In The Name of God

Cervical intraepithelial neoplasia treatment & follow up

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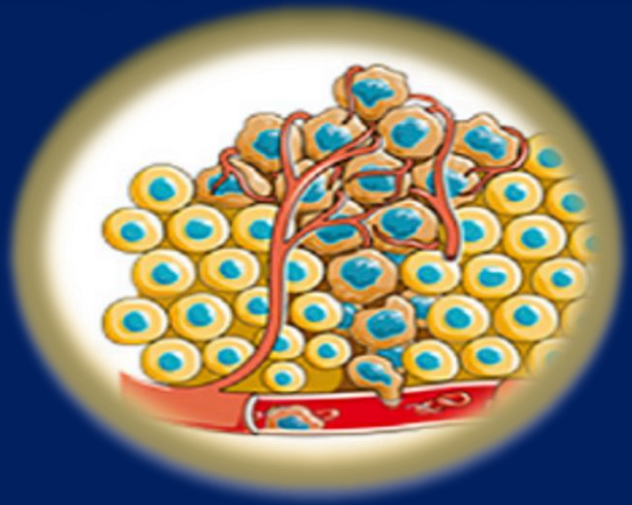
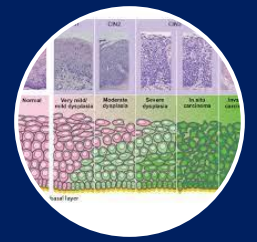


Objectives

- Discuss choosing between excision and ablation for treatment.
- Discuss the prognosis after this treatment.
- Discuss the recommendations for follow-up.
- The overall approach to management of CIN.
- ✓ Surveillance versus observation versus treatment

Cervical intraepithelial neoplasia (CIN)

Recommendations are based on risk, not results.



- CIN is a premalignant lesion of the uterine cervix that is classified as low grade (CIN 1) or high grade (CIN 2,3) based on the risk of progression to malignancy.

- In managing patients with CIN, the goal is:
  - To prevent possible progression to invasive cancer while avoiding overtreatment of lesions that are likely to regress.

- Surveillance or observation is appropriate for some patients with low-risk lesions whereas treatment with an excisional or ablative procedure is recommended for patients with higher risk lesions.

The treatment of dysplasia with ablative or excisional procedures is key to cervical cancer prevention.

The choice of operative technique should be made based on the lesion factors (such as location, size, and suspicion for underlying malignancy), as well as patient factors (such as age, parity, and fertility desires) and cost.

Finally, as with any procedure, physician preference, practice setting, and skill should be taken into consideration.

Use of p-16 staining may improve risk stratification of these lesions.

P16 is able to aid in diagnosis.

P-16 status is not universally available.

p16 is a cyclin-dependent kinase-4 inhibitor that is expressed in a limited range of normal tissues and tumors.

LAST System[1]	Cytology	LSIL	HSIL		
	Histology	LSIL	p16 staining should be performed*	HSIL	
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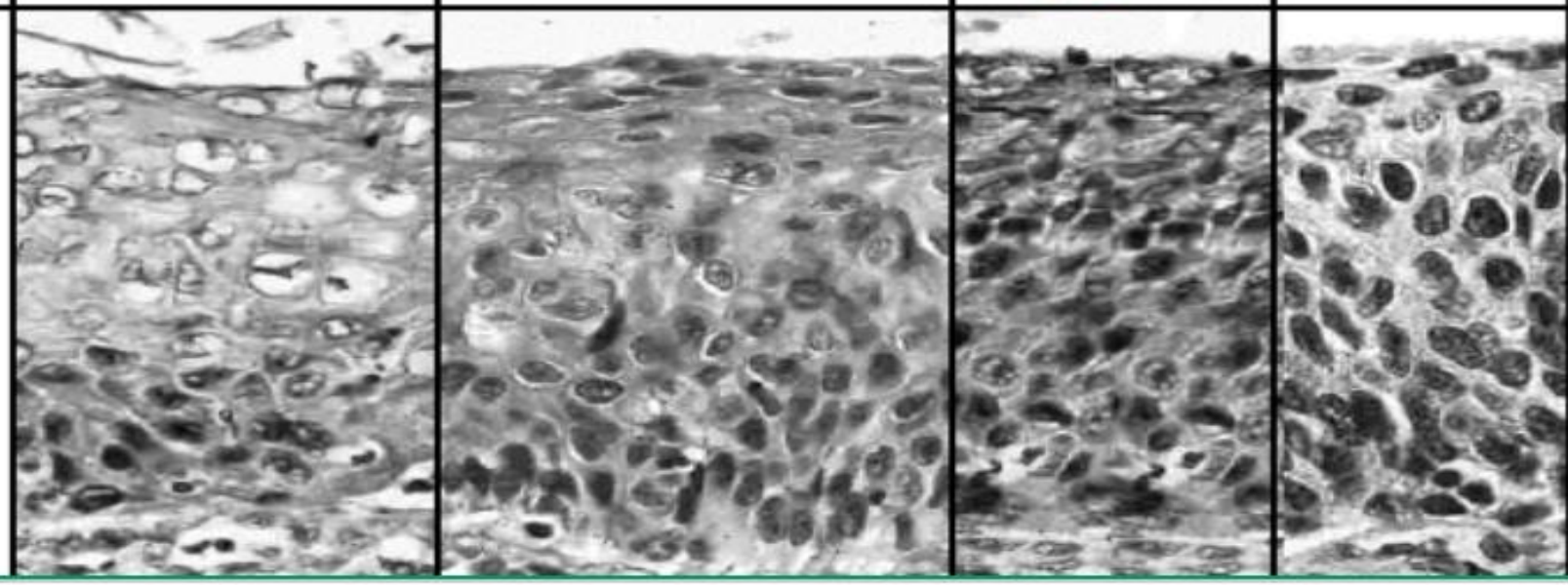
Histologic images					

Terminology regarding cytologic and histologic precancerous changes of the uterine cervix. The corresponding terminology from the previous classification systems is shown. Images of the histologic correlates for each category are also shown.

