Management Guidelines for Cervical Screening & Preinvasive Disease of the Cervix

FOREWORD:

Foreword by Past Chairperson (Prof Ho Tew Hong)

As I conclude my tenure as the Chairperson of the National Cervical Cancer Screening Programme Operations Committee, I reflect on the tremendous progress we have made in our fight against cervical cancer. Over the past several years, our collective efforts have significantly contributed to the steady decline in the incidence and mortality rates of cervical cancer in Singapore. From 2011 to 2015, cervical cancer was the 10th most common cancer among women, a remarkable improvement from being the 4th most common female cancer in the 1970s.

This progress is a testament to the effectiveness of our screening programs, particularly the widespread adoption of the Pap smear since its introduction in 1964. The positive attitude of Singaporean women towards cervical screening has been instrumental in this success. However, while we celebrate these achievements, we must acknowledge that there is still much work to be done to further reduce cervical cancer rates.
The landscape of cervical cancer screening has evolved significantly since the first publication of our Management Guidelines in 2002. Advances in molecular technology, particularly in Human Papillomavirus (HPV) testing and genotyping, along with the introduction of HPV vaccines, have revolutionized our approach to cervical cancer prevention. Over the past decade, key trials and updated national guidelines have provided us with more cost-effective and efficient strategies for cervical cancer screening.

This revised edition of our guidelines incorporates the latest advancements, emphasizing the importance of integrating HPV testing as a primary screening modality. The combination of liquid-based cytology and HPV DNA testing represents a significant advancement in our screening strategy, ensuring that we remain at the forefront of cervical cancer prevention.

I extend my heartfelt gratitude to the dedicated team who worked tirelessly on these guidelines, with special thanks to A/Prof Jeffrey Low (taking over the mantle), and Dr.

Ida Ismail-Pratt for leading the clinical management guideline workgroup. I also thank the Health Promotion Board for their unwavering support and for providing us with the opportunity to revisit and enhance these critical public health guidelines.
As I step down, I am confident that A/Prof Jeffrey Low will continue to lead the National Cervical Cancer Screening Programme Operations Committee with the same dedication and passion, driving further progress in our mission to eradicate cervical cancer. A death from cervical cancer is a death from neglect, and together, we will strive to ensure that no woman in Singapore has to suffer from this preventable disease.

Prof. Ho Tew Hong
Clinical Professor
Past Chairperson
National Cervical Cancer Screening Programme Operations Committee
March 2024

Foreword by Chairperson (A/Prof Jeffrey Low)

It is with great honor and a sense of responsibility that I assume the role of Chairperson of the National Cervical Cancer Screening Programme Operations Committee from April 2024. Building on the solid foundation laid by my predecessor, we are poised to make further strides in our fight against cervical cancer, a disease that has significantly impacted women's health in Singapore.

Over the past few decades, we have witnessed a remarkable decline in the incidence and mortality rates of cervical cancer. Our efforts in public health education, in making cervical screening widely available in Singapore with substantial subsidies for all citizens and PRs, and advances in the evaluation and treatment of preinvasive disease have reduced the incidence of cervical cancer from being the 4th most common female cancer in the 1970s to the 10th most common from 2011 to 2021.

However, our mission is far from complete. With the advent of new technologies and methodologies, it is imperative that we continue to innovate and adapt our strategies to stay ahead in the fight against cervical cancer. The integration of Human Papillomavirus (HPV) testing and genotyping in population screening, along with the implementation HPV vaccination in our school-based health program, has revolutionized our approach to screening and prevention. These advancements necessitate a continuous update of our clinical management guidelines to reflect the latest evidence and best practices.

The revised 2024 edition of our clinical management guidelines aims to provide comprehensive and up-to-date recommendations for the management of preinvasive cervical disease. By incorporating HPV self-testing as an additional alternative screening modality alongside physician-led HPV testing, we are taking a significant step forward in enhancing the population coverage of cervical screening in Singapore.

I would like to express my deepest appreciation to the outgoing Chairperson, Professor Ho, for his invaluable contributions and leadership. I also extend my gratitude to the dedicated team of experts, including Dr. Ida Ismail-Pratt, whose efforts have been instrumental in the development of these updated guidelines. Additionally, I thank the

Health Promotion Board for their continuous support and commitment to cervical cancer prevention.

As we move forward, I am committed to working closely with all stakeholders to ensure that our screening programs remain robust and effective. Together, we will strive to achieve our ultimate goal of eliminating cervical cancer as a public health issue in Singapore. Let us continue to work tirelessly towards a future where no woman has to suffer from this preventable disease.

A/Prof. Jeffrey Low Jen Hui
Chairperson
National Cervical Cancer Screening Programme Operations Committee
April 2024

Foreword by Ida Ismail-Pratt MBChB(Glasgow), FRCOG, BSCCP

Clinical Management Guidelines Workgroup Lead

Cervical cancer is preventable.

In order to save our women from this terrible preventable disease, effective screening, diagnosis and treatment needs to work together as all three aspects of screening are crucial in detecting and eradicating early preinvasive cervical disease and cervical cancer.

In 2019, our national cervical cancer screening program entered the new era of screening with Human Papillomavirus (HPV) testing for women 30 years and above. The superior sensitivity of the HPV test compared to cytology only screening for this age group allows for earlier detection and treatment of preinvasive cervical disease. HPV test also allows practitioners to predict the risk of future cervical cancer by using the presence or absence of the different types of High-risk HPV infection as a surrogate for cancer risk prediction, giving practitioners the capability to manage and counsel their patients better.

As the evidence on HPV and innovations in cervical cancer screening continues to evolve, so does our guideline. To remain up to date with current practice, a clinical guideline review group was set up to look at current evidence in cervical cancer screening to allow better guidance for Singapore cervical cancer screening practitioners.

The clinical guideline review group comprises of a multidisciplinary team of clinicians, academicians and cytopathology/molecular diagnostics partners from restructured hospitals and private sectors, polyclinic groups (NHGP, NUP and SHP), and public health/academic sector. The group were also privileged to be able to work with international experts in systematic review and meta-analysis.

In addition, the tremendous amount of work that was required to develop an evidence-based up-to-date guideline for all Singaporean practitioners, would not be able to be

completed without the passion and commitment from our junior doctors and academicians who will one day themselves be leaders in this field.

I would like to thank all those that have volunteered their time and commitment to the development of this guideline. A special thank you and appreciation to Professor Natasha Howard, from Saw Swee Hock School of Public Health, Singapore for her leadership and guidance in the systematic review and meta-analysis done by the review group.

I would also like to thank Professor Ho Tew Hong, our chairman for the the National Cervical Cancer Screening Programme Operations Committee for his continued leadership and vision in pushing the evolution of the guideline to continue to serve and guide our healthcare providers with the most up-to-date evidence-based information to save our women from this preventable disease.

Cervical cancer is not a woman's problem. It is everybody's problem. Let's not leave any woman behind.

Dr. Ida Ismail-Pratt
MBChB(Glasgow), FRCOG, BSCCP
Clinical Management Guidelines Workgroup Lead
National Cervical Cancer Screening Programme Operations Committee

[Table of Contents]

Cytology group

- **Clinical group lead:**
- **Systemic review/Metanalysis clinical lead:**
- **Systemic review/metanalysis academic lead:**
- **Review group committee members:**

HPV group

- **Clinical group lead:**
- **Systemic review/Metanalysis clinical lead:**
- **Systemic review/metanalysis academic lead:**
- **Review group committee members:**

Immunocompromised group

- **Clinical group lead:**
- **Systemic review/Metanalysis clinical lead:**
- **Systemic review/metanalysis academic lead:**
- **Review group committee members:**

Preinvasive management group

- **Clinical group lead:**
- **Systemic review/Metanalysis clinical lead:**
- **Systemic review/metanalysis academic lead:**
- **Review group committee members:**

Health Promotion Board (HPB)

Glossary and Terminology

Pre-requisite for HPV assay for cervical cancer screening in Singapore.

References

Cytology group

HPV test group

Immunocompromised group

Preinvasive cervical disease group

Supplementary 1: cytology group

Supplementary 2: HPV group

Supplementary 3: Immunocompromised group

Supplementary 4: Preinvasive group

EXECUTIVE SUMMARY: 2024 UPDATES ON GUIDELINE

Cytology group recommendations

Comparing the safety of HPV DNA testing versus cytology-only screening for women aged 18-29 years: a systematic review and meta-analysis

Main review question:
Does HPV primary screening more accurately detect CIN+ compared with cytology-only screening for women aged 18-29years?

Summary of recommendation

Recommendation 1:

There is insufficient evidence to recommend HPV DNA testing over liquid-based cytology for the purpose of primary cervical cancer screening in women less than 30 years old.

Recommendation 2:

Establishing a national database for cervical cancer screening and management of preinvasive cervical disease will allow for a more accurate future longitudinal analysis of effectiveness and safety of HPV DNA and cytology screening for women below 30 years of age.

Recommendation 3:

Further research focusing on the effectiveness, safety, cost-effectiveness, and the impact of current cervical cancer screening and preinvasive cervical disease management, are needed in Singapore to identify the best primary screening strategy for women under age 30.

For full report, refer to Supplementary 1: Cytology Group.

HPV test group recommendations

Comparing the safety, effectiveness, and acceptability between self-sampling and physician sampling for HPV testing of women aged 25-69: A systematic review and meta-analysis.

Main review question:

1. Are HPV DNA test using vaginal self-sampling tools effective in detecting high-risk HPV strains (HR HPV) compared to physician collected samples for women aged 25 – 69 years old for primary cervical cancer screening?

2. Is HPV DNA test using vaginal self-sampling tools acceptable among eligible women and could this lead to higher uptake of HPV screening and thus better detection?

3. Is there any adverse events associated with vaginal self-sampling?

4. Which HPV self-sampling tools are commonly used?

Summary of recommendation

Recommendation 1:

Vaginal self-sampling for HPV DNA test can be an alternative to physician sampling for primary cervical cancer screening in healthy women aged 30 – 69 years old with no history of previous cervical pathologies.

HPV DNA test using vaginal self-sampling and physician sampling are comparable in terms of efficacy in detecting HPV DNA, with higher degrees of agreement in HR HPV strains including HPV 16/18. We recommend vaginal self-sampling modality only. Other modalities of screening including urine and anal testing. are not recommended due to insufficient evidence.

HPV DNA test using vaginal self-sampling must be performed with a validated HPV deoxyribonucleic acid (DNA) assay using a validated vaginal self-sampling method. In view of insufficient evidence, other assays including HPV messenger ribonucleic acid (mRNA) are not recommended.

Reflex cytology cannot be processed with vaginal self-sample as this requires cervical sampling under direct visualisation during a formal pelvic examination. Patients with HR HPV non-type 16/18 should

be referred to primary care for pap smear testing while patients with HR HPV type 16/18 should be referred to colposcopy.

Recommendation 2:

Based on the current available evidence, or lack thereof, no obvious trends seem to suggest superiority of any particular type of vaginal self-sampling tool

While there are a variety of vaginal self-sampling tools available on the market, comparative data on different vaginal self-sampling tools is limited, and there is little evidence over which vaginal self-sampling tools are superior.

Recommendation 3:

Given high patient acceptability levels of HPV DNA testing using vaginal self-sampling, eligible women could have the option to choose this approach.

Recommendation 4:

As HPV self-sampling is safe to use with no associated adverse events, it should be considered for eligible women.

For full report, refer to Supplementary 2: HPV Group.

Immunocompromised group recommendation

Review on risk of progression to high-grade lesions and cervical cancer patients who are immunocompromised and/or taking Immunosuppressants.

Main review question:
Are patients with autoimmune conditions on immunosuppressants at risk of progression to high-grade lesions / cervical cancer compared to the healthy population?

Summary of recommendation

Recommendation 1:

Definition of Immunosuppression

Suppression of the body's immune system and its ability to fight infections and other diseases. Immunosuppression may be deliberately induced with drugs, as in preparation for bone marrow or other organ transplantation, to prevent rejection of the donor tissue[27].

Recommendation 2:

High risk immunosuppressive clinical conditions requiring more frequent screening includes:

- HIV positive women and women with primary immunodeficiency syndromes
- Women who have undergone solid organ or hematopoietic stem cell transplant
- Women who have clinical conditions requiring them to take at least one immunosuppressive medication long-term other than steroids such as
    - Anti-metabolites (e.g. mycophenolate-based, azathioprine, methotrexate, cyclophosphamide)
    - Calcineurin and mTOR inhibitors (e.g. tacrolimus, cyclosporine, sirolimus, everolimus)
    - Biologics (e.g TNF-α antagonists)
- However, steroids alone and hydroxychloroquine are not associated with a higher risk of cervical cancer

Recommendation 3:

Screening Recommendations:

- While initial, primary cervical cancer screening can be performed at all Screening Centres, screening and subsequent follow-up for abnormal cervical screening results should ideally be centralised at a hospital-based Assessment Centre.
- Screening age should be from age 25 and to continue lifelong.
- Screening modality should be as follows:
    - 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.
      If positive for any high-risk HPV strains, refer directly for colposcopy instead of doing cytology triage
- Vulvar or anal cancer screening should be conducted at each review. This should minimally include history taking, and ideally inspection and physical examination.

