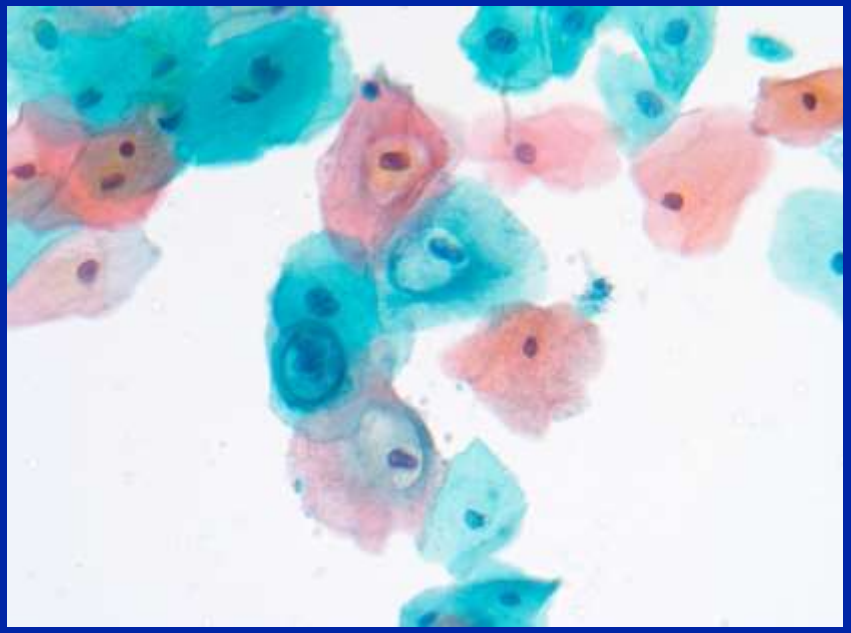
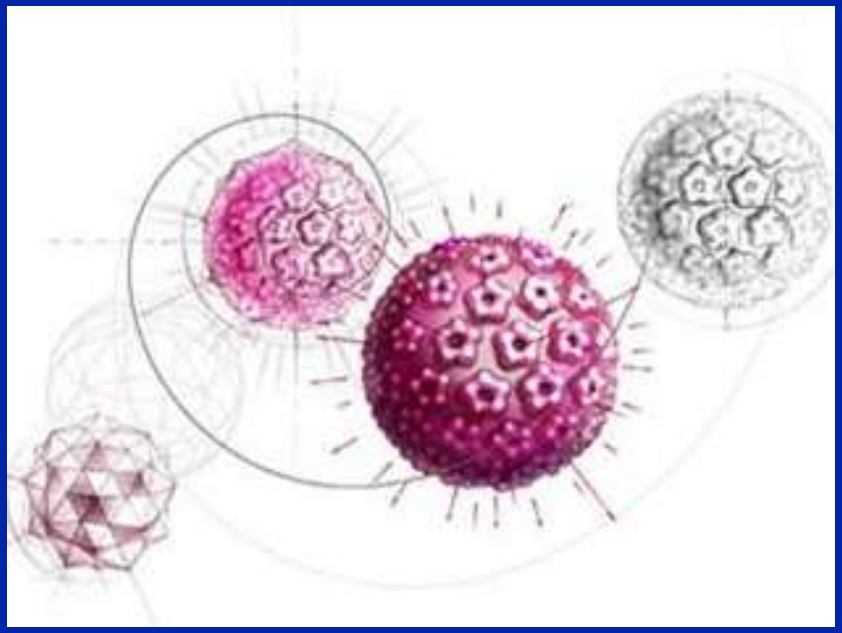
HPV Primary Screening



