

Guidelines for Cervical Cancer Prevention and Screening

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1 INTRODUCTION

The Guidelines on the Management of Abnormal Cervical Cytology was last updated in 2008. Since then, there have been several important new developments including Human Papillomavirus (HPV) vaccines, the expanded role of HPV testing in screening, new technologies in HPV testing as well as new World Health Organization (WHO) nomenclature for histological classification of squamous intraepithelial neoplasia. This current revision has incorporated these changes. As the scope of the guidelines has expanded, it is renamed as “HKCOG guidelines for cervical cancer prevention and screening”.

In this revision, the main changes include new information on :

- i) Guidance on primary cervical cancer prevention by HPV vaccination
- ii) Guidance on the use of HPV testing as a stand-alone test or as part of ‘co-test’ with cytology for primary screening
- iii) WHO 2014 nomenclature
- iv) 2014 Bethesda system
- v) Details of different available HPV tests

2 PRIMARY PREVENTION – PROPHYLACTIC VACCINE

Primary prevention of cervical cancer is now possible through the use of prophylactic vaccination against HPV. There are three vaccines currently available: the bivalent (Cervarix) against HPV 16/18, the quadrivalent (Gardasil) against HPV 6/11/16/18 and the nonavalent (Gardasil 9) against HPV 6/11/16/18/31/33/45/52/58. All of

them offer protection against HPV types 16 and 18 (the two most common strains in cervical cancer) which account for about 70% of cervical cancer. [1, 2], Furthermore, it is estimated that the nonavalent vaccine could prevent 87% of cervical cancers worldwide in women who are naïve to HPV infection [3]. **Cervical cancer screening is still relevant to vaccinees as current vaccines cannot offer full protection.** The quadrivalent and nonavalent vaccines also offer protection against genital wart caused by HPV types 6 and 11. The vaccines offer no effect on viral clearance in women with preexisting infection [4] but there is evidence to suggest that vaccine can reduce the risk of developing subsequent disease by 35–46% irrespective of causal HPV type after an excisional procedure for cervical intraepithelial neoplasia [5]. Meta-analysis has demonstrated that prophylactic vaccines are highly efficacious in preventing vaccine type HPV infections and associated precancerous cervical lesions [6]: 95% efficacy against persistent HPV 16 and 18 infections, 97–98% in preventing HPV 16 and 18 associated CIN1+ and over 90% for CIN2+ in the per-protocol population which approximates pre-sexually active young adolescents naïve to vaccine type HPV with perfect or nearly perfect compliance to vaccination. However, the efficacy in the intention-to-treat population which mimics young women in the general population who may have been exposed to vaccine type HPV infection and have less than perfect compliance with vaccination protocol is reduced to 75–85%, 57–78% and 50% for persistent HPV 16 and 18 infections, HPV 16 and 18 associated CIN1+ and CIN2+ respectively. Therefore, these prophylactic vaccines work best for adolescents before sexual debut and they should be the target population for HPV vaccination. WHO recommends primary target population to be girls within the age range of 9 or 10 years through to 13 years [7]. In 9–13 year olds, the number of bivalent and quadrivalent doses of HPV vaccine can be reduced from three

to two doses as researches demonstrated that antibody response to two doses in 9-14 years old girls is as good as a three dose course [8, 9] WHO position paper (2014) recommended a 2-dose schedule with a 6-month interval between the doses for females younger than 15 years. There is no maximum recommended interval between the doses but an interval no greater than 12-15 months is suggested to complete the schedule. Clinical trial demonstrated non inferiority of the anti-HPV immune responses for all 9 types in girls and boys 9-14 years of age who received 2 doses as compared to young women 16-26 years of age who received 3 doses schedule. Both bivalent and quadrivalent vaccines induce partial cross-protection against infection and disease caused by a limited number of phylogenetically-related non-vaccine types [10]. WHO's Global Advisory Committee on Vaccine Safety (GACVS) concluded that all vaccines had good safety profiles but the vaccines are not recommended for pregnant women. Efficacy against infection and cervical lesions associated with HPV-16/18 has been shown to last at least 9 years and boosters are not required.

Other strategies to reduce the risk of HPV acquisition, like practicing safer sex (reducing the number of sexual partners and the use of condom) and avoidance of smoking, would also help to prevent cervical cancer. Cigarette smoking by women is associated with an increased risk for squamous cell carcinoma and the risk increases with the duration and intensity of smoking [3].

Summary of Recommendations:

- Prophylactic HPV vaccines are most effective in women with no prior exposure to the virus (i.e in never-sexually active women)
- Women aged 15 or above should be given a 3-dose regime
- Girls under the age of 15 can be given a 2-dose regime
- HPV vaccine should not be given to pregnant women
- Cervical cancer screening is still necessary after HPV vaccination

3.1 Target population

The target population encompasses all women from **age 25 or the time of commencing sexual activity (whichever is later) until the age of 64**. In view of the rarity of cervical carcinoma in women below 25 years of age and the relatively high proportion of cytological abnormalities that spontaneously regress, screening before this age is less cost-effective and could result in unnecessary interventions. Nevertheless, women aged below 25 years with high-risk profile may be screened after assessment by doctor. Screening may be discontinued in women aged 65 or more if all routine screens within the last 10 years are normal and they were not previously diagnosed to have HSIL histologically. Women over 65 years who have never had cervical cytology and have a history of being sexually active, should be screened. (Table 1)

Taking a cervical cytology sample during pregnancy may induce bleeding and cause anxiety to the woman and hence this is not the best time to perform cervical cancer screening. Nevertheless, this may be an opportunity to perform a cytology test in pregnant women who have never been screened.

Particular emphasis should be given to recruit those women at greatest risk of developing cervical cancer - those who have never had cervical cytology screening, and those who have not had one for more than 3 years.

Women who have hysterectomy with removal of cervix for benign diseases and without a prior history of cervical dysplasia can discontinue screening.

3.2 Screening Interval (Cytology)

The percentage reduction in the cumulative incidence of cervical cancer is 93% with an annual or biennial screening interval, 91% if performed every 3 years, 84% if performed every 5 years and 64% if performed every 10 years. Screening at 3-

yearly intervals is less costly and does not significantly reduce the efficacy of preventing invasive cervical cancer compared to that achieved with annual screening [11]. **Screening at 3-yearly intervals, after 2 consecutive normal annual cytology tests, is recommended.** Chronically immunosuppressed women will need annual screening[12].

3.3 Methods of screening

3.3.1 Methods of screening - Cervical Cytology

Cervical cytology remains the main tool for screening cervical cancer in Hong Kong. The quality of the cytology sampling has a major influence on the sensitivity of the cervical cytology. The presence of inflammatory cells, blood or debris, the type of cell collector used and the skill of the operator will affect the quality of the cytology. Cytology sampling during menstruation should be avoided. Use of a broom type device will optimize cell sampling from the endocervical canal and ectocervix, and thus the transformation zone.

Both conventional cytology using the glass slide and liquid based cytology (LBC) are acceptable methods for screening. LBC also has the advantage of allowing “reflex” HPV testing be performed if necessary. In conventional cytology, despite adequate collection of cervical cells, poor and uneven transfer of cells to the slide may hamper assessment because of insufficient cells or a thick smear. Mucus, blood or inflammatory cells may also obscure the cervical cells. The cytology smear should be immediately and properly fixed after the slide is prepared, either in 95% alcohol or using a spray fixative. LBC minimizes the problems mentioned above and reduces the rate of unsatisfactory cytology sampling. Liquid based specimens should be collected according to the manufacturer’s instructions.