  History should cover 1) abnormal bleeding or discharge per vaginum or per rectum, 2) persistent anogenital itching, or 3) pain upon defaecation or intercourse. If any of these are positive, a digital anorectal examination is needed and a referral for specialist evaluation may be required.

Recommendation 4:

Specific Situations:

- Patients with immunosuppression condition who are post-cervical excision & post-hysterectomy may require individualized cervical screening follow-up at a hospital-based Assessment Centre.

Recommendation 5

- All immunocompromised women between age 9-45 should receive a 3-dose course of HPV vaccination.

For full report, refer to Supplementary 3: Immunocompromised Group.

Preinvasive cervical disease group recommendations.

To examine the safety and effectiveness of conservative management of women with cervical intraepithelial neoplasia grade 1 (CIN1)

Main review question:
What is the evidence on safety and effectiveness of conservative management of CIN 1 beyond 2 years?

Summary of recommendation

Recommendation 1:

Patients with Low Grade Cytology *and HPV/ CIN 1 on biopsy with adequate colposcopy can be observed with a repeat Pap and HPV DNA test in 12 months' time. If a repeat HPV test is negative in 12 months' time, the patient can be discharged to routine screening.

Recommendation 2:

Patients with Low Grade Cytology * and HPV/CIN1 on biopsy with adequate colposcopy, with persistent HPV infection (HPV 16/18/others) may have a higher risk of progression of the disease to CIN2 or CIN3, thus they should be listed for discussion at a multi-disciplinary team after 2 years of persistent HPV infection for further management.

Recommendation 3:

Patients with Low Grade Cytology and HPV/CIN 1 on biopsy with adequate colposcopy and has persistent low-grade cytology with negative HPV tests can be safely observed for up to 5 years.

Recommendation 4

Patients with High Grade Cytology** and HPV/CIN 1 on biopsy with adequate colposcopy, a cytopathological review is recommended. An excisional biopsy should be considered for diagnostic purposes.

For full report, refer to Supplementary 4: Preinvasive Group.

Chapter 1: Screening Population

Cervical cancer screening criteria and intervals

1.1 Eligibility for 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

The frequency of cervical cancer screening 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.

1.3 Women who have never had sexual intercourse.

Women who have never had sexual intercourse do not need to go for cervical screening. However, if these women have any symptoms e.g. abnormal vaginal bleed, they should consult a doctor.

1.4 Immunocompromised women including those taking immunosuppressants.

Refer to Chapter 3 – Management of immunocompromised individuals.

1.5 Women who have had HPV vaccination.

Screening should proceed as per non-vaccinated women.

1.6 Discharge from Screening

A woman may be discharged from screening at 69 years of age if she has:

- 2 consecutive negative HPV tests in the last 10 years, with the most recent test occurring within last 5 years.

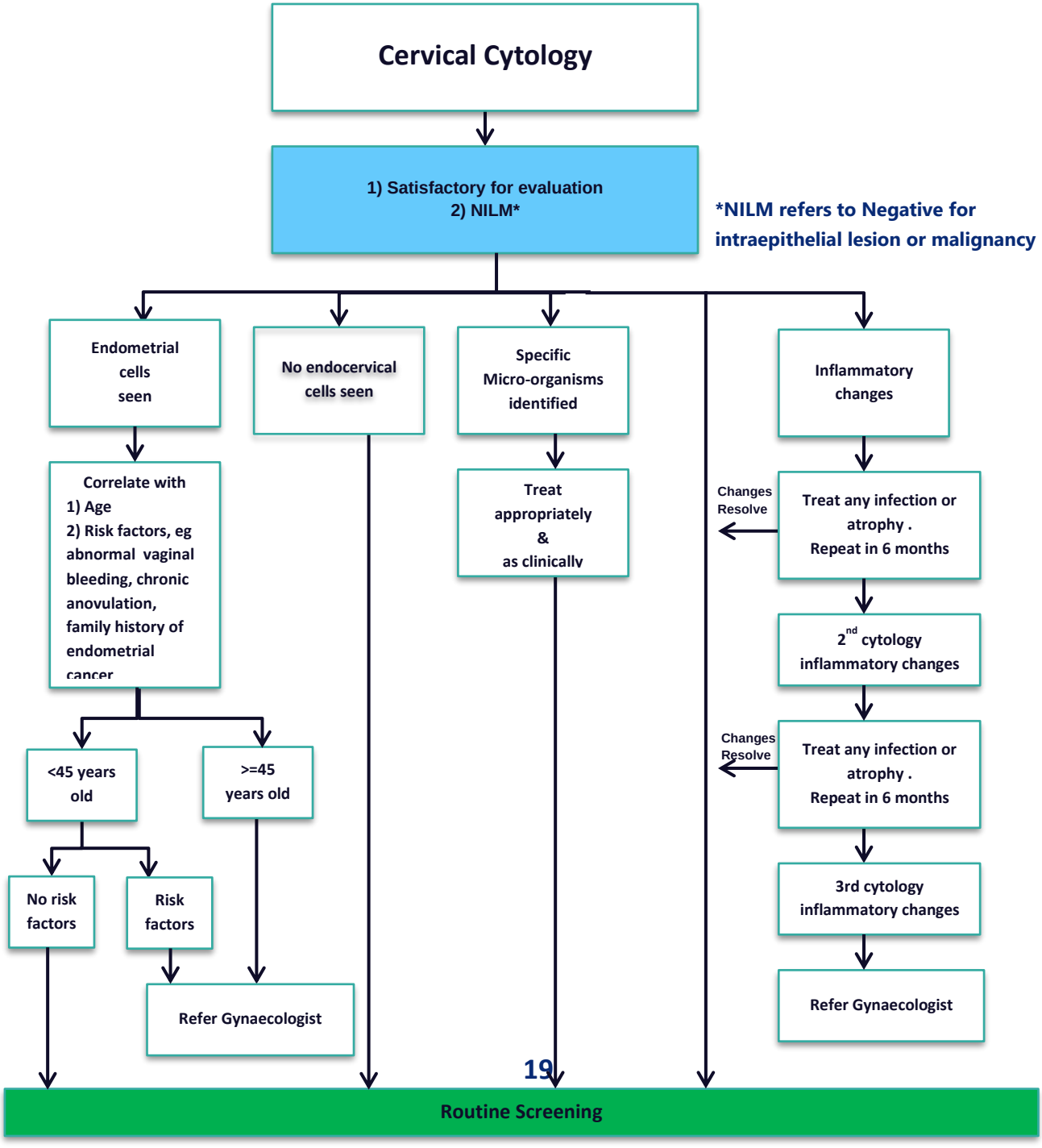
For women who had history of treatment for CIN2, CIN3 or AIS, routine screening should continue for at least 20 years, even if it extends beyond 69 years of age.

For women who are immunocompromised or talking immunosuppressants, screening continues for life.

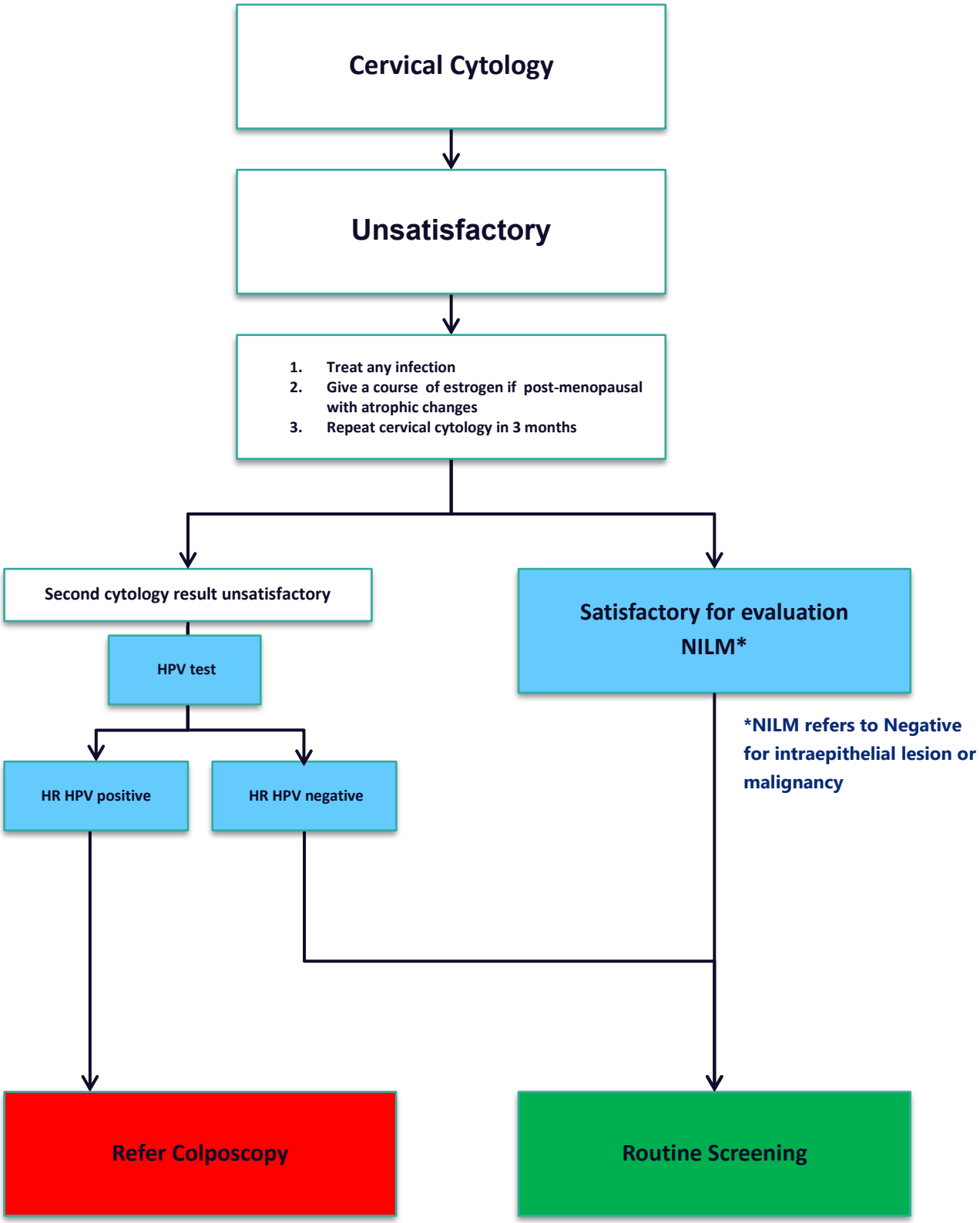
Chapter 2: Recommended management for (primary) cervical cancer screening in healthy population

2.1: Cervical cytology (Papanicolaou test) only method (25-29 year olds)

