesirable effects, certainty of the evidence, and balance of the effects, values given to the outcome by patients, resources required, cost effectiveness, certainty of evidence on costs, equity, feasibility, and acceptability. If required by at least one of the panel members, the judgement was expressed through voting. Voting options could be restricted to those that were considered plausible after the evidence evaluation.

The same procedure was adopted for the final recommendation (Table 3, Ref. [21]). Strong recommendation could be given only if at least 75% of the panel voted for it and after the panel assessed that the presented evidence satisfied the conditions for a strong recommendation. This was particularly important when the certainty of the evidence was low or very low.

Adoption of existing recommendations

At the time of implementation of the new methodological requirements for guidelines development by the Italian National Institute of Health, six recommendations had already been developed by a Panel of Experts from the GISCi society, following the GRADE method, and published online in the GISCi website [19]. Since the methodology used by GISCi was consistent with the one required by the ISS, the CTS decided to follow the formal process of adoption defined by the GRADE method [26] for adopting or, eventually, adapting these recommendations in the “Multisociety Italian Guidelines for cervical cancer prevention”. The panel evaluated all the SoF and EtD table to confirm or not each single judgement and to formulate the final recommendation. Adopted/adapted recommendations underwent the same review process required for publication in the SNLG database [19]. Up to February 2021, these recommendations completed the adoption process and are under review by external experts.

2.2.6 External review

The methodology of systematic literature review, the process of evaluating the evidence, and of the development of the recommendation underwent external review by the experts in the field identified by the CTS.

The main aim of the external review was to assess the correctness of methodology implementation and the quality of reporting for each development process phase.

The comments from the review phase were discussed in plenary with panel members to define how to integrate them into the final documents.

Reviewers' comments and panel decisions were attached to the documentation sent to the SNLG for final approval.

2.2.7 Guidelines approval and publication

The document including scope, PICO, systematic reviews and plenary sessions' outputs in SoF and EtD tables and the final recommendations, together with COI and external reviewers' contribution, was sent to the SNLG for assessment and approval.

Comments from the reviewers of the SNLG and related answers and revisions were integrated in the final document in an iterative process, which could imply supplementary plenary sessions for discussion with panel members, until SNLG approval.

The approved recommendations were then published on the SNLG ISS Web site, available for free for all healthcare professionals and patients [11].

2.2.8 Guidelines updating process

The GDG is committed to reviewing and updating the recommendations when required by new European Guidelines, under request by the Italian Ministry of Health, or every 3 years to assess whether new evidence becomes available.

3. Discussion

The process to develop the “Multisociety Italian Guidelines for cervical cancer prevention” started in May 2018. The first recommendation, which is in a single chapter, on adjuvant HPV vaccination in women treated for CIN2 or CIN3 has already been published, and other chapters on post treatment follow up, use of biomarkers in triaging HPV-positive women, and conservative management of low risk CIN2 are in the pipeline [11].

The guidelines are the product of a collaboration between all the involved scientific societies and endorsed by The National Centre for Screening Monitoring (ONS). This endorsement, the multidisciplinary participation, and the rigorous methodology adopted brought to their recognition by the SNLG.

Given their public health nature, the guidelines were born in the framework of the recommendation of higher level, developed by European Commission and by national governmental agencies (Ministry of Health and ONS). This was the case of recommendations for screening regarding age, test to be used and screening intervals, reported in the European Guidelines published in 2008 (and updated in 2015) and contextualised to our Country by the Italian HTA report and by the National Prevention Plan [3–5, 27]. The basic recommendations on HPV vaccination were provided by the National Immunization Plan drafted by the Italian Ministry of Health [28].

Moreover, in Italy both HPV vaccination and cervical cancer screening are included in the Essential Levels of Care set by the Ministry of Health [2].

Table 2. Summary of Judgements on Evidence-to-Decision Criteria, layouts by GRADEpro [21].

a. Framework used for questions comparing two interventions.							
Judgement							
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know
b. Framework used for questions comparing two diagnostic procedures.							
Judgement							
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of the evidence of test accuracy	Very low	Low	Moderate	High			No included studies
Certainty of the evidence of test's effects	Very low	Low	Moderate	High			No included studies
Certainty of the evidence of management's effects	Very low	Low	Moderate	High			No included studies
Certainty of the evidence of test result/management	Very low	Low	Moderate	High			No included studies
Certainty of effects	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table 3. Type of Recommendation table layout from GRADEpro [21].

Type of recommendation				
Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

, an empty box that can be checked to define the type of recommendation.

Therefore, the “Multisociety Italian Guidelines for cervical cancer prevention” Working Group are bound to develop recommendations in accordance with superordinated documents, for all the clinical questions that had not been addressed yet.