Factors that are important and can affect the interpretation of a cytology test include age, hormonal status (e.g. postnatal,

postmenopausal), use of hormonal contraceptives or an Intrauterine Contraceptive Device (IUCD), pregnancy, the date of last menstrual period, history of previous abnormal cervical cytology and histology results, the type of treatment received, and relevant clinical signs and symptoms such as abnormal cervical appearance, postcoital, intermenstrual or postmenopausal bleeding. Such information should be indicated on the request form. The sample should also be properly labeled.

The use of oestrogen in postmenopausal women and the treatment of a pre-existing infection may improve the quality of the cytology sample.

3.3.1.1 The 2014 WHO classification and 2014 Bethesda system

There has been no change in nomenclature between the *2014 Bethesda System for Reporting Cervical Cytology* and the previous edition. The minor change in the current edition is in the reporting of benign endometrial cells. Presence of benign-appearing endometrial cells should be reported for women aged ≥ 45 years, instead of the previous recommended ≥ 40 years so as to improve the predictive value for any underlying endometrial hyperplasia or adenocarcinoma [13-16]. In the last decade, suggestions of introducing an intermediate category for cases of LSIL with equivocal HSIL (so-called LSIL, cannot exclude HSIL or LSIL-H) was rejected by 2014 Bethesda working group and therefore should not be used. For these cases, reporting of LSIL with a second component of ASC-H is recommended [13].

Histologic reporting of squamous intraepithelial neoplasia will be changed from the traditional 3-tier classification (e.g. CIN1 to 3, VaIN 1 to 3 and VIN 1 to 3) into a two-tier system of low- and high grade squamous intraepithelial lesions (LSIL, HSIL respectively, irrespective of cervix, vagina or vulva), which are identical to

the Bethesda System for Reporting Cervical Cytology. This has proven to be more reproducible and divides patients into two managerial subgroups [17-19]. The change was a result of the work done by *The 2012 Lower Anogenital Squamous Terminology (LAST)* project working groups, and supported by the *2014 WHO Classification of Tumours of Female Reproductive Organs* working groups. LAST also recommended that p16 immunostain may be utilized in histologically indeterminate biopsies (HSIL versus “CIN1-2”, and HSIL versus atypical squamous metaplasia). Nonetheless, the p16 positive stain pattern should be ‘diffuse block staining’[20].

Although the histologic categories of abnormal cervical glandular lesions have been redefined in the *2014 WHO Classification of Tumours of Female Reproductive Organs*, the cytologic categories of ‘atypical glandular cells, NOS’, ‘atypical endocervical cells’, or ‘atypical glandular cells, favour neoplastic’ remain unchanged from the last edition in the *Bethesda System for Reporting Cervical Cytology* [21].

3.3.1.2 Computer-assisted screening of cervical cytology

Computer-assisted screening increases a laboratory’s productivity by replacing the labour-intensive job of screening and also reduced the likelihood of human errors with manual screening. Computer-assisted cervical cancer screening devices may be broadly divided into two types: location-guided screening and risk-stratification devices. Currently, commonly used computer-assisted devices in Hong Kong include the ThinPrep™ Slide Imager and AutoPap/FocalPoint™ slide profiler which are both approved by FDA for use for primary screening. The laboratories which use these devices should have established quality control for rescreening methods. Irrespective of the type of device being used, cases with abnormal cells found and cases with significant clinical concerns have to be

referred to pathologists for evaluation and reporting. If a case is examined by a computer-assisted device, the *2014 Bethesda System for Reporting Cervical Cytology* recommendation is to specify the device together with the findings in the cytology report.

3.3.2 Methods of screening – HPV testing

Cervical cancer is caused by persistent infection with high-risk HPV, with HPV 16 and HPV 18 account for about 70% of all cases. HPV testing can be used in the following setting:

- i) As a triage for ASCUS smears
- ii) As primary screening
 - As part of co-testing with cytology
 - As a stand-alone test in primary screening
- iii) As a test of cure (Section 5)

The major advantage of HPV testing is its high sensitivity in detecting precancerous lesions. Various studies have shown that HPV-based screening has greater sensitivity than cytology in detecting CIN3 or more severe lesions [22]. Moreover, being a more objective test than cytology, HPV testing has a higher reproducibility and the test can be automated. However, the drawback is the lower specificity leading to an increase in retesting, procedures (colposcopy and biopsy), over-treatment and psychological burden, in particular among young women where HPV infection is usually transient.

The efficacy and cost-effectiveness of using HPV test as a primary screening method, either as a co-test or a stand-alone test, differ in different clinical and social – economical settings. Therefore, the benefits of a HPV-based screening programme should be based on large scale local data and cost-analysis. While local population data is being collected, individual health care practitioner should assess his /her own setting to decide if HPV testing should be

used. The following information aims to provide some guidance in the subsequent management of the results when HPV tests are employed.

HPV Testing should only target at high-risk oncogenic HPV types. Testing for low-risk HPV types has no clinical role in cervical cancer screening or management of abnormal cytology.

The presence of high-risk HPV DNA can be detected by commercial kits, polymerase chain reaction (PCR), dot-blot or sequencing. HPV RNA detection denotes presence of active infection, and can be achieved by RNA transcription of specific HPV genes using RT-PCR or real time PCR. **Only analytically and clinically validated HPV tests should be used.** The performance characteristics vary among these HPV tests. Laboratory standard operating procedures and quality assurance programs should ideally be in place for use of any HPV testing procedures.

(See Appendix 1 for currently available HPV tests)

3.3.2.1 HPV testing as a triage for ASCUS smears (Fig2)

Patients present with ASCUS who are positive for high-risk HPV are more likely to carry high grade lesions (CIN 2-3). High-risk HPV can be found in around 50% of ASCUS [23, 24]. Reflex HPV testing in triaging patients with ASCUS is an alternative to repeat cytology at 6 months in decision for colposcopy referral [25], except in women 20 years of age and younger. Colposcopy is indicated for women with ASCUS cytology and HPV-positive test.

Women with ASCUS cytology and HPV-negative can be followed up with co-testing or cytology alone at 3 years [15].

HPV-16/18 genotyping of HPV-positive women with ASCUS did not appear to lead to different management since the risk for CIN 3+ had exceeded the

threshold for colposcopy even in women with ASCUS who have high-risk HPV types other than 16 or 18 [15].

Reflex HPV testing has limited role in triaging patients with LSIL for colposcopy because over 80% of LSIL has high risk HPV [24]. Even in older age groups, reflex HPV testing for LSIL to triage for colposcopy is not recommended since HPV positivity among women with LSIL decreased only slightly with age (30 to 34 vs 60 to 64 years, 88% vs 72%) [26].

3.3.2.2 HPV testing as primary screening

Application of HPV testing in primary screening includes **co-testing with cytology or HPV as a stand-alone test.**

Incorporating HPV testing into screening strategies has the potential to increase disease detection and increase the length of screening interval. However, the improved sensitivity must be balanced against the potential risks of unnecessary testing, procedures and treatment.

HPV infection is highly prevalent below the age of 30 and most of them are transient. Detection of these transient infections can be harmful since this may cause anxiety, stigmatization, discomfort and bleeding during diagnostic and treatment procedures, and pregnancy complications such as preterm delivery due to unnecessary treatment. **Taking into account of the high prevalence of HPV in young women and the median age of cervical cancer patients in Hong Kong, HPV testing should not be used before the age of 30 for primary screening, either as a co-test or stand-alone test.**

3.3.2.2.1 HPV testing as a co-test with cytology for primary screening

HPV and cytology co-testing can be considered as an alternative to cytology alone for cervical cancer screening. In many studies, addition of HPV testing to cytology resulted in

increased sensitivity for detecting CIN 3 at the first round of screening and a decrease in CIN 3 or cancer detected in subsequent rounds of screening [22, 27-29].