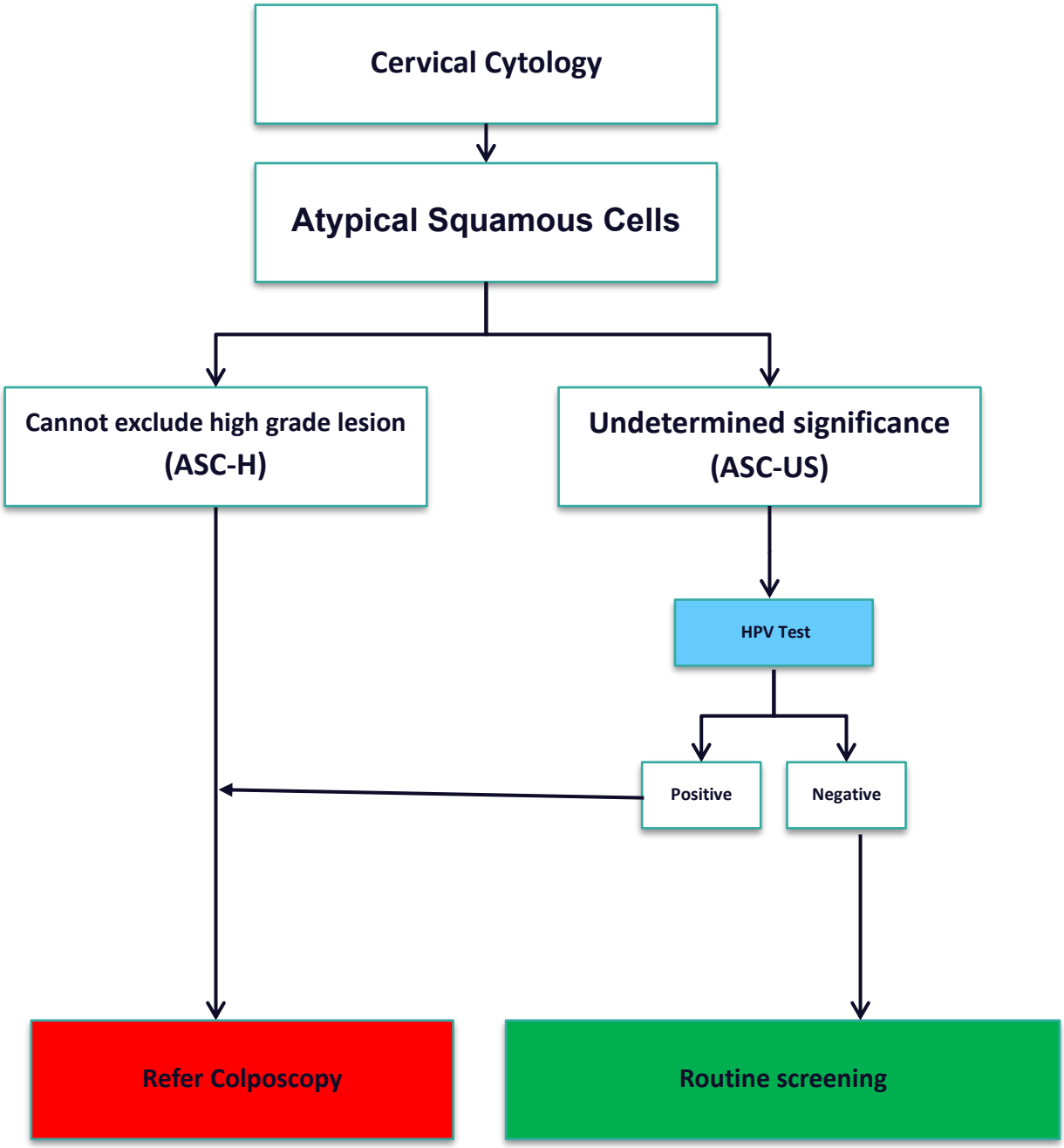
2.1.1: NILM* + other findings



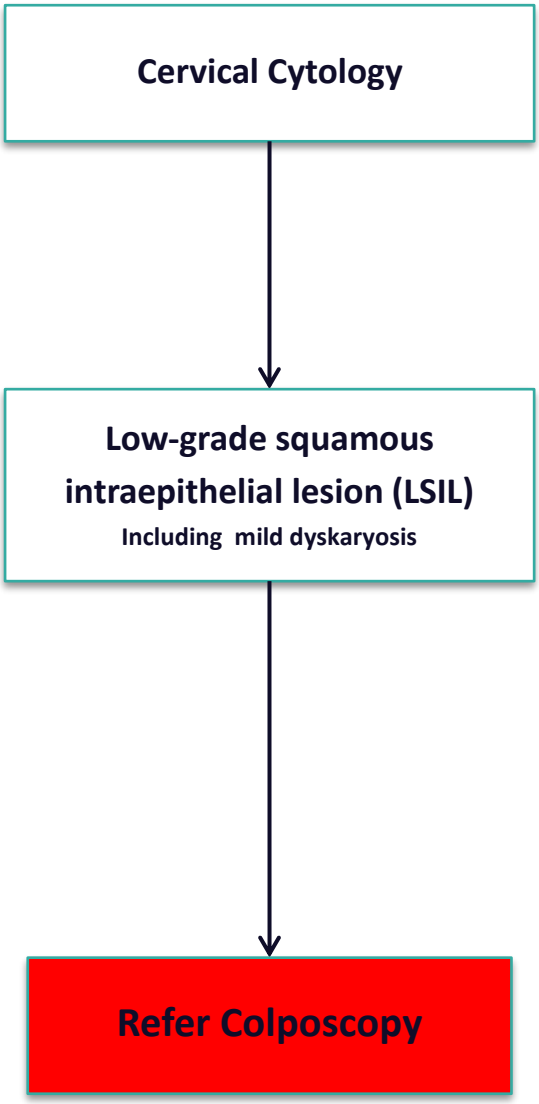
2.1.2: Management of Unsatisfactory Cytology Results



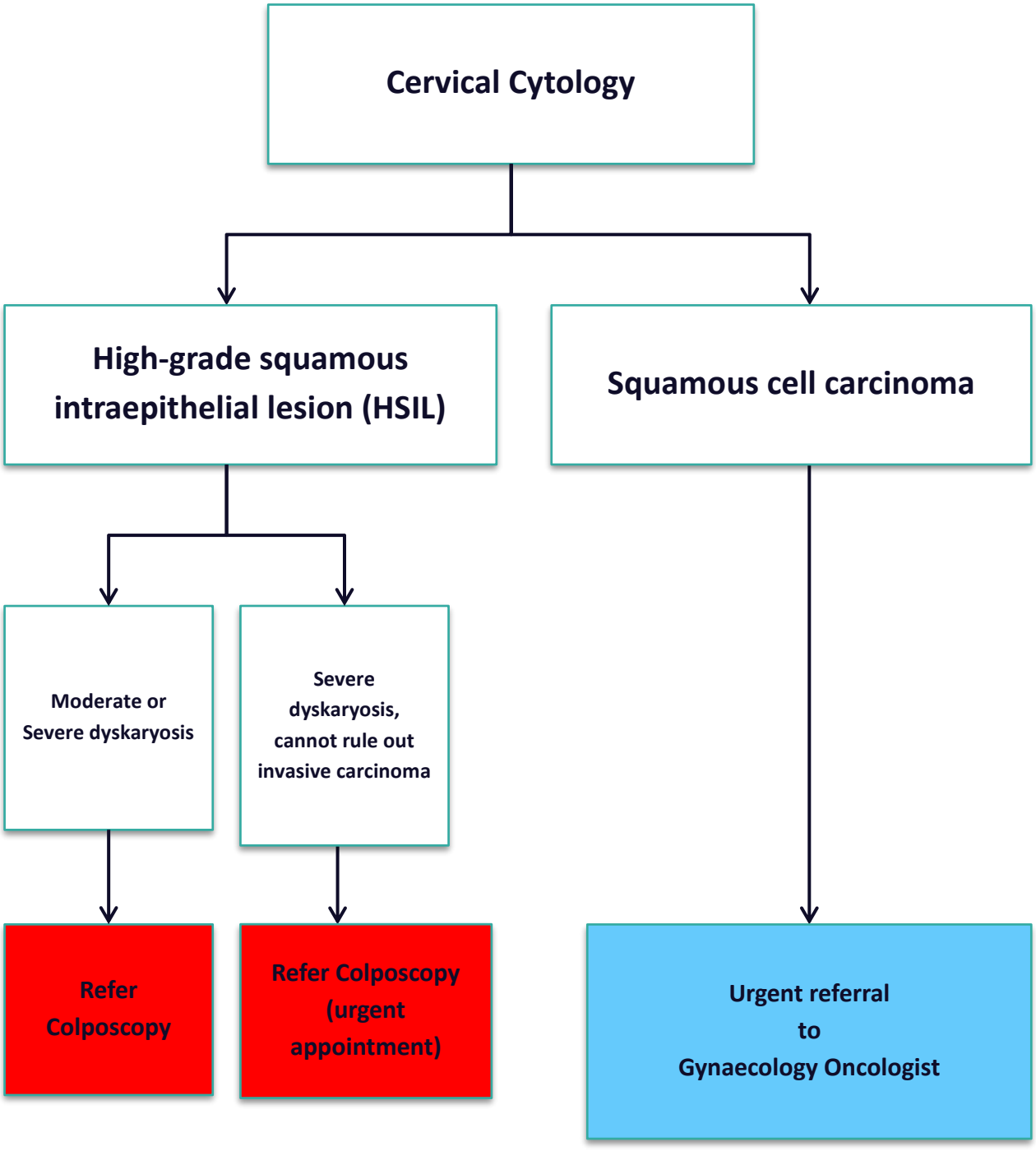
2.1.3: Management of Abnormal Cytology Results: Atypical squamous cells



2.1.4: Management of low-grade squamous intraepithelial lesions (LSIL)

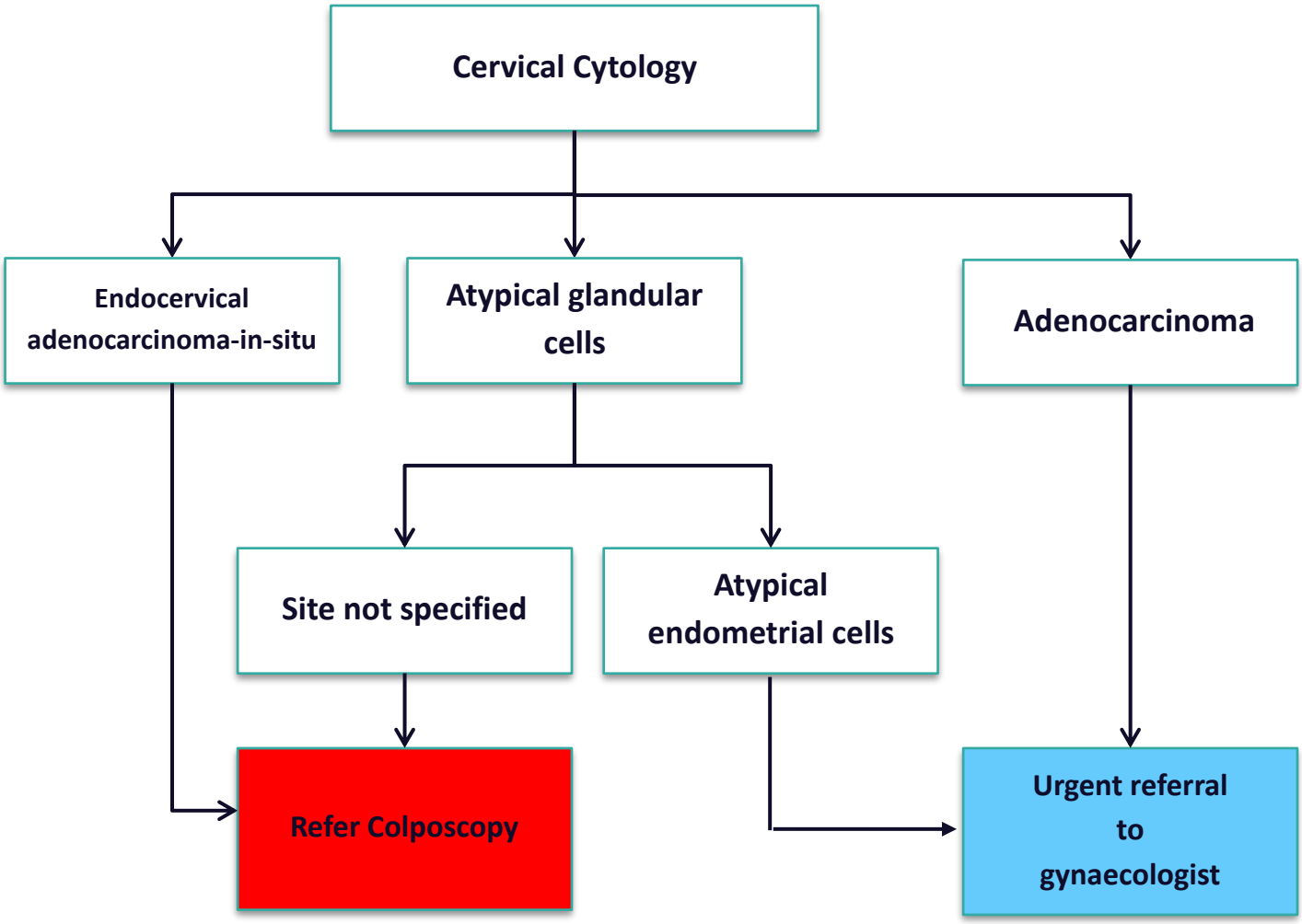


2.1.5: Management of high-grade squamous intraepithelial lesions (HSIL)



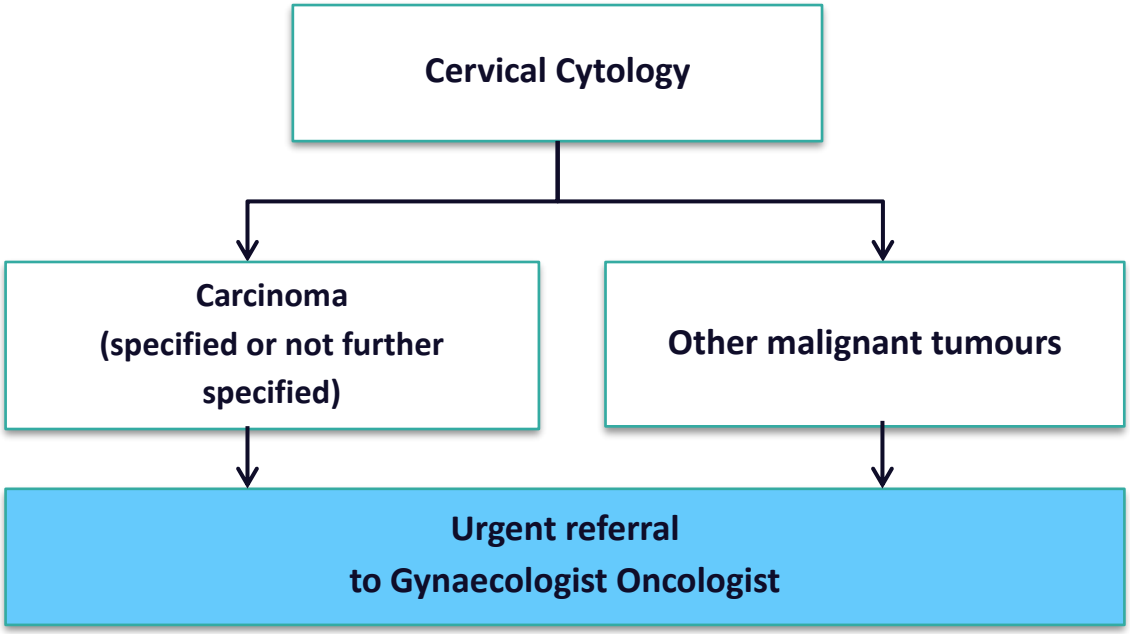
2.1.6: Glandular abnormalities on cytology

