Gynecologic Cancer Screening Update

Dennis Yi-Shin Kuo, MD, FACOG

Associate Director, Division of Gynecologic Oncology

Associate Professor, Department of Obstetrics and Gynecology and Women's Health

Montefiore Medical Center, Albert Einstein College of Medicine

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Montefiore

Disclosure

- **I served once as a proctor for Intuitive surgical.**

Objectives

- Have an understanding of updates on the Pap test for screening and HPV natural history
- Be able to convey the updates on screening in low risk women, pregnant women, and adolescents
- Be able to convey the updates on HPV testing and HPV genotyping
- Be aware of changes in cervical cancer screening in other areas of the globe

Cervical Cancer: Worldwide Prevalence, Incidence, and Mortality Estimates

Prevalence: 2,274,000 women have cervical cancer[1]

Incidence: 510,000 new cases each year[1]

2000 estimated incidence of invasive cervical cancer by selected region[2]

Mortality: Second leading cause of female cancer-related deaths (288,000 annually)[1]

1. World Health Organization. Geneva, Switzerland: World Health Organization; 2003:1–74. **2.** Bosch FX, de Sanjosé S. *J Natl Cancer Inst Monogr.* 2003;31:3–13.

Epidemiology

- Incidence: 1975 14.8 per 100,000
  2006 6.5 per 100,000
- Mortality: 2009 11,270 new cases in the US
  4070 deaths in 2009
- Mortality: 500,000 new cases and 240,000 deaths per year in the world
- Cervical cytology screening programs reduce incidence of cervical cancer
- What is the best available evidence on screening for cervical cancer

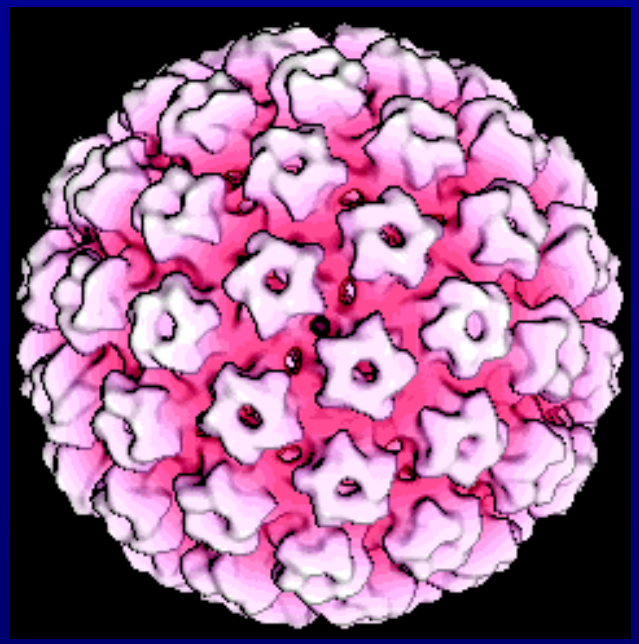
Background

- 50% of the women with cervical cancer never had cervical cytology testing.
- Another 10% had not been screened within the 5 years before diagnosis.
- Although rate of cervical cancer are on the decline in US born women, immigrants of US from countries without routine cervical cytology screening remain a high-risk group

Natural History of Cervical Intraepithelial Neoplasia (CIN)

- Infection with human papillomavirus (HPV): Essential in the development of cervical neoplasia.
- Most HPV-infected women will never develop cervical abnormalities.
- Most young women have effective immune response that clears the infections or reduce the viral load in an average of 8-24 months.
- Cigarette smoking and a compromised immune system are factors that may disrupt this immunity.

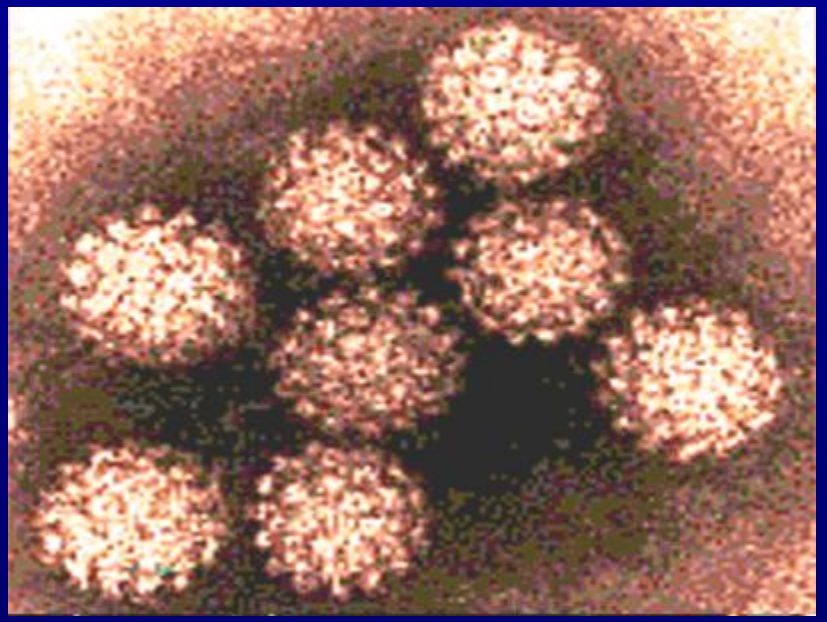
Human Papillomavirus



- Circular, double-stranded DNA virus
- Highly species specific and epithelialtropic
- Many cancer-causing or ‘high risk’ HPV types
  - Most common types in US are HPV 16 and 18

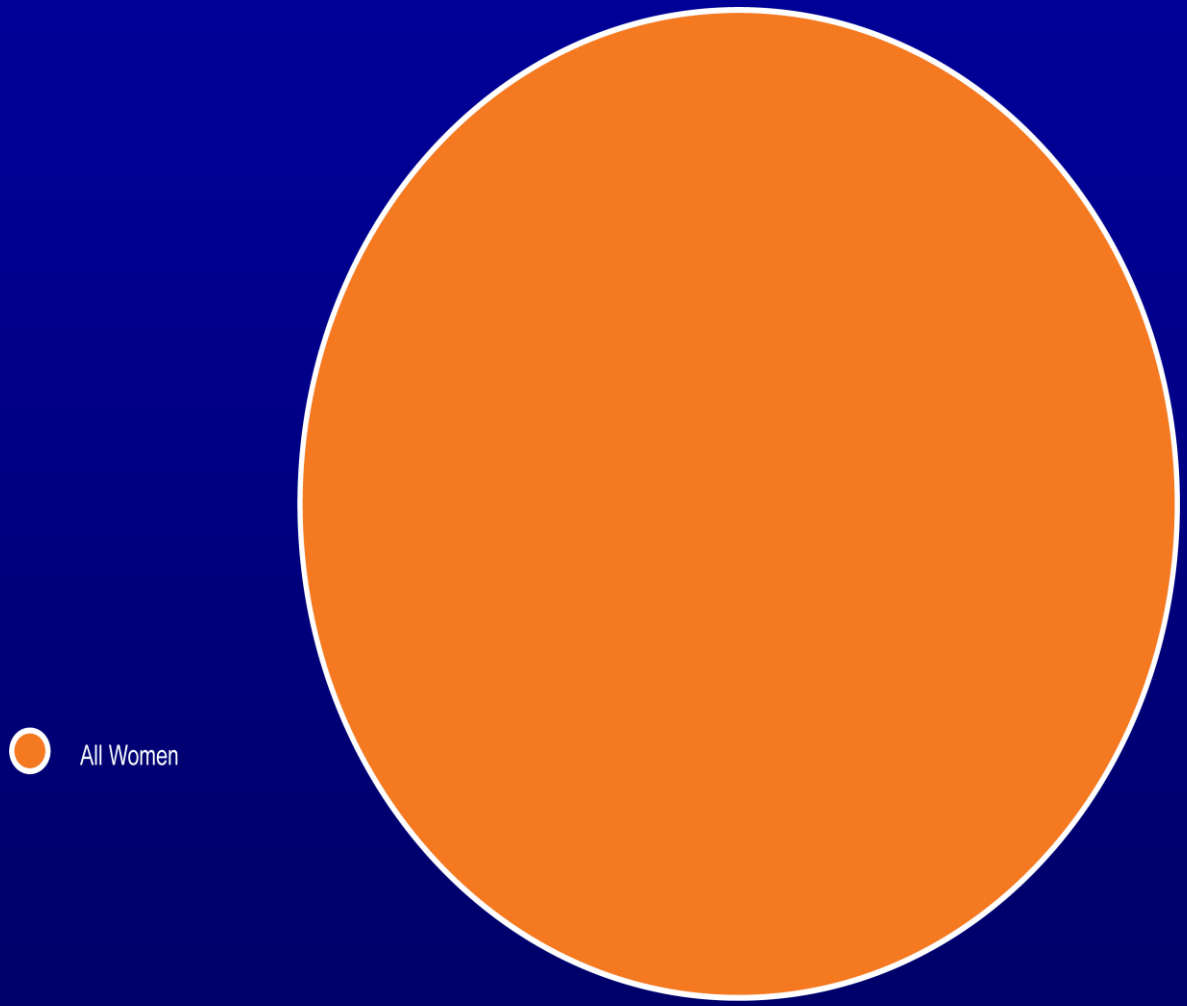
Human Papillomavirus is Necessary for Cervical Cancer

- HPV DNA sequences detected in more than 99% of invasive cervical carcinomas[1]
  - The association between HPV and cervical cancer is higher than that between smoking and lung cancer
- Most common sexually transmitted infection



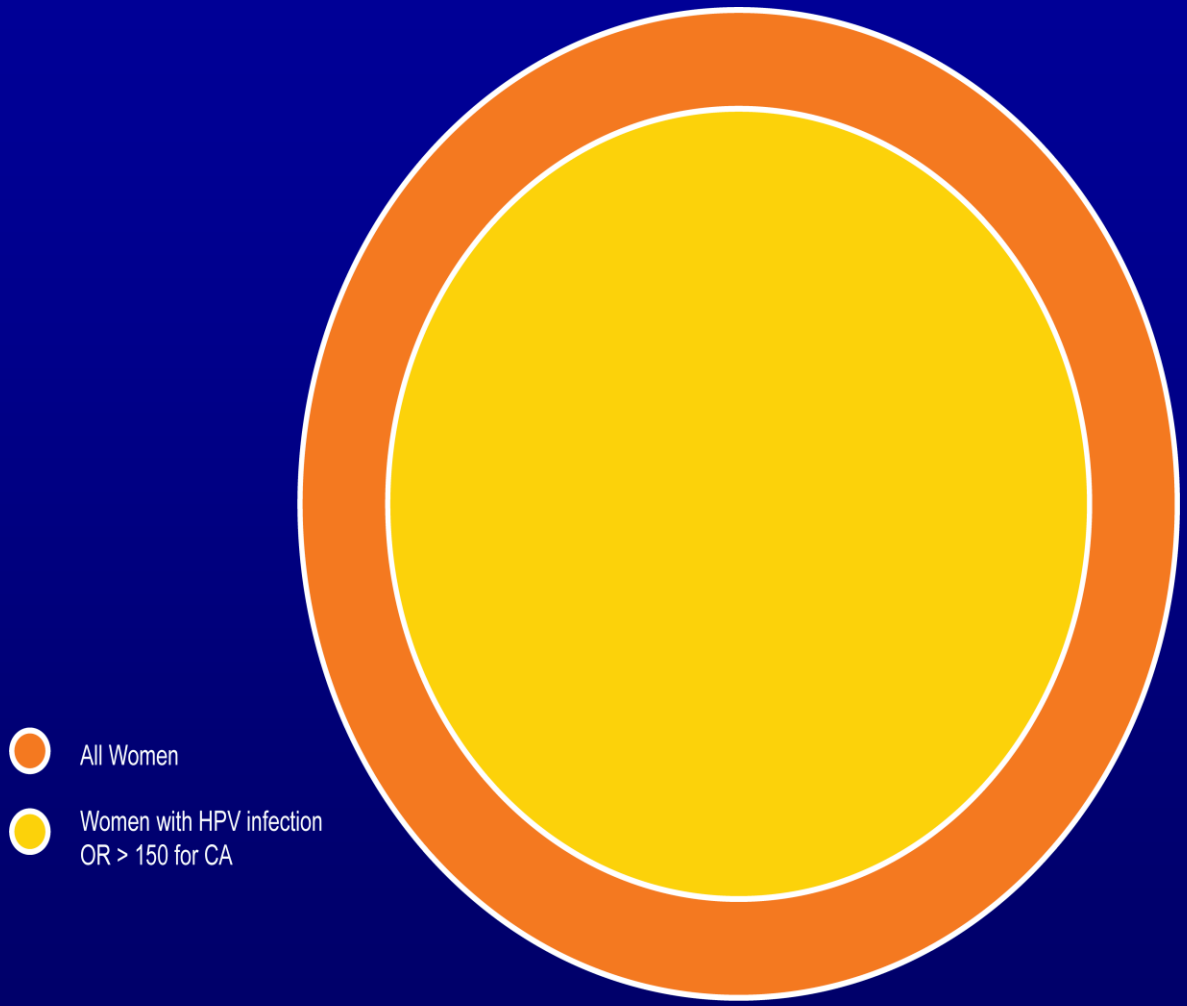
[1]Walboomers JM, Jacobs MV, Manos MM, et al. *J Pathol* 1999;189(1):12-9.

HPV and Cervical Cancer



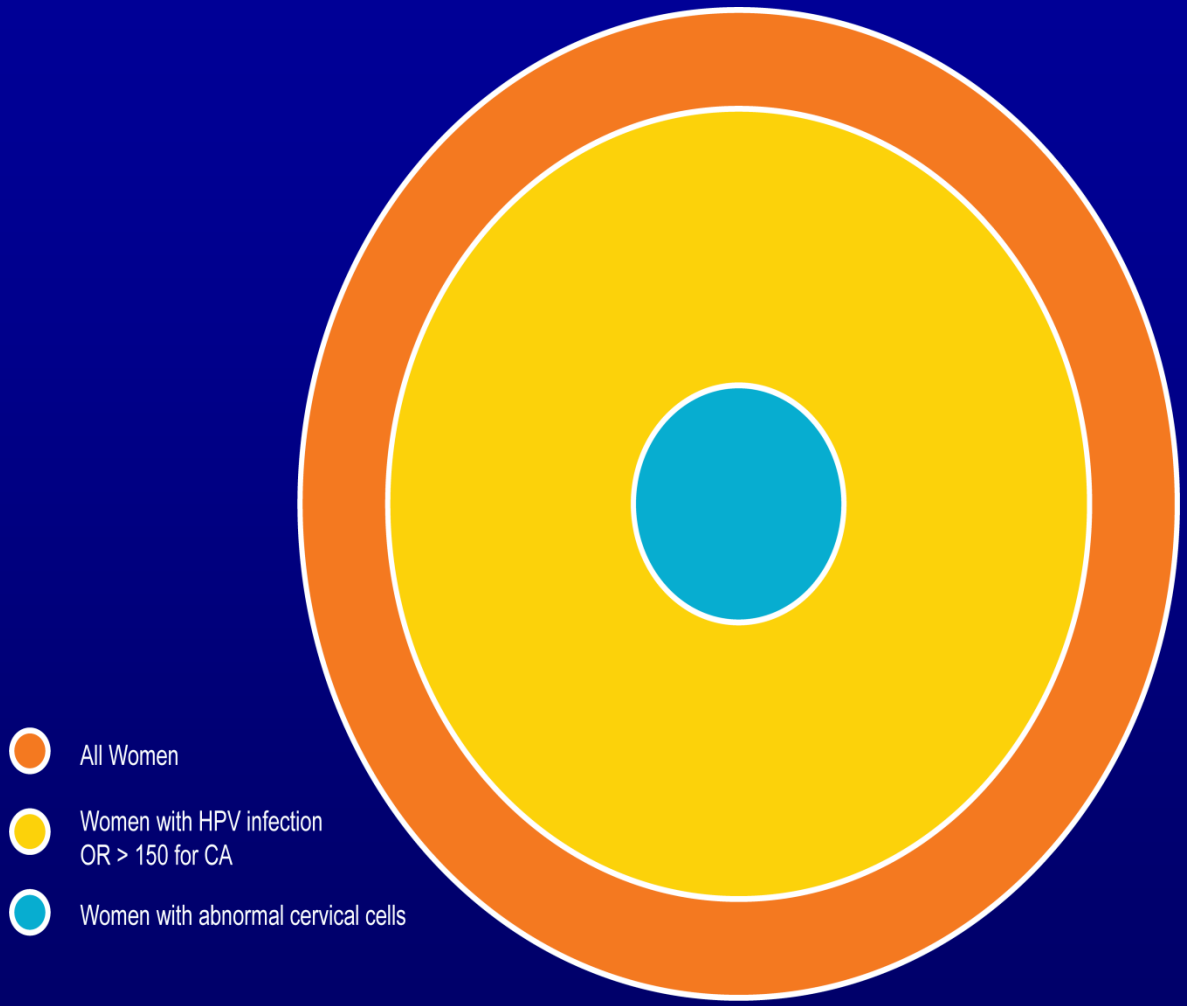
Munoz N, Bosch FX, de Sanjose S, et al. *N Engl J Med* 2003;348:518-27.