LAST: lower anogenital squamous terminology; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions; CIN: cervical intraepithelial neoplasia.
* CIN 2 that is p16-positive is classified as HSIL. CIN 2 that is p16-negative is classified as LSIL.

Excisional treatments vs Ablative treatments

- Excisional treatments are referred to as cone biopsies or cervical conization and include:

  - Cold knife conization,
  - Loop electrosurgical excision procedure (LEEP; also called large loop excision of the transformation zone [LLETZ]), and
  - Laser conization.

- Ablative treatments include:

  - Cryotherapy,
  - CO2 laser ablation, and
  - Thermal ablation (eg, diathermy, cold coagulation).

Hysterectomy

- Hysterectomy is unacceptable as a primary treatment for CIN but is an option for patients who are:
- Incompletely treated with
- • Excision or
- • Ablation or
- • Who have recurrent CIN.

Choosing the treatment approach

- Factors to consider in choosing excision versus ablation
- In the United States, excision, specifically with loop electrosurgical excision procedure (LEEP), has largely replaced the practice of ablation.
- In practice, when treatment is performed, it is preferred excision over ablation for all CIN grades because it provides a diagnostic specimen, which is reviewed even when a diagnostic specimen is not essential.

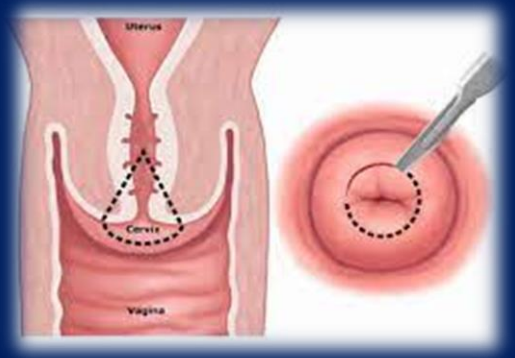
Choosing the treatment approach

- Factors to consider in choosing excision versus ablation

  This is consistent with the WHO, which recommends LEEP over cryotherapy in settings where LEEP is available.

- By comparison, the American Society for Colposcopy and Cervical Pathology states that excision or ablation is acceptable treatment for CIN 1 (when treatment is indicated) but prefers excision over ablation for CIN 2,3.

Clinicians and patients should consider the following factors when choosing a treatment approach.



- Is a diagnostic specimen needed?
- Therefore an excisional procedure is required:
  - A lesion extends into the cervical canal and cannot be fully visualized.
  - A lesion covers >75 % of the ectocervix or is beyond the reach of the cryoablation tip .
  - The endocervical curettage demonstrates CIN 2+ (or CIN that cannot be graded).

Is a diagnostic specimen needed?

- The patient has had a **previous excision for CIN 2+**
- **Glandular disease** (AIS) is present:

- Glandular disease may be located in the **transformation zone** or **endocervical canal**, and lesions are often not contiguous ("**skip lesions**"); therefore, an excisional biopsy is needed to confirm the diagnosis and assess the extent of disease.

Is a diagnostic specimen needed?

- **There is diagnostic uncertainty:**

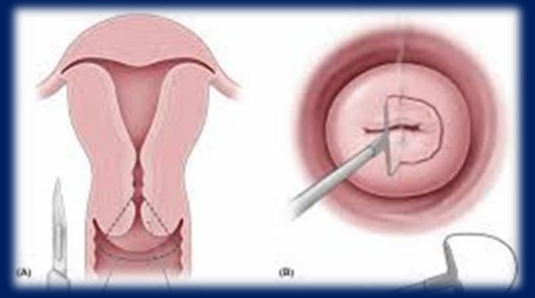
  Patients with an inadequate colposcopic examination (eg, the entire squamocolumnar junction or lesion cannot be visualized).

- Patients with **inconsistent findings on cytology versus colposcopy** (ie, HSIL) on cervical cytology followed by a colposcopic finding of CIN 1 in patients 25 years and older.

Is a diagnostic specimen needed?

- There is a high risk of invasive disease :
- For patients in whom cervical cancer is suspected, it is crucial to obtain diagnostic information and evaluation of surgical margins.
- Use of p16 staining of the colposcopic biopsy specimen may improve classification and risk stratification of these lesions.
- However, reporting of p16 status is not universally available.

Is excision more effective than ablation?



- In patients with high-grade disease (CIN 2,3), use of any therapy other than excision should be supported by high-quality evidence showing that forgoing the diagnostic information provided by excision does not worsen prognosis; however, there are few high-quality data comparing outcomes of excision versus ablation in this setting.
- There are some data to suggest that cryotherapy is less effective in women with HIV with success as low as 37% in HIV-positive women compared to 77% to 93% effectiveness in HIV-negative women.

Is excision more effective than ablation?

- Although the efficacy rate (eg, residual disease after treatment) for both ablation and excision has been reported to be approximately 90 to 95 %, A meta-analyses indicates that it remains unclear whether ablation is as effective as excision.
- Therefore, many practices and societal organizations prefer excision.

Is future pregnancy planned?

- Patients planning a future pregnancy may choose to avoid excision because of adverse obstetric outcomes (second trimester pregnancy loss, preterm pre-labor rupture of membranes, preterm delivery) in large observational studies.
- Ablation, in theory, has a lower risk of adverse obstetric outcomes given that the cervix is better preserved than with excision.
- However, CIN itself may pose an increased risk of preterm birth, regardless of treatment method. Patients should be counseled about these issues.

Does excision have greater morbidity than ablation?

- **Excisional methods** are typically thought to be associated with **greater morbidity** than ablative therapy.