- HPV-Negative, Cytology-Negative Co-test (Fig 1)

Women who are co-tested negative have a low chance of having concurrent CIN 2+ (negative predictive value of 0.988-1.000) [30] and cervical cancer (3.2/100,000 women per year over 5 years) [31]. These women should continue with routine screening. **A 5-year screening interval is recommended after a negative co-test.** Studies had showed that the 5-year risk of CIN 3+ and cancer following a negative co-test (0.16% and 0.0087% respectively) were comparable to or even less than the 3-year risk of CIN 3+ and cancer following a negative cytology alone (0.17% and 0.0154% respectively) [29, 31].

- HPV-Positive, Cytology-Negative Co-test (Fig 1)

Immediate colposcopy for HPV-positive, cytology-negative women is discouraged since the immediate risk of CIN 3 in these women is low (<1%-4.1%) [31, 32] . However, the 5-year risk of CIN 3+ increased to about 6% [22, 31] .

Either repeat co-testing in 12 months or immediate HPV genotyping for HPV 16 alone or HPV16/18 is acceptable.

Since most transient HPV infections (about 67%) are cleared by 12 months [33], repeat co-testing at 12 months is one of the options. If co-testing is repeated at 12 months, colposcopy is indicated if HPV positive or ASCUS or above. Women can return to 3 yearly co-testing or 3 yearly cytology if HPV test and cytology are both negative.

If immediate HPV genotyping is performed, colposcopy is indicated if HPV 16 or HPV16/18 positive. The risk of developing CIN 3 or cancer is found to be highly genotype-dependent. HPV-16 and HPV-18 account for two-thirds of all invasive cervical cancer [32]. The short term (within 12 weeks) risk of CIN 3+ in these women is about 10% [32]. The 10-year cumulative incidence rate of CIN 3+ were 17% among HPV16+ women, 14% among HPV 18+ women, but only 3% for those with other high risk HPV infection [34].

If HPV 16 alone or HPV 16/18 is negative, co-testing or cytology is repeated at 12 months. Although the short term (within 12 weeks) risk of CIN 3+ for oncogenic HPV genotypes other than HPV 16/18 (2.4%) [32] do not warrant immediate colposcopy, they should be followed at 12 months since the risk is higher than those co-tested negative.

If HPV testing is not available, cytology should be repeated 6 - monthly for 3 times before returning to routine screening. If the repeat cytology is abnormal, then it should be managed according to the abnormality (eg if cytology in 6 months is ASCUS, then the management for ASCUS should be followed ie repeat cytology in 6 and 12 months and refer to colposcopy if there are two ASCUS smears.)

- HPV-Negative, Cytology-ASCUS Co-tests (Fig 2)

Women with negative HPV and ASCUS cytology will need repeat co-testing or cytology in 3 years.

- HPV-Negative, Cytology LSIL Co-tests (Fig 3)

Either immediate colposcopy or repeat co-testing in 12 months is acceptable. The risk of CIN 3+ for these women is low and similar to that

of ASCUS alone without knowledge of HPV status (2% vs 2.6%) [26]. If co-testing is repeated at 12 months and both tests are negative, women can have co-test or cytology in 3 years before returning to routine screening. Otherwise, colposcopy is indicated for either HPV-positive or ASCUS or above.

- HPV-Positive, Cytology-Positive Co-tests

Women with HPV-positive and ASCUS or above should be referred for colposcopy. (see also section 3.3.2.1).

3.3.2.2.2 HPV testing as a stand-alone test for primary screening (Fig 4)

Co-testing with HPV test and cytology can improve the sensitivity for detection of high grade pre-malignant lesions but it means each woman will need 2 tests instead of 1, with significant resources and cost implications. Alternatively, HPV testing as a stand-alone test has also been considered for primary cervical cancer screening. The lower specificity associated with HPV testing is the major drawback. The problem of lower specificity can be overcome by using a second triage test to identify those who have a higher risk in developing precancerous and cancerous lesions. The appropriateness of HPV test as a stand-alone test requires further verification.

- Negative Stand-alone HPV test

Limited data suggest that a negative HPV test has a high negative predictive value. Negative co-testing has an extremely small 5-year cumulative risk of CIN 3+ of 0.2%. (see section on Co-testing). There is insignificant difference (0.1%) in the 5-year cumulative risk of CIN3+ between a negative HPV test alone and a negative co-test [35, 36]. Therefore, a negative HPV test may provide

greater reassurance against CIN 3+ over the next 5 years than cytology alone and is nearly as reassuring as a negative co-test. Women with a negative stand-alone test can have routine screening (no less than every 3 years).

- Positive Stand-alone HPV test

Immediate referral of HPV test positive women to colposcopy without further triage tests is NOT recommended. Due to the lower specificity of HPV stand-alone test, it is not appropriate to refer women with a positive HPV test directly to colposcopy because this will increase the colposcopy rate significantly (from 2.5% to 5.8% in age 35-60 and from 3.6% to 13.1% in age < 35 [37]) and possible over-treatment of non-progressive lesions leading to unnecessary complications.

A second triage test should be done to better predict which of these women would be at high risk of developing CIN 2+ and hence need referral for colposcopy. It is still uncertain what the best triage test is. Literatures suggested a variety of different triage strategies, including the use of cytology, HPV 16/18 genotyping, and biomarkers.

- Triage with cytology. The subsequent management would be the same as for co-test with HPV and cytology. **Those with positive cytology (\geq ASCUS) should be referred to colposcopy. Those with negative cytology should perform co-testing at 12 months (see Section on Co-testing) or repeat smear in 6 months for 3 times (Fig 1)**
- Triage with genotyping for HPV 16 and/or 18. **Those who are HPV 16/18 positive should be referred to colposcopy** (see section on co-testing with immediate HPV 16/18 genotyping). **Those who are HPV**

16/18 negative can either perform co-testing at 12 months or reflex cytology. Referral to colposcopy should be considered at the level of ASCUS +. Adding a further cytology triage test to those positive other than HPV16/18 could increase the sensitivity of the test by 14-20% at the expense of increasing the number of colposcopies performed [38]. However, current evidence on this triage strategy is still limited. Therefore, the effectiveness of this management strategy is still uncertain.

- Triage with biomarkers. Tests employing HPV E6/E7 mRNA may help to distinguish transient from persistent HPV infection. Immunostains p16, ProEx C, ki-67, or p16/ki-67 dual staining may help to identify equivocal or HPV+/cytology negative cases for referral to colposcopy. However, none of these tests to date have been approved for use by FDA for primary cervical cancer screening [39].

Although the use of HPV testing as a standalone test for cervical cancer screening appears promising, the optimal management strategy of HPV positive women is still yet to be defined. Currently, there is a lack of long-term follow-up data on the safety and efficacy of these approaches and the potential harms associated with these approaches are not well studied. Further research is required in order to support HPV test as a standalone test for cervical cancer screening.

4 MANAGEMENT OF NORMAL AND ABNORMAL SMEARS

Please refer to Fig 1-3 for summary of management of normal and abnormal low grade smears.

Patients with high grade smears (HSIL) should be referred to colposcopy. Immediate loop electrosurgical excision procedure (See and LEEP) can be offered if high grade lesion can be seen in colposcopy (except for adolescents). Review of cytology slides is recommended if no high grade lesion can be found.

Suggested actions for other cervical cytology results are shown in Table 2.

5 COLPOSCOPY AND TREATMENT FOR CIN

The colposcopist's role is to examine the transformation zone, define the extent of the lesion, and biopsy the most abnormal area for tissue diagnosis. In addition to the cervix, the vagina should also be examined.

