

Cervical Cancer: How Can We Prevent A Preventable Disease?

Legislative Women's Caucus

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Relevance of Cervical Cancer Today

Cervical Cancer Screening as a Model for Disease Screening

Evolution of Cervical Cancer Screening

The Role of HPV in Screening

What is Important in a Screening Strategy?

Current Options for Cervical Cancer Screening

Cytology (Pap)

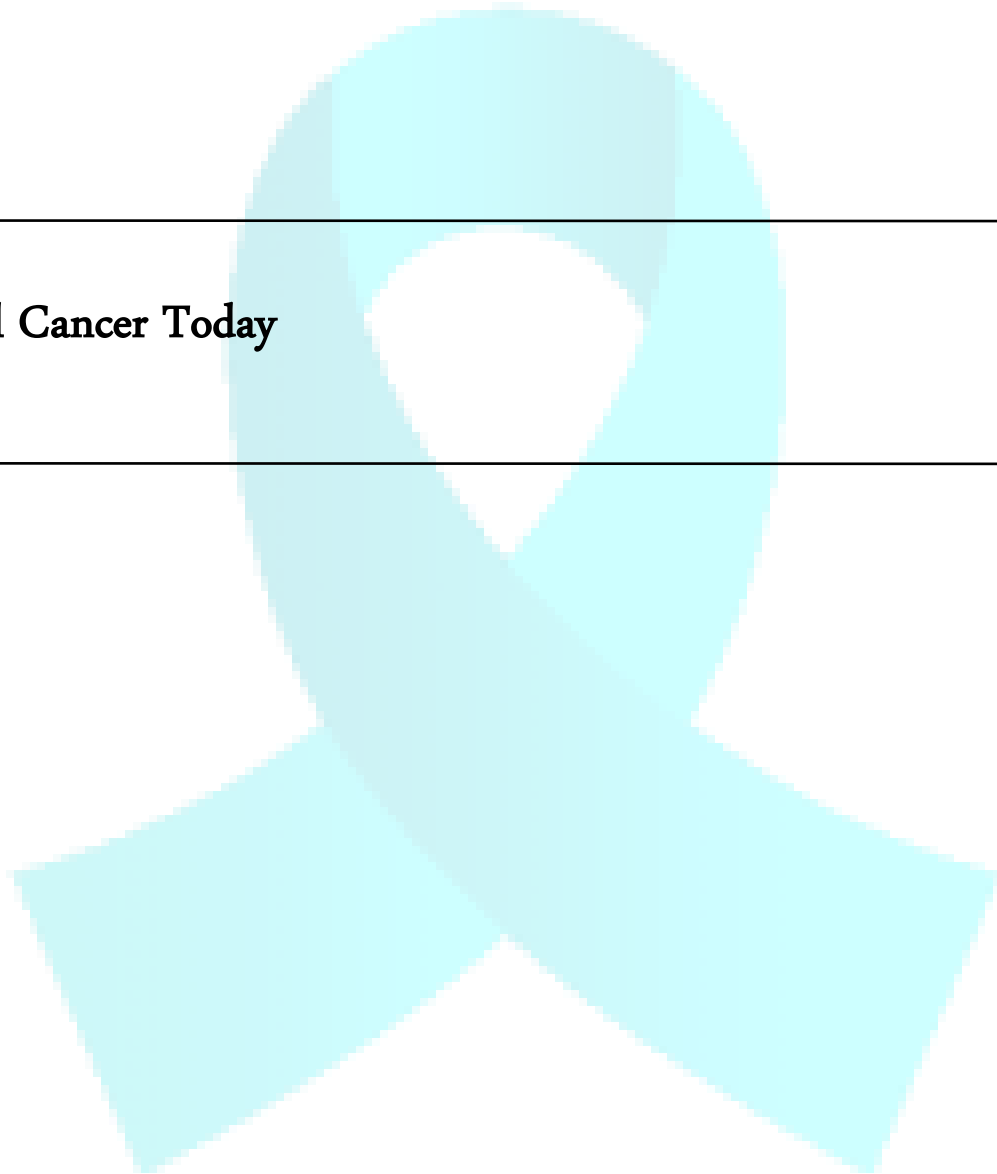
Cotesting (Pap & HPV Testing)

HPV Primary Screening

Cervical Cancer Screening in California

HEDIS

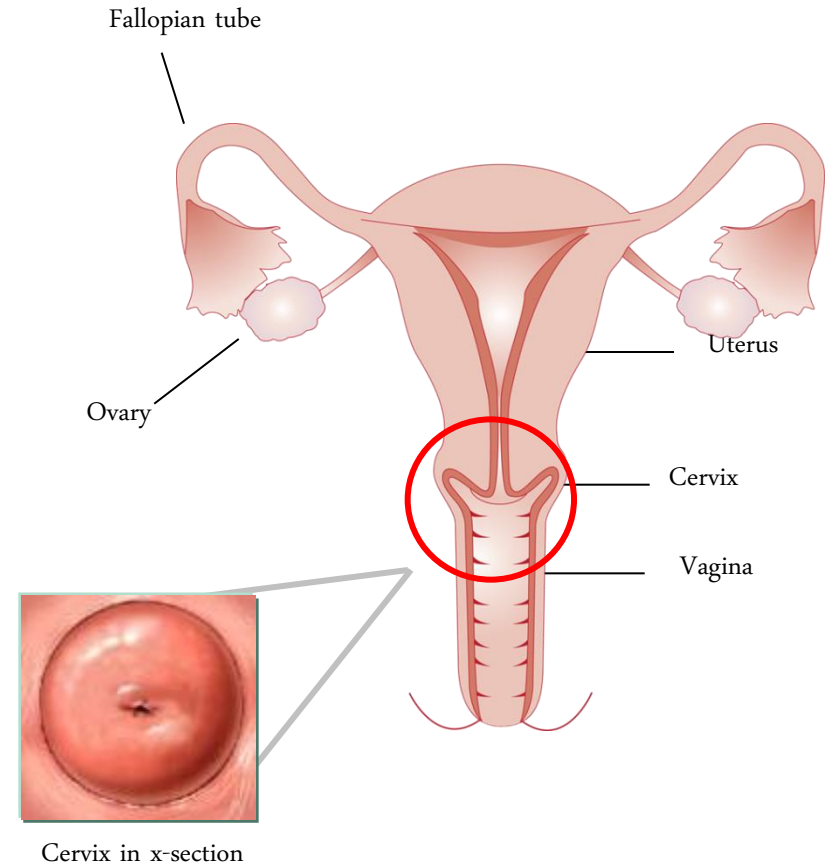
Every Women Counts



Relevance of Cervical Cancer Today

Anatomy of the uterus

- The cervix forms the entry into the uterus
- Most cervical precancers and cancers are asymptomatic
- Only advanced disease may present with vaginal bleeding
- Screening asymptomatic women can help prevent cancer or promote detection at an early stage



Screening terminology: Pap, Colposcopy and Biopsy

The primary goal of screening is to determine which women need to go to colposcopy