Management of atypical glandular cells, adenocarcinoma, and endocervical adenocarcinoma-in-situ



2.1.7: Malignant cells and other indication for referral *

** other indications for referral, such as abnormal vaginal bleeding and clinically suspicious-looking cervix, regardless of the cervical cytology result.*

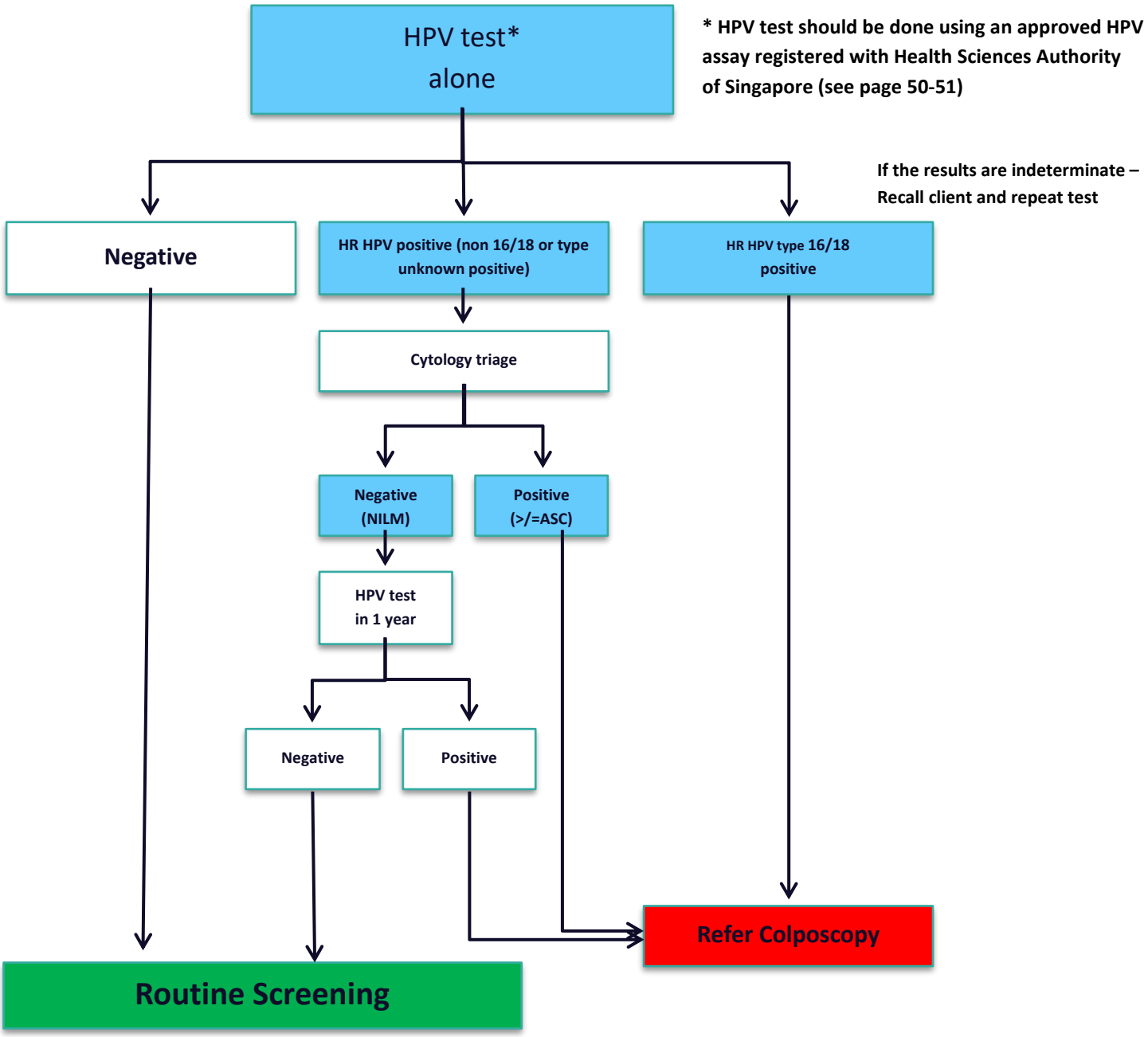


Other indications for referral:

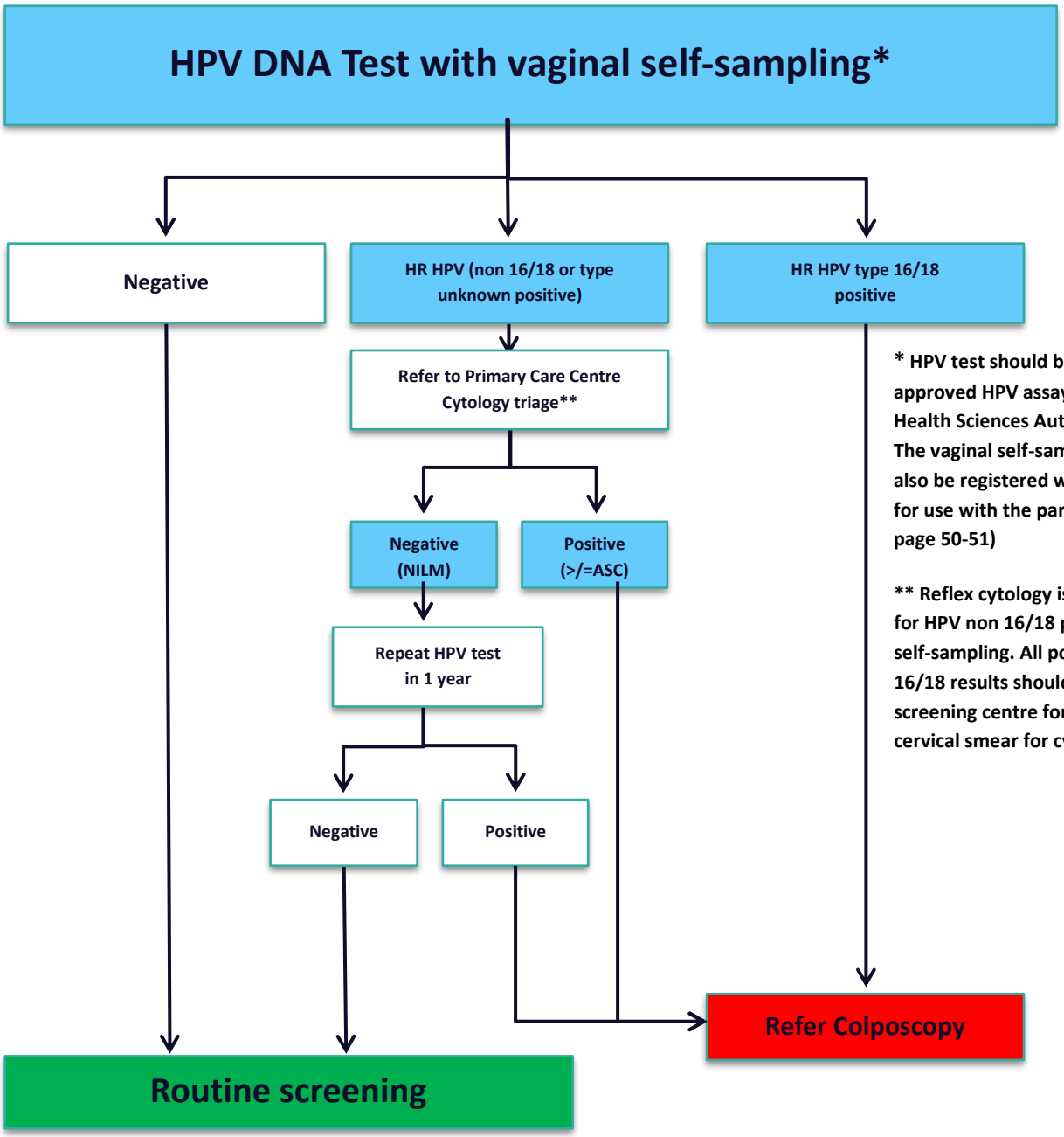
- Abnormal vaginal bleeding, e.g. post-coital, post-menopausal or inter-menstrual, should always be investigated and the woman referred for a gynaecologist opinion.
- Clinically suspicious looking cervix irrespective of the cervical cytology result must be referred for colposcopy.

2.2: HPV primary screening (30-69 years old)

2.2.1: Human Papillomavirus (HPV) testing by a physician or certified nurse



2.2.2: Human Papillomavirus (HPV) DNA test using vaginal self-sampling method[1]



* HPV test should be done using an approved HPV assay registered with Health Sciences Authority of Singapore. The vaginal self-sampling method must also be registered with HSA and validated for use with the particular HPV test (see page 50-51)

** Reflex cytology is not recommended for HPV non 16/18 positive using vaginal self-sampling. All positive HPV non 16/18 results should be referred back to screening centre for physician-led cervical smear for cytology triage.

[1] HPV self-sampling is currently not offered under the national cervical cancer screening programme.

2.3: Primary screening for other circumstances

2.3.1: Women who has had a Hysterectomy

2.3.1.1 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

2.3.1.2 Subtotal hysterectomy

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

2.3.1.3 Hysterectomy where histology not known

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

2.3.1.4 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
    - Yearly vault smears for five years
    - Two yearly subsequently

2.3.1.5 Women previously treated for VAIN, or invasive gynaecological malignancy.

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

2.3.2: 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.

Chapter 3: Recommended Management of Immuno-compromised Individuals

3.1 Definition of immunosuppression

Suppression of the body's immune system and its ability to fight infections and other diseases. Immunosuppression may be deliberately induced with drugs, as in preparation for bone marrow or other organ transplantation, to prevent rejection of the donor tissue.

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

- HIV positive women and women with primary immunodeficiency syndromes
- Women who have undergone solid organ or haematopoietic stem cell transplant
- Women who have clinical conditions requiring them to take at least one immunosuppressive medication long-term **other than steroids** such as
    - Anti-metabolites (e.g. mycophenolate-based, azathioprine, methotrexate, cyclophosphamide)
    - Calcineurin and mTOR inhibitors (e.g. tacrolimus, cyclosporine, sirolimus, everolimus)
    - Biologics (e.g TNF-α antagonists)
- However, steroids alone and hydroxychroloquine are not associated with a higher risk of cervical cancer

3.2.1 Screening recommendation:

3.2.1.1 Screening site:

- While initial, opportunistic screening can be performed at all Screening Centres, screening and subsequent follow-up should ideally be centralised at a hospital-based Assessment Centre

3.2.1.2 Screening age

- Screening age should be from age 25 and to continue lifelong

3.2.1.3 Screening modality and frequency:

Age Group	Screening Modality	Screening Frequency
25 to 29-years-old	Cervical cytology	Annually
30-years-old & above	HPV primary screening	3 yearly

If positive for any high-risk HPV strains, refer directly for colposcopy instead of doing cytology triage

3.2.1.4 Screening of other anogenital area

- Vulvar or anal cancer screening should be conducted at each review.
- This should minimally include clinical history taking, and ideally inspection and physical examination.
- Clinical history should cover
  - abnormal bleeding or discharge per vaginum or per rectum,
  - persistent anogenital itching, or
  - pain upon defaecation or intercourse.

  If any of these are positive, a digital anorectal examination is needed and a referral for specialist evaluation may be required.