Histological confirmation of the colposcopic diagnosis is advisable before treatment. In patients with a colposcopic diagnosis of high grade lesion, a "see and treat" approach[40], i.e. perform loop excision without a biopsy, is adopted by some colposcopists. Although this practice decreases the need for another visit, it carries the risk of over-treating patients with low grade lesions. The rate of over-treatment depends on the expertise of the colposcopist.

Majority of low grade lesions will regress spontaneously over 2 years and immediate treatment may not be necessary [41, 42]. About 15% of patients may progress to high grade lesions and require treatment later.

If a low grade lesion is confirmed by colposcopy and biopsy, the patient can be followed up with cytology every 6 months. If LSIL / ASCUS persists, colposcopy can be repeated between 12 to 18 months. Patients can resume routine screening after having 3 consecutive normal cytology results.

HPV testing may be used as an adjunct to cytology testing in the follow up management after colposcopy or treatment. It can be used as a test of cure at 12 months after colposcopy. A meta-analysis had shown that HPV testing was significantly more sensitive (ratio of 1.25; 95% CI: 1.15-1.36) but not less specific (ratio of 0.97; 95%

CI: 0.93-1.02) compared to cytology to predict residual or recurrent CIN 2+ after treatment [22].

Instead of 6 monthly smears, the patient can have co-testing in 12 months. If both HPV and cytology are negative, co-testing can be repeated in 3 years and the patient can return to routine screening afterwards. (Fig 5)

Routine screening should be continued for at least 3 times even if the woman has reached the age of 65.

For those who had a high grade smear but colposcopic directed biopsy only showed a low grade lesion, review of material is recommended. If confirmed to be low grade, co-testing in 12 months and 24 months should be done before returning to 3 yearly co-testing and subsequent routine screening. If either test is positive during the 24 months period, colposcopy may be recommended. (Fig 5)

In patients with LSIL involving more than 2 quadrants of the cervix or if the patient is unable or unwilling to return for follow-up, then treatment should be considered. If the lesion persists for more than 2 years, treatment is recommended. If the final histology from treatment confirms low grade lesions, the patient should be followed up similar to other patients with low grade lesions on cervical biopsies.

The reason for treating HSIL is that these lesions could progress to invasive cancer if left untreated. The time of progression to cancer is variable and can take from months to years [23]. The risk of HSIL (CIN 3) progressing to an invasive lesion is about 12% over a period of 10 years [43].

Treatment for CIN can be carried out under local anaesthesia on an outpatient basis in 90% patients.

Ablative methods including electrocoagulation diathermy, cryosurgery, cold coagulation and laser vaporization, are undesirable because they do not provide a specimen for histology examination.

The current recommended method is - LEEP. This has the advantage of providing a tissue specimen that is generally of sufficient quality for histological exclusion of occult invasion. Complications include intraoperative and postoperative bleeding (1-8%), infection, cervical

stenosis (1%), cervical deformity and cervical incompetence [43] and rarely injury to vagina, bladder and ureter. Reports showed an association with preterm delivery, low birth weight and premature rupture of membranes but there was no significant increase in neonatal morbidity [44].

Hysterectomy is not recommended for the treatment of HSIL unless there are concomitant gynaecological problems that warrant a hysterectomy. Hysterectomy should not be performed for cytological abnormality without proper colposcopy examination & biopsy.

After treatment for high grade CIN, patients should be followed up by cervical cytology for 3 times at 6-months intervals & then annually for 10 years, then return to lifelong routine screening. Exit from lifelong routine screening may be considered after 20 years if all routine screening smears are negative and the woman has reached the age of 65.

Alternatively, co-testing can be repeated at 12 and 24 months. If both are negative, co-testing can be repeated in 3 years, then return to routine screening. (Fig 6)

If patient has ASCUS/LSIL on cervical cytology within 12 months, continue follow up with cervical cytology is acceptable. If the low grade cytological abnormalities persist for more than one year, colposcopy has to be repeated. Colposcopy should be repeated any time when HSIL is found on cervical cytology.

For patients who had hysterectomy for CIN with clear margin, vaginal cytology should be taken at 6 & 18 months. If both results are normal, no further vaginal cytology is necessary. If excision was incomplete or clearance of margin is uncertain on hysterectomy, or if the patients had VAIN, vaginal cytology should be taken at 6 and 12 months then yearly for 10 years followed by lifelong 3-yearly cytology tests.

6 MANAGEMENT IN SPECIAL CATEGORIES

6.1 Adolescent (age 20 or less)

High prevalence of HPV infections is found in adolescence. The cytological

abnormalities are usually of minor-grade (ASCUS & LSIL) and the prevalence of cervical cancer is very low in this population.

Because most HPV infections clear spontaneously within 2 years, immediate colposcopy for minor cytological abnormalities in adolescents is discouraged, as there could be potential harm due to over-investigation and over-treatment.

For ASCUS/LSIL, repeat cervical cytology 12-monthly. If HSIL or persistent abnormal cytology for 2 years, colposcopy should be performed. If high grade lesion is confirmed on biopsy, LEEP is indicated. If no high grade lesion was found on a satisfactory colposcopy examination, cytology should be repeated 6 monthly. If HSIL persists at one year, colposcopy should be repeated. If HSIL persists for 2 years, LEEP should be considered.

If colposcopy for HSIL is unsatisfactory, cytology and colposcopy should be repeated in 6 months. If HSIL persists and colposcopy is still unsatisfactory at one year, LEEP should be offered.

6.2 Pregnant women

The only indication of therapy for cervical neoplasia in pregnant women is invasive cancer.

Cancer risk is relatively low among pregnant women with ASCUS/LSIL; hence deferring colposcopy for ASCUS/LSIL is acceptable (at least beyond 6 weeks after delivery).

Pregnant women with HSIL or atypical glandular cells (AGC) should have a colposcopic examination as non-pregnant women to rule out malignancy. Endocervical curettage is contraindicated. Repeat colposcopy at early 3rd trimester may be considered.

Treatment for high grade disease can be deferred to the postpartum period.

Colposcopy guided biopsy or cone biopsy is indicated only if malignant lesion is suspected.

6.3 Chronically Immunocompromised

Women who are chronically immunosuppressed are at higher risk of persistent HPV infection, leading to progression to CIN and cervical cancer. They need annual screening. Treatment for high grade abnormal cytology in this group should be the same as in immunocompetent women. Low grade lesions should be observed as they respond poorly to treatment. These should be monitored regularly for progression.

7 LOCAL CERVICAL SCREENING PROGRAMME

The Department of Health of the Government of the Hong Kong Special Administrative Region launched a territory-wide Cervical Screening Programme (CSP) in March 2004 in collaboration with local health care professionals to facilitate and encourage women to have regular cervical cancer screening. Demographic data and cytology results of women who have joined the CSP are entered into the Cervical Screening Information System (CSIS). The CSIS is a computerized central registry for capturing and retrieving data related to cervical cancer screening of registrants. The functions of the CSIS include maintenance of a reminder system, allowing sharing of cytology results among relevant health care providers for better and continuity of patient care, facilitating timely follow-up, treatment and re-screening, tracking utilization, evaluating overall programme coverage, and supporting service-related research. Registered women can view their own records online, and receive reminder letters when they are due for next screening. Registered health care providers as well as laboratory technicians can also use the CSIS to view the test records of their clients upon women's authorization [45].

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This guideline was produced by the Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practicing in Hong Kong. The guideline does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognized clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that clinical management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice. Particular attention is drawn to areas of clinical uncertainty where further research may be indicated.

