



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Screening for and Preventing HPV & Cervical Cancer

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CONTINUING MEDICAL EDUCATION DEPARTMENT OF MEDICINE



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL



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Clinical focus: gynecologic cancers

- Research focus: development of infrastructure for cancer care for women in resource limited countries; structural violence against women and reproductive outcomes

Disclosures

NONE

Objectives

- Understand risk-based format for 2019 cervical cancer screening guidelines
- Understand risk-based format for management of screening results 2019 cervical cancer screening guidelines





OUTLINE

Background – Cervical
Cancer Statistics

Introduction to Screening

2019 Guidelines



Background

Cervical Cancer Statistics 2021

Globocan 2021

Worldwide: 604,127 women diagnosed with invasive cervical cancer

Worldwide: 341,831 women will die from cervical cancer

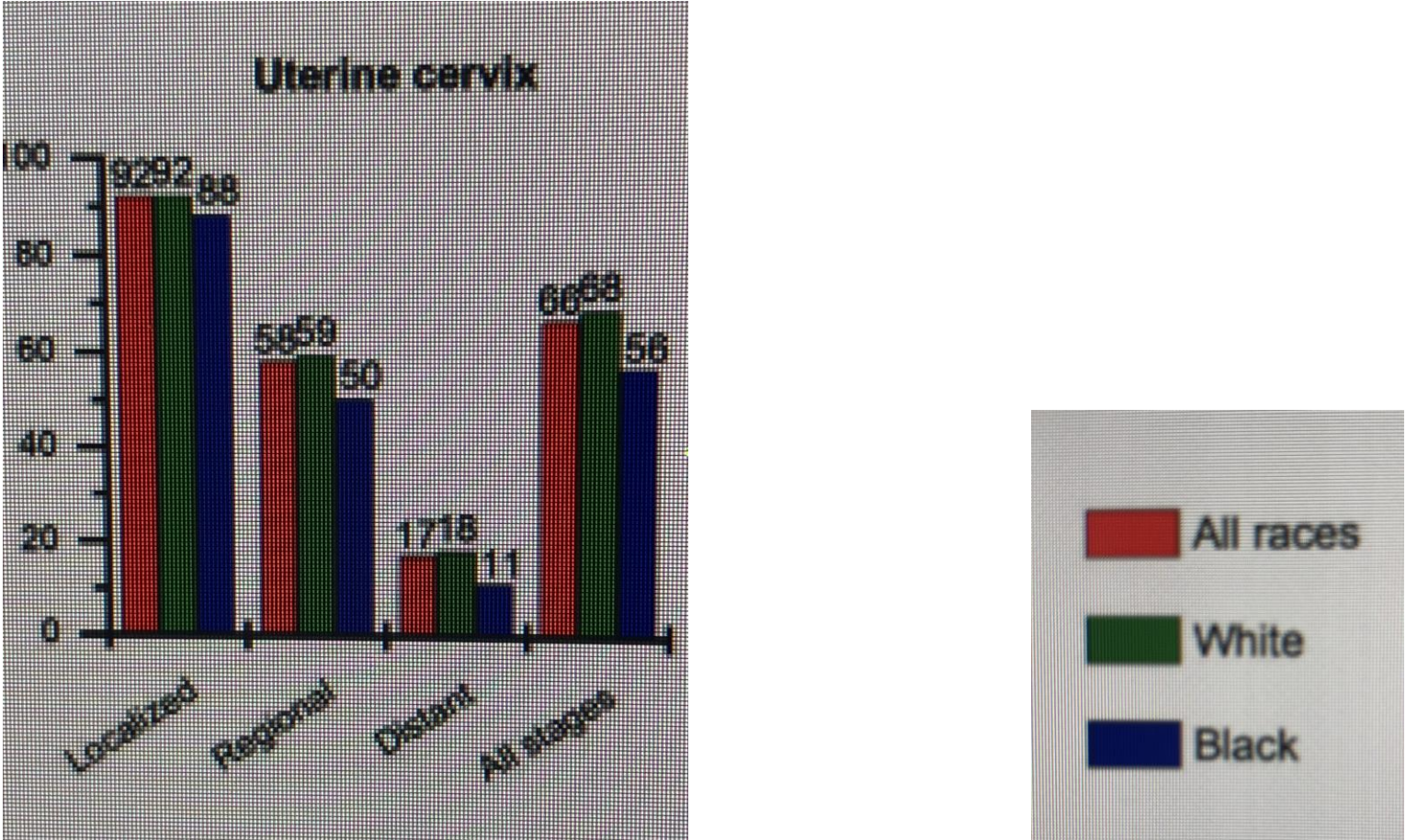
United States: 14,480 women diagnosed with invasive cervical cancer

United States: est. 4290 women will die from cervical cancer

Probability of developing cervical cancer (birth to death): 1 in 158 women in USA (0.6%)



2021: Five-Year Survival Cervical by Race USA



Background Rationale for Screening

Cervical cancer has a long preinvasive phase

There are effective and cheap screening tests for preinvasive and invasive cervical cancer

Cervical cancer can be prevented with adequate screening



The Consequences of Over-Screening Treatment of lesions that have a high probability of spontaneous regression

80 percent of low-grade lesions will
spontaneously regress
63 percent of CIN 2 lesions regress by three
years



The Consequences of Over-Screening

Scarring of cervix

Cervical stenosis

Shortening of cervix

Traumatic

Dyspareunia

Pain

Infertility

Cervical Incompetence
during pregnancy

Inability to perform
adequate screening



The Consequences of Over-Screening

Long Term Changes : **CERVICAL STENOSIS**



The Consequences of Over-Screening Long Term Changes: **CERVICAL INCOMPETENCE**

LEEP Procedure and Preterm Birth

- one LEEP: 7.2% preterm deliveries (between 28 and 37 weeks)
- No LEEP: 4.6%
- Two LEEPs: preterm risk increases 3x
 - *Obstet Gynecol vol121:1063-1067, 2013*



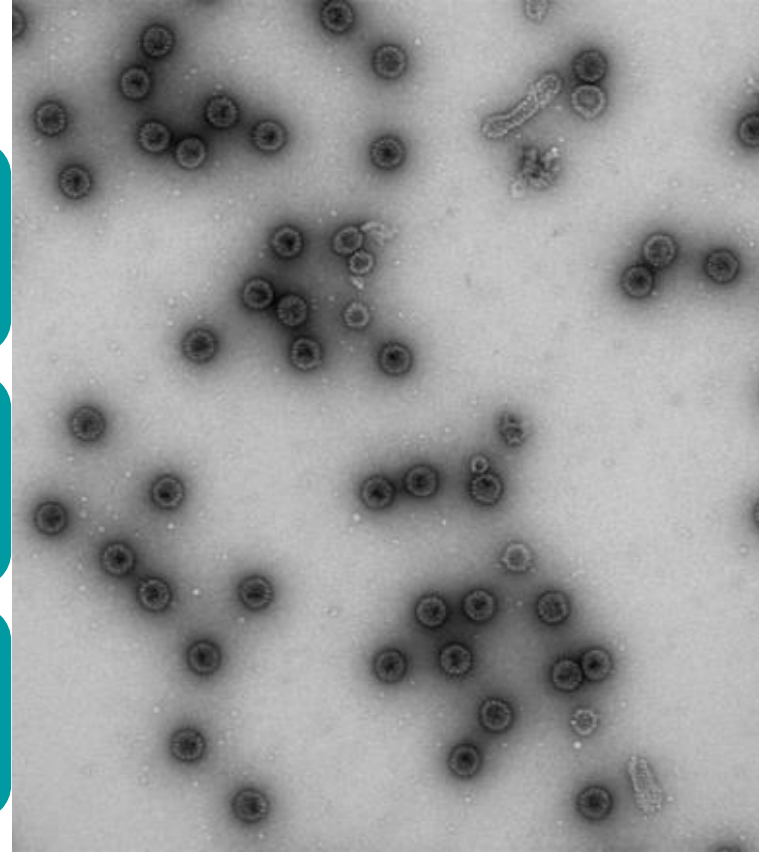
Cervical Cancer Screening

HPV SUBTYPES

45 mucosal/genital subtypes

high risk : HPV - 16, 18, 31, 33, 35,
39, 45, 51, 52, 56, 58, 59, 66, 68

low risk: HPV - 6, 11, 40, 42, 43,
44



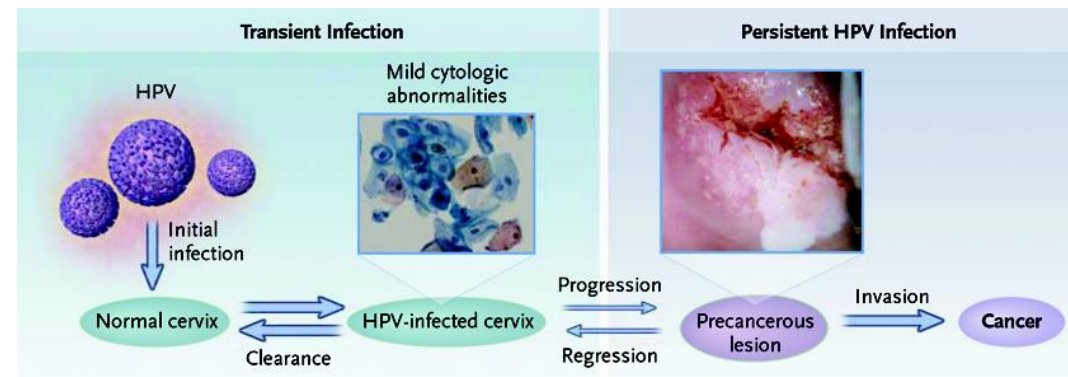
HPV(HIGH RISK) NATURAL HISTORY

-3–8-month incubation period

-80% cleared in 12 months

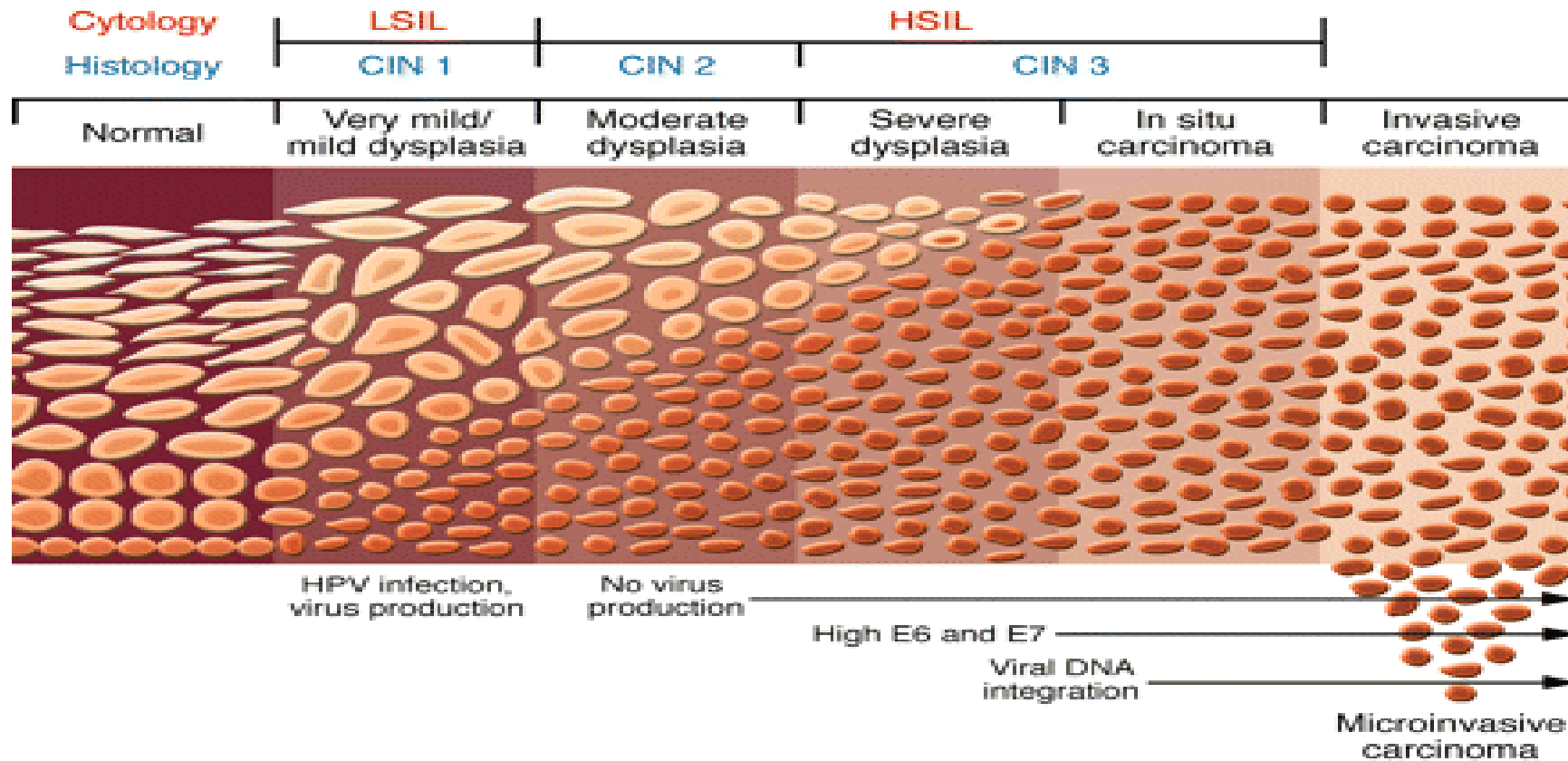
-95% cleared by three years

Less than 1% of all HPV high risk infections lead to invasive cancer-



Cervical Cancer Screening

Preinvasive Disease





Cervical Cancer Screening

Techniques of Screening

- Physical Exam
- Visual Inspection with Acetic Acid
- Pap Smear
- HPV Testing
- Cervical Biopsies

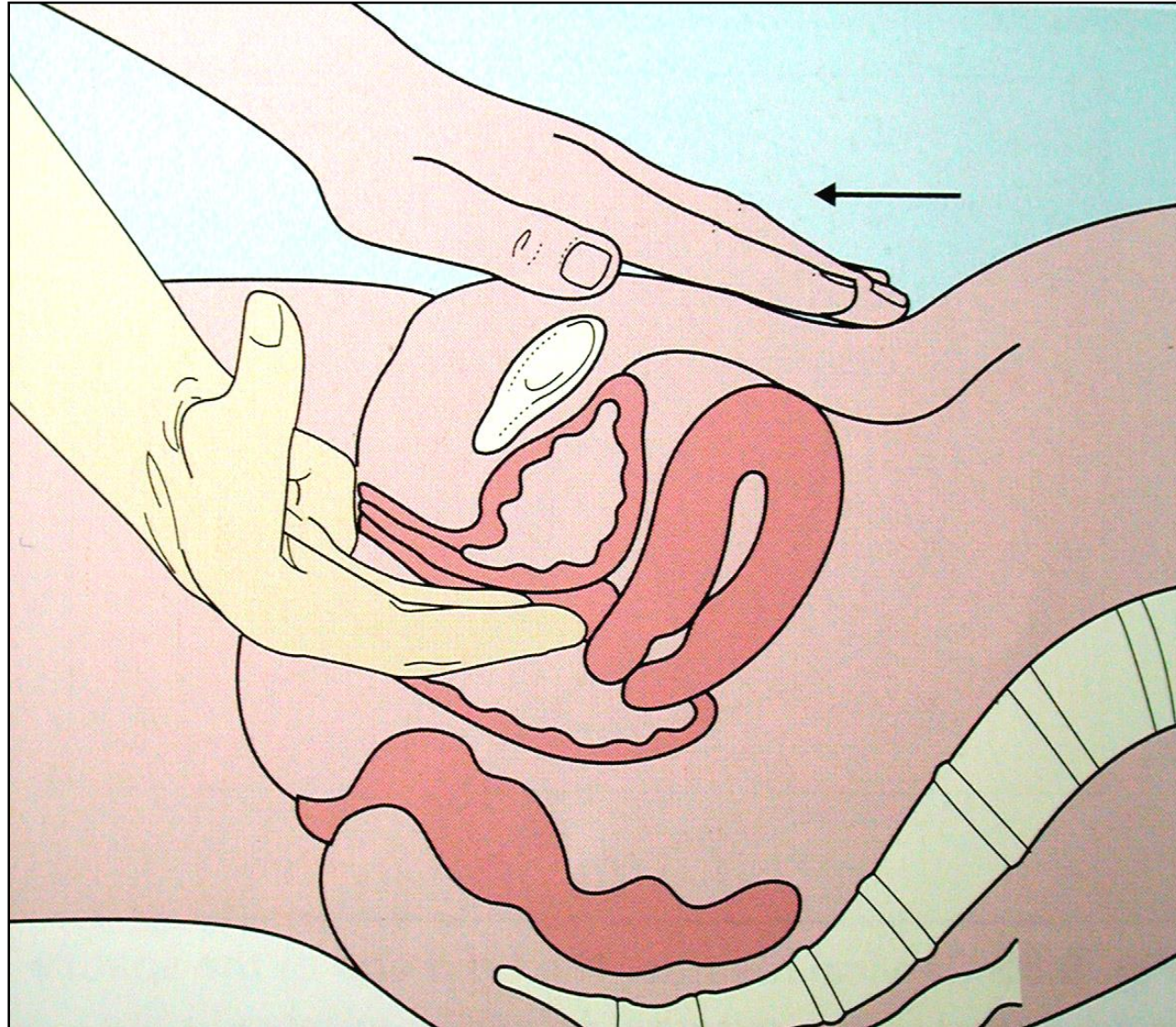


Techniques of Screening Physical Exam

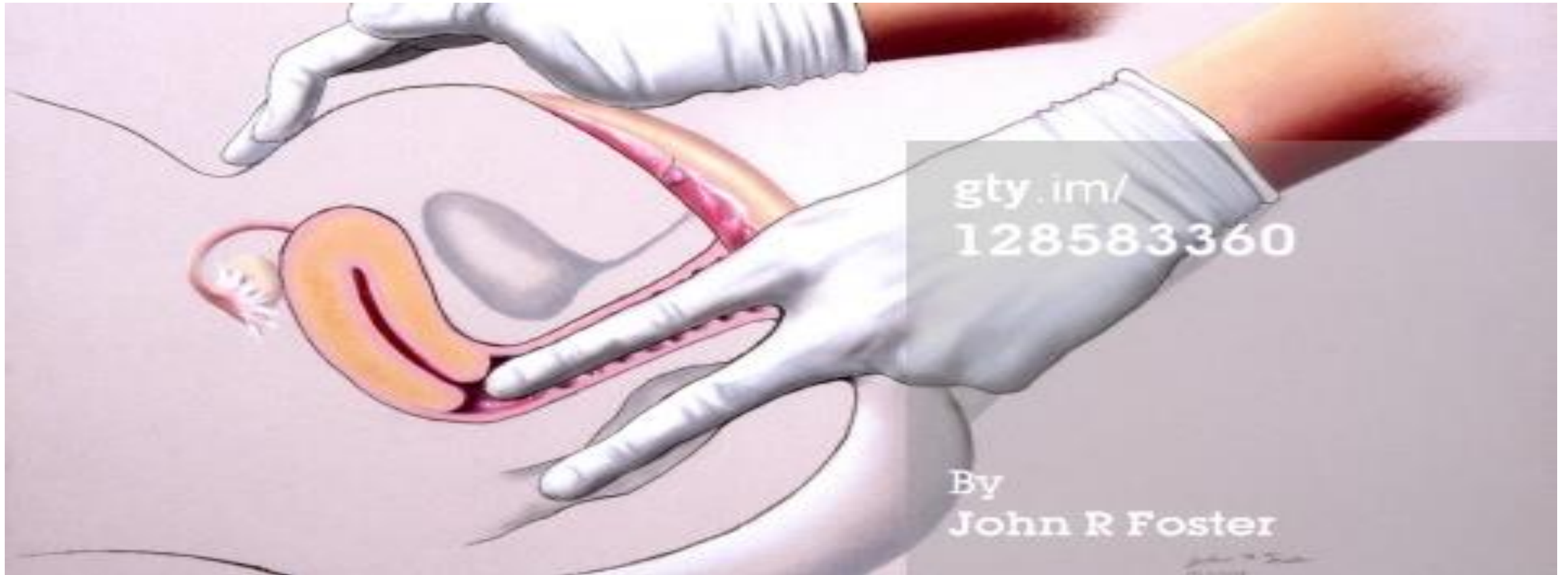
Examine	Visually examine the vulva and perianal region
Insert	Insert the speculum into the vagina
Examine	Visually examine the cervix and the walls of the vagina
Palpate	Palpate the cervix and the walls of the vagina.
Palpate	Palpate the parametria and uterosacral ligaments by rectovaginal exam



Position of the uterus



Rectovaginal exam



Techniques of Screening Pap Smear

With a spatula, rotate the spatula 360 degrees around the exocervix

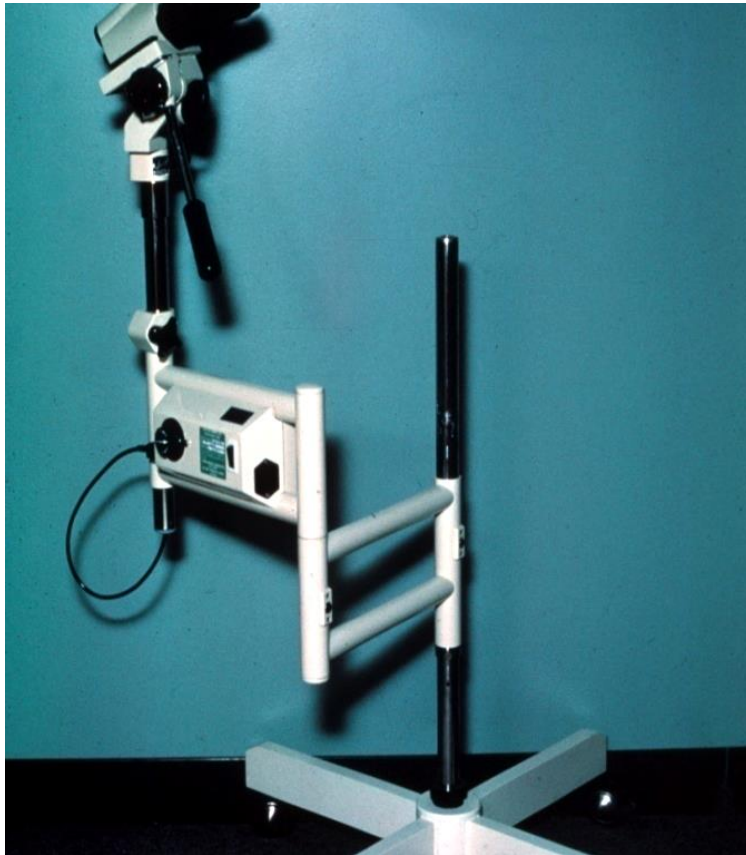
With a cytobrush, place the brush within the endocervix and rotate 360 degrees

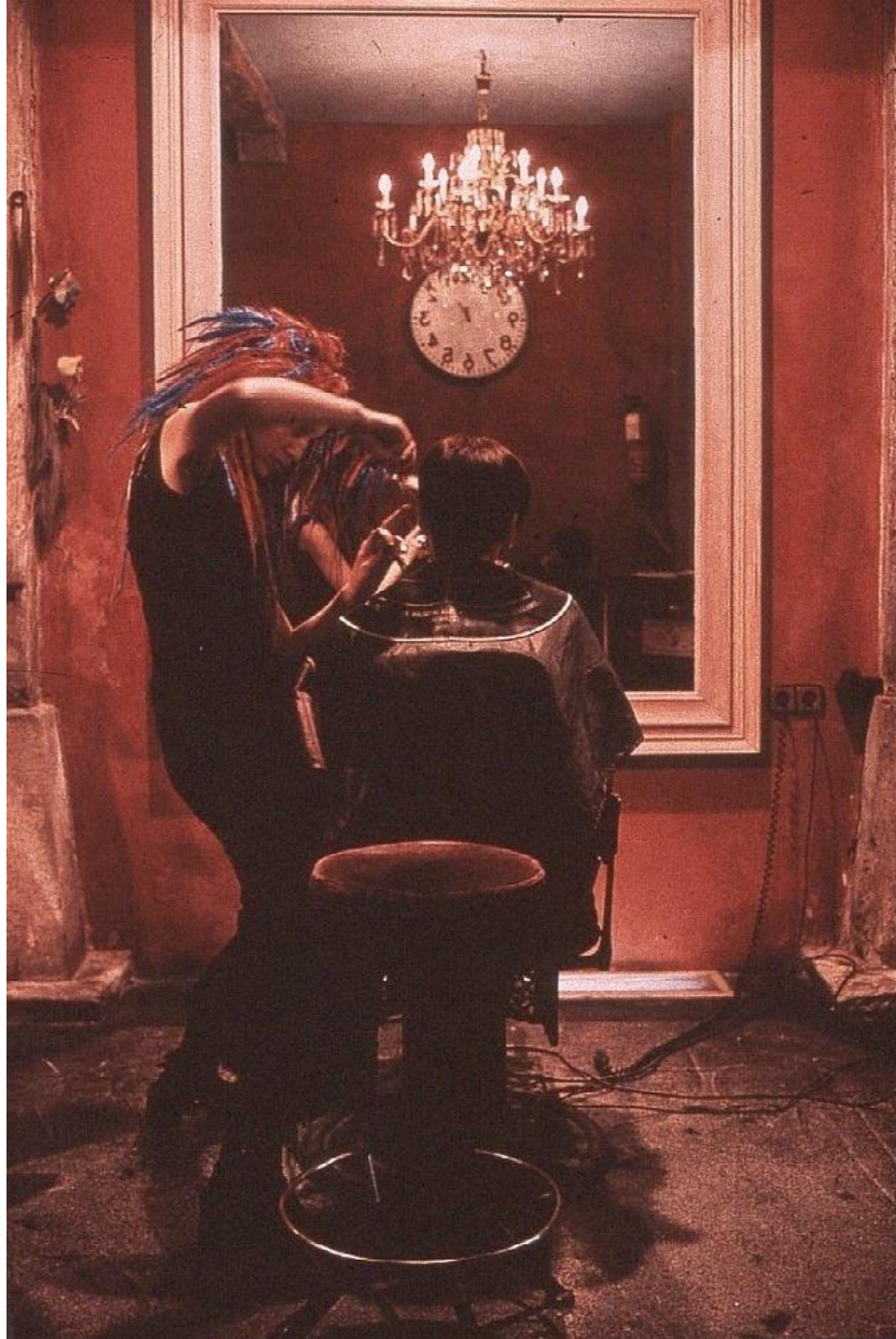
Apply both the spatula and cytobrush to a slide and then apply fixative

Or place spatula and cytobrush into liquid-based solution and break off the tips



Techniques of Screening Colposcopy & Cervical Biopsies





Guidelines History – pre-2001*

Annual Pap testing

- Possibly spacing out after > 2 negative tests

Colposcopy for any abnormality

Guidelines reflect a combination of ACS, ACOG, ASCCP, USPSTF guidelines



Guidelines – 2001- 2012*

2001 ASCCP Consensus Management Guidelines:

- 12 pages
- 8 pages of actual text
- No figures

Screening using cytology alone or cytology + HPV testing

Management

- NILM/HPV+
- ASC then HPV testing + vs –
- HSIL then colposcopy vs “see and treat”

Treatment

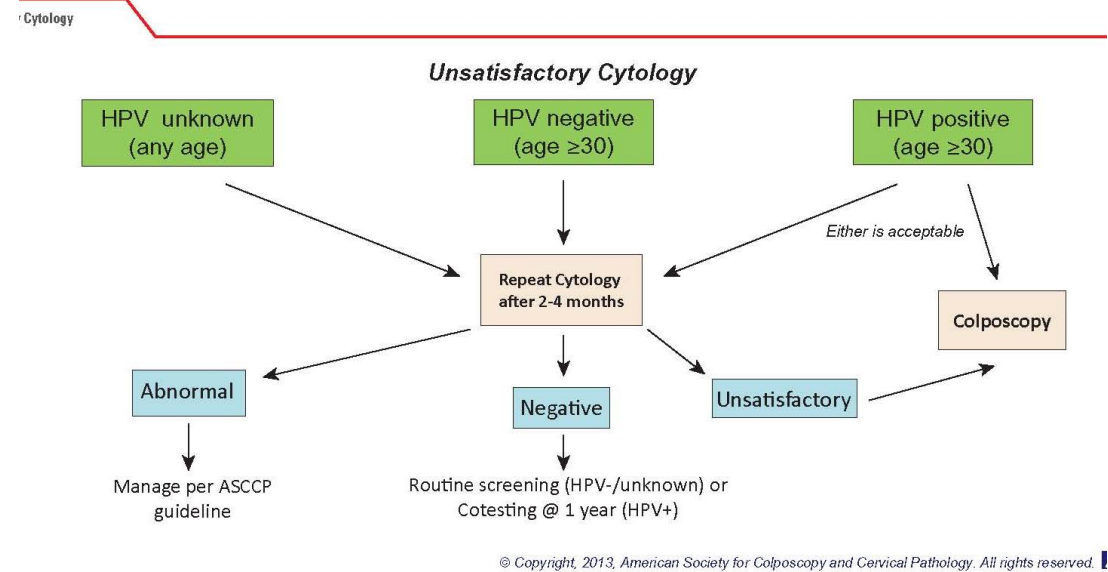
- High grade
- Pap/ colposcopy discrepancy
- AIS adenocarcinoma in situ



Guidelines –2012*

2012 ASCCP Consensus Management Guidelines:

- 27 pages
- 22 pages of actual text
- 18 figures



Screening using cytology or cytology + HPV

Increasing interval of screening

Management /Treatment

ASC/LSIL in patients <25

LSIL & HPV testing

CIN2/3 management



Guidelines reflect a combination of ACS, ACOG, ASCCP, USPSTF guidelines

Guidelines 2019 (2020)

8 individual articles

11 pages explaining the statistics

30 pages of actual guidelines

- 25 pages of text
- 13 figures

applies **ONLY to individuals with a cervix who do not have any signs or symptoms of cervical cancer*

***DOES NOT APPLY** to high-risk individuals*

-dx of precancerous lesion

-in utero exposure to DES

-immunocompromised individuals

Population*	Recommendation
Aged less than 21 years	No screening
Aged 21-29 years	Cytology alone every 3 years
Aged 30-65 years	Anyone of the following --Cytology alone every 3 years --FDA-approved primary high-risk HPV testing alone every 5 years --cotesting (HPV & cytology) every 5 years
aged greater than 65 years	No screening after adequate negative prior screening results
Hysterectomy with removal of the cervix	No screening in individuals who do not have a history of high grade cervical precancerous lesions or cervical cancer



Objectives

Understand

Understand how HPV epidemiology drives risk-based cancer prevention

Learn

Learn fundamentals of risk-based guidelines for managing patients

Understand

Understand why risk-based management represents an improvement in care



How Were the Guidelines Created?

Took 2 years

Representatives from multiple organizations are recruited

Workgroups formed (treatment, colpo, surveillance, risk modification, etc.)

Phone meetings

In person meetings

Voting

Writing

publishing

4 Patient Advocacy Organizations
Federal Agencies

- CDC
- NCI

13 Medical Professional Societies



New Terminology

Inclusivity

“individuals with a cervix”

“patients with concerns about the effect of treatment on future pregnancy”

The Data

Where does it come from?

How do we know it is applicable across the spectrum of patients

Model building

- What to include?

HPV infection



What Data Were Used/ How Do We Know They Are Representative?

Kaiser Permanent Northern California Data (KPNC)

Validation of risk & risk-based management with other cohorts (New Mexico; CDC; BD Onclarity trial)

Largest/longest real clinical experience with HPV-based screening in the world

- Over 1.5 million patients with routine co-testing from 2003-2017
- HPV genotyping for approximately 19,000 patients

Provides risk-based evidence for most of the common decision points that occur in screening

- Long length of follow-up allows use of past history for more personalized management

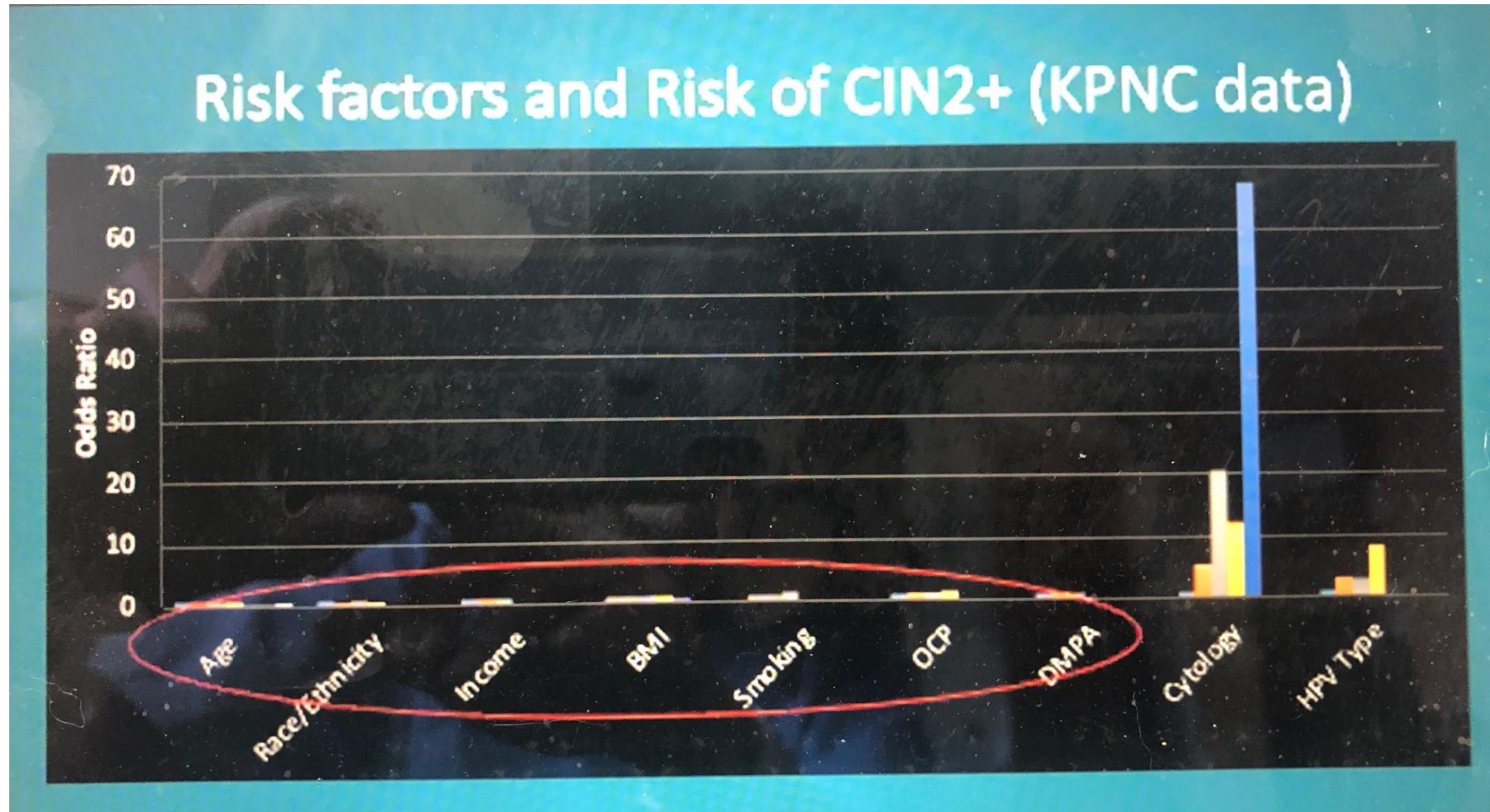
Cheung LC et al J Low Genit Tract Dis 2020; 24(2): 90-101



Free Version of Guidelines
<https://www.ascp.org/mobile-app>



Which Risk Factors Influence pre-cancer development?



Fundamental Concept #1

Persistent HPV Infections is important

The longer an HPV infection has been present, the higher the risk of pre-cancer and cancer

- Time matters
- Type matters (HPV 16 most dangerous)
- Other patient factors don't matter if you know about HPV
- CLINICAL CORRELATE: Colposcopy is always needed following two consecutive positive HPV tests



Applying the Data – “Guiding Principles”

Is Immediate CIN 3 risk 4% or Higher?

- Yes
 - Look at immediate CIN 3 risk for management
 - Expedited treatment (60-100% risk)
 - Expedited treatment or colposcopy acceptable (25-60% risk)
 - Colposcopy recommended (4-24% risk)
- No
 - Look at 5-year CIN 3 risk for management
 - Return in one year ($> 0.55\%$ risk)
 - Return in 3 years ($> 0.15\%$ risk)
 - Return in 5 years ($< 0.15\%$ risk)

Equity

Safety

- Focus resources
- Avoid loss to follow-up
- Avoid unnecessary procedures

Enduring



Fundamental Concept # 2:

Management is based on risk, not results

Establish a risk threshold for colposcopy and treatment options

In past , management based on results, for instances: all ASCUS/HPV+ goes to colposcopy

Two basic thresholds:

- Screening intervals
- Referral to colposcopy



Surveillance Intervals in 2019 Management Guidelines

Goal = simplicity and excellent care

No compelling reason to change intervals

Providers are familiar with 1, 3 and 5-year follow-up intervals

Health systems/tracking features built around these intervals



ASSUMPTION: Intervals for retesting should reflect underlying risk (equal management for equal risk)

Define	Define surveillance intervals
Define	Define threshold to release patients back to general population screening
Define	Define risk thresholds for short interval follow up at 1 and 3 years
Determine	<p>Determine which tests to use for surveillance and at what intervals</p> <ul style="list-style-type: none">•HPV alone•HPV/cytology contesting•Cytology (Pap alone)



Where do these thresholds come from?

Prior Guidelines

ASCUS/HPV+ or LSIL

Negative Cytology

Negative HPV testing (no prior history)

Follow-up

Colposcopy

3-year follow-up

5-year follow-up



Where do these thresholds come from?

Prior Guidelines

ASCUS/HPV+ or LSIL

- Immediate Risk CIN 3 : 4%

Negative Cytology

- 5-year risk CIN 3: 0.33-0.55%

Negative HPV testing (no prior history)

- 5-year risk CIN 3: 0.12-0.14%

Follow-up

Colposcopy

3-year follow-up

5-year follow-up



Patients Stratified by Risk

Is Immediate CIN 3 risk 4% or Higher?

- Yes
 - Look at immediate CIN 3 risk for management
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 - Return in one year ($> 0.55\%$ risk)
 - Return in 3 years ($> 0.15\%$ risk)
 - Return in 5 years ($< 0.15\%$ risk)



2019 Management Guidelines Colposcopy Threshold

When individuals have an estimated immediate risk of diagnosis of CIN3+ of 4.0% or greater based on prior history and current results, referral to colposcopy is recommended



30-year-old with no prior screening is found to have ASCUS/HPV+ screening

2012 guidelines

colposcopy

2019 guidelines

HPV	Pap	Immediate Risk of CIN3+	Recommendation
Pos	LSIL	4.3%	colposcopy
Pos	ASC-US	4.4%	colposcopy

Expedited treatment (60-100% risk)

Expedited treatment or colposcopy acceptable (25-60% risk)

Colposcopy recommended (4-24% risk)



30-year-old with negative HPV on prior screening is found to have ASCUS/HPV+ screening

2012 guidelines

colposcopy

2019 guidelines

HPV	Pap	Immediate Risk of CIN3+	Recommendation
Pos	LSIL	2.1%	1 year follow-up
Pos	ASC-US	2.0%	1 year follow-up

Return in one year (> 0.55 % risk)

Return in 3 years (> 0.15% risk)

Return in 5 years (< 0.15% risk)





Clinical Situation



Testing



Recommendation

Age

Under 25
YEARS**25 to 29**
YEARS**30 to 65**
YEARS**Over 65**
YEARS

Clinical Situation

Management of routine screening results >

Return visit during pre-colposcopy surveillance >

Evaluation of a colposcopic biopsy >

Management of results during post-colposcopy surveillance >

Follow-up after treatment >

Special situation: Rarely screened patients >

Special situation: Symptomatic patients >

Special situation: Immunosuppressed patients >

Next >

55-year-old with no prior screening is found to have LSIL/HPV negative screening

2012 Guidelines

1 year follow-up

2019 Guidelines

HPV	PAP	Immediate risk of CIN3+	5 year risk of CIN3+	Recommendation
negative	LSIL	1.1%	2%	1 year follow-up

Return in one year (> 0.55 % risk)

Return in 3 years (> 0.15% risk)

Return in 5 years (< 0.15% risk)



55-year-old with no prior screening is found to have LSIL/HPV negative screening -2019 Guidelines

HPV	PAP	Immediate risk of CIN3+	5-year risk of CIN3+	Rec	5-year risk of CIN3+	Rec
		Unknown prior HPV status	Unknown prior HPV status		Prior neg HPV	
negative	LSIL	1.1%	2%	1 year follow-up	0.25%	3-year follow-up

Return in one year (> 0.55 % risk)

Return in 3 years (> 0.15% risk)

Return in 5 years (< 0.15% risk)



Follow up - Colposcopy

2012

- 40-year-old with LSIL/HPV+
- Colposcopy: Endocervical curettage – CIN 1
- RTC co-testing in 1 year: ASCUS/HPV+
- RECOMMEND: Repeat colposcopy

2019

- With low grade pap and colposcopy showing less than CIN2
- And repeat co-testing showing ASC-US
- Immediate CIN 3 risk is 3.1%
- 5-year CIN 3 risk is 6.0 %
- RECOMMEND: 1 year follow-up

Return in one year (> 0.55 % risk)

Return in 3 years (> 0.15% risk)

Return in 5 years (< 0.15% risk)



Immediate & 5-Year Risks of CIN3+ Post-colposcopy at which CIN2+ was not found, after referral for low grade results

Egemon et al J Lower Genital Tract Disease 2020

Current HPV	Current cytology	Number of patients = N (%)	CIN 3+ cases	CIN3+ immediate risk/ 5-year risk	Recommended management (confidence score %)
negative	NILM	32,361 (55)	56	0.00 / 0.42	3-year follow-up (99)
negative	ASC-US/LSIL	2,937 (5)	14	0.05 / 0.92	1-year f/u (93)
negative	High grade	149 (0.25)	4	1.6 / 4/1	colposcopy
negative	ALL (HPV negative)	35,603 (60)	74	0.01 / 0.51	3-year f/u (73)
positive	NILM	9,352 (16)	272	2.1 / 5.2	1-year f/u (100)
positive	ASC-US/LSIL	12,843 (22)	445	3.1 / 6.8	1-year f/u (100)
positive	High grade	1,294 (2.2)	276	23 / 31	Colposcopy (94)
	TOTAL	58,936 (100)	1,067		



Safer: Avoid Unnecessary Procedures In Low-Risk Patients

Colposcopy with Biopsy of the cervix is based on risk, not just test results
Avoid the pain, anxiety, and resource utilization in low-yield colposcopies



Define High Risk Patients to Focus Resources

- Histologies HSIL (CIN2+) on biopsy remains the threshold for treatment in the general population
- CIN 3 should always be treated (except in pregnancy)
- CIN 2 has the option of treatment or observation with colposcopy/biopsy in those concerned with treatment effects on future pregnancy



High Risk Patients

High-grade cytology with HPV 16 infections are highest risk

- >75 % risk of any precancer (CIN 2 or histologic HSIL)
- >60 % risk of highest grade precancer (CIN3+)

Recommendation: Expedited treatment

- See and treat
- Treating without requiring colposcopy with confirmatory biopsies



High Risk

Is Immediate CIN 3 risk 4% or Higher?

- Yes
 - Look at immediate CIN 3 risk for management
 - Expedited treatment (60-100% risk)
Expedited treatment or colposcopy acceptable (25-60% risk)
 - Colposcopy recommended (4-24% risk)

Immediate Risk of CIN 3+	Recommendation	Examples
<25%	Level below which colposcopy & biopsy is preferred	ASCUS/HPV+ LSIL/HPV+
>25%-59%	Immediate* excisional treatment or treatment after confirmatory biopsies are acceptable	HSIL?HPV+ (49%) HSIL/HPV- (25%) ASC-H/ HPV+ (26%)
>60%	Immediate* excisional treatment is preferred ; treatment after confirmatory biopsies are acceptable	HSIL, HPV 16+ (60%)

**Not recommended for patients younger than age 25 or currently pregnant*



Guidelines Enduring: Designed to accommodate future changes

Reduced Cervical Cancer

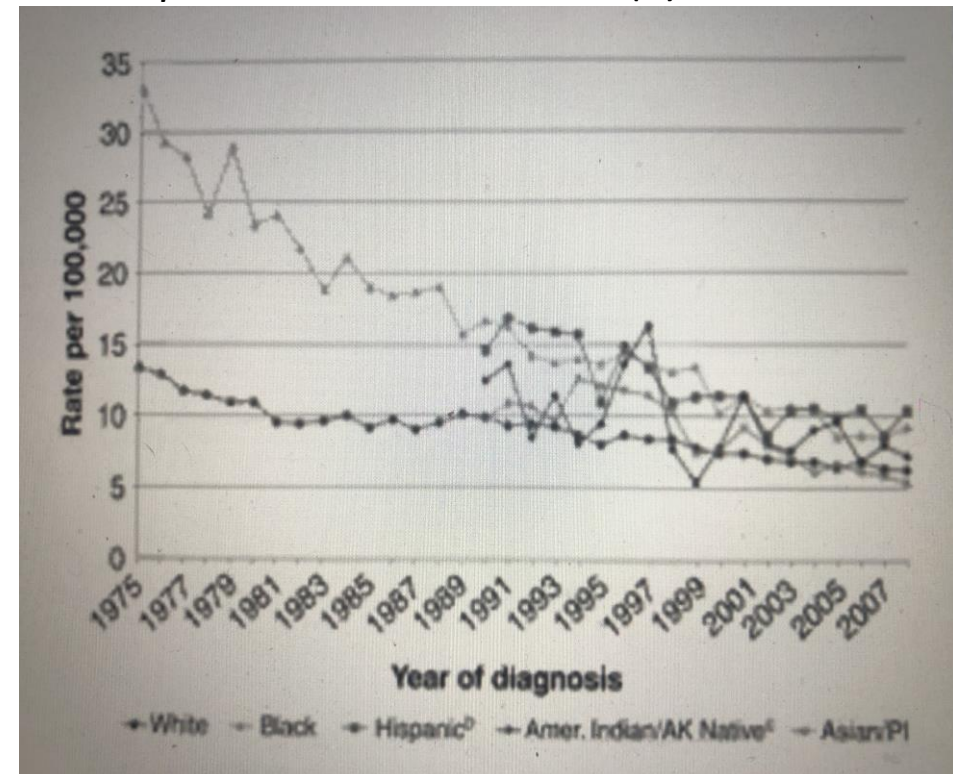
Programs based on cervical cytology (Pap tests) with colposcopy have been very successful

Risk of LSIL decreases with prior negative HPV test

The risk of malignancy may vary differently based on HPV vaccine status

Cervical Cancer Rates in USA

Pierce Campbell et al 2012 CEPB 21(9): 1402



Enduring: defined risks for referrals to colposcopy and treatment based on successful historical standards

2019 Guidelines Framework designed to preserve cancer prevention while decreasing unnecessary colposcopy in the setting of

- Decreasing CIN 3+ prevalence as vaccinated populations age into screening cohorts
- Decreasing CIN3+ prevalence as populations undergo multiple rounds of HPV-based screening



2019 Guideline Changes in Screening/ Surveillance

All positive HPV tests should have additional reflex triage cytology performed from the same laboratory specimen

- Allows for more accurate determination of immediate CIN 3+ risk
- Determines eligibility for expedited treatment

HPV based testing is preferred

- Cytology is acceptable if HPV testing is unavailable

HPV based testing interval	Cytology alone Interval
1 year	6 months
3 years	1 year



2019 Changes to Treatment Recommendations

2012

CIN2, CIN 3, and adequate colposcopy: both excision & ablation are **acceptable** treatment modalities

If CIN 1 persists for at least 2 years, either continued follow-up or treatment is **acceptable**

2019

Excision treatment is **preferred** to ablative treatment for histologic HSIL (CIN 2, CIN 3) in the United States

With histologic LSIL diagnosed at consecutive visits for 2 years, observation is **preferred** but treatment is **acceptable**



2019 Changes to follow-up after treatment of CIN 2/3

- HPV-based testing at 6 months (Best predictor of recurrence), if negative then annually for 3 years
- Continued surveillance with HPV testing or co-testing at 3-year intervals for at least 25 years
- Continued surveillance at 3-year intervals beyond 25 years is acceptable for as long as the patient's life expectancy and ability to be screening are not compromised due to serious health issues



HPV Vaccination: Important but NOT included (yet) in screening guidelines

HPV vaccination prior to age 18 reduces the CIN3+ risk by 50%

HOWEVER: 2015 was the first time that 50% of those age eligible to receive first dose of vaccine

These patients are just reaching their early 20s, a group already conservatively managed

Documentation of vaccine status and age of vaccination is challenging

Vaccination will likely impact age to start screening in the future



By The Way: The over 65-year crowd...

Mills et al “Eligibility for cervical cancer screening exit” Gynecol Oncol 2021

Ages greater than 65: No Further Pap Smear Testing **ONLY IF**

- who have had > 3 consecutive normal pap tests
- or > 2 consecutive negative HPV tests and pap tests in last 10 years with the most recent pap occurring within the last 5 years
- or women who have had hysterectomies for benign disease

Most older women do not meet criteria to stop cervical cancer screening

Analysis of national insurance claims: only 22% of 600,000 women met criteria to stop screening

- 37% had too few screens to meet exit criteria
- 21.5% had medical or screening history that precluded screening exit

No patient should ever discontinue screening based on age alone without their HCP completing a thorough review of records



SUMMARY: 2019 Management of Screening Results

There are Six Categories

Immediate risk of
CIN 3+ > 60%

Immediate risk of
CIN 3+ 25% -60%

Immediate risk of
CIN 3+ 4-25%%

5-year risk of CIN3+
<0.15%

5-year risk of CIN3+
0.15 –
0.55%

5-year risk of CIN3+
>0.55%

Use website or app
to calculate risk



Thank You!!

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<https://www.massgeneral.org/obgyn/research/strength-and-serenity>

