MANAGEMENT GUIDELINES FOR CERVICAL SCREENING & PREINVASIVE DISEASE OF THE CERVIX

February 2019

Preface

Foreword

The incidence of cervical cancer in Singapore has steadily declined over the last four decades. From 2011-2015 cervical cancer was the 10th most common cancer occurring among women. It was the 4th most common female cancer in the 1970s. The age-standardised incidence rate of newly diagnosed cervical cancer in females has been declining since 1976. It has dropped by more than half from 17.3 per 100,000 person-years in the period 1976-1980 to 7.1 per 100,000 person-years in the period 2011-2015. It is accompanied by the decline in the mortality rates as well. The impact of cervical cytology screening on reducing the incidence and mortality of cervical cancer is well documented in observational studies, in particular, in countries with well organised screening programmes.

The Papanicolaou smear or the Pap smear has been widely available since its first introduction into Singapore in 1964. The positive attitude of Singapore women towards screening contributed toward the improvement in cervical cancer control in Singapore.

Whilst the incidence of cervical cancer in Singapore has declined over the decades, more can still be done to reduce the rates of cervical cancer further.

Since the first publication of the Management Guidelines for Abnormal Pap Smear & Preinvasive Disease of the Cervix in 2002 by the Health Promotion Board for its CervicalScreen Singapore Programme, much has changed in the way we look at the management of the abnormal Pap smear as well as the future of cervical cancer screening. In addition to the advent of new molecular technology in Human PapillomaVirus (HPV) and viral genotyping, the availability of the HPV vaccines has further revolutionised the approach to this most preventable cancer.

Within the past decade, several sentinel trials have been performed to help triage management of patients. In addition, updated national guidelines have been published to provide a more cost-effective approach to cervical cancer screening. The future of screening for Cervical Cancer is evolving and the role of HPV testing as a primary modality is being adopted by Singapore and many other countries including the Netherlands, Australia and UK.

This second edition aims to provide an update to the management of preinvasive disease of the cervix and address the roles played by liquid based cytology and the HPV DNA testing. Cytology has served us well in the past but incorporating HPV technology into our screening strategy is a pathway to advance cervical cancer screening.

I would like to express my heartfelt gratitude to the team that helped to draw up the guidelines. Special mention to Dr Chia Yin Nin, A/Prof Timothy Lim and Dr Ida Ismail-Pratt. In coming up with the revision of the older guidelines published many years before, I would also like to thank the Health Promotion Board for giving us the opportunity to revisit this very important public health issue in cervical cancer prevention. A death from cervical cancer is a death from neglect.

Professor Ho Tew Hong

Chairman

CervicalScreen Singapore Advisory Committee

January 2019

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Acknowledgements

Disclaimer:
This guideline serves as a guide to clinician and may not cover every clinical scenario. Management should be individualised and tailored to each patient's condition and wishes.

1 Cervical Screening Guidelines

Age Group to be Screened and Screening Interval

1.1 Entry to Cervical Cancer Screening

All women who have ever had sex are advised to have their first cervical cytology test from the age of 25

1.2 Frequency of Screening

- Under the National Cervical Cancer Screening Programme, the frequency is as follows:
  - Age 25 – 29 years: Cervical cytology taken once every 3 years
  - Age 30 - 69 years : HPV test alone every 5 years for a negative HPV test.
- Options for age >= 30 years in non-national cervical screening programmes:
  - Cervical cytology alone every 3 years
  - HPV test alone every 5 years
  - Co testing with cervical cytology and HPV test every 5 years

1.3 Discharge from Screening

- A woman can be discharged from screening at 69 years of age if she has :
  - 3 consecutive negative cervical cytology tests
  - or 2 consecutive negative HPV tests in the last 10 years, with the most recent test occurring within last 5 years
  - or 2 consecutive negative Co-tests in the last 10 years, with the most recent test occurring within last 5 years
- **For Women who had history of CIN2, CIN3 or AIS, routine screening should continue for at least 20 years, even if it extends beyond 69 years of age**

1.5 Women who have never had Sexual Intercourse

- Women who have never had sexual intercourse need not have screening
- However if these women have any symptoms, they should consult a doctor

1.6 Women with high risk characteristics

- Refer to section 6 - Management of Immunocompromised Individuals

1.7 Women who have had HPV vaccination

- Screening should proceed as per non vaccinated women

2 Terminology for Cervical Cytology (Pap Smear) Reporting

List of Terminology

2.1 Unsatisfactory for evaluation

2.2 Negative for intraepithelial lesion and malignant cells.

2.3 Abnormal Cytology

2.3.1 Squamous Lesions

- Atypical squamous cells (see note).
  - Atypical squamous cells of undetermined significance (ASC-US).
  - Atypical squamous cells, cannot exclude high grade lesion (ASC-H)
- Low-Grade Squamous Intraepithelial Lesion (LSIL)
  - HPV effect
  - Mild dyskaryosis (indicative of CIN 1)
- High-Grade Squamous Intraepithelial Lesion (HSIL)
  - Moderate dyskaryosis (indicative of CIN2)
  - Severe dyskaryosis (indicative of CIN3)
  - Severe dyskaryosis (indicative of CIN3) cannot exclude invasive carcinoma
- Squamous cell carcinoma

2.3.2 Glandular Lesions

- Atypical (see note)
  - Atypical endocervical cells
    - Not Otherwise Specified (NOS)
    - cannot exclude neoplasia
  - Atypical endometrial cells
    - NOS
    - cannot exclude neoplasia
  - Atypical glandular cells (Site not specified)
    - NOS
    - cannot exclude neoplasia
- Endocervical adenocarcinoma-in-situ
- Adenocarcinoma
  - Endocervical
  - Endometrial
  - NOS
  - Extrauterine

2.3.3 Carcinoma

- Others-specify
- NOS

2.3.4 Other malignant tumours

- Specify
- NOS

Note: In certain instances, the reporting pathologist may wish to further qualify his/her findings with additional comments. Further management of the patient may take into account the additional information provided.

Explanatory Notes

2.1 Unsatisfactory:

- A cytology sample that is unreliable for the detection of cervical epithelial cell abnormalities.
- Criteria for adequacy:
  - Conventional smear:
    - A satisfactory smear should show at least 10, 000 well-preserved and well-visualised squamous cells.
    - If fewer that these are seen because of paucity of cells, poor preservation, air-drying artefact, thick smearing or covering of blood, inflammatory exudate or other obscuring agents, the smear is considered unsatisfactory.
  - Liquid based cytology:
    - A satisfactory preparation should have a minimum of 5, 000 well-preserved and well visualised squamous cells.
- A smear comprising mainly endocervical cells is also considered unsatisfactory, unless the smear was intended to specifically evaluate the endocervical canal.

2.2 Negative for intraepithelial lesion and malignant cells

- The cytology shows no dyskaryotic or malignant cells i.e. no cells indicative of CIN (SIL), glandular neoplasia or malignancy.
- This category includes those in which cells showing reactive changes are present, those in which micro-organisms are identified, those which contain morphologically benign endometrial cells and those which show changes related to therapy (radiation therapy and / or chemotherapy)

2.3 Abnormal Cytology Results

2.3.1 Squamous Lesions:

- Atypical squamous cells
  - These are cells showing cytologic changes suggestive of a dysplastic squamous lesion but are quantitatively or qualitatively insufficient for a definitive interpretation.
- Low-Grade Squamous Intraepithelial Lesion (LSIL)
  - HPV effect:
    - Squamous cells showing stringent criteria of HPV effect i.e: koilocytosis in superficial or intermediate squamous cells or sharply delineated perinuclear halos in parabasal cells.
  - Mild Dyskaryosis:
    - Cytologic changes indicative of CIN 1
- High-Grade Squamous Intraepithelial Lesion (HSIL)
  - Moderate Dyskaryosis:
    - Cytologic changes indicative of CIN 2
  - Severe Dyskaryosis:
    - Cytologic changes indicative of CIN 3
  - Severe Dyskaryosis, cannot rule out invasive carcinoma:
    - Cytologic changes indicative of at least CIN 3, but with features of possible invasive tumour.
- Squamous cell carcinoma:
  - Cytologic changes indicative of an invasive squamous cell carcinoma.

2.3.2 Glandular Lesions:

- Atypical:
  - These are glandular cells showing cytologic changes which exceed those of a definite benign or reactive process, could reflect a dysplastic glandular lesion but are quantitatively or qualitatively insufficient for a definitive interpretation. Where possible, these are qualified as to whether the abnormal cells are of endocervical or endometrial origin.
- Endocervical adenocarcinoma-in-situ:
  - Cytologic changes indicative of endocervical adenocarcinoma–in-situ.
- Adenocarcinoma:
  - Cytologic changes indicative of an invasive adenocarcinoma. Where possible, these are qualified as to whether the abnormal cells are of endocervical, endometrial or extrauterine origin.

2.3.3 Carcinoma

- Describe accordingly.

2.3.4 Other Malignant Tumours:

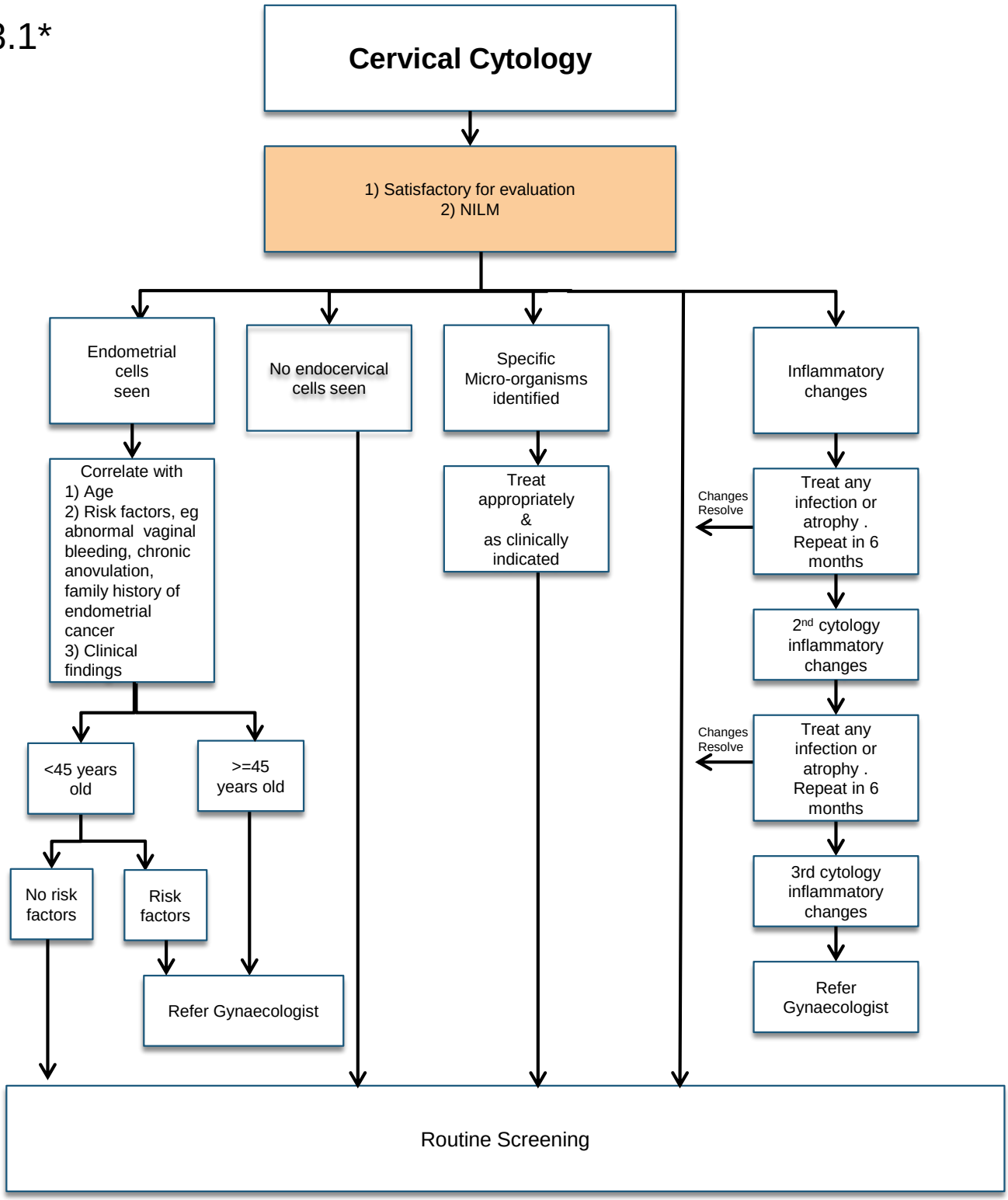
- Describe accordingly.