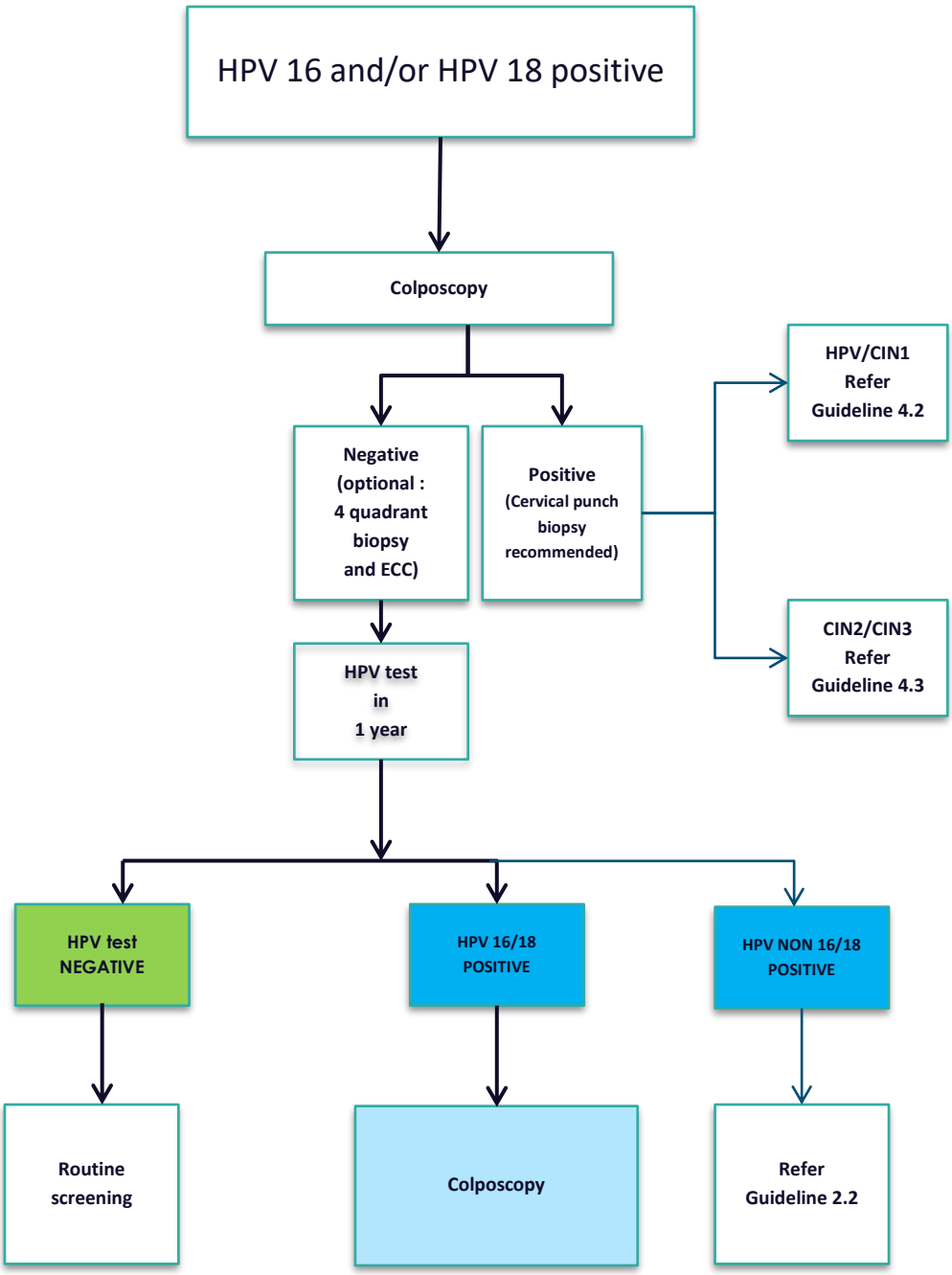
3.2.1.5 Special Situations:

- Patients with immunosuppression condition who are post-cervical excision & post-hysterectomy may require individualized cervical screening follow-up at a hospital-based Assessment Centre
- Immunocompromised women between age 9-45 should receive a 3-dose course of HPV vaccination

Chapter 4: Recommended Management of Preinvasive Disease of the Cervix

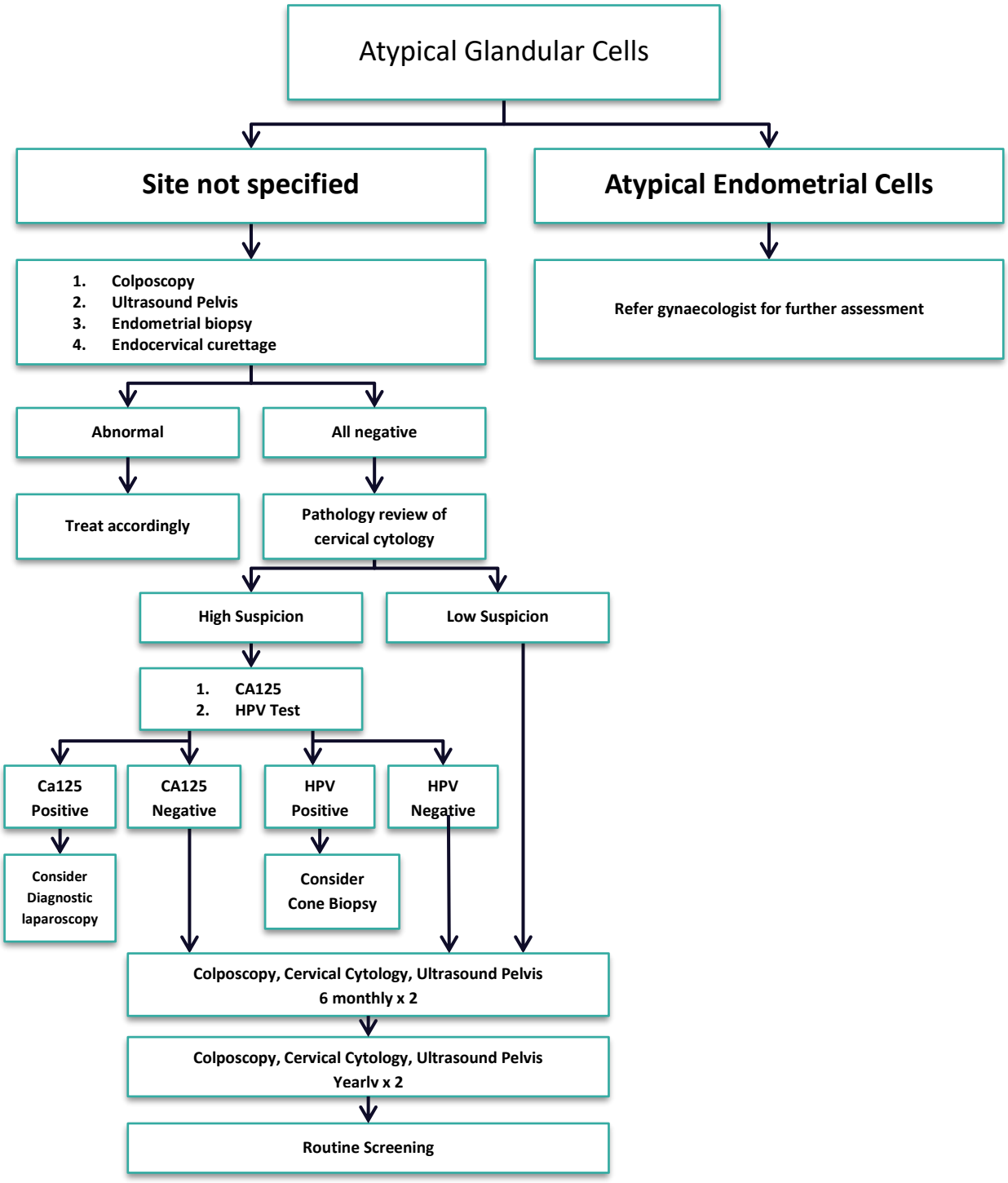
4.1: Management of abnormal cervical screen results

4.1.1: HPV Type 16 and/or Type 18 positive

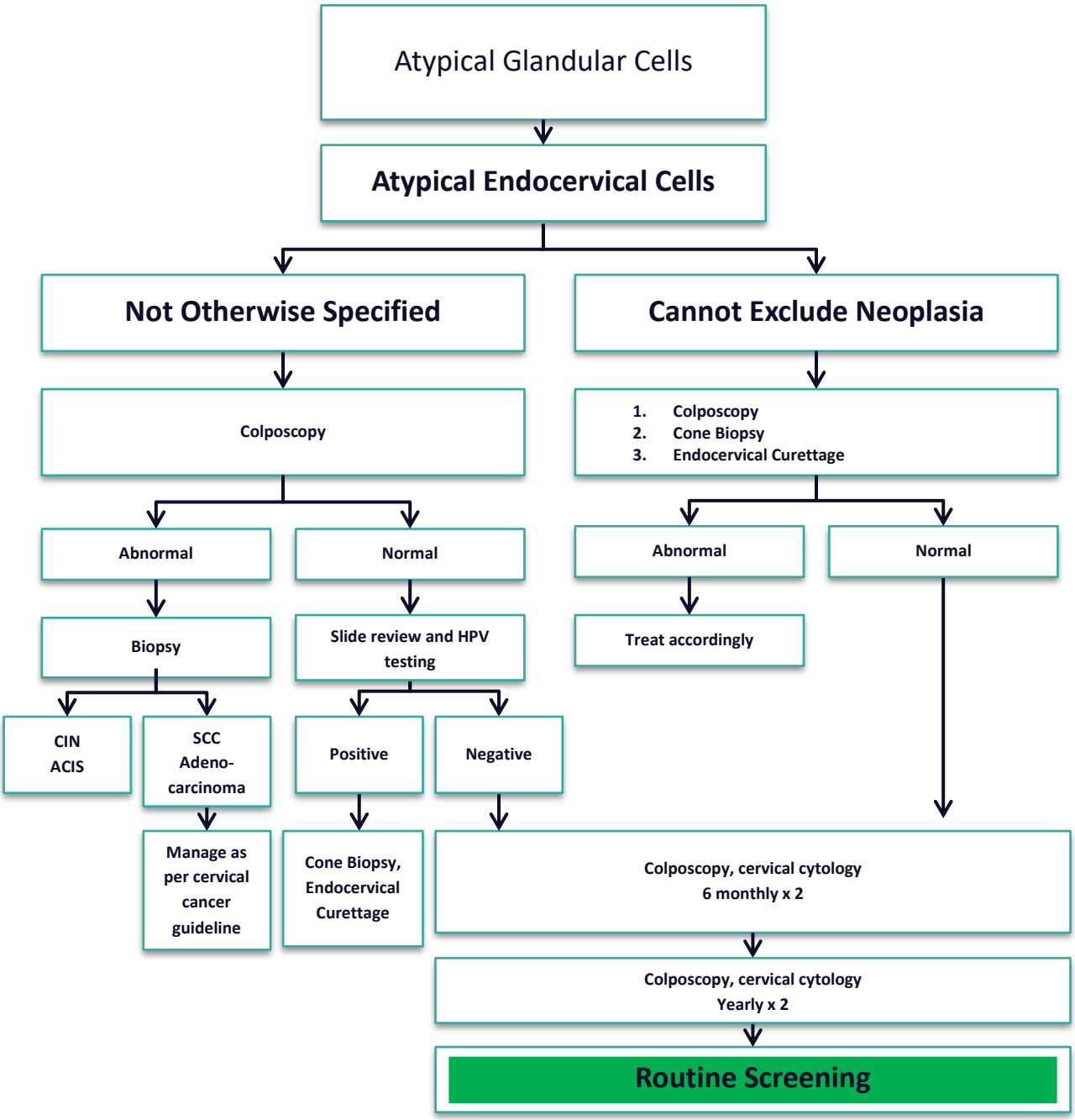


4.1.2: Atypical Glandular Cells

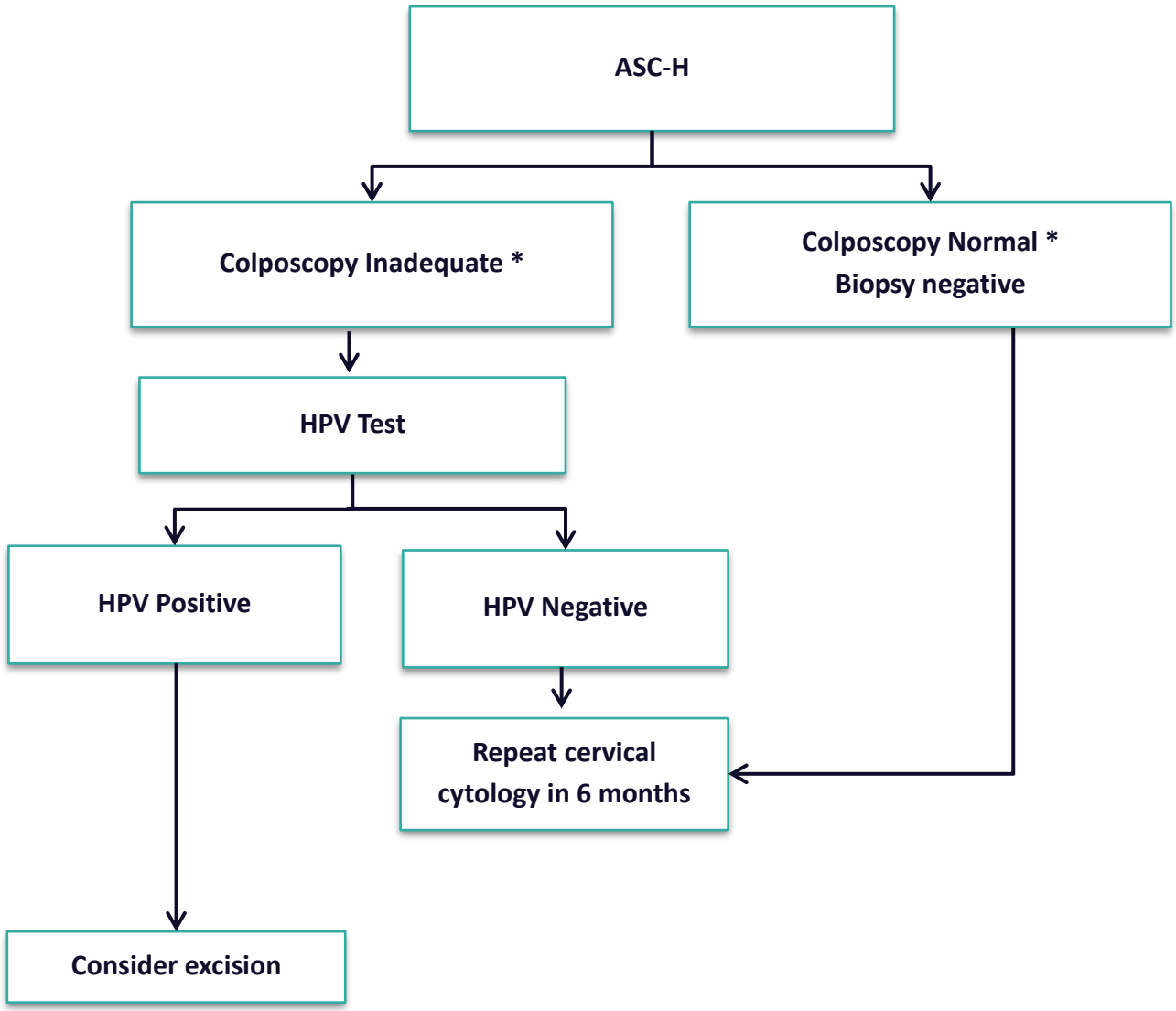
Atypical Glandular Cells: Site not specified & Atypical Endometrial Cells