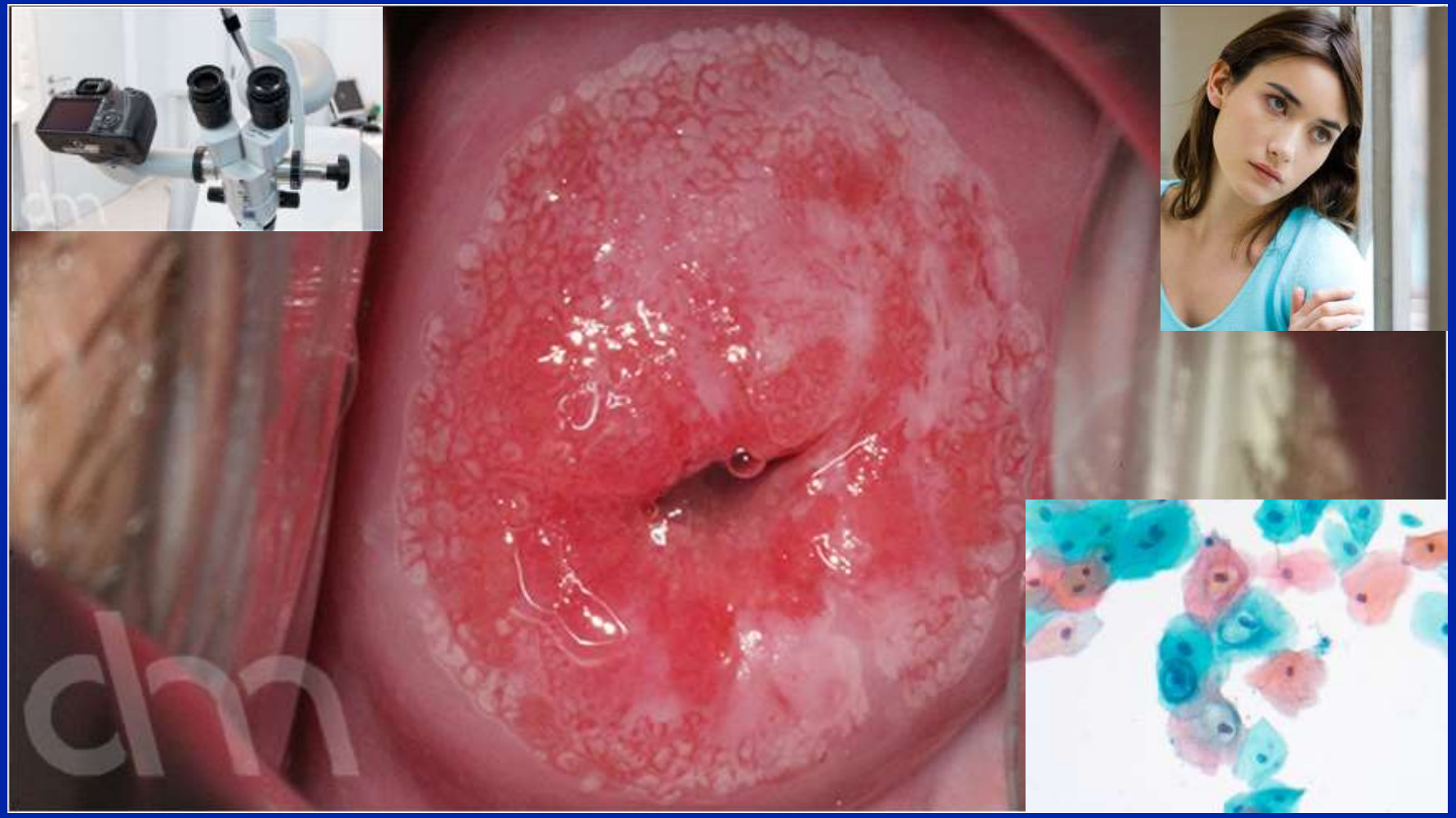


High-risk HPV Types

International Agency for Research on Cancer High-risk HPV Types

- **HPV 16**
- **HPV 18**
- **HPV 31**
- **HPV 33**
- **HPV 35**
- **HPV 39**
- **HPV 45**
- **HPV 51**
- **HPV 52**
- **HPV 56**
- **HPV 58**
- **HPV 59**
- **HPV 68**

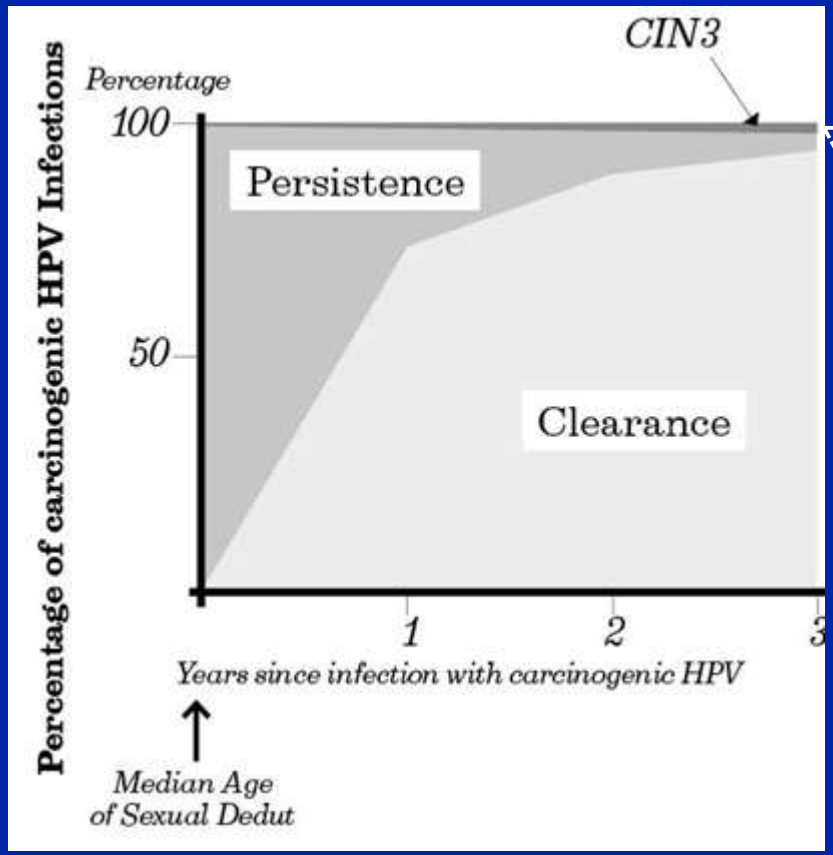
30 y.o., Pap test: LSIL



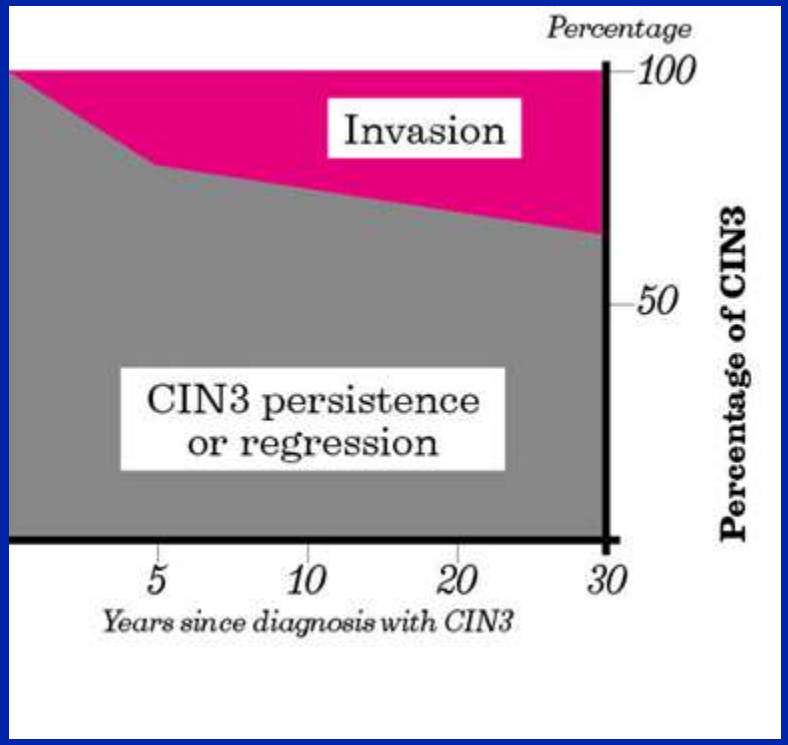
How do we see risk in medical practice?