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Table 1 Routine screening recommendation

Under 25	Screen as per physician's assessment of risk
25-29	Cytology annually for 2 consecutive years, then 3 yearly cytology
30-64	Cytology annually for 2 consecutive years, then 3 yearly cytology OR Co-test (Cytology + high risk HPV test) every 5 years
≥65 & previous negative screening	Can discontinue screening if routine screening results are negative within the last 10 years
≥ 65, never had cervical cancer screening and with history of being sexually active	Offer routine screening
Previous LSIL (histological findings)	Continue follow up as per guidelines Exit from screening at the age ≥ 65 provided that all routine screening are negative for the last 10 years.
Previous HSIL (histological findings)	Continue follow up as per guidelines Exit from screening at the age ≥ 65 provided that all routine screening smears are negative for the last 20 years.
Have hysterectomy with removal of cervix for benign diseases and without a prior history of cervical dysplasia	Can discontinue screening
Chronically immunosuppressed should be screened regardless of age when they have become sexually active	

Table 2.1 Management of Cytology results- Squamous lesions

Cervical cytology	Suggested actions
Normal (Fig.1)	<p>Cytology alone : repeat cytology every 3 years (after 2 initial annual screen)</p> <p>Co-testing :</p> <p>If high risk HPV(hrHPV) negative, repeat co-testing every 5 years</p> <ul style="list-style-type: none"> - If hrHPV negative, but history of hrHPV positive/ or smear abnormality in the last screening, repeat screening (co-testing or cytology) in 3 years - If hrHPV positive , then 3 options <ul style="list-style-type: none"> ▪ Repeat smear in 6 months for 3 times ▪ Repeat co-testing in 12 months ▪ Do genotyping for HPV16/18. <ul style="list-style-type: none"> • If HPV 16/18 positive, refer colposcopy. • If HPV 16/18 negative, repeat co-testing or smear in 1 year, then 3 years, then routine screening
ASCUS (Fig. 2)	<p>Cytology alone : repeat cytology in 6 months and 12 months</p> <p>HPV triage or co-testing :</p> <ul style="list-style-type: none"> - hrHPV positive, refer for colposcopy - hrHPV negative, repeat screening (co-testing or cytology) in 3 years
LSIL(Fig.3)	<p>Cytology alone : refer for colposcopy</p> <p>Co-testing :</p> <ul style="list-style-type: none"> - hrHPV positive , refer for colposcopy - hrHPV negative , repeat co-testing in 12 months <ul style="list-style-type: none"> ○ If either abnormal – refer for colposcopy ○ If both normal, repeat co-testing or cytology in 3 years , then routine screening
ASC-H (Fig. 7)	<p>Refer for colposcopy.</p> <ul style="list-style-type: none"> - Obtain endocervical sampling if unsatisfactory colposcopy. - If no lesion identified, review of material is recommended. If no change in diagnosis, repeat cytology 6 monthly. - Repeat colposcopy if persistent abnormal cytology. - Refer back to routine screening if cytology is normal twice.
HSIL	Refer for colposcopy
Invasive cancer	Biopsy if frank growth, otherwise early referral for colposcopy and biopsy

Table 2.2 Management of Cytology results- Glandular lesions and others

AGC-NOS (Fig. 8)	Refer for colposcopy, endometrial biopsy and, endocervical sampling. (Endometrial sampling first for AGC NOS, endometrial cells) For AGC –FN and AIS : if there is no significant pathology explaining the source of abnormal cells, a diagnostic cold knife cone is recommended. Ablative procedure is unacceptable.
AGC-favor neoplasia (FN)	
Adenocarcinoma in situ (AIS)	
Benign looking endometrial cells	Women after menopause : further investigations Premenopausal women \geq 45 years : further investigations if symptomatic Women < 45years- Treat as normal
Unsatisfactory	Cytology alone : repeat cytology in 2-4 months. If 2 consecutive unsatisfactory cytology , refer for colposcopy Co-testing : -If hrHPV positive, refer for colposcopy. -If hrHPV negative, repeat cytology in 2-4 months. If 2 consecutive unsatisfactory cytology , refer for colposcopy
Normal but transformation zone absent	Manage as normal smears.

APPENDIX . Different types of laboratory HPV tests

HPV test	Manufacturer	HPV Detection	HPV Genotyping	Identifying multiple infections in a single test
Hybrid Capture 2*	Qiagen	13 HR HPV	NA	NA
Amplicor	Roche	13 HR HPV	NA	NA
Cervista*	Hologic	14 HR HPV	HPV16/18	NA
Cobas HPV**	Roche	14 HR HPV	HPV16/18	NA
Realtime HR HPV*	Abbott	14 HR HPV	HPV16/18	NA
Aptima HPV	GenProbe	14 HR HPV	NA	NA
Linear Array	Roche	Multiple HPV	Yes	Yes
HPV Chips	Various	Multiple HPV	Yes	Yes
PCR-Sequencing		Yes	Yes	NA

HR, high-risk. HPV, human papillomavirus. NA, not available.

* denotes FDA approved tests ** denotes FDA approved for primary screening

Fig. 1 Management of normal cytology with or without HPV test

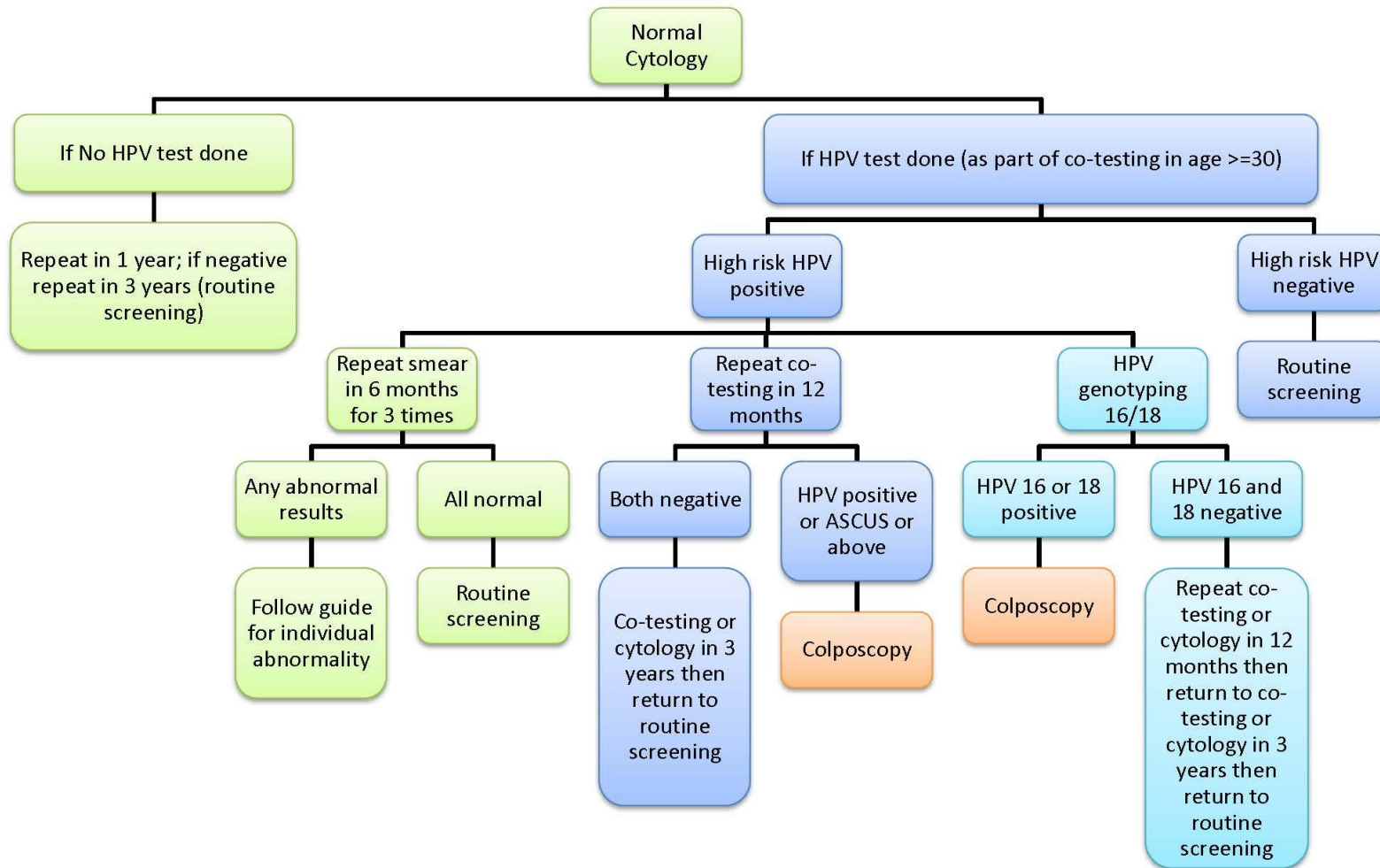


Fig. 2 Management of ASCUS smear (with or without HPV triage or co-testing)