Elements to be included in the report

- Satisfactory/Unsatisfactory cytology results
- Endocervical/Metaplastic squamous cells present/absent
- Interpretation of cytology (includes documentation of findings other than epithelial cell abnormalities eg micro-organisms, treatment effect, etc)
- Recommendation for follow up

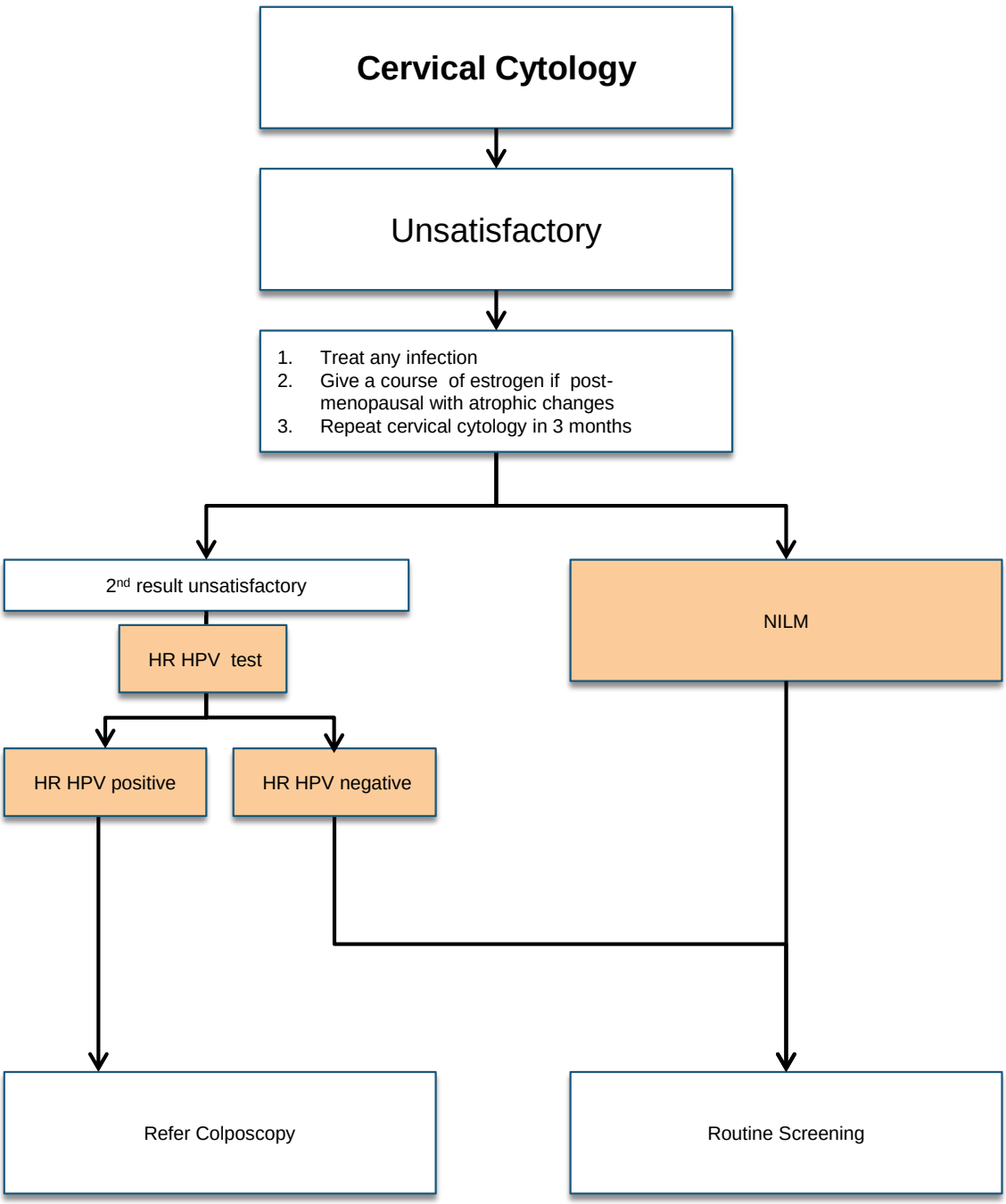
3 Management of Cervical Cytology (Pap Smear) Screening

3.1*



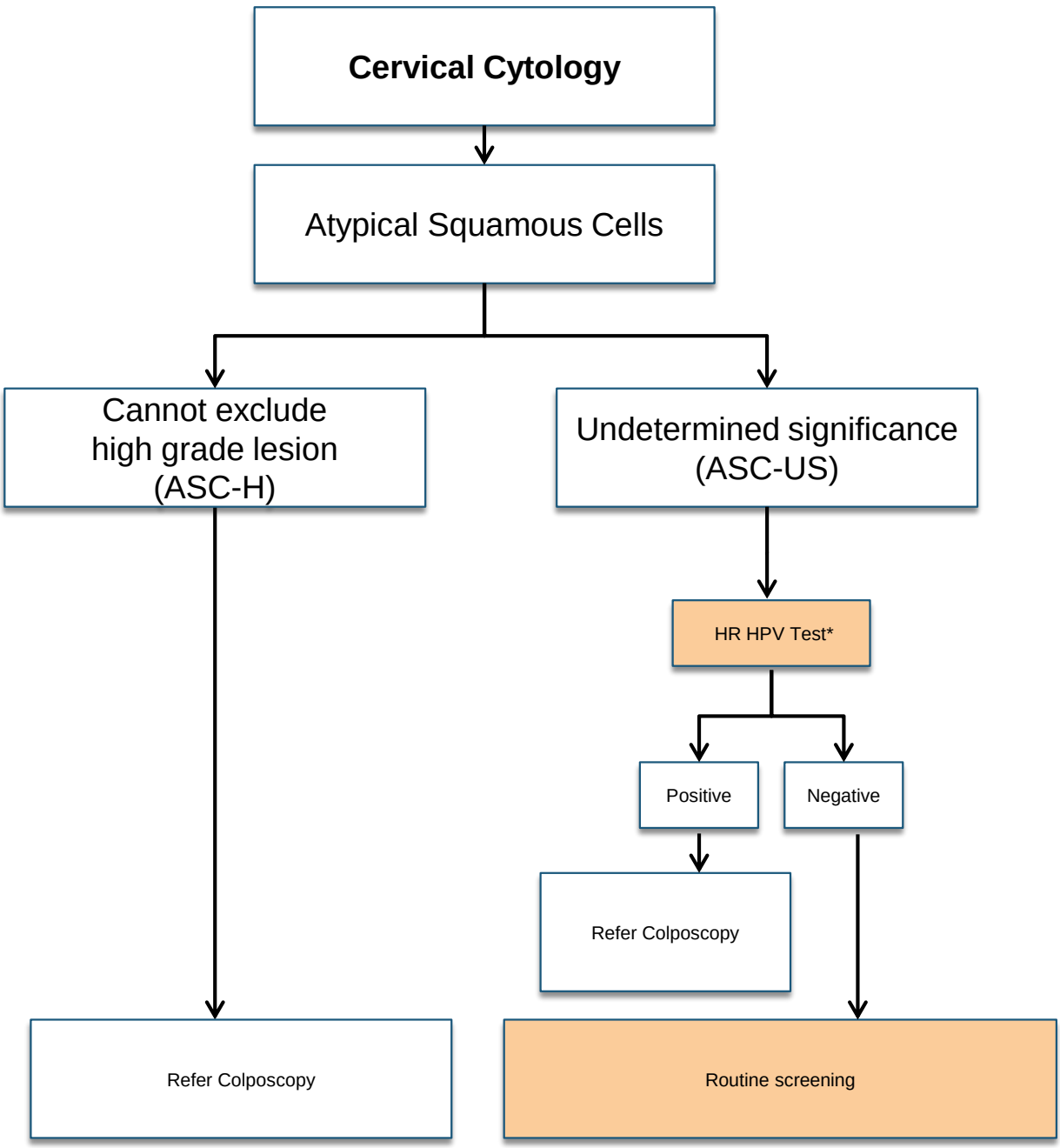
*Workflow adopted by the National Cervical Cancer Screening Programme for women who are between 25 to 29 years old

