The Future Role for Colposcopy in Europe

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■ **Abstract:** Improvements in the performance of cervical screening may be limited by the diagnostic performance of colposcopy. Nonetheless, colposcopy remains the best available tool to assess women considered at high risk for having or developing cervical cancer. The provision and role of colposcopy across Europe is variable. Introduction of vaccination against human papillomavirus (HPV) types 16 and 18 as well as the possible switch to HPV-based screening is likely to change the profiles of women presenting to colposcopy services and provide management difficulties for the colposcopist.

The standard of colposcopy in Europe can be maintained or improved despite a variable availability of screening. The prevalence of cervical intraepithelial neoplasia grade 3 may decrease for women having had HPV vaccination. The incidence of cervical intraepithelial neoplasia grade 3 and cervical cancer in second and subsequent rounds of HPV-based screening are likely to decrease compared to cytology-based screening. In HPV-based screening, the numbers of women with no detectable or minor abnormalities at colposcopy and with screen-detected glandular disease are likely to increase. We have considered how these issues will affect states that have varying implementation of organized cervical screening programs and varying degrees of implementation of HPV testing or vaccination.

The development of quality assurance across Europe accompanying these program changes is discussed. ■

Key Words: colposcopy, human papillomavirus 16, human papillomavirus 18, health care quality assurance, early detection of cancer

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Well-organized screening reduces the incidence and death rate from cancer of the cervix. Incorporation of quality assurance for all aspects of the screening program seems essential to ensure this outcome. Colposcopy has a subjectivity that may see its performance as the gold standard for diagnosis lag behind advances in screening and secondary testing. Cytology-based screening has a moderate sensitivity to detect high-grade cervical intraepithelial neoplasia (CIN) and several developments are at various stages of implementation, which will soon impact on cervical screening programs.

Throughout Europe, there is a variation of practice with colposcopy supported by quality control procedures predominantly in Northern and parts of Western Europe. Cervical screening and colposcopy services are less organized elsewhere in Europe and there seems to be a wide variation in the availability of colposcopists (see Figure 1). This article seeks to explore the likely changes of performance of colposcopy in an environment of human papillomavirus (HPV) vaccination and testing as well as consider the practicalities of ensuring colposcopists throughout Europe have adequate expertise and support to fulfill their role.

CHALLENGES TO THE DIAGNOSTIC PERFORMANCE OF COLPOSCOPY

The sensitivity for colposcopic biopsy to detect precancer of the cervix for women with abnormal cytology is around 70% [1]. Colposcopy has a modest reproducibility and accuracy and may be more of a problem for women having had HPV vaccination in preventing the development of most cervical precancers. Similarly, women who participated in HPV screening trials had a significantly lower prevalence of CIN 3+ in subsequent screening rounds compared with cytology-based screening. As a result, the positive predictive value (PPV) for colposcopy is likely to decline as the prevalence of disease drops [2], and with a high sensitivity of HPV testing, specificity of any secondary screen (such as colposcopy) within an HPV-based screening program will become a priority.

Mitchell et al. [3] in a meta-analysis revealed a high sensitivity of colposcopy (85%), but a low specificity of 69%, resulting in a high rate of false-positive diagnosis of high-grade lesions. More recent studies suggest a much poorer sensitivity for high-grade CIN of 49% to 61% [4–9]. Earlier articles introduced bias as biopsies tended to be taken in areas of suspected abnormality