Risk can viewed as the probability of getting a disease over a certain period of time

Nguyen T, Eisman J Fracture Risk Assessment: From Population to Individual Clin Densitom 2017,20 (3)

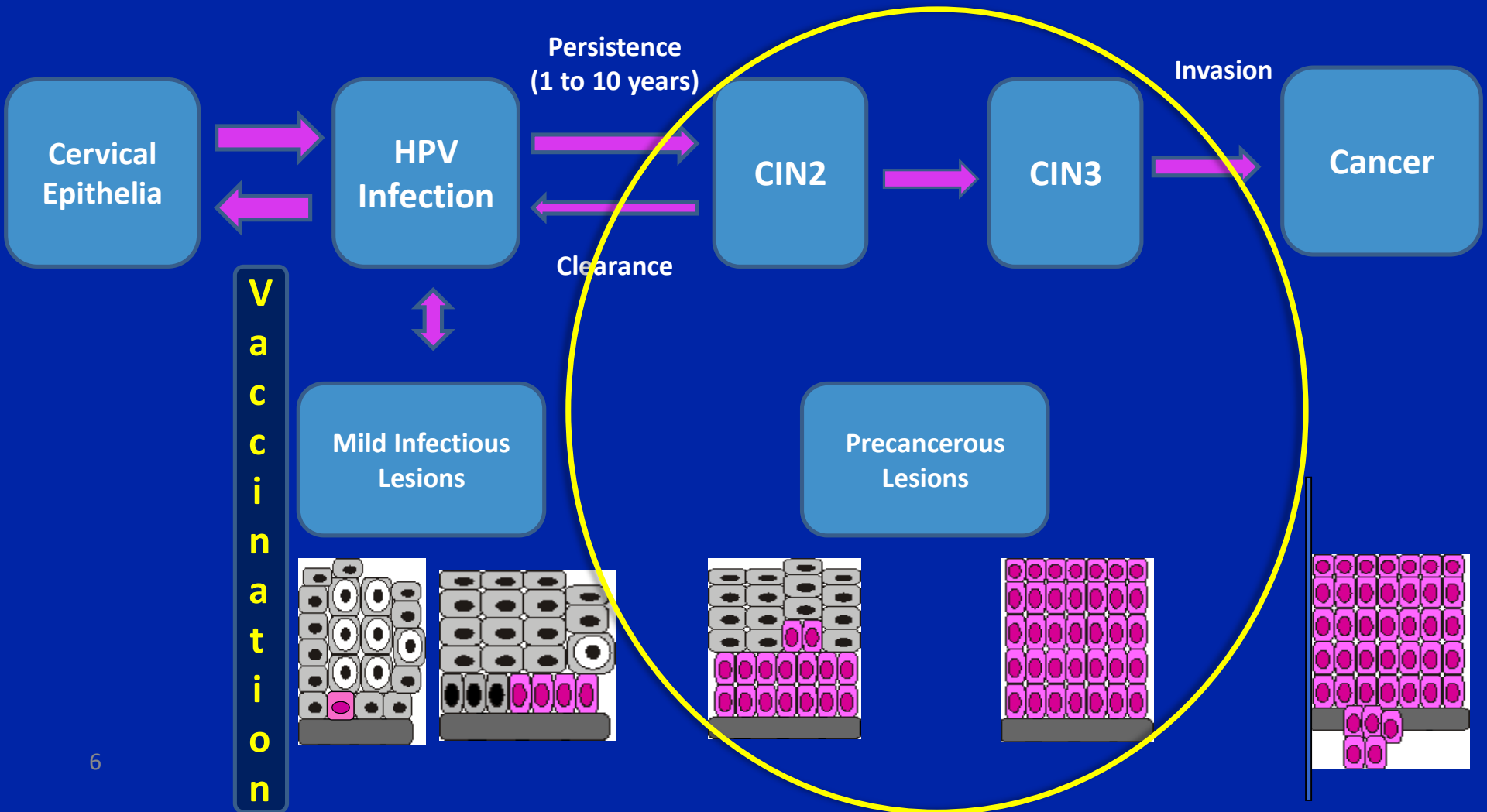


~10 years



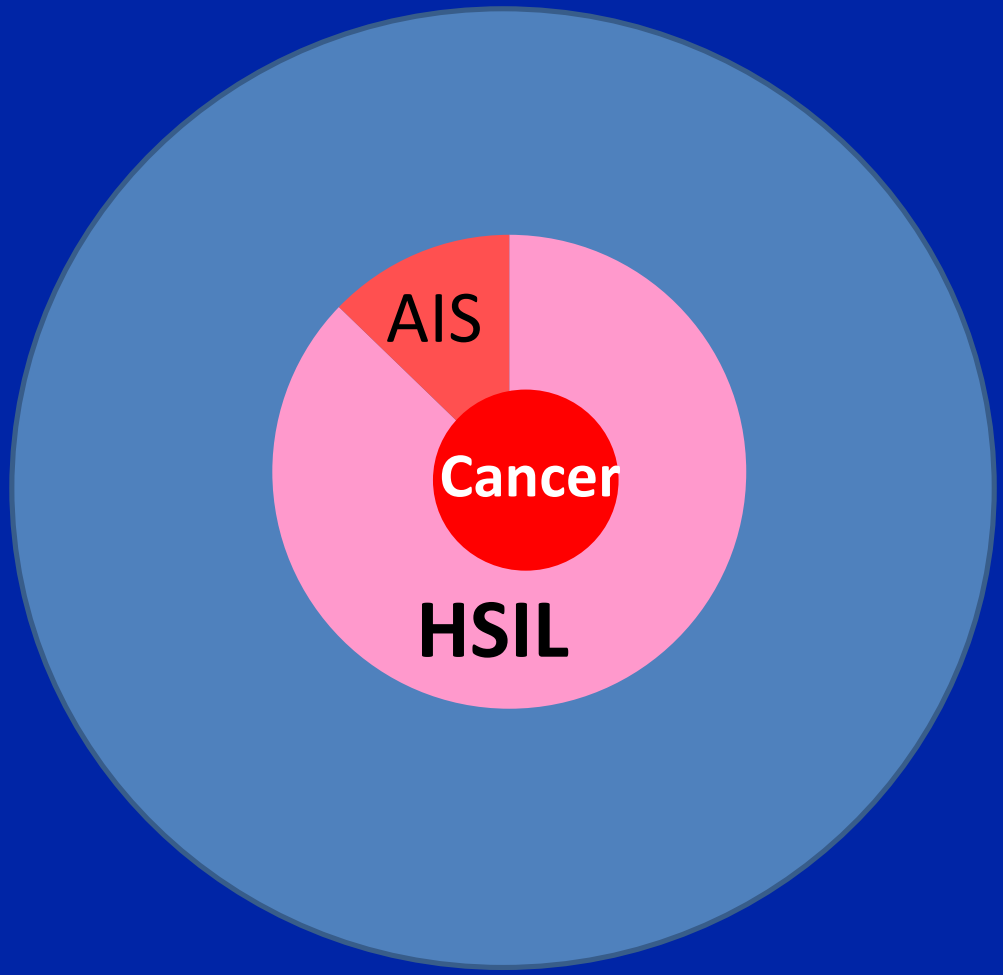
Mark Schiffman, 2011

The Natural History of Cervical Carcinogenesis



Secondary Prevention of Cervical Cancer

Screening → Colposcopy →



Cervical Cancer Screening

Fundamental goals[19]

1. Prevent morbidity and mortality from cervical cancer.
2. Identify precursors likely to progress to cancer (maximize the benefits of screening).
3. Avoid detection/treatment of transient HPV infections and lesions that will not become cancerous (minimize potential harms of screening).