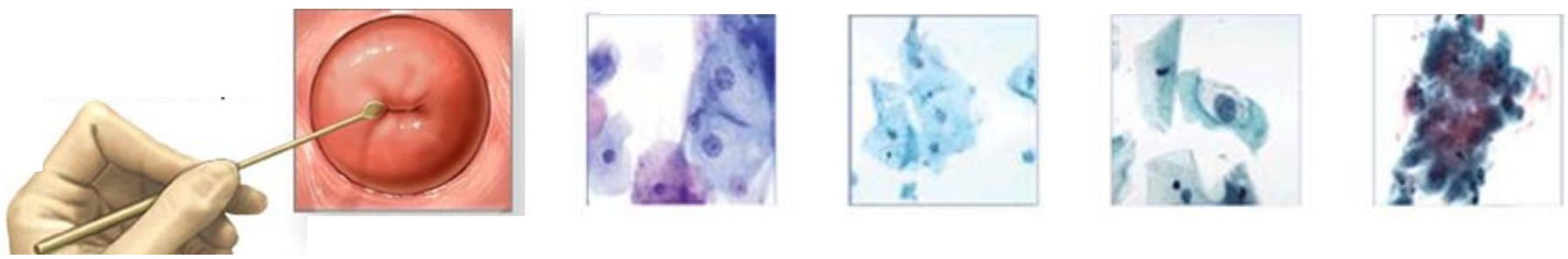
Pap Smear Results

Normal

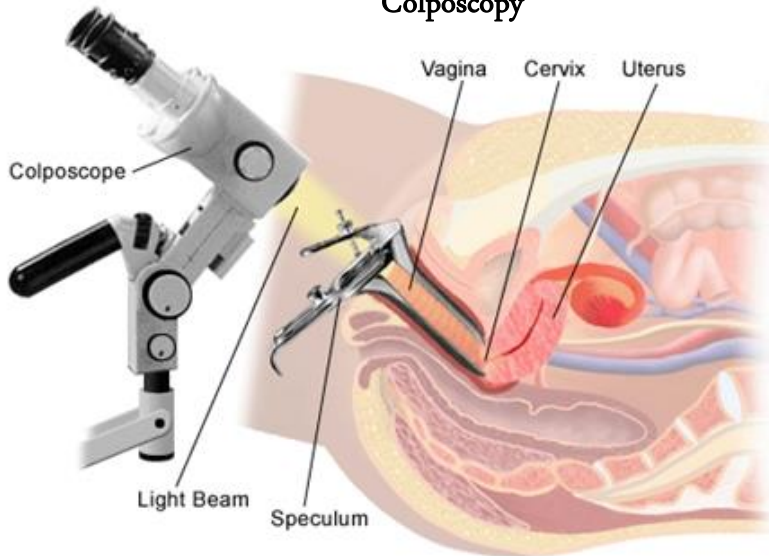
**Borderline
(ASCUS)**

Low Grade

High Grade



Colposcopy



Biopsy

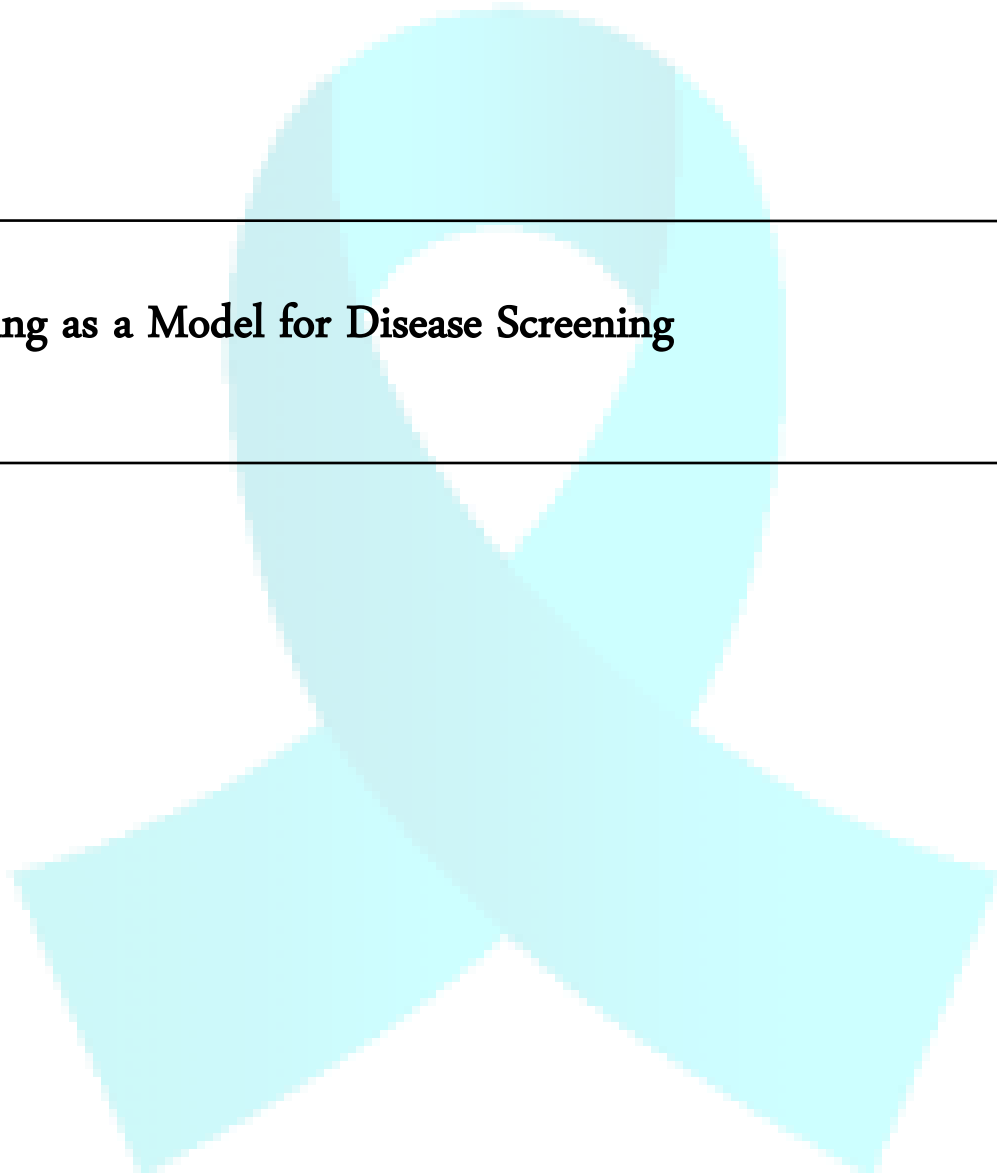


What do we know?

- >99% of cervical cancers are caused by HPV:
 - Of the ~14 oncogenic types, HPV 16 & HPV 18 are responsible for ~70% invasive cancers
- HPV is the most common sexually transmitted infection:
 - 80% of women will be infected sometime during their lifetime; persistence of infection increases risk
- Cervical cancer: 3rd most common cancer in women and 5th cause of cancer death world wide
- Despite screening:
 - ~12,000 cases and ~4,000 deaths annually in US
 - ~500,000 cases and >250,000 deaths world wide

Worldwide, a women dies from cervical cancer every 2 minutes ...





Cervical Cancer Screening as a Model for Disease Screening

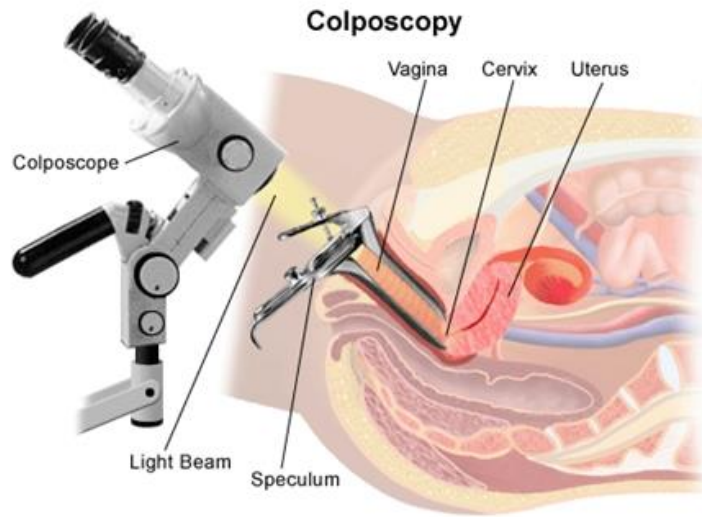
Cervical Cancer Screening:

A Perfect Model for Screening

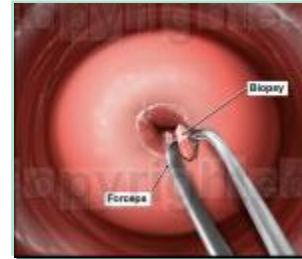
- We understand the natural history of cervical cancer
 - caused by the HPV virus
- Cervical cancer has a long precancerous stage
 - It takes ~10 years to progress from precancer to cancer
- We have effective screening tests
- The cervix is easily accessible to testing
- We have effective methods for treating precancer when it is detected

Evolution of Cervical Cancer Screening

Who needs referral to colposcopy?