HPV and Cervical Cancer



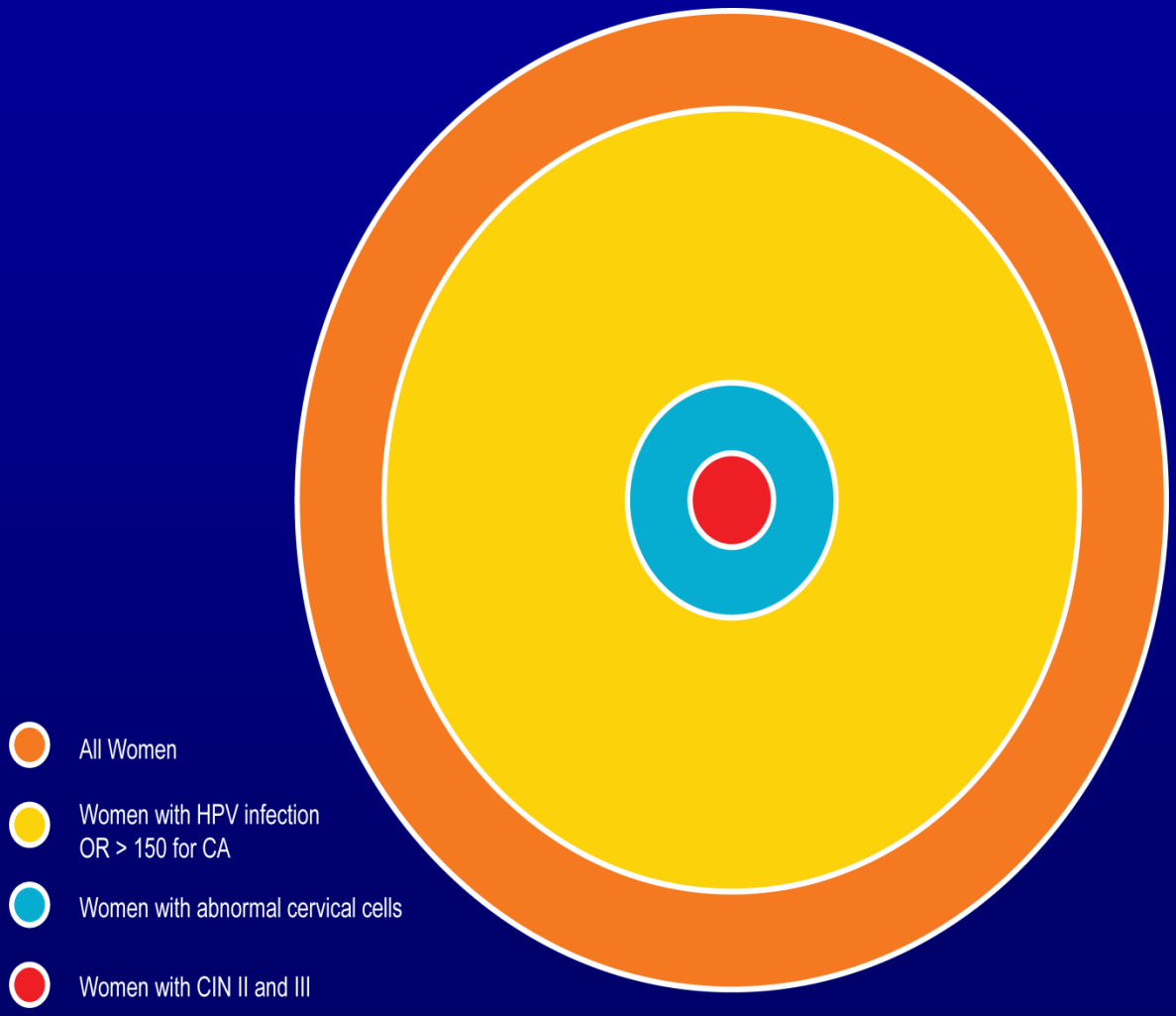
Munoz N, Bosch FX, de Sanjose S, et al. *N Engl J Med* 2003;348:518-27.

HPV and Cervical Cancer



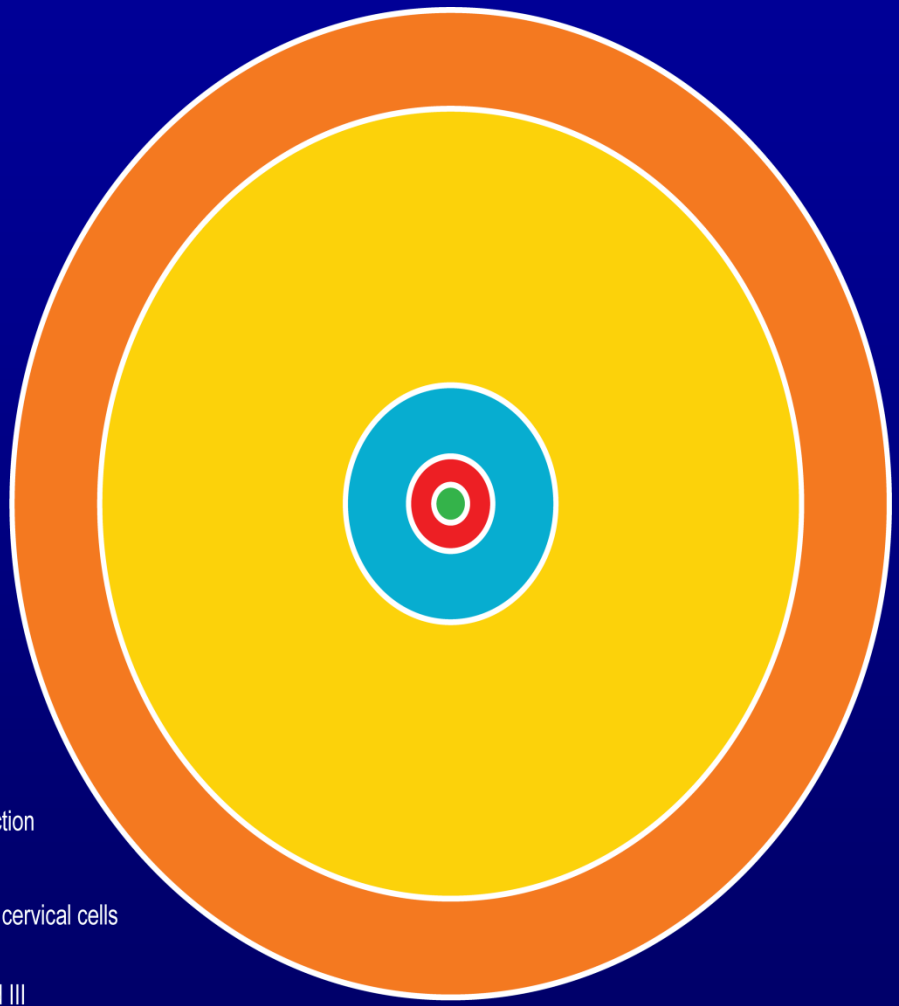
Munoz N, Bosch FX, de Sanjose S, et al. *N Engl J Med* 2003;348:518-27.

HPV and Cervical Cancer



Munoz N, Bosch FX, de Sanjose S, et al. *N Engl J Med* 2003;348:518-27.

HPV and Cervical Cancer



All Women

Women with HPV infection
OR > 150 for CA

Women with abnormal cervical cells

Women with CIN II and III

Women with cervical cancer

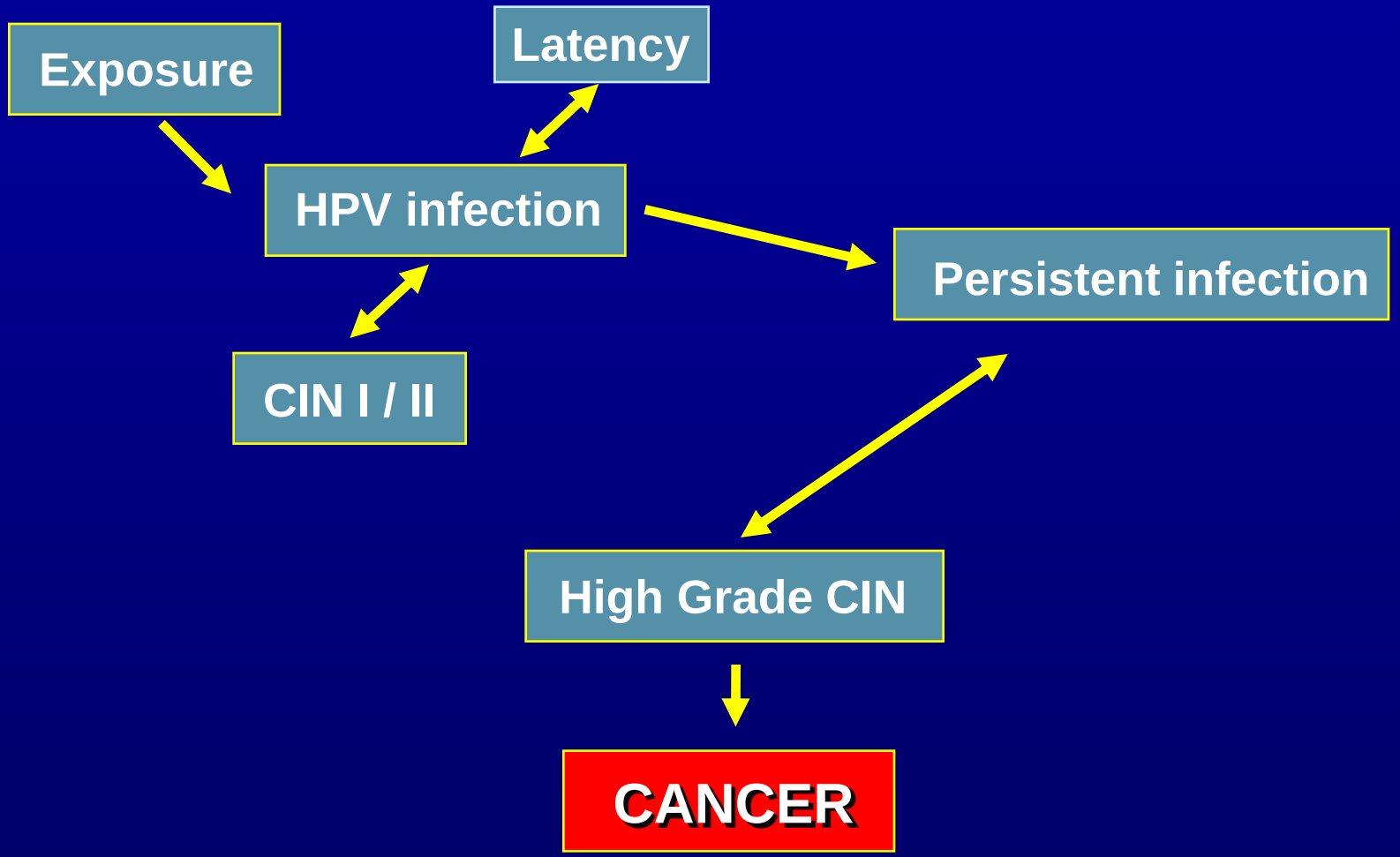
Munoz N, Bosch FX, de Sanjose S, et al. *N Engl J Med* 2003;348:518-27.

US HPV Statistics

- Lifetime risk for sexually active men and women approaching 80%.[1]
- Point prevalence rate of HPV infection around 27%[2]
- about 34% of 14-24 year olds infected with HPV [2]
- Condoms are, at best, only marginally effective for preventing HPV infection[3]
  - Social barriers also limit condom effectiveness[4]

1. Centers for Disease Control and Prevention. Rockville, Md: CDC National Prevention Information Network; 2004.
2. Dunne et al. JAMA 297 (8): 813-819. 2007.
3. Winer et al. NEJM 354:2645-54. 2006.
4. Holmes KK et al. Bull WHO 82:454-61.2004.

Pathway to Cervical Cancer



Adopted from Einstein and Burk, *Papillomavirus Report*, 2001

Cytologic Reporting

- The Bethesda System: Proposed in 1988, revised in 1991.
- Specimen adequacy: Satisfactory or unsatisfactory for interpretation
- Atypical Squamous Cells: The degree of nuclear atypia is insufficient to warrant a precancerous diagnosis
  - Atypical Squamous cells of undetermined significance (ASC-US)
  - Atypical squamous cells cannot exclude a high grade squamous intraepithelial lesion (ASC-H)

Cytologic Reporting

- Atypical Glandular Cells: Used to be called Atypical glandular cells of undetermined significance (AGUS), potentially more aggressive work-up.
- Low-grade squamous intraepithelial lesions
- High-grade squamous intraepithelial lesions
- Squamous cell carcinoma

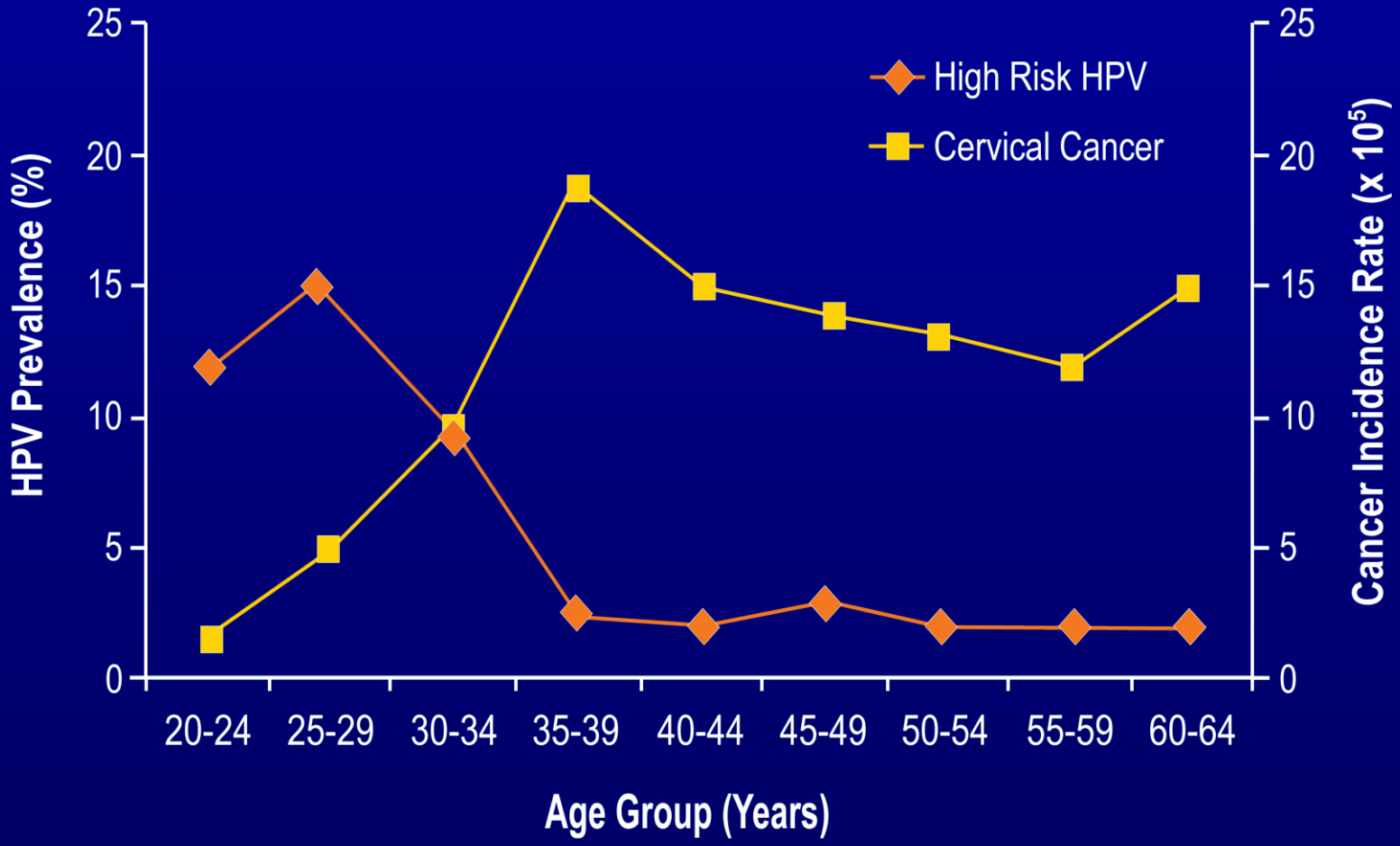
Natural History of HPV Infection[1]

	Koutsky et al. 1992	Ho et al. 1998	Woodman et al. 2001	Moscicki et al. 2001
# Patients Followed	241	608	1075	496
# Patients HPV (-)	198	399	1075	105
Average age of population	26 ± 7	20 ± 3	18 ± 1	20 ± 2
Median Duration of F/U	25 months	36 months	36 months	26 months
% of HPV(+) patients developing CIN	28% with CIN 2-3	26% with any CIN	44%	22%
Likelihood of developing CIN if HPV(+) (Relative Risk)	11	3	8	7
Median duration of HPV infection	N.D.*	8 months (7-10)	14 months (8-25)	N.D.

