cancer screening committee

Recommendations on screening strategies for cervical cancer: HPV testing compared to cytology

Appraisal report

August 2021

cancer screening committee

Impressum

Geschäftsstelle Cancer Screening Committee

lic. phil. Yvonne Grendelmeier (Leitung)

Dr. Nicole Steck (wissenschaftliches Sekretariat)

Tel: +41 31 631 55 76
office@cancerscreeningcommittee.ch
www.cancerscreeningcommitte.ch

Cancer Screening Committee
c/o Krebsliga Schweiz
Effingerstrasse 40
CH-3001 Bern

cancer screening committee

Table of contents

cancer screening committee

Executive Summary - English

The benefit of cervical cancer screening is undisputed, but different screening strategies are available, including cytology and/or HPV-testing-based approaches using different combinations or algorithms. Based on an assessment report, the Swiss Cancer Screening Committee has appraised the evidence on women's attitudes and preferences as well as the clinical effectiveness and cost-effectiveness of the different methods of cervical cancer screening. The appraisal has been made following the Evidence to Decision (EtD) framework. Based on this appraisal, the Committee issued the following recommendations for women, non-binary persons, and transgender men with a cervix:

1. *For persons in the target groups aged 30 to 70, the committee suggests HPV primary testing with subsequent cytology triage as the method for cervical cancer screening (GRADE weak recommendation).* While the current state in terms of values and preferences of the persons in the target groups remains unclear and likely variable, the current body of evidence suggests that HPV primary testing is clinically more effective as well as cost-effective, compared with cytology.
2. *For persons in the target groups aged 21 to 29 years, the committee recommends cervical cancer screening with cytology (GRADE strong recommendation).* In these young ages, due to the frequent occurrence of asymptomatic HPV infections that often resolve without consequences, cytology-based screening (which is the current practice) remains more appropriate.
3. *Regardless of the age group, the committee recommends a screening interval of three years instead of one year (GRADE strong recommendation).* A three-year interval for cervical screening is already recommended today, although high practice variations remain. The committee found that there is no indication for a clinical advantage of yearly screening, whereas longer intervals lower the burden of screening, and are more cost-effective.
4. *Regardless of the age group, the committee also suggests a screening interval of five years, as opposed to three years (GRADE weak recommendation).* The evidence for clinical effectiveness and harm does not point to any clinically meaningful differences between three- or five-year intervals, whereas longer intervals lower the burden of screening, and are more cost-effective.
5. *The committee recommends reimbursement of the HPV test as a screening test by the statutory health insurance (GRADE strong recommendation).* The reimbursement of the HPV-based screening within a defined framework ensures equity of access.

To implement the recommendations and reduce existing inequalities in screening coverage, a targeted information campaign should address all target groups as well as gynaecologists and other important stakeholders in the healthcare system. The evidence only allows for weak recommendations on several issues, and limited data are available on the preferences of women. This emphasises the need for shared decision-making to identify the options in line with the target persons' own values and preferences.

Appraising and summarising the evidence for the implementation of an organised screening program was not within the scope of the committee. However, it believes that an organised program would allow for the harmonisation of practices throughout the healthcare system, ensure quality of the testing, and allow exemption from the deductible according to the standard rules of the statutory health insurance; this would increase accessibility and equity.

The possibility of self-sampling with the HPV test needs to be further explored, especially since it could lower the burden of screening and reach target populations that do currently not undergo screening.

cancer screening committee

Executive Summary - German

Der Nutzen des Gebärmutterhalskrebs-Screenings ist unbestritten. Es stehen verschiedene Screening-Strategien zur Verfügung, darunter auf Zytologie und/oder HPV-Tests basierende Ansätze in unterschiedlichen Kombinationen. Das Expertengremium Krebsfrüherkennung hat die verschiedenen Screening-Methoden basierend auf einem Assessment-Bericht verglichen und bewertet. Es beurteilte die Evidenz zu den Einstellungen und Präferenzen von Frauen sowie die klinische Wirksamkeit und Kosteneffektivität der verschiedenen Methoden gemäss dem Evidence to Decision Framework (EtD). Auf der Grundlage dieser Bewertung gibt das Gremium folgende Empfehlungen für Frauen, nicht-binäre Personen und Transgender-Männer mit Gebärmutterhals heraus:

1. *Für Personen der Zielgruppen im Alter von 30 bis 70 Jahren schlägt das Gremium den HPV-Primärtest mit anschliessender zytologischer Triage als Methode des Gebärmutterhalskrebs-Screenings vor (GRADE schwache Empfehlung).* Der aktuelle Wissensstand bezüglich Werte und Präferenzen der Personen in der Zielgruppe lässt keinen eindeutigen Schluss zu. Die Evidenz weist jedoch darauf hin, dass der HPV-Primärtest im Vergleich zur Zytologie klinisch effektiver und auch kosteneffektiv ist.
2. *Für Personen der Zielgruppen im Alter von 21 bis 29 Jahren empfiehlt das Gremium ein Gebärmutterhalskrebs-Screening mit Zytologie (GRADE starke Empfehlung).* Da in diesem Alter HPV-Infektionen sehr häufig sind und meist von alleine abheilen, ist das heute in der Schweiz gemachte Zytologie-basierte Screening angemessener als ein HPV-basiertes Screening.
3. *Unabhängig von der Altersgruppe empfiehlt das Gremium ein Screening-Intervall von drei anstatt einem Jahr (GRADE starke Empfehlung).* Bereits heute ist in der Schweiz für das Gebärmutterhalskrebs-Screening ein Drei-Jahres-Intervall empfohlen. Die Praxis ist jedoch nicht einheitlich. Das Expertengremium fand keinen Hinweis auf einen klinischen Vorteil von jährlichem Screening, während längere Intervalle die Belastung durch das Screening reduzieren und kosteneffektiver sind.
4. *Unabhängig von der Altersgruppe schlägt das Gremium ein Screening-Intervall von fünf anstatt drei Jahren vor (GRADE schwache Empfehlung).* Die Evidenz bezüglich klinischer Wirksamkeit zeigt für drei- und fünfjährige Intervalle keine klinisch relevanten Unterschiede, hingegen reduzieren längere Screening-Intervalle die Belastung durch das Screening und sind kosteneffektiver.

5. *Das Gremium empfiehlt die Erstattung (Kostenübernahme) des HPV-Tests als Screening-Test durch die obligatorische Krankenpflegeversicherung (GRADE starke Empfehlung).* Die Kostenübernahme des HPV-basierten Screenings ist eine Voraussetzung für die Zugangsgerechtigkeit.

Um die Empfehlungen umzusetzen und um bestehende Ungleichheiten im Zugang zum Screening zu reduzieren, sollten mit einer Informationskampagne sämtliche Zielgruppen, aber auch Gynäkologinnen und Gynäkologen und andere Akteure im Gesundheitswesen angesprochen werden. Die Evidenz ist in vielen Belangen nicht eindeutig und erlaubt deshalb nur schwache Empfehlungen. Zudem gibt es nur wenig Daten zu den Präferenzen der Personen in den Zielgruppen. Dies betont die Bedeutung einer partizipativen Entscheidfindung der betreffenden Personen zusammen mit dem Gesundheitspersonal (shared decision making). Damit können die individuellen Präferenzen in Bezug auf die verschiedenen Möglichkeiten identifiziert werden.