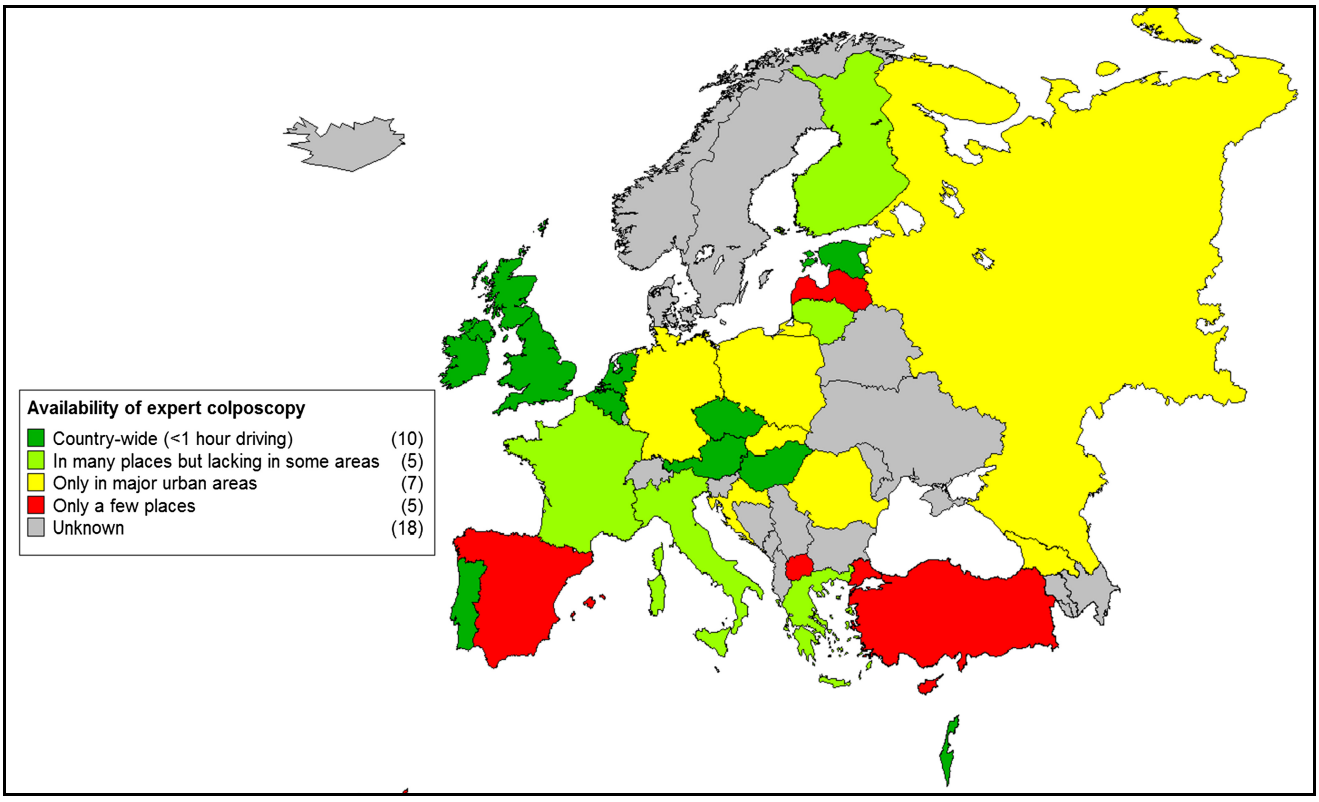

Figure 1. Availability of colposcopists in EFC states.

with an assumption that those cases without biopsies did not have high-grade CIN. Colposcopic opinion also seems to be influenced by prior knowledge of the cytology [10]. Unlike PPV, sensitivity is difficult to calculate for colposcopic opinion unless all colposcopies are accompanied by a biopsy or biopsies. In general, throughout Europe, biopsies are not usually taken from a normal-appearing transformation zone if referral cytology is low grade, which accounts for around 50% of all colposcopic referrals [11, 12]. This effect will tend to inflate colposcopic sensitivity, which will be inflated further in clinical practice as the choice of punch biopsy site depends on the skill of the colposcopist [10]. Random biopsies from the squamocolumnar junction with or without accompanying endocervical curettage do not improve the diagnostic yield of high-grade CIN for low-grade referrals and should be discouraged [4]. Furthermore, there is an enormous variation in colposcopic practice across Europe with its use either in conjunction with screening (including where colposcopy may form part of an annual gynecologic assessment at the level of an individual gynecologist's practice) or as an investigatory tool for abnormal cytology. In both circumstances, the prevalence of high-grade CIN is substantially different with a difference in anticipated colposcopic performance.