**ND, not described in publication*

[1]Einstein MH and Burk RD. *Papillomavirus Report*, 2001

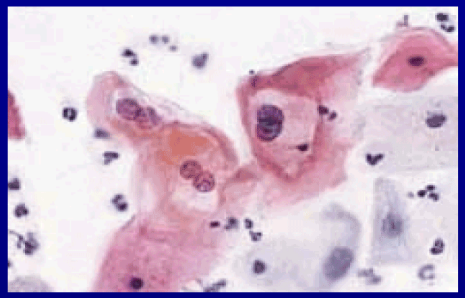
Age-Specific Rates of HPV Infection and Cervical Cancer



Castle PE, et al. *Obstet Gynecol.* 2009;113:595–600.

Model of Progressive Cervical Dysplasia

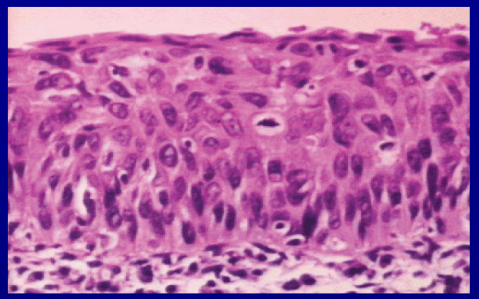
Regression 50-60%
Progress 11%



CIN1/HPV

Months-Years

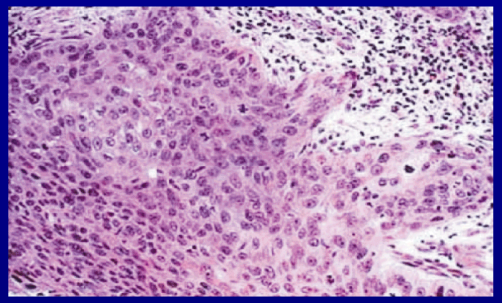
Regression 32-43%
Progress 14-22%



CIN 2, 3

Months-Years

HPV Clearance



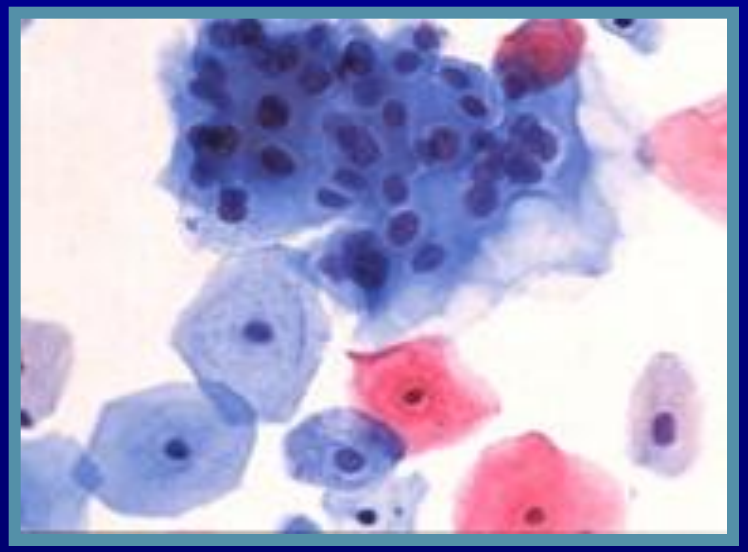
Cancer

Years-10s of Years

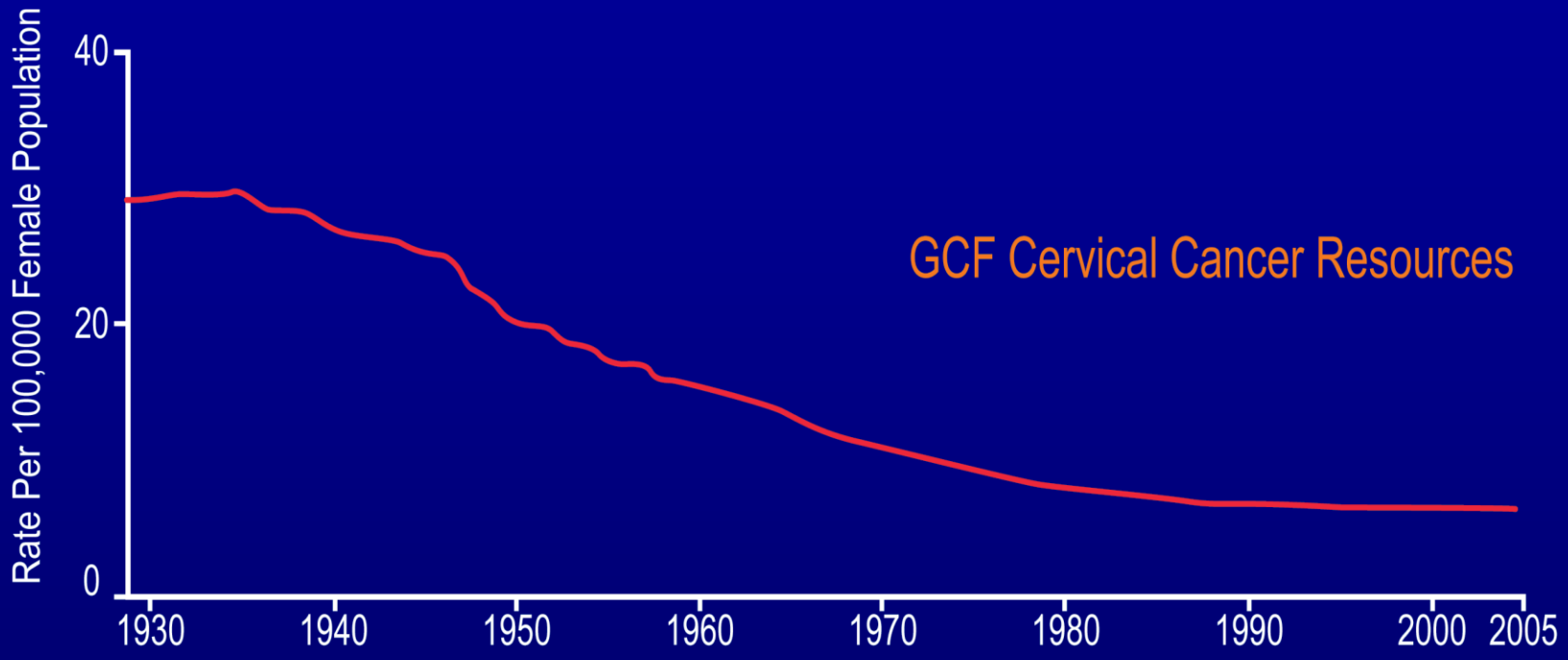
Schiffman MH, Brinton LA. *Cancer*. 1995;76:1888-1901.

The Papanicolaou (PAP) Test

Dr. Papanicolaou

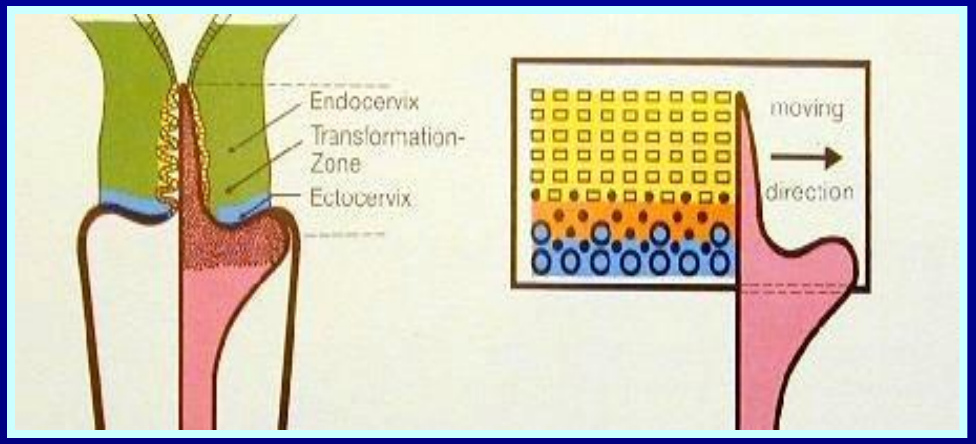


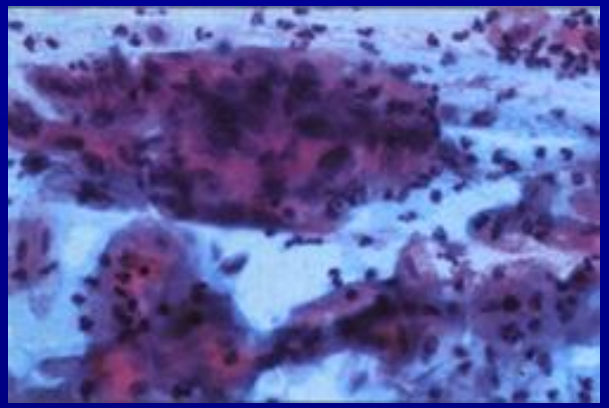
Decreasing Trends of Cervical Cancer Incidence in the U.S.



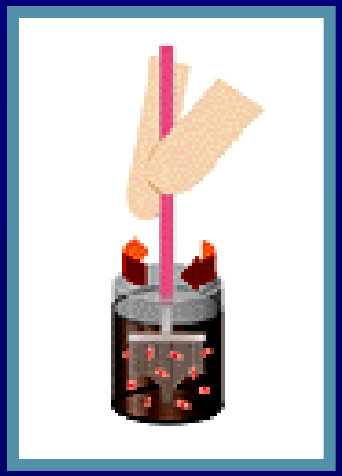
- With the advent of the Pap smear, the incidence of cervical cancer has dramatically declined.
- The curve has been stable for the past decade because we are not reaching the unscreened population.

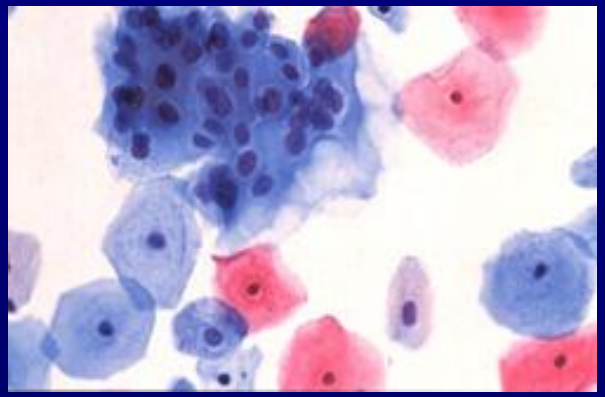
Pap Test Technology





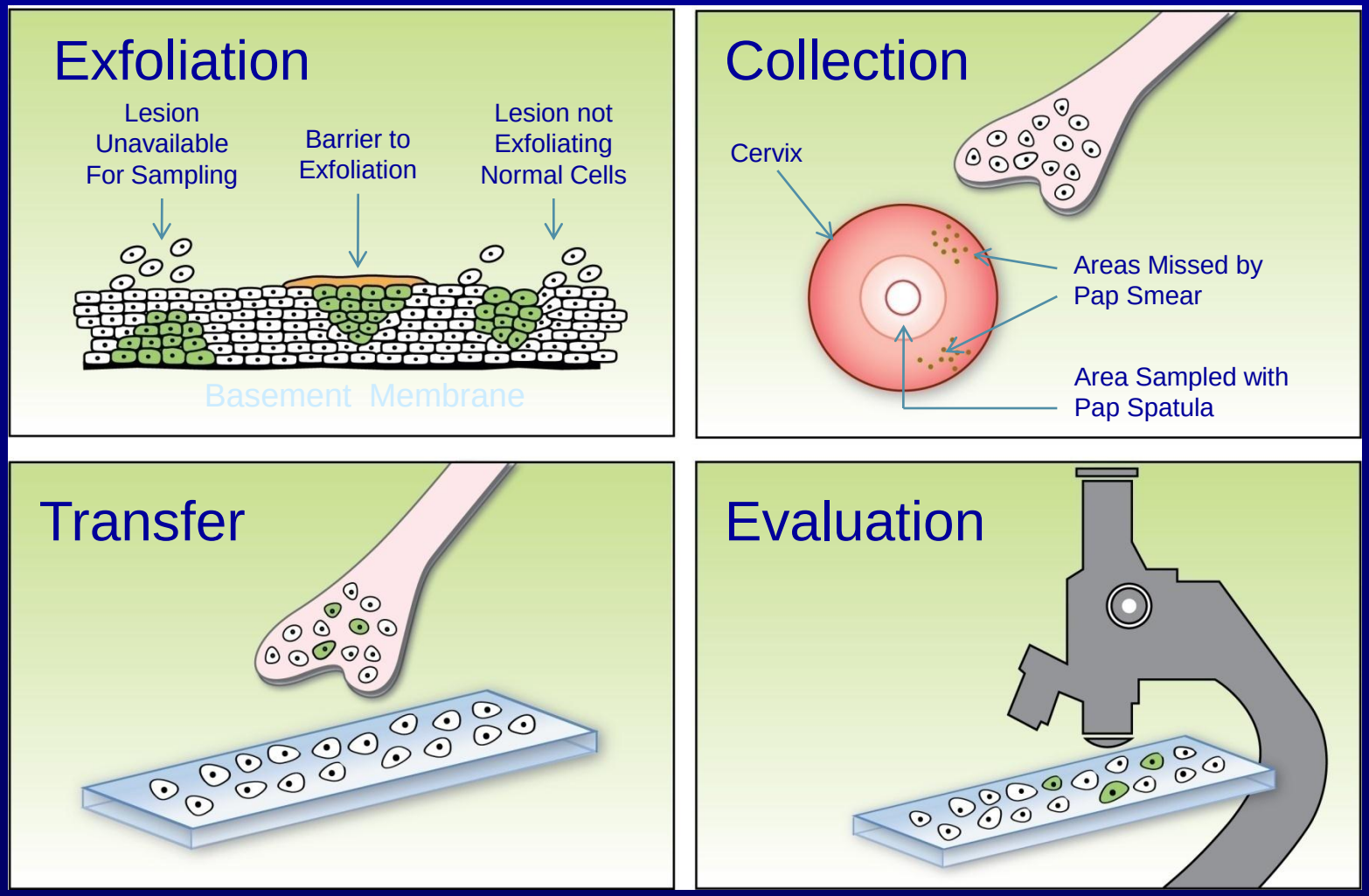
Conventional Smear





Liquid Based Pap Test

Why Do Pap Tests Fail?