3.2 Management of Unsatisfactory Cytology Results

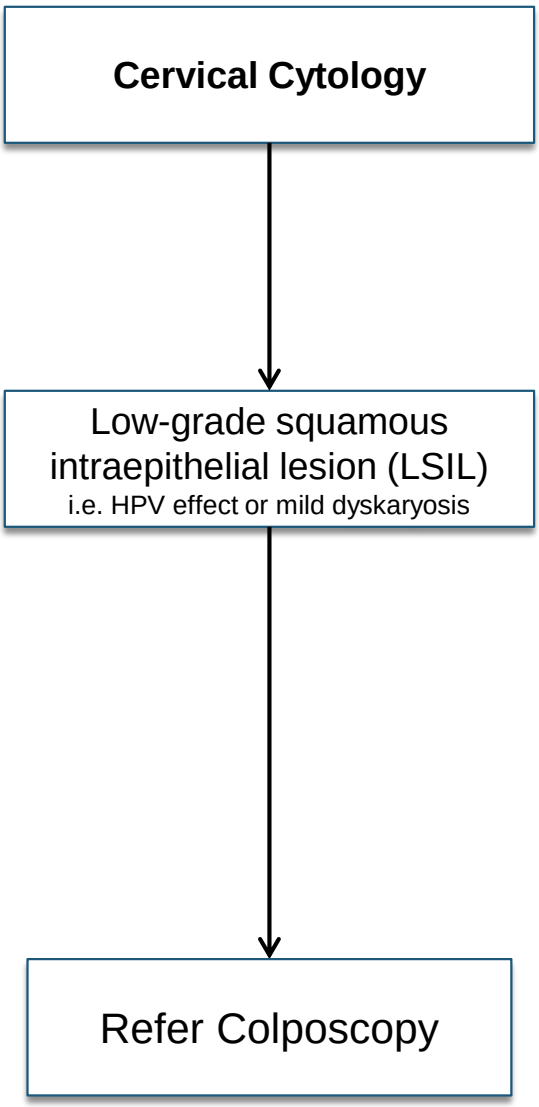


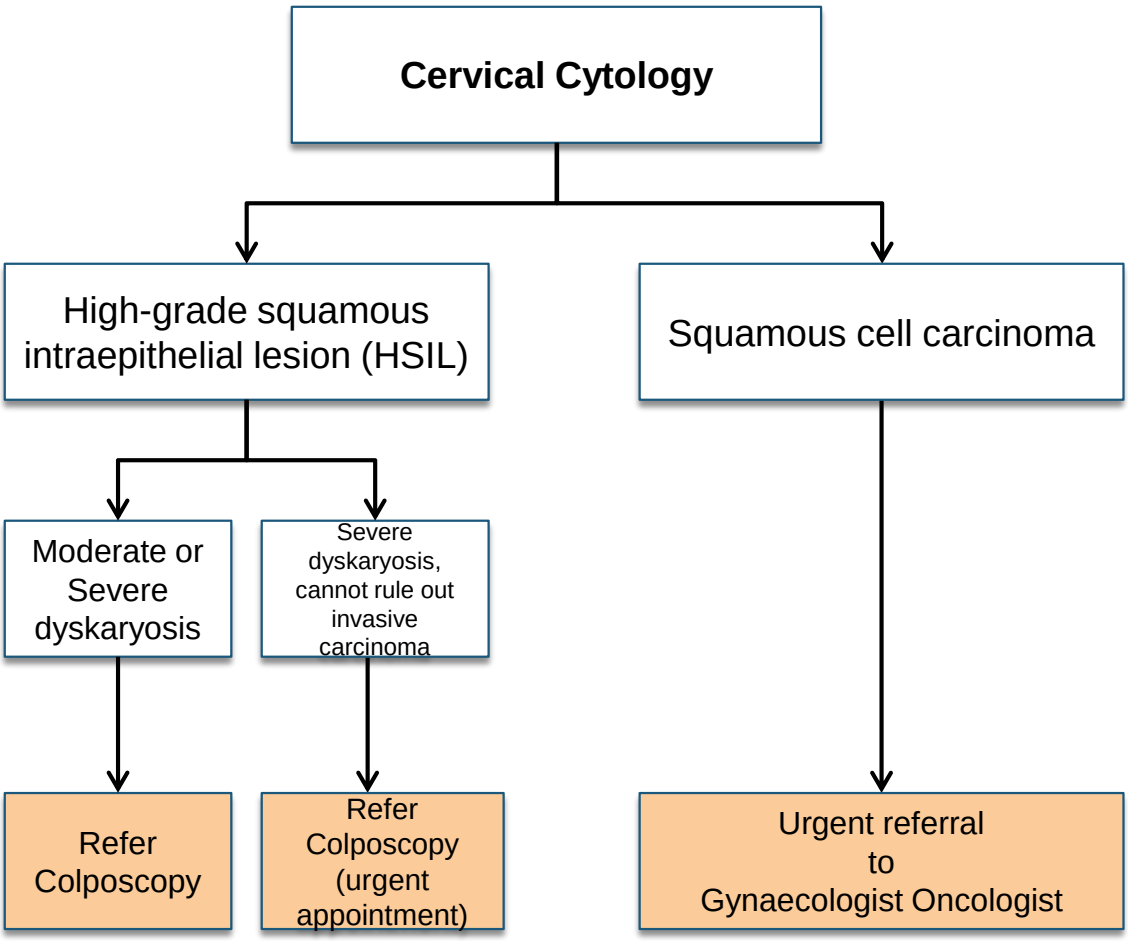
3.3 Management of Abnormal Cytology Results

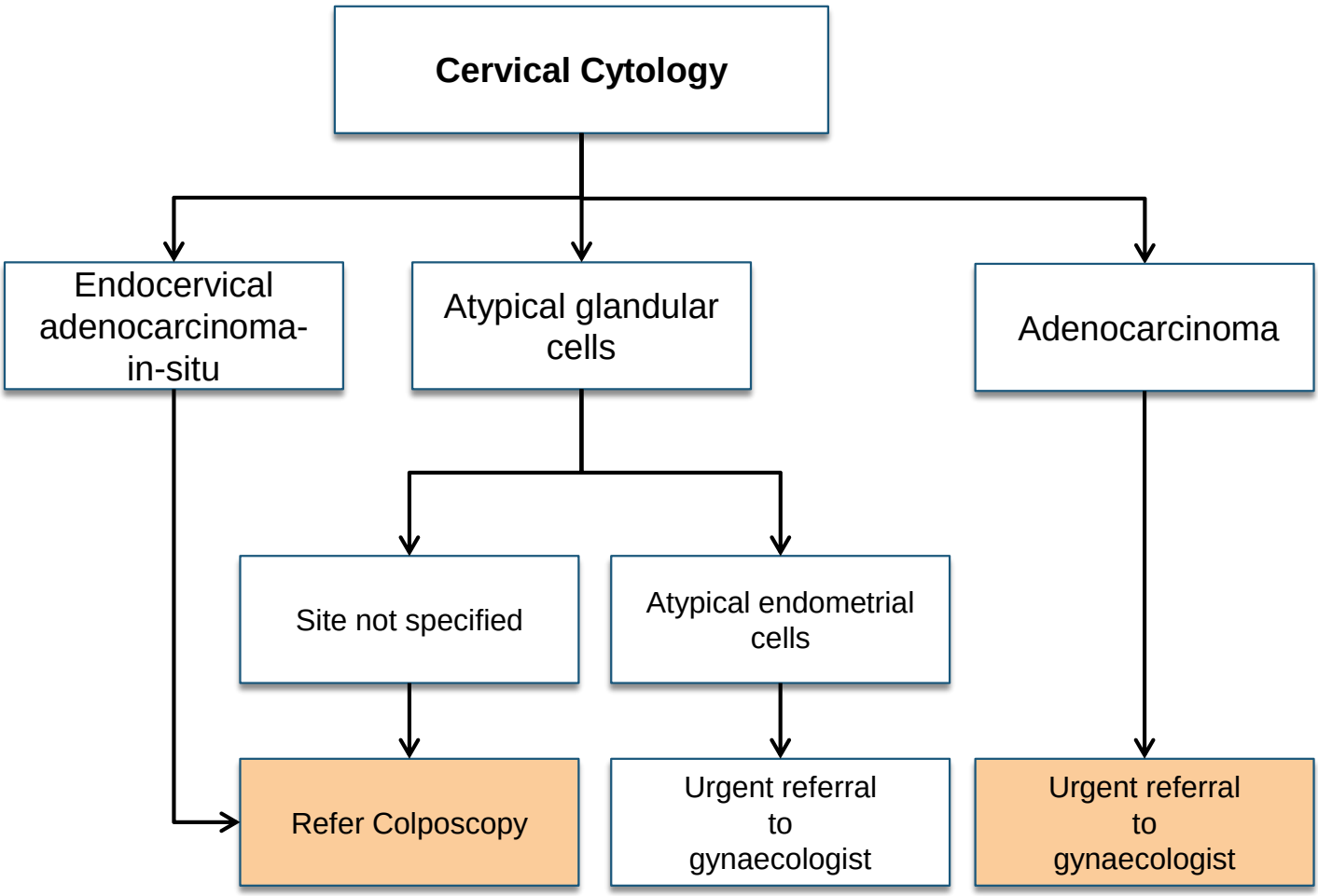
3.3.1 Management of abnormal cytology results with no past history of CIN or genital tract cancer

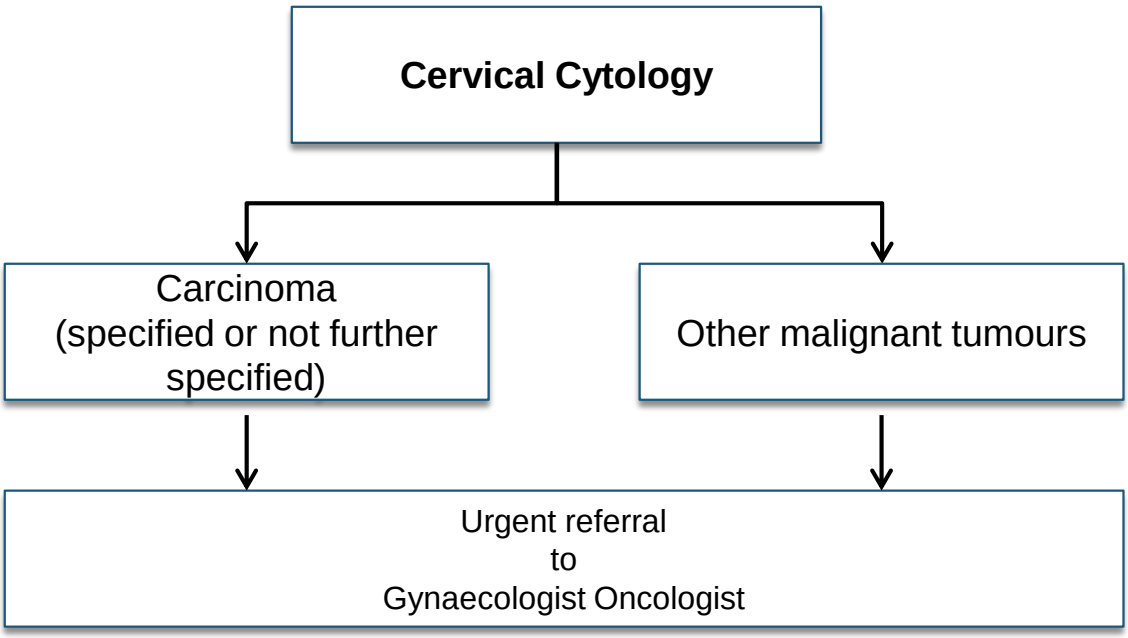


*Workflow adopted by the National Cervical Cancer Screening Programme for women who are between 25 to 29 years old


Cervical Cytology
Low-grade squamous intraepithelial lesion (LSIL)
i.e. HPV effect or mild dyskaryosis
Refer Colposcopy


Cervical Cytology
High-grade squamous intraepithelial lesion (HSIL)
Squamous cell carcinoma
Moderate or Severe dyskaryosis
Severe dyskaryosis, cannot rule out invasive carcinoma
Refer Colposcopy
Refer Colposcopy (urgent appointment)
Urgent referral to Gynaecologist Oncologist