4.1.2: Atypical Glandular Cells: Atypical Endocervical Cells

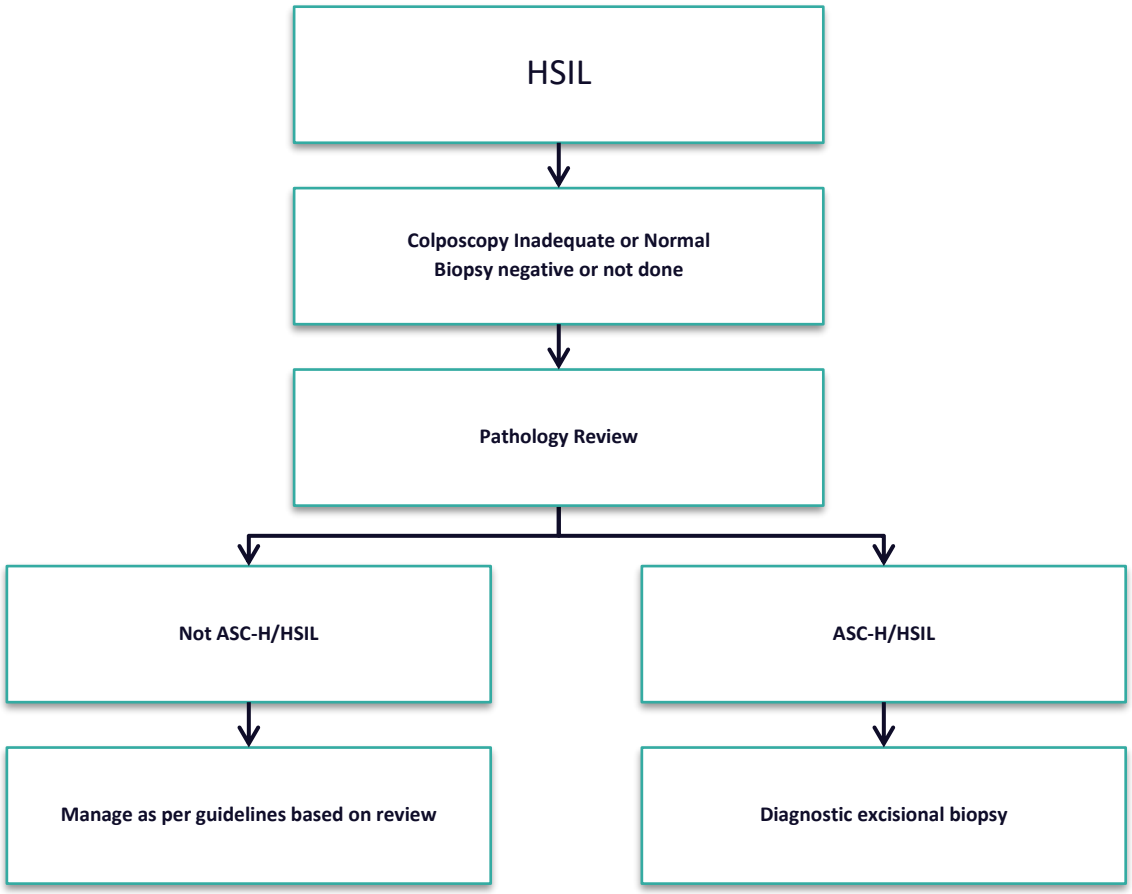


4.1.3: Abnormal Cytology (ASC-H/HSIL) & Inadequate or Normal Colposcopy



* Consider Pathology Review when necessary

HSIL Cytology & Unsatisfactory or Normal Colposcopy



4.2: Management of histologically proven preinvasive cervical diseases

4.2.1: CIN1 with low grade cytology

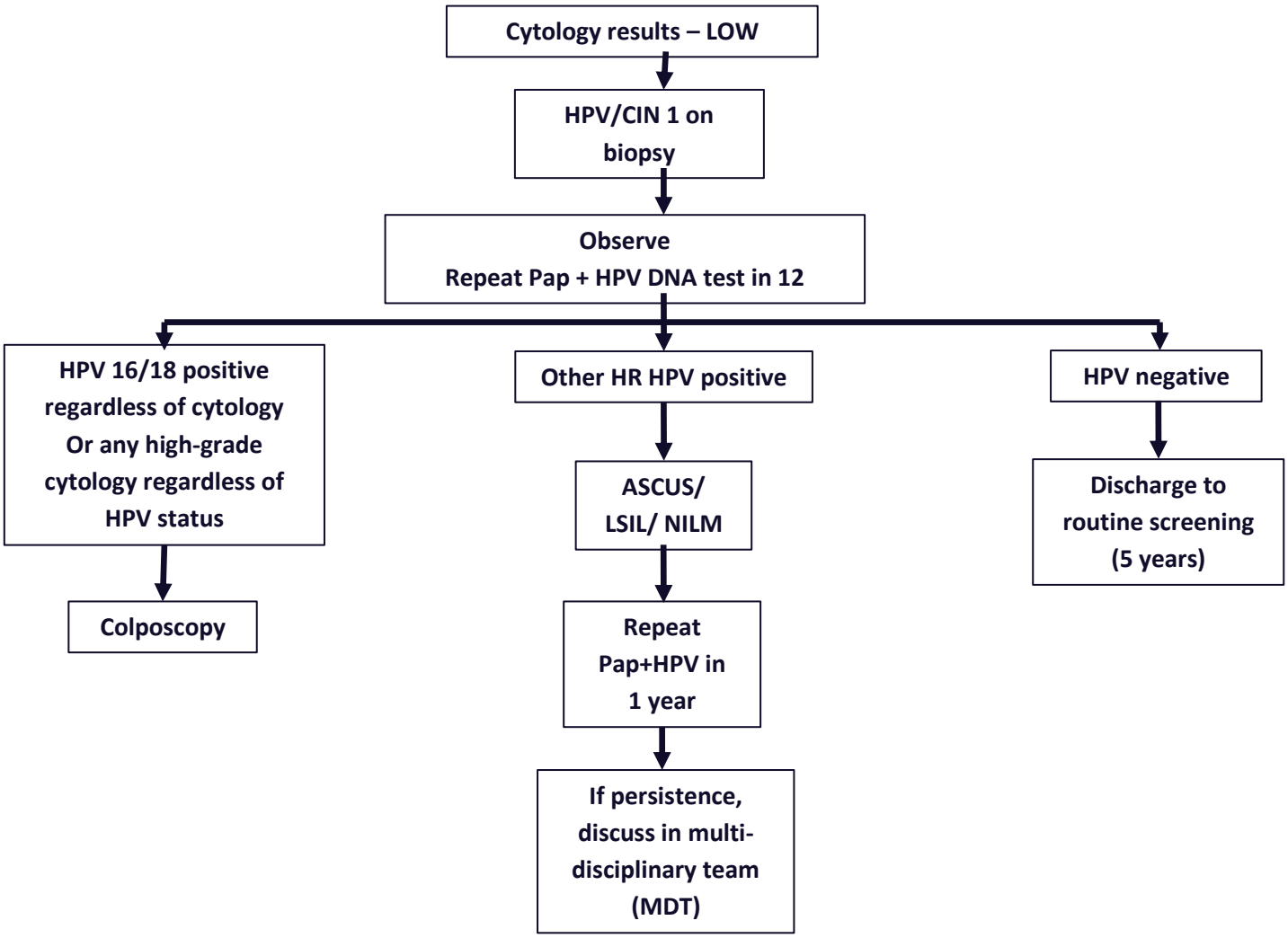


Figure 1: Workflow for patients with Low Grade Cytology* and HPV/CIN 1 on biopsy
***Definition of Low Grade: HPV others positive + ASCUS, LSIL, HPV others positive x2 (1 year apart), normal cytology**