- In 2 meta-analyses, no significant difference in complications (eg, hemorrhage) or selected adverse effects (eg, pain) were found, but the analyses were not powered to detect small differences in these outcomes for specific techniques.
- Adverse effects that are typically reported include:

  - Excision - Intraoperative bleeding, infection, and delayed hemorrhage (usually 1-2 weeks postoperatively).
  - Ablation - Posttreatment bleeding and infection; a prolonged, heavy, watery vaginal discharge can occur after cryotherapy, and minor cramping during the procedure.

Cryotherapy results in destruction of local tissue, and ice should be seen extending approximately 5 mm from the probe. The entire transformation zone should be covered

- The most common risk of cryotherapy is minor cramping during the procedure. This is generally a limited side effect.
- Up to 20% of patients will report diffuse watery discharge.
- Light spotting can occur and is most commonly noted 12 -15 days following the procedure.
- Pelvic rest is recommended for 2 weeks to minimize bleeding and infection.
- Long-term complications include a risk of cervical stenosis in 1% - 4% of patients.
- This procedure does not affect pregnancy outcomes.
- Major bleeding or infection occurs less frequently than with excisional procedures.

- The key benefit of LEEP, which resulted in its wide uptake, was the ability to perform the procedure in the outpatient setting under local anesthesia. This is made possible by the excellent hemostasis provided by performing the excision with the electrosurgical wire.
- This procedure is performed in the outpatient setting with significant reductions in cost.
- It is also easy to perform, teach, and learn. Not all patients are appropriate candidates for LEEP, however.
- Cervical anatomy should be compatible with use of the preset loop sizes. Further, significant patient anxiety may preclude performing the procedure in the office setting and may require that the procedure be performed in the operating room.
- Because of the ease of performing the LEEP technique, some providers have moved to using a "see and treat" strategy going straight from high-grade pap to LEEP without colposcopic biopsies. This is an important strategy in clinics with high no-show rates or low resources such as low-income countries.
- However, this is not acceptable in young women with desire for future fertility or lowgrade abnormalities on cytology procedure of choice for treatment of dysplasia.
- **Loops are available ranging from 15- 25 mm in electrode diameter (width)**. Size should be chosen based on the size of the cervix, lesion, and extent of transformation zone.

- Loop size is chosen based on anatomy, transformation zone, and lesion size. The electrode should be activated prior to touching the tissue. The electrode is then gently passed through the tissue while maintaining the current until the pass is complete.
- Loss of current during the procedure stops the cutting wave, and reinitiation of the current from the opposite direction can result in bleeding at the junction of where the two passes meet.
- Similarly, reactivation of the current can result in increased thermal artifact. The loop can either be passed from side to side or from top to bottom.
- Some favor starting at the area of most concern based on the preprocedure biopsy or visualized lesion to ensure the best pathologic assessment at this location.
- Starting the excision from top to bottom can result in the specimen falling into operative field and obscuring the view.
- The depth of excision should be greater than 5 mm, ideally at least 7 to 8 mm, to allow for excision of the underlying endocervical glands. This depth has been shown to remove most preinvasive lesions without adding undue risk for complications such as preterm birth.

Other factors

- Additional deciding factors that require shared decision making between the provider and patient include cost, availability, and convenience.

For example,

laser ablation equipment is costly, requires additional specialized training, and a laser procedure may require general or regional anesthesia in an inpatient setting.

The benefits of CO2 laser include targeted lesion therapy, ability to treat lesions that extend onto the vagina, rapid healing, and lower cervical stenosis rates than cryotherapy.

The disadvantages of the CO2 laser are the equipment acquisition expense, training required for use, and maintenance cost for the laser.

Potential candidates for hysterectomy

- Hysterectomy is not a first-line treatment for CIN because the risk of significant morbidity is higher than with less invasive, yet effective, treatment modalities (eg, excision and ablation).

Potential candidates for hysterectomy

- CIN 2,3 and positive excisional margins who have completed childbearing.
- In whom an additional excisional procedure cannot be performed.
- Recurrent or persistent CIN 2,3 who have completed childbearing.
- In whom a repeat excisional procedure is not feasible or desired.
- Scarring or shortening of the cervix from prior treatments that prohibits a repeat excisional procedure.
- Unwillingness or inability to comply with long-term follow-up.

Scarring may increase the risk of complications of a repeat excisional procedure or limit the results of further testing (ie, scarring may obscure premalignant cells).

Potential candidates for hysterectomy

- If invasive disease is suspected, a diagnostic excisional procedure may be performed and sent for frozen section prior to hysterectomy to confirm that cervical cancer is not present and that a radical hysterectomy is not indicated.

Prognosis after excision or ablation

- Poor prognostic factors.
- Higher rates of persistent disease are associated with:
  - Positive margin status.
  - HPV DNA positivity, especially with HPV 16, 6 months or more posttreatment.
  - Large lesion size (eg, greater than two-thirds of the surface of the cervix).
  - Endocervical gland involvement.

Margin status, when available, is a predictor of both disease persistence and recurrence.

Prognosis by margin status

- Negative margins
  — CIN appears to have a high rate of cure when the entire lesion has been excised, but few long-term studies are available.

- In one study of over 4400 patients with negative margins after an excisional procedure for CIN 3, a new high-grade cytologic or histologic lesion developed in only 0.35 % of patients after a median of 8.9 years (range 3.3 to 16.8 years).

Positive margins

- Studies have consistently shown that patients with positive margins after an excisional procedure, compared with negative margins, are at significantly higher risk for *residual* or *recurrent disease*.

- Recurrence can occur years after treatment; the mean time to recurrence was almost 4 years in one study.