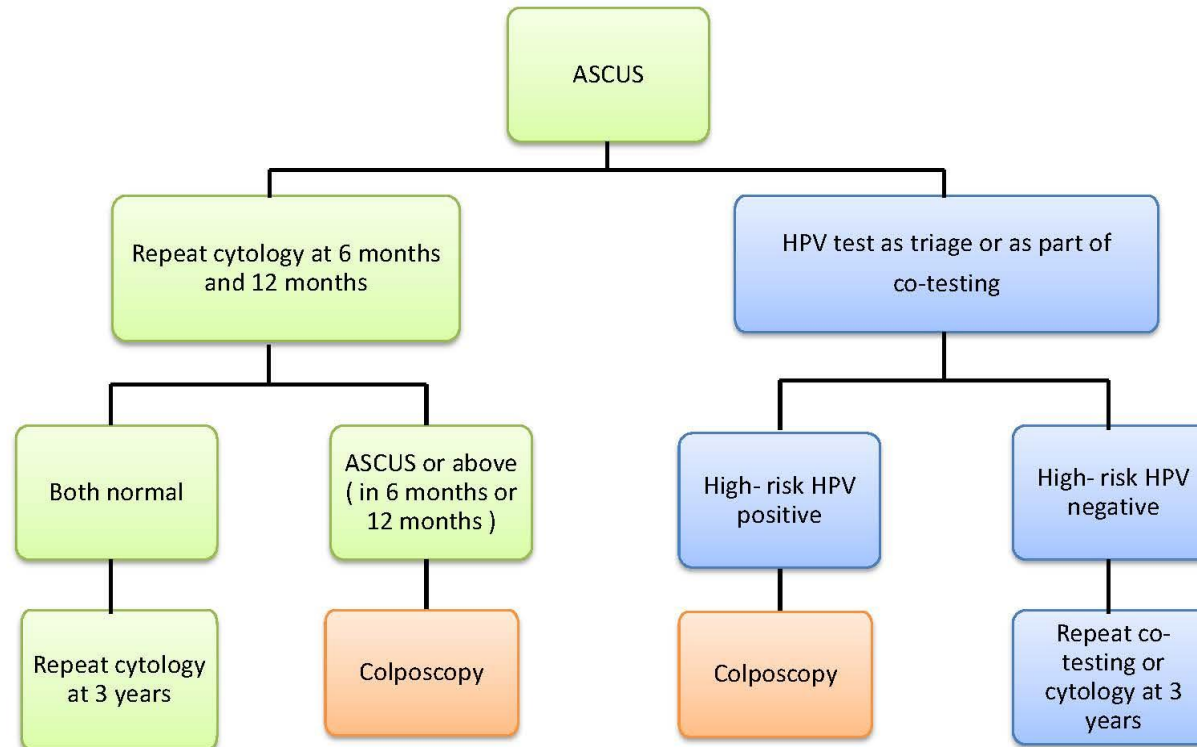


Fig. 3 Management of LSIL smears

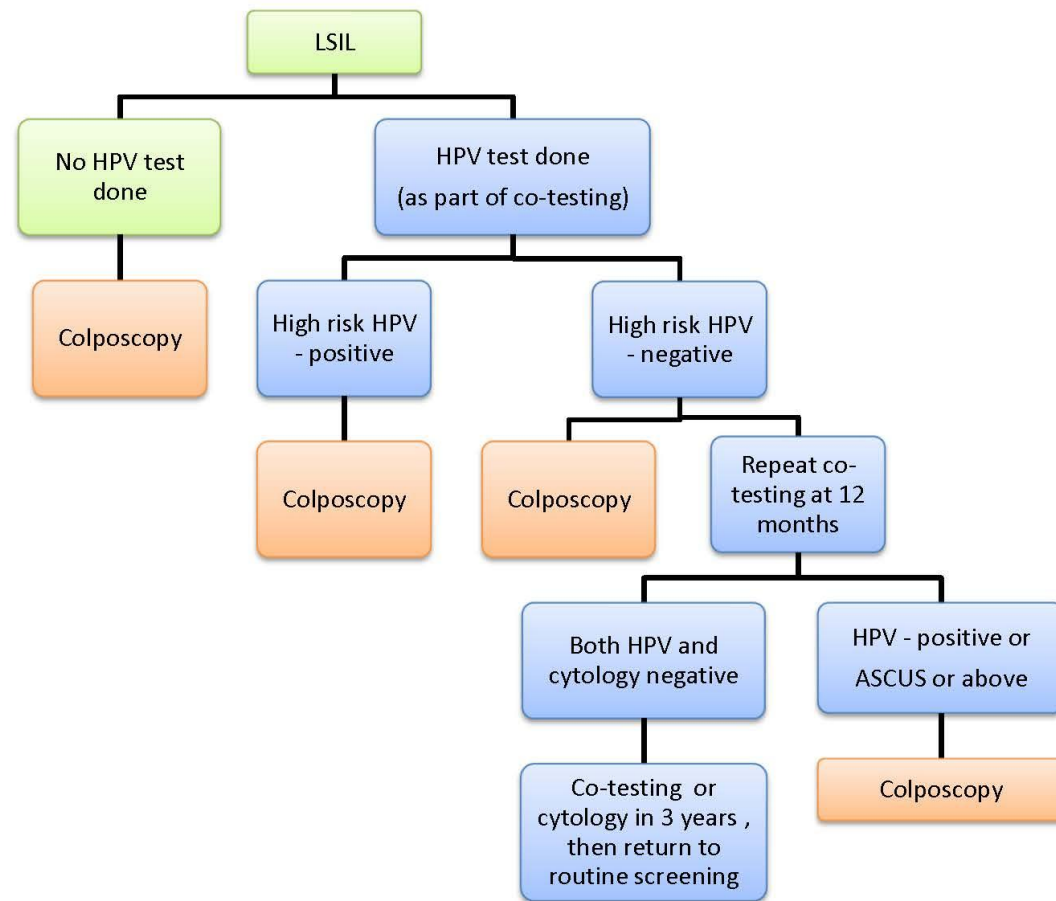
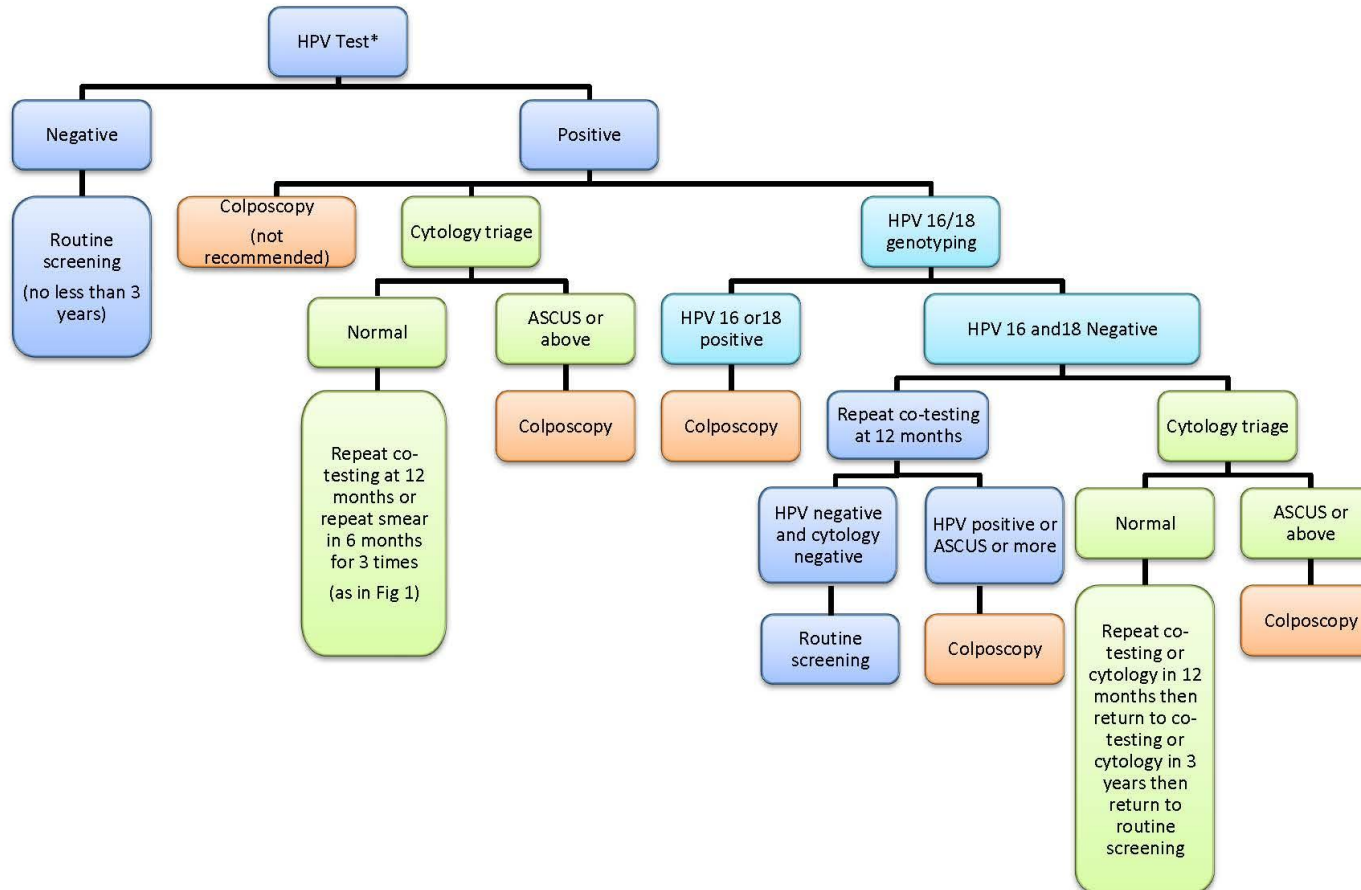
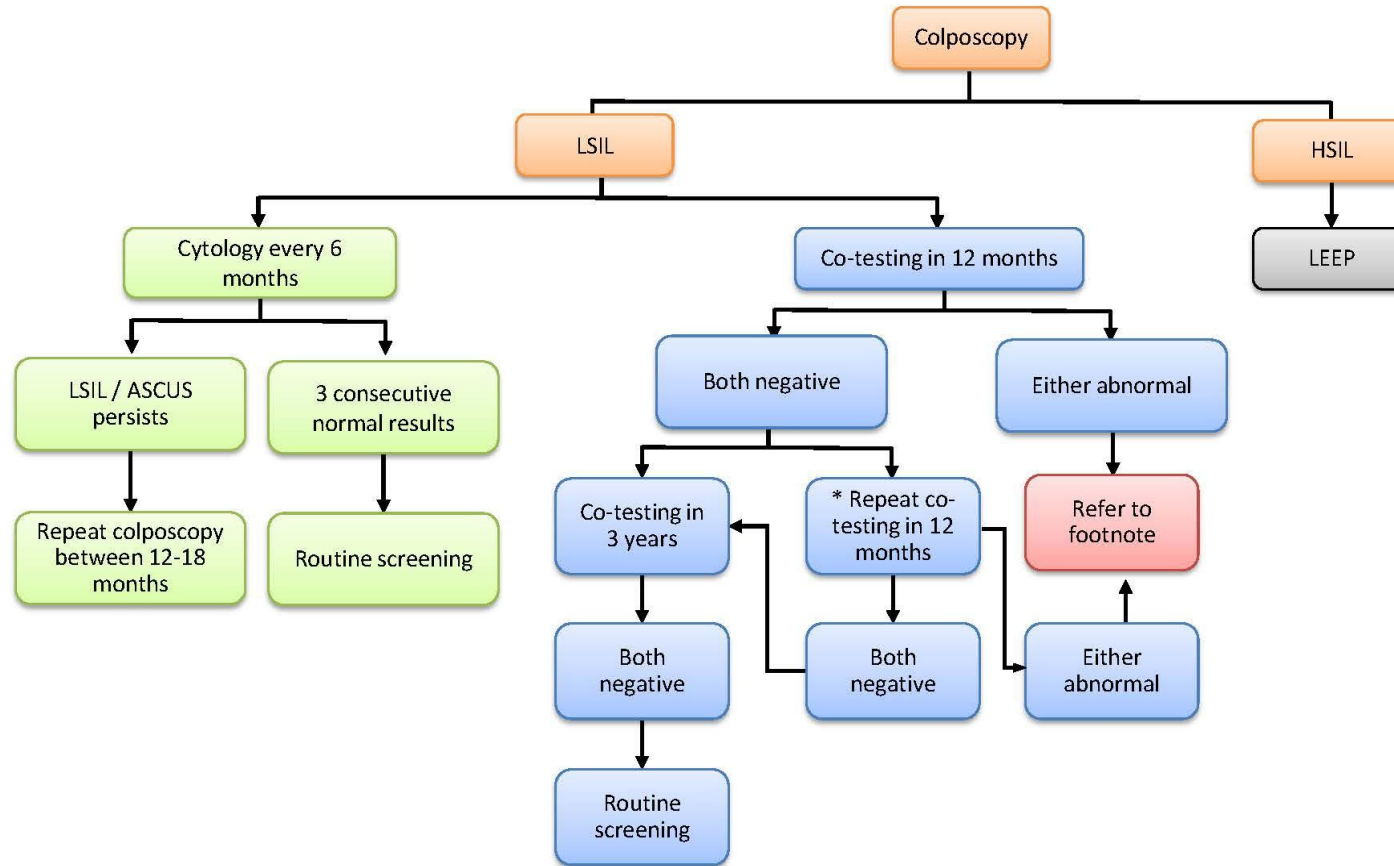


Fig. 4 Management options in HPV as a stand-alone test
 (The appropriateness of HPV test as a stand-alone test requires further verification)



* Only applies to specific tests approved for primary screening (Refer to Appendix)

Fig. 5 Management after colposcopy



Footnote:

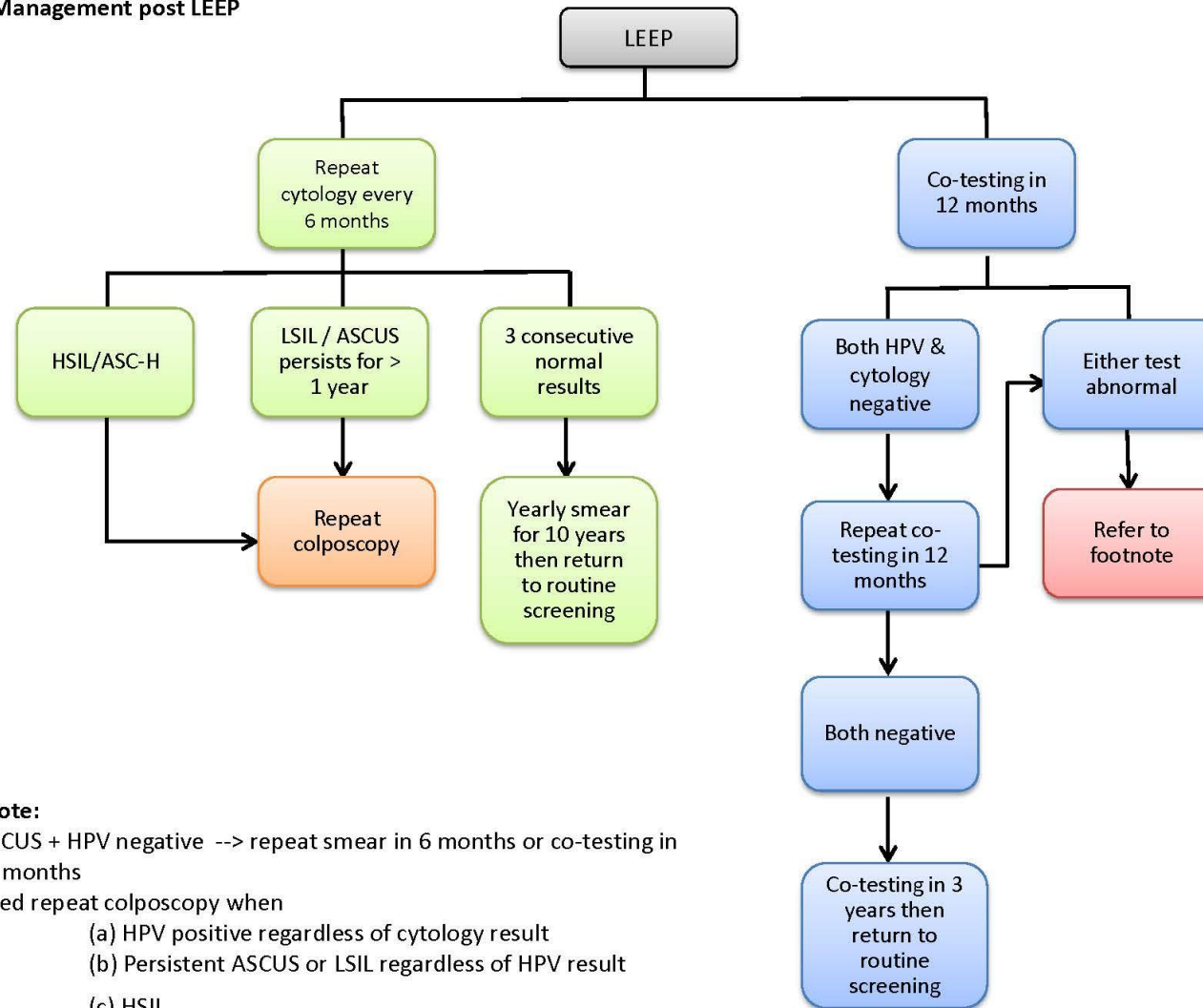
(1) ASCUS + HPV negative --> repeat smear in 6 months or co-testing in 12 months

(2) Need repeat colposcopy when

- (a) HPV positive regardless of cytology result
- (b) Persistent ASCUS or LSIL regardless of HPV result
- (c) HSIL

* For those who had previous high grade smear leading to colposcopy

Fig. 6 Management post LEEP



Footnote:

- (1) ASCUS + HPV negative --> repeat smear in 6 months or co-testing in 12 months
- (2) Need repeat colposcopy when
 - (a) HPV positive regardless of cytology result
 - (b) Persistent ASCUS or LSIL regardless of HPV result
 - (c) HSIL

Fig. 7 Management of women with Atypical Squamous Cells-Cannot Exclude High grade SIL (ASC-H)

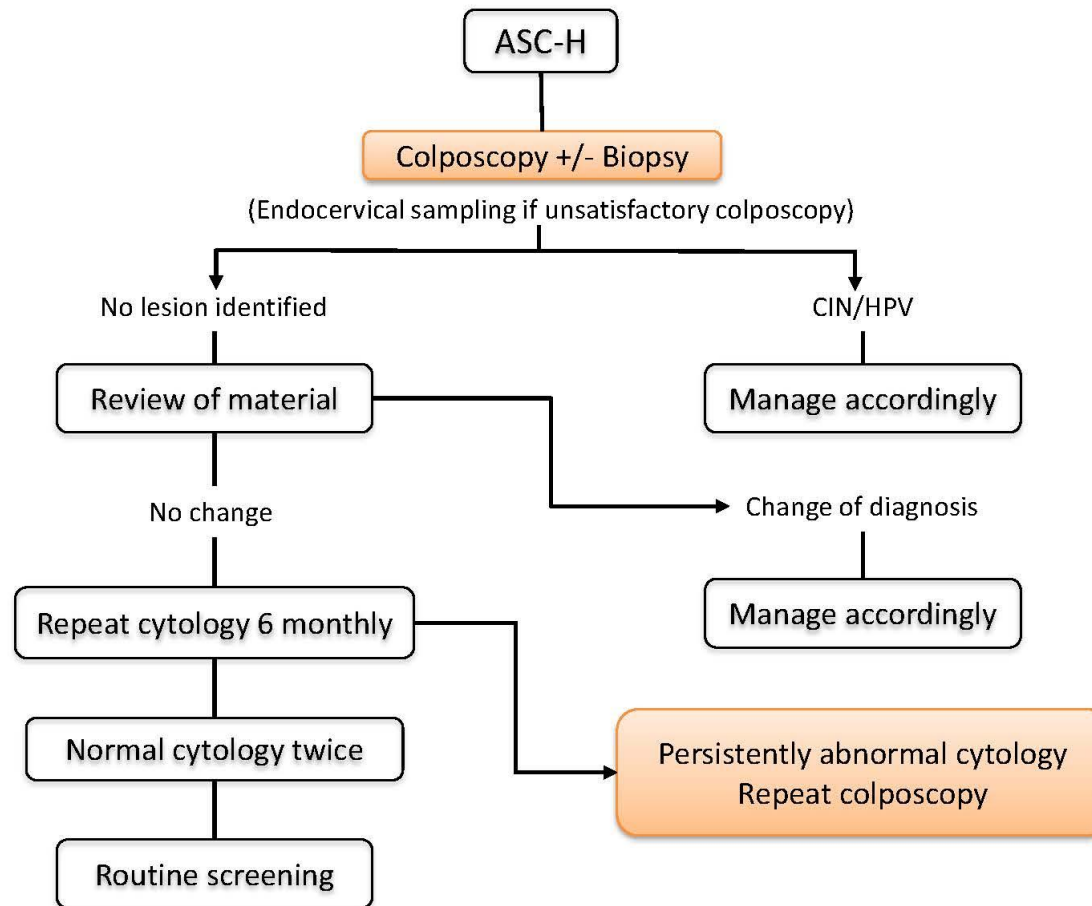


Fig. 8 Management of women with Cytology showing Atypical Glandular Cells