Liquid Based versus Conventional Pap

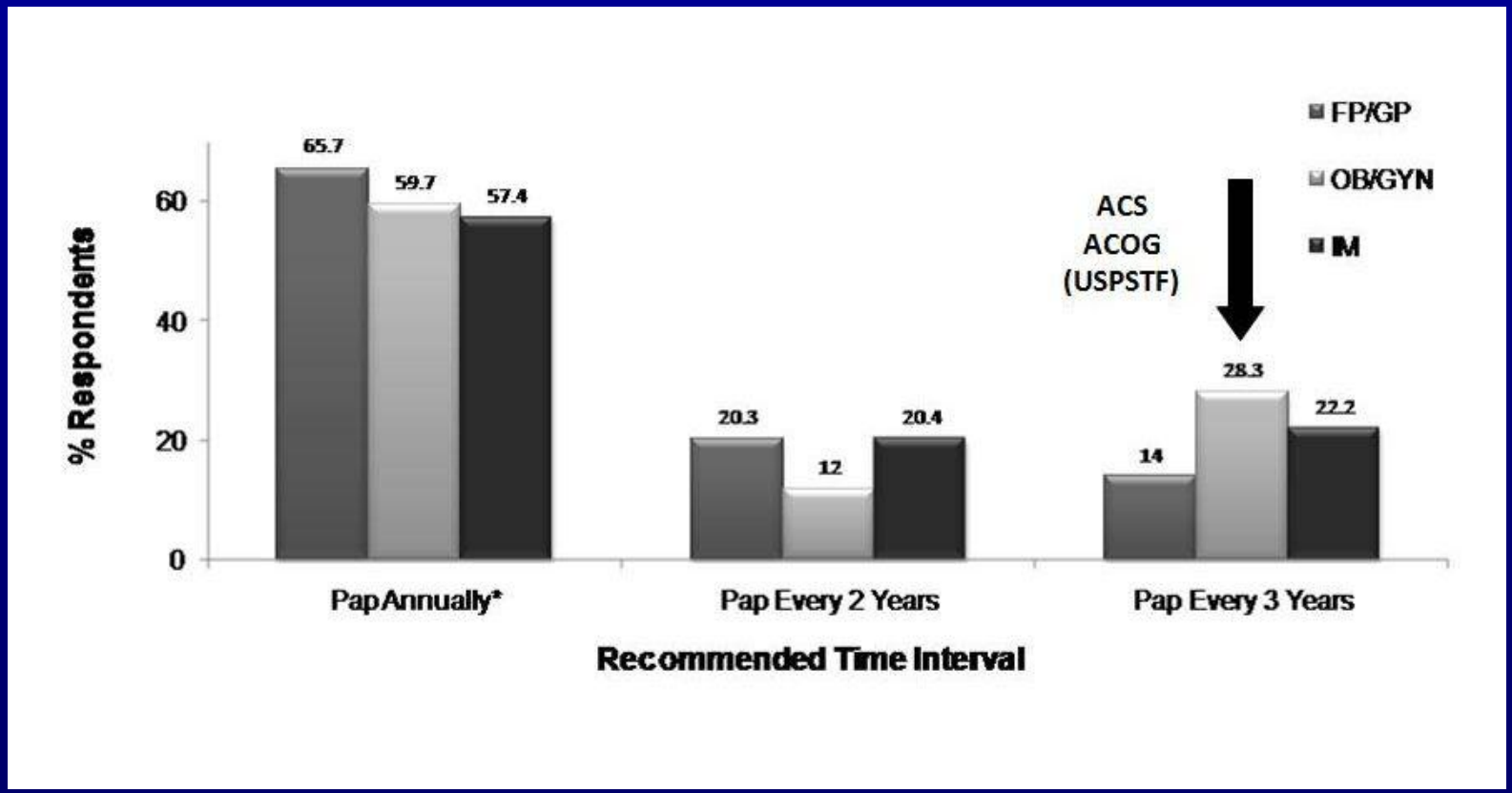
- Performance of conventional cytology requires avoidance of contaminating blood, lubricants, discharge
  - Minimal difference in performance
- Liquid based cytology filters out artifact
- Nearly 90% of Pap performed in the US is liquid based
- Benefits of liquid based cytology include molecular testing of HPV and other STDs

ACOG Practice Bulletin Number 109, December 2009

Issues with screening algorithms and additional molecular testing

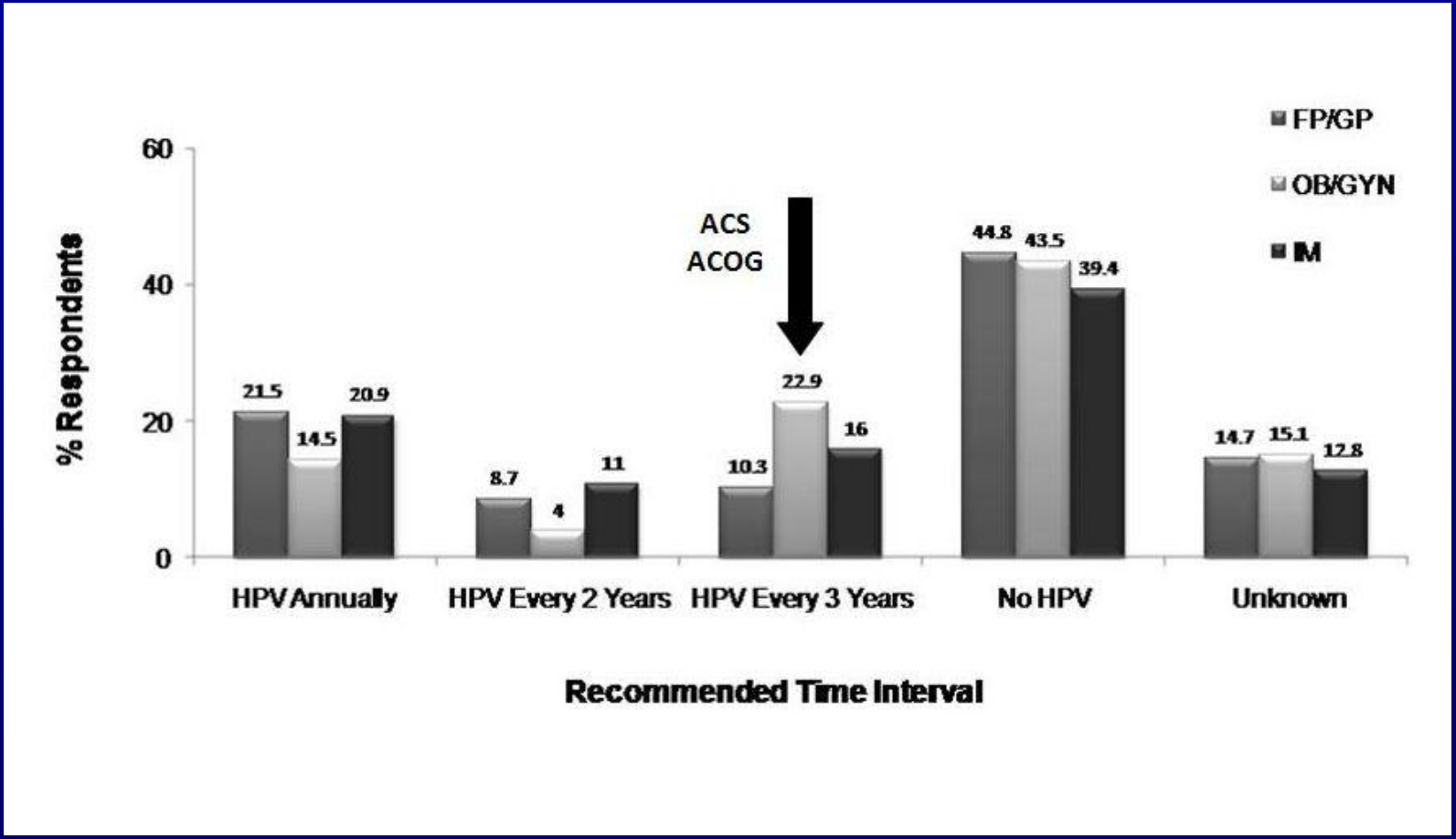
- Too complicated
- Future algorithms and additional molecular testing meant to maximize identification of clinically relevant disease while minimizing:
  - Equivocal Paps (ASCUS and LSIL)
  - Colposcopy
  - Overtreatment, particularly in young women
- Medical-legal fears of providers in missed disease or patient non-compliance

Recommended times for a follow-up Pap test for a 35 year-old female with normal Pap tests and HPV negative



Herzog TJ, Huh W, Einstein MH. *Gynecol Oncol.* 2010.

Recommended times for a follow-up HPV test for a 35 year-old female with normal Pap tests and HPV negative



Herzog TJ, Huh W, Einstein MH. *Gynecol Oncol.* 2010.

CIN3 is the Most Significant Clinical Target for Screening

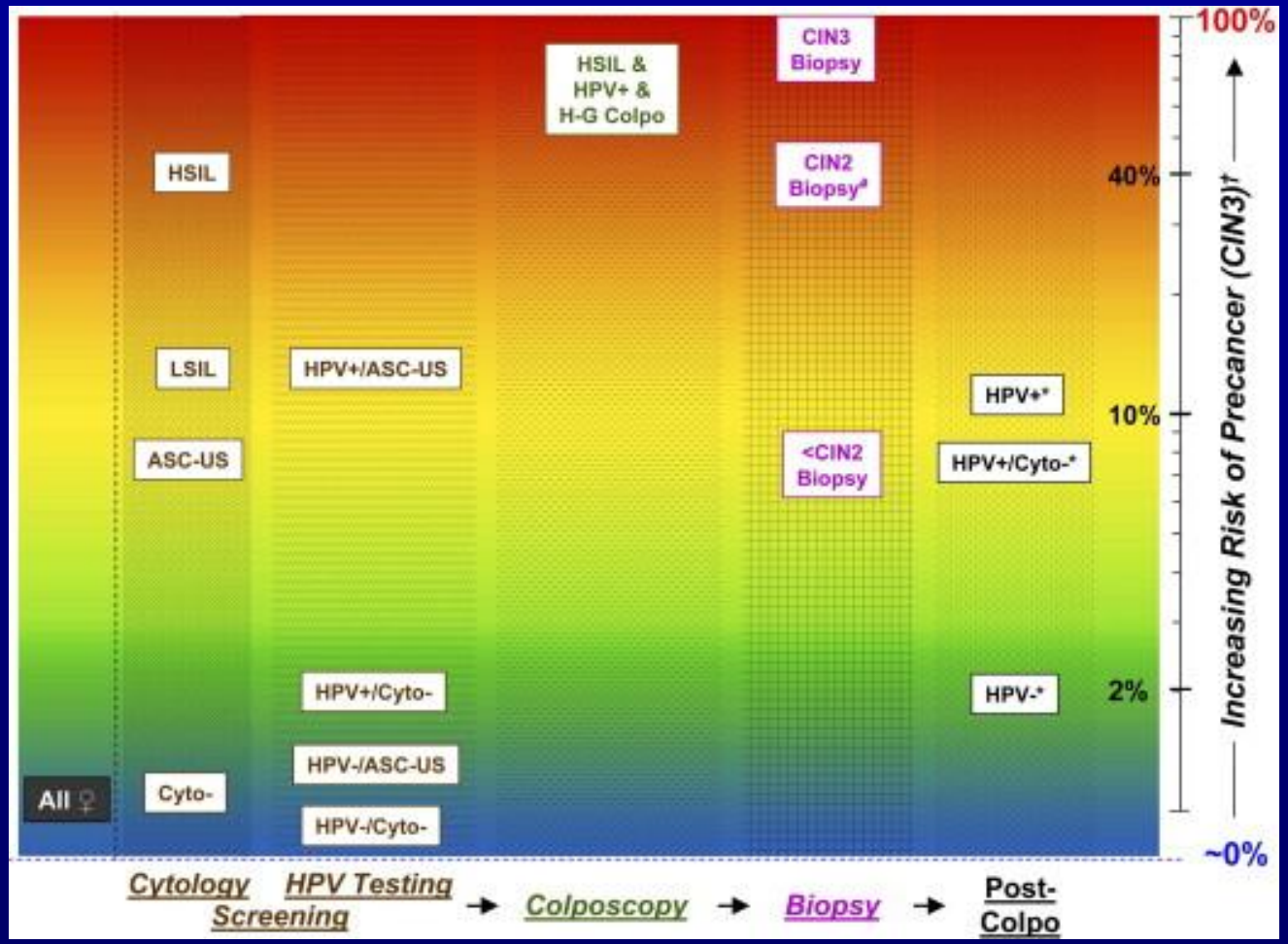
- Although not all CIN3 lesions will progress to cancer, it is generally considered to be a cancer precursor[1]
  - CIN3 prevalence peaks between ages 25 years and 30 years[2]
  - Progression to cancer usually takes at least a decade or longer
- The significance of CIN2 is less clear[2]
  - The risk of progression to CIN3 or cancer appears greater for women with CIN2 than for women with CIN1
  - However, many women with CIN2 will have regression of their lesions without therapy[3]
  - Opportunities for biomarker development

[1]McCredie et al *Lancet Oncology*, 2008
[2]ACOG Practice Bulletin No. 99. *Obstet Gynecol*. 2008
[3]Castle P et al, *Obstet Gynecol*. 2009.

Biomarkers under development for prediction of progressive CIN

- $P16^{INK4A}$ +/- Ki-67
- 3q26 gain
- mRNA
- Epigenetic profiling

Risk of cervical precancer and results of screening and clinical management for cervical cancer prevention



Castle et al. J Low Genit Tact Dis 2008

Cytologic Abnormalities in Adolescents

- Adolescent = 20 years of age and younger (ASCCP)
- High prevalence of HPV and minor cytologic abnormalities
- Very low risk of invasive cervical cancer
- Majority of HPV infections spontaneously clear in 2 years

Cytologic Abnormalities in Pregnant Patients

Abnormality	Management
ASC-US	-Identical to non-pregnant -Can defer colposcopy until 6 weeks postpartum -ECC unacceptable
LSIL	-Colposcopy preferred -Can delay colposcopy until 6 weeks postpartum -No CIN 2 or 3, follow-up postpartum
HSIL	-Colposcopy -Biopsy lesions consistent with CIN 2 or 3 -Repeat evaluation 6 weeks postpartum

Cervical Cancer Screening Recommendations for Low Risk Women

	American Cancer Society (2002)	American College of Obstetricians and Gynecologists (2009)
Initiation	3 yrs after intercourse. Not later than age 21	Age 21
Age < 30	Every other year	Every other year
Age ≥ 30	▪Cytology annually ▪Liquid-based every other year*	Every 3 years with liquid-based or conventional cytology*
When to stop if low risk	▪Age 70 ▪3 consecutive negative cytology	▪Age 65 or 70 ▪3 consecutive negative cytology

*Establish 'low risk' classification and less frequent screening if HPV co-test negative

Saslow D et al CA Cacner J Clin 2002.
ACOG Practice Bulletin #109. 2009

Cervista®

- FDA approved March 2009
  - Cervista™ HPV HR[1]
  - Cervista™ HPV 16/18
- Enzymatic DNA amplification with fluorescent read out
  - Approved for use with ThinPrep

Einstein et al. Gynecol Oncol. 2010

Cervista® HPV HR

- Detection of 14 high risk HPV types
  - 16, 18, 31, 33, 35, 39, 45 ,51, 52, 56, 58, 59, 68 and 66
  - Similar to 13 of Hybrid Capture 2 plus HPV 66
- FDA-approved indications:
  - Used adjunctively with cervical cytology to screen women 30 years and older to assess the presence or absence of high-risk HPV types
  - To screen patients with ASC-US cervical cytology results to determine the need for referral to colposcopy

ASCCP HPV Genotyping Clinical Update.

Cervista® HPV 16/18

- Specific detection of HPV 16 and 18
- FDA-approved indications:
  - In women 30 years and older the test may be used adjunctively with the Cervista™ HPV HR test in combination with cervical cytology to assess the presence or absence of specific high-risk HPV types
  - Used adjunctively with the Cervista™ HPV HR test in patients with ASC-US cervical cytology results to assess the presence or absence of specific high-risk HPV types. The results of this test are not intended to prevent women from proceeding to colposcopy ASCCP HPV Genotyping Clinical Update.