Prognosis

- Prognosis when the entire excisional specimen is negative:

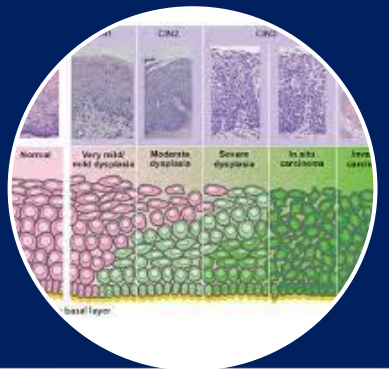
  - A completely negative excisional specimen raises concern that the lesion was missed, and, therefore, these patients should be followed similarly to those with positive margins.

Prognosis

- Prognosis when HPV is positive on follow-up testing:

- HPV status following treatment also appears to predict risk of recurrence, and HPV-based testing is now the primary follow-up testing technique after treatment for CIN.

CIN
Follow-up



- In managing and following of the patients with CIN, the goal is:
  - To prevent possible progression to invasive cancer while
  - Avoiding overtreatment of lesions that are likely to regress.

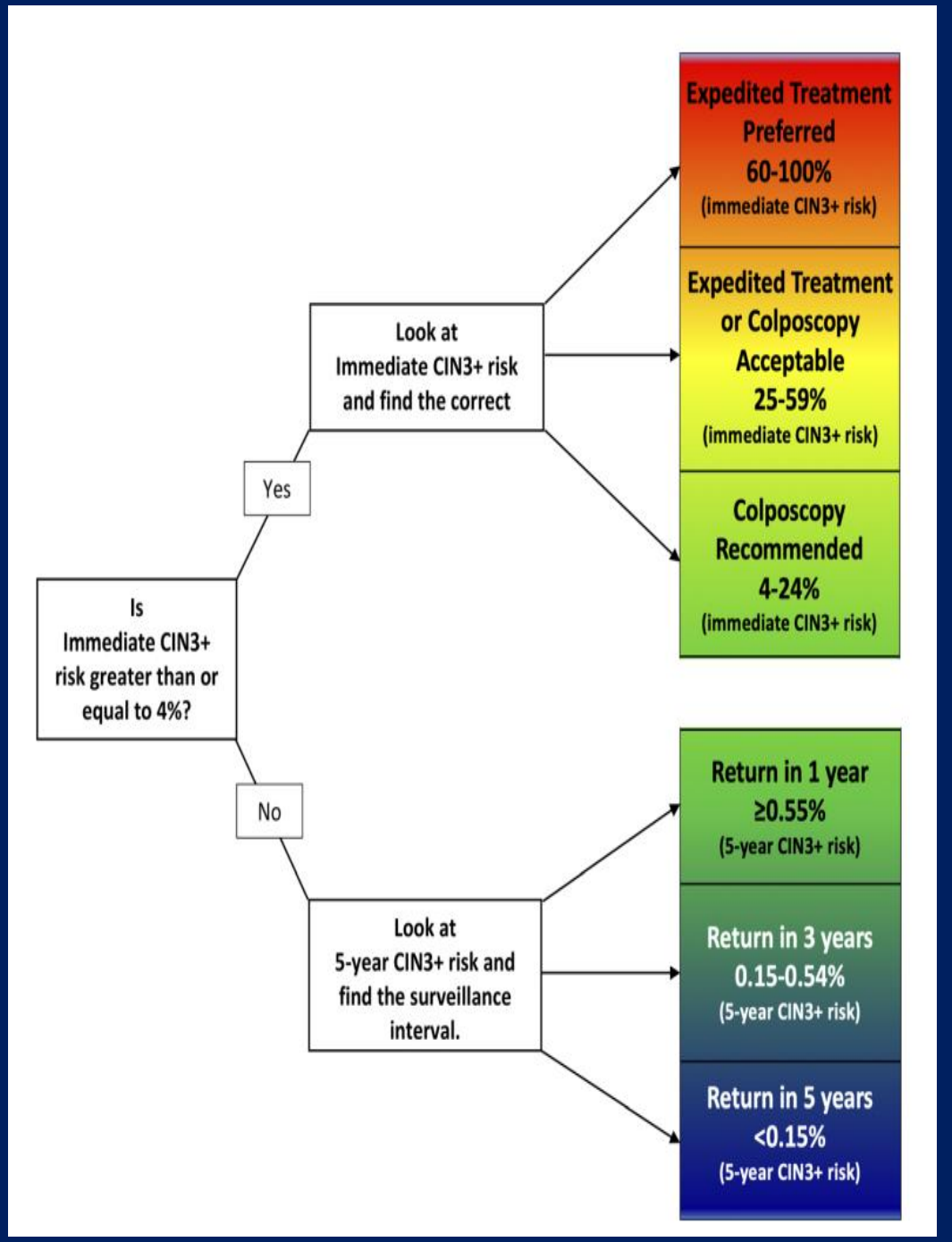
Recommendations are based on the risk of progression to malignancy, not results.