Die Zusammenfassung und Beurteilung der Evidenz hinsichtlich einer Implementierung eines organisierten Screening-Programms war nicht Aufgabe des Expertengremiums. Die Mitglieder des Gremiums sind jedoch der Ansicht, dass ein organisiertes Programm eine Harmonisierung der Praxis erwirken, die Qualität des Screenings gewährleisten sowie die Franchisen-Befreiung ermöglichen würde. Dies würde den Zugang zum Screening erleichtern und insbesondere die Zugangsgerechtigkeit erhöhen.

Ob und in welchem Rahmen allenfalls HPV-Selbstabstriche zum Screening geeignet sind, muss noch untersucht werden. Sie könnten die mit dem Screening verbundenen Belastungen reduzieren. Zudem haben sie das Potenzial Zielgruppen zu erreichen, die heute nicht am Screening teilnehmen.

cancer screening committee

Executive Summary - French

Le bénéfice du dépistage du cancer du col de l'utérus est incontestable. Il existe plusieurs stratégies de dépistage, parmi lesquelles des approches fondées sur un examen cytologique et/ou un test HPV selon différentes combinaisons. Le comité d'experts du dépistage du cancer a comparé les différentes méthodes de dépistage à partir d'un rapport d'évaluation (Assessment). Il a analysé les données scientifiques relatives aux appréhensions et aux préférences des femmes ainsi qu'à l'efficacité clinique et au rapport coût/efficacité des différentes approches à la lumière de l'Evidence to Decision Framework (EtD). Sur la base de cette évaluation approfondie, le comité d'experts formule les recommandations ci-après pour les femmes, les personnes non-binaires et les hommes transgenres ayant un col de l'utérus.

1. *Pour les personnes des groupes cibles âgées de 30 à 70 ans, le comité d'experts propose un test HPV primaire suivi d'un triage cytologique comme méthode d'examen du frottis du col de l'utérus (GRADE recommandation faible).* Les connaissances actuelles concernant les valeurs et les préférences des personnes de ce groupe cible ne permettent pas de formuler une conclusion péremptoire. Les études scientifiques réalisées ont cependant démontré que le test HPV primaire est cliniquement plus efficace qu'un examen cytologique et qu'il présente aussi un bon rapport coût/efficacité.
2. *Pour les personnes âgées de 21 à 29 ans, le comité d'experts recommande de procéder à un examen cytologique pour dépister le cancer du col de l'utérus (GRADE recommandation forte).* Les infections à papillomavirus humains sont très fréquentes à cet âge et guérissent, pour la plupart, spontanément. Un dépistage fondé sur un examen cytologique, tel qu'il est pratiqué aujourd'hui en Suisse, est donc plus approprié qu'un dépistage par test HPV.
3. *Le comité d'experts recommande, pour toutes les tranches d'âge, un intervalle de dépistage de trois ans au lieu d'un an (GRADE recommandation forte).* Aujourd'hui déjà, l'intervalle de dépistage du cancer du col de l'utérus recommandé est de trois ans en Suisse. La pratique est loin d'être uniforme. Le comité d'experts n'a identifié aucune indication démontrant l'avantage clinique d'un dépistage annuel alors que des dépistages moins fréquents réduisent le stress y associé et présentent un meilleur rapport coût/efficacité.
4. *Le comité d'experts propose, pour toutes les tranches d'âges, un intervalle de dépistage de cinq ans au lieu de trois ans (GRADE recommandation faible).* Il ne ressort des données disponibles aucune différence clinique importante entre un intervalle de dépistage de trois

ou de cinq ans. En revanche, un intervalle de dépistage moins fréquent diminue le stress y associé et présente un meilleur rapport coût/efficacité.

5. *Le comité d'experts recommande le remboursement (la prise en charge des coûts) par les caisses d'assurance maladie du test HPV au titre d'examen de dépistage (GRADE recommandation forte).* La prise en charge des coûts du dépistage fondé sur un test HPV par l'assurance obligatoire des soins est indispensable pour garantir un accès équitable.

Pour mettre en œuvre les recommandations et réduire les inégalités existantes en matière d'accès au dépistage, il faudrait déployer une campagne d'information qui s'adresse non seulement à l'ensemble des groupes cibles mais aussi aux gynécologues et autres acteurs du système de santé. Sur plusieurs questions, les données scientifiques ne permettent de formuler que de faibles recommandations. En outre, il n'existe que peu de données sur les préférences des personnes des différents groupes cibles. Ce double constat souligne l'importance d'une prise de décision participative entre la personne concernée et le professionnel de santé (shared decision making). Une telle démarche permettra d'identifier les préférences individuelles en fonction des possibilités offertes.

La compilation et l'évaluation des données scientifiques en vue d'une mise en œuvre d'un programme de dépistage organisé ne relevait pas de la compétence du comité d'experts. Les membres du comité considèrent néanmoins qu'un programme organisé contribuerait à une harmonisation des pratiques, garantirait la qualité du dépistage et permettrait l'exonération des franchises. Un tel programme faciliterait dès lors l'accès au dépistage et améliorerait, en particulier, l'égalité en la matière.

Des études doivent encore être réalisées pour déterminer si et dans quelle mesure des auto-prélèvements HPV pourraient être utilisés dans le cadre du dépistage. L'utilisation de ce type de prélèvements pourrait réduire le stress associé au dépistage et permettait d'atteindre des groupes cibles qui, aujourd'hui, ne bénéficient pas du dépistage.

cancer screening committee

1. Mandate of the Cancer Screening Committee

The National Cancer Screening Committee was established within the framework of the National Strategy against Cancer in Switzerland. The Trusteeship Council is composed of Oncosuisse, the Federal Office of Public Health (FOPH), the Conference of Cantonal Directors of Public Health (GDK-CDS), and Public Health Schweiz. In February 2019, the executive board elected the members of the panel (Table 1).

The mandates entrusted to the committee are as follows:

- It operates as an independent advisory body.
- It addresses questions of cancer screening (population-based screening).
- It appraises the evidence previously assembled by third-party assessment teams and formulates recommendations for screening strategies.
- It takes into account medical, epidemiological, economic, legal, and ethical aspects from a societal and patient-centred perspective.
- It monitors and considers relevant developments in Switzerland and abroad.
- It prepares recommendations for relevant political and professional stakeholders involved in cancer screening.

The committee works in a scientifically rigorous, trustworthy, balanced, and independent manner.