[19]Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Low Genit Tract Dis. 2012;:16(3):179-204

Why Isn't Just "Finding Lesions" the Objective of Screening?

- We do not know which lesions will progress to cancer; most will not.
- Issues of concern:
  - Persistent hrHPV infections
  - CIN3 (treatment required)
  - CIN2 in older women (no risk to pregnancies if beyond reproductive age)
  - Persistent CIN2 and CIN2,3 in women of reproductive age

A new era in Cervical Cancer Prevention

"Risk Assessment"
"Risk Based Management"

Cervical Cancer Incidence by Age Group, USCS*, 1998-2002

Age	Rate per 100,000
0-19	0.1
20-29	4.5
30-39	13.9
40-49	16.5
50-64	15.4
65+	14.6
All ages	9.4

*United States Cancer Statistics includes data from CDC's National Program of Cancer Registries and NCI's Surveillance, Epidemiology and End Results Program.

Saraiya M et al. Obstet Gynecol 2007;109:360-70

ALTS trial: Data from Kaiser Permanente Northern California

- By far **the longest/largest real clinical experience with HPV testing and co-testing (**Cotesting started in 2003;)
  - **Over 1 million women age 30+ undergoing co-testing**
    - **440 cancers, 3231 CIN3+, 7581 CIN2+**
  - **Nearly 400k women age<30 with cytology and HPV triage of ASC-US**
    - **26 cancers, 1231 CIN3+, 4193 CIN2+**
- KPNC has high follow-up rates

Calculating Risk in KPNC

- **Total** or cumulative **risk** is the sum of two pieces:
  - **Immediate risk** if the condition is referred for immediate colposcopy
  - **Future risk** over the next 5-years of follow-up

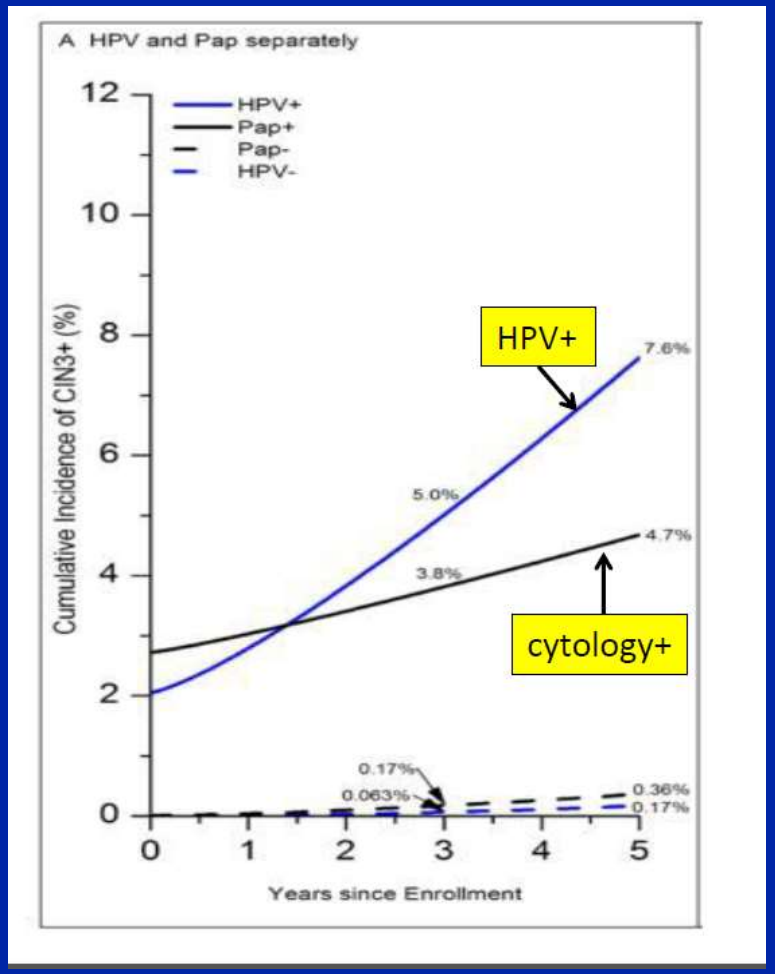
- **Example: 1000 women aged 30+ with LSIL**
  - **24** are diagnosed with CIN3+ at their immediate colposcopy: **2.4% immediate risk**
  - **29** more are diagnosed with CIN3+ **over the next 5 years (2.9%)**
  - **Cumulative risk:** 2.4% + 2.9% = **5.3%** CIN3+ risk over 5 years

- Logistic-Weibull model and the Logistic-Cox model

Cheung et al, Stat Med, 2017 ; Hyun et al, Ann Appl Stet, 2017 , Landy et al, Prev Med,2018