Strengths and limitations

Among the strengths of the GRADE approach, extensively described elsewhere [12, 25], the GDG emphasised the following:

- Role of the multidisciplinary experts in all phases, from evidence synthesis to development of the final recommendations;
- Inclusion of patients as full voting members in the Panel of Experts;
- Inclusion of methodological experts to guide clinical experts in the guideline’s development method;
- Transparency on all phases, criteria, and justification, that makes the final recommendation easy to be adopted in each context and easy to be updated in the future;
- Flexibility in clinical implementation with inclusion of subgroup and implementation considerations;
- Support for decision makers and healthcare manager with Monitoring and evaluation considerations;
- Support for future development and for overcoming existing gaps of knowledge, enlisting Research priorities.

In particular, patients’ voice was relevant in giving a judgement on how outcomes are valued. For this specific point scientific literature is almost always missing; therefore the panel is called to express a subjective judgement. Including patients as full voting members in the panel gives to women the opportunity to talk as peer in a field where they have much more direct expertise than the experts.

Furthermore, explicating the single judgements underlying the final recommendation allows transparency about which criteria mostly guided the decision, avoiding to stress the interpretation of the evidences. This is particularly useful to develop implementation and subgroup considerations that can support the best way to apply conditional recommendations.

Among the limitations, the GDG missed a specific expertise in cost effectiveness analysis. However, the impact of such lack was limited by the experience of panel experts in different fields including health policy and management and health technology assessment.

Finally, guidelines are often criticized for taking too long to become available [12]. This is particularly true when the

process is structure and proceduralized, as the GRADE approach implies. In the first experience of this project, the recommendation about adjuvant HPV vaccination [29], the most time consuming steps were the two sequential external reviews, one by the expert reviewers identified by the CTS and the second by the SNLG. These steps could be more efficiently managed if conducted in parallel as usually external review of content and method are conducted in scientific publication.

4. Conclusions

To increase timeliness of publication, this project will produce guidelines organized in chapters, grouping sets of meaningful recommendations that will be processed and published independently. This implies that a final, comprehensive manual will never be published, while an ongoing online publication will be available, as a result of a continuous production process that follows the topics timely prioritized.

Abbreviations

CIN, Cervical Intraepithelial Neoplasia; CNEC, National Centre for Clinical Excellence, Quality and Safety of Care; CTS, Technical Scientific Committee; ERT, Evidence Review Team; GDG, Guidelines Development Group; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HPV, Human Papillomavirus; ONS, National Centre for Screening Monitoring; RCT, Randomized Controlled Trials; SNLG, National System for Guidelines.

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Ethics approval and consent to participate

The work described in this paper did not need ethical approval. 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/>.

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Conflict of interest

The authors declare no conflict of interest.

References

- [1] The Council of the European Union. Council Recommendation of 2 December 2003 on cancer screening. 2003. Available at: <http://data.europa.eu/eli/reco/2003/878/oj> (Accessed: 28 March 2021).
- [2] Presidente del Consiglio dei Ministri. Decreto del Presidente del Consiglio dei Ministri 29 novembre 2001. Definizione dei livelli essenziali di assistenza. 2002. Available at: <https://www.gazzettaufficiale.it/eli/id/2002/02/08/02A00907/sg> (Accessed: 28 March 2021).
- [3] Arbyn M, Anttila A, Jordan J, Schenk U, Ronco G, Segnan N, et al. European guidelines for quality assurance in cervical cancer screening. Second edition. *Annals of Oncology*. 2010; 21: 448–458.
- [4] Anttila A, Arbyn A, De Vuyst H, Dillner J, Dillner L, Franceschi S, et al. European guidelines for quality assurance in cervical cancer screening. Office for Official Publications of the European Union. *Annals of Oncology*. 2010; 21: 448–458.
- [5] Ronco G, Biggeri A, Confortini M, Naldoni C, Segnan N, Sideri M, et al. Health technology assessment report: HPV DNA based primary screening for cervical cancer precursors. *Epidemiologia E Prevenzione*. 2012; 36: e1–e72.
- [6] Italian Ministry of Health. Screening oncologici. Raccomandazioni per la pianificazione e l'esecuzione degli screening di popolazione per la prevenzione del cancro della mammella, del cancro della cervice uterina e del cancro del colon retto. 2006. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_774_allegato.pdf (Accessed: 28 March 2021).
- [7] Regione Veneto, DGR n. 1557 del 17 novembre 2020, Bur n. 183 del 27 novembre 2020. 2020. Available at: <https://bur.regione.veneto.it/BurServices/pubblica/DettaglioDgr.aspx?id=434569> (Accessed: 1 April 2021).
- [8] Giunta Regionale Regione Toscana. Delibera N 193 del 18-02-2019. Regione Toscana. 2019. Available at: http://www.301.regione.toscana.it/bancadati/atti/Contentut.o.xml?id=5208700&nomeFile=Delibera_n.193_del_18-02-2019 (Accessed: 1 April 2021).
- [9] Cuschieri K, Ronco G, Lorincz A, Smith L, Ogilvie G, Mirabello L, et al. Eurogin roadmap 2017: triage strategies for the management