The recommendations of the committee will aim to provide rigorous and independent guidance for evidence-based policy by political and professional stakeholders (Swiss Confederation, cantons, service providers, insurers, professional societies, patient organisations, and non-governmental organisations (NGOs)).

cancer screening committee

Table 1. Members of the Committee of Experts on Cancer Screening

Appraisal Committee of Experts on Cancer Screening

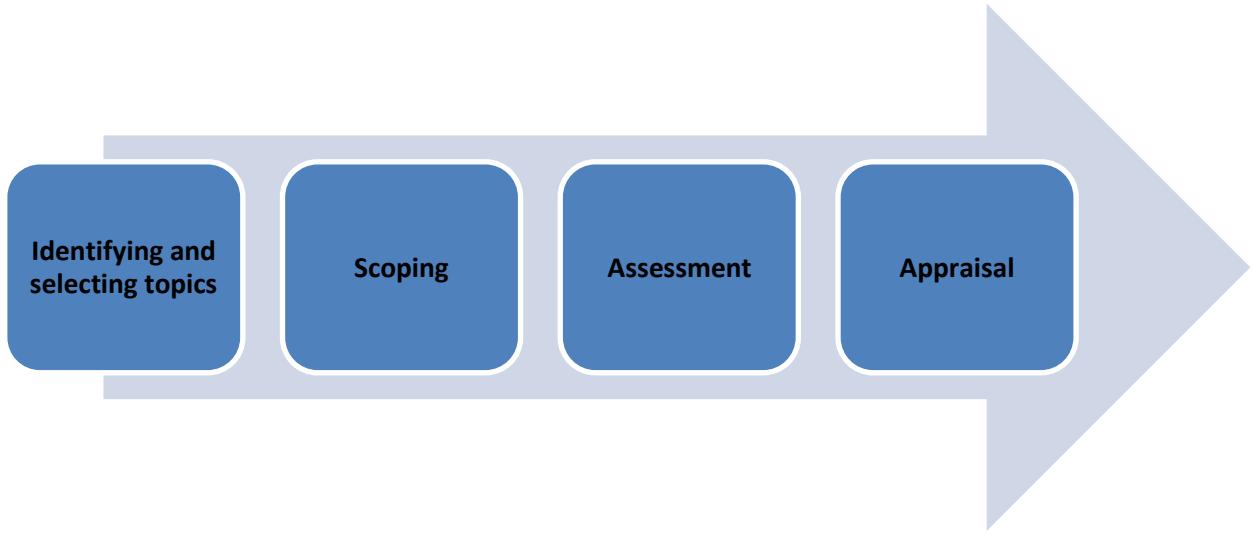
EXPERT	FIELD OF EXPERTISE
Prof. Dr. Marcel Zwahlen Institute for Social and Preventive Medicine, University of Bern (Chairman) **Prof. Dr. med. Thomas Agoritsas** Divisions of Internal Medicine & Clinical Epidemiology, Geneva University Hospitals	Epidemiology, Methodology, Statistics
Prof. Dr. med. Stefan Aebi Chief Physician of Medical Oncology, Lucerne Cantonal Hospital **Prof. Dr. med. Reto Auer** Institute of Primary Health Care (BIHAM), University of Bern, Center for Primary Care and Public Health (Unisanté), Lausanne **Dr. med. Reto Guetg** Independent Medical Examiner, Medical Advisor Federal law on Health Insurance, Bern	Medicine (Clinical Practice and Prevention)
Dr. med. Jacques Fracheboud Retired, formerly Erasmus University Medical Center, Rotterdam, The Netherlands	Screening
Prof. Dr. Matthias Schwenkglenks Institute of Pharmaceutical Medicine, University of Basel; Institute of Epidemiology, Biostatistics and Prevention, University of Zurich	Health Economics
Prof. Dr. med. Samia Hurst-Majno Institute for Ethics, History and the Humanities, University of Geneva	Ethics
lic. iur. MAE Michelle Salathé Medicine Ethics Law, Basel	Law and Ethics
David U. Haerry Chairman, Positive Council, European Patients Academy (EUPATI), Zurich	Patient partner

For the recommendations presented here, there are no financial or other conflicts of interest among the members of the committee.

2. Methods

The Cancer Screening Committee follows nationally and internationally established guidance for the assessment of medical procedures (i.e. “health technology assessment”) [1,2]. The development of the present recommendations followed four steps (fig. 1).

Figure 1: Working process of the Cancer Screening Committee



a. Topic identification and selection

Based on a broad survey of the interested parties, the Cancer Screening Committee prioritised specific topics, considering the current body of evidence, burden of disease, burden of screening (as time and money invested, but also unnecessary worries and further medical clarifications due to false positive or unclear results), and whether there was a current policy reason to address each specific issue. Based on the committee’s proposal, the Trusteeship Council identified the topic of HPV-based screening for cervical cancer as the first topic to be addressed.

In recent years, testing for high-risk human papillomavirus (hrHPV) has been developed and has been proposed by some organisations as an alternative to cytological screening [3,4].

The US Preventive Services Task Force and other organisations have reviewed the evidence quantifying the benefits and harms of cervical cancer screening [3,5,6]. The optimal approach to cervical cancer screening might depend on the age of the screened person (<30 years, 30-35 years, >35 years), the findings of previous screening rounds, and the HPV vaccination status.

In Switzerland, there is currently no structured cervical cancer screening program in place. There are also no reliable data on how many women undergo screening and how often. However, data from health insurance companies and the Swiss Health Survey suggest both the occurrence of over-screening in certain population groups, while other groups are under-screened or even never undergo any screening [7,8].

b. Scoping

The Cancer Screening Committee invited about 20 potential mandate holders to formulate a scoping report on cervical cancer screening in the Swiss context. The question to be addressed by the scoping report was as follows: "*What is the relative performance of different cervical cancer screening strategies that may contain cytology-based and/or HPV-testing based components in different combinations and algorithms?*" The Institute for Evidence in Medicine, Medical Center, University of Freiburg, Germany submitted an offer according to the specifications. An evaluation team composed of Prof. Marcel Zwahlen, Chair Cancer Screening Committee; Aline Flatz, MD, MPH, Scientific Collaborator Swiss Cancer League, Scientific Office; Dr. rer. nat. Rolf Marti, Swiss Cancer League, Head of Research, Innovation and Development, Member of the Managing Board; and Yvonne Grendelmeier, lic. phil., Head Office of the Cancer Screening Committee evaluated the offer according to the award criteria. They considered that the scoping review would help to ensure the rigour and accuracy of the retrieved results. On proposal of the evaluation team, the Cancer Screening Committee commissioned the Institute for Evidence in Medicine, University of Freiburg, Germany, to conduct the scoping.

In the scoping report [9], the questions to be answered were refined and the methods concerning search methods, study identification, review of clinical effectiveness, health-related values and preferences, and health economics were defined (Table 2, PICO). The population of interest was defined as asymptomatic women aged 20 to 70 years. The following screening strategies were to be compared: HPV testing without cytology-testing, HPV testing in combination with cytology (either conventional cytology [Pap smear] or liquid-based cytology [LBC]), and HPV testing with cytology-based triage. For the clinical review, the outcomes of interest were defined as follows: disease-specific and/or overall mortality, morbidity (cervical intraepithelial neoplasia [CIN], cervical cancer) referrals to colposcopy/treatment, false-positive and false-negative screening results, psychological harms, and adverse effects.