Biopsy



- 1950's: PAP test (Cytology) introduced

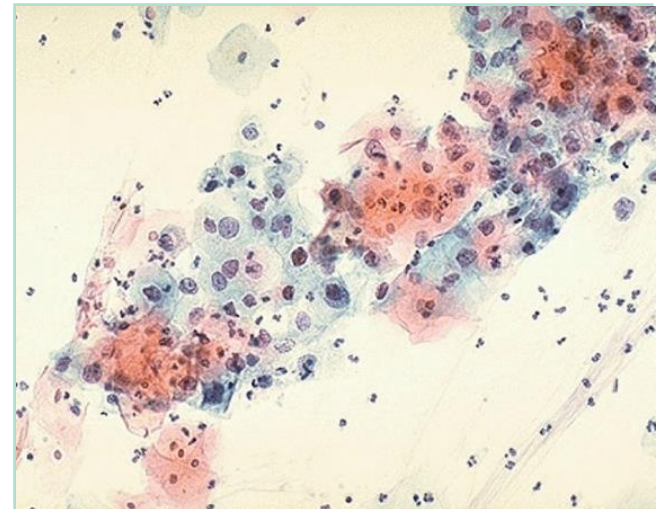
Introduction of cytology (Pap smear) for cervical cancer screening



- George Papanicolaou published atlas of cervical cytology in 1954
- By 1960's industrialized countries began to use the Pap smear for cervical cancer screening
- It has continued as a screening methodology in developed countries

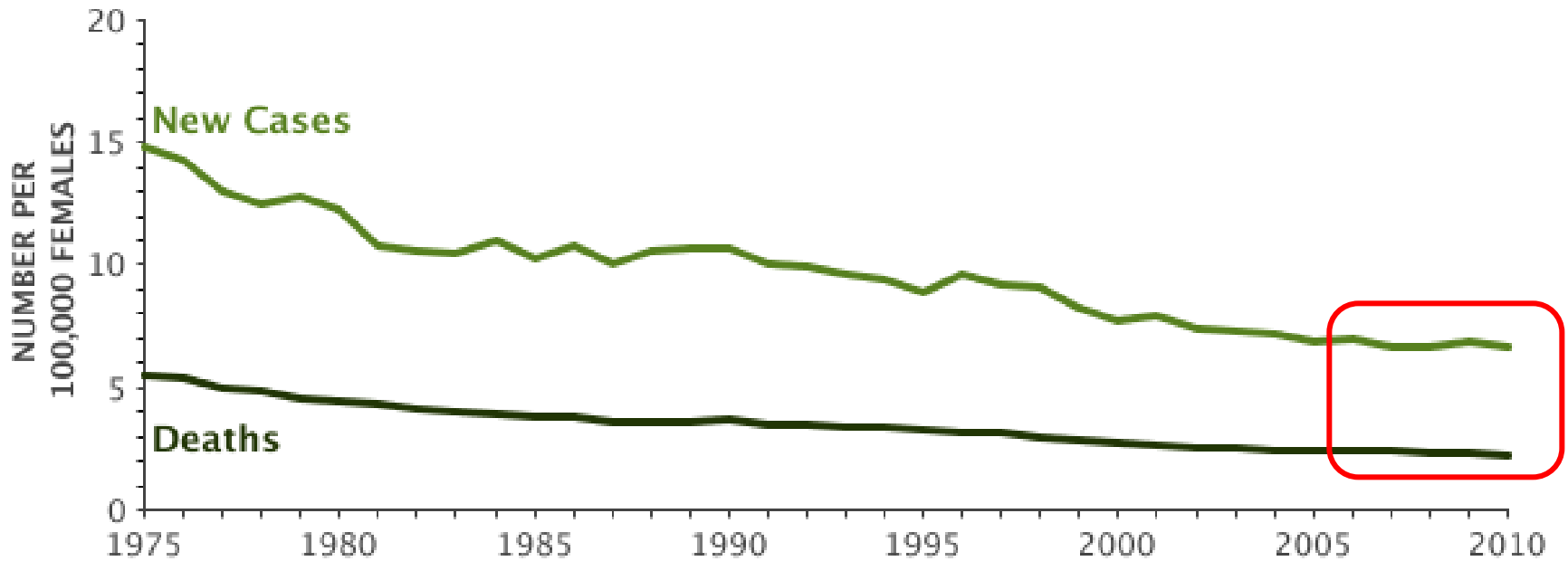


George Papanicolaou



PAP Testing Has Reduced Cervical Cancer Incidence

But has it reached the limitations of effectiveness?



| Year | 1975 | 1980 | 1985 | 1989 | 1993 | 1997 | 2001 | 2005 | 2010 |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 5-Year Survival | 68.1% | 67.9% | 66.4% | 71.0% | 70.9% | 71.6% | 70.4% | 68.0% | 67.9% |

Screening history of women diagnosed with invasive cervical carcinoma

| Cause | Kaiser ¹ | Swedish audit ² |
|---|---------------------|----------------------------|
| No recent screen | 464 (56%) | 789 (64%) |
| Cytology detection failure | 263 (32%) | 300 (24%) |
| Failure of follow-up of abnormal cytology | 106 (13%) | 91 (7%) |

¹Leyden WA, et al. *J Natl Cancer Inst* 2005; 97:675–683;

²Andrae B, et al. *J Natl Cancer Inst* 2008; 100:622–629.

The role of HPV in cervical cancer

- In 1975, Professor zur Hausen hypothesized that HPV was a necessary cause of cervical cancer¹
- By 1990s it was confirmed that virtually all cervical cancers were caused by HPV²
- 2003 screening guidelines support HPV testing as part of screening
- In 2008, Professor Hausen received the Nobel Prize for Medicine in recognition of his work



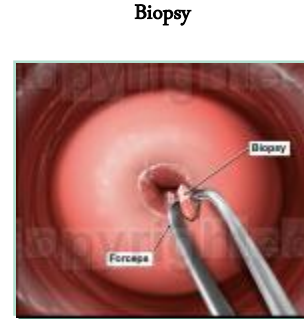
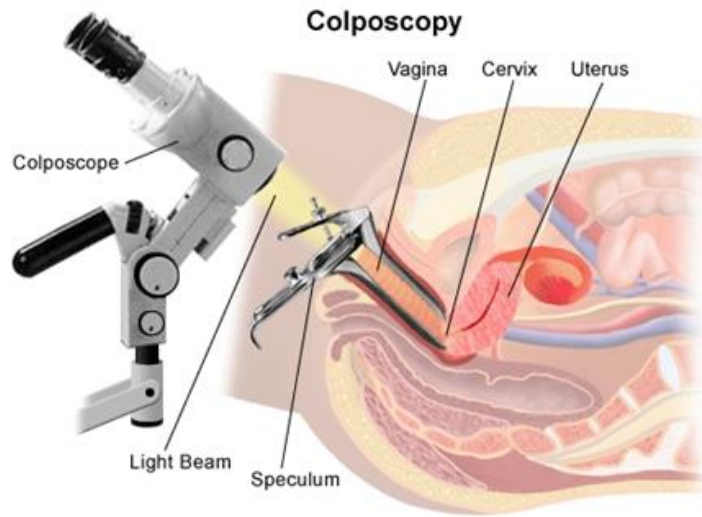
Professor Harald zur Hausen

¹ zur Hausen et al. Bibl. Haematol. 1975

² Walboomers et al. J Pathol. 1999

Evolution of Cervical Cancer Screening

Who needs referral to colposcopy?



- 1950's: PAP test (Cytology) introduced
- 1990's: HPV determined to be responsible for cervical cancer

The Challenge of Cervical Cancer Screening

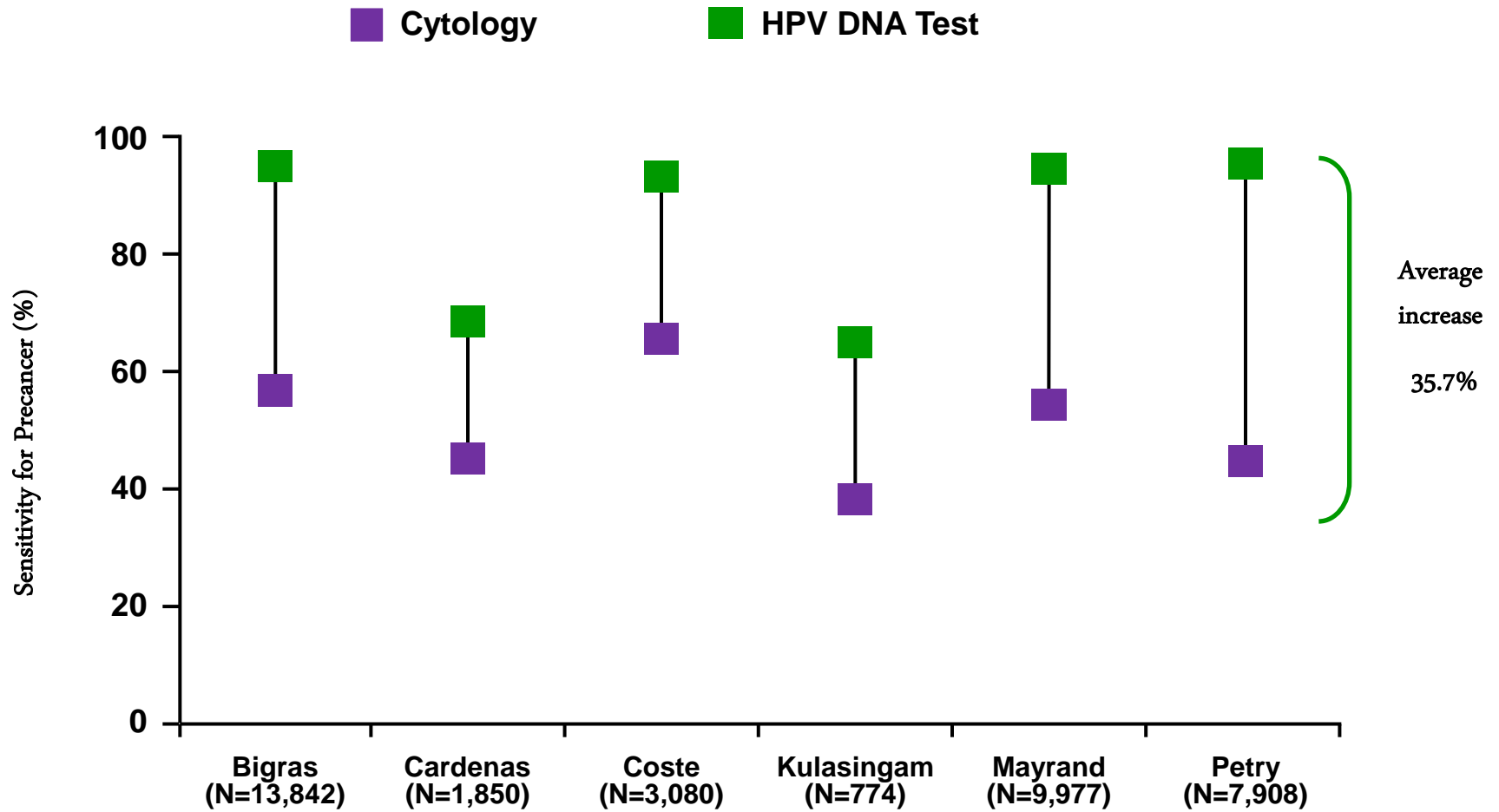
What is Important in a Screening Strategy?

- The initial screening test should be as sensitive as possible so that all those at risk can be identified
 - followed by a more specific test that identifies who needs additional testing or treatment
 - an optimal balance between Sensitivity and Specificity needs to be found

Cytology Consistently Has a Lower Clinical Sensitivity than HPV DNA



Can HPV be an effective tool for screening?



Studies performed in developed countries in women 30 years and older.

Certain HPV types are more specific for cervical precancer & cancer

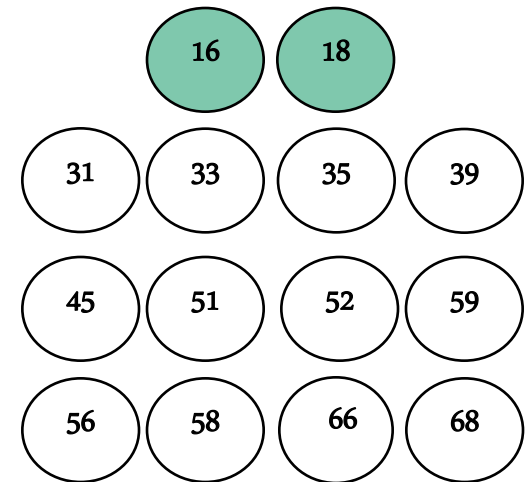
There are >140 known HPV types (genotypes)

- A subset of genotypes is frequently associated with invasive cervical cancer – these are called high-risk HPV genotypes^{1,2}

Among the high-risk genotypes, HPV 16 and HPV 18 are the 2 most oncogenic

- Infection with these types places women at the highest risk for developing cervical cancer
- They are responsible for causing ~80% of all cervical cancers

High-risk HPV genotypes



¹Walboomers J, *et al.* 1999

²Burk R, *et al.* 2009;

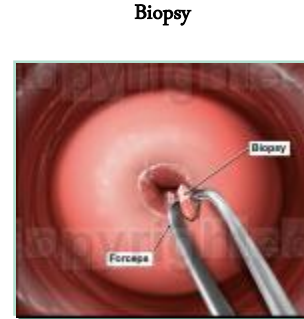
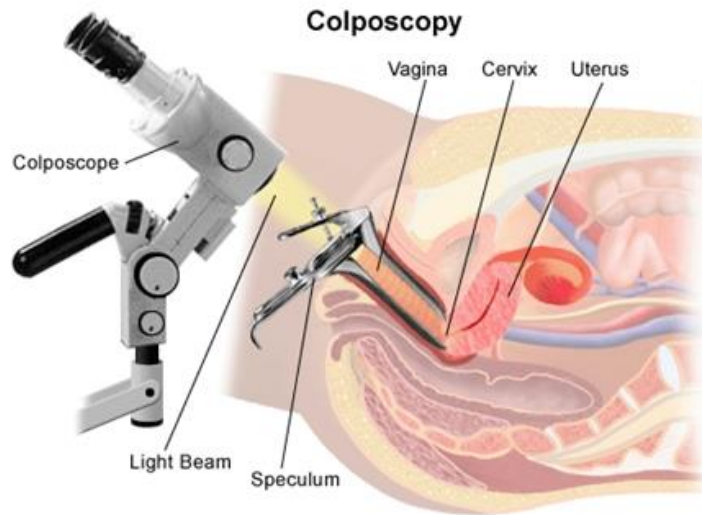
The Challenge of Cervical Cancer Screening *Who needs referral to colposcopy?*



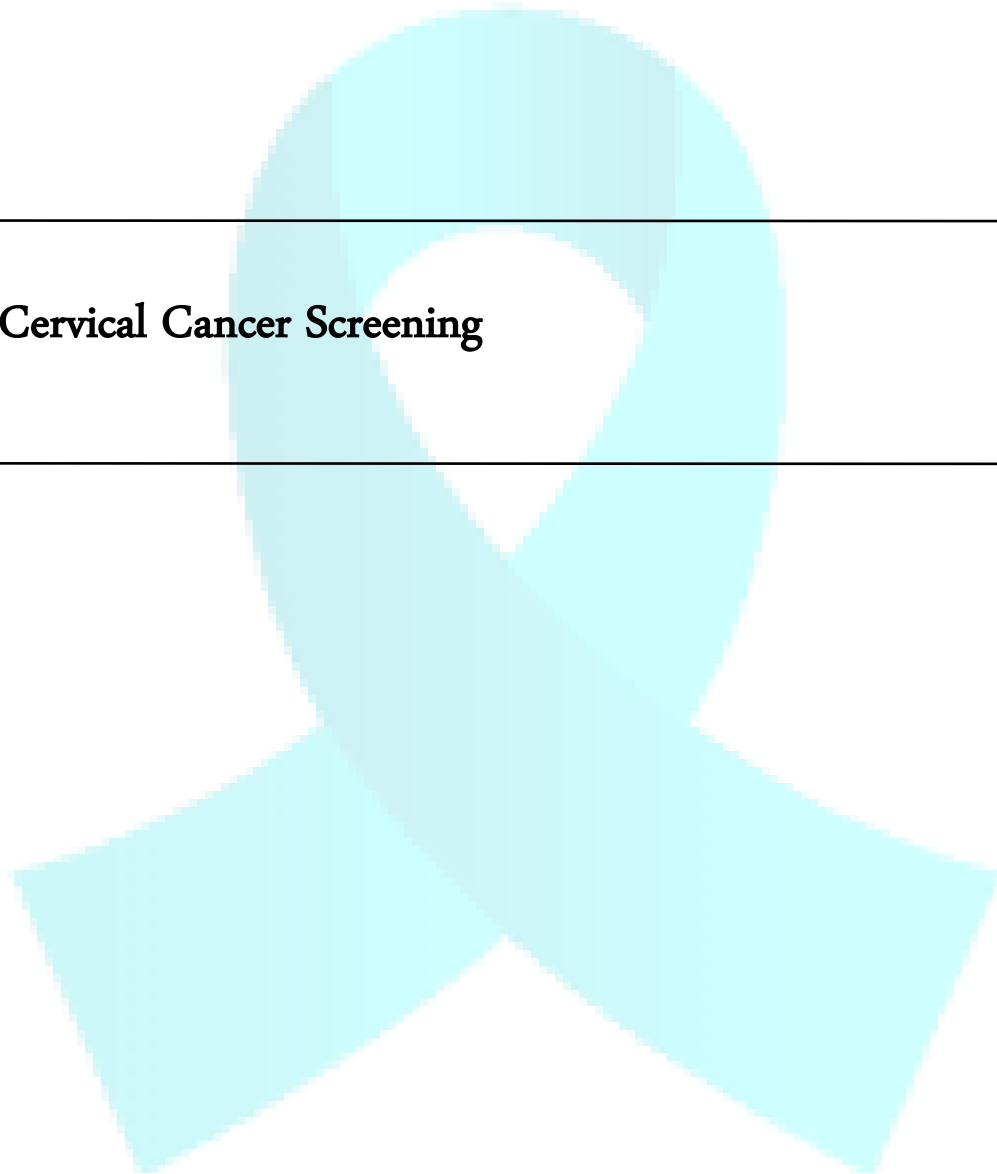
- The initial screening test should be as sensitive as possible so that all those at risk can be identified
 - followed by a more specific test that identifies who needs additional testing or treatment
 - an optimal balance between Sensitivity and Specificity needs to be found
- HPV:
 - identifies women who are at **risk** for cervical disease
 - is sensitive, but not very specific
- Pap smear (Cytology):
 - identifies women who already have **disease**
 - is more specific

Evolution of Cervical Cancer Screening

Who needs referral to colposcopy?



- 1950's: PAP test (Cytology) introduced
- 1990's: HPV determined to be responsible for cervical cancer
- 2001: Triage of borderline abnormal PAPs with HPV (ASC-US Triage)
- 2006: Cotesting (HPV + PAP), 16/18 Genotyping
- 2007 – 2013: Studies from Canada and Europe suggest HPV as the first-line primary screen
- 2014: FDA approves HPV as the first-line primary screen



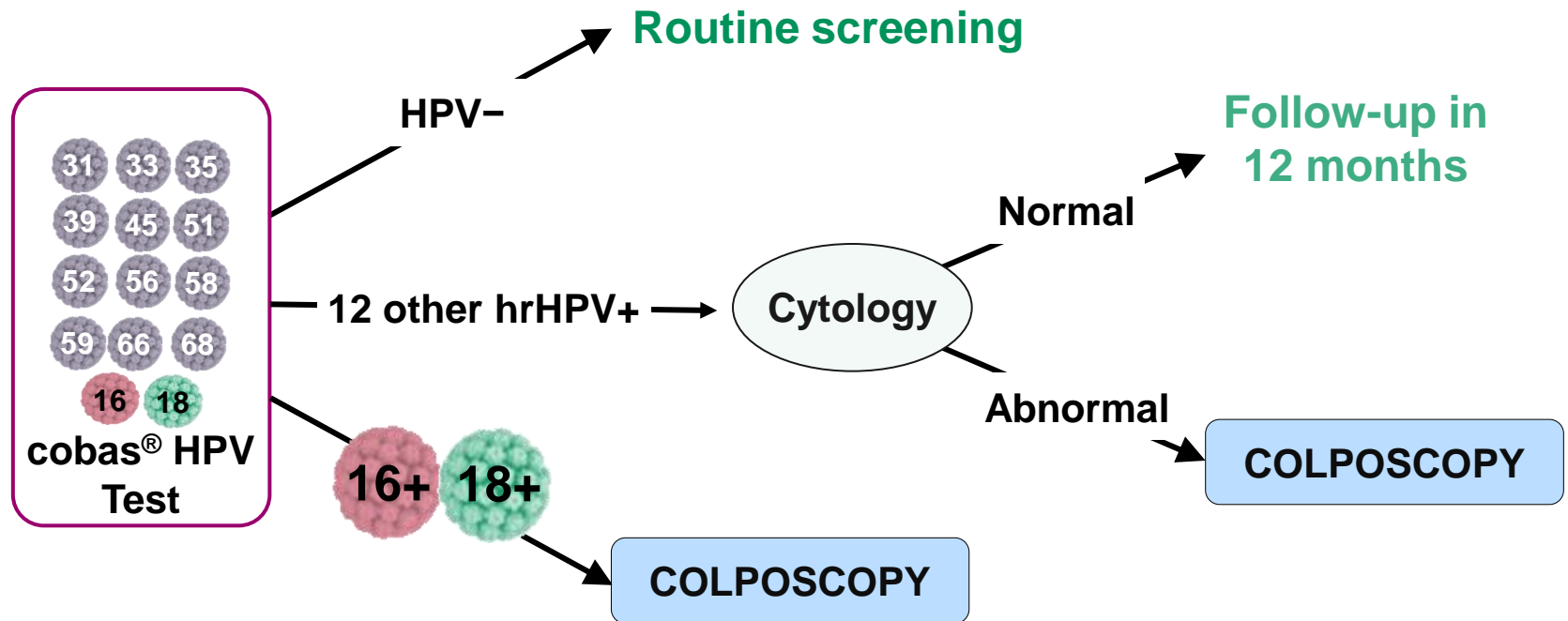
Current Options for Cervical Cancer Screening

Current Options for Cervical Cancer Screening

- Pap smear
 - Women ≥ 21 years every 3 years
- Cotesting: *preferred* option by current guidelines
 - Pap smear + HPV testing in women ≥ 30 years every 5 years
- HPV Primary Screening
 - cobas® HPV Test as the first-line test in women ≥ 25 years every 3 years
 - Supported as a screening option by Society of Gynecologic Oncologists and American Society of Colposcopy and Cervical Pathology

FDA Approved HPV Primary Screening Algorithm:

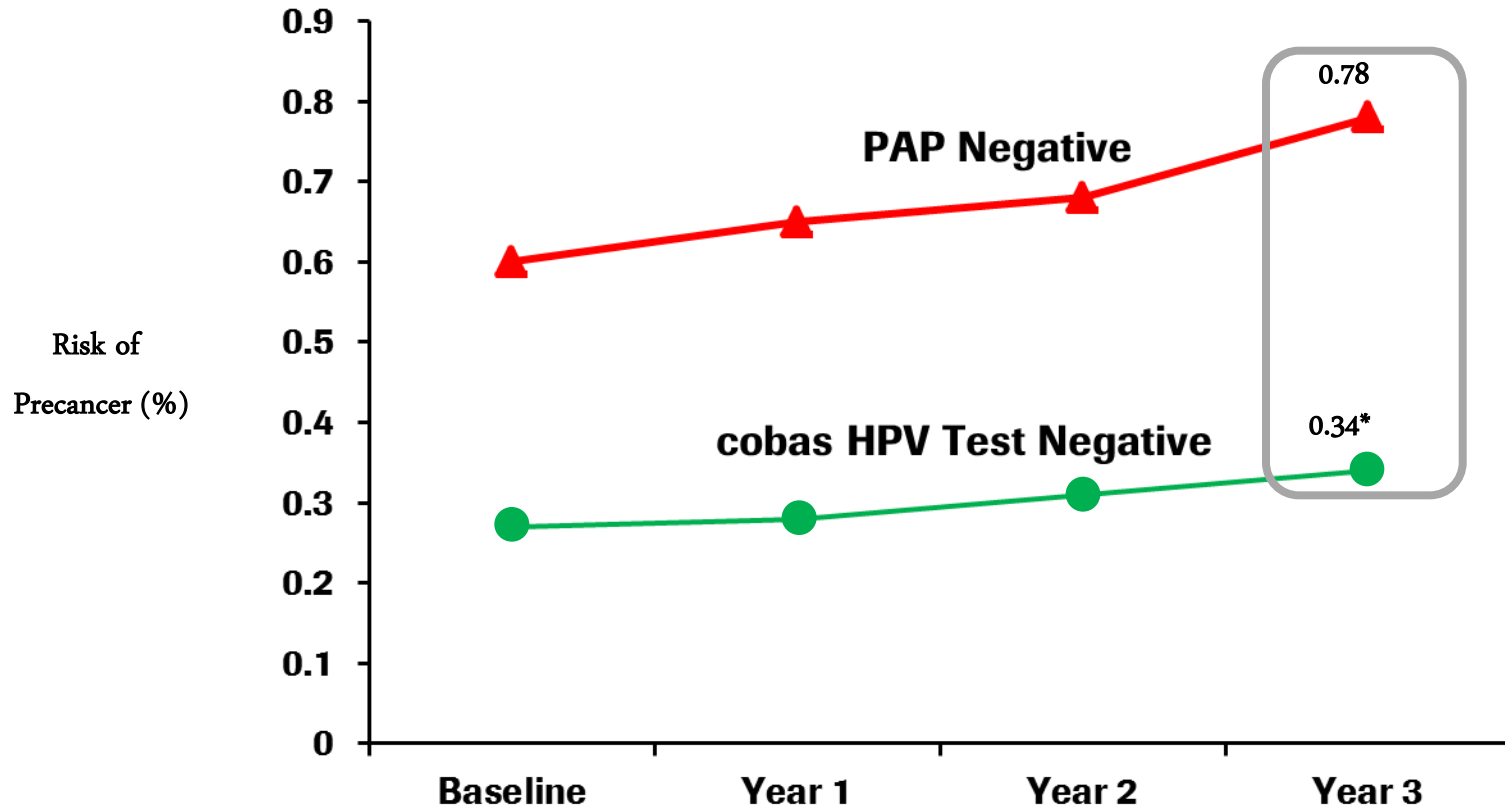
cobas[®] HPV Test with HPV 16/18 genotyping and reflex PAP in women ≥ 25 years



Risk of Precancer over 3 Years after a Negative Screen (*ATHENA trial*):

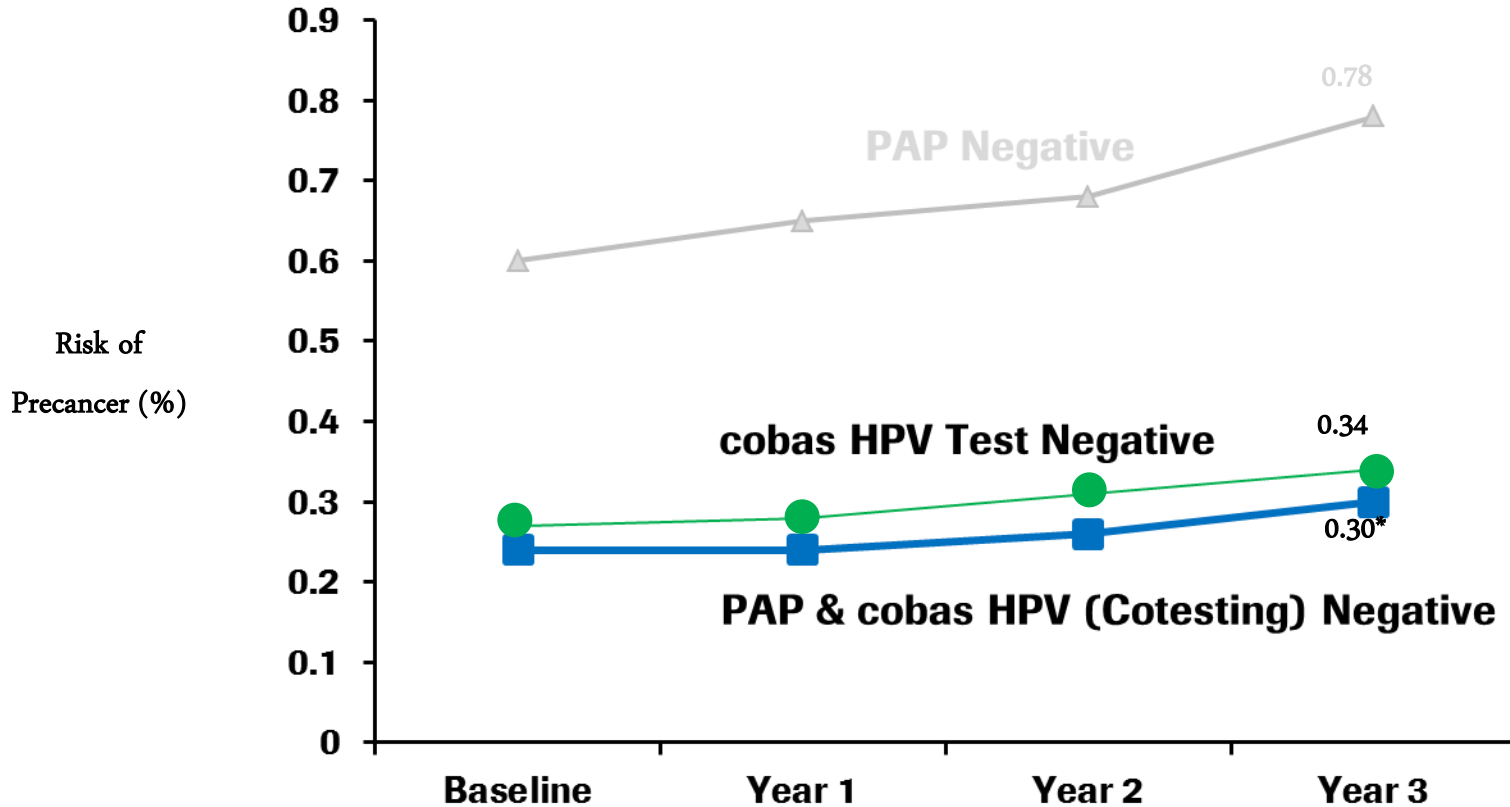


HPV negative vs. PAP negative at baseline (90% of the population)



The risk of \geq CIN 3 over 3 years in women with a negative HPV result at baseline is 1/2 the risk in women with a negative Pap result

Risk of Precancer over 3 Years after a Negative Screen: *HPV negative vs. Cotesting negative at baseline*



A negative Pap result added to a negative hrHPV result at Baseline adds little benefit and increases the colposcopy rate from 4.6% to 5.4%

Comparison of Performance of Strategies to Detect Precancer in Women

Aged \geq 25 Years

(10% of population who screen positive)

| Strategy | Relative Sensitivity | Relative Specificity |
|------------------------------|----------------------|----------------------|
| Pap (Cytology) | 1.00 | 1.00 |
| HPV Primary Screening | 1.33* | 0.99 |

* Significantly higher than cytology.

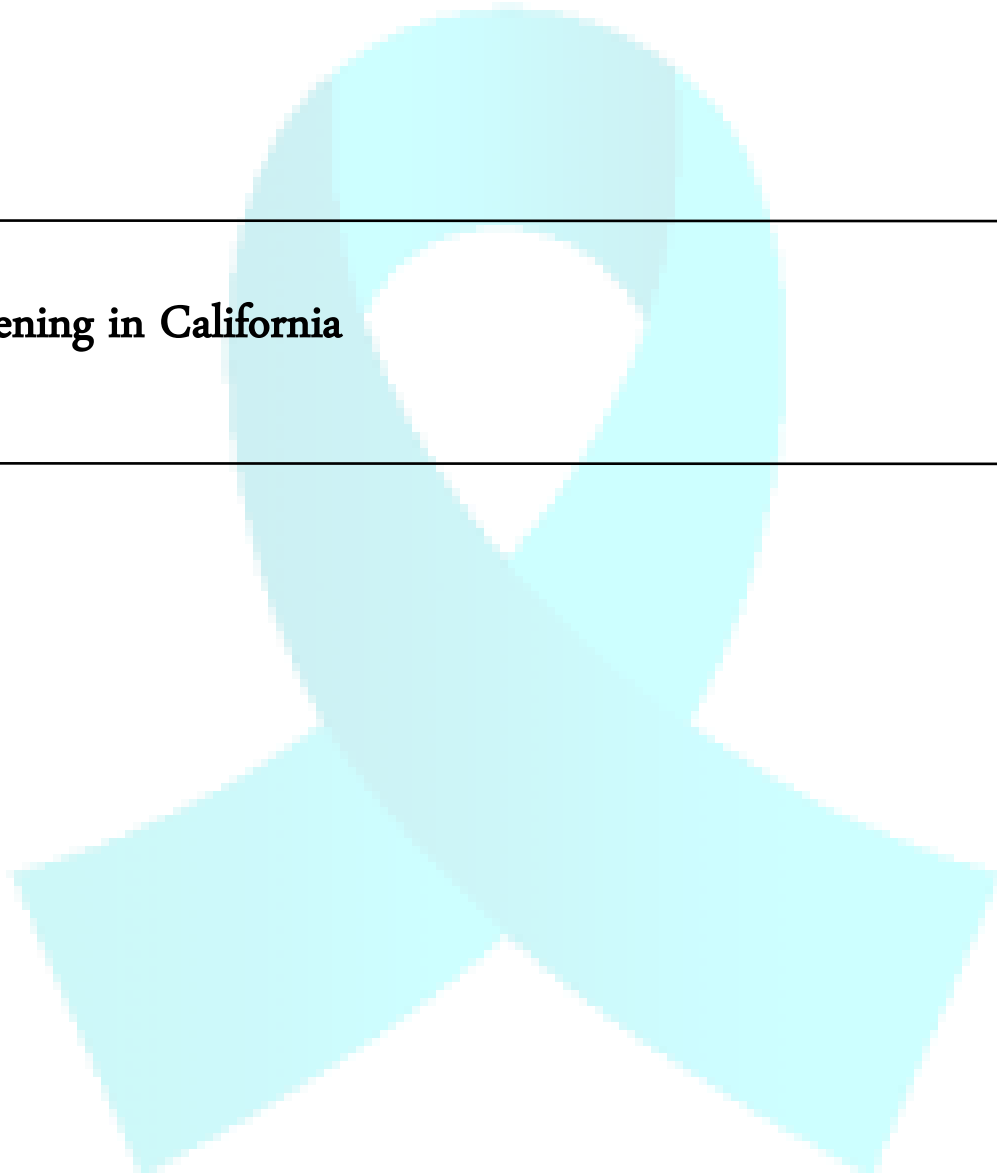
Comparison of Strategies in Women



Aged ≥ 25 Years

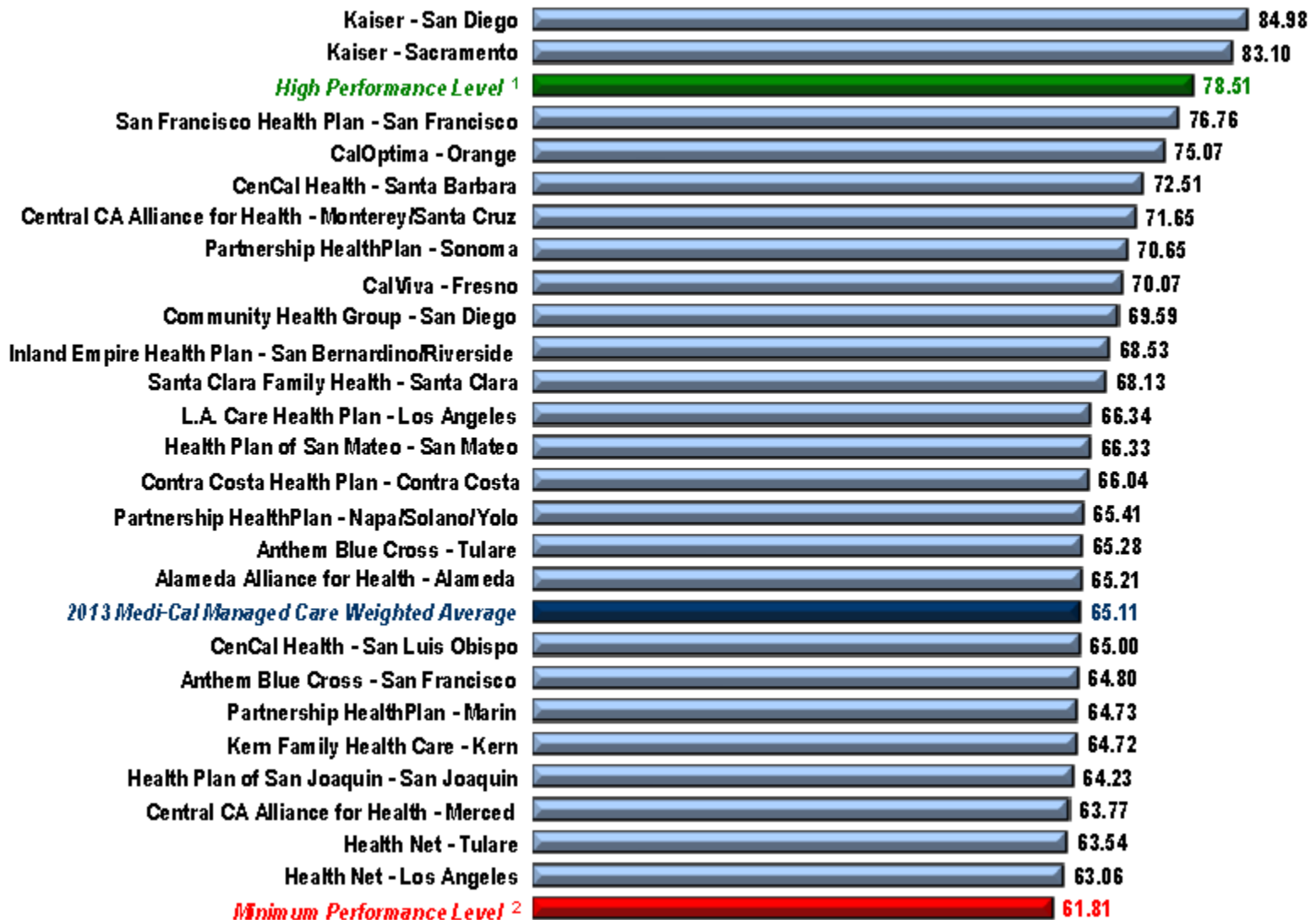
Tradeoffs Between CIN3+ Detected and Colposcopy

| Strategy | Screening Tests | Precancer Cases Detected | Screening Tests per Precancer Case Detected | Colpos | Colpos per Precancer Case Detected |
|-----------------------|-----------------|--------------------------|---|--------|------------------------------------|
| Pap (Cytology) | 43,562 | 167 | 260.9 | 1431 | 8.6 |
| HPV Primary Screening | 44,009 | 233 | 190.1 | 1887 | 8.2 |



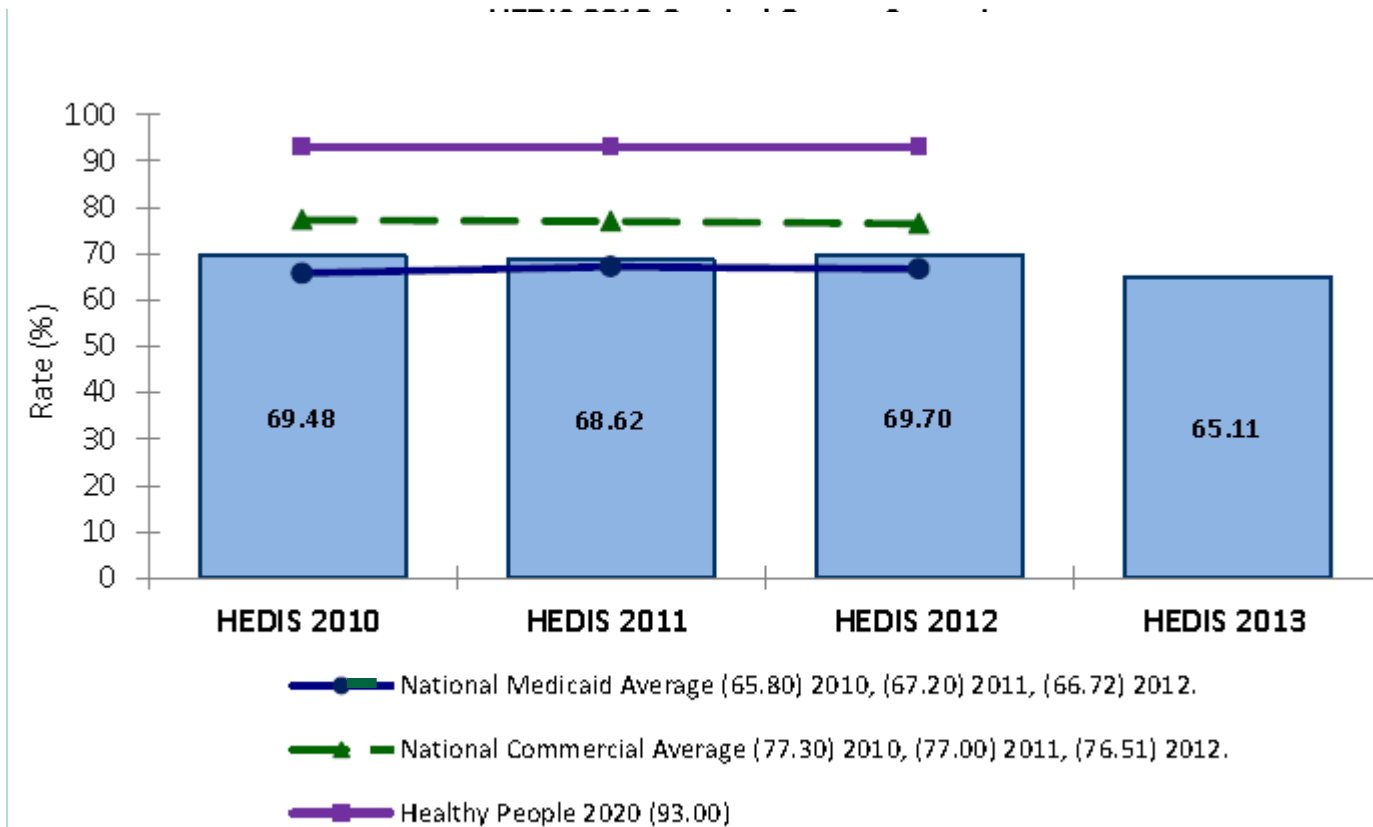
Cervical Cancer Screening in California

Medi-Cal Managed Care HEDIS 2013 Cervical Cancer Screening: *Screening rate ranks above the Minimum Performance Level, but in the lower 1/3 of all health plans*



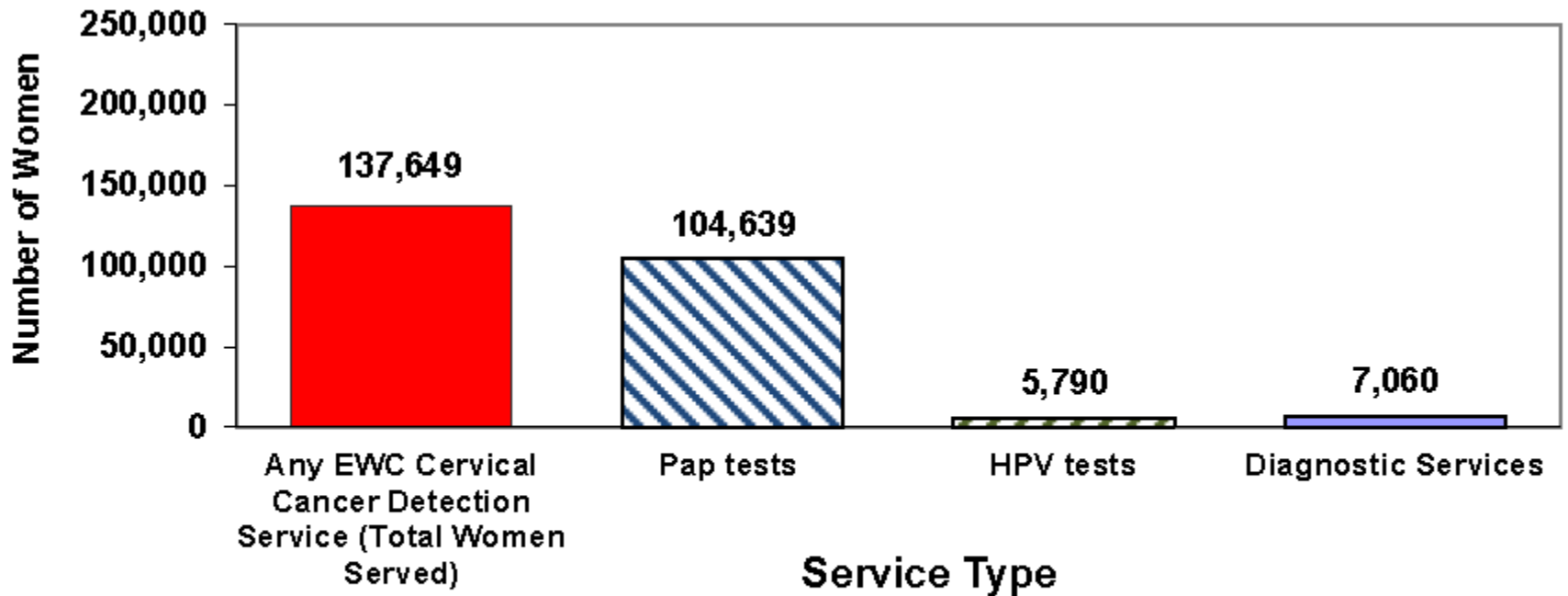
HEDIS 2013 Medi-Cal Managed Care Weighted Average Comparison to State and National Benchmarks:

Weighted average was lower than Healthy People 2020 Objective and showed a decrease relative to Medicaid & National Commercial Average

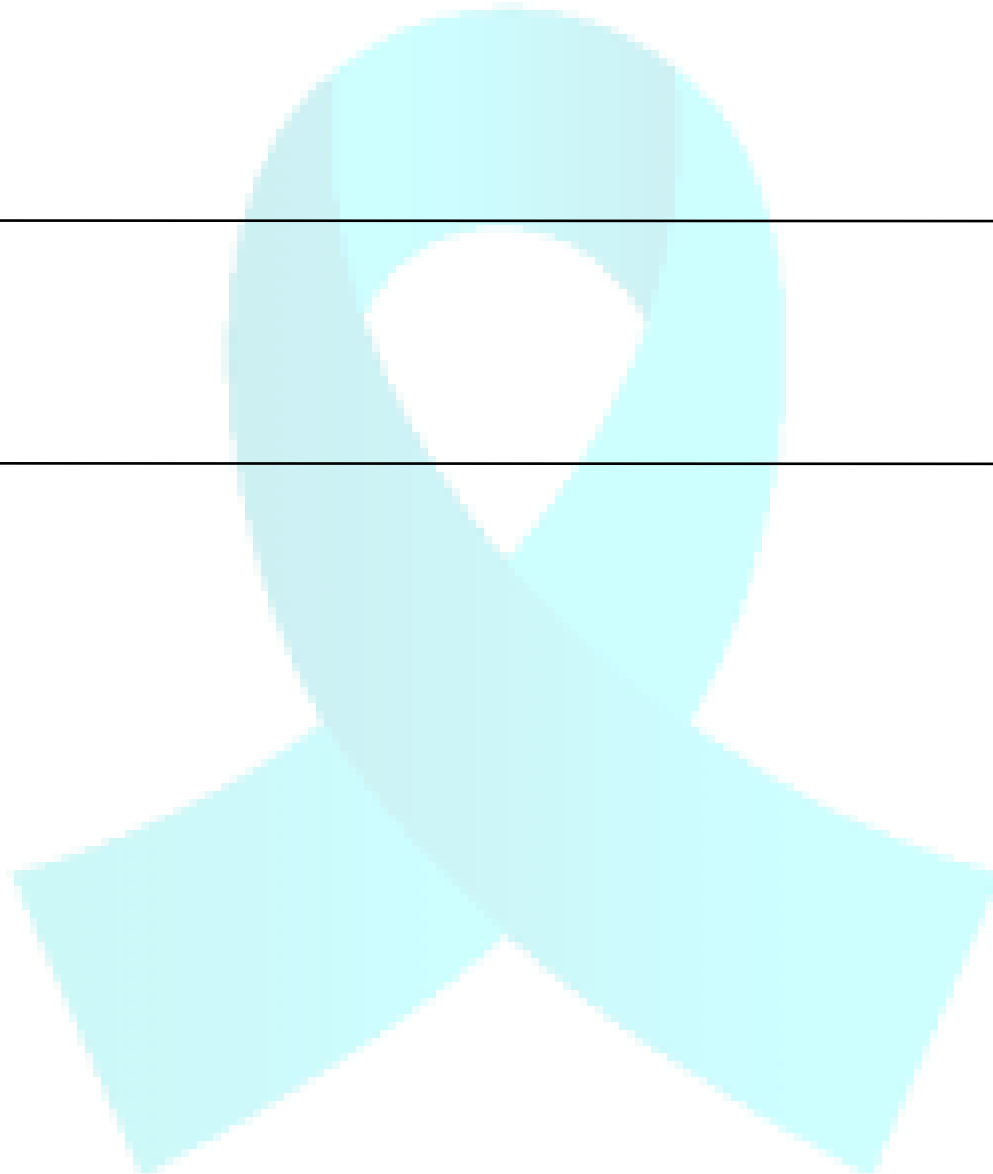


Every Woman Counts Cervical Cancer Screening and Diagnostic Services, 2010-2011:

HPV testing lagging well behind Pap testing



Notes: 1) EWC clinical testing for 2010-2011, reported as of October 2012; 2) "Diagnostic Services" includes colposcopy with or without cervical biopsy(s), endocervical curettage, lesion excision with or without fulguration, endometrial sampling and other diagnostic procedures.



Conclusions

Cervical Cancer Screening:

- When implemented and effective, can prevent cervical cancer
- Has evolved from the Pap smear to using combinations of Pap and HPV testing
- Should include HPV testing either as a cotest or a first line stand-alone test
- Needs to be improved in California so that rates rise at least to the national Medicaid average and closer to Healthy People
 - Educate physicians/other health care providers and women
 - Identify and implement the most cost effective screening options

The solution to preventing cervical cancer ...



Effective screening...
one woman at a time

Doing now what patients need next