

# Cervical Cancer Screening

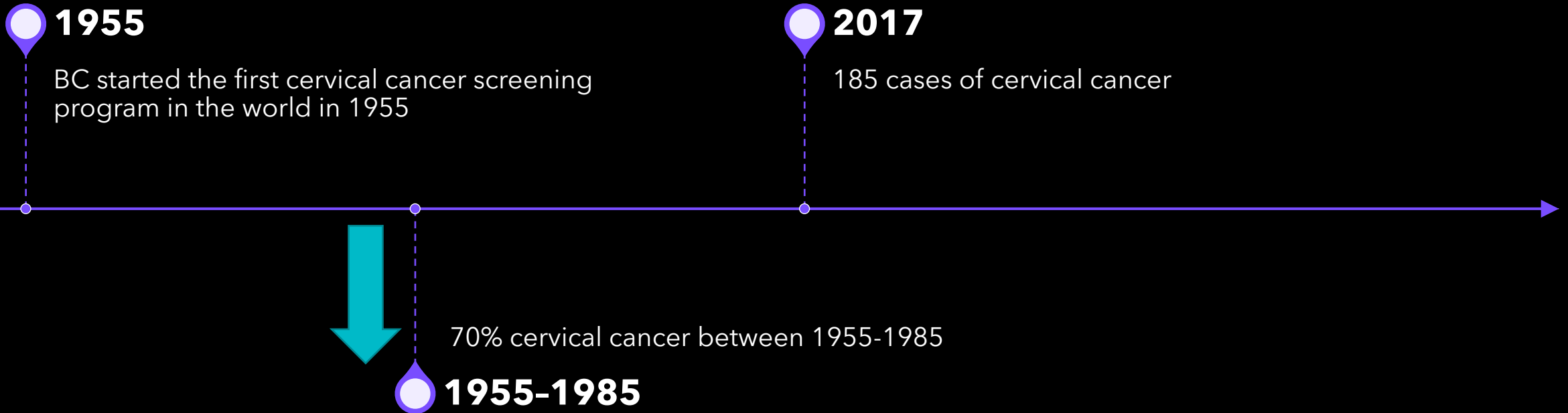
HOW SHOULD WE SCREEN?



# 3 Cases:

- 22 year old- post coital bleeding, unusual appearance to her cervix
- Never had a pap smear, not vaccinated against HPV
  
- 42 y.o. G3P3, Obese, T2DM-
- pap AGC- NOS
  
- 56 yo. Hx of warts, kidney transplant, long list of meds including immune modulators -
- Pap shows ASC-H

# BC History



# HUGE SYSTEM



# HUGE SYSTEM

325000 paps  
per year

Vancouver-  
then every  
health authority

Labs

QI

QA

Recall letters

# When does screening work?

- Ability to DX preinvasive lesions
- Tx is available
- Time from preinvasive lesion to cancer is slow
- The disease is COMMON enough

# Pros/Cons of Screening

## **BENEFITS**

Reduce severity of  
disease and treatments

Reduce incidence

Reduce deaths

## **HARMS**

Overdiagnosis/  
Overtreatment


False Negatives

False Positives

COST- diverting health  
resources

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# What is a pap smear?

A microscopic view of a Pap smear showing various cervical cells. The image displays a variety of cell types, including large, flat, squamous cells with distinct nuclei and some smaller, more rounded cells. The cells are stained, with nuclei appearing dark purple and cytoplasm or extracellular material in shades of pink and blue. The background is a gradient of light blue and green.

CYTOLOGY:  
Cells that are taken off  
the top layer of the  
cervix



# Number Needed to Screen to Prevent One Cervical Cancer Case Ontario Population 4.5M

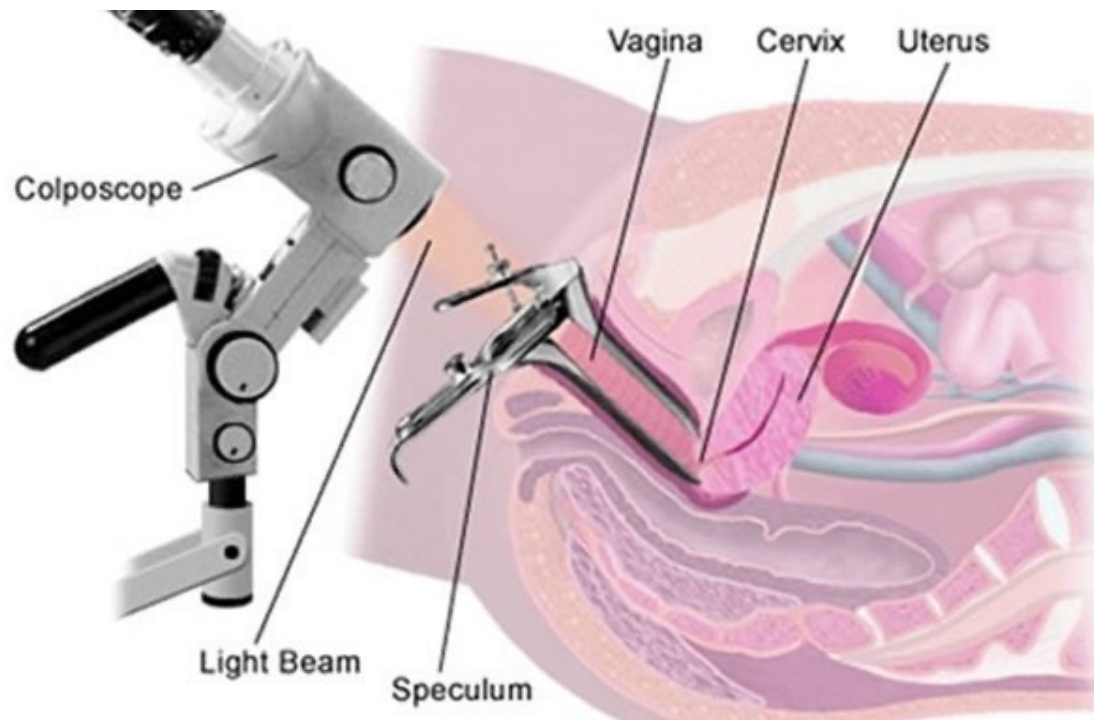
## Number Needed to Screen

Number Needed to Screen by Age Group: 2010-2015

Year	21-29	30-39	40-49	50-59	60-69	All Ages
2010	19,688	3,612	2,514	3,351	4,138	3,973
2011	12,991	4,095	3,724	3,763	4,086	4,624
2012	27,309	5,071	2,802	3,863	5,312	4,885
2013	26,766	5,022	3,663	3,545	6,236	5,330
2014	23,554	5,177	4,203	3,833	5,530	5,592
2015	25,244	3,831	3,817	5,222	6,954	5,676

# How many paps to prevent one cervical cancer?

- Ontario Data
- About 4000-5500 Paps to prevent one cancer



# COLPOSCOPY

- Site directed biopsy that provides HISTOLOGY

# How many COLPOSCOPY appointments to detect one CIN3+

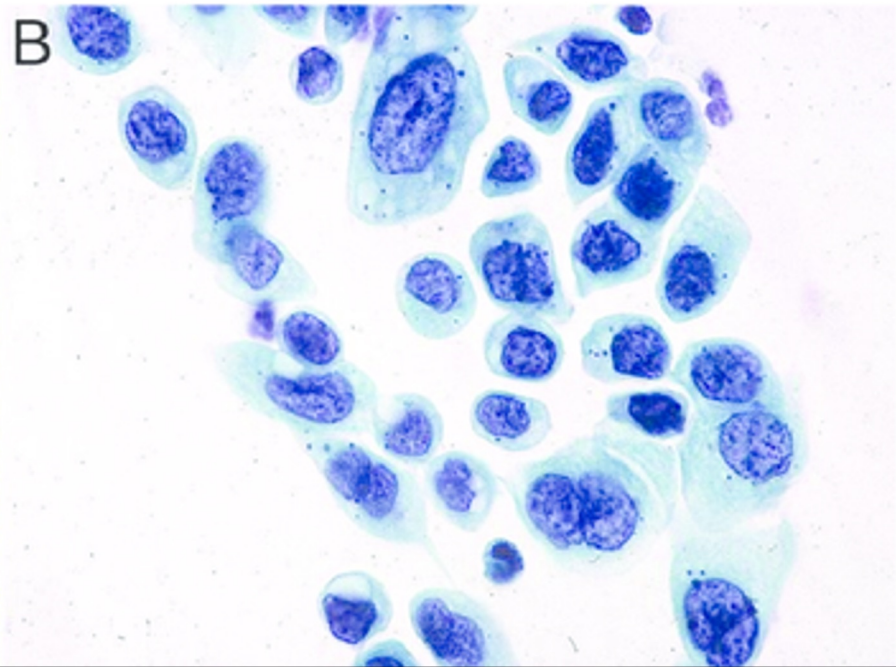
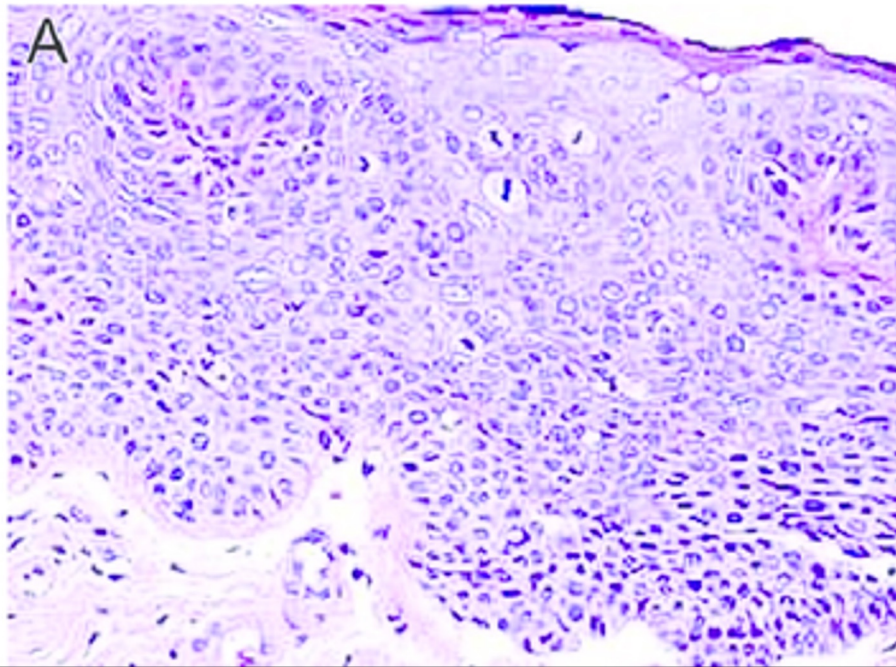
- **NNT:**

- Number of **colposcopies** needed to detect one carcinoma in situ/invasive cancer

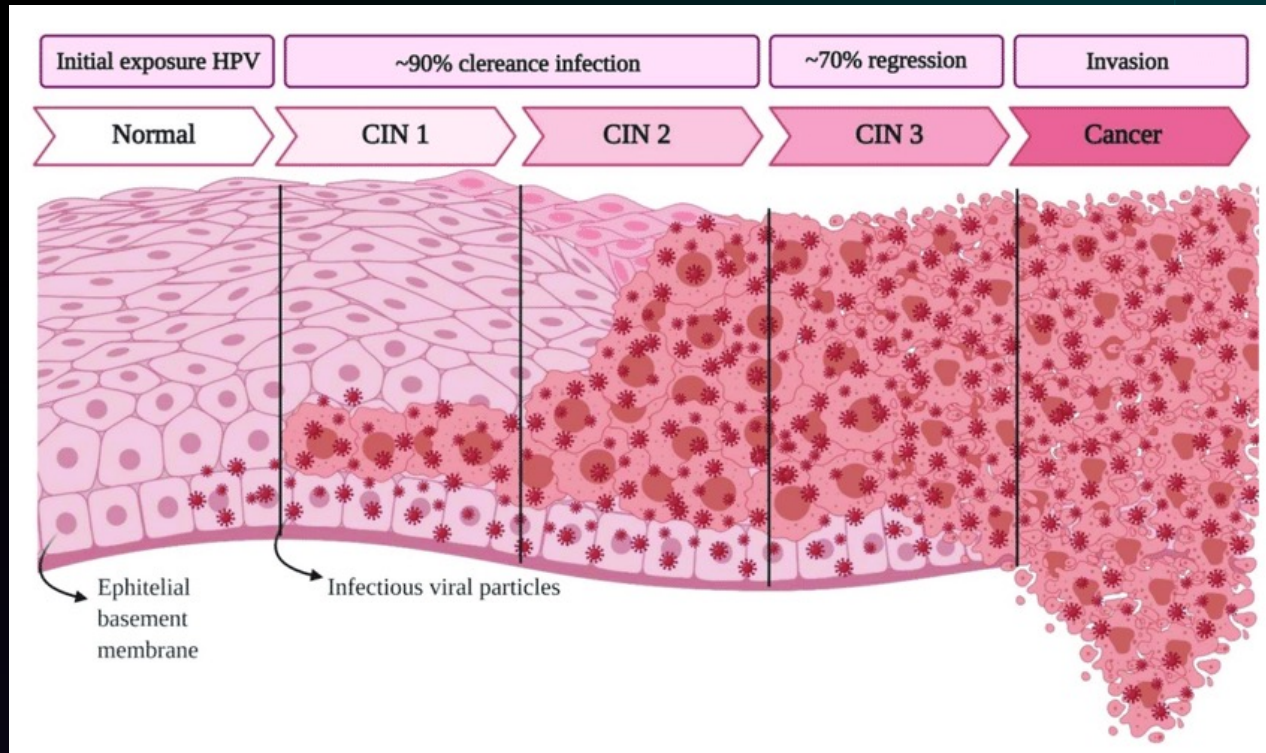
Index ASCUS	Index LSIL
12-20	14

# Histology- full thickness biopsy

CYTOLOGY- EXFOLIATED INDIVIDUAL CELLS



# TERMINOLOGY- So confusing



- ASCUS
- LSIL
- HSIL
- ASC-H
- AGC NOS
- AGC favour neoplasia
- CIN????

We are trying  
to simplify and  
use **ONLY**  
cytology  
terms

**Table 1. Cervical Cytologic and Histologic Terms**

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**Cytology**

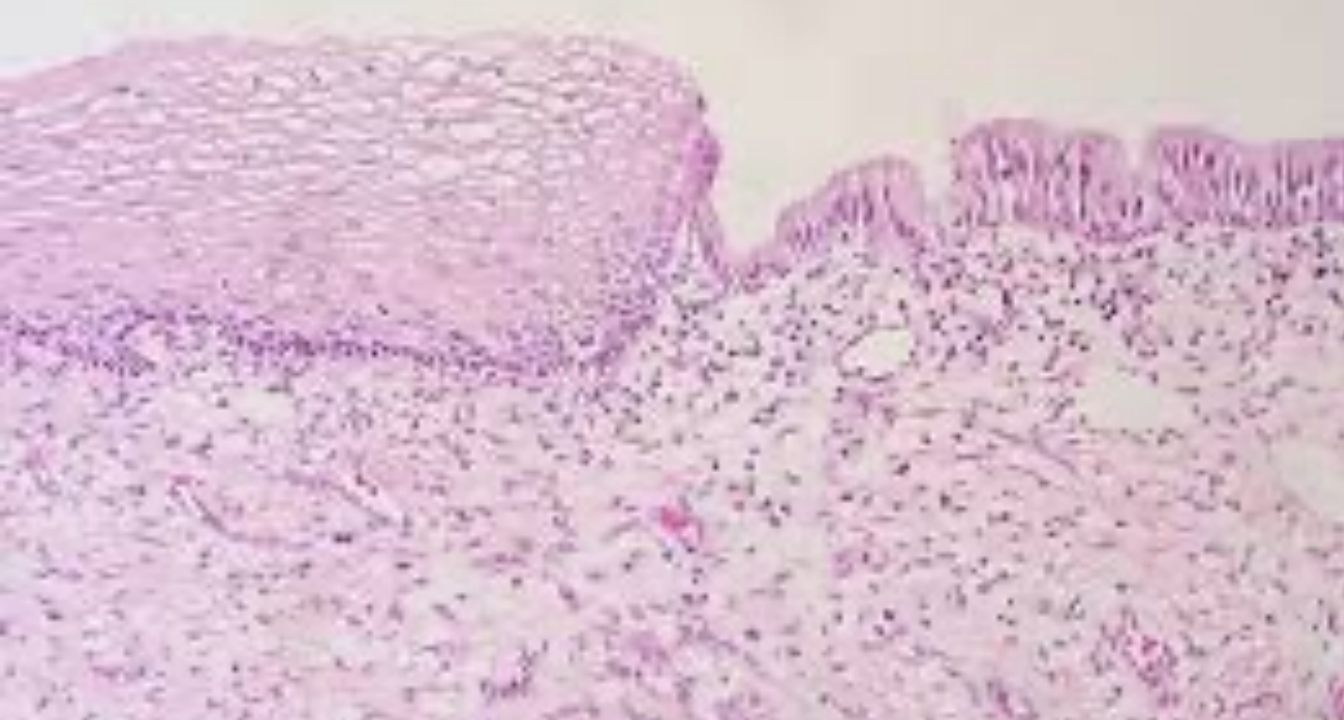
ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells—cannot exclude HSIL
LSIL	Low-grade squamous intraepithelial lesion
HSIL	High-grade squamous intraepithelial lesion
AGC	Atypical glandular cells
AIS	Adenocarcinoma in situ

**Histology**

CIN 1	Cervical intraepithelial neoplasia, grade 1
CIN 2	Cervical intraepithelial neoplasia, grade 2
CIN 3	Cervical intraepithelial neoplasia, grade 3
AIS	Adenocarcinoma in situ

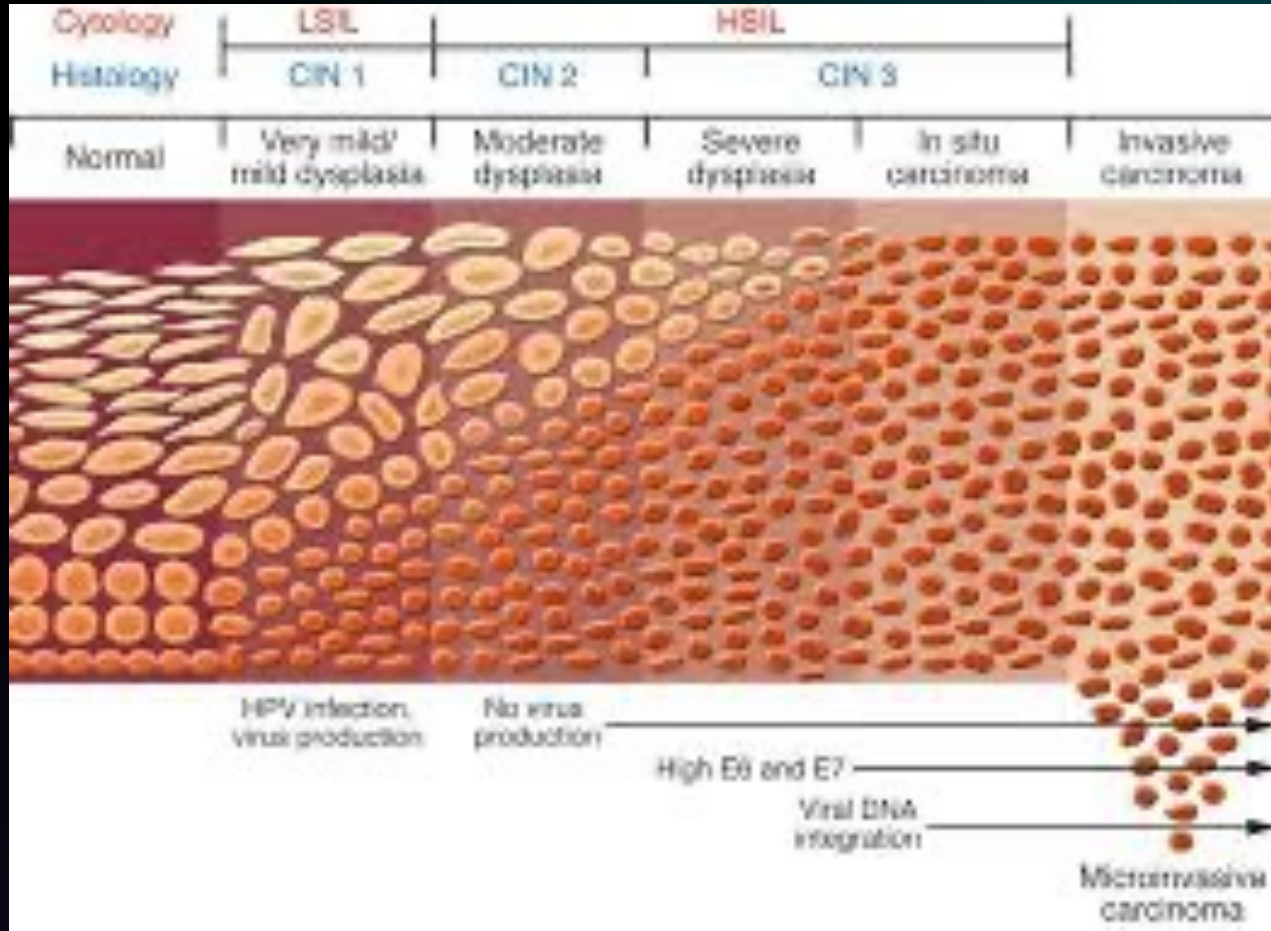
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*Information from references 5 through 8.*



## Transformation Zone

- Where squamous cells transition to glandular cells
- 2 kinds of abnormalities of the cervix
- From these 2 kinds of cells
- Squamous
- Glandular



Squamous  
90%





NO JOB IS FINISHED  
UNTIL THE PAPERWORK  
IS DONE

# If you take a Pap Smear

YOU ARE RESPONSIBLE

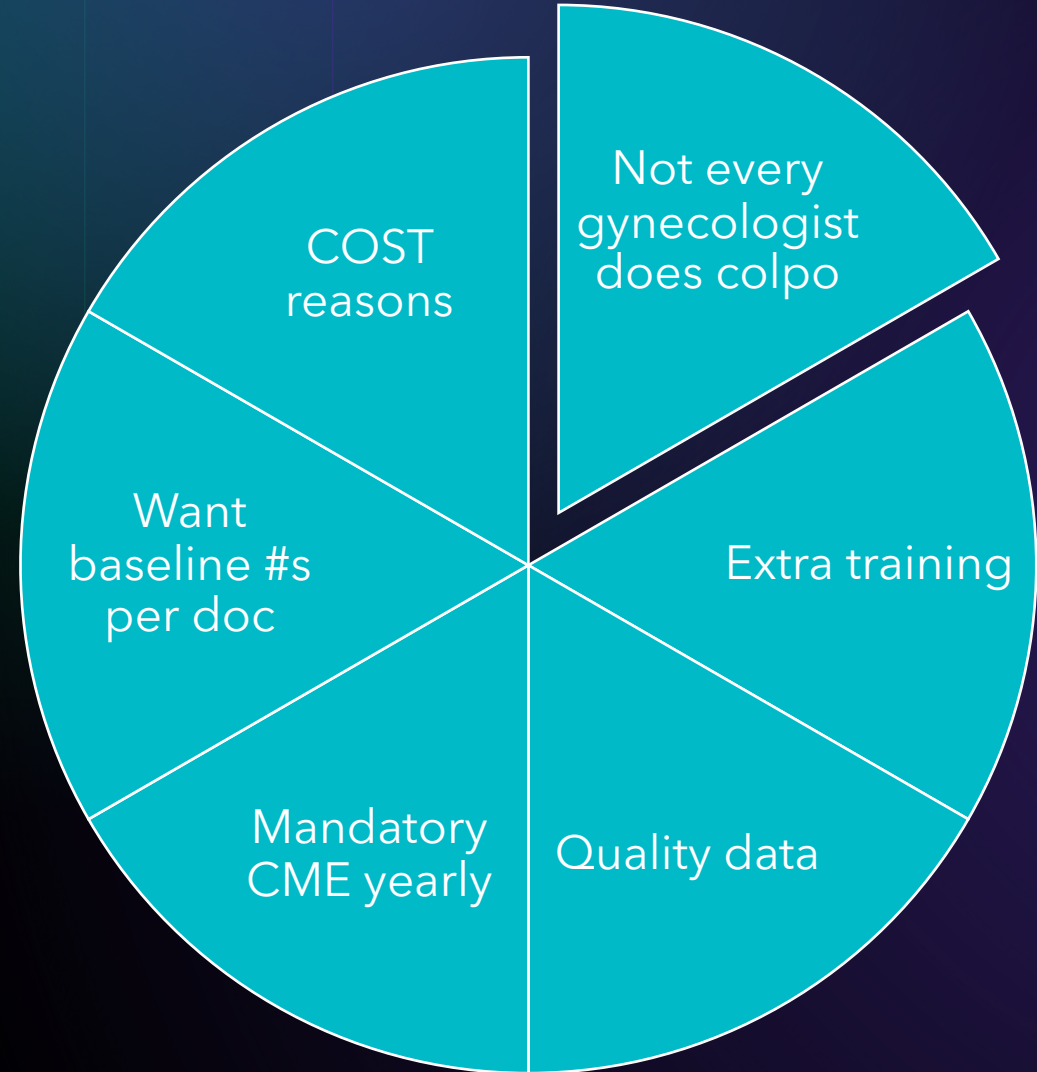
ENSURE RESULT RECEIVED

TELL PATIENT RESULT

COORDINATE ANY FURTHER CARE REQUIRED

RECALL FOR SCREENING AS NEEDED

# COLPO clinics



# Screening

- 25-69
- Any person with a cervix
- Who has ever had sex- genital, oral, digital, penetrative
- With a partner of any gender



# WHY age 25?

- Risk Cx ca by age
- 20 yo -0.5/100 000
- 20-24yo -1.35/ 100 000
- Younger patients often detect cancer by symptoms (postcoital bleeding, constant spotting)
- HARM: detect cin2/3 that would regress and get LEEP



# WHY every 3 years?

**Table 1: Effect of different screening intervals.**

*Effect of Different Screening Policies on Cervical Cancer Incidence, ages 20-64*

<i>Age Range</i>	<i>Interval (years)</i>	<i>Lifetime tests</i>	<i>% Reduction in Incidence of Cervical Cancer</i>	<i>Test per Cervical Cancer Prevented</i>
20-64	1	45	93%	3,030
20-64	3	15	91%	1,042
25-64	3	13	90%	917

Adapted from IARC working group evaluation.<sup>7</sup>



# Why Stop at age 69

- Incidence cervical ca low
- Age expectancy
- Protection of lifetime of screening
- Most women that get cervical cancer after age 65 did NOT participate well in screening over their lifetime

# RESULTS?

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With any pap

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# RISK?

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What is the risk that you  
have precancer now?

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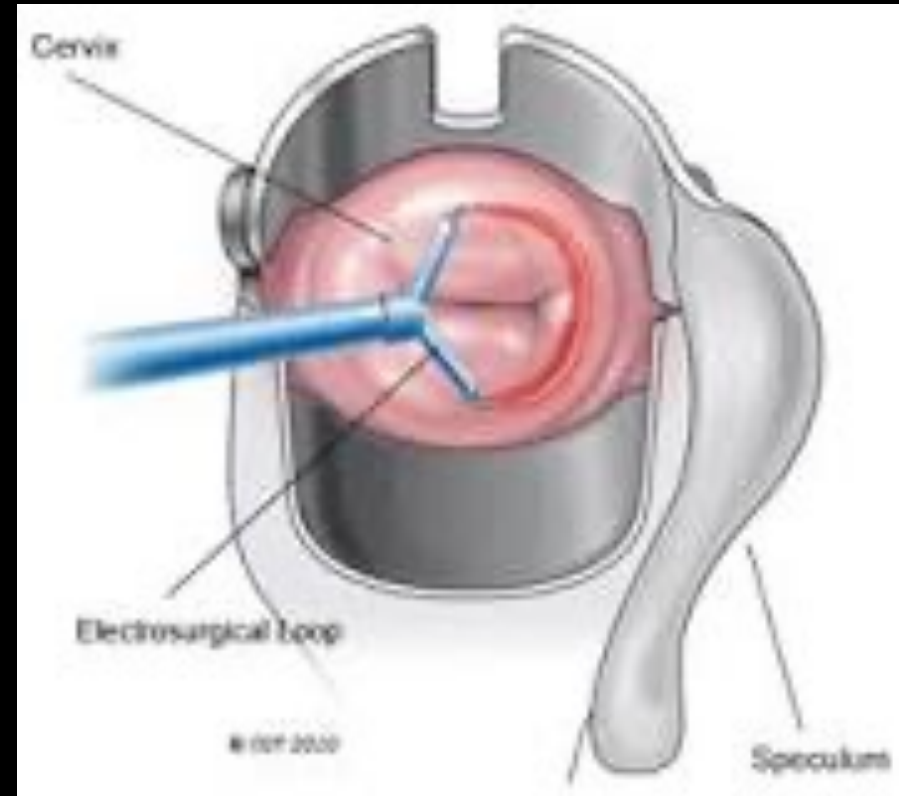
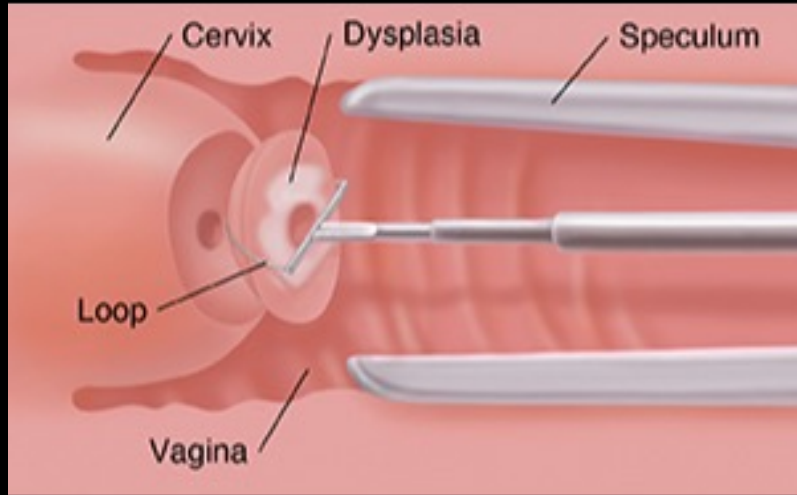
What is the risk you  
have cancer right now?

## 8.13 Summary of Positive Predictive Values of Cytology Results

**Table 4: Positive Predictive Value of Cytology Result**

Cytology Result	PPV for CIN 2, CIN3 or Cancer	PPV for CIN 3 or Cancer	PPV for Cancer
ASCUS	20.20%	9.02%	0.08%
LSIL	27.25%	11.99%	0.05%
ASC-H	53.99%	35.19%	0.90%
HSIL (moderate dysplasia)	67.00%	39.16%	0.42%
HSIL (severe dysplasia)	88.36%	75.35%	4.18%
AGC-NOS	18.60%	14.14%	2.42%
AGC-FN	70.13%	66.23%	23.12%
AIS	81.82%	81.82%	36.36%
Squamous cell carcinoma	90.79%	90.79%	34.21%
Adenocarcinoma	67.86%	67.86%	42.86%





# LEEP- what is it? Risks?

- RISKS OF LEEP
- INFECTION <5%
- BLEEDING <5%
- PRETERM LABOUR

# LEEP

## Cervix Screening Program: Program Overview

**Table 2: Reproductive risk of excisional treatments.**

	Anticipated Absolute effects		Relative Risk
	Risk (per 1000) [Comparison]	Risk (per 1000) [Intervention] (95% CI)	Intervention/ comparison
<i>Pre term birth (&lt;37 weeks)</i>	54	95 (85 - 106)	1.75 (1.57 - 1.96)
<i>Pre term birth (&lt;37 to 34 weeks)</i>	14	32 (26 - 40)	2.25 (1.79 - 2.82)
<i>Pre term birth (&lt;28 to 30 weeks)</i>	3	7 (5 - 11)	2.23 (1.55 - 3.22)
<i>Low birth weight (&lt;2500 gram)</i>	37	66 (58 - 76)	1.81 (1.58 - 2.07)
<i>Perinatal mortality</i>	7	11 (8 - 14)	1.51 (1.13 - 2.03)

Adapted from Kyrgiou et. al. <sup>18</sup>

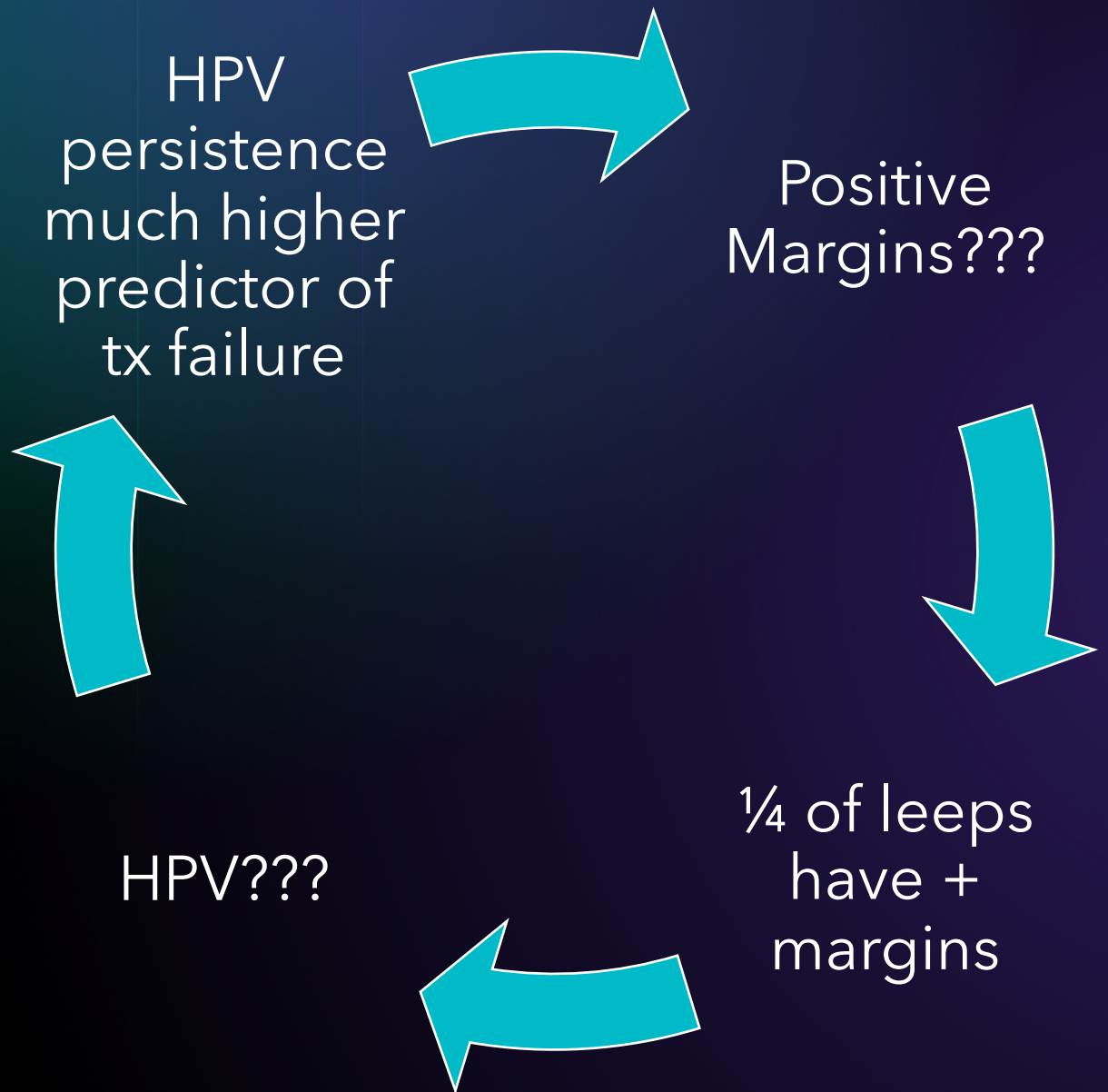
# Recurrence risk

AFTER HAVING YOUR LEEP WHAT  
IS THE CHANCE - YOU HAVE  
PRECANCER AGAIN???

CIN 3  
6.6%

AIS 9%

# Why does it recur???



# HPV persistence

POST LEEP HPV PERSISTS

3 mos- 27%

6 mos 20%

12 mos 15%

24 mos 10%

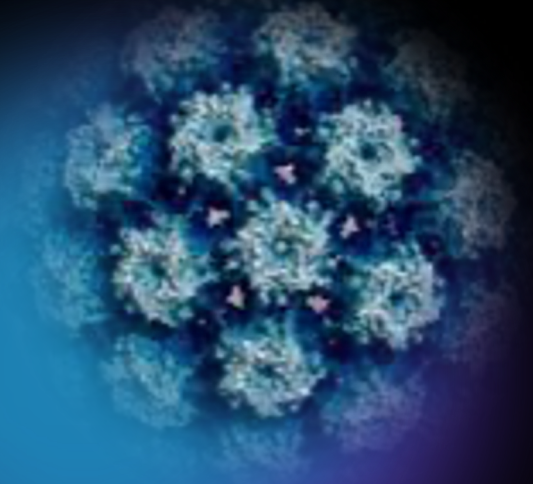




# Persistence of HPV

- 2 roads
- 1. CLEAR HPV- don't get disease
- 2. HPV persists- get CIN2+
- CONCLUSION: women with HPV persistence over 7 years either develop CIN 2+ or become HPV negative

# What can we do to clear HPV infection?



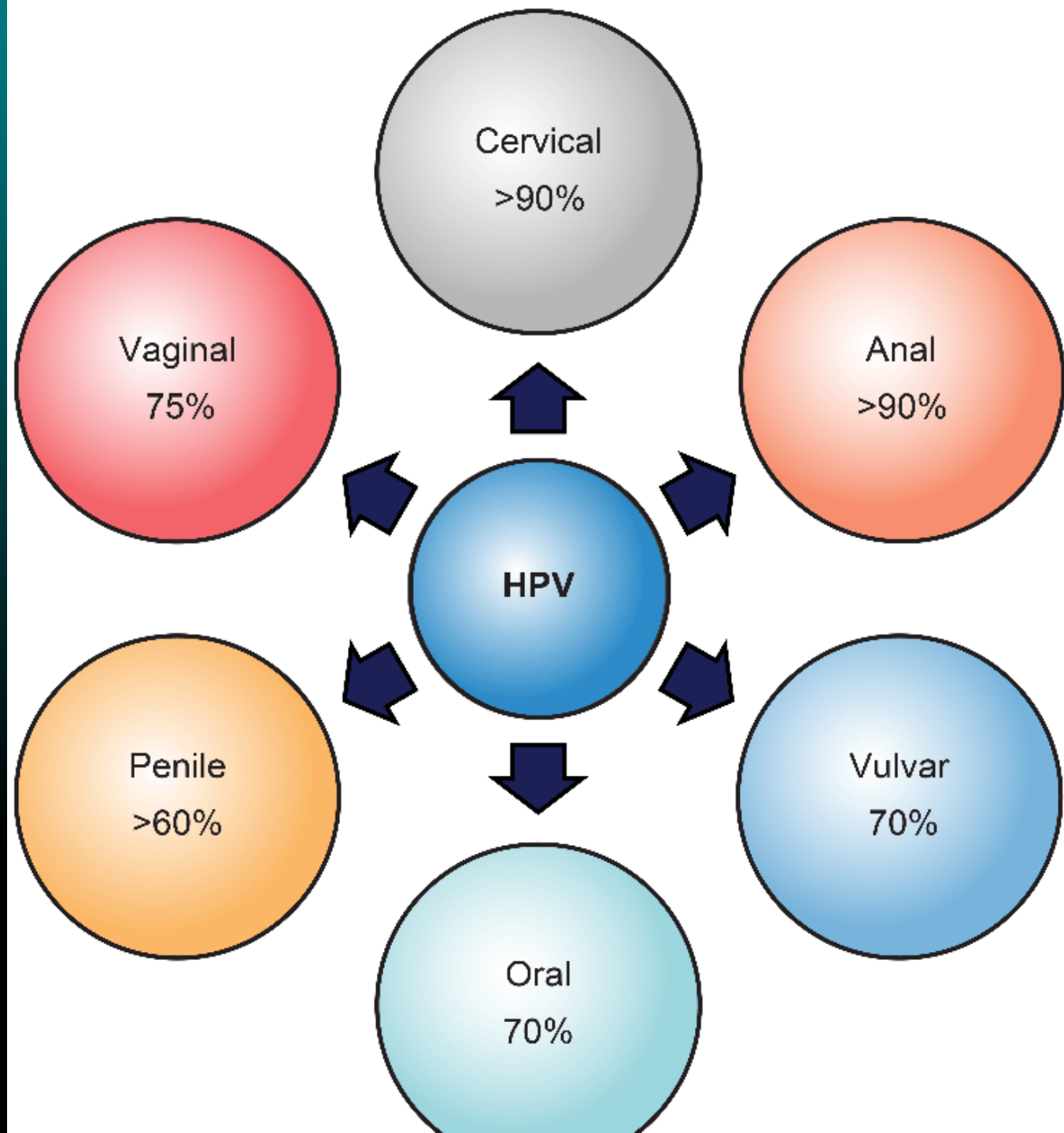
- Stop Smoking
- ?Get vaccinated
- ?effect of leep
- BEST is to PREVENT with Primary vaccination
- We don't know

A microscopic image showing several large, light-colored, rounded cells. On the surface of these cells, there are several bright red, spherical particles. Each particle is composed of many smaller, repeating units, giving it a textured, bumpy appearance. The background is a soft, out-of-focus blue and purple gradient.

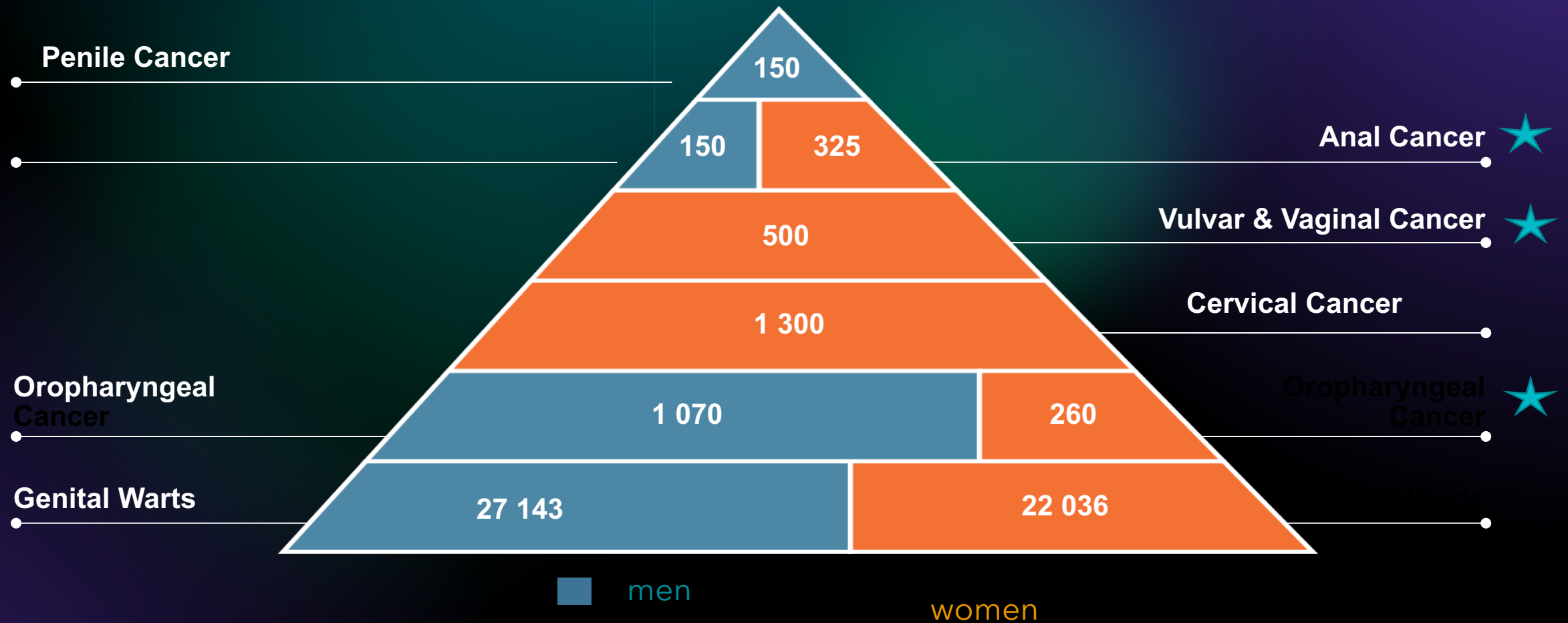
Let's talk  
more  
about  
HPV



# HPV causes Cancer



# Annual Estimated Number of Cases



# HPV 101

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cervical cancer is caused by HPV (>90%)

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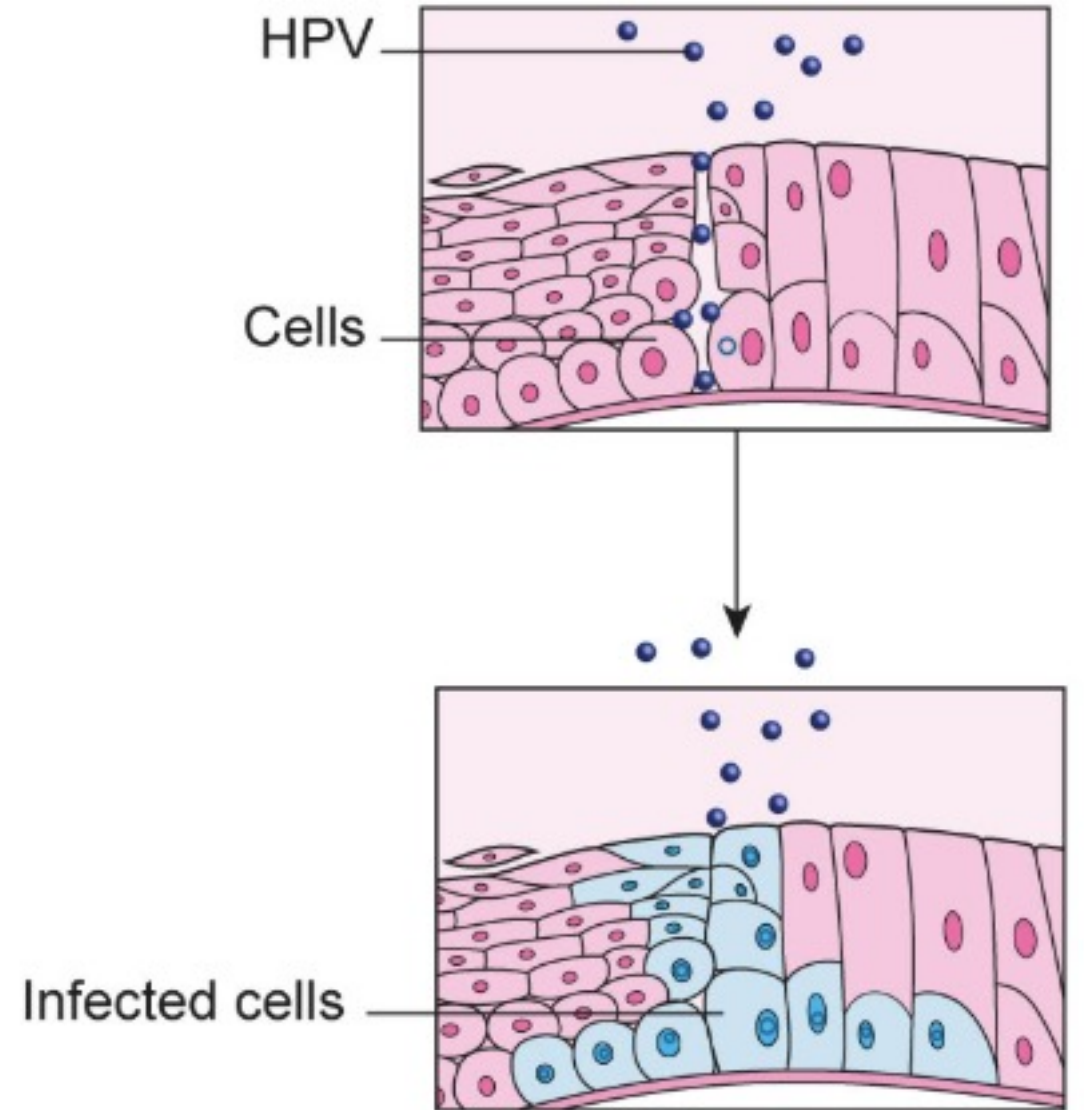
There are over 150 types of HPV

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13 genotypes have been shown to cause cervical cancer

# HPV Virology

- Non enveloped, DS DNA virus
- HPV Infectivity:
  - Epithelium infected
  - Doesn't kill the cells
  - Hides in basal cells



# Sophisticated evasion of the Immune System

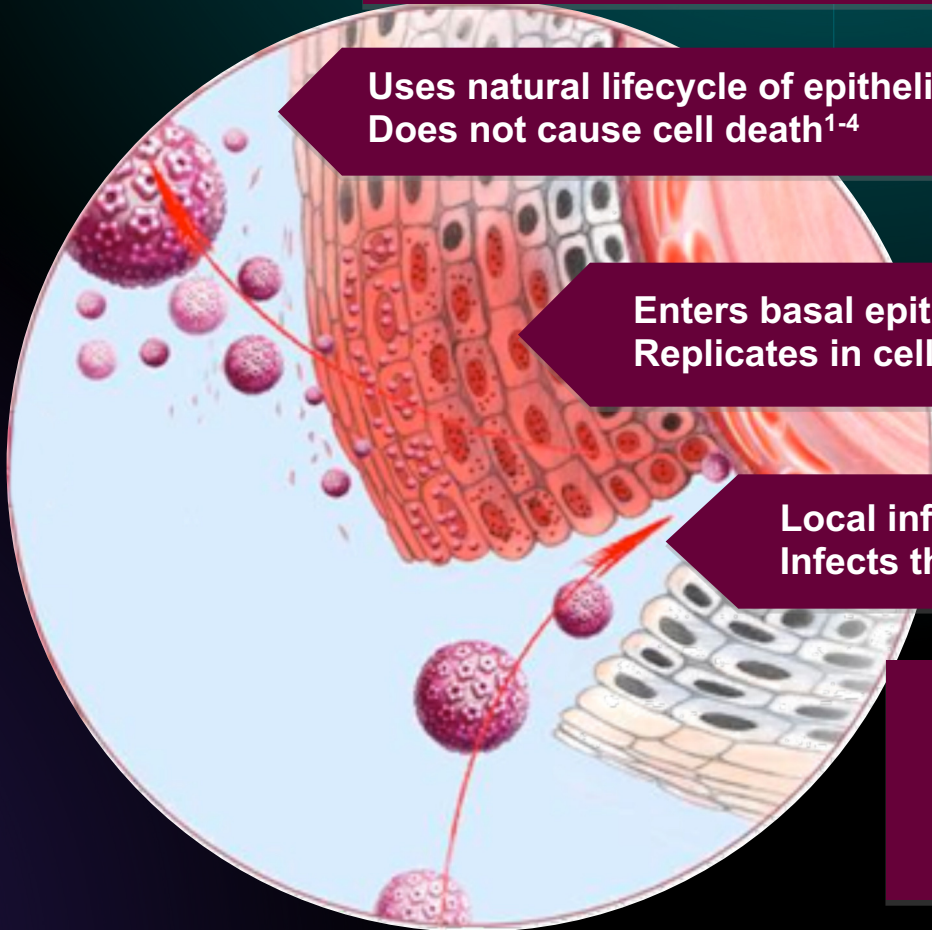
**Poor exposure to antigen presenting cells**

**Uses natural lifecycle of epithelial cells to release new viruses<sup>1-4</sup>  
Does not cause cell death<sup>1-4</sup>**

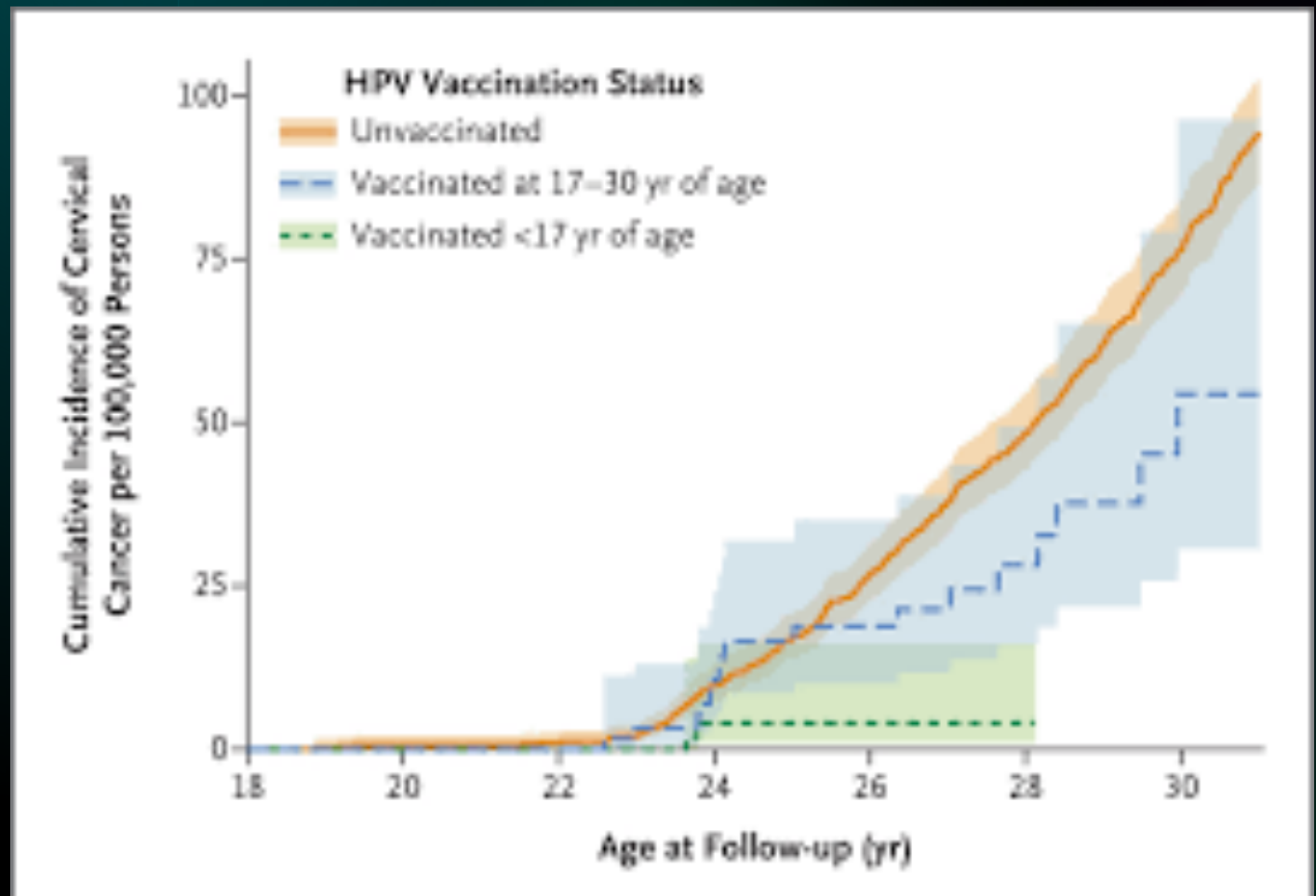
**Enters basal epithelial cell, integrates DNA in host cell<sup>1-4</sup>  
Replicates in cells; remains intraepithelial<sup>1-4</sup>**

**Local infection<sup>1-4</sup>  
Infects the epithelium through micro abrasions<sup>1-4</sup>**

**Infection with HPV is not  
reliably protective against  
future infection**



# Vaccines work

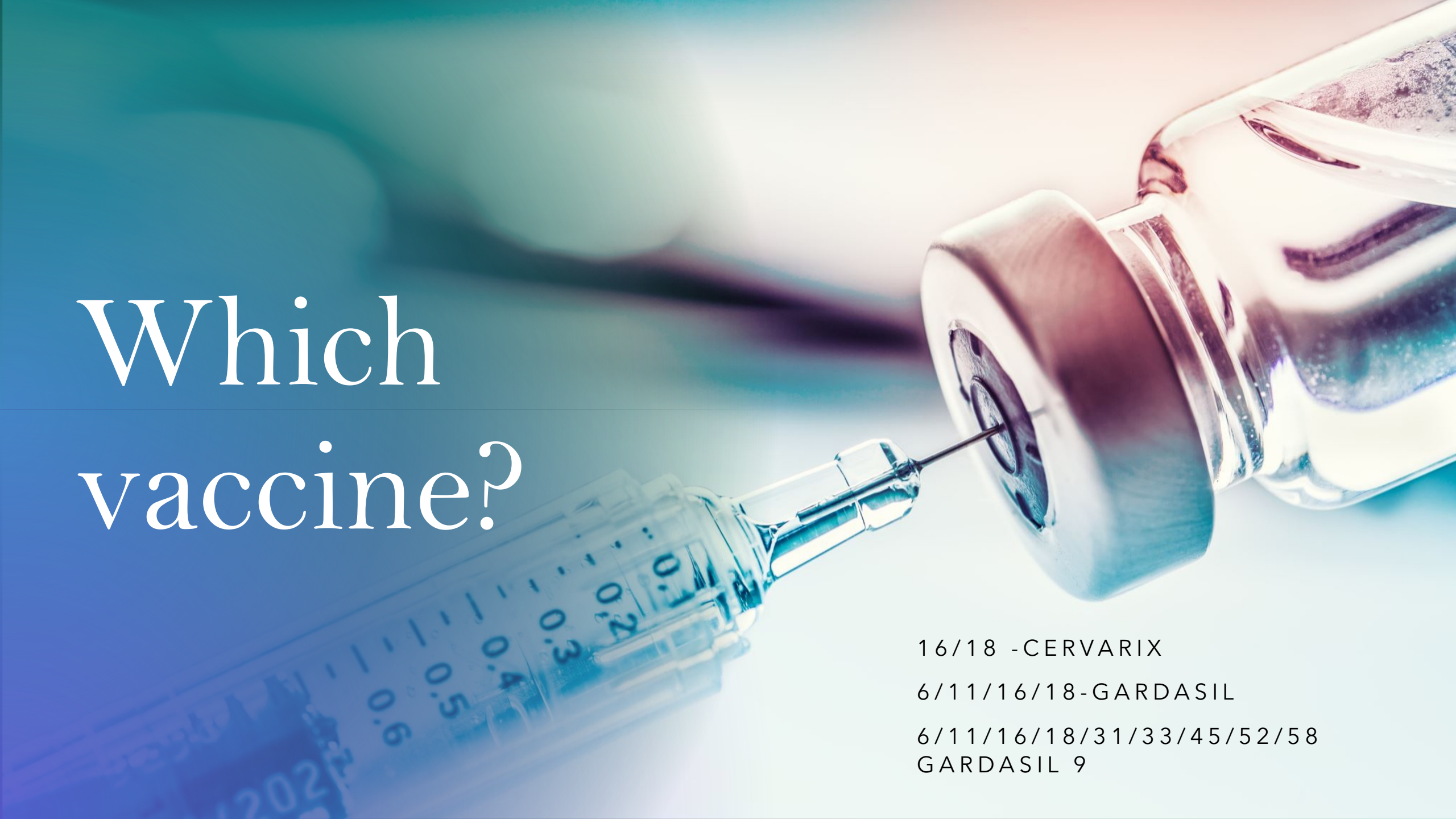


BC data: 1  
dose HPV  
vaccine  
(between  
age 9-14)

57% reduction  
CIN2+

73% reduction  
in CIN3

# Which vaccine?



16/18 -CERVARIX

6/11/16/18-GARDASIL

6/11/16/18/31/33/45/52/58  
GARDASIL 9





ALL 3 =  
Excellent

- Safety
- Efficacy
- effectiveness

# Target

# age

# 11-12 yo

<15 years old- 2  
doses 6 months apart  
(0, 6-12 months)

>15 years old- 3  
doses, 0, 2, 6 months

# Interval



- <15 yo want at least 6 months between doses
- 6-12 month range given as want dose prior to sexual activity
- 20% 9<sup>th</sup> grade/55% 12<sup>th</sup> grade are sexually active



# HPV : catch up (didn't get it yet)

- Regardless of sexual activity
- Regardless of prior HPV exposure
- Regardless of sexual orientation

# Safety

270 M doses worldwide since 2006

Arm swelling, erythema

Syncope common

Serious adverse events= RARE

# MESSAGING



Everyone who has sex gets HPV- we all have sex, we all have HPV

This is a cancer prevention vaccine

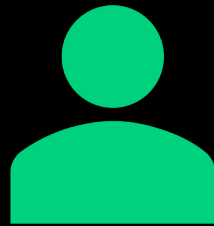
I have had it, My boys have both had it

HPV evades our immune system-vaccine GIVES you immunity you do not get with natural infx

# MESSAGING BOTTOM LINE



IT IS SAFE



IT WORKS



I HIGHLY RECOMMEND  
IT

# BC 2017-2018

67% OF ELIGIBLE GRADE 6 GIRLS RECEIVED THEIR FULL HPV  
VACCINATION





Now that you  
understand how  
we do things  
now-  
**EVERYTHING**  
is about to  
change

## HPV Based Cervical Cancer Screening

Benefit of Cervical Screening with HPV: Greater Sensitivity

HOW DOES THE NEW HPV TEST COMPARE WITH THE TRADITIONAL CERVICAL TEST?

FOR EVERY **1000**  **WOMEN SCREENED:** 

Around 20 women **will have** precancerous changes.

**18** The HPV test will correctly identify 18 of these women

**15** The traditional cervical test will identify 15 of the women

# HPV testing

IS THE FUTURE

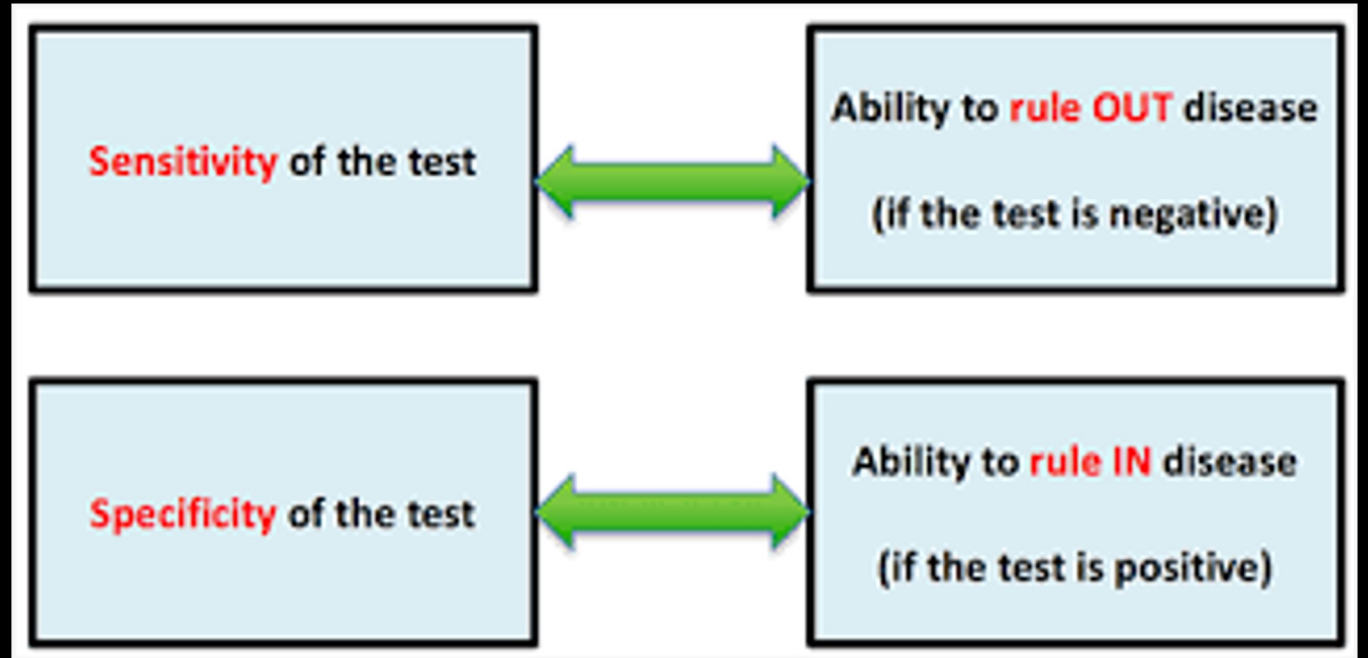
# HPV vs CYTOLOGY

	HPV testing	CYTOLOGY
One time sensitivity	96%	53%
One time Specificity	90%	96%
Detects	Oncogenic types of HPV	Abnormal cell changes in the cervix (from low and high risk HPV)
Interpretation	Objective and reproducible	subjective

# SNOUT & SPIN

HPV – highly sensitive –  
if negative—rules out  
disease

But lower specificity  
means if HPV is positive  
does **NOT** rule in that  
you will have CIN3+



# HPV testing

- MUCH higher sensitivity (if negative is a TRUE negative)
- Lower specificity (positive HPV does not mean you have the disease ...yet...)
- Will lead to higher numbers in our system at first
- Every 5 years
- Will be able to self test with SWAB only
- AUSTRALIA has already changed to HPV as primary screen

# Advances in pathology

- P16 staining= surrogate marker for oncogenic HPV infection- \*inactivation of Rb by the viral E7 oncoprotein following viral integration into host genome leads to overexpression of p16,
- In plain English: Shows the virus has integrated into the HOST DNA.
- Ki-67- DENOTES CELL PROLIFERATION
- COMBINING P16 and ki-67 shows a lot of promise

# P16= HPV has integrated into DNA of host

## Moderate Dysplasia (CIN2)

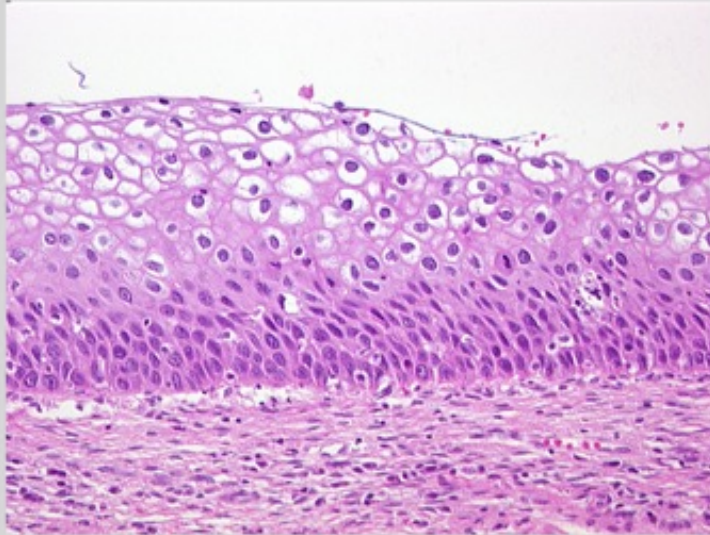


Figure 2. H&E. Dysplastic cells in the lower half of the epithelium

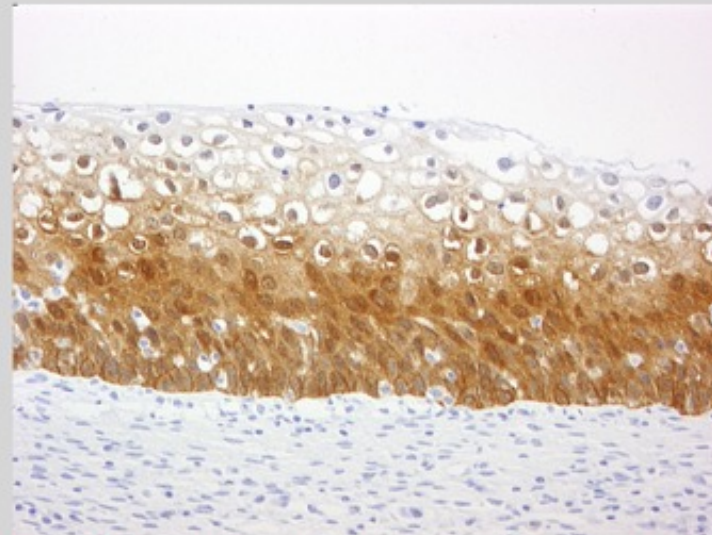
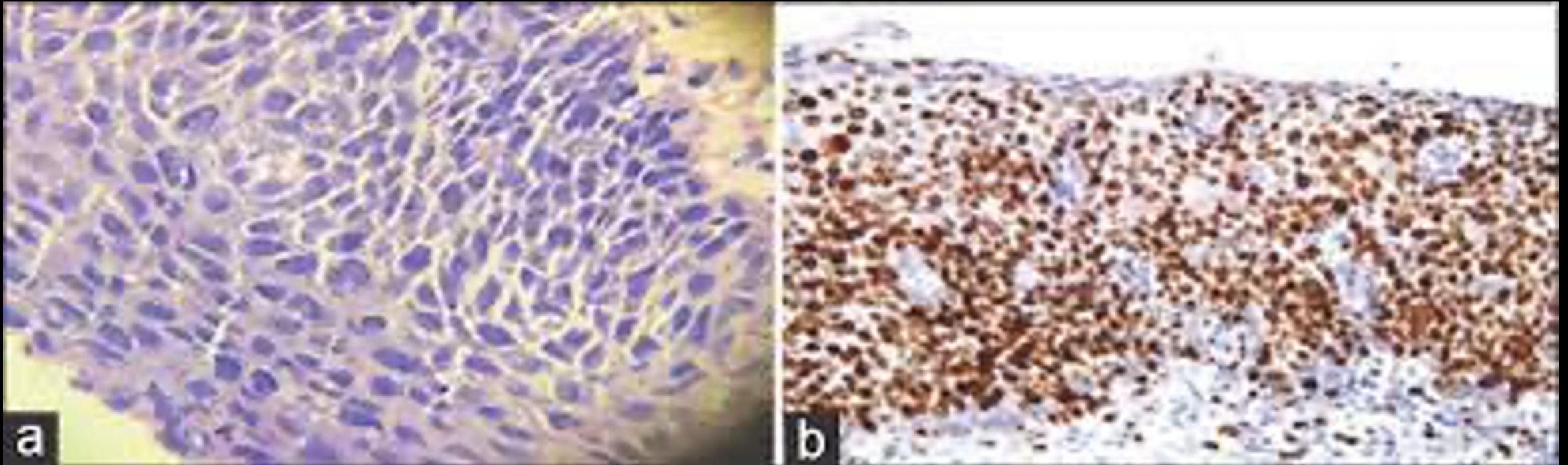


Figure 3. Dysplastic cells show cytoplasmic and nuclear p16<sup>INK4a</sup> positivity in a diffuse distribution in the lower half of the epithelium. The cells in the superficial layers show no or only weak p16<sup>INK4a</sup> positivity.

# Ki-67 = CELL PROLIFERATION





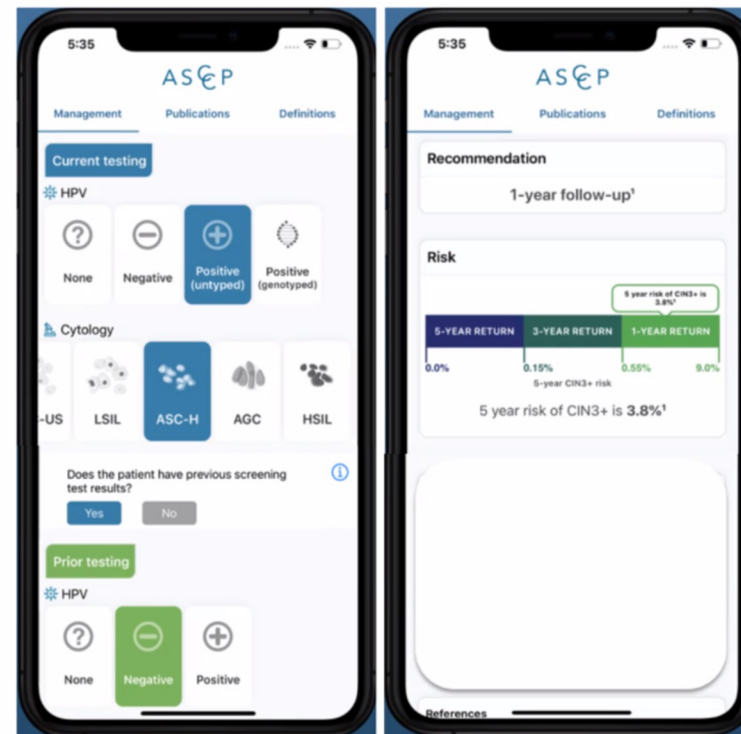
# Results versus RISK based screening

## 2012 Result-Based Guidelines

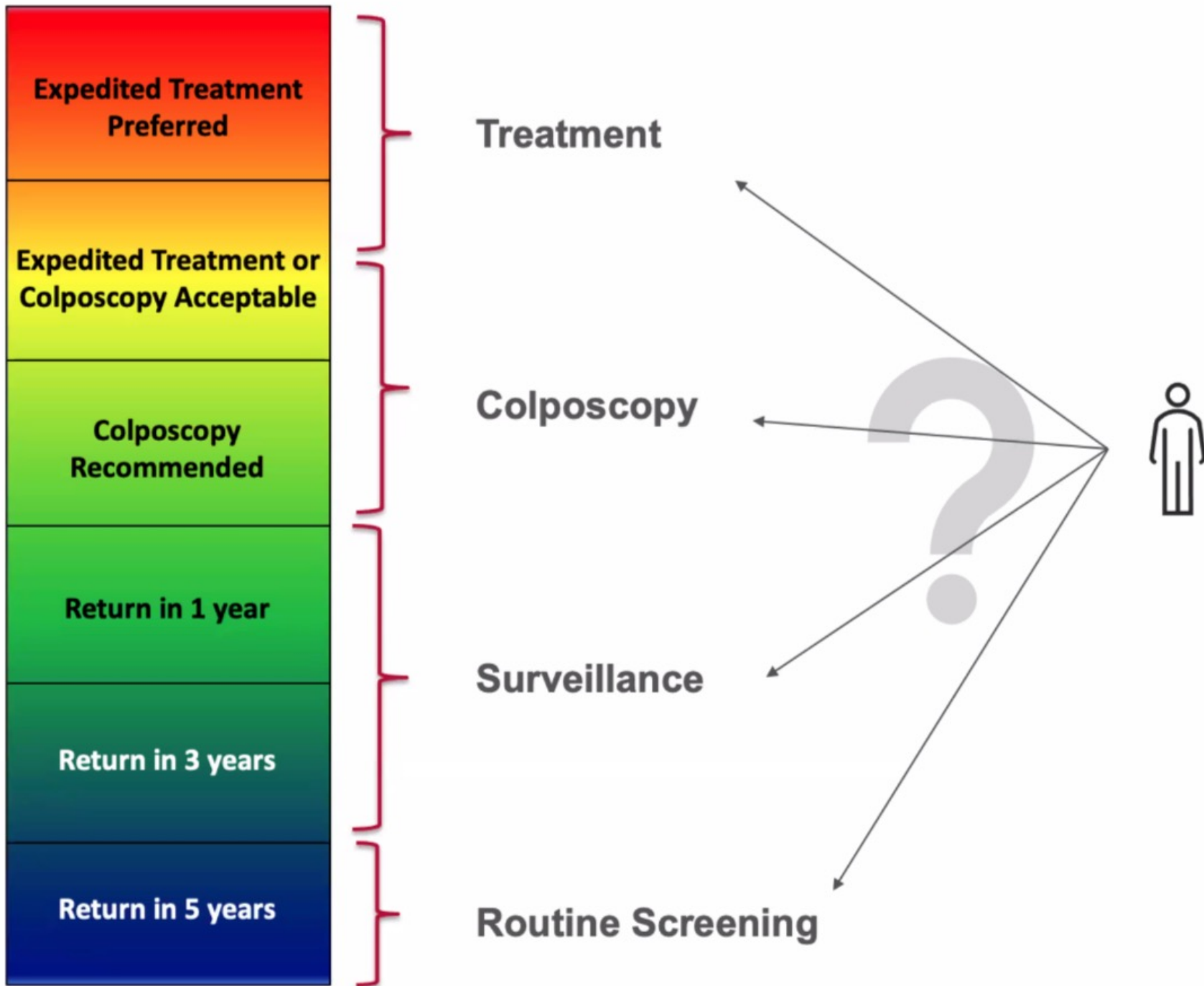


Massad et al. JLGTD 2013

## 2019 Risk-Based Guidelines

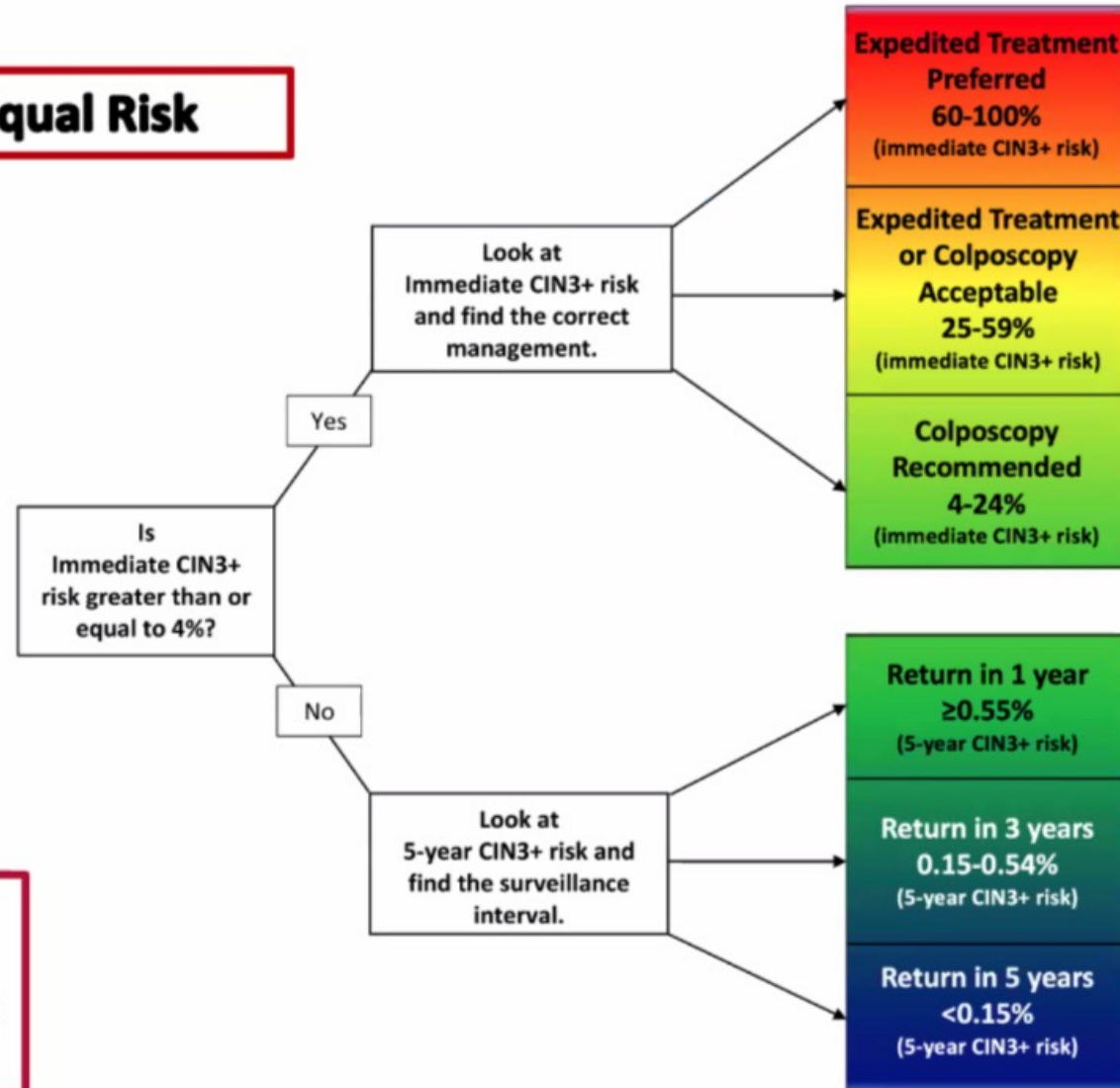


Egemen et al. JLGTD 2020  
Perkins et al. JLGTD 2020



# 2019 ASCCP Risk-Based Management Consensus Guidelines

## Equal Management of Equal Risk



**Immediate risk** – chance of having CIN3+ today  
**5-year risk** – chance of CIN3+ 5 years from today



[www.cervicalrisk.com](http://www.cervicalrisk.com)

# The FUTURE: promote vaccines Advocate for HPV testing

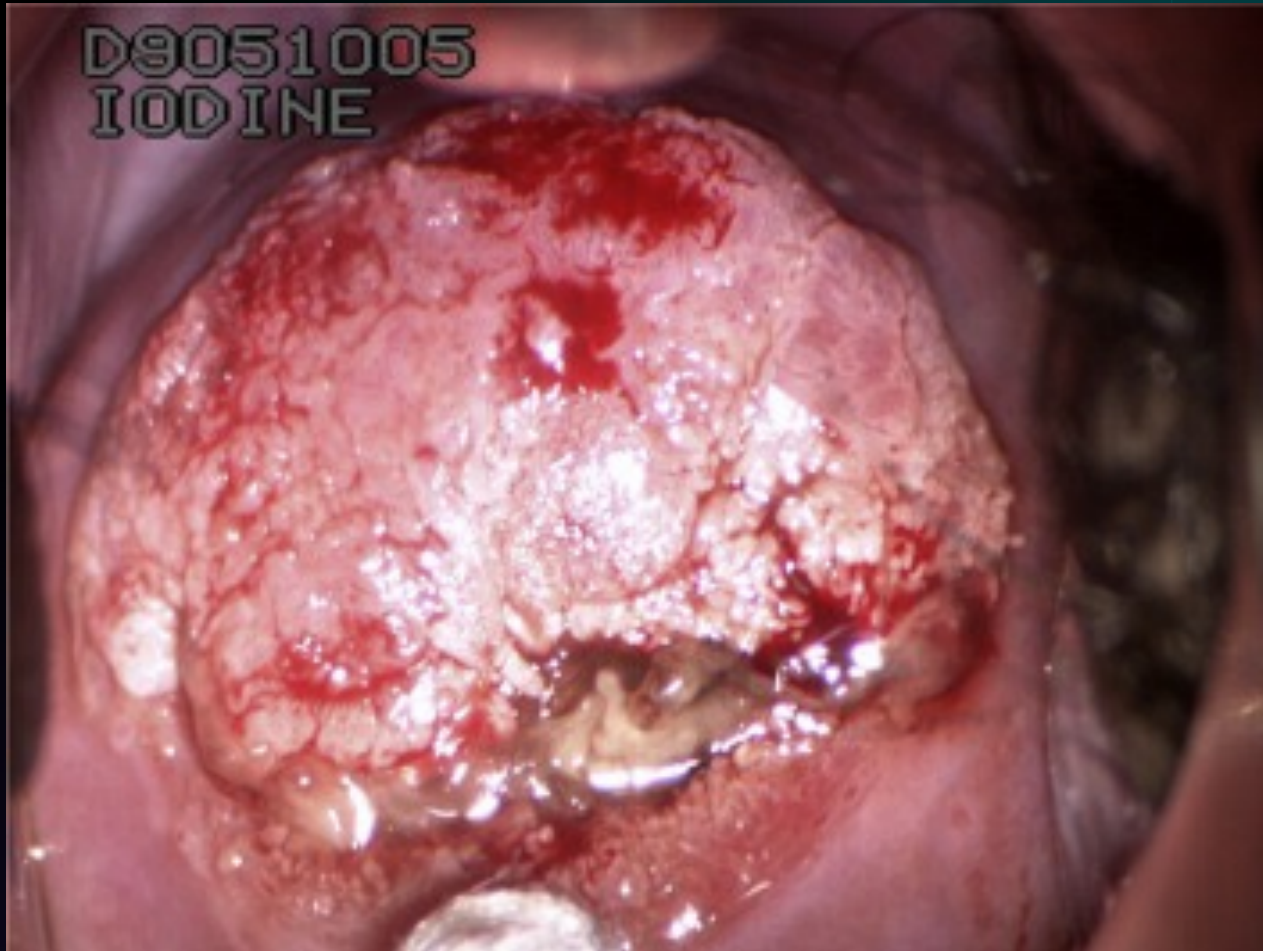
- We can do better!!! HIGHER VACCINATION NUMBERS
- We can advocate for HPV testing
- RISK based? Versus RESULT based programs
- P16 STAINING
- HPV TYPE SPECIFIC TESTING

# STAY TUNED...

RESEARCH IS BLOWING UP IN THIS AREA

Most change in my 16 years of practice

With increased precision - cost is higher COMPLEXITY



# REMEMBER- screening works for pre cancer

- IF IT looks like cancer already- pap may not pick it up.
- SEND anything that looks funny to us

IF it looks **FUNKY** refer!!!





I'm a gynecologist- that's my job



If it looks funny- send it to us

I'm a  
gynecologist

That's my  
job



<http://www.bccancer.bc.ca/screening/documents/cervix-program-overview.pdf>

## This global strategy to eliminate cervical cancer proposes:

- a vision of a world where cervical cancer is eliminated as a public health problem;
- a threshold of 4 per 100 000 women-years for elimination as a public health problem;
- the following 90-70-90 targets that must be met by 2030 for countries to be on the path towards cervical cancer elimination:

**90%**

of girls fully vaccinated  
with HPV vaccine by  
age 15 years.

**70%**

of women are screened  
with a high-performance  
test by 35 years of age and  
again by 45 years of age.

**90%**

of women identified with cervical  
disease receive treatment  
(90% of women with precancer  
treated, and 90% of women  
with invasive cancer  
managed).

# 3 Cases:

- 22 year old- post coital bleeding, unusual appearance to her cervix
- Never had a pap smear, not vaccinated against HPV
  
- 42 y.o. G3P3, Obese, T2DM-
- pap AGC- NOS
  
- 56 yo. Hx of warts, kidney transplant, long list of meds including immune modulators -
- Pap shows ASC-H

*22 yo.*



# NO Pap smear required

DO swabs - cervicitis much more common than cancer

Risks of cancer is 1.35/ 100 000

Counsel re: HPV vaccine

Send to colpo- let us decide re: pap smear and biopsy

Refer to gyne re: PCB- long differential- usually nothing in this age group

# 42 yo G3P3, obese, T2DM, PAP AGC-NOS

Glandular lesions  
are much worse  
then squamous

Precolpo risk of  
cancer and cancer  
14% (cancer 2.4%)

Higher risk of  
endometrial lesion-  
she will get  
endometrial biospy



# 56 yo –hx of warts, kidney transplant- pap ASC-H

Ascus versus ASC-H

ASCUS- follow guidelines repeat x 3 prior to colpo - odds of cancer 0.08%

Odds of precancer 12%

ASC-H odds of cancer 0.9%

Odds of precancer 35%

Treat ASC-H like HSIL (Moderate)

# Yearly pap smears

HIV

Organ transplant

Immune modulators  
(autoimmune disease) still  
every 3 years!

# 56 yo- kidney transplant

COLPO shows CIN3

LEEP - CIN3

Fu at 6 mos - negative, HPV 16 +

Fu at 1 year- no visible lesion, HPV 16+, ECC positive CIN3

REPEAT Leep done

?will she ever clear the HPV???

Questions???