Table 2. Patients, Intervention, Comparator, Outcome (PICO) defined in the scoping report

Population	Asymptomatic women aged 20 to 70 years
Intervention	HPV testing without cytology-testing HPV testing in combination with cytology (either conventional cytology or LBC) HPV testing with cytology-based triage
Comparator	Cytology-based testing (either conventional cytology or LBC) without HPV triage Cytology-based testing (either conventional cytology or LBC) with HPV triage
Outcomes	Women's preferences and attitudes: - Preferences related to the healthcare organization - Preferences related to desired, undesired, and competing outcomes - Screening strategy preferences - Treatment preferences (after a positive result) Clinical effectiveness: - Mortality (disease-specific and/or overall) - Morbidity (CIN, cervical cancer) - Referrals to colposcopy/treatment - False-positive and false-negative screening results - Psychological harms - Adverse effects Health economic assessment - Costs per QALY gained - Costs of different HPV-based screening strategies - Costs of different cytology-based screening strategies

HPV=Human Papillomavirus; LBC=liquid-based cytology; CIN=cervical intraepithelial neoplasia; QALY=quality-adjusted life year

Medical societies and other stakeholders were invited to comment on the drafted questions, and changes were made accordingly (available on www.cancerscreeningcommittee.ch).

c. Assessment

The Cancer Screening Committee appointed the Institute for Evidence in Medicine, University of Freiburg to undertake the systematic collection and assessment of the available evidence based on the scoping report.

For the assessment report, systematic searches were performed in seven databases to identify randomised trials and non-randomised studies focusing on different aspects of cervical cancer screening, as follows:

i. Women's attitudes towards HPV screening
ii. Clinical assessment
iii. Health economic assessment

Searches for existing systematic reviews and guidelines were also performed using different platforms. The risk of bias and applicability of the results of the included studies concerning women's attitudes were assessed using the Mixed Methods Appraisal Tool (MMAT) for Evaluating Primary Research Studies [10,11]. The certainty of evidence regarding patient-important clinical outcomes defined in the PICO was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [12]. In the health economics part, the methodological quality of the economic evaluations was assessed using the "Phillips checklist" [13,14], or the "Evers checklist" in case of economic evaluations not applying economic modelling [15]. The quality of reporting of the identified health economic studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [16]. A budget impact analysis for Switzerland was performed.

The assessment report was completed in December 2020 [17]. Stakeholders were invited to comment on the report in writing by January 2021. The full assessment report has been published on the committee website.

d. Appraisal

The Cancer Screening Committee appraised the synthesised evidence in three meetings as per the EtD framework [18,19], considering the following: (1) women's attitudes, values, and preferences (including their variability and uncertainty); (2) the balance of the estimated benefits and harms; (3) the certainty of these estimates (i.e. quality of the evidence); (4) resource considerations; (5) health equity; (6) acceptability; and (7) feasibility of implementing the interventions. In addition to the assessment report, the committee took into account the feedback received from the stakeholders, the expert letter from the Swiss Society for Gynaecology and Obstetrics [8], and guidelines from other countries. In the first two appraisal meetings, external

experts[1] were present during part of the meeting to answer technical and practical questions from the committee.

After the second appraisal meeting, the first version of this recommendation report was drafted and discussed among the members of the committee. The report was finalised at the third appraisal meeting. The committee issued recommendations based on acceptability, clinical effectiveness, harms, cost-effectiveness, and budget impact of HPV-based screening. Health equity, accessibility, and feasibility were also considered. The committee followed the GRADE approach, in which recommendations can either be strong or weak (also known as conditional). The key determinants of the strength of a recommendation are based on the EtD framework to balance the desirable and undesirable consequences of alternative management strategies. The committee used the GRADE wording “we recommend” for strong recommendations and “we suggest” for weak recommendations, with either “weak recommendation” or “strong recommendation” mentioned in brackets at the end of each given statement for further clarity.

In the absence of a detailed analysis of ethical, legal, and social implications (ELSI) aspects in the specific context of HPV and in the context of cervical cancer screening in general, the assessment report did not examine these aspects. However, the expert committee has commented on ELSI aspects that may be relevant, and these comments have been presented in Chapter 6.

[1] Dr. med. Brigitte Frey Tirri, Chief Physician, Specialist in Gynaecology and Obstetrics FMH, Cantonal Hospital Baselland;
Dr. André Kind, Deputy Chief Physician Gynaecology, Head Physician Policlinic and Gynaecological Dysplasia Unit, University Hospital Basel;
Prof. Patrick Petignat, Department of Women-Children-Teenagers, Division of Gynaecology HUG

3. Background on cervical cancer

The information presented here is a summary of the chapter “1. Background” in the assessment report [17].

a. Epidemiology of cervical cancer

Cervical cancer is a major public health problem worldwide and the fourth most common cancer affecting women [20]. In 2018, the age-standardised incidence per year ranged from 4 per 100,000 women in Switzerland (one of the lowest incidences worldwide) and approximately 9 per 100,000 in Germany, England, and the Netherlands, to more than 40 per 100,000 in some parts of Africa [8,21,22]. In developed countries, the number of women who die from cervical cancer has decreased by almost 50% over the past 30 years. In Switzerland, approximately 70 women die from cervical cancer every year [23]. The 5-year and 10-year survival rates are approximately 70% and 66%, respectively [23]. The average age at diagnosis of invasive cervical cancer is 55 years.

b. Risk factors for cervical cancer

The main cause of cervical cancer is persistent infection with sexually transmitted human papillomaviruses (HPV), and approximately 99% of cervical cancers are associated with these viruses [20,24,25]. There are over 100 different HPV types; the prevalence rates of HPV infection vary widely between different geographic regions, countries, and age groups, and reach a peak between the ages of 20 and 24 [26–28]. Asymptomatic HPV infections are common, and usually resolve without any consequences. Persistent infections with high-risk viruses (HPV genotypes with oncogenic potential, particularly HPV16 and HPV18) account for approximately 70% of all cases of cervical carcinoma [29,30].

Cervical cancer generally develops over many years, and is associated with characteristic precancerous changes in the cervical tissue denoted as cervical intraepithelial neoplasia (CIN). CIN is categorised as CIN1 (mild dysplasia), CIN2 (moderate to marked dysplasia), and CIN3 (severe dysplasia to carcinoma in situ) [31,32]. CIN2+ is defined as CIN grade 2 or worse (CIN3, adenocarcinoma in situ, invasive cervical cancer). Approximately one out of 100 cases of CIN1 and 12 to 30 out of 100 cases of CIN2 or CIN3 progress to invasive cervical cancer [32].

c. Early detection and prevention measures of cervical cancer

Among all malignant tumours, cervical cancer is one that can most effectively be prevented by screening [33,34]. Cervical cancer screening has conventionally been based on cytological testing. In conventional cytology (commonly known as the smear test, Pap test, or Pap smear), cells are sampled from the cervix using a spatula or brush and transferred directly onto a glass slide for microscopic examination. In liquid-based cytology, the sampled material is deposited in a preservative solution [35]. More recently, there has been a rapid increase in the development of testing systems to detect the presence of hrHPV. A review from 2020 [36] identified 193 commercially available HPV tests based on DNA or hrHPV E6/E7 mRNA analysis. In HPV-based screening, two main strategies can be distinguished, as follows:

- Cotesting is a combination of HPV testing and conventional or liquid-based cytology with a defined procedure for each combination of test results.
- Primary HPV testing implies primary HPV testing only, with cytology triage in HPV-positive cases.

d. Current screening situation in Switzerland and abroad

Most international guidelines recommend that women between the ages of 25 and 65, 70, or 74 should be invited for cervical cancer screening every three to five years [37]. However, there are variations in how these guidelines are implemented by individual countries, based on age [8], testing modality (cytology or HPV), and screening interval. Germany has implemented an organised screening programme in 2020. Women between the ages of 20 and 34 years are entitled to one cytological examination per year. From the age of 35 (no upper age limit), women can undergo a combined screening test consisting of a cytological examination and a HPV test once every three years [38]. However, invitations for the screening program are only sent out every five years.