4.2.2: CIN1 with high grade cytology

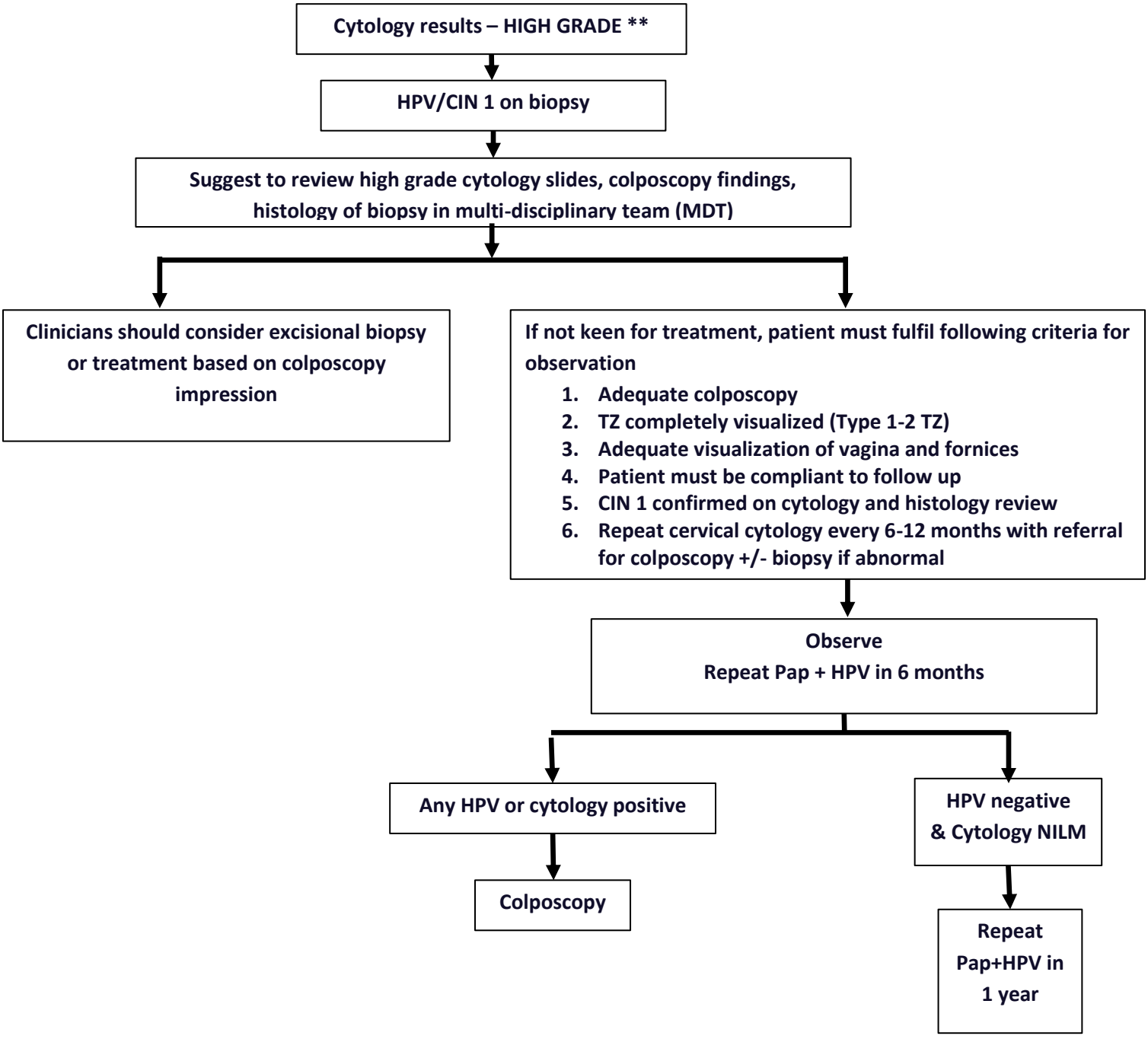
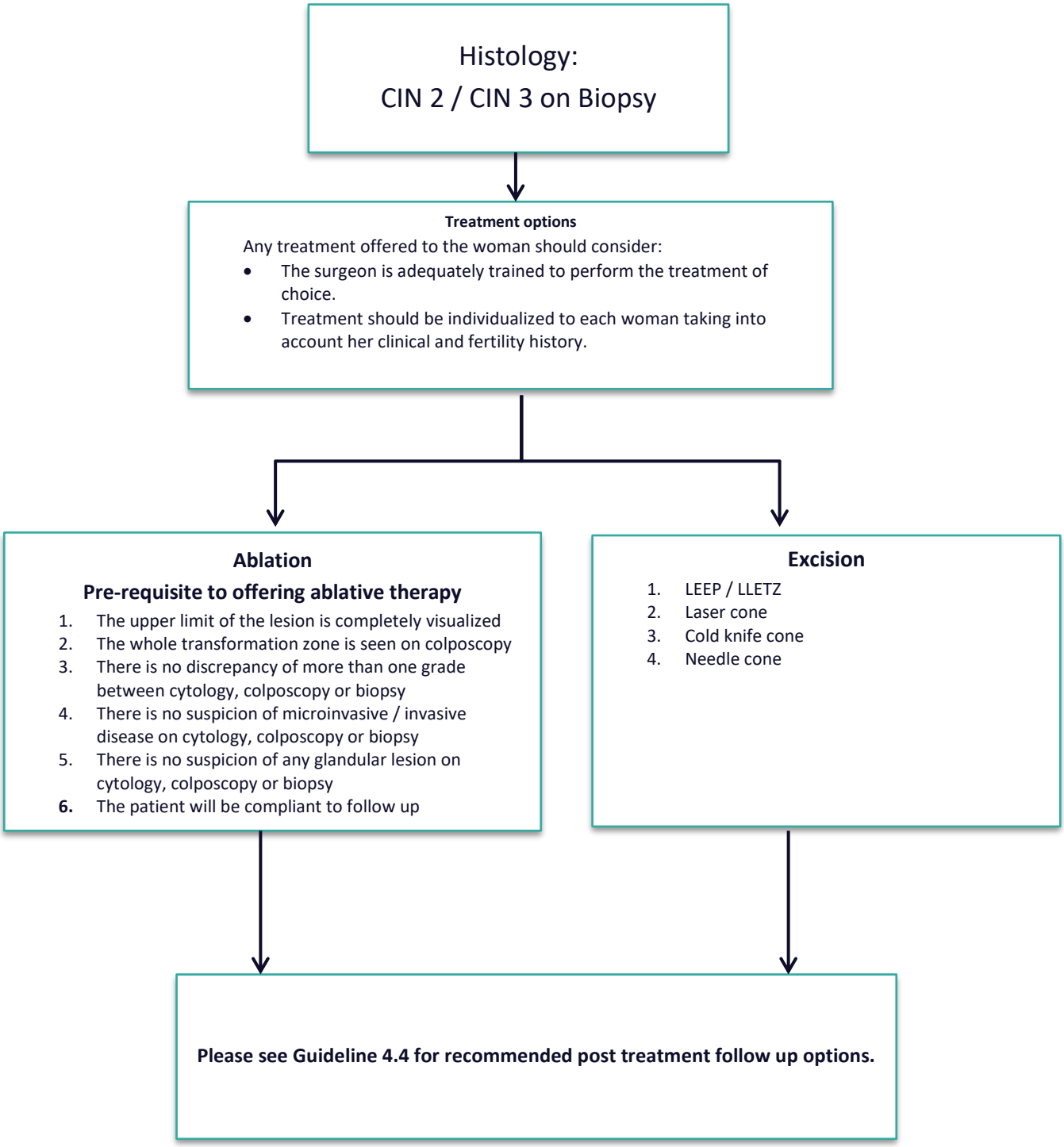


Figure 2: Proposed workflow for patients with High Grade Cytology and HPV/CIN 1 on biopsy**

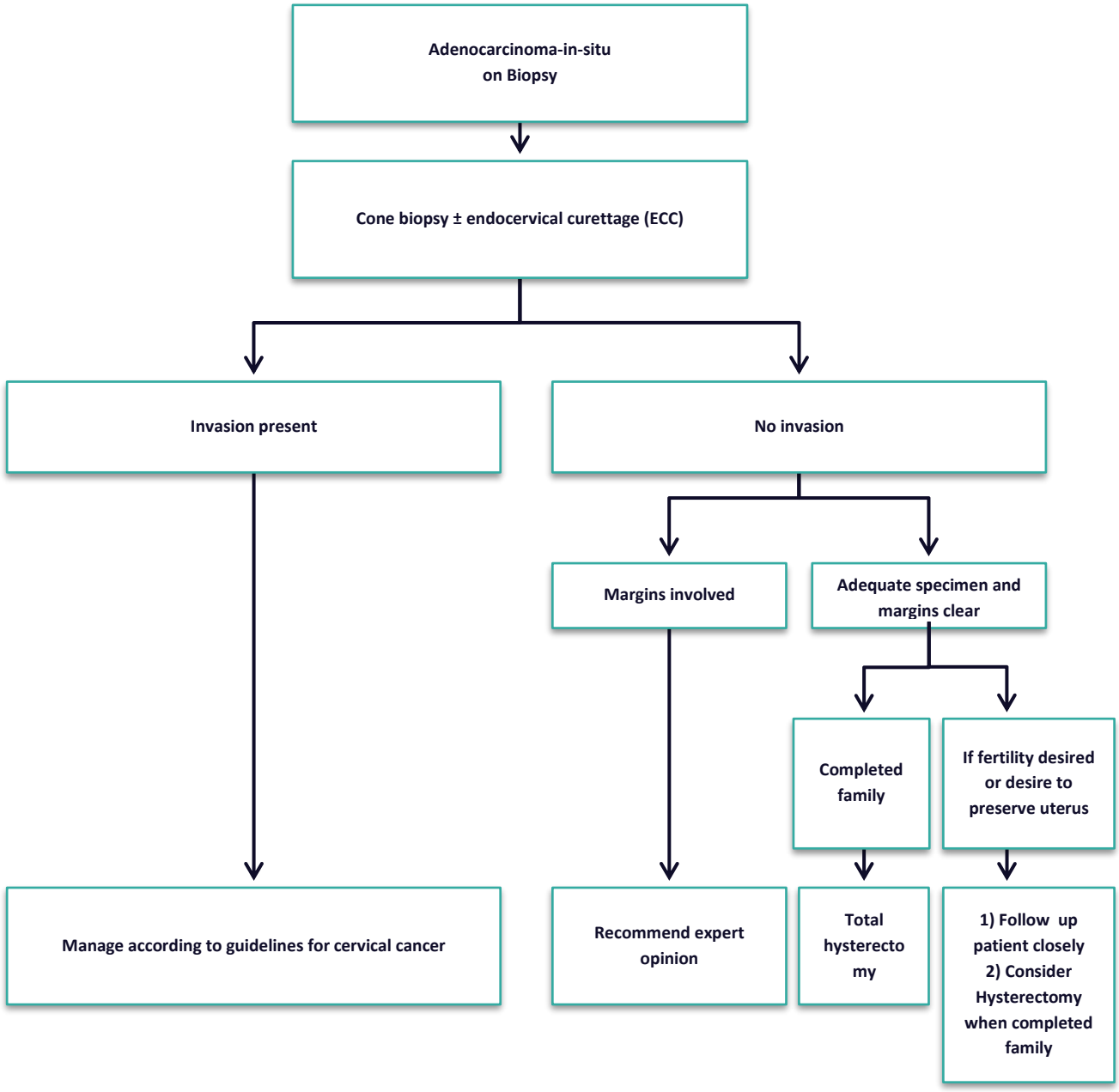
**** Definition of High Grade: ASC-H, HSIL +**

4.3: Management of histologically proven high-grade CIN (CIN 2/3)

4.3.1: CIN 2 / CIN 3 on cervical biopsy

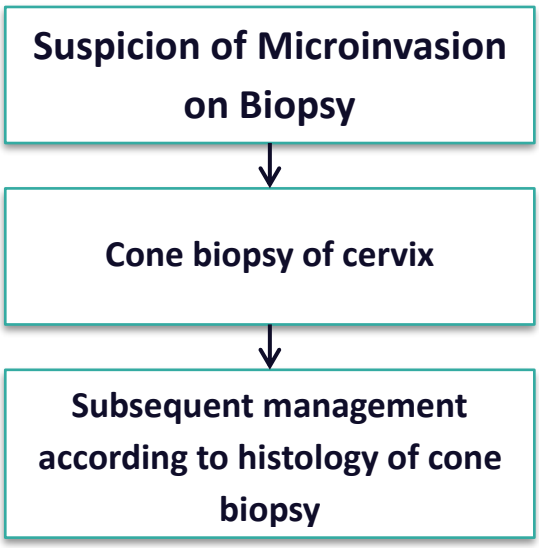


4.3.2: Adenocarcinoma-in-situ



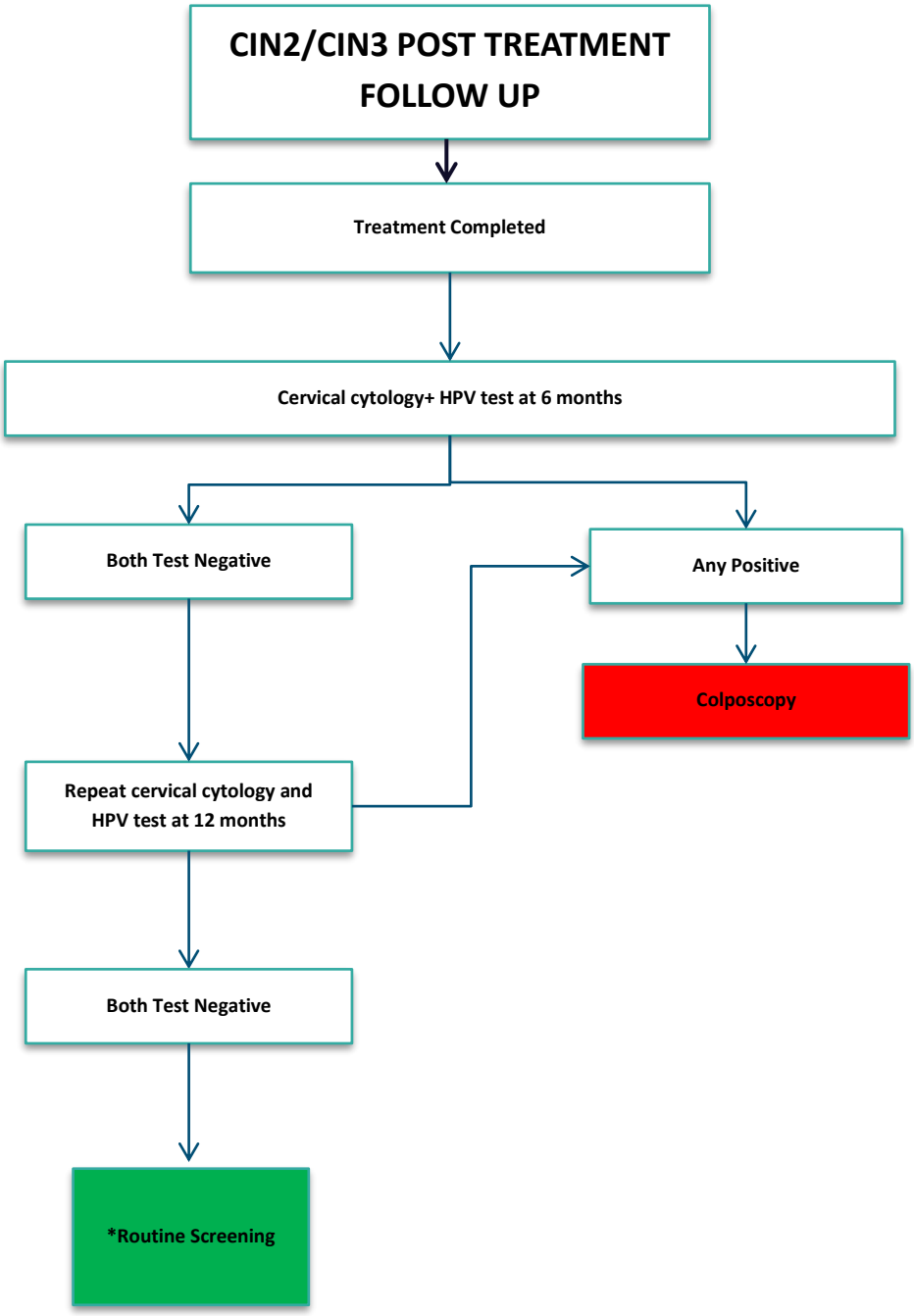
Note :For cone biopsy for adenocarcinoma-in-situ, a single large specimen with clear margins is necessary for adequate histopathological interpretation. A LEEP may not be adequate. A cone biopsy is preferred.