As the incidence of cervical cancer is expected to decline with HPV vaccination and HPV-based screening, community-based clinicians and junior gynecologists will not have seen many cases of overt cervical cancer limiting expertise in diagnosing microinvasive or clinical disease.

DIFFICULTIES FOR FUTURE COLPOSCOPISTS

Colposcopic performance may be adversely affected by 3 changes to the screening program: the introduction of vaccination, a change to HPV-based screening, and consideration of the types of secondary triage tests as part of that screening program.

I. HPV Vaccination

The consequences of vaccination on colposcopic practice are difficult to determine with any clarity. The incidence of high-grade CIN and the need for treatment of CIN will be reduced by at least 50% if there is uptake of all the eligible population. A decline in high-grade CIN and cervical glandular intraepithelial neoplasia (cGIN) has been shown already in real life analysis [13].The effect on low-grade disease is more difficult to predict, but currently, there is no evidence of a different effect between the 2 vaccines on the development of CIN 1. HPV types 6 and 11 account for most condylomata, but CIN 1 has a variety of causative HPV types. HPV-16 may be found in approximately 20% of CIN 1 [14]. If screening becomes HPV-based then women with only oncogenic HPV infection will be referred for colposcopy. However, with continued cytology-based screening up to 19% (range = 12%–25%) of women with low-grade cytology harbor high-grade CIN [15]. At least half of these women would be prevented from developing high-grade CIN by vaccination and would not be referred for colposcopy. Overall, the future referral rates to colposcopy for women having had either of the 2 vaccines will be lower than in the nonvaccinated population, but we do not know the exact magnitude of this decline. Nonetheless, the PPV for the colposcopic diagnosis of CIN 2+ will decline in vaccinated women.

The specific major colposcopic changes (intense acetowhite, distinct sharp margins, coarse mosaic or punctation, and lesion size) may not be a feature of high-grade CIN but of HPV and, in particular, may be a feature of HPV-16. Twenty expert colposcopists identified by the American Society for Colposcopy and Cervical Pathology reviewed images from the Atypical Squamous Cells of Undetermined Significance (ASCUS) and Low-Grade Squamous Intraepithelial Lesion (LSIL) Triage Study (ALTS) after application of 5% acetic acid. There was more agreement if the lesions were HPV-16 related rather than by CIN grade, but otherwise, the associations between HPV type and lesion recognition were weak. Visual appearances may be accountable to HPV-16 infection per se rather than grade of CIN [16]. In a study examining dynamic spectral imaging in 177 women referred for colposcopy, HPV-16–positive lesions had biopsies taken more often than non–HPV-16 lesions despite colposcopists being unaware of HPV status (88.1% vs 72.5%). However, this effect was not statistically significant (p = .066) but was independent of lesion size. The authors suggested that this may have been due to more intense acetowhitening, which was detected by dynamic spectral imaging [9]. An unpublished poster presentation from Cruickshank et al. (2011) described 105 women referred for colposcopy in Scotland who had their colposcopic impression compared to histologic outcome by HPV type. The PPV for CIN 2+ was higher for lesions containing HPV-16 (82%) or -16/18 (85%) than for those which were neither HPV type (50%), but the numbers were small. Perhaps some high-grade CIN not visualized at colposcopy is non–type 16 CIN.