In the UK, the screening interval is three years up to the age of 49 years, and five years for women aged 50 years or older. Primary HPV-based screening was fully implemented in 2019. In this screening test, a sample is first tested for HPV, and if the test result is positive, a cytology assessment is additionally performed.

Switzerland provides opportunistic screening, which relies on the initiative of the individual person or her physician. It remains unclear how many persons in the target groups make use of screening today. Approximately 500,000 screening examinations are invoiced annually via health insurance

funds [17]. However, this figure does not take into account out-of-pocket payments. In the Swiss Health Survey 2017, approximately 50% of women of screening age reported that they had undergone a screening examination in the last 12 months. This would result in 1.4 million examinations. The actual uptake is probably somewhere between 500,000 and 1.4 million examinations.

According to Article 12e, Paragraph b of the Ordinance on Health Care Services, gynaecological examinations including cytology-based screening are reimbursed by the statutory health insurance at annual intervals for the first two times, and thereafter at three-year intervals. HPV detection is not covered as a cervical screening modality. However, the HPV test is paid for by health insurance after a pathological result of cytology-based screening. Since cytology-based screening is not carried out within an organised screening program, it is subject to deductibles and retention fees according to the standard rules of the statutory health insurance.

In March 2018, the Swiss Society for Gynaecology and Obstetrics published an expert letter summarising its recommendations for cervical cancer screening [8]. The letter recommends a screening test every three years for those aged 21 to 70 years; this screening test consists of cytological screening for those aged below 30 years, and cytological screening or primary HPV-based screening for those aged 30 to 70 years. However, the authors point out that the HPV test in primary screening is currently not covered by the statutory health insurance in Switzerland. The expert letter adds that in primary HPV-based screening, cervical cytology is performed in the case of hrHPV positivity. Further procedures must be determined according to a defined algorithm. The collecting physician should be responsible for the follow-up and determination of the procedure in case of abnormal findings. The experts also stated that only validated tests may be used for HPV-based screening.

In contrast to organised screening, opportunistic cervical cancer screening is often characterised by heterogeneous quality and high coverage in selected populations that are screened too frequently, while socioeconomically deprived population groups are often screened less frequently.

e. HPV vaccination

In addition to cervical cancer screening, the Federal Office of Public Health and the Federal Commission for Vaccinations recommend that girls and boys should be vaccinated against HPV, preferably between the ages of 9 and 14 [22,39]. In Switzerland, approximately 59% of all 16-year-old girls and 17% of 16-year old boys were completely vaccinated against hrHPV in 2019 [40]. Since the introduction of the vaccination recommendation for young women in 2007, the vaccine

has been modified several times, as not all high-risk types were initially covered. With increasing vaccination coverage in the Swiss population, the benefits and conditions for cervical cancer screening may need to be reassessed.

4. Evidence from the assessment report

The Cancer Screening Committee commissioned an assessment report comparing HPV-based screening approaches with cytology-testing considering clinical effectiveness, screening-related harms, women's attitudes towards HPV-based screening, cost-effectiveness, and budget impact [17]. The results are summarised below:

a. Women's attitudes, values, and preferences towards HPV-based screening

Few data are available on women's attitudes, values, and preferences towards HPV-based screening. Three qualitative studies and one quantitative study met the inclusion criteria. In total, 742 women aged 18 to 65 years were included across all studies. The qualitative studies investigated attitudes towards HPV testing with a special focus on personal implications, using in-depth interviews and/or focus group discussions. The quantitative study compared the preferences of women related to HPV testing and conventional cytology using an "interviewer-administered" survey.

The assessment report identified three specific factors impacting women's attitudes towards HPV-based screening strategies, as follows: (i) Understanding the personal risk of a HPV infection. For example, many women who felt that they were not at risk for a sexually transmitted infection (owing to their lifestyle) felt no need to undergo HPV-based screening. (ii) Understanding the definition of HPV (related to its transmission). In the available studies, a majority of women were sceptical towards an HPV-based screening strategy because HPV is a sexually transmitted disease; they felt that being tested may lead to stigmatisation. (iii) Understanding the purpose of screening. Women who understood the purpose of screening appreciated the benefits of HPV testing.

b. Evidence on clinical effectiveness and harm

For the clinical assessment, ten randomised trials including 447,105 women were identified. The women's age at enrolment varied between 25 and 64 years across most trials. The intervals between screening rounds were three and four years for trials with two screening rounds. Furthermore, five non-randomised studies comparing primary HPV testing with cytology were eligible for the assessment, and included a total of 678,631 women.

Clinical effectiveness outcomes

There were no trials/studies reporting *overall or cancer-related mortality*.

Pooled evidence from the randomised controlled trials comparing HPV-based screening with cytology is shown in Table 3.

There was no difference in the risk of being diagnosed with *cervical cancer* between women screened with HPV-testing (in any combination) and those screened with cytology-testing.

Compared to cytology-testing, HPV-testing (in any combination) detected four more *cases of CIN2+* per 1000 women (ranging from one to seven more, moderate certainty) and one more *case of CIN3+* per 1000 women (ranging from zero to three more in primary HPV-based testing, moderate certainty; and from zero to two more in cotesting, low certainty). In the second screening round (follow-up screening), HPV-based testing (in any combination) compared to cytology-testing detected fewer cases of precancerous lesions (Table 3).

In the first round of screening, the effect estimates indicate that more women across all ages undergoing HPV-testing may be *referred for colposcopy*, in comparison with those receiving cytology-testing, as follows: about three more per 1,000 women (ranging from one fewer to eight more, low certainty) in primary HPV-testing, and one more (ranging from three fewer to seven more, moderate certainty) in cotesting. Similarly, in the first round of screening, seven more per 1,000 women with CIN2+ or adenocarcinoma in situ (ranging from one to 21, moderate certainty) undergoing HPV-based testing may be *referred for treatment* with primary HPV testing, compared to women undergoing cytology testing. Data from the second round of screening indicated that women undergoing HPV-based testing may be equally or less likely to be referred for treatment compared to women receiving cytology testing (Table 3).

The proportion of women showing *psychological distress* evaluated using self-reported General Health Questionnaires did not differ between the screening groups, either in randomised trials or in the non-randomised study.

cancer screening committee

Table 3. Evidence from randomised controlled trials comparing HPV-based screening with cytology-based screening by screening strategy and screening round