- of HPV-positive women in cervical screening programs. *International Journal of Cancer*. 2018; 143: 735–745.
- [10] Tornesello ML, Buonaguro L, Giorgi-Rossi P, Buonaguro FM. Viral and cellular biomarkers in the diagnosis of cervical intraepithelial neoplasia and cancer. *BioMed Research International*. 2013; 2013: 519619.
- [11] Istituto Superiore di Sanità. Sistema Nazionale Linee Guida dell'Istituto Superiore di Sanità. 2021. Available at: <https://snlg.iss.it/> (Accessed: 28 March 2021).
- [12] Schünemann HJ, Lerda D, Dimitrova N, Alonso-Coello P, Gräwingholt A, Quinn C, *et al*. Methods for development of the european commission initiative on breast cancer guidelines. *Annals of Internal Medicine*. 2019; 171: 273–280.
- [13] Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, *et al*. GRADE evidence to decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLPMENT. *Journal of Clinical Epidemiology*. 2017; 81: 101–110.
- [14] Schünemann HJ, Best D, Vist G, Oxman AD. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. *Canadian Medical Association Journal*. 2003; 169: 677–680.
- [15] Schünemann HJ, Wiercioch W, Etxeandia I, Falavigna M, Santesso N, Mustafa R, *et al*. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *Canadian Medical Association Journal*. 2014; 186: E123–E142.
- [16] Schünemann HJ, Woodhead M, Anzueto A, Buist AS, Macnee W, Rabe KF, *et al*. A guide to guidelines for professional societies and other developers of recommendations: introduction to integrating and coordinating efforts in COPD guideline development. an official ATS/ERS workshop report. *Proceedings of the American Thoracic Society*. 2012; 9: 215–218.
- [17] Woolf S, Schünemann HJ, Eccles MP, Grimshaw JM, Shekelle P. Developing clinical practice guidelines: types of evidence and outcomes; values and economics, synthesis, grading, and presentation and deriving recommendations. *Implementation Science*. 2012; 7: 61.
- [18] LEGGE 8 marzo 2017, n. 24. Disposizioni in materia di sicurezza delle cure e della persona assistita, nonché in materia di responsabilità professionale degli esercenti le professioni sanitarie. (17G00041) *Gazzetta Ufficiale Serie Generale n.64 del 17-03-2017*. Available at: <https://www.gazzettaufficiale.it/> (Accessed: 28 March 2021).
- [19] SNLG- ISS. Methodological manual for the production of clinical practice guidelines. 2019. Available at: https://snlg.iss.it/wp-content/uploads/2019/04/MM_v1.3.2_apr_2019.pdf (Accessed: 28 March 2021).
- [20] GISCI Working Group. “Utilizzo del test HPV-HR nel triage delle ASC-US, delle LSIL in donne con più di 35 anni, nel follow-up delle donne con citologia ASC-US+ dopo un approfondimento di secondo livello negativo per CIN2+ e nel follow-up dopo trattamento delle lesioni CIN2-3: aggiornamento 2018”. 2018. Available at: https://gisci.it/documenti/documenti_gisci/Utilizzo_test_HP-V-HR_2018_def2.pdf (Accessed: 28 March 2021).
- [21] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al*. *Cochrane handbook for systematic reviews of interventions*, second edition. The Cochrane Collaboration. 2019.
- [22] Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, *et al*. Completing ‘summary of findings’ tables and grading the certainty of the evidence. *Cochrane Handbook for Systematic Reviews of Interventions*. 2019; 170: 375–402.
- [23] Schünemann HJ, Al-Ansary LA, Forland F, Kersten S, Komulainen J, Kopp IB, *et al*. Guidelines international network: principles for disclosure of interests and management of conflicts in guidelines. *Annals of Internal Medicine*. 2015; 163: 548–553.
- [24] GRADEpro GDT online platform. 2020. Available at: <https://gradepro.org/> (Accessed: 28 March 2021).
- [25] Schünemann HJ, Brozek J, Guyatt G, Andrew Oxman. *Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach*. 2013. Available at: <https://gdt.gradepro.org/app/handbook/handbook.html> (Accessed: 28 March 2021).
- [26] Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, *et al*. GRADE evidence to decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLPMENT. *Journal of Clinical Epidemiology*. 2017; 81: 101–110.
- [27] Italian Ministry of Health. Piano Nazionale della Prevenzione 2014–2019. 2014. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2285_allegato.pdf (Accessed: 28 March 2021).
- [28] Italian Ministry of Health. Piano Nazionale della Prevenzione Vaccinale 2017–2019. 2017. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf (Accessed: 28 March 2021).
- [29] Multisociety Italian Guidelines for cervical cancer prevention Working Group. HPV vaccination in women treated for Cervical Intraepithelial Neoplasia grade 2 or 3: evidence-based recommendation from the Multisociety Italian Guidelines for cervical cancer prevention. *European Journal of Gynaecological Oncology*. 2021.