ALTS: HPV testing predicts future risk better than cytology

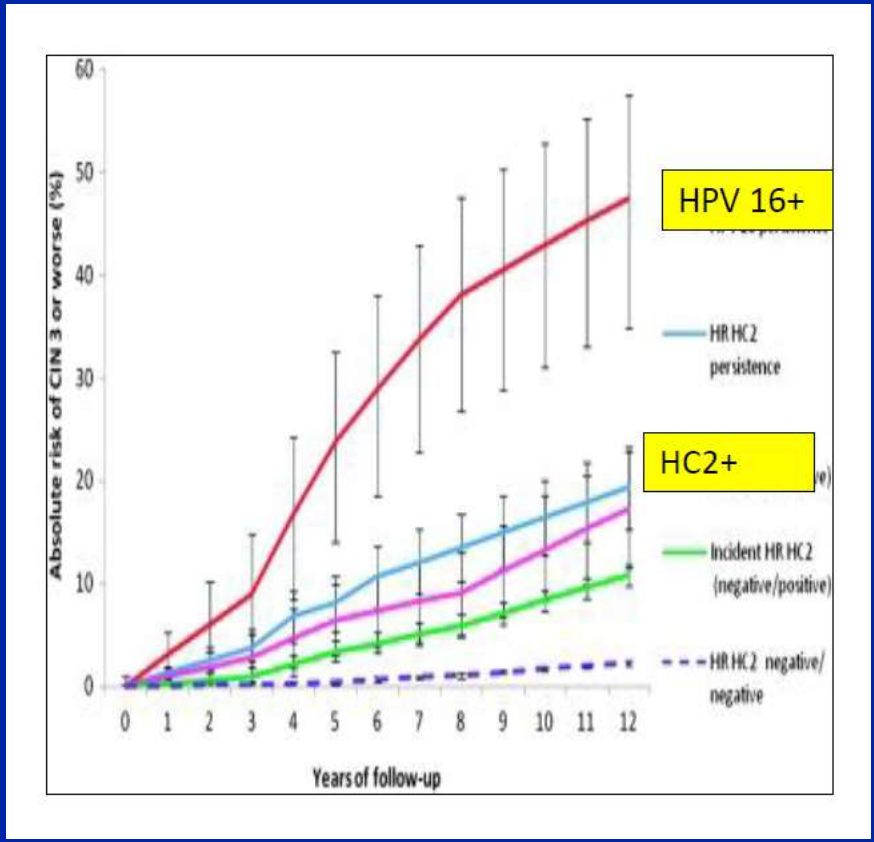
- 331.818 women over 2003-2009
- Followed for 5 years for CIN3+
- Both HPV and cytology predicted risk on the date of screening
- *HPV predicted future risk of CIN3 and cancer over 5 years*



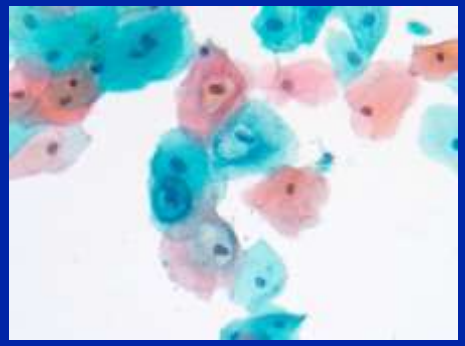
Katki et al J Low Genit Tract Dis. 2013 Apr;17(5 Suppl 1): S28-35

Persistent HPV is especially high risk

- 8656 women age 20-29 underwent co-testing 2 years apart
- Followed for 12 years for CIN3+
- **Risk of CIN3+**
  - **47% persistent HPV16+**
  - 19% persistent HC2
  - HPV neg 2%
- ***HPV history is an important risk modifier***



Kjaer, et al. J Nati Cancer Inst 2010 Oct 6; 102(19):1451-3



Limitations of Cervical Cytology

- False-positive results common; most ASC-US and LSIL not associated with CIN3+.
- Sensitivity for CIN3+ is only 44—71% depending on the specific study.
- High variability in labs' abnormal rates and interpretation of individual cases.
- Identifies current disease, but not future risk of disease.

Sensitivity of Cytology for CIN2+

Oregon review for 2012 USPSTF guidelines[21]

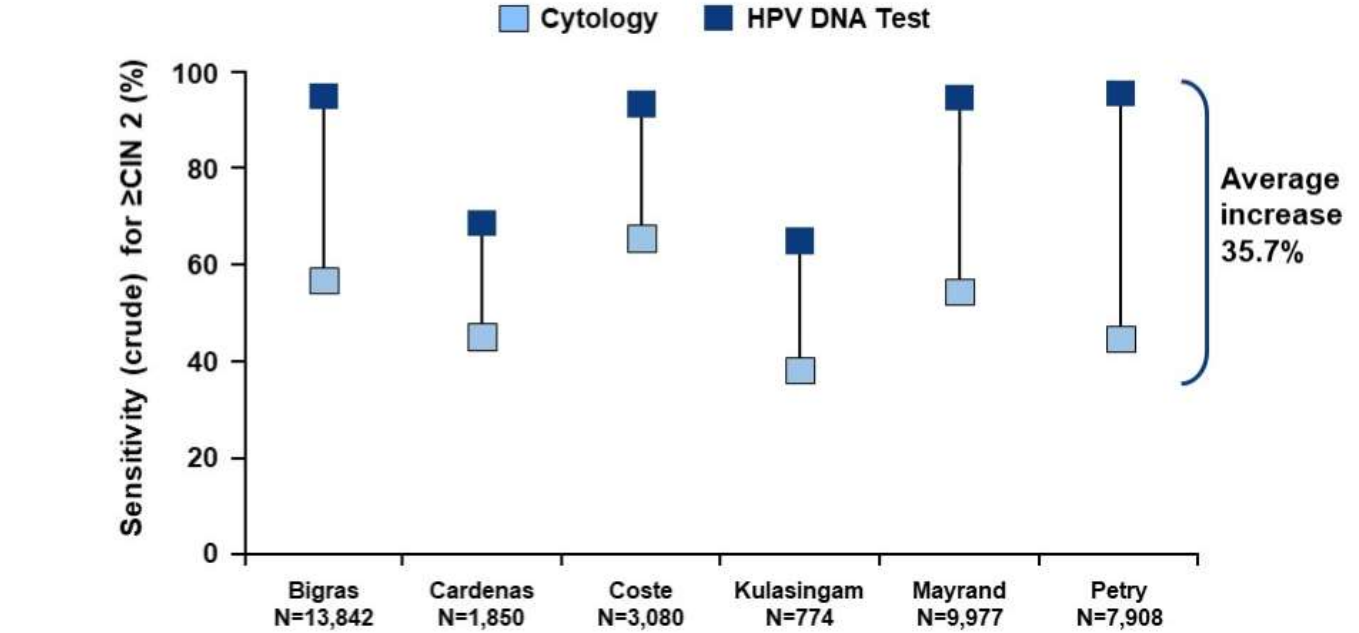
Author	Year	Number	Method	Sensitivity	95% CI
Petry	2003	7,908	Conv	44%	(30-58)
Coste	2003	3,080	Conv	65%	(50-80)
Bigras	2005	13,842	LBC	59%	(49-68)
Taylor	2005	3,114	LBC	71%	(58-81)
Mayrand	2007	9,977	Conv	56%	NA
Cardenas-Turanzas	2008	1,850	LBC	44%	(20-70)

CI = confidence interval, Conv = conventional cytology; LBC = liquid-based cytology

[21]Whitlock EP, Vesco KK, Eder M, Lin JS, Senger CA, Burda BIJ. Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155(10):687—697.