Outcome	Overall certainty (GRADE)	Relative risk (95% CI)	Risk with cytology	Risk difference HPV-cytology (95% CI)
Primary HPV, 1st round			**per 1.000 women**	
CIN2+	moderate	1.81 (1.22-2.68)	4	4 more (1-7 more)
CIN3+	moderate	1.78 (1.15-2.75)	2	1 more (0-3 more)
Cervical Cancer	low	0.89 (0.55-1.44)	0	0 (0-0)
Colposcopy referrals	low	1.36 (0.93-2.00)	8	3 more (1 fewer – 8 more)
Treatment referrals	moderate	3.59 (1.52-8.49)	3	7 more (1-21 more)
Primary HPV, 2nd round				
CIN2+	moderate	0.35 (0.18-0.67)	1	1 fewer (1 fewer -0)
CIN3+	moderate	0.25 (0.10-0.68)	1	1 fewer (1 fewer -0)
Cervical Cancer	low	0.15 (0.01-2.81)	0	0 fewer (0-0)
Treatment referrals	moderate	0.35 (0.18-0.67)	1	1 fewer (1 fewer -0)
Cotesting, 1st round				
CIN2+	moderate	1.40 (1.12-1.76)	9	4 more (1-7 more)
CIN3+	low	1.07 (0.91-1.26)	6	1 more (0 -2 more)
Cervical Cancer	low	0.57 (0.18-1.87)	0	0 (0-0)
Colposcopy referrals	moderate	1.07 (0.83-1.39)	18	1 more (3 fewer-7 more)
Treatment referrals	moderate	1.36 (1.01-1.84)	10	4 more (0 -9 more)
Cotesting, 2nd round				
CIN2+	moderate	0.74 (0.57-0.97)	3	1 fewer (1 fewer-0)
CIN3+	low	0.69 (0.48-1.00)	2	1 fewer (1 fewer-0)
Cervical Cancer	low	0.38 (0.06-2.21)	0	0 (0-0)
Treatment referrals	low	0.83 (0.59-1.18)	2	0 (1 fewer -0)

CI=confidence interval; CIN=cervical intraepithelial neoplasia; CIN2+=moderate to marked dysplasia; CIN3+=severe dysplasia to carcinoma in situ; GRADE=Grading of Recommendations, Assessment, Development, and Evaluation; HPV=human papillomavirus; Cotesting=combination of HPV testing and conventional or liquid-based cytology; Primary HPV testing=HPV testing, with cytology triage only in HPV-positive cases

c. Health economic assessment

The assessment report identified 21 economic evaluations – 18 primary studies and three Health Technology Assessments (HTAs). These evaluations were model-based cost-effectiveness analyses using input data from the literature, and measured the additional costs per quality-adjusted life year (QALY) gained over long time horizons, expressed as the incremental cost-effectiveness ratio (ICER). Not all studies reported absolute differences in costs and effects; this may be considered as a methodological deficit.

All studies included in the assessment report were conducted in industrialised countries that are socioeconomically comparable to Switzerland. The majority of this heterogeneous set of studies (screening intervals were between three and five years in majority of the cases) showed that HPV-based screening is more cost-effective than cytology-based screening, according to the standards of the respective jurisdictions. Switzerland has no formal threshold for the acceptable cost for the gain of a QALY. However, the ICERs reported in the international studies indicate that three- to five-yearly HPV-based screening may be cost-effective and acceptable in Switzerland. Firm conclusions addressing the optimal screening interval and women's age in terms of cost-effectiveness could not be derived conclusively, though longer intervals seem to be more cost-effective. In addition, the data suggested that the ICER did not worsen and possibly even improved when vaccinated women were screened, probably due to the decreased need for colposcopies.

The financial impact of adopting new screening tests and strategies was approximated based on recent data from Santésuisse. The base-case scenario aimed to reflect current cervical cancer screening in Switzerland, and the estimated total costs were 22 CHF million per year for the tests alone. Assuming that no additional gynaecologist visits are needed and testing costs remain constant, a shift towards cotesting would be associated with an increase in total testing costs to 110 CHF million per year (budget impact, CHF 88 million per year). A shift to primary HPV testing would be associated with an increase in total testing costs to 91 CHF million per year (budget impact, CHF 69 million per year). The underlying assumptions on screening participation were probably an underestimation, as there are individuals who chose a higher deductible level, and pay for the test themselves. The real number of tests and the extent of out-of-pocket payments are not known. The budget impact results do not consider the effect of a potential change in the screening intervals.

For the budget impact analysis, costs of CHF 40 for a cytology-based screening test and CHF 180 for a HPV test were assumed. The price for the HPV test is substantially higher in Switzerland than

in neighbouring countries, even considering the generally higher cost level in Switzerland. The price of the HPV test is crucial for the cost-effectiveness of the screening strategy.

5. Recommendations

The recommendations are aimed at the following target groups: women, non-binary persons, and transgender men with a cervix aged 21 to 70 years.

I. **For persons in the target groups aged 30 to 70 years, the committee suggests primary HPV-testing with subsequent cytology triage as the method of cervical cancer screening (GRADE weak recommendation).**

Justification: The values and preferences of persons in the target groups remain unclear and are likely to vary. With primary HPV testing followed by cervical cytology in cases of hrHPV positivity, approximately six more precursor lesions per 1,000 women could be detected and treated than with cytology-based screening. The data from the health economic assessment indicate that primary HPV testing is likely cost-effective compared to cytology-based screening. The HPV test has certain practical advantages; it opens up the option of sample collection by the target persons themselves, without the need for a visit to a gynaecologist for the sampling. This may considerably reduce the burden of screening and could improve accessibility. However, there is no clear evidence of the effectiveness of HPV tests compared to cytology concerning hard outcomes, and the certainty for a reduction in cancer incidence is low; overall and cancer mortality is not reported in the available trials.

Cotesting as an alternative HPV testing strategy would require defining algorithms for the work-up of different combinations of test results. This would add substantial complexity to the implementation. Cotesting would likely result in higher costs. The assessment report identified no direct comparison between primary HPV testing and HPV cotesting. However, each strategy was compared with cytology, showing a similar range of effectiveness in preventing precancerous lesions to cytology (low to moderate certainty).

In this context and the absence of reliable data on the target persons' preferences, the committee believed that a majority, but not all, informed persons concerned would opt for primary HPV testing, and thus has issued a weak recommendation in favour of primary HPV testing.

II. **For persons in the target groups aged 21 to 29 years, the committee recommends cervical cancer screening with cytology (GRADE strong recommendation).**

Justification: Cervical cancer screening with cytology has already been recommended for ages 21 years and above. The majority of target persons acquires an HPV infection between the ages of 20 and 30 years [41]. In this young age, primary HPV-based screening is unfavourable due to the frequent occurrence of asymptomatic HPV infections that often resolve without any consequences. For this reason, it is more appropriate and less harmful to work up only cytological abnormalities in younger persons, rather than following up every HPV infection.

III. **Regardless of age group, the committee recommends a screening interval of three years instead of one year (GRADE strong recommendation).**

Justification: Although a three-year interval is already recommended for cervical cancer screening, many women are still annually examined using cytology, with a large variability in practice. The data considered in the assessment report do not allow for a direct comparison of screening intervals with reference to clinical effectiveness. However, there is no indication of a clinical advantage of yearly screening. Short screening intervals increase the likelihood of harm due to more frequent false-positive results, whereas longer screening intervals lower the burden of screening. Although the health economic assessment did not directly compare interval lengths, the data suggest that longer intervals are more cost-effective.

IV. **Regardless of age group, the committee suggests a screening interval of five years, as opposed to three years (GRADE weak recommendation).**

Justification: The evidence of clinical effectiveness and harm does not point to any clinically meaningful differences between the three- and five-year screening intervals. From an economic point of view, a five-year screening interval is more cost-effective than a three-year interval. However, given that many women are still screened annually today, a switch to five-year intervals outside of an organised screening program may not be acceptable to all stakeholders. There is also a lack of data on the preferences and values of the target groups with regard to screening intervals, even though one could expect that a longer interval would lower the burden of screening.