4.3.3: Suspicion of Microinvasion on Cervical Biopsy



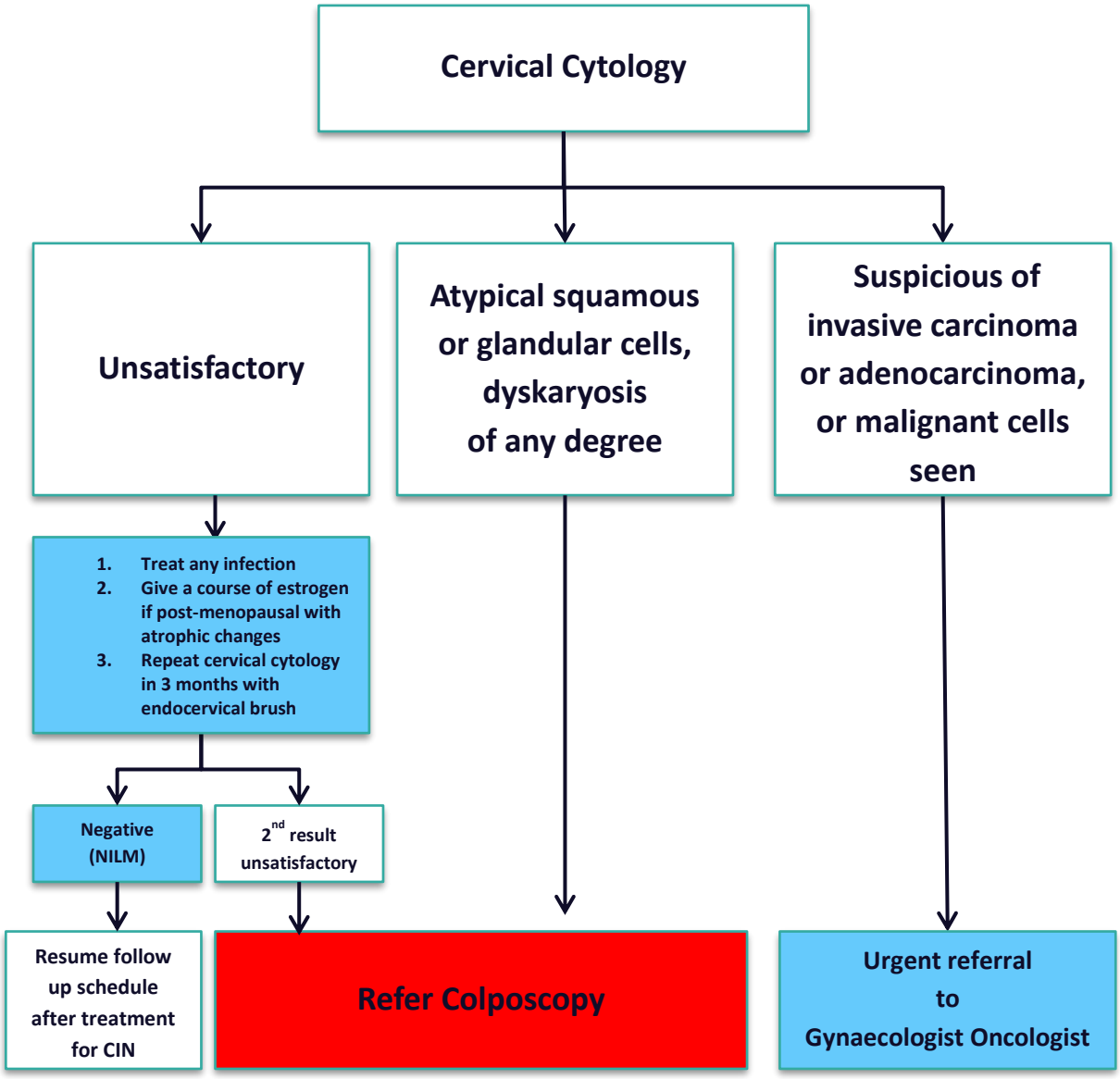
Note: For suspected microinvasion a single large cone biopsy specimen with clear margins is necessary for adequate histopathological interpretation. A LEEP may not be adequate. A cone biopsy is preferred.

4.4: Recommendation for follow up after treatment for high grade CIN (CIN2/CIN3)



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

4.5: Management of Abnormal Cytology Results following treatment for Preinvasive cervical disease (CIN or CGIN)



Acknowledgement

The successful revision of the Clinical Management Guidelines was made possible through the collaborative efforts of various dedicated teams and individuals. We extend our deepest gratitude to everyone involved for their invaluable contributions.

National Cervical Cancer Screening Programme Operations Committee

We thank the members of the Committee for their leadership and strategic oversight, which have been critical in guiding the direction of the revised guidelines.

- **Prof. Ho Tew Hong**
- **A/P. Low Jen Hui Jeffrey**
- **Dr. Ida IsmailPratt**
- **Dr. Timothy Lim**
- **Dr. Ravichandran**
- **Dr. Wong Wai Loong**
- **Dr. Lim Li Min**
- **Dr. Kanneganti Abhiram**
- **Dr. Ng Lai Peng**
- **Dr Lynette Oon Lin Ean**
- **Dr. Chew Sung Hock**
- **Dr. Desmond Ong**
- **Dr. Wang Junjie**
- **Dr. Ong Ai Li**

Guideline Review Committee

Our appreciation goes to the Guideline Review Committee for their diligent work in reviewing and refining the guidelines, ensuring they reflect the most current clinical evidence and best practices.

- **Lead: Dr. Ida Ismail-Pratt**

Clinical Lead & Academic Lead

Special thanks to our Clinical and Academic Leads for their expertise and dedication in integrating research findings with clinical insights, which have been instrumental in shaping the guidelines.

- **Professor Natasha Howard**

Cytology group

We acknowledge the Cytology Group for their comprehensive review and contributions, which have strengthened the cytology components of the guidelines.

- **Clinical group lead: Dr. Ida Ismail-Pratt**
- **Systemic review/Metanalysis clinical lead: Dr. Jeannie Yap & Dr. Tan Ying Hao**
- **Systemic review/metanalysis academic lead: Ms. Manar Marzouk & Miss Mandi Lee**
- **Review group committee members: Dr. Amanda Tan, Dr. Diana GZ Lim, Dr. Ng Lai Peng, Dr. Zeenathnisa Aribou, Dr. Abhi Kanneganti, Miss Reem Malouf, Miss Sim Zi Ying, Mr. Walter Lam,**

HPV group

Our thanks to the HPV Group for their critical analysis and input, ensuring that the guidelines are informed by the latest developments in HPV-related care.

- **Clinical group lead: Dr. Lim Li Min**
- **Systemic review/Metanalysis clinical lead: Dr. Jania Wu**
- **Systemic review/metanalysis academic lead: Miss Manar Marzouk**
- **Review group committee members: Dr. Lee Kai Wei, Dr. Lynette Oon, Dr. Desmond Ong, Dr. Justin Lee, Dr. Lam Sze Tung, Dr. Zeenathnisa Aribou, Lin Pan, Reem Malouf**

Immunocompromised group

We extend our gratitude to the Immunocompromised Group for their focused work in addressing the needs of immunocompromised individuals, an essential aspect of the guidelines.

- **Clinical group lead: Dr Kanneganti Abhiram**
- **Systemic review/Metanalysis clinical lead: Dr Claudia Tong**
- **Systemic review/metanalysis academic lead: Professor Natasha Howard**
- **Review group committee members: Dr Wong Wai Loong, Dr Teh Kailin, Dr Caitlin O'Hara, Dr Andrea Tan, Dr. Ida Ismail-Pratt**

Preinvasive management group

We appreciate the Preinvasive Management Group for their thorough review and contributions, which have enhanced the guidelines related to preinvasive cervical conditions.

- **Clinical group lead: Dr. Timothy Lim Yong Kuei**
- **Systemic review/Metanalysis clinical lead: Kwek Lee Koon**
- **Systemic review/metanalysis academic lead: Miss Manar Marzouk**
- **Review group committee members: Lim Poh Ting, Chong Jia Ying, Sumbal Shahbaz, Lam Sze Tung, Ravichandran Nadarajah, Chew Sung Hock, Ida Ismail-Pratt**

Health Promotion Board (HPB)

Finally, we acknowledge Health Promotion Board (HPB) for their essential support in coordinating the review process, ensuring that all aspects of the guideline revision were efficiently managed.

Glossary and Terminology

Explanatory Notes

Unsatisfactory:

- A cytology sample that is unreliable for the detection of cervical epithelial cell abnormalities.
- Criteria for adequacy:
  - 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.

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)

Abnormal Cytology Results

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.

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.

Carcinoma

- Describe accordingly.

Other Malignant Tumours:

- Describe accordingly.

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.

Pap smear/test (Cervical Cytology) -

- **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)

Prerequisite for HPV assay for HPV primary screening

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
- If vaginal self-sampling is performed, the procedure for self-sampling with a specific commercial kit must be registered with Health Sciences Authority of Singapore (HSA) and validated by the performing laboratory. HPV mRNA tests are not recommended to be used together with vaginal self-sampling.

References

1. Debbie Saslow, Diane Solomon, Herschel W. Lawson et al. *American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening guidelines for Prevention and Early Detection of Cervical Cancer.* Am J Clin Pathol 2012;137:516-542.
2. ASCUS-LSIL Triage Study (ALTS) group. *A randomized trial on the management of LSIL cytology interpretations.* Am J Obstet Gynecol 2003;188: 1393-400.
3. DC Rijkaart, J Berkhof, and L Rozendaal. *Human Papilloma virus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomized controlled trial*. Lancet Oncol (2011) 10.1016/S1470-2045(11) 70296-0.
4. Mark H Stoler, Thomas C Wright Jr, Abha Sharma and the ATHENA (Addressing The Need for Advanced HPV Diagnostics) HPV study group. *High–Risk Human Papillomavirus Testing in women With ASC-US Cytology*. Results from the ATHENA HPV study
5. Bansal N, Jason D, Wright, Carmel J. Cohen, Thomas J. Herzog. *Natural history of established low grade CIN 1 lesions*. Anticancer Redearch 28:1763-1766 (2008).
6. Thomas Cox, Mark S, Diane S. *Prospective follow-up suggests similar risk of subsequent CIN grade 2 or 3 among women with CIN grade 1 or negative colposcopy and directed biopsy*. University of California. 25th March 2003.
7. Philip E. Castle, Julia C. Gage, Cosette M. Wheeler, Mark S. *The clinical meaning of a CIN 1 biopsy.* ACOG 2011; 118(6): 1222-1229.
8. Coupe VMH, Berkhof J, Verheijen RHM. *Cost-effectiveness of HPV testing after treatment for CIN.* BJOG 2007;114:416-424.
9. Flannelly G, Bolger B, Fawzi H. *Follow up after LLETZ.* BJOG 2001; 108:1025-1030.
10. Kitchener HC, Walker PG, Nelson L. *HPV testing as an adjunct to cytology in the follow up of women treated for CIN*. BJOG 2008;115:1001-1007
11. Massad, L. Stewart; Einstein, Mark H.; Huh, Warner K.; Katki, Hormuzd A.; Kinney, Walter K.; Schiffman, Mark; Solomon, Diane; Wentzensen, Nicolas; Lawson, Herschel W.; for the 2012 ASCCP Consensus Guidelines Conference. *2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer*

Screening Tests and Cancer Precursors. Journal of Lower Genital Tract Disease. 17():S1-S27, April 2013.

12. Kathryn E. Sharpless, MD, PhD, David M. O'Sullivan, PhD, Peter F. Schnatz, DO, FACOG. *The Utility of HumanPapillomavirus Testing in the Management of Atypical Glandular Cells on Cytology.* Journal of Lower Genital Tract Disease, Volume 13, Number 2, 2009, 72Y78.
13. Peter F. Schnatz, DO, FACOG, Kathryn E. Sharpless, MD, PhD, David M. O'Sullivan, PhD. *Use of Human Papillomavirus Testing in the Management of Atypical Glandular Cells.* Journal of Lower Genital Tract Disease, Volume 13, Number 2, 2009, 94Y101.
14.. David L. Greenspan, MD, Marina Cardillo, MD, Diane D. Davey, MD, Debra S. Heller, MD, and Ann T. Moriarty, MD. *Endometrial Cells in CervicalCytology: Review of CytologicalFeatures and Clinical Assessment* .Journal of Lower Genital Tract Disease, Volume 10, Number 2, 2006, 111Y122.
15. Melissa K. Frey, MD; Divya Gupta, MD. *Evaluation of WomenWith Atypical Glandular Cells on Cervical Cytology*. The Female Patient | Vol 36 September 2011.
16. *Evidence summary for Cervical dysplasia and cancer - abnormal cytology following routine cervical Screening* . NHSCSP 21-Jul-2011.
17. *Guidelines for cervical screening New Zealand.* Published in August 2008 by the National Screening Unit, Ministry of Health.

Supplementary (project reports)

Documents attached separately.