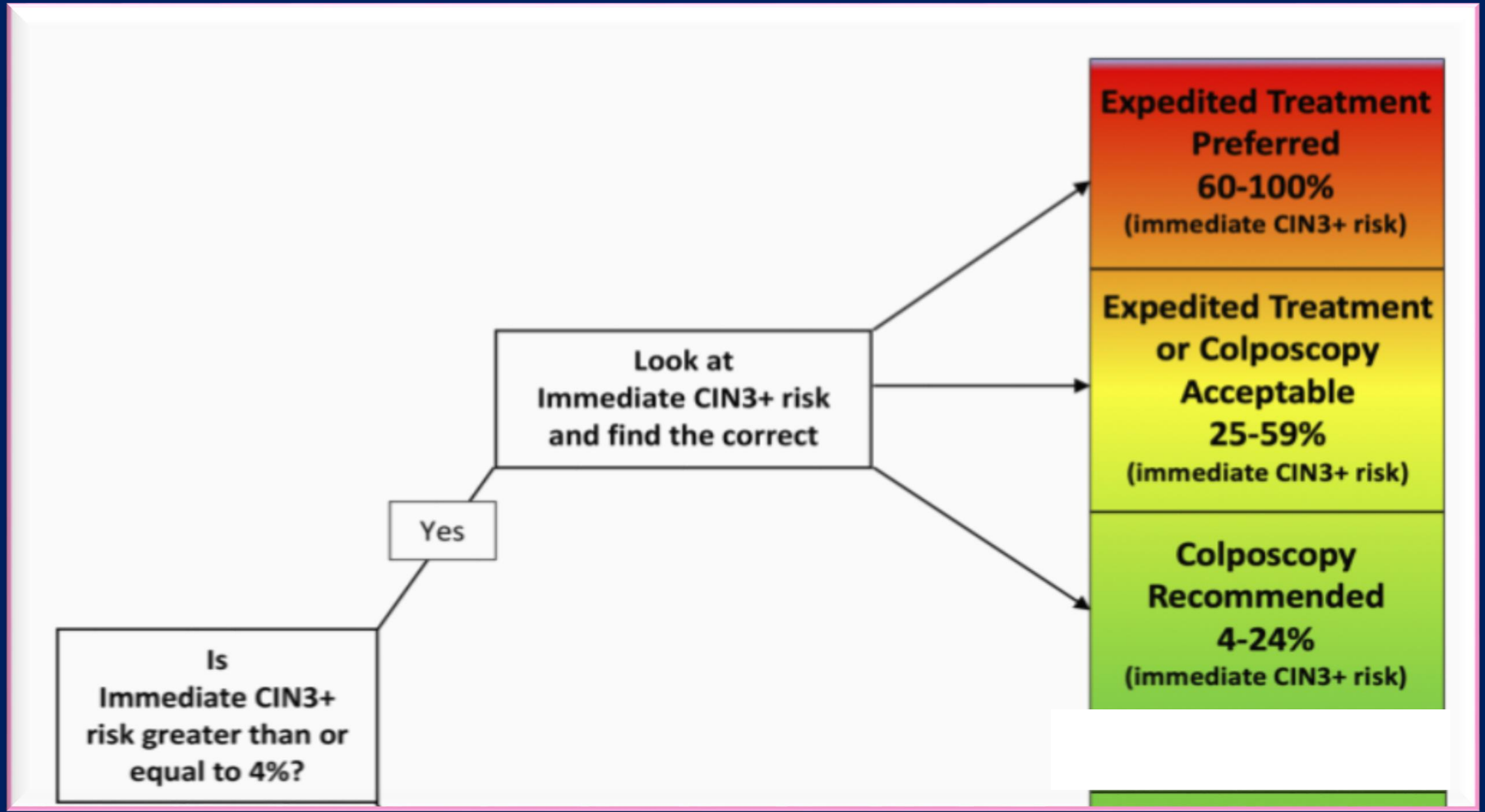
These risk estimates were generated using long-term observational screening and management data set from Kaiser Permanente of Northern California (KPNC), allowed precise risk estimation over long follow-up periods.

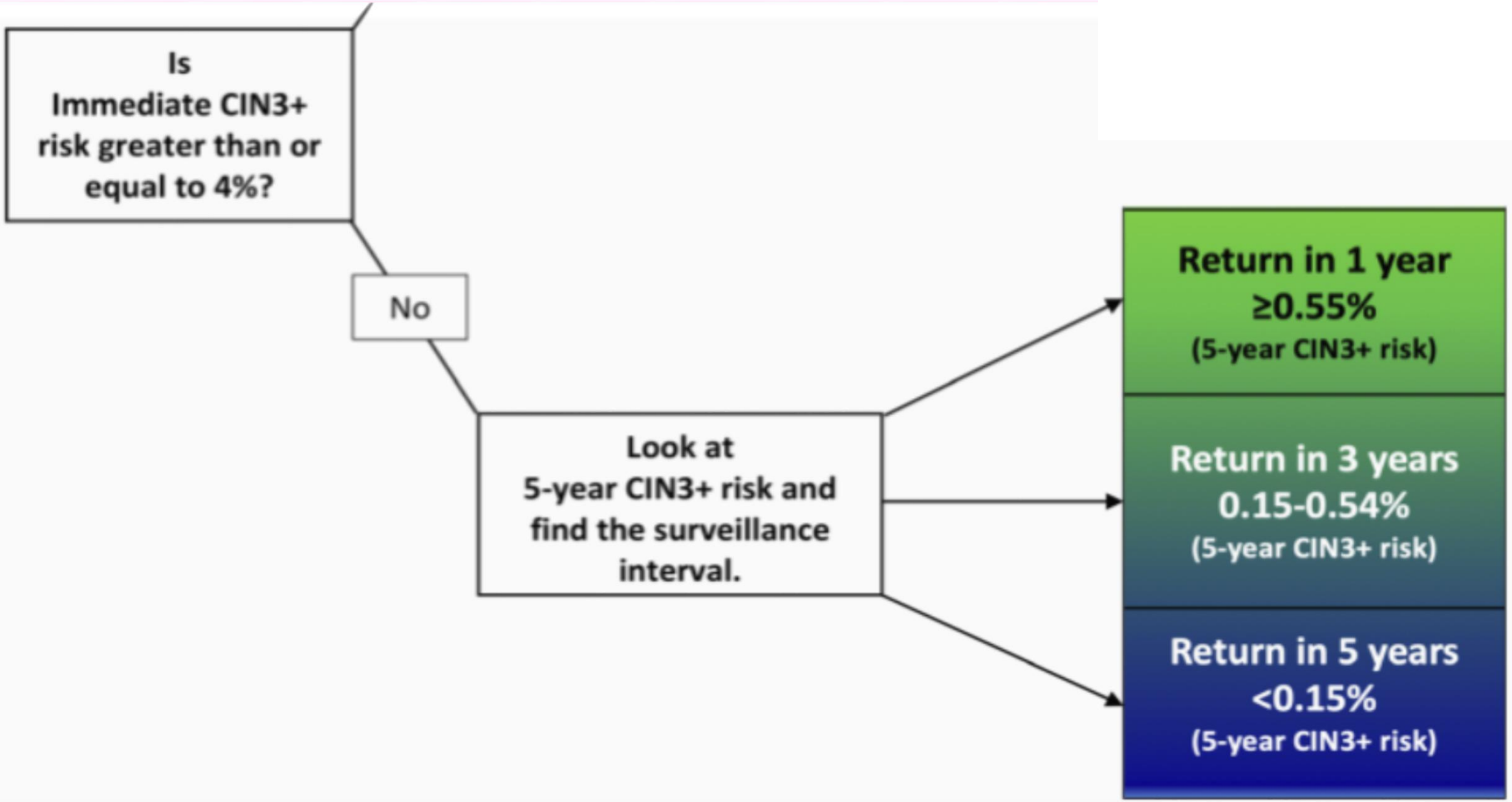
Risk estimates were based on data from more than 1.5 million KPNC patients who received cotesting with cytology and HPV testing, age and any combination of history and current or recent past test results between 2003 and 2017.