Using HPV Testing to Improve Sensitivity*

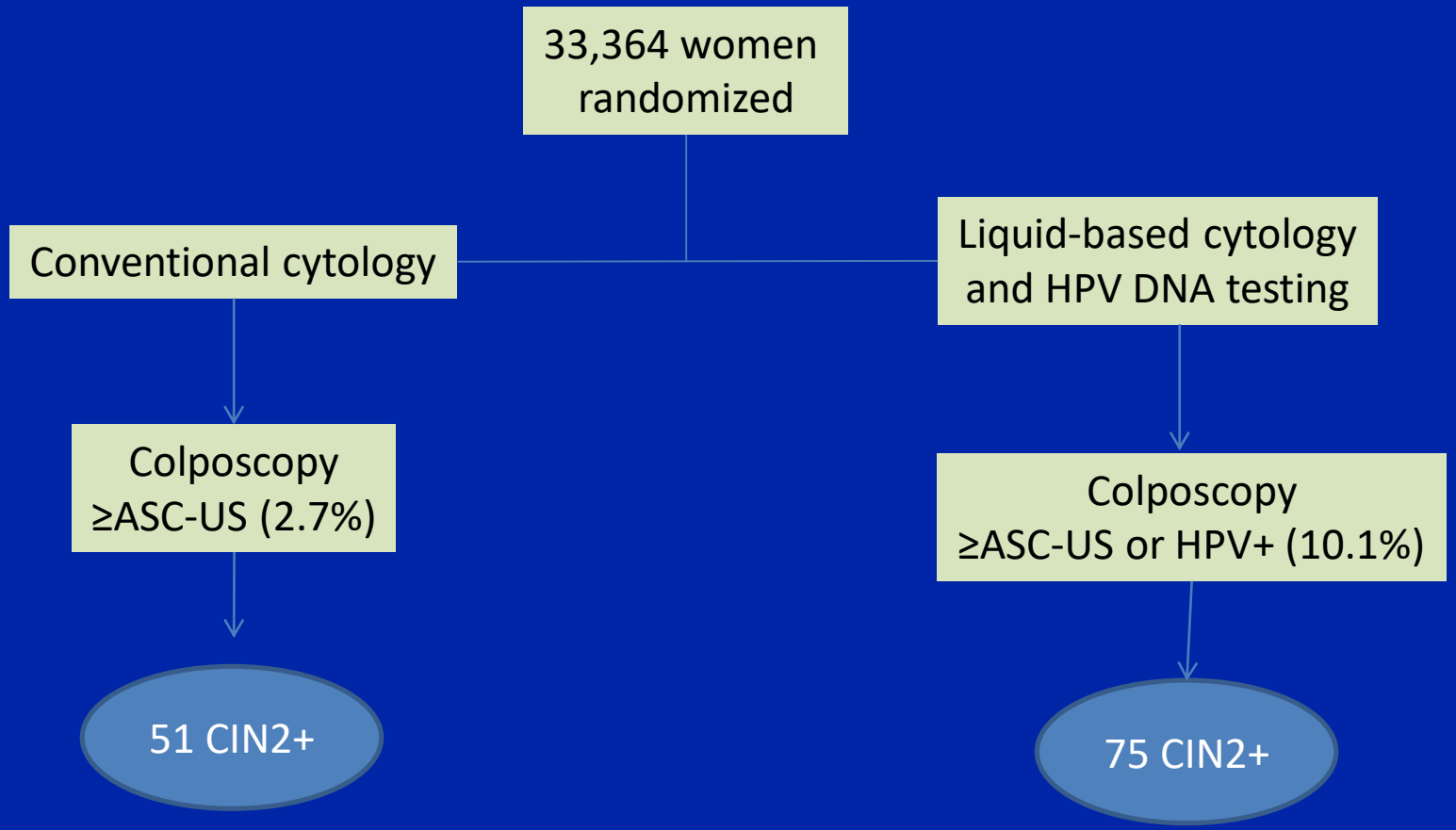
Oregon review for 2012 USPSTF guidelines[21]



[21]Whitlock EP, Vesco KK, Eder M, Lin JS, Senger CA, Burda BIJ. Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155(10):687—697.

Co-testing With Cytology and HPV Testing

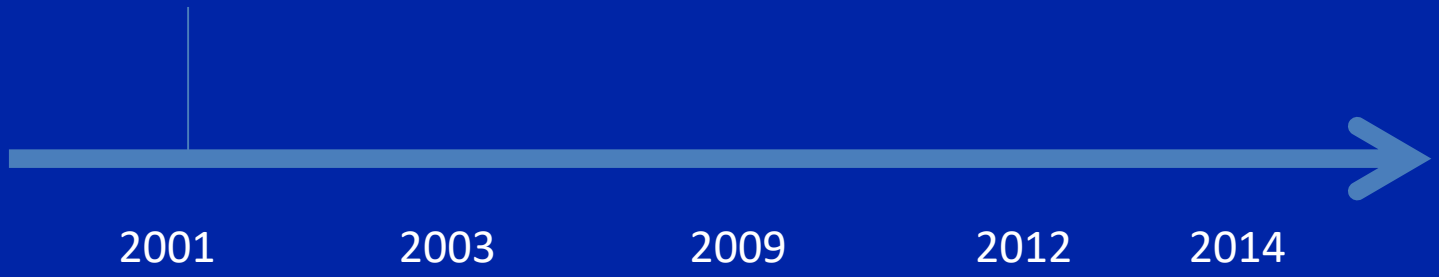
NTCC findings by study arm [31]



[31] *Ronco G, Segnan N, Giorgi-Rossi P, et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. Journal of the National Cancer Institute 2006;98:765-74 .*