Cervista® HPV HR Compared to hc2®

	hc2	*Cervista HPV*
Year of FDA Approval	1999	2009
Internal Control	No	Yes[1]
HPV Types Detected	13 High-Risk Types	14 High-Risk Types (genotypes covered by hc2 plus HPV 66)
Sample Size Requirement	4 mL	2 mL[1]
Cross-Reactivity With Common Low-Risk Types	Yes[4,5]	None[1]
Genotyping	No	Yes; same 2mL sample[1]
CIN3 Sensitivity	96.3% (CI: 91.6%-98.8%)[3]	100% (CI: 85.1%-100%) [1,2]

[1]Cervista HPV HR package insert #15-3100. Madison, WI: Third Wave Technologies, Inc; 2009.

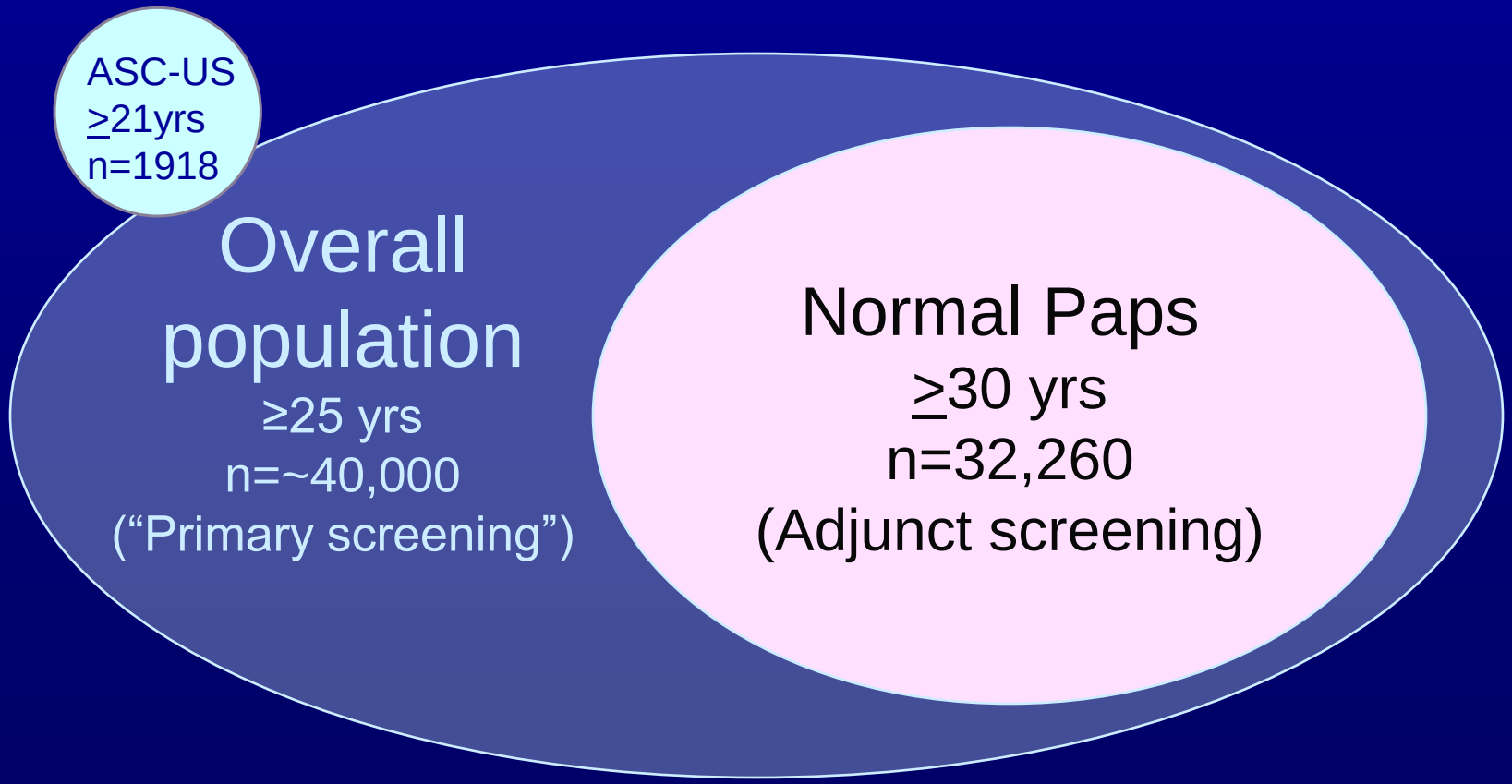
[2]Einstein MH et al, *Gynecol Oncol*. 2010.

[3]Solomon D, Schiffman M, Tarone R, et al. *J Natl Cancer Inst*. 2001 Feb 21;93(4):293-9.

[4]Castle PE, Solomon D, Wheeler CM, et al. *J Clin Microbiol*. 2008 Aug;46(8):2595-604.

[5]Poljak M, Marin IJ, Seme K, Vince A. *J Clin Virol*. 2002 Dec;25:S89-97.

ATHENA HPV study populations
Clinical validation of cobas 4800 HPV test



ATHENA HPV Study results: cobas 4800 HPV Test and hc2 in ASC-US: Detection of CIN2+ in side by side comparison

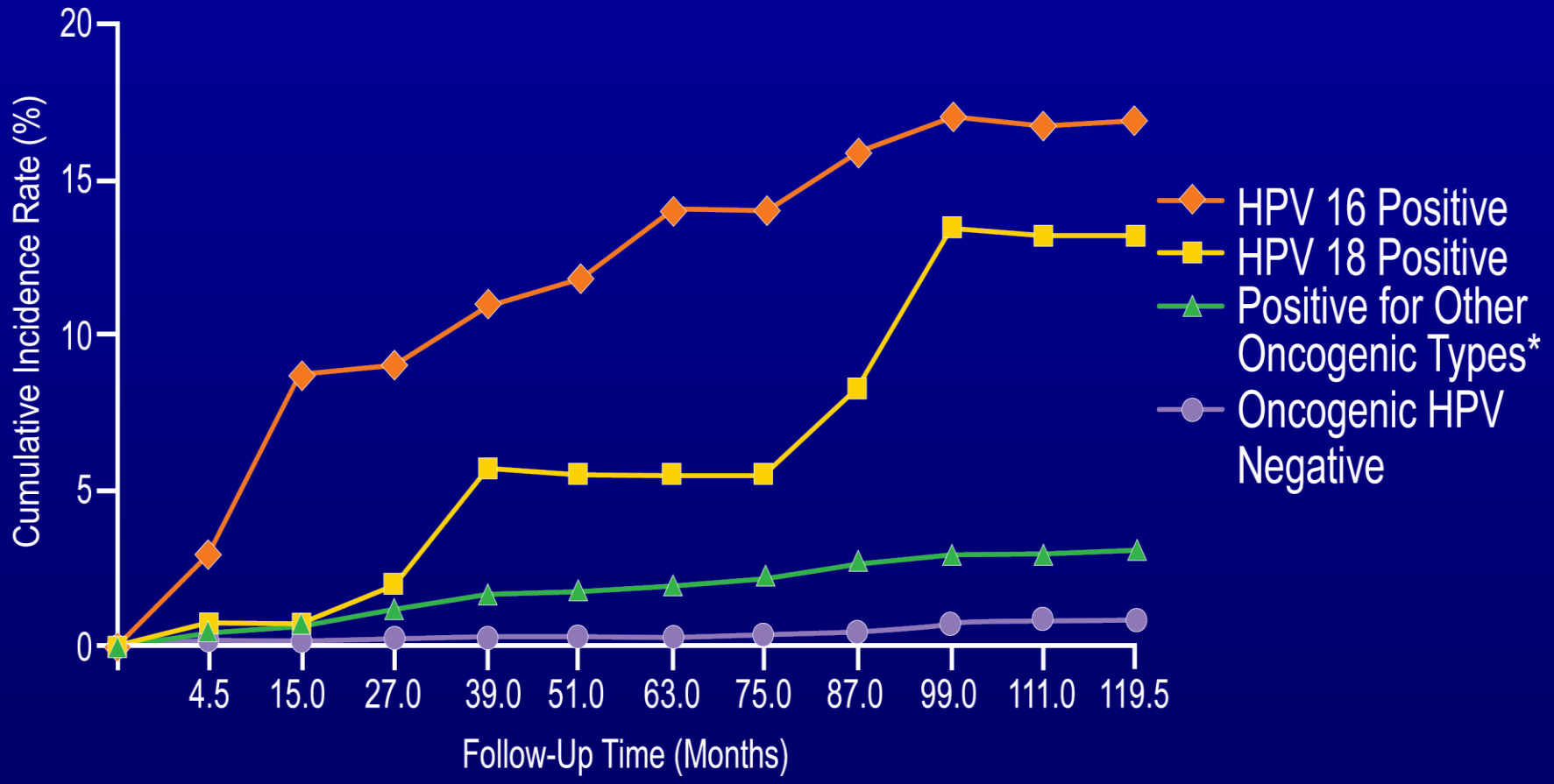
	cobas 4800 HPV Test		hc2	
	Point Estimate	95% CI	Point Estimate	95% CI
Sensitivity (%)	90.0 (72/80)	(81.5, 94.8)	87.2 (68/78)[1]	(78.0, 92.9)
Specificity (%)	70.5 (1,056/1,498)	(68.1, 72.7)	71.1 (1,056/1,485)[2]	(68.8, 73.4)
PPV (%)	14.0 (72/514)	(12.8, 15.3)	13.7 (68/497)	(12.4, 15.1)
NPV (%)	99.2 (1,056/1,064)	(98.6, 99.6)	99.1 (1,056/1,066)	(98.3, 99.5)

[1]Two subjects with CIN2+ had indeterminate results; [2]Thirteen subjects with <CIN2 had indeterminate results

*FDA approval of cobas 4800 for cervical cancer screening April, 2011

Stoler M, *et al.* Presented at IPV 2010. Montreal, Canada

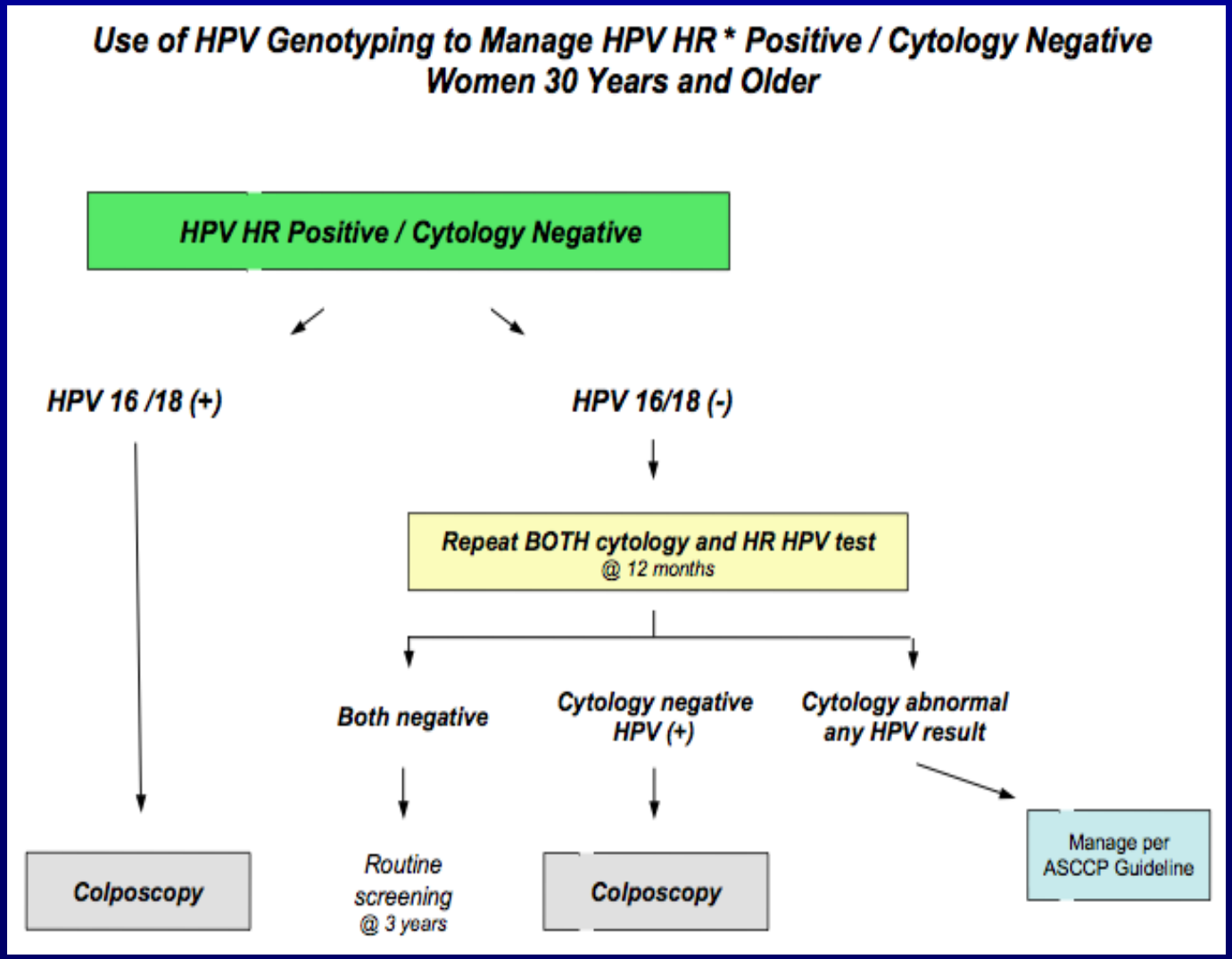
Risk of Cervical Precancer and Cancer in Women with HPV 16 or 18



*Positive for the non-HPV 16/18 types in Hybrid Capture 2.

Kahn, MJ, Castle PE, Lorincz AT, et al. *J Natl Cancer Inst*. 2005;97:1072-1079..

HPV 16/18 Genotyping



ASCCP HPV Genotyping Clinical Update.

HPV 16/18 for ASC-US

- ALTS two-year cumulative risk of CIN 2+: 25%
  - HPV 16/18 positive ASC-US risk of CIN 2+: 40%
  - Other (non 16/18) HPV positive ASC-US risk of CIN 2+: 20%
  - Similar patterns for women 21-29 and those 30 and older
- HPV genotyping *does* stratify risk of CIN 2+
- The risk of CIN 2+ remains high enough in non HPV 16/18 + ASC-US that colposcopy is *still* warranted
- ASCCP do ***NOT*** recommend HPV genotyping in women with HPV-positive ASC-US

ASCCP HPV Genotyping Clinical Update.