The committee issues a weak recommendation, emphasising the need for shared decision-making with persons in the target groups.

V. The committee recommends the reimbursement (coverage) of the HPV test as a screening test by the statutory health insurance (GRADE strong recommendation).

Justification: The data on the preferences of women, clinical effectiveness, and health economic assessment show that primary HPV testing is slightly superior to cytology-based screening at acceptable costs. To ensure equity of access to cervical cancer screening with primary HPV testing, HPV-testing in people in the target groups should be reimbursed by the health insurers.

6. Ethical, legal, social, and implementation considerations

a. Information and reachability of the target groups

Available data suggests that a substantial proportion of the target population is over-screened, and undergoes annual screening tests. However, others may not undergo any screening. This cannot be solved solely through issuing recommendations for a particular test. A range of initiatives are needed to alter the situation. Therefore, the change from cytology-based screening to primary HPV testing should be accompanied by information campaigns tailored in particular to those who have not had access to screening so far, or did not use it. To implement the recommendations, gynaecologists and other important players in the healthcare system must also be targeted. In addition, the campaigns would need to be well coordinated with the HPV vaccination campaign to exploit synergies, and additionally to explain the need for both vaccination and screening.

b. Shared decision-making

As the evidence only allows for weak or conditional recommendations on most issues, different choices will be appropriate for different persons according to their own context, values, and preferences. Therefore, sound information and shared decision-making are critical. To implement this, the development of standardised decision aids would be helpful. Healthcare professionals should also receive dedicated training on shared decision-making and the use of such decision aids in clinical encounters. These decision aids can support individuals in the target groups with reference to decisions on the strategy that meets their specific needs and health priorities.

c. Test costs

The price of a HPV test in Switzerland is 180 CHF; this is significantly higher than the cost in the neighbouring countries, even considering the higher cost of living in Switzerland. There are two aspects to pricing, as follows: first, the market price for a test, and second, the amount laboratories are allowed to charge for a test. With a higher number of tests, the price per test may decrease. The maximum reimbursement will need to be set by the statutory health insurance if HPV testing for cervical cancer screening gets covered. The outcomes of these processes are conditional on the decisions taken by governmental authorities. It is unclear how many of the tests are paid out-of-pocket today, but these out-of-pocket payments exist and contribute to inequality in access to screening.

To prevent economically driven disparities in access to care, financial barriers for persons participating in the screening such as deductibles, should be abolished. Deductibles have been set up to reduce demand for care, and this concept is out of line in the context of screening or prevention where high participation is desired.

d. Organized screening program

The optimum way to increase accessibility and to appeal to the widest possible range of persons in the target groups is to introduce a well-organised screening program. Comparing opportunistic screening as it currently exists in Switzerland with an organised screening program was beyond the scope of this report. Therefore, the committee cannot make formal recommendations for this broader question. However, as confirmed by the input of the stakeholders and based on discussions with external experts, the committee shares a consensus that such a program is clearly preferable. The introduction of a new organised program would facilitate a change in the screening method and the implementation of a three-year (or a five-year) screening interval. Most importantly, a well-organized screening program would increase accessibility and equity. This would make it easier to exempt cervical cancer screening from requiring a deductible, and thus reduce disparities caused by economic status. On the other hand, the committee is aware that the introduction of an organised screening program at the national level would be a novelty in the Swiss system, and would require strong political support.

e. Self-sampling

One advantage of HPV testing is the feasibility of self-sampling, which is possible without compromising on quality. This option needs to be carefully considered and discussed, especially because it could possibly reach sub-populations within the target groups who do not undergo screening examinations currently, and do not see a gynaecologist regularly. In addition, the importance of self-testing for early cancer detection was emphasised in the wake of the coronavirus disease (Covid-19) pandemic during which many screening programmes were temporarily interrupted, and doctor visits were postponed [42,43].

f. Vaccination

With the increase in the number of people who are vaccinated against hrHPVs, the milieu for cervical cancer prevention is changing, with implications at different levels. The awareness of the causal association between HPV and cervical cancer is likely to increase with time. It can also be

assumed that vaccinated individuals may be more willing to consider longer test intervals. With the increase in the number of vaccinated people, the number of CIN+, and correspondingly the diagnostic accuracy may decrease [44]. Approaches to testing strategies may thus need to be further revised in the future.

g. Persons in the target groups age 71 and older

The screening strategy for persons older than 70 years was not within the scope of this HTA. There is limited data pertaining to this population. The potential benefits of screening for older women can only be speculated upon; such speculations will be based on the indirect application of evidence from younger populations and assumptions about the exposure of this population to HPV and the subsequent risk of developing invasive cancer in their lifetime.

7. References

1 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE: Going from evidence to recommendations. BMJ. 2008;**336**:1049–51. doi:10.1136/bmj.39493.646875.AE

2 Alonso-Coello P, Schünemann HJ, Moberg J, *et al.* GRADE Evidence to Decision (EtD) frameworks: A systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ* 2016;**353**. doi:10.1136/bmj.i2016

3 Melnikow J, Henderson JT, Burda BU, *et al.* Screening for cervical cancer with high-risk human papillomavirus testing updated evidence report and systematic review for the us preventive services task force. *JAMA - J Am Med Assoc* 2018;**320**:687–705. doi:10.1001/jama.2018.10400

4 Rebolj M, Rimmer J, Denton K, *et al.* Primary cervical screening with high risk human papillomavirus testing: Observational study. *BMJ* 2019;**364**. doi:10.1136/bmj.l240

5 Koliopoulos G, Nyaga VN, Santesso N, *et al.* Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database Syst. Rev. 2017;**2017**. doi:10.1002/14651858.CD008587.pub2

6 Curry SJ, Krist AH, Owens DK, *et al.* Screening for cervical cancer us preventive services task force recommendation statement. *JAMA - J Am Med Assoc* 2018;**320**:674–86. doi:10.1001/jama.2018.10897

7 Zwahlen M. Früherkennung. In: Oncosuisse, ed. *Nationales Krebsprogramm für die Schweiz 2011-2015*. 2011. 48–61.

8 Frey Tirri B, Patrick P, Jacot-Guillarmod M, *et al.* Empfehlungen für die Gebärmutterhalskrebsvorsorge. 2018. https://www.sggg.ch/fileadmin/user_upload/Formulardaten/akt_50_D_Gebaermutterhalskrebsvorsorge_01.03.18.pdf

9 Schmucker C, Kaier K, Rücker G, *et al.* Cervical Cancer Screening with Human Papillomavirus Testing - Scoping report. Freiburg: 2020. https://cancerscreeningcommittee.ch/wp-content/uploads/2019/11/scoping-report-HPV-screening20191024.pdf

10 Pluye P, Hong QN. Combining the power of stories and the power of numbers: Mixed methods research and mixed studies reviews. In: *Annual Review of Public Health*. Annual Reviews Inc. 2014. 29–45. doi:10.1146/annurev-publhealth-032013-182440

11 Hong QN, Fàbregues S, Bartlett G, *et al.* The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. *Educ Inf* 2018;**34**:285–91. doi:10.3233/EFI-180221

12 Guyatt GH, Oxman AD, Vist GE, *et al.* GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–6. doi:10.1136/bmj.39489.470347.ad

13 Philips Z, Bojke L, Sculpher M, *et al.* Good practice guidelines for decision-analytic modelling in health technology assessment: A review and consolidation of quality assessment. Pharmacoeconomics. 2006;**24**:355–71. doi:10.2165/00019053-200624040-00006

14 Cooper N, Coyle D, Abrams K, *et al.* Use of evidence in decision models: An appraisal of health technology assessments in the UK since 1997. J. Heal. Serv. Res. Policy. 2005;**10**:245–50. doi:10.1258/135581905774414187

15 Evers S, Goossens M, De Vet H, *et al.* Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5. doi:10.1017/s0266462305050324

16 Husereau D, Drummond M, Petrou S, *et al.* Consolidated health economic evaluation reporting standards (CHEERS) statement. *Value Heal* 2013;**16**:e1. doi:10.1016/j.jval.2013.02.010

17 Schmucker C, Nury E, Rücker G, *et al.* Cervical Cancer Screening with Human Papillomavirus Testing-

Health Technology Assessment. 2021.