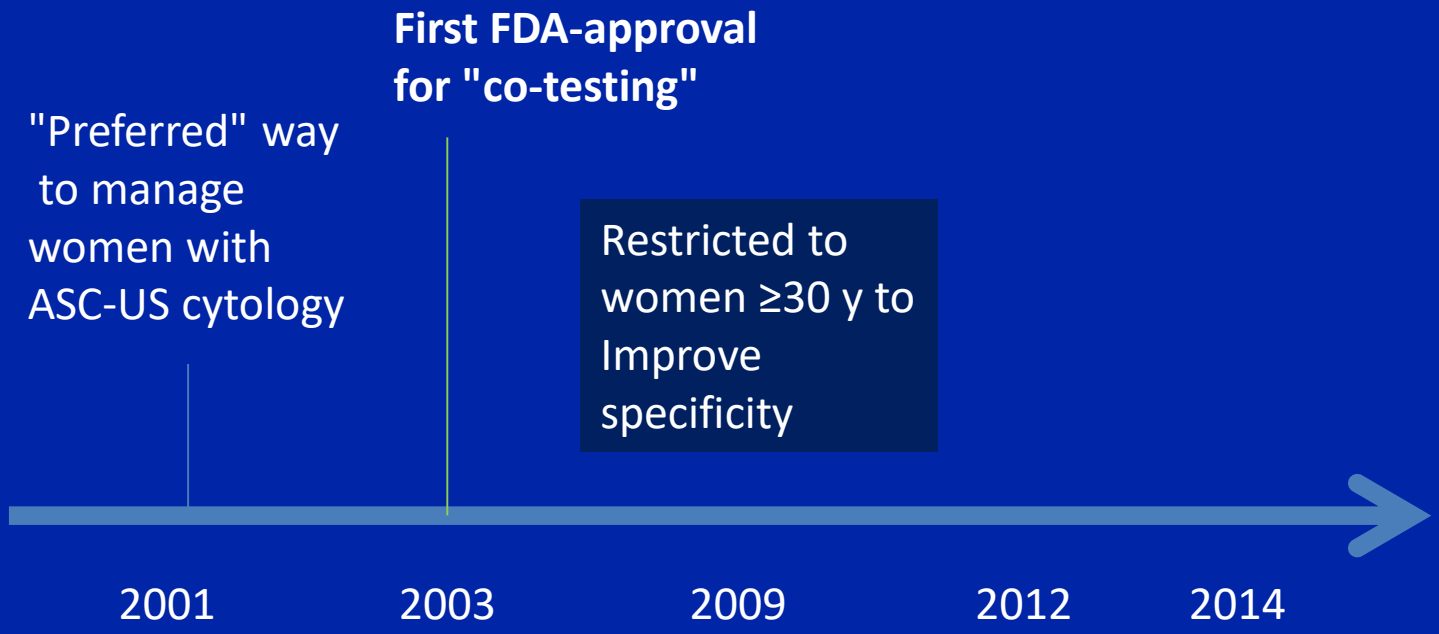
Timeline: Clinical Uses of High-risk HPV Testing

"Preferred" way to manage women with ASC-US cytology



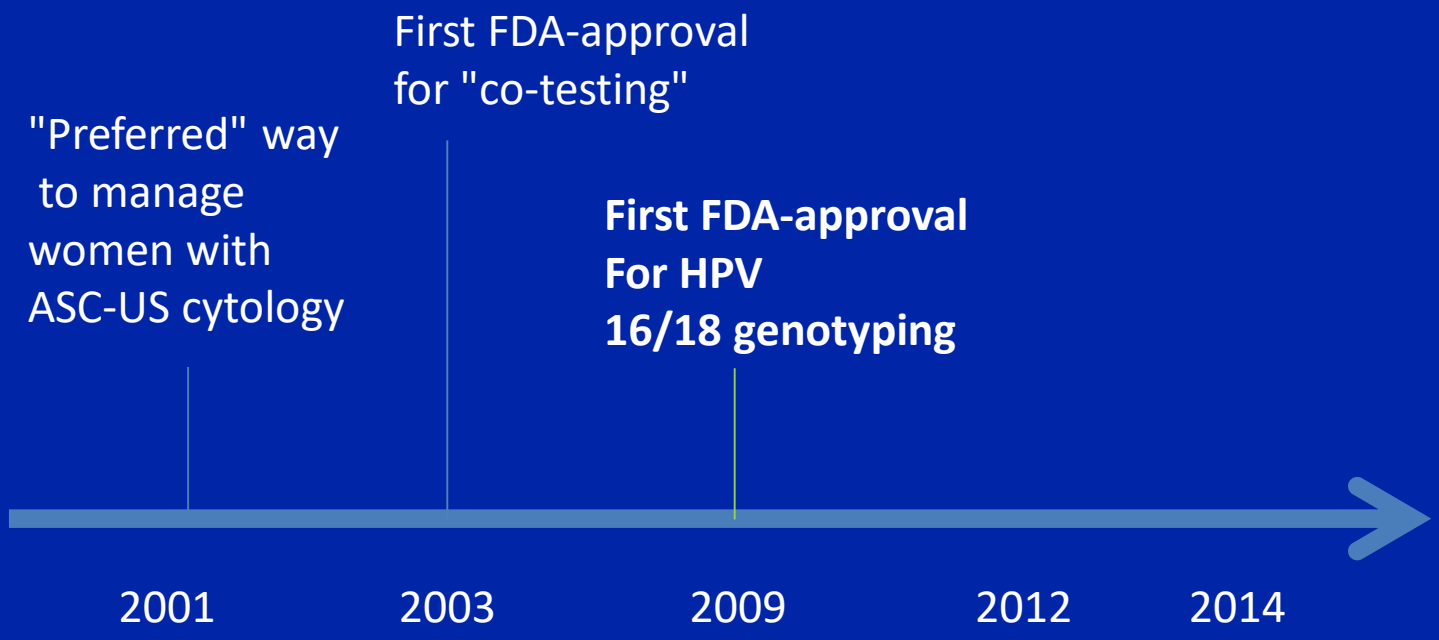
Helped fix the problem of massive numbers of ASC-US diagnoses