HPV Testing in Primary Screening

- HPV testing used in combination with cytology as primary screening in women 30 years of age and older
- Pooled screening study data on HPV testing
  - Sensitivity for CIN 2+: 95%
    - Higher when using combination
  - Specificity for CIN 2+: 93%
- Women negative by cytology and HPV testing have less than 1 in 1000 chance of having CIN 2+

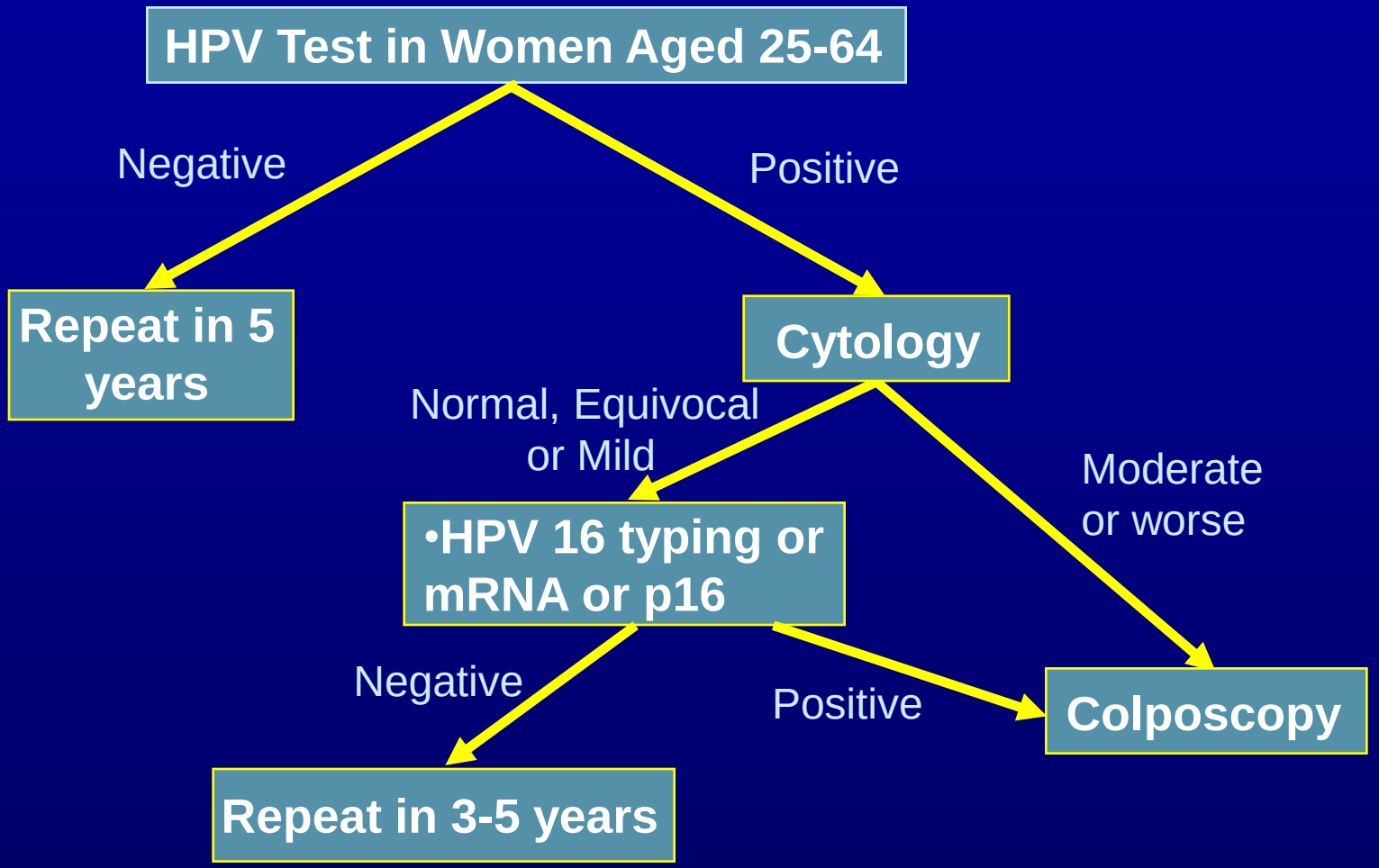
Wright, TC, Massad LS, Dunton CJ, et al. Am J Obstet Gynecol 2007.

HPV Testing in Primary Screening

- Cytology and HPV negative
  - Should not be re-screened before 3 years
- Cytology negative, HPV positive
  - Review of over 213,000 women over 30 yo found 6.5% HPV positive (58% negative cytology)
  - Risk of CIN 2+ 2.4-5.1%
  - Most become HPV negative
  - Repeat cytology and HPV testing at 12 months
    - Persistently HPV positive women should undergo colposcopy

Wright, TC, Massad LS, Dunton CJ, et al. Am J Obstet Gynecol 2007.

Potential Future Screening Algorithm



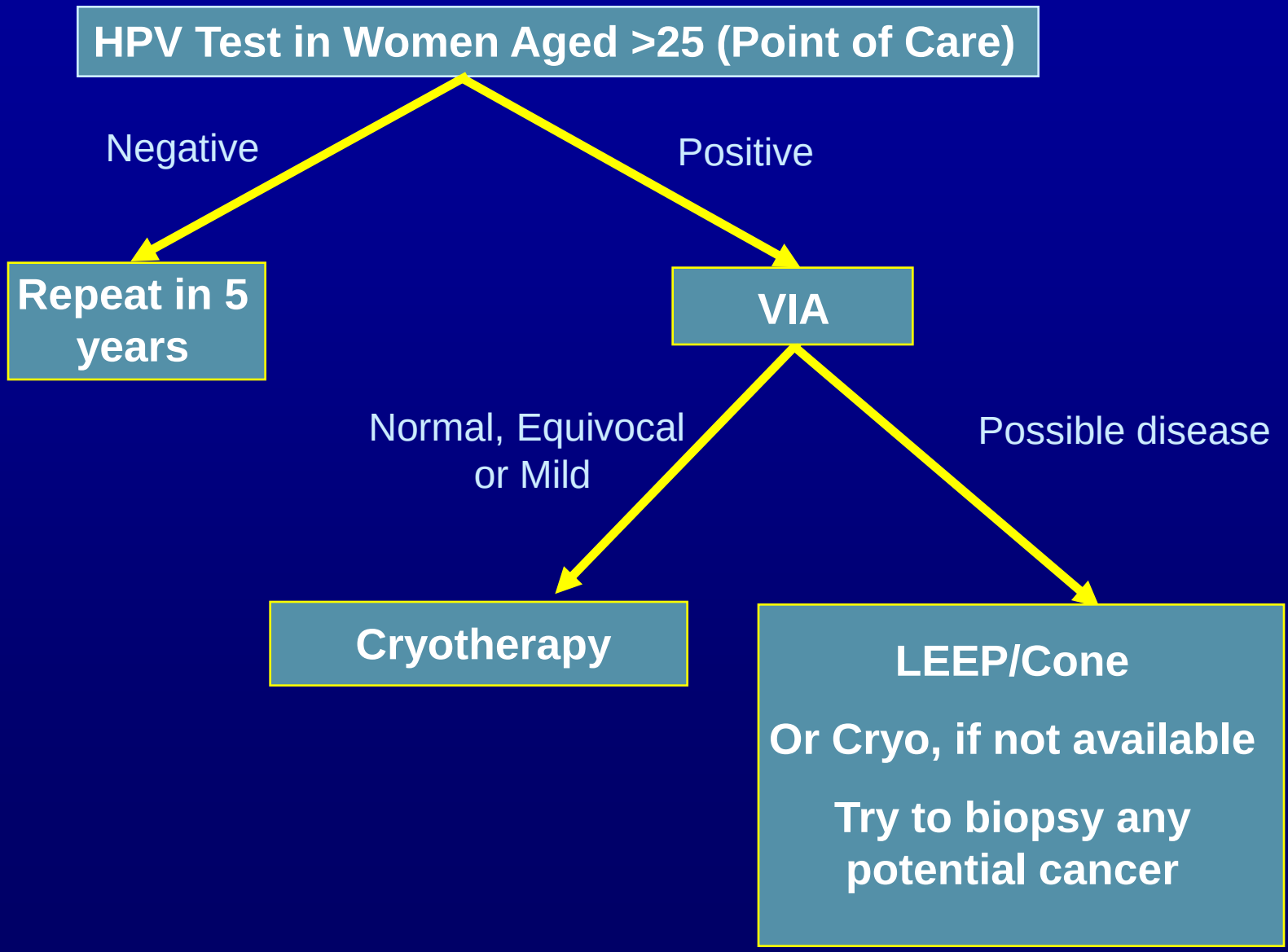
Adopted from Cuzick J. et al. Eurogin 2009. Nice, France

HPV Testing in Primary Screening

- Used in Rural India in over 130,000 women between 30 and 59 randomized to one of 4 groups: HPV testing, cytologic testing, VIA, or standard care (control group)
- Cervical cancer diagnosed more frequently in the HPV testing group (127) compared with 118 in the control group (of which 82 had advanced disease). No significant reductions in death in the VIA or standard cytology group
- In a low-resource setting, a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer

Sankaranarayanan R et al NEJM, 2009

HPV/VIA Screening/Treatment Algorithm



Conclusions

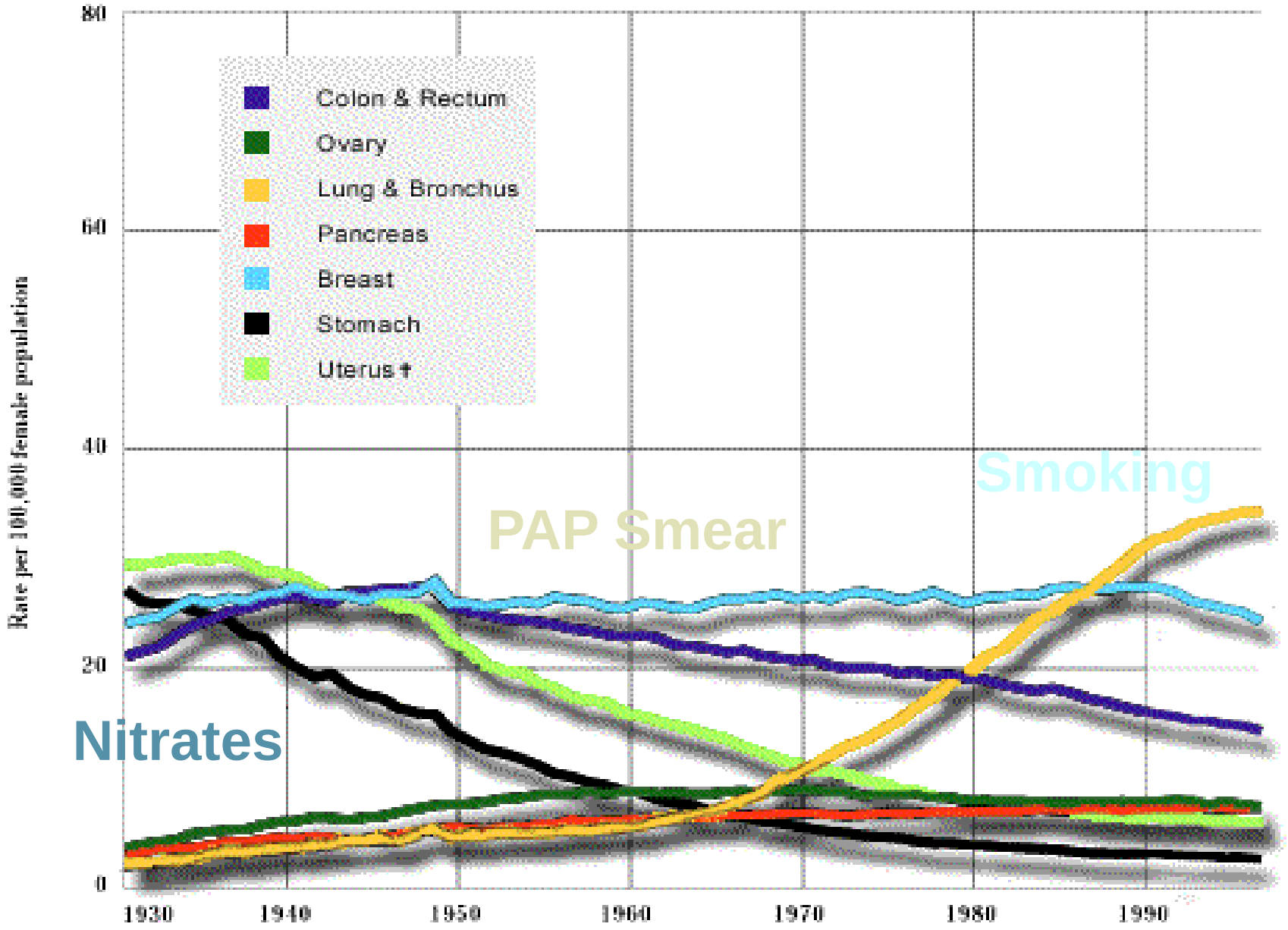
- All guidelines are shifting to doing more with less testing
- Future guidelines will be targeting even less frequent intervals
  - Also the potential for alternate algorithms in 'vaccinated patients'
- Do little in adolescents and pregnant patients, particularly with equivocal cytology
- HPV 16/18 genotyping has triage role
- HPV testing as a primary screen appears to be an effective strategy, but not being considered in US screening for now

Ovarian Cancer Screening and Prevention

‘Early diagnosis of ovarian cancer is a matter of luck rather than a triumph of scientific approach’

Hugh Barber

Trends in US Female Cancer Death Rates



What Are My Chances?

- Lifetime probability of developing OC is 1.8%
- With one first degree relative - 5%
- With two or more first degree relatives - 7%
- Ashkenazi Jewish - 16.5% lifetime risk

Struewing, *NEJM* 336:1401-8, 1997

Risk Assessment

- Genetic risk factors
  - - Family History
  - - Site-specific ovarian syndromes
- Environmental risk factors
- Hormonal risk factors

Clinical Classification of Familial Ovarian Cancer: 1970s

- Site-specific ovarian cancer syndrome
- Breast /ovarian cancer syndrome
- Lynch type II syndrome (HNPCC)

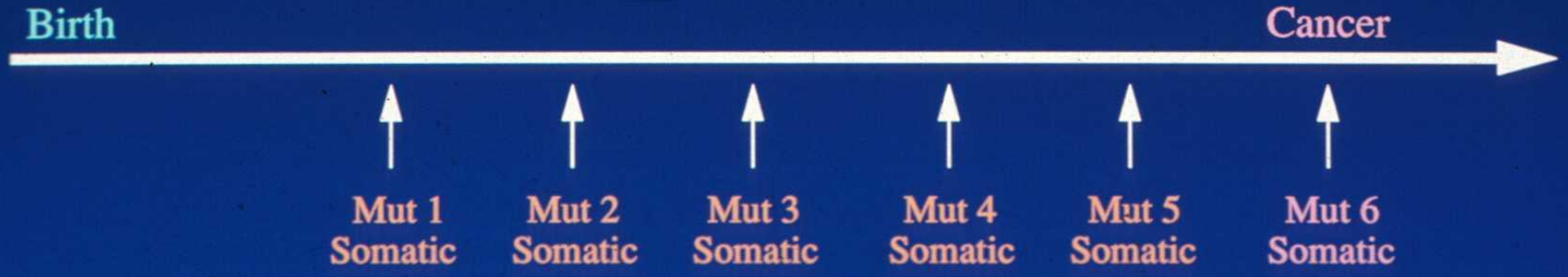
Genetic Classification of Familial Ovarian Cancer: 1990s

- Site-specific ovarian cancer syndrome
  - – - BRCA1 and BRCA2
- Breast /ovarian cancer syndrome
  - - BRCA1 and BRCA2
- Lynch type II syndrome (HNPCC)
  - - MSH2 and MLH1

All Cancers are Genetic

"Hereditary" Cancer:

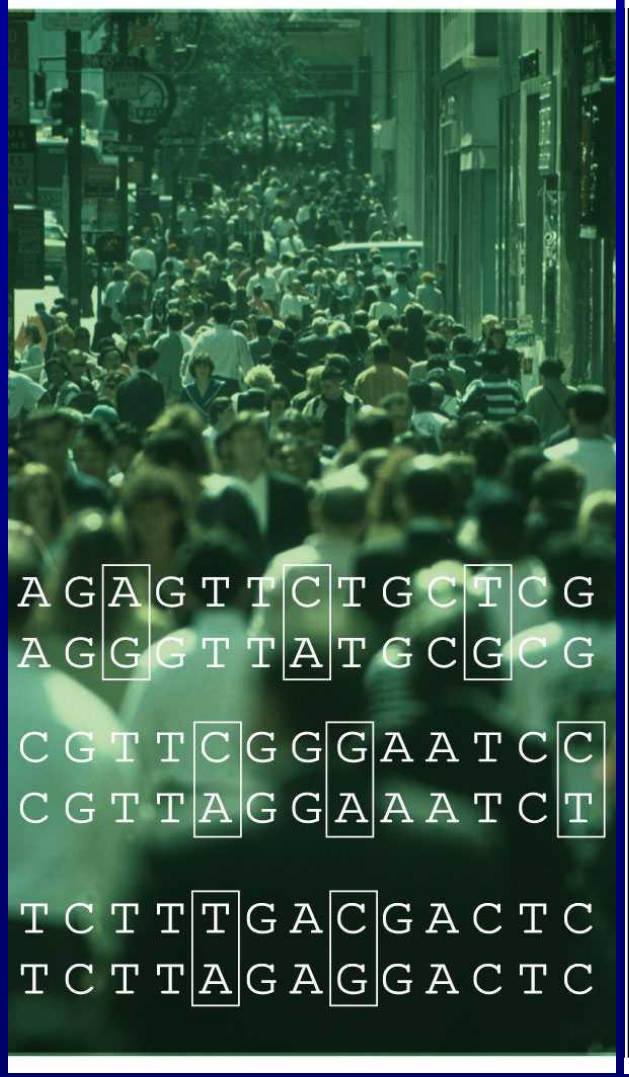
"Sporadic" Cancer:



Genetic Predisposition to Ovarian Cancer

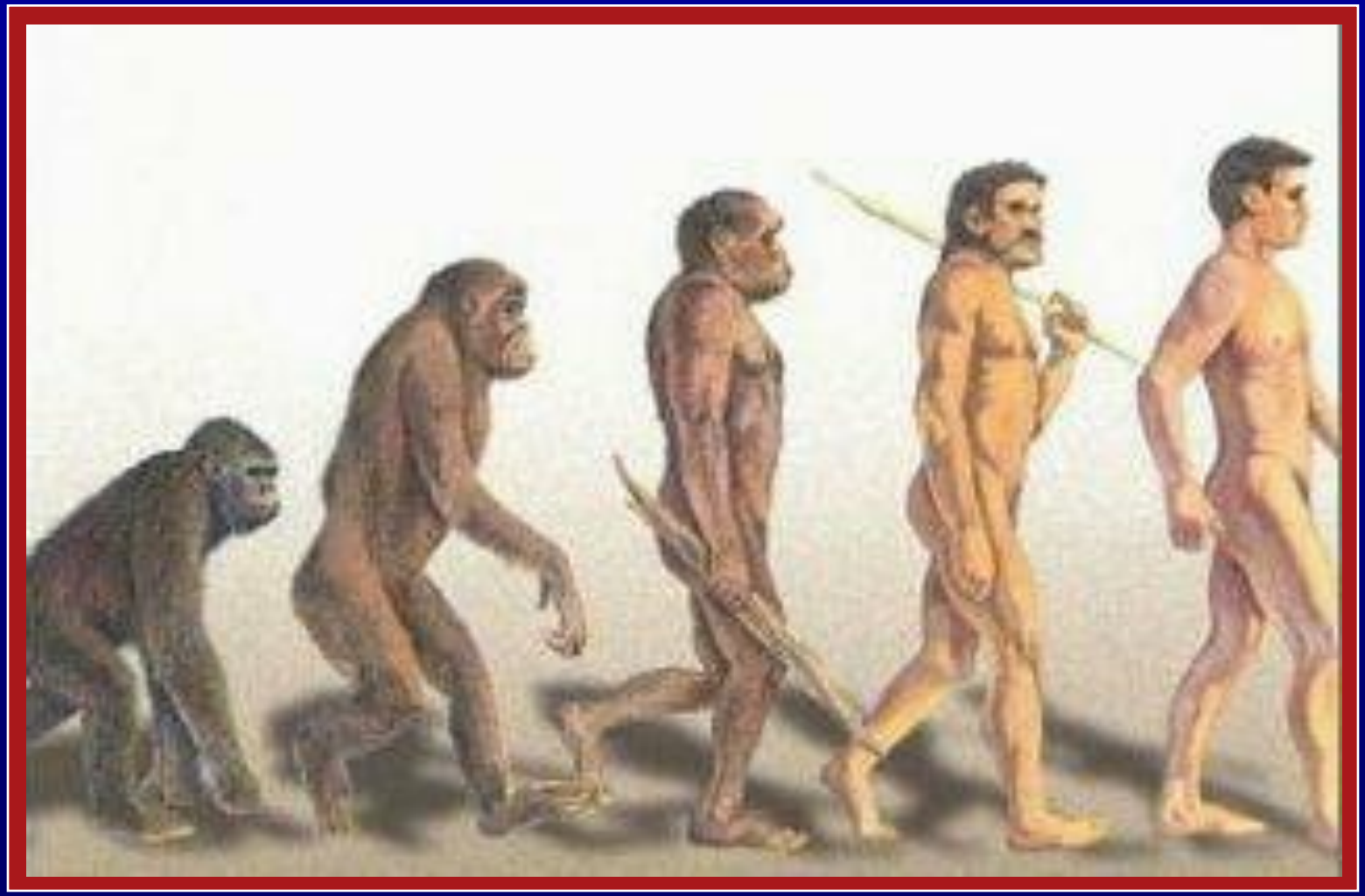
Alteration	Prevalence	RR	CA Fraction
BRCA1	<0.5%	10-20 fold	6%
BRCA2	<0.5%	5-10 fold	3%
DNA repair	<0.5%	3-5 fold	1%
Polymorphisms	?5-45%	2-3 fold	?15%
TOTAL			*25%*

Genetic Diversity - Polymorphisms



- Polymorphism - a genomic locus that varies between individuals
- Causes - extrinsic (UV, chemicals), intrinsic (hydrolysis, replication errors)
- Change must escape DNA repair to be fixed in the genome
- Drives evolution and accounts for variation between individuals within a species

Evolution



Genetic Diversity

1%

Chimpanzee

30 million bases

Human

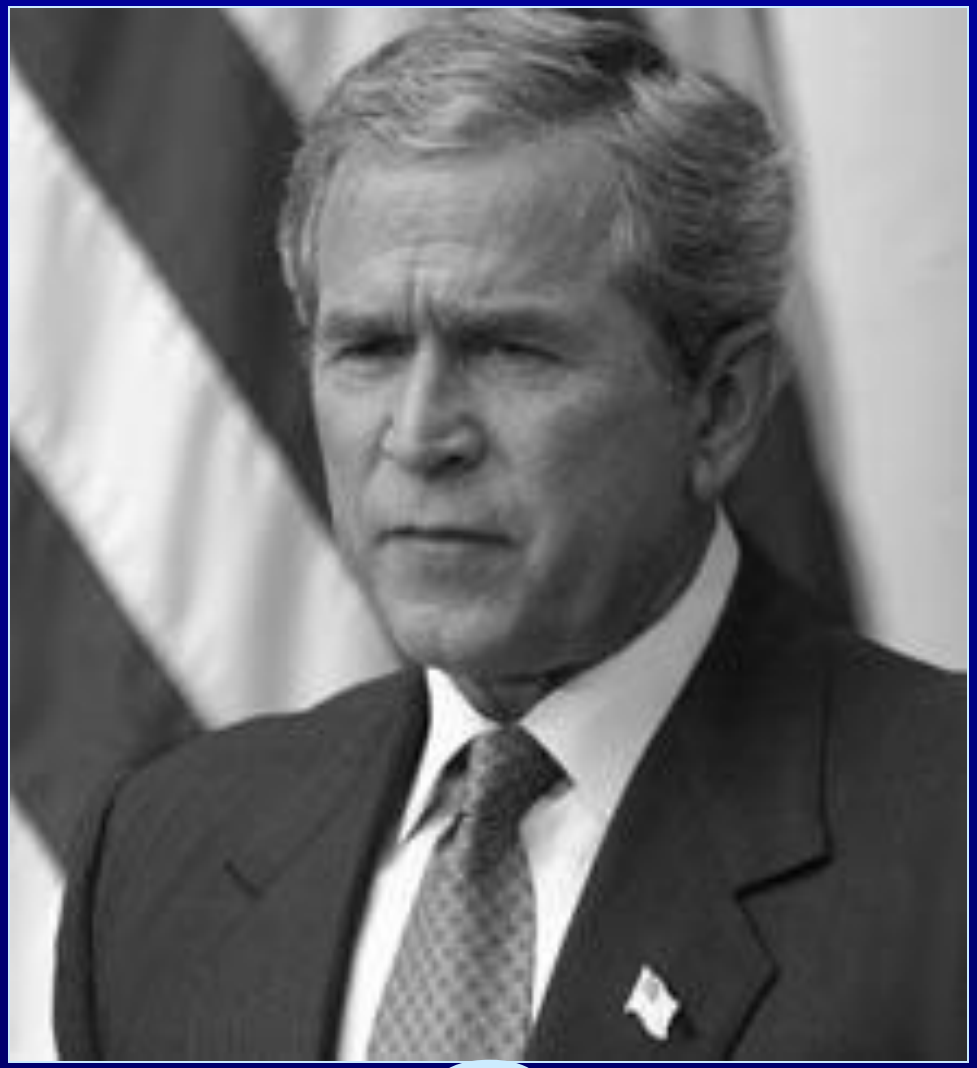
Human Genetic Diversity

0.1%

Honest Abe

3 million bases

Slick Willie

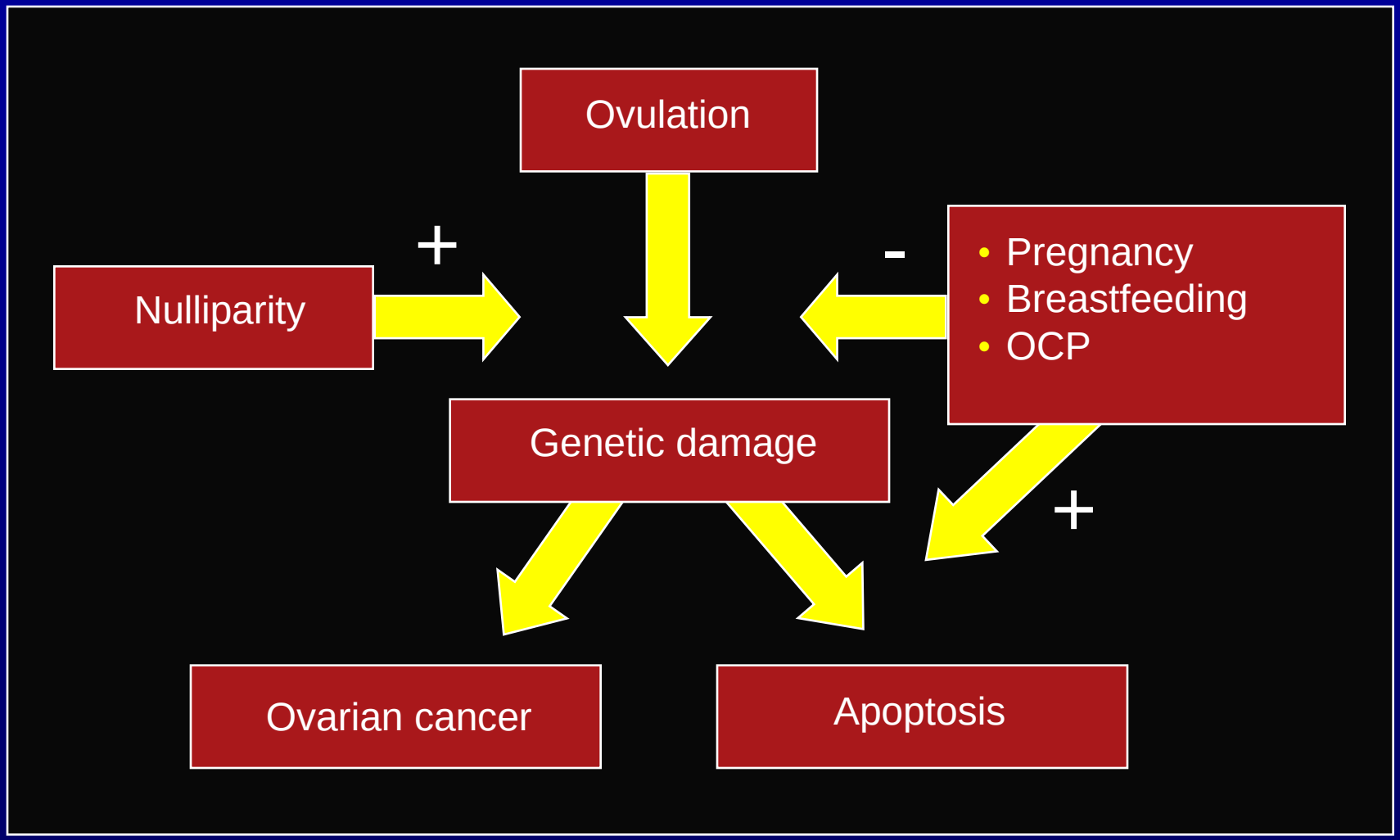


?

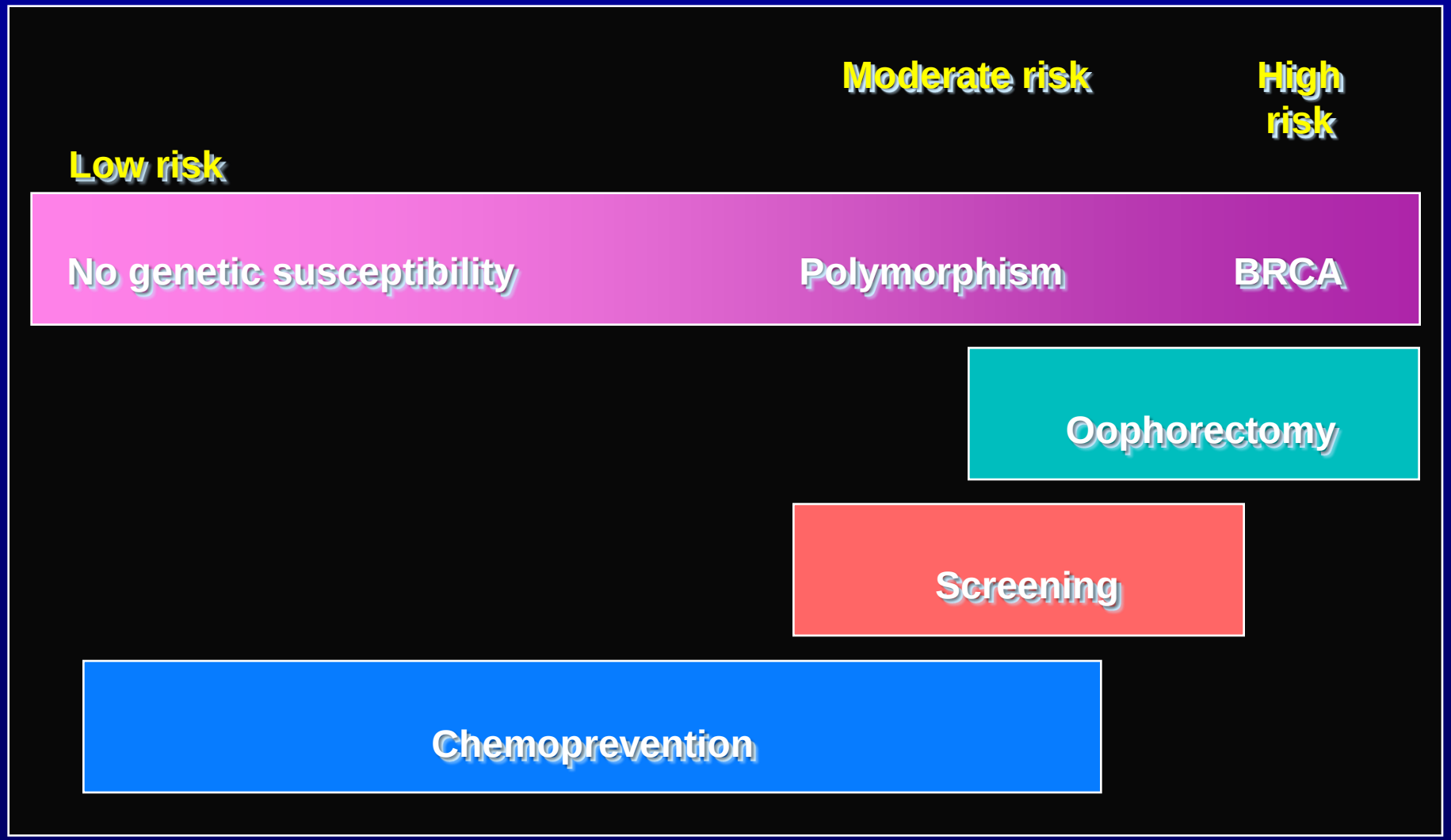
Single Nucleotide Polymorphisms (SNPs)

- SNPs account for 80% of genetic variations between individuals
- Several hundred thousand in the human genome
- Most are relatively ancient and 80% have rare allele frequencies >10%
- Most SNPs are either outside genes or silent

Pathogenesis of Ovarian Cancer



Strategies for Primary and Secondary Prevention of Ovarian Cancer



Criteria for an Effective Screening Test

- Large burden of disease
- Recognizable preclinical stages
- Curative potential much greater in early stages
- Acceptable to the screener and the person being screened
- Reasonable sensitivity, specificity, predictive values
- Improvement in cause specific mortality

CA-125

- Antigenic determinant on a high molecular weight glycoprotein
- Recognized by the muring monoclonal antibody OC-125
- Derived from coelemic epithelium
  - - In tubal, endometrial, and endocervical epithelium
- 85% of pts with levels >35 U/ml have OC
- PPV-4%

Benign Conditions Which Elevate CA-125

- Pregnancy
- Menstruation
- PID
- Endometriosis
- Fibrocystic disease of the breast
- Liver disease
- Renal failure

Risk of Ovarian Cancer Algorithm

- Not only elevated levels, but the rate of elevation
- Based on logarithmic rises in CA-125
- Higher slopes

Skates, *Cancer* 76(10):2004-2010, 1995.