In the 2019 ASCCP Risk-Based Management Consensus Guidelines, clinical management decisions are based on immediate and 5-year CIN 3+ risk estimates based on HPV testing and cytology.

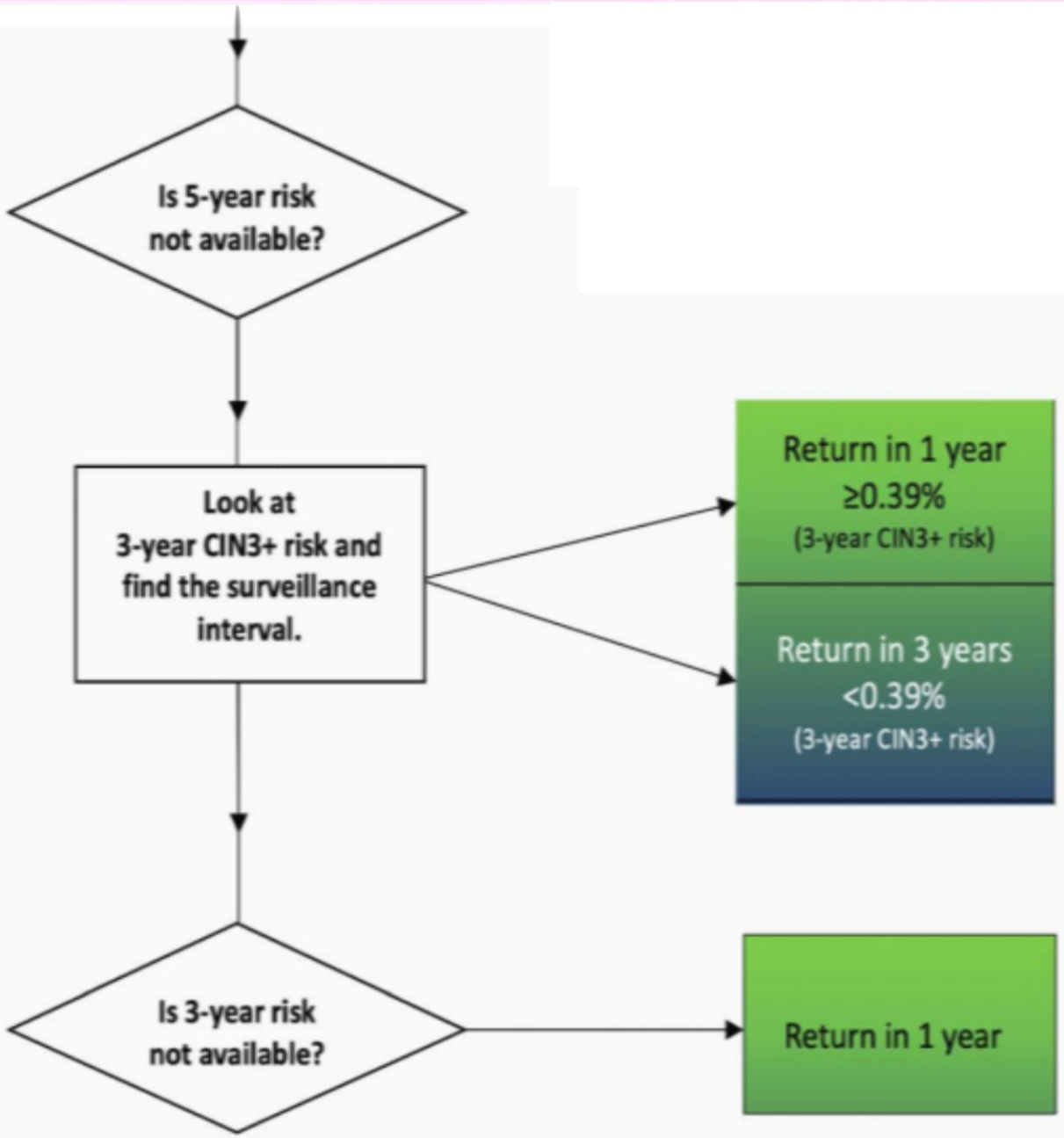
- This figure demonstrate how patient risk is evaluated.
- For given current results and history combination (past history, including unknown history), the immediate CIN3+risk is examined.
- If this risk is 4% or greater, immediate management via colposcopy or treatment is indicated.
- If the immediate risk is less than 4%, the 5-year CIN3+risk is examined to determine whether the patients should return in 1, 3, or 5 years.




Is
Immediate CIN3+
risk greater than or
equal to 4%?
Yes
Look at
Immediate CIN3+ risk
and find the correct
Expedited Treatment
Preferred
60-100%
(immediate CIN3+ risk)
Expedited Treatment
or Colposcopy
Acceptable
25-59%
(immediate CIN3+ risk)
Colposcopy
Recommended
4-24%
(immediate CIN3+ risk)



Risk_Based_Cervical_Consensus_data Methods addendum to the 2019 Guidelines and confirmed on July 12, 2021


Is 5-year risk not available?
Look at 3-year CIN3+ risk and find the surveillance interval.
Return in 1 year ≥0.39% (3-year CIN3+ risk)
Return in 3 years <0.39% (3-year CIN3+ risk)
Is 3-year risk not available?
Return in 1 year

HPV 16/18

Clinical : HPV 16 or 18 positivity is the highest risk scenario and is an indication for immediate referral to colposcopy and, if combined with a high-grade squamous intraepithelial lesion (HSIL), expedited treatment with an excisional procedure

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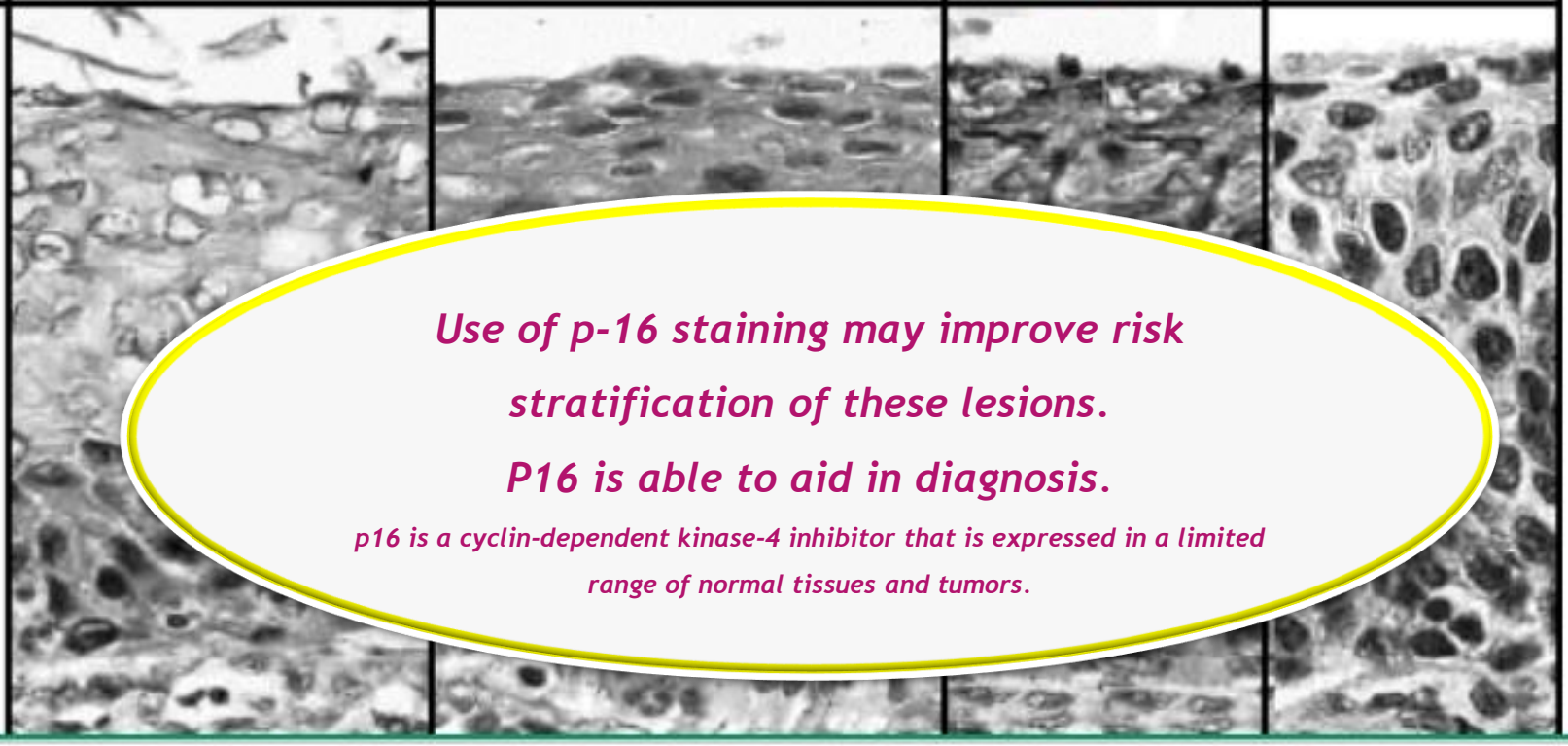
Histologic images					

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Persistent positive result

- Defined as consecutively positive HPV results at least 12 months apart is a necessary pathogenetic step for progression to clinically relevant disease.
- Most, if not all, patients with persistent HPV infection will be diagnosed with (CIN 2+) or more within 5-7 years, many in as few as two years.
- Patients with persistent positive results, but in whom further work-up (with cytology and colposcopic biopsies) is reassuring, are evaluated with vaginal colposcopy.
- If vaginal colposcopy is negative, continued surveillance with cervical cytology and colposcopy is prudent as the patient remains at risk for cervical cancer.

Follow-up after treatment

- Type and duration of testing:
  - The evaluation approach presented here is provided by the 2019 consensus guidelines of the (ASCCP) (ACOG), the Society of Gynecologic Oncology, the American Cancer Society (ACS), the Centers for Disease Control and Prevention, and the National Cancer Institute.

Follow-up after treatment

- Studies have consistently reported that posttreatment HPV-based testing is more sensitive than cytology alone in detecting persistent/recurrent CIN .
- Therefore, HPV-based testing, rather than cytology alone, should be used for surveillance in patients 25 years and older.
- When cytology is used, either in patients younger than 25 years or in settings where HPV-based testing is not available, cytology should occur at more frequent intervals (eg, 6-month intervals when one-year HPV-based testing is recommended, and one-year intervals when three-year HPV-based testing is recommended).

FOLLOW-UP patients with CIN (all grades) treated with ablation or excision (and with negative margins)

- For patients ≥25 years:
- HPV-based testing at six months; cervical cytology is acceptable only if HPV-based testing is not available.
- If HPV is positive, then colposcopy and biopsies should be performed and managed based on these results.
- If HPV is negative, then HPV-based testing should occur annually for 3 years.
- If HPV remains negative, then HPV-based testing can occur every 3 years for at least 25 years.

For patients <25 years

- For patients <25 years : Cervical cytology at 6 months.
  If cervical cytology is HSIL or ASC-H, then colposcopy with biopsies should be performed and managed based on these results.
- If cervical cytology is LSIL or less (HPV-positive ASC-US) and persists, then colposcopy with biopsies should be performed and managed based on these results.
- If cytology is negative, then cytology should occur at 6-month intervals for 3 years.
- If cytology remains negative, then cytology can occur annually. When the patient reaches the age of 25, testing can transition to the HPV-based model and occur every three years, as above.

Patients with CIN 2,3 treated with excision (and with margins and/or ECC that is positive for CIN 2+) should be followed with;

- HPV-based testing in 6 months is preferred; colposcopy and ECC at six months are acceptable.
- If HPV is negative, then HPV-based testing should occur annually for 3 years then at 3 year interval for at least 25 years.
- If HPV is positive, then colposcopy and targeted biopsies should be performed and managed based on these results.

  - If CIN 2+ continues, repeat excision should be performed.
  - If repeat excision is not feasible or desired, hysterectomy is recommended.

  Repeat excision is acceptable for patients who are 25 years and older and in whom future pregnancy and potential obstetric outcomes are not a primary concern.

If hysterectomy is performed, management is as follows:

- Patients with CIN 2,3 on hysterectomy specimen or patients who underwent a hysterectomy for a history of CIN 2,3 have an increased risk of disease recurrence and should be followed with:

- HPV-based testing annually for 3 years.
  If HPV is positive, cytology should be performed.

-

- If HPV is negative for ***3 consecutive years***, long-term follow-up with HPV-based testing at ***3-year intervals*** is performed ***for 25 years***.

- Patients with **CIN 1 or less** on the hysterectomy specimen and no history of CIN 2+ can ***discontinue follow-up*** testing.

Patients in whom a complete history is not available

- In practice, all patients are asked about their cervical cancer screening history and obtain medical records whenever possible.

- The medical record is important because many patients do not recall:
  - Their abnormal pap history,
  - May not have been told a specific diagnosis, or
  - May incorrectly report a normal screening history.

If the medical records cannot be obtained, it should be relied on the patient's reported results:

- If a patient is certain that an excisional procedure or ablation has been performed, it is regarded this as a positive history of CIN 2,3 and follow the patient as described for patients with CIN (all grades) treated with ablation or excision (and with negative margins).

- If a patient reports a history of "an abnormal Pap smear," it is regarded the history as uncertain and begin age-based cervical cancer screening.

Evidence

- Patients who have a history of CIN 2,3 or adenocarcinoma in situ and who have been appropriately treated or
- Who had spontaneous regression of cervical neoplasia should have follow-up testing for at least 25 years following diagnosis, even if this extends screening past age 65 years, based on guidelines from ACOG, ASCCP, ACS, and the American Society for Clinical Pathology.

- Testing may be discontinued earlier in patients in poor health and with a limited life expectancy.

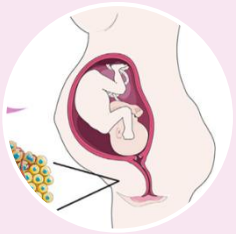
Evidence

- Longitudinal studies have shown that patients with a history of CIN 2,3 have a 5- to 10-fold higher risk of cervical cancer compared with the general population.

- While most disease recurrence presented within 2 years, the risk persisted as long as 20 to 25 years.

Timing of future pregnancy

- There are few studies regarding how long patients should wait to conceive after treatment.



- It is suggested an interval of 3 months or longer from an excisional procedure to conception.

Summary and recommendations

- The mainstays of treatment of (CIN) are excision or ablation of the transformation zone of the cervix.
- Factors to consider when choosing between treatment with excision or ablation include:

  - Whether a diagnostic specimen is needed,
  - Future pregnancy plans,
  - Complications and side effects, and
  - Efficacy.

- In practice, it is preferred excision over ablation in almost all instances because it provides a diagnostic specimen.

Summary and recommendations

- Hysterectomy is not a first-line treatment for CIN.
- Hysterectomy is a reasonable option only for patients with CIN 2,3 who have:

  - A positive excisional margin and
  - In whom an additional excisional procedure cannot be performed,
  - Have completed childbearing, and
  - Are unwilling or unable to comply with long-term follow-up.

Summary and recommendations

- **Higher rates of persistent disease after excision or ablation** are associated with:
  - Positive margin status,
  - HPV DNA positivity posttreatment,
  - Large lesion size, and
  - Endocervical gland involvement.

A completely negative excisional specimen raises concern that the lesion was missed. These patients should be followed similarly to those with positive margins.

Summary and recommendations

- After treatment with excision or ablation, follow-up testing is determined based on CIN grade and margin status, if available.

- In general, patients 25 years or older are followed with HPV-based testing, and patients younger than 25 years are followed with cervical cytology until age 25 when HPV-based testing can begin.

- If results are negative, testing should continue for at least 25 years given there is a 5- to 10-fold risk of developing cervical cancer in these patients compared with the general population.


ANY
QUESTIONS?

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