Timeline: Clinical Uses of High-risk HPV Testing



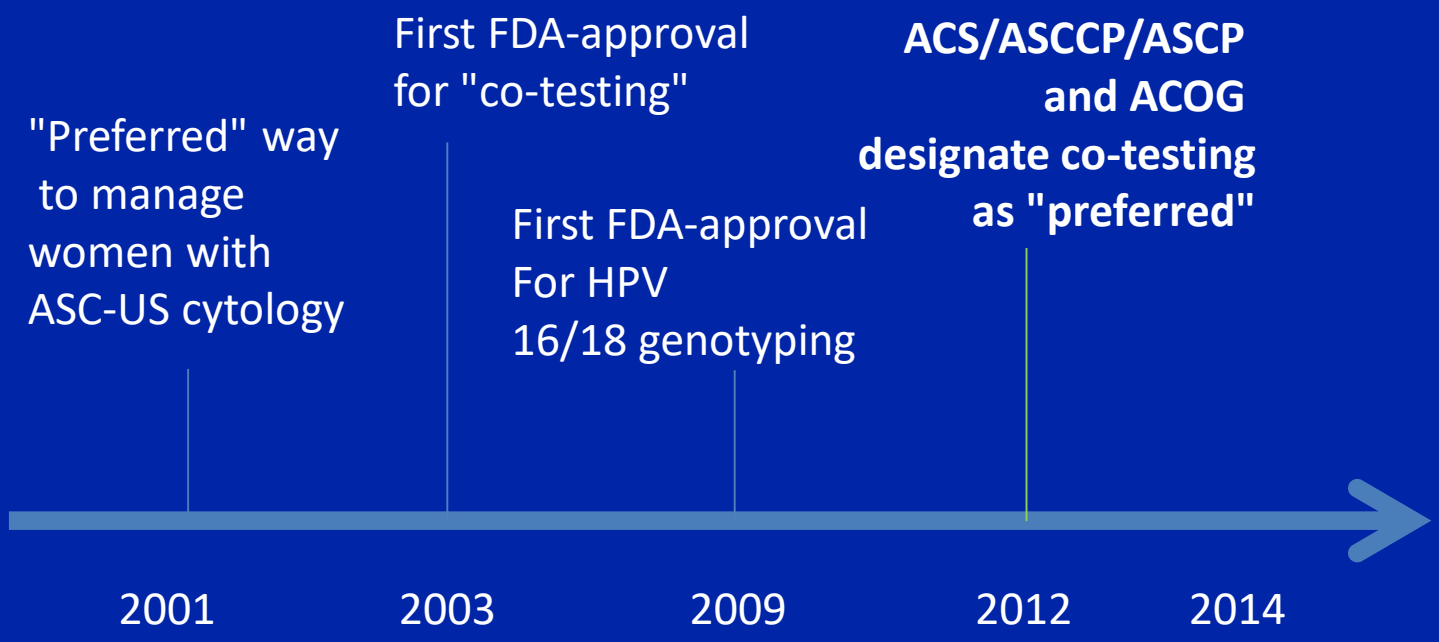
Goal was to compensate for the poor sensitivity of cytology

Timeline: Clinical Uses of High-risk HPV Testing



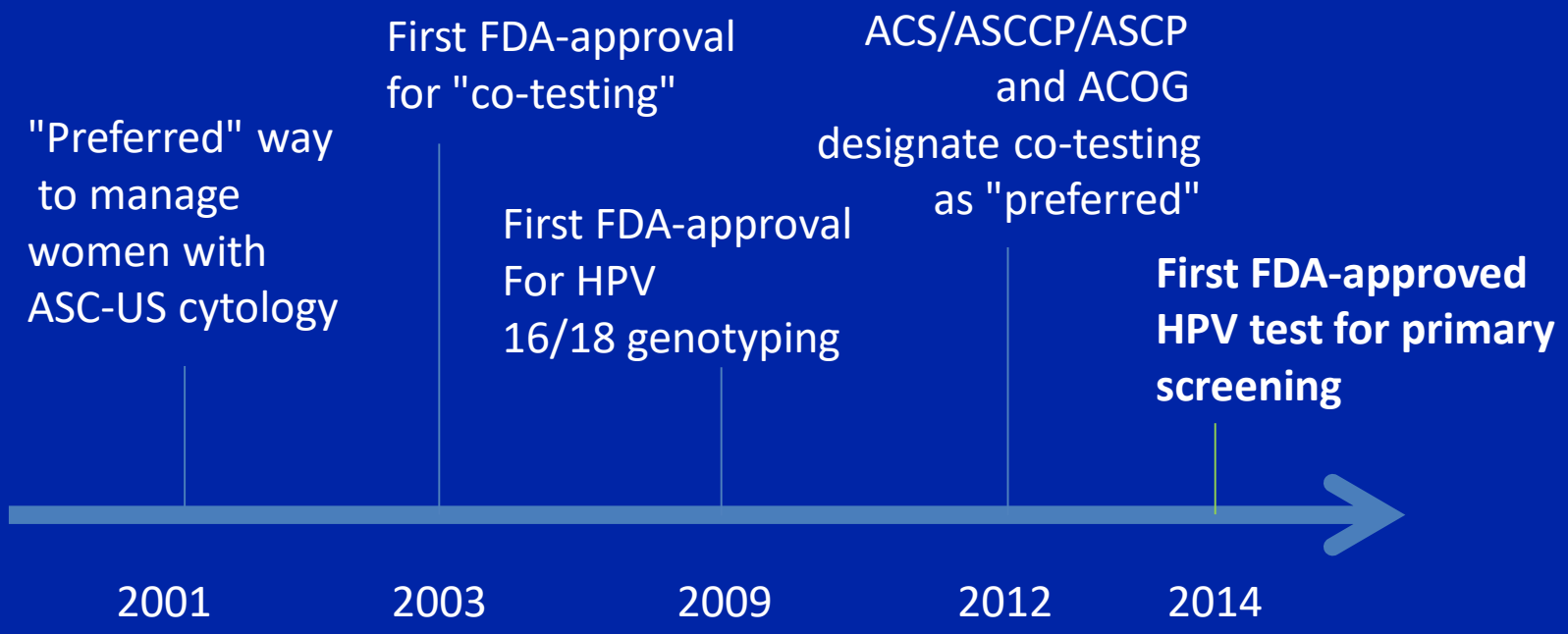
Co-testing became more
Acceptable as women at
Greatest risk immediately
Identified for colposcopy

Timeline: Clinical Uses of High-risk HPV Testing



"Preferred" designation is a powerful driver of adoption

Timeline: Clinical Uses of High-risk HPV Testing



Opportunity to simplify screening, use one test

2014 FDA Approval for Primary hrHPV Testing for Cervical Cancer Screening [24]

Rationale

- **More sensitive** and reproducible than cytology alone.
- Assesses current and future risk.
- More cost-effective for large-volume screening.
- Primary hrHPV screening is safe and effective based on ATHENA.[29, 30]
- May be more useful in women vaccinated against HPV.

[24]Huh WK, Ault KA, Chelmow D, e tal. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. J Low Genit Tract Dis. 2015;19(2):91— 96.
[29]Wright, T. C., Jr., Stoler, M. H., Sharma, A., Zhang, G., Behrens, C., & Wright, T. L. (2011). Evaluation of HPV-16and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. AmJ Clin Pathol, 136(4), 578-586.
[30]Ronco, Dillner, Elfstrom, K. M., Tunesi, S., Snijders, P. J., Arbyn, M., ... Meijer