Other Tumor Markers

- CA 19-9
  - - Antigen that is part of the Lewis blood group
  - - Elevated in ovarian, pancreatic, GI, lung, and EMCA
- CA 15-3
  - - Tumor associated antigen in milk fat
  - - Elevated in breast cancer
- TAG 72-3
  - - Glycoprotein surface antigen
  - - Found in colon, gastric, and ovarian cancers

Tumor Markers

- Tetranectin
  - - Binds to kringle 4 of plasminogen
  - - Enhances t-PA
  - - Influences cells to proliferate
- CASA
  - - Assay which uses antibody which binds to MUC1 receptor on mucin cells
- OVX1
  - - Monoclonal antibody generated by immunizing mice with multiple ovarian cancer cell lines
  - - Does not bind to normal epithelium

Tumor Markers

- LASA
  - - Lipid-associated sialic acid
  - - Assay which determines glycoprotein-bound sialic acid
  - - Positive in leukemia, sarcoma, melanoma, oropharyngeal tumors and ovarian cancer
- VEGF
  - - Vascular endothelial growth factor
  - - Promoter of angiogenesis

Ultrasound

- Multiple scoring systems
  - - Solid vs. cystic
  - - Septations
  - - Color Doppler Imaging (CDI)
- All agree that papillary vegetations are a poor prognostic sign
- Due to time and expense, USS cannot be used as more than a second-level modality for screening

Uncontrolled Trials of Ovarian Cancer Screening

General Population Volunteers

Report	Country	Participants	Ovarian Cancer Stage I	Ovarian Cancer Total
Einhorn et al. (1992)	Sweden	5,550	2	6
Campbell et al. (1990)	UK	5,479	5	9
Jacobs et al. (1993)	UK	21,959	3	11
DePriest et al. (1993)	USA	3,220	2	3
TOTAL	All	36,208	12	29

Uncontrolled Trials of Ovarian Cancer Screening

Volunteers with Positive Family History

Report	Location	Participants	Ovarian Cancer Stage I	Ovarian Cancer Total
Bourne et al. (1993)	UK	1,601	5	6
Karlan et al. (1993)	Los Angeles	597	1	1
Schwartz et al. (1991)	Connecticut	>200	-	-
Muto et al. (1993)	Boston	386	-	-
Crade (1993)	Long Beach	389	-	-

Multimodal Screening Equations

Royal College of London Study

- 22,000 women randomized
- Screened women were offered three annual screens that included CA-125 and USS
  - - If 30 U/ml or more, or ovarian volume more than 8.8 ml, referral to gynecologist

Results of Study

- 16 total cancers identified in screened group
- 20 cancers identified in control group
- Slight survival benefit in screened group and no difference in mortality

Further Trials

- Expanding the Royal College Study
- NIH PLCO (Prostate, Lung, Colon, Ovary)
  - - Larger study
  - - Older women
- Multiple small studies

Management of Hereditary Cancer

- Obtain personal and family history of cancer
- Confirm cancer diagnosis in affected individuals
- Estimate risk of hereditary cancer syndrome
- Education and informed consent
- Genetic testing
- Post test counseling and follow-up

Screening Guidelines for Genetic Testing

- Breast and OC in same family
  - - Particularly if in same woman
- Cases of male breast cancer
- Multiple cases of early onset disease
- Bilateral breast cancers

Based on statistical models, a patient should have at least a 10% probability of carrying a mutation before genetic testing is recommended

Statement from ASCO-*JCO* 14:1730-6, 1996.

Risk Factors for BRCA Mutations

- Two or more affected first degree relatives
- Early onset of breast cancer (<50 years old)
- Male breast cancer (BRCA2 only)
- Ovarian cancer at any age
- Ashkenazi Jewish heritage

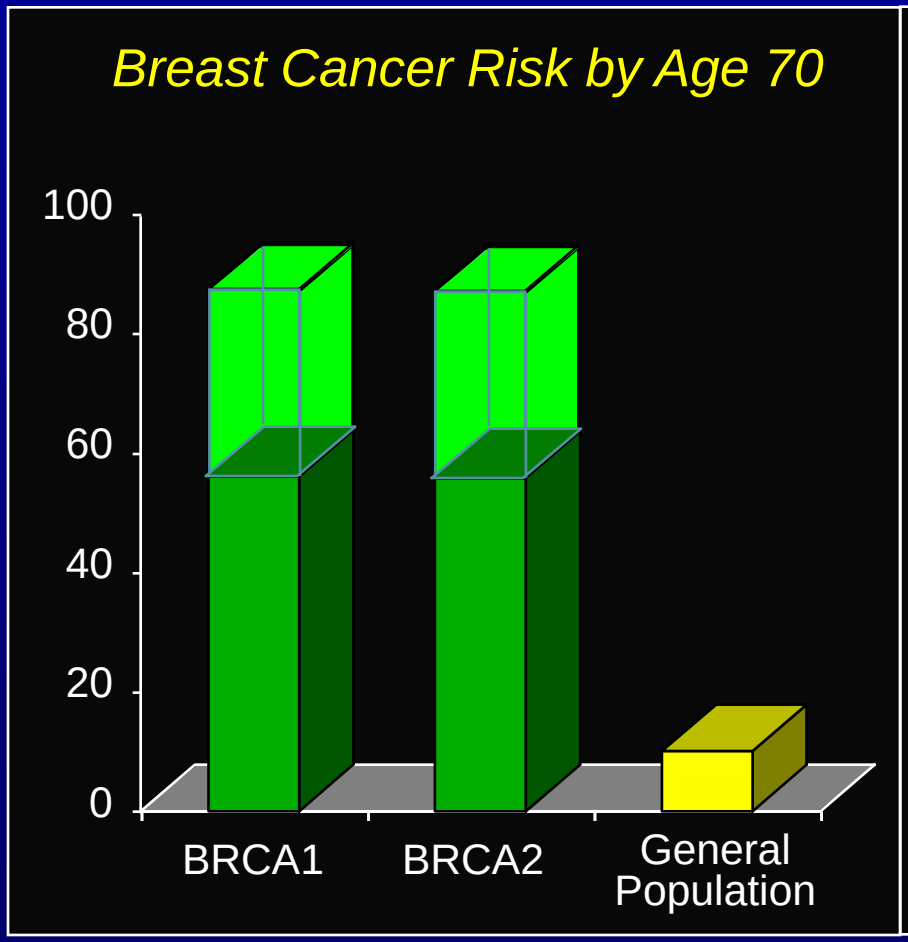
Testing

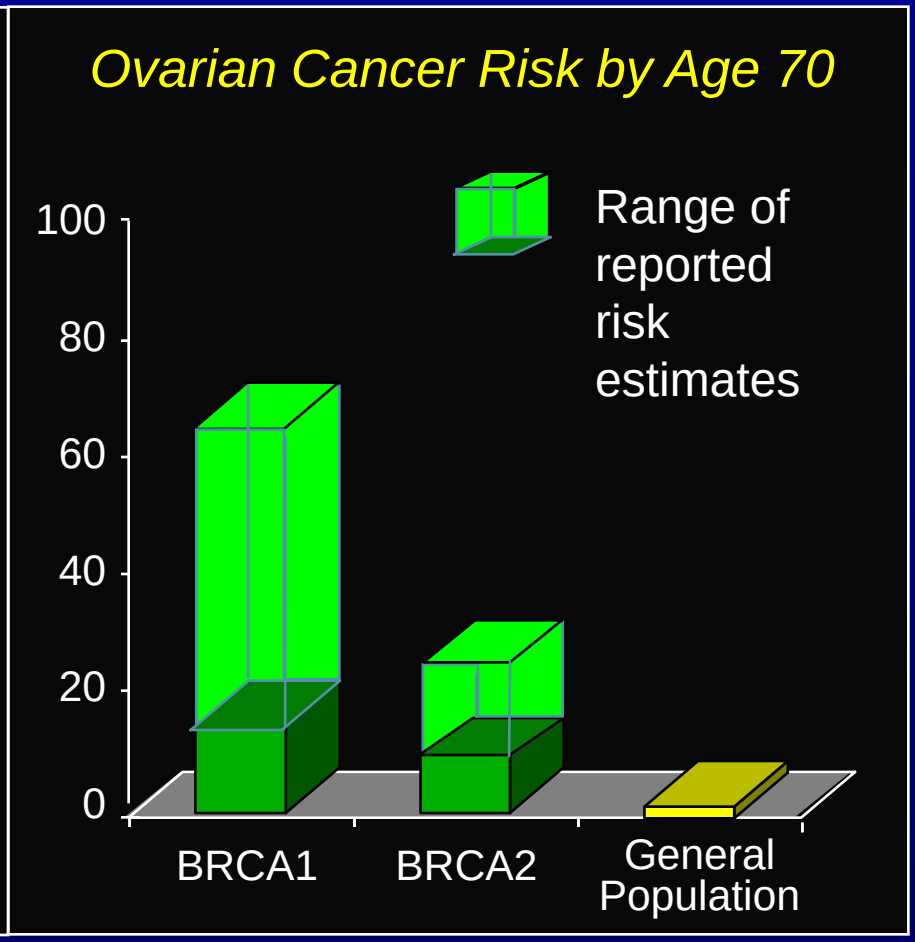
Test a living affected member

185delAG 5382 insC	*BRCA1*	17q21
6174delT	*BRCA2*	13q

–If no mutations identified, full sequencing can be offered

Inherited Mutations in BRCA1 and BRCA2 Increase the Risk of Breast and Ovarian Cancer





Lancet 343:692, 1994
Am J Hum Genet 56:265, 1995

New Engl J Med 336:1401, 1997
Am J Hum Genet 62:676, 1998

Stage and Diagnosis and Prevalence of Screen Detected Ovarian Cancer in High Risk Women

Author	N	Screen Detected OC [LMP]	Prevalence Screen Detected OC per 100,000	Proportion Diagnosed at Stage 1
Bourne (1993)	1601	6 [3]	375	5/6
Muto (1993)	384	0	0	
Schwartz (1995)	247	0	0	
Belinson (1995)	137	1	730	0/1
Dorum (1996)	180	7 [3]	3889	3/7
Karlan (1999)	1261	10 [2]	793	3/10
All Studies	3810	24 [8]	630	11/24 (46%)
Excluding [LMP]		16	420	3/16 (19%)

Adapted from Bell R et al. *Brit J Obstet Gynecol* 1998;105:1136-1147.

Ovarian Cancer Screening in Women Who Carry BRCA1 and 2 Mutations

- CA 125 and ultrasound screening are not approved for population screening
- The relative risk of ovarian cancer is increased at least 10-fold in BRCA1 and BRCA2 carriers
- Ovarian cancer screening in mutation carriers with ovaries seems reasonable

BRCA1 and 2 Sequencing in Women with Ovarian Cancer at Myriad Genetics

- Mutations were found in 34% of 824 women with ovarian cancer (199 BRCA1, 82 BRCA2)
- 60% frameshift, 25% nonsense, 12% intronic, 3% missense
- Median age at diagnosis was 49 for BRCA1 and 55 for BRCA2

Frank TS et al, *J Clin Oncol,* Vol 20, pg 1480, 2002.

Social, Ethical and Legal Implications of BRCA1/2 Testing

- Anxiety, depression and guilt
- Insurance concerns
- Medical record documentation
- Obligation to inform other family members
- Reproductive strategies

Tubal Ligation

- Decreases ovarian cancer risk
- Relationship between tubal ligation and decreased risk is strong, but based on subjective data.
  - - Nurses health study

Chemoprevention

- OC's
  - - Use of OC's 6 or more years decreased risk of hereditary ovarian cancer by 60%.
  - • The longer the use, the greater the risk reduction
  - • Risk protective for 15 years[1]
  - - Low-dose OC's have weaker protection
- ASA
  - - Small, subjective studies
  - - Possibly COX-II specific
- Retinoids
  - - Cell line data
  - - Phase II trials beginning 2001

[1] Narod, *NEJM* 339:424-8, 1998

Oral Contraceptives May Prevent Ovarian Cancer in BRCA1 and 2 Carriers

- 207 BRCA1/2 carriers with ovarian cancer
- 163 sisters without ovarian cancer
  - 53 mutation carriers
  - 42 non-carriers
  - 66 not tested
- Risk of ovarian cancer

- < 3 years OCP	0.7
- 3-6 years OCP	0.4
- > 6 years OCP	0.3

Narod et al, *N Engl J Med,* 1998.

Prophylactic Oophorectomy

- 1000 ovarian cancer cases would be prevented if PO were done at the time of hysterectomy in all women over 40 in the U.S.[1]
- Should be encouraged in all women with hereditary forms of ovarian cancer after childbearing.
  - - Decreases risk by at least 50%[2]
  - - Still at risk for primary peritoneal cancer
- Should be performed on women at increased risk who are having other abdominal surgery

[1] Lepine, *Mor, Mortal Wkly Rep CDC Surveillance Summary* 46:1-15, 1997

[2] Struewing, *J NCI monographs* 33-5, 1995.

Should Prophylactic Oophorectomy Be Performed at Laparotomy / Laparoscopy For Non-Gynecologic Indications?

- Women ≥40 years
- Family history of breast, ovarian, endometrial or colon cancer
- At time of colorectal surgery
- Cholecystectomy
- GYN / GYN Onc consult pre- or intraop

Laparoscopic Prophylactic Oophorectomy

Surgical Issues

- Discuss risks: anesthesia, infection, bleeding and damage to adjacent organs
- Discuss potential conversion to laparotomy
- Discuss concomitant hysterectomy
- Remove both ovaries and tubes completely
- Perform pelvic peritoneal cytology
- Multiple blocks from each tube and ovary

Prophylactic Oophorectomy in BRCA Carriers

Pros

- Decreases ovarian cancer incidence and mortality
- Can be delayed to allow completion of childbearing
- Ease of laparoscopic approach
- Acceptable effect on body image and self esteem
- Estrogen replacement can prevent surgical menopause
- Lowers breast cancer risk

Prophylactic Oophorectomy in BRCA Carriers

Cons

- Surgery may not be covered by insurance
- Potential for surgical morbidity and mortality
- Potential for primary peritoneal carcinoma
- Premature surgical menopause

Breast Cancer Risk After Prophylactic BSO in BRCA1 Mutation Carriers

- Surgery Subjects (n=43)
  mut*BRCA1* and Prophylactic BSO
- Control Subjects (n=79)
  mut*BRCA1* but no BSO
- Result: Reduction in breast cancer risk with surgery
  HR = 0.53 (95% CI: 0.33 - 0.84)
- HRT did not negate the risk reduction

Rebbeck TR et al. *JNCI* 1999;91:1475-79.

Prophylactic Oophorectomy and HRT

- Compliance — Varies — 31-89% up to 5 years; 13-71% >5 years
- Risks — Osteoporosis /cardiac disease vs. breast cancer
- Speroff — ↓ life expectancy with non compliance
- ERT vs. combined HRT

Cost-Effectiveness

- Cost per screen highest in the first year
- At the lowest (in 1997) screening costs per patient is $39 US
- Costs per life saved may be more than $10 million

Conclusions

- Few women are at increased risk of ovarian cancer
- Screening should be reserved for those at risk
- Surgical or chemopreventive options are available