II. HPV-Based Screening

HPV-based screening will select a group of women who differ from patients referred for cytology-based screening programs in clinical aspects that may increase the failure rate of colposcopy:

1. The proportion of women without any cervical lesion or with minor colposcopic changes is increased. In a pilot project in Wolfsburg, the rate of HPV-positive women without any lesion was 36% (normal colposcopy and/or histology without any atypia). Cytology-negative/ HPV-positive women were not immediately examined in this pilot, and so the proportion could be significantly higher. A further problem is the performance of colposcopy in subsequent HPV screening rounds because the prevalence of CIN 3+ as well as the PPV of colposcopy will decline significantly. There have been no published data as yet but one might speculate that seeing many healthy women without lesions or with low-grade changes only might distract the attention needed for colposcopy in a high-risk population. Colposcopy would be likely to perform with increasing difficulty in the vaccinated and HPV-based screening population. Its use should be confined to the diagnostic setting for women with abnormal screening such as HPV-positive women with abnormal cytology.
2. Only women with persistent infections with high-risk HPV types will develop new CIN 3 and cervical cancer. Compared with the follow-up of women with ASCUS or LSIL cytology, the risk of new lesions is increased in these patients [17, 18]. If the evaluation of colposcopy is based on the subsequent risk for developing CIN 3+, this risk will be increased in HPV screening compared to cytology-based screening.
3. More cGIN will be identified by HPV testing compared with cytology-based screening [19]. These lesions are more difficult to be detected at colposcopy.

With more patients referred for colposcopy, more women without CIN 2+ may have treatment with subsequent morbidity such as pain, vaginal discharge, and irregular bleeding. A single excisional treatment may be associated with preterm delivery [20, 21]. Furthermore, there is the worry and inconvenience of having abnormal screening tests with a need for more frequent follow-up. Therefore, refined triage of positive HPV testing is required. Colposcopic experience in detecting CIN is almost exclusively based on decades of Pap smear screening. It is unclear if lesions with positive cervical cytology permit easier colposcopic diagnosis than lesions associated with normal cervical cytology. Within the ATHENA trial investigating the utility of HPV testing in primary screening for cervical cancer in 47,208 women, as well as in the FUTURE vaccine trials, colposcopic prediction showed an underestimation of CIN 3+ in up to 57% of cases [22] (Wright, Stoler, and Castle, personal communication). Adherence to current colposcopic principles of identifing the extent of the transformation zone, obtaining biopsies from areas of abnormality, excision of an incompletely visualized transformation zone in the presence of high-grade referral cytology, and having quality-assured practice should avert a decline in sensitivity for the detection of high-grade CIN seen with cytology-based screening. This seems to be supported by a review of a primary HPV screening pilot project over 5 years that rigorously followed these principles. The failure rate of colposcopy defined as CIN 3 lesions missed at the first colposcopy assessment was significantly increased in HPV-positive women with normal cytology compared with patients with abnormal cytology. However, the overall failure rate of less than 5% was assumed to be acceptable. Remarkably, most failures were related to type 3 transformation zones and not explained by false-negative biopsies [23].

Castle et al. [24] considered that colposcopy is appropriate if the cumulative risk of CIN 3+ over 2 years is at least 10%, offering a risk-based referral to colposcopy instead of one based on algorithm. The threshold for referral for colposcopy set by Castle et al. should be challenged. Should there be a prevalent risk for CIN 3+ at 10%; should this be for CIN 2+ or should the threshold for colposcopy be changed? Ideally, colposcopy should be reserved exclusively for the management of precancerous lesions (i.e., CIN 3 and cGIN). Until ideal algorithms for referral to colposcopy are devised within an HPV-based screening program, then the definition of Castle et al. seems wise but should be reappraised when suitable performance data become available. Indeed, a risk-based model would allow addition of further tests such as p16 and other biomarkers to be added without having to rewrite existing algorithms for all outcomes of testing.

III. Use of Triage Tests for HPV-Based Screening

With a paradigm of carcinogenesis of HPV acquisition, persistence, and progression from HPV infection to precancer and then to invasion over several years, testing for the presence or absence of HPV seems a crude marker for cancer risk. More colposcopy referrals and associated psychological morbidity [25] would be anticipated with an HPV-based screening test positive rate ranging from around 5% to 16% [19, 26–28]. This represents an approximate doubling of the referral rate

to colposcopy for cytology-based screening with ASCUS or worse [29].

Cervical cytology with its high specificity could provide triage and has been chosen in most of the population pilot trials. An algorithm chosen by the Netherlands and by Italy uses 2 cytology samples at 6 and 12 months. The cumulative risk at 14 years for CIN 3 among cytologically normal women with high-risk HPV at entry was 28%, with 50% of these women detected at the next screening round in a longitudinal study of 7,278 women [30]. In this study, the prevalence of CIN 3 was highest in those with HPV-16, with an odds ratio 3 to 4 times higher than for other HPV types. HPV-16 was also more than twice as likely to persist than any other HPV type. HPV genotyping may therefore provide an alternative triage tool with up to 27% of all HPV-positive cases being due to HPV-16 [31–33], accounting for up to 54% of all HPV-positive CIN 3 [32, 34]. The ATHENA study reported on 4,219 women who were high-risk HPV-positive but cytology-negative and who were at least 30 years of age. The prevalent CIN 2+ rate on those having HPV testing who were HPV-16/18-positive was 11.4%, whereas those who were high-risk HPV-positive (but not HPV-16/18-positive) was 6.1%, and those who were HPV-negative was 0.8%. The rate of CIN 2+ seems age-dependent for 16/18 with the rate dropping with increasing age [33]. Long-term follow-up shows the same effect in the Kaiser Permanente population, with a cumulative risk for CIN 3+ in a cytologically negative population with HPV-16 at 10 years of 20.7%, 17.7% for HPV-18, and 1.5% for high-risk HPV-negative women [35]. Similar results for risk at 12 years were reported by Kjaer et al. [18] from Denmark. In this latter study, if a repeat test 2 years later remained positive for HPV-16, then the 10-year risk increased to 47.4%, but if the repeat test was negative, the 10-year risk dropped to 3.0%. ATHENA data for women 30 years or older shows that HPV-16/18 positivity as a triage to colposcopy was equivalent to ASCUS+ cytology and no HPV testing with a sensitivity of 59.3% and a PPV of 15.5% for CIN 3+ [34]. Other high-risk HPV types have an absolute risk of CIN 3 of around 6% after 12 years of follow-up [18]. The ATHENA study has an incident risk of CIN 3+ for negative cytology and HPV-16/18+ of 9.8% and colposcopy seems appropriate in this setting. Repeat HPV testing and cytology in 12 months seems appropriate for high-risk HPV-positive (but HPV-16/18-negative) cases.

A further alternative to cytology and genotyping for triage of HPV-positive cases is the use of biomarkers. A suitable candidate biomarker is p16, which had a sensitivity of 88% for CIN 2+ in HPV-positive women in the Italian NTCC study, with a relative sensitivity compared to cytology of 1.53 for CIN 2+ in women 35 to 60 years without an increase in referral rate to colposcopy [36, 37]. However, there is an element of subjectivity in assessing the degree of interpretation of p16 immunostaining, which is used with cytology or histology. There seems to be wide variation in positivity when applied to ASCUS and LSIL [38]. A combined immunostain for p16 and Ki-67 has a high sensitivity and specificity for CIN 3 and could be considered as a triage for HPV testing if it proves to be reliable in clinical practice [29]. Dual staining with p16/Ki-67 has been shown to be reliable in diagnosing the remaining CIN 2+ in the group of HPV-positive, cytology-negative patients within a German primary HPV screening pilot project [39]. In this study, 25% of the HPV-positive, cytology-negative population were p16/Ki-67-positive and dual staining detected 90% of the remaining high-grade CIN. Cytology may be suitable as a triage test if its referral rate to colposcopy is no more than 2% in the general population [40]; otherwise, genotyping or use of biomarkers could be considered. Immediate testing is preferable to reduce anxiety. In addition, any repeat testing risks default.

POSSIBLE ASSISTANCE FOR FUTURE COLPOSCOPISTS

There is a prospect of improving the objectivity and performance of colposcopy with dynamic spectral imaging (DySIS). Measurement of acetowhitening and modeling of a color-coded map assists the identification of high-grade CIN by localizing and grading the severity of any cervical lesion. Several studies with DySIS-assisted colposcopy have shown promising results [7, 41, 42]. In a recent Dutch study, the sensitivity of DySIS colposcopy to identify women with CIN 2+ was 79% versus 55% for conventional colposcopy. When a DySIS color-coded map was combined with conventional colposcopy, the sensitivity was 88% [8]. Despite some technical issues that may limit visualization of potential CIN (such as excessive blood or mucus hindering a complete view of the transformation zone), it seems that DySIS may have a future in cervical screening. Indeed, the National Institute for Health and Clinical Excellence has provided a draft recommendation that DySIS is a cost-effective method of cervical assessment, and colposcopy units should consider replacing colposcopes with DySIS despite the extended examination time and cost in procuring the technology [43]. There are

several other optical and electrical impedance real-time devices under development, but as yet, none are ready for introduction into clinical practice.

THE CURRENT USE OF COLPOSCOPY IN EUROPE—A WAY FORWARD

During a European Federation for Colposcopy (EFC) satellite meeting in May 2011 in Berlin, authorized representatives of 24 member societies answered questions on the role of colposcopy in their home states. The rationale was to determine current practice and agree basic standards for benchmarking performance across Europe to encourage support for colposcopy services where this was lacking. An objective was to support the development of reports and guidelines to generate political interest in the development of national screening programs. From their responses, colposcopy in Europe is mostly used as assessment of abnormal screens, although it is occasionally used as part of routine gynecologic assessment (6 states). A large minority of states permit colposcopy to be performed by all gynecologists (7 states).

Six preliminary quality standards were also selected as indicators for best practice (see Table 1), and a list of final quality indicators will be identified by an EFC Delphi consultation. Such standards must be applicable to all colposcopists, whatever their circumstances and however well organized their national screening may be. The criteria for satisfying the standards must be achievable, measureable, observable, understandable, and reasonable. All women with abnormal screens must be investigated by colposcopy if treatment is planned with liberal use of colposcopically guided punch biopsies if high-grade CIN is suspected. There should be a record of all colposcopic findings with an adequate PPV for a colposcopic prediction of CIN 2+. Overtreatment of CIN must be avoided, and there should be suitable negative cytology or HPV status after treatment. It is unclear how these standards will perform in an environment of HPV testing.

Multidisciplinary team meetings involving the cytologist, the pathologist, and colposcopist are required to review cases where there is discrepancy between cytology and histology, for glandular cases and for cancers. Regular quality reports should be produced for each colposcopist, local service, and state. Regular national audits and perhaps a pan-European audit of cervical cancer detected within the screening age range also should be encouraged. This is in place in the United Kingdom. An Internet-based voluntary quality assurance system is being piloted in Germany. The EFC can coordinate consensus building among member societies in defining minimum standards on training and practicing colposcopy as well as recommending tools to assess and control the quality of all parts of colposcopy management and education. Although the EFC is not in a position to assess directly whether standards are being satisfied, member societies can be advised how to achieve a transparent and comparable quality assessment that will lead to standardized high-quality colposcopy in all EFC member states.

However, at present, data collection is limited and practice is variable. Few states within Europe have colposcopists expected to see a defined number of patients. Only Belgium, France, Germany, Italy, Israel, Netherlands, Spain, and the United Kingdom reported seeing at least 30 cases per year per colposcopist. In Eastern Europe, no qualifications are needed to practice colposcopy. Practicing colposcopists should have regular review of their

Table 1. The Berlin 2011 Consensus Quality Indicators

1. Quality of colposcopic examination / identification of SCJ
Aim: Description/documentation of squamocolumnar junction and type of TZ (IFCPC classification)
Indicator:
- Proportion of documented colposcopies with description of SCJ and type of TZ of all documented colposcopies (100%).

2. Quality of colposcopic prediction
Aim: A high PPV of colposcopic findings classified as major changes for a histopathologic diagnosis of CIN 2+
Indicator:
- Colposcopic findings classified as major changes should correlate with a histologic diagnosis of CIN 2+ in most cases (>75%).

PPV = (colposcopic opinion CIN 2+) / total CIN 2+ cases seen by that colposcopist) $\times$ 100

3. Quality of indication for invasive therapy
Aim: Good selection of CIN 2+, avoidance of overtreatment
Indicators:
- Relation of CIN 2+ to ≤CIN 1 among all women who underwent invasive treatment (CIN 2+ should outnumber ≤CIN 1).
- High proportion of CIN 2+ of all treatment at first visit cases (>85%).

4. Preference of minimal invasive therapy
Aim: Avoidance of cold knife conizations and hysterectomies in the treatment of CIN
Indicator:
- Proportion of LLETZ or laser cone/ cold knife conization or hysterectomy in the treatment of CIN (>98%).

5. Colposcopic guidance of minimal invasive CIN therapy
Aim: Minimal invasive therapies should be done under colposcopic guidance
Indicator:
- Proportion of treatment procedures for CIN performed by a trained colposcopist under colposcopic guidance/total treatments for CIN (>95%).

6. Proof of cure following invasive treatment of CIN
Aim: Assessment of the effectiveness of treatment
Indicator:
- Proportion of treated CIN 2+ cases with negative tests (HPV or cytology) 6–12 months after treatment (>85%).

SCJ, squamocolumnar junction; TZ, transformation zone; IFCPC, International Federation for Cervical Pathology and Colposcopy; PPV, positive predictive value; CIN, cervical intraepithelial neoplasia; LLETZ, large loop excision of the transformation zone.

performance. All selected standards should be challenged by a few good centers to see how the standards perform.

If screening programs are introduced in Eastern Europe then more women will meet colposcopists who are poorly trained and certification would be useful here for young colposcopists where age is equated to experience. Sufficient junior colposcopists must be trained and registered to sustain screening programs and allow adequate access for women to have colposcopy. Use of paper-based or electronic training logbooks could facilitate these processes. Trainees from states with no organized colposcopy training may train elsewhere to return home with their skills and disseminate their expertise locally. Colposcopy needs to be of a high standard with practice of a small number of colposcopists being nominated as experts in their area of practice and training should provide the wherewithal to be an expert colposcopist.

New innovations and technologies such as modified screening algorithms, screening or triage tests, and the use of DySIS can be added with measurable effect to quality-assured screening and colposcopy services. Approaches to improve cervical screening must be to enhance and not undermine existing national programs. This is indeed a daunting challenge but a task to which pan-European health organizations have gained expertise. The European Cervical Cancer Association and the European Union are encouraging opportunities for screening among member states. The EFC and its affiliated national colposcopy societies are collaborating to provide workable standards for colposcopic practice as well as providing training particularly for trainees from Eastern Europe.

OUTLOOK AND CONCLUSIONS

Mass screening has to be available and it has to be quality assured. Successful screening with a reduction in the burden of cervical cancer is undoubtedly a desired outcome but colposcopists must be prepared for the changes imposed on practice. HPV vaccination and HPV screening will reduce the burden of cervical cancer and CIN 3 but will create new challenges with a lower PPV for colposcopy and higher failure rates as well as an increased risk of overtreatment, although the effects on the appearance of CIN lesions currently remain speculative. There will be fewer gynecologists who will have seen or be familiar with the gross and colposcopic appearances of cervical cancer. Adherence to agreed quality standards for best practice in colposcopy will help colposcopists manage cases at perceived increased risk for cervical cancer and precancer in a standardized way, although ongoing research is required to ensure that following these colposcopic principles is sufficient to address all challenges imposed by new cervical cancer prevention programs. We should not be deterred from providing high-quality training and standards of practice for colposcopists throughout Europe because whatever screening scenarios will be chosen, colposcopy will remain the tool to diagnose precancerous lesions after a positive screen. There is no better alternative to colposcopy, but there is no alternative for colposcopy than better and more sophisticated standardized quality assurance. This may then realize the greatest benefit from modified screening strategies translated into improved cervical cancer diagnosis and mortality.

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