18 Moberg J, Oxman AD, Rosenbaum S, *et al.* The GRADE Evidence to Decision (EtD) framework for health system and public health decisions. Heal. Res. Policy Syst. 2018;**16**. doi:10.1186/s12961-018-0320-2

19 Alonso-Coello P, Schünemann HJ, Moberg J, *et al.* GRADE Evidence to Decision (EtD) frameworks: A systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ* 2016;**353**. doi:10.1136/bmj.i2016

20 Cervical cancer. https://www.who.int/health-topics/cervical-cancer#tab=tab_1 (accessed 12 Apr 2021).

21 Arbyn M, Weiderpass E, Bruni L, *et al.* Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Heal* 2020;**8**:e191–203. doi:10.1016/S2214-109X(19)30482-6

22 Robert Koch-Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. Krebs in Deutschland 2015/2016: Robert Koch-Institut, 2019 - Google Suche. https://www.google.com/search?client=firefox-b-d&q=Robert+Koch-Institut%2C+Gesellschaft+der+epidemiologischen+Krebsregister+in+Deutschland+e.V.+Krebs+in+Deutschland+2015%2F2016%3A+Robert+Koch-Institut%2C+2019 (accessed 12 Apr 2021).

23 Nationale Krebsregistrierungsstelle NKRS. Statistiken. 2020. https://www.nkrs.ch/de/stat/

24 Walboomers JMM, Jacobs M V., Manos MM, *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;**189**:12–9. doi:10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F

25 Crosbie EJ, Einstein MH, Franceschi S, *et al.* Human papillomavirus and cervical cancer. Lancet. 2013;**382**:889–99. doi:10.1016/S0140-6736(13)60022-7

26 Baussano I, Franceschi S, Gillio-Tos A, *et al.* Difference in overall and age-specific prevalence of high-risk human papillomavirus infection in Italy: Evidence from NTCC trial. *BMC Infect Dis* 2013;**13**. doi:10.1186/1471-2334-13-238

27 Sargent A, Bailey A, Almonte M, *et al.* Prevalence of type-specific HPV infection by age and grade of cervical cytology: Data from the ARTISTIC trial. *Br J Cancer* 2008;**98**:1704–9. doi:10.1038/sj.bjc.6604324

28 Dunne EF, Unger ER, Sternberg M, *et al.* Prevalence of HPV infection among females in the United States. *J Am Med Assoc* 2007;**297**:813–9. doi:10.1001/jama.297.8.813

29 Schiffman M, Castle PE, Jeronimo J, *et al.* Human papillomavirus and cervical cancer. Lancet. 2007;**370**:890–907. doi:10.1016/S0140-6736(07)61416-0

30 Clifford G, Franceschi S, Diaz M, *et al.* Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases. *Vaccine* 2006;**24**. doi:10.1016/j.vaccine.2006.05.026

31 McCredie MR, Sharples KJ, Paul C, *et al.* Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol* 2008;**9**:425–34. doi:10.1016/S1470-2045(08)70103-7

32 Tota JE, Bentley J, Blake J, *et al.* Introduction of molecular HPV testing as the primary technology in cervical cancer screening: Acting on evidence to change the current paradigm. *Prev Med (Baltim)* 2017;**98**:5–14. doi:10.1016/j.ypmed.2016.11.029

33 Arbyn M, Rebolj M, De Kok IMCM, *et al.* The challenges of organising cervical screening programmes in the 15 old member states of the European Union. *Eur J Cancer* 2009;**45**:2671–8. doi:10.1016/j.ejca.2009.07.016

34 Murphy J, Kennedy EB, Dunn S, *et al.* HPV Testing in Primary Cervical Screening: A Systematic Review and Meta-Analysis. *J Obstet Gynaecol Canada* 2012;**34**:443–52. doi:10.1016/S1701-2163(16)35241-0

35 Denton KJ. Liquid based cytology in cervical cancer screening. Br. Med. J. 2007;**335**:1–2. doi:10.1136/bmj.39262.506528.47

36 Poljak M, Oštrbenk Valenčak A, Gimpelj Domjanič G, *et al.* Commercially available molecular tests for human papillomaviruses: a global overview. Clin. Microbiol. Infect. 2020;**26**:1144–50. doi:10.1016/j.cmi.2020.03.033

37 Arbyn M, Anttila A, Jordan J, *et al.* European guidelines for quality assurance in cervical cancer screening. Second edition-summary document. Ann. Oncol. 2010;**21**:448–58. doi:10.1093/annonc/mdp471

38 Richtlinie für organisierte Krebsfrüherkennungsprogramme und Krebsfrüherkennungs-Richtlinie: Programm zur Früherkennung von Zervixkarzinomen - Gemeinsamer Bundesausschuss. https://www.g-ba.de/beschluesse/3597/ (accessed 12 Apr 2021).

39 Human papillomavirus vaccines: WHO position paper, May 2017 - PubMed. https://pubmed.ncbi.nlm.nih.gov/28530369/ (accessed 12 Apr 2021).

40 Bundesamt für Gesundheit. Durchimpfung von 2-, 8- und 16-jährigen Kindern und Jugendlichen in der Schweiz, 2017–2019. *BAG-Bulletin 16* 2021;:12–9.file:///C:/Users/Nsteck/AppData/Local/Temp/2101044_BAG_Bulletin_DE_16_2021_Durchimpfung.pdf

41 Burger EA, Kim JJ, Sy S, *et al.* Age of acquiring causal human papillomavirus (HPV) infections: Leveraging simulation models to explore the natural history of HPV-induced cervical cancer. *Clin Infect Dis* 2017;**65**:893–9. doi:10.1093/cid/cix475

42 Gorin SNS, Jimbo M, Heizelman R, *et al.* The future of cancer screening after COVID-19 may be at home. Cancer. 2021;**127**:498–503. doi:10.1002/cncr.33274

43 Jaklevic MC. Pandemic Spotlights In-home Colon Cancer Screening Tests. JAMA - J. Am. Med. Assoc. 2021;**325**:116–8. doi:10.1001/jama.2020.22466

44 Lei J, Ploner A, Lehtinen M, *et al.* Impact of HPV vaccination on cervical screening performance: a population-based cohort study. *Br J Cancer* 2020;**123**:155–60. doi:10.1038/s41416-020-0850-6