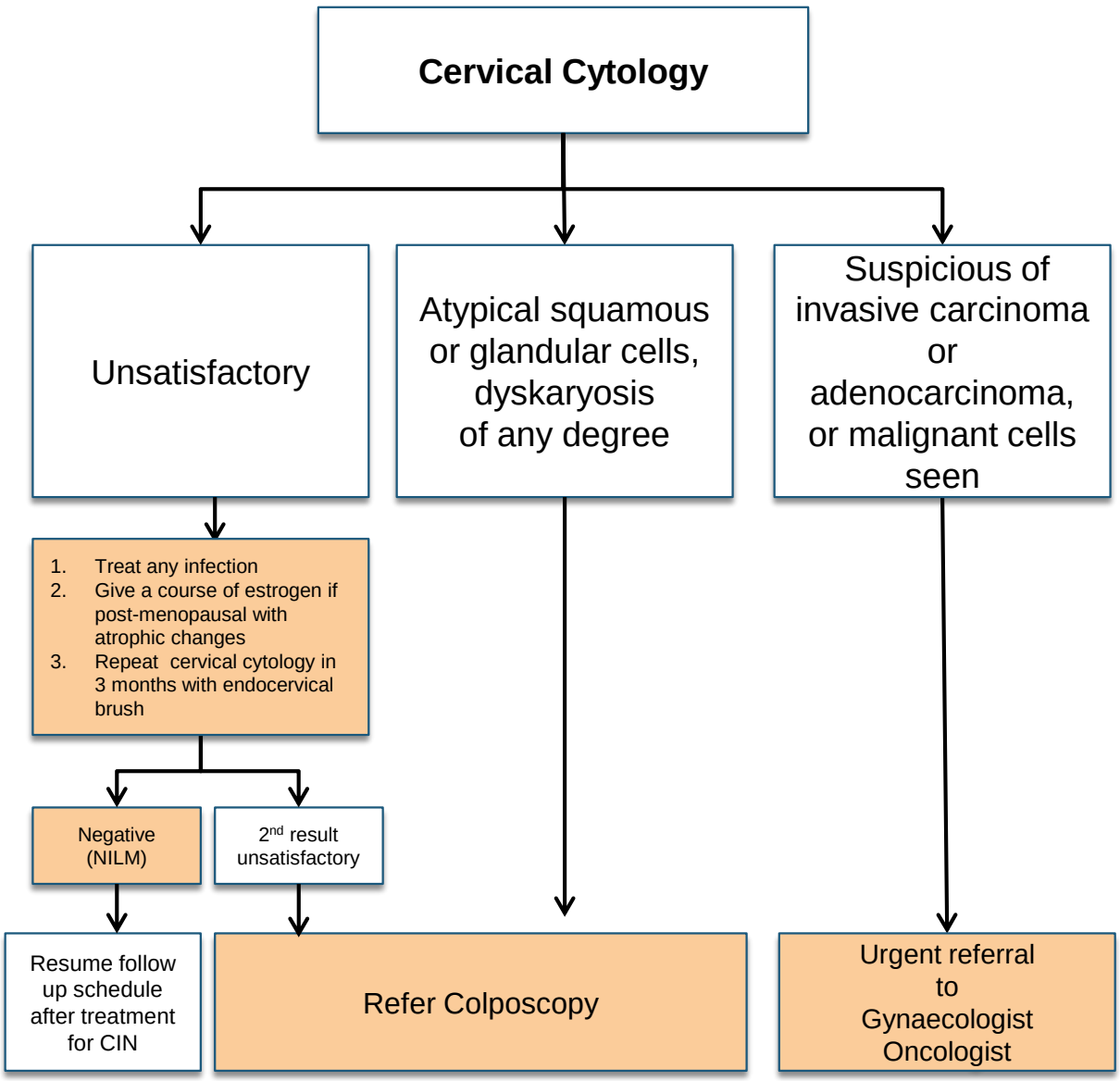

Cervical Cytology
Endocervical adenocarcinoma-in-situ
Atypical glandular cells
Adenocarcinoma
Site not specified
Atypical endometrial cells
Refer Colposcopy
Urgent referral to gynaecologist
Urgent referral to gynaecologist



Other indications for referral :

- Abnormal vaginal bleeding, e.g. post-coital, post-menopausal or inter-menstrual, should always be investigated and the woman referred for a specialist opinion.
- Clinically suspicious looking cervix irrespective of the cervical cytology result must be referred for colposcopy.

3.3.2 Management of Abnormal Cytology Results following treatment for CIN or CGIN



3.3.3 Management of the Abnormal Cytology in Pregnancy

- The same as in the non-pregnant patient

3.4 Cervical Cytology After Hysterectomy

3.4.1 Hysterectomy for benign disease

- Women meeting the following criteria, in the absence of symptoms, need not have any further cervical cytology
  - Normal cervical cytology history
  - Histopathology of cervix known and is benign with no dysplastic/ neoplastic changes

3.4.2 Subtotal hysterectomy

- Should continue to have cervical cytology according to the screening programme

3.4.3 Hysterectomy where histology not known

- One base-line cervical cytology of vaginal vault
- If this is normal, then no further cervical cytologies are required

3.4.4 Immunosuppressed women (due to disease or therapy – refer to section 6)

- Should continue to have cervical cytology of the vault at yearly intervals

3.4.5 Women with a past history of CIN

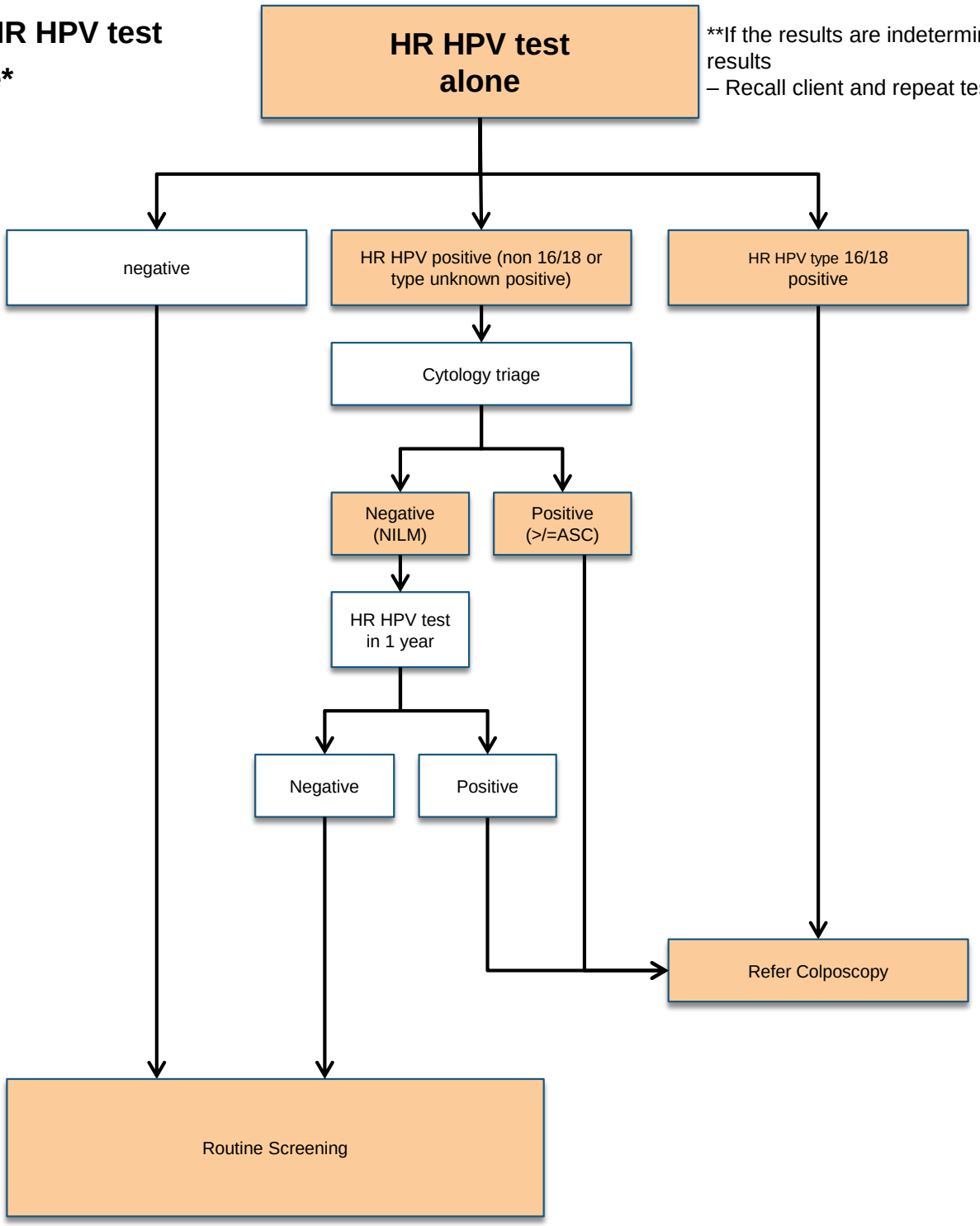
- If excision margin was involved or not adequately assessed histologically
  - Follow up should be at the discretion of the gynaecologist
  - Vault smears should in general be taken at least yearly
- CIN (CIN 1 / 2 / 3) completely excised at hysterectomy
  - Vault smears for five years yearly
  - Two yearly subsequently

3.4.6 Women previously treated for VAIN, or invasive gynaecological malignancy

- These women should be followed up by the treating gynaecologist/ gynaecological oncologist.

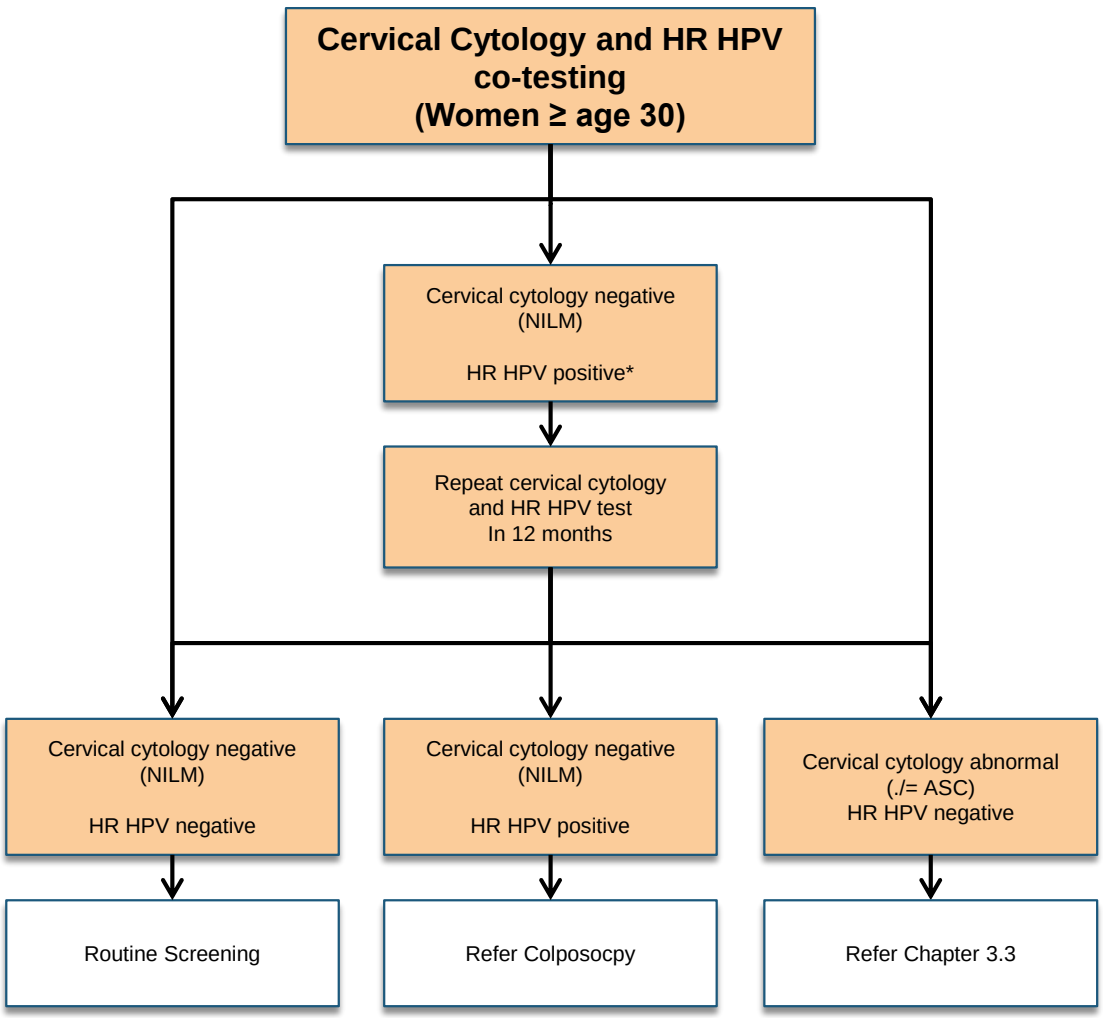
4 Management of HPV Test Screening

4.1: HR HPV test alone*



*Workflow adopted by the National Cervical Cancer Screening Programme for women who are 30 years and above

5 Management of Cervical Cytology (Pap Smear) and HR HPV Test Co-Testing



* If HPV 16 or 18 positive, you may refer for colposcopy

6 Management of Immunocompromised Individuals

6.1 Definition of immunosuppression

Immunosuppression is defined as the partial or complete suppression of the immune response in an individual to fight infection.

6.2 High risk Immunosuppressive clinical condition requiring more frequent screening includes:

- All HIV positive women.
- All women who had undergone solid organ transplant (SOT)
- All women with clinical conditions requiring them to take 2 or more immunosuppressive medication

6.3 Screening recommendation:

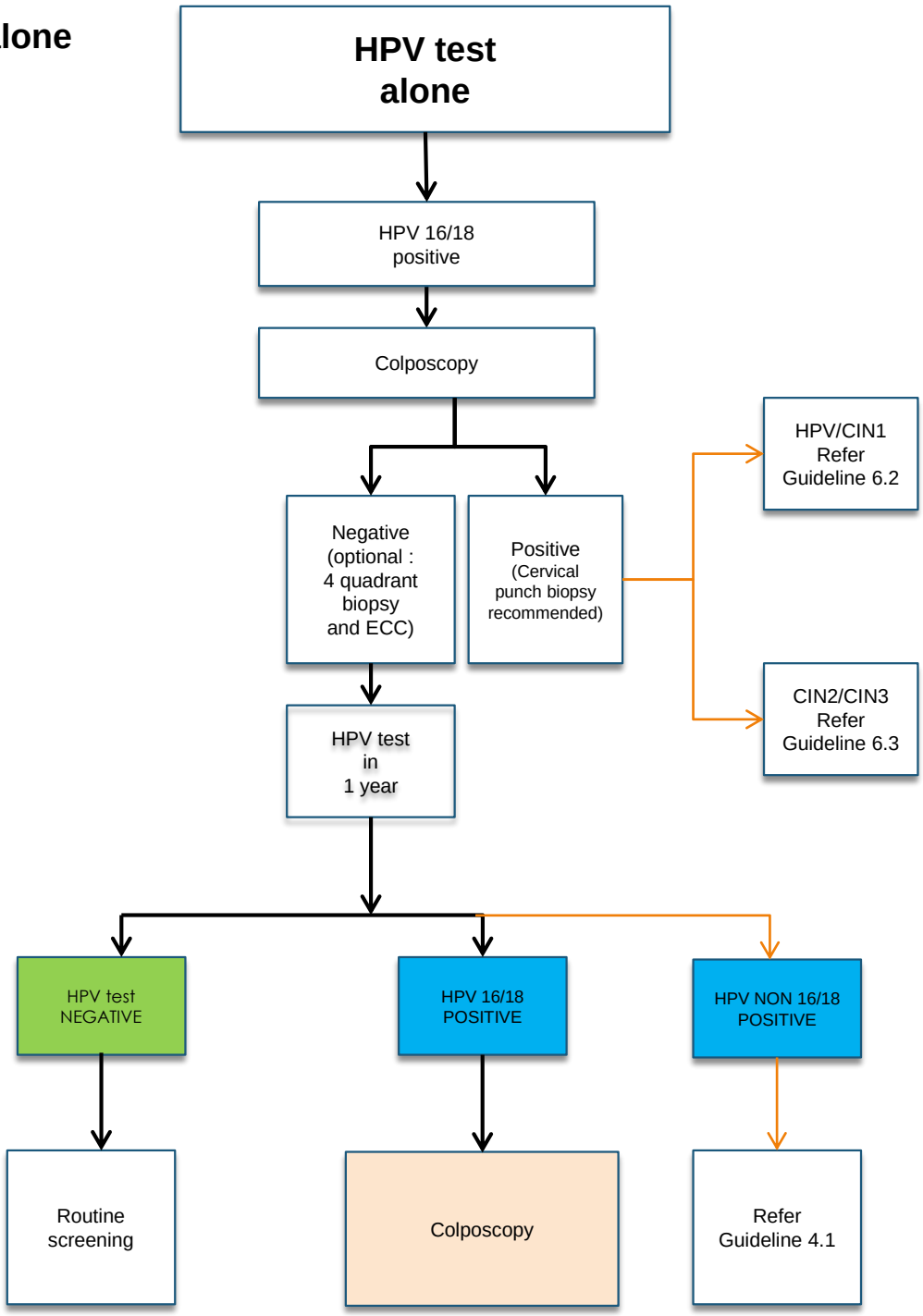
- Age to start screening: As per national guideline at 25 years old
- Screening modality:

  - Annual cervical cytology for women between 25 to 29 years old
  - 3 yearly HPV primary screening for women who are 30 years old and above

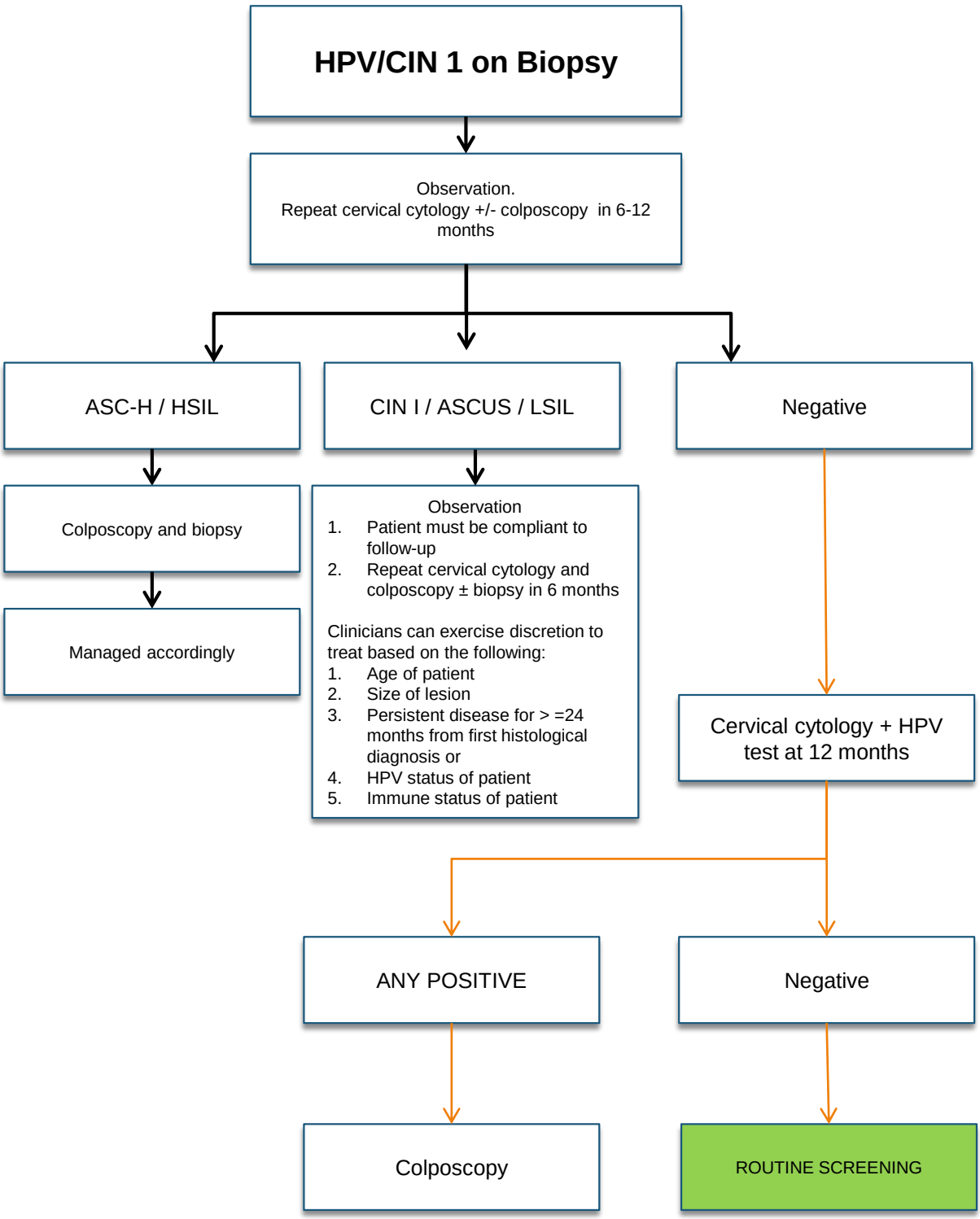
    : Those who are tested with any high risk HPV strains should be sent for colposcopy instead of doing a cytology triage
- Age for discharge from screening: Lifetime screening

7 Management of Preinvasive Disease of the Cervix

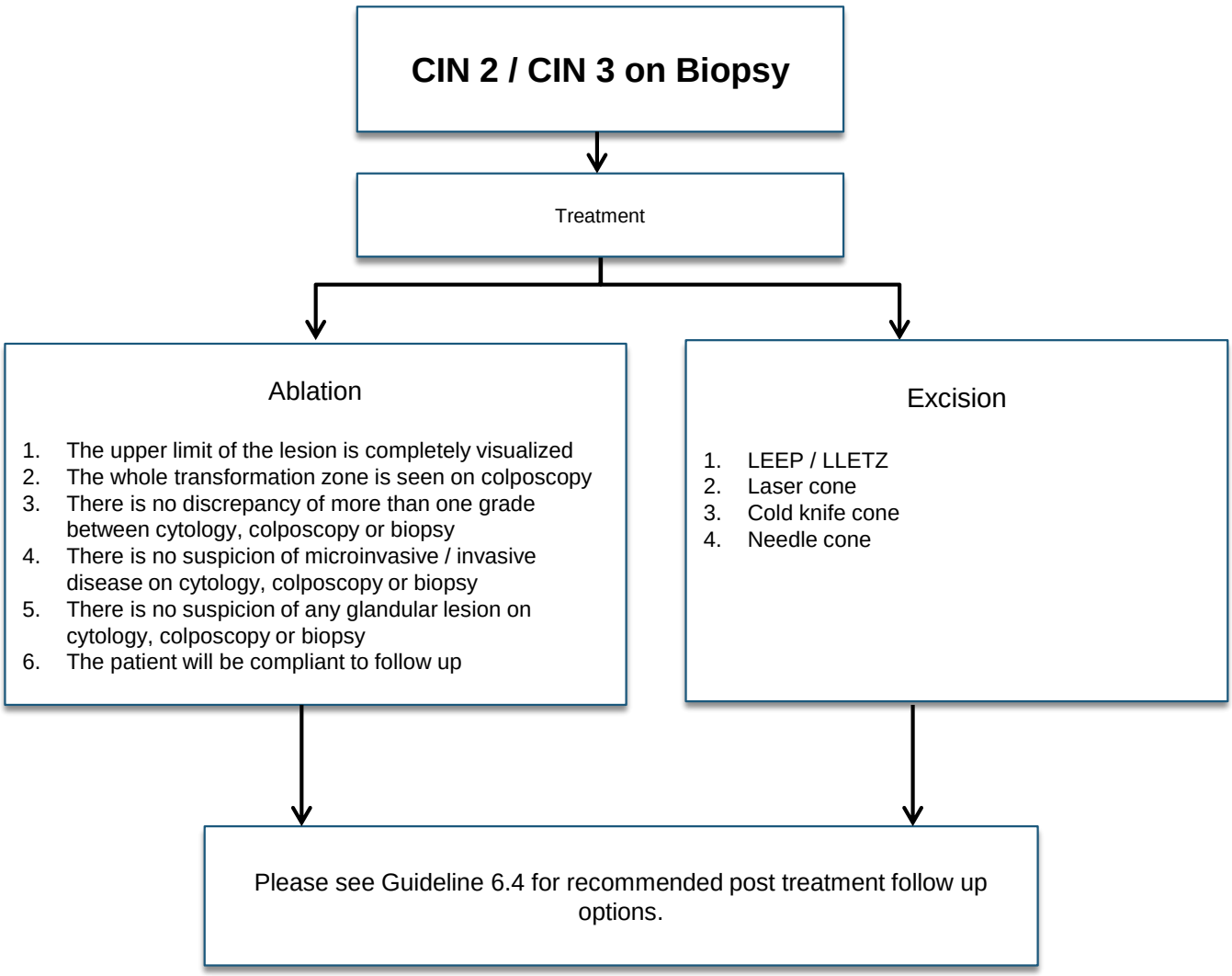
7.1 HPV test alone



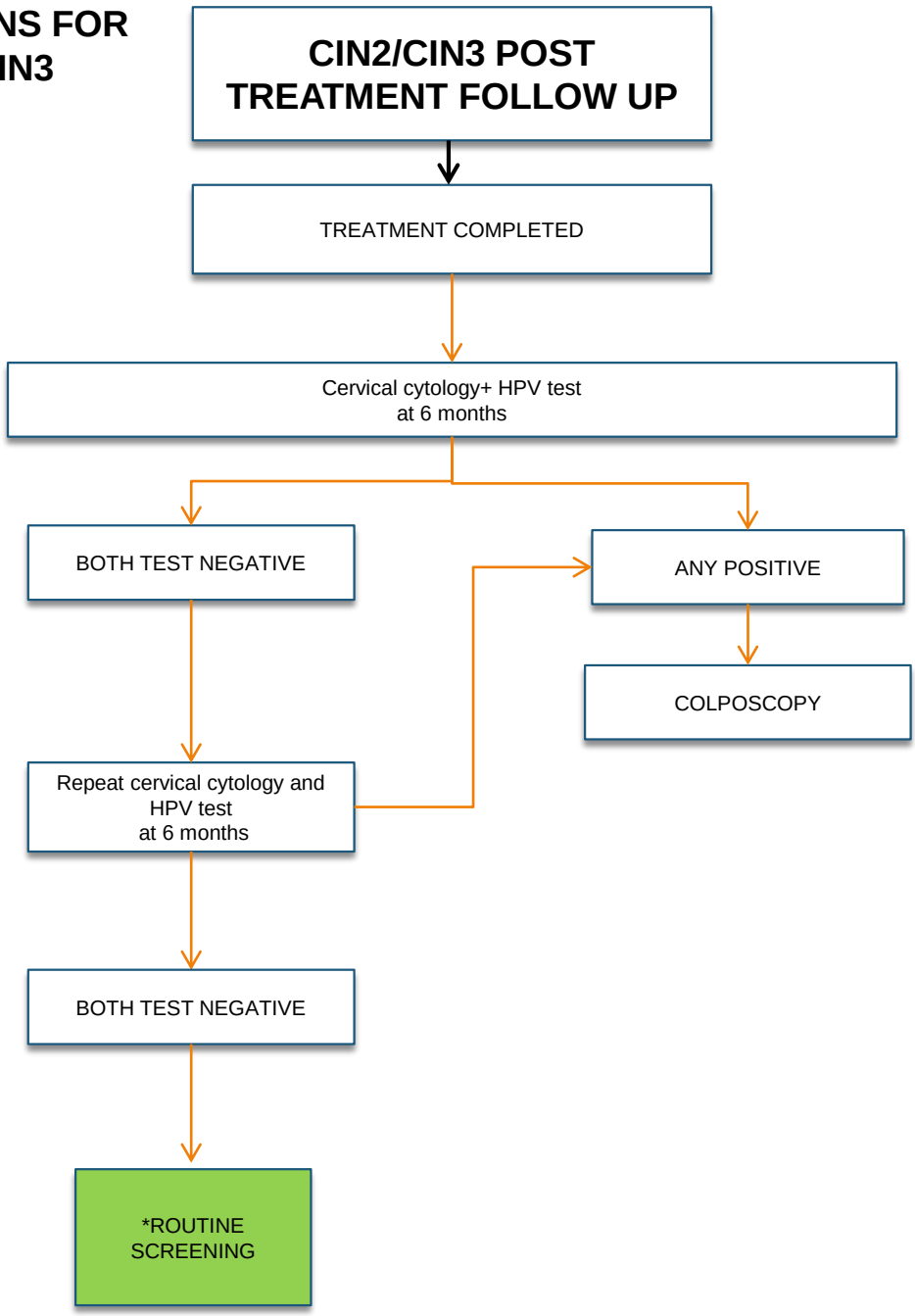
7.2 HPV/CIN 1


HPV/CIN 1 on Biopsy
Observation.
Repeat cervical cytology +/- colposcopy in 6-12 months
ASC-H / HSIL
CIN I / ASCUS / LSIL
Negative
Colposcopy and biopsy
Managed accordingly
Observation
1. Patient must be compliant to follow-up
2. Repeat cervical cytology and colposcopy ± biopsy in 6 months
Clinicians can exercise discretion to treat based on the following:
1. Age of patient
2. Size of lesion
3. Persistent disease for > =24 months from first histological diagnosis or
4. HPV status of patient
5. Immune status of patient
Cervical cytology + HPV test at 12 months
ANY POSITIVE
Negative
Colposcopy
ROUTINE SCREENING

7.3 CIN2 / CIN3

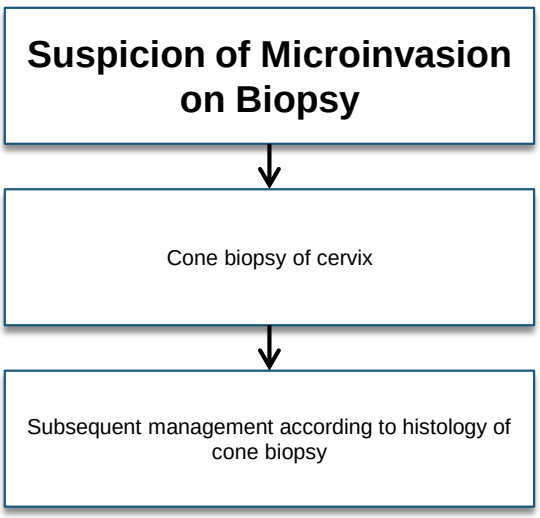

CIN 2 / CIN 3 on Biopsy
Treatment
Ablation
1. The upper limit of the lesion is completely visualized
2. The whole transformation zone is seen on colposcopy
3. There is no discrepancy of more than one grade between cytology, colposcopy or biopsy
4. There is no suspicion of microinvasive / invasive disease on cytology, colposcopy or biopsy
5. There is no suspicion of any glandular lesion on cytology, colposcopy or biopsy
6. The patient will be compliant to follow up
Excision
1. LEEP / LLETZ
2. Laser cone
3. Cold knife cone
4. Needle cone
Please see Guideline 6.4 for recommended post treatment follow up options.

7.4 TREATMENT OPTIONS FOR CIN2/CIN3



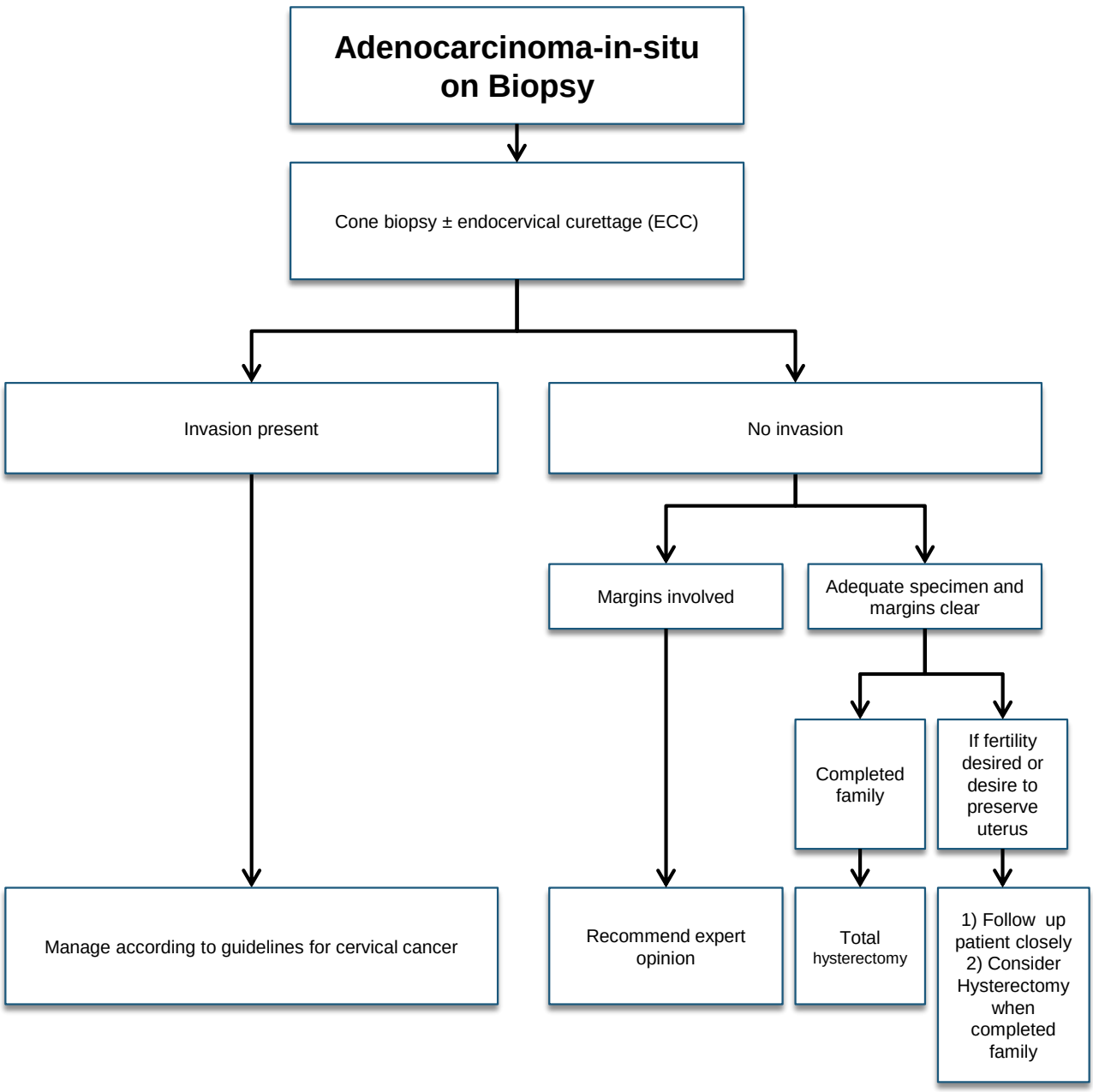
**** Clinician may return patient back to routine screening in community providing is compliant to regular cervical cancer screening.***

7.4 Suspicion of Microinvasion on Cervical Biopsy



Note : For suspected microinvasion a single large cone biopsy specimen with clear margins is necessary for adequate histopathological interpretation. A LEEP may not be adequate. A cone biopsy is preferred.

7.5 Adenocarcinoma-in-situ

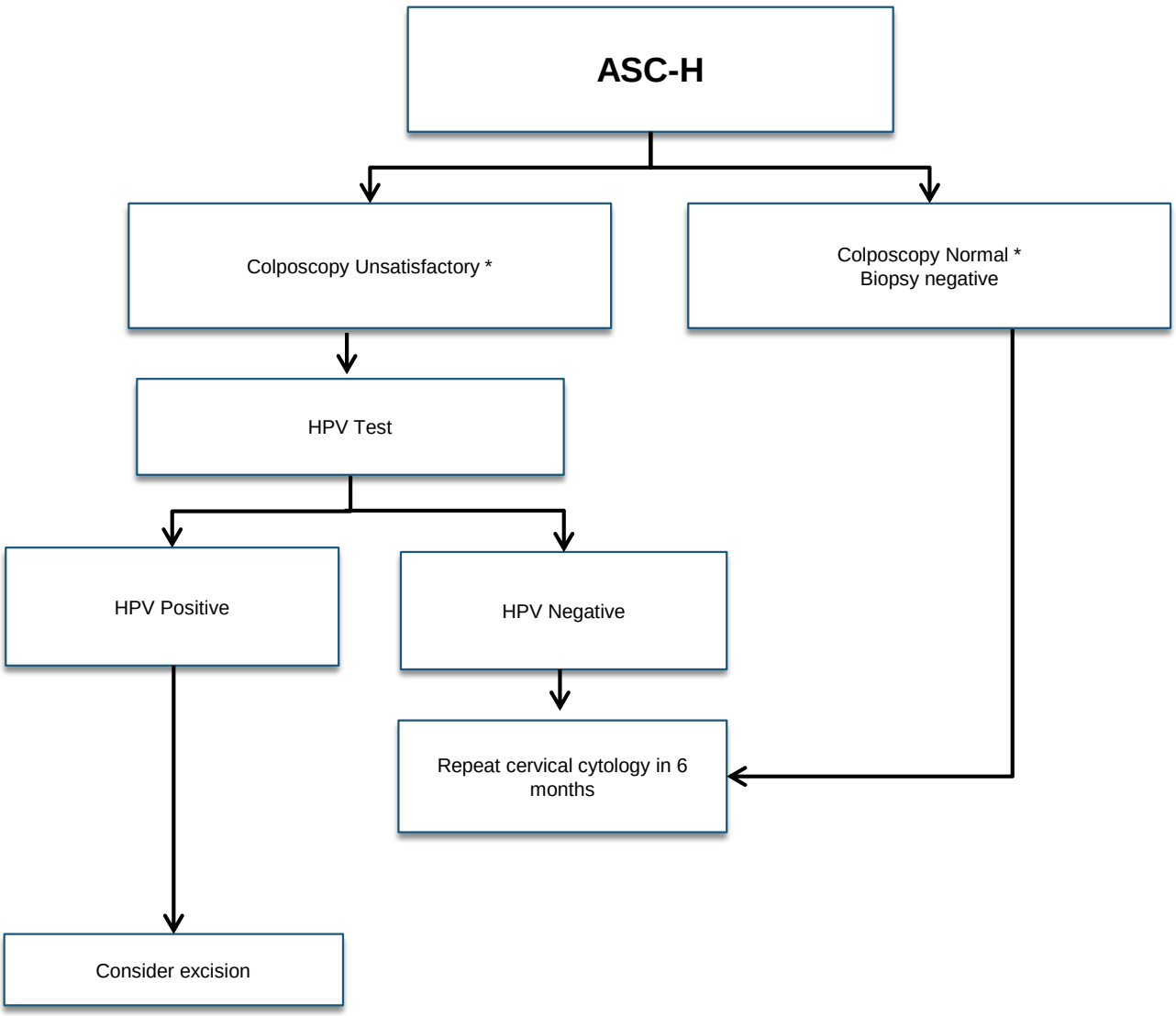


Note : For cone biopsy for adenocarcinoma-in-situ, a single large specimen with clear margins is necessary for adequate histopathological interpretation. A LEEP may not be adequate. A cone biopsy is preferred.

8 Special Situations

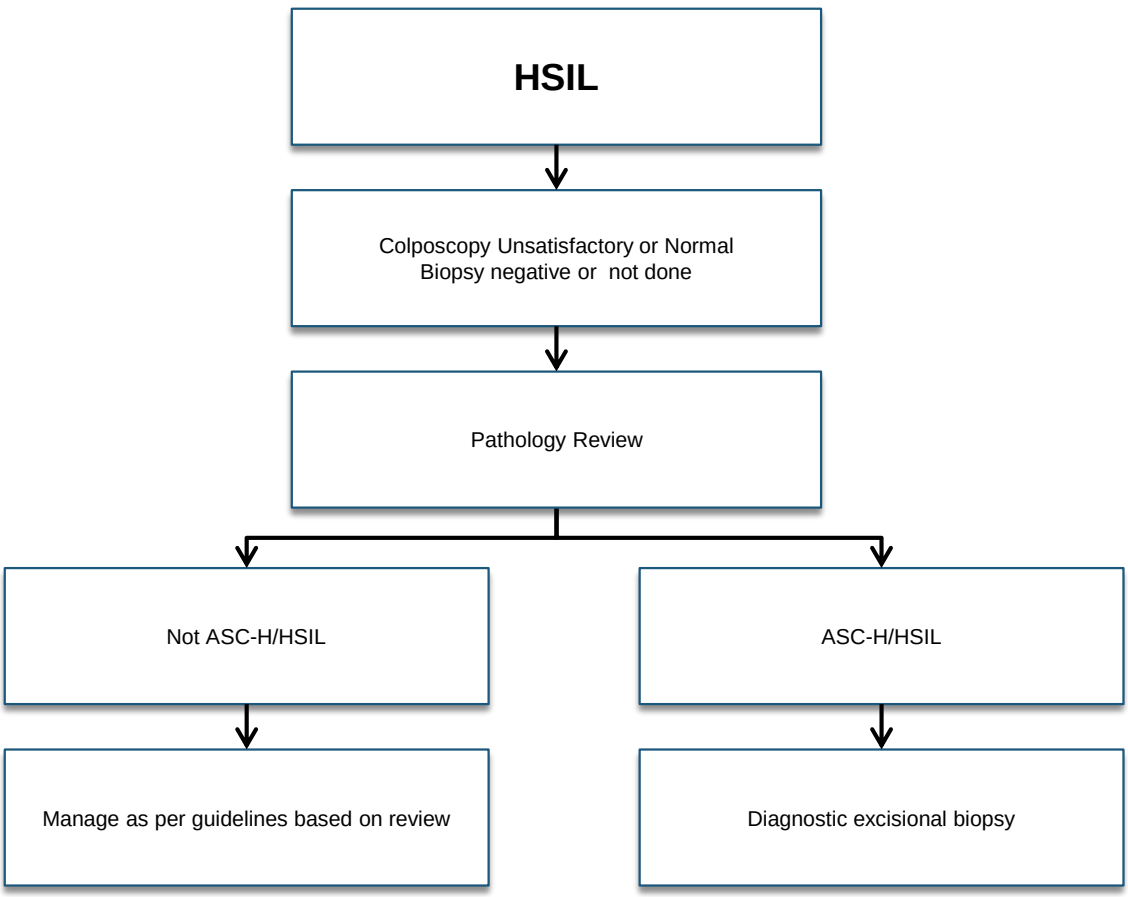
8.1 Abnormal Cytology (ASC-H / HSIL) & Unsatisfactory or Normal Colposcopy

8.1.1 ASC-H Cytology Result & Unsatisfactory or Normal Colposcopy



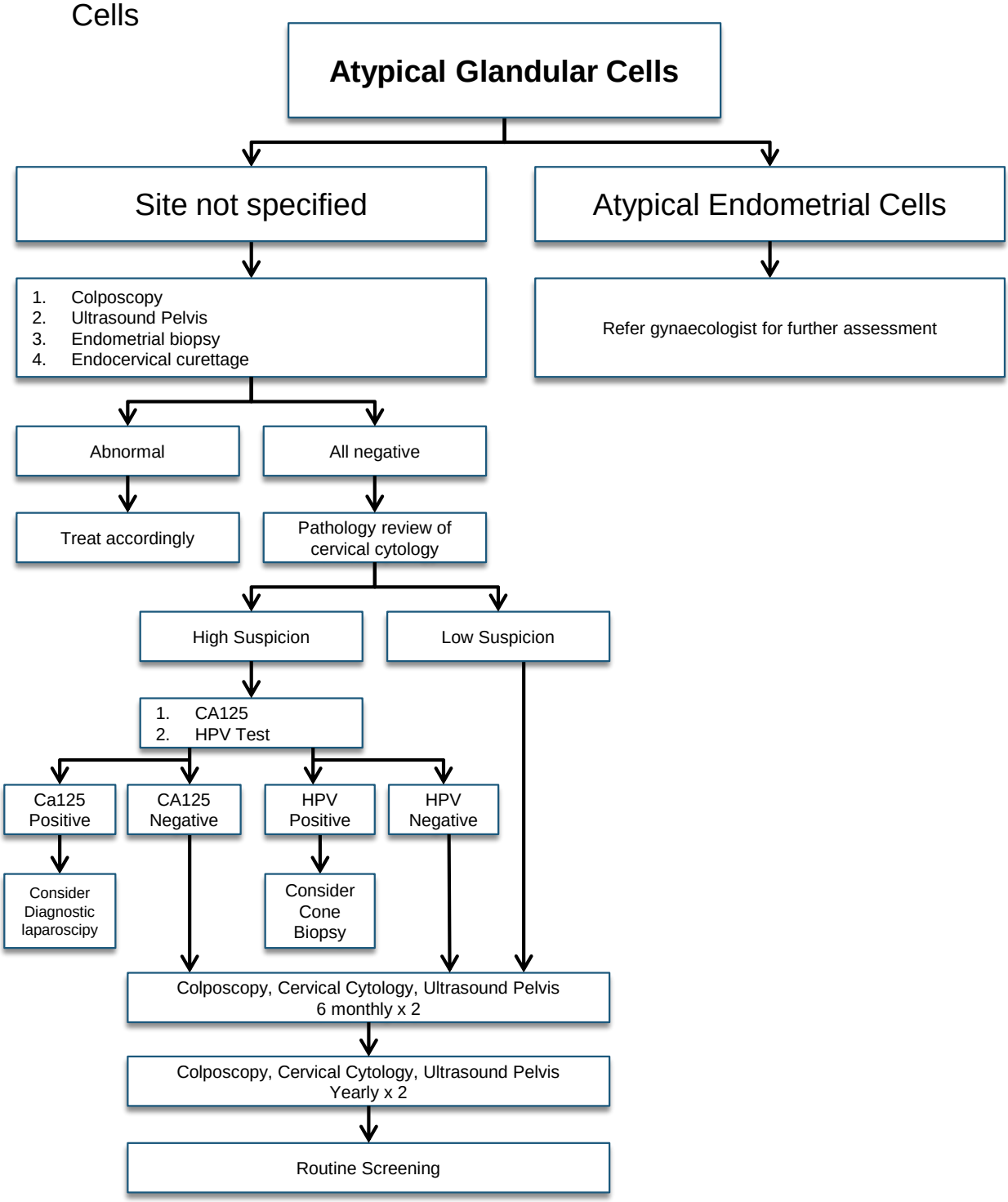
- Consider Pathology Review when necessary

8.1.2 HSIL Cytology & Unsatisfactory or Normal Colposcopy

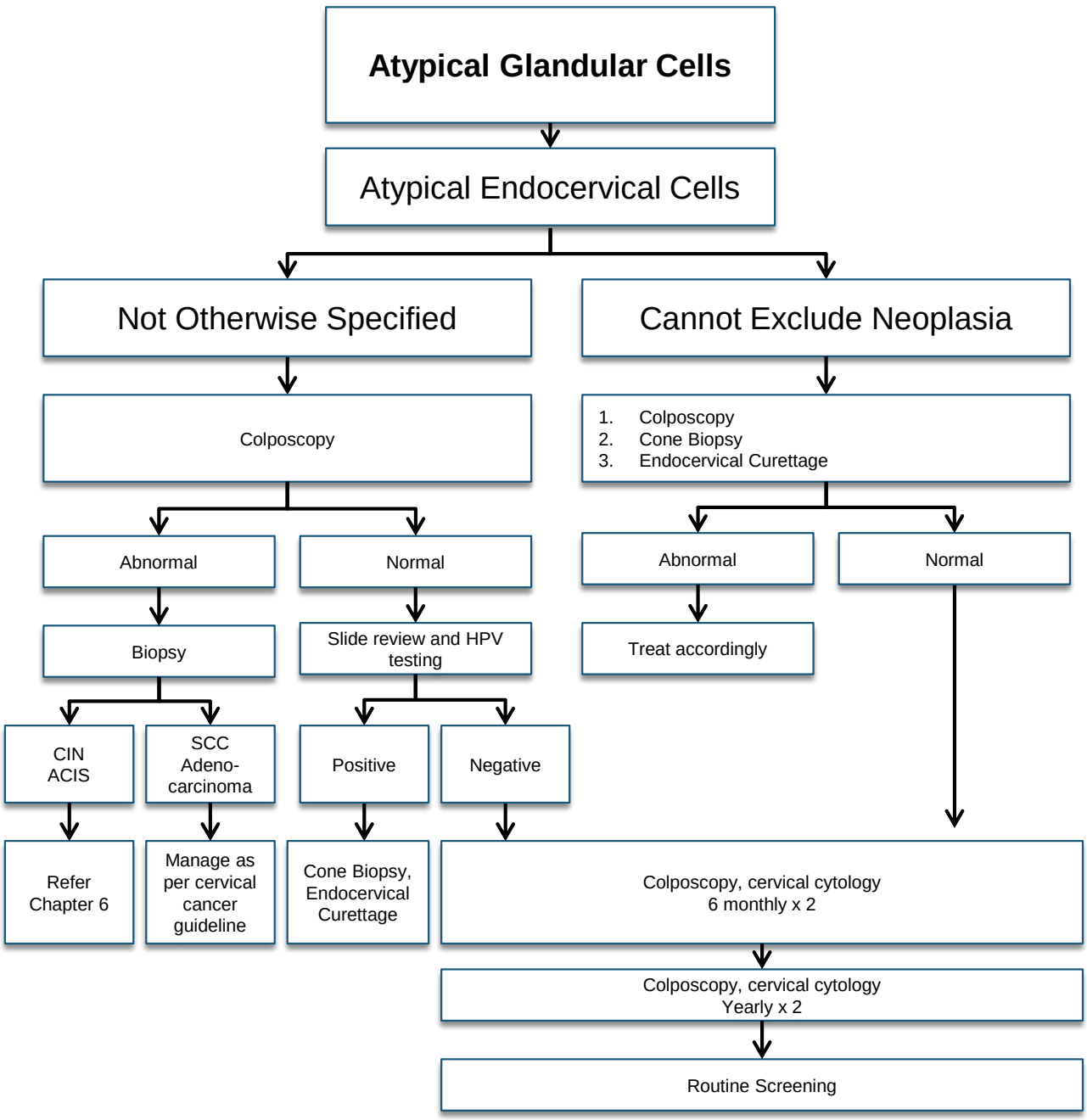


8.2 Atypical Glandular Cells

8.2.1 Atypical Glandular Cells: Site not specified & Atypical Endometrial Cells



8.2.2 Atypical Glandular Cells : Atypical Endocervical Cells



8.5 Management of the Abnormal Cytology and CIN in Pregnancy

- Colposcopic evaluation should be undertaken to exclude invasive disease, by a colposcopist experienced in colposcopy in pregnancy.
- If a high grade lesion is suspected on colposcopy, a biopsy is indicated to exclude possible invasive disease. Cervical biopsy is safe in pregnancy.
- If CIN 2 or 3 is present, colposcopic review should be done every trimester to exclude any possible progression to invasive disease.
- Treatment of CIN should be deferred till at least 8 weeks post-partum, when the lesion should be reassessed. If the patient is breast feeding, local application of estrogen before the colposcopic reassessment may assist accurate evaluation.
- The management of labour is not influenced in any way by the presence of CIN, irrespective of severity.

Glossary

- **Adenocarcinoma in situ (AIS)** - High-grade precancerous changes to glandular cells of the cervix.
- **Cervical intraepithelial neoplasia (CIN)** - abnormal changes of squamous cell on the cervix. CIN 2 and 3 are considered pre-malignant. This is a histological diagnosis that can only be made on a tissue specimen.
- **Colposcopy** - examination of the cervix and vagina with a magnifying instrument called a colposcope.
- **Cone biopsy** - Surgical removal of a cone-shaped section of the cervix. The procedure may be used to diagnose or treat cell changes.
- **Co-testing** - use of both cervical cytology and HPV testing for high risk HPV types at one visit for cervical screening.
- **Dyskaryosis** – nuclear abnormalities in cell morphology detected on cervical cytology.
- **Glandular lesion** - abnormality seen in glandular cells.

Glossary

- **Human Papillomavirus (HPV)** is a virus of over 100 types. Approximately 40 types infect the genital tract and the subtype determines the clinical manifestations of the infection and the oncogenic potential (low or high risk).

HPV tests – The "HR HPV test positive" term in this document refers to a positive result for high-risk (HR) HPV types that cause cervical cancer. High-risk HPV types are detected in 99% of cervical cancers and worldwide approximately 70% of cervical cancers are due to HPV types 16 and 18. The other high-risk HPV types are HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

These tests are currently approved for two indications only – for follow-up testing of women with abnormal cervical cytology test results and for cervical cancer screening. Unfortunately, there are no approved tests for the detection of HPV infections in men.

HPV tests used for primary cervical cancer screening should meet the following criteria:

- Only commercial HPV nucleic acid amplification tests that are analytically and clinically validated for primary population-based screening should be used.
  - The laboratory must confirm that the manufacturer's kit insert lists population based primary screening as an intended use, in combination with the chosen collection medium.
  - Laboratories must follow manufacturer's instructions and no modifications are allowed.
- The HPV test must detect at least 13 high risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Detection of HPV66 is also desirable.
- HPV 16 and HPV 18 specific genotyping is required.
- The HPV assay must be registered with Health Sciences Authority of Singapore (HSA).
- HPV tests must be analytically and clinically validated for primary screening with proven acceptable reproducibility, clinical sensitivity, specificity, positive predictive value and negative predictive value for cervical cancer and verified precancer (CIN 2,3) as documented by publication in peer-reviewed scientific literature. If a clinical trial has not been done, the performance of the assay has to be reported in peer-reviewed literature to be equivalent to assays that have been clinically validated for primary screening, according to the guidelines in Meijer et al, 2009 (Int J Cancer 2009;124:516-520).
  - Sensitivity of candidate test for ≥CIN2 should be at least 90% of sensitivity of the Qiagen HC2 or an equivalent validated test for primary HPV screening. (Require 60 samples for power of 80%)
  - Specificity of candidate test for ≥CIN2 should be at least 98% of the specificity of HC2 or an equivalent validated test for primary HPV screening. (Require 800 samples for power of 80%)
  - Intra- and inter-laboratory agreement should be not less than 87%. (Require at least 500 samples, of which 30% are HPV positive)
- The assay must have an internal control to monitor inhibition and/or assay failure.
- The assay must have an internal control for cellularity to detect inadequate or empty cervical samples

Glossary

Pap smear/test (Cervical Cytology) -

Named after the pathologist who first developed the test in 1943, Dr. George Papanicolaou. Cells scraped from the cervix are examined under the microscope. The term ‘cervical cytology’ comprises of one of the following:

- Conventional Pap - "smear" of cervical cells is placed directly on a slide for examination.
- Liquid-based Cytology (brand names ThinPrep® or SurePath®), the cervical cells are suspended in a solution before being placed on the slide.

- **LLETZ (Large Loop Excision of the Transformation Zone)** - Treatment for abnormal cervical cells using an electrical wire loop to remove abnormal cervical cells under local anaesthesia.
- **Transformation zone** - the area in the cervix where the squamous cells meet the glandular cells.
- **Vaginal vault smear** - A smear taken from the top of the vagina after a hysterectomy. (See chapter 7 for indications of vaginal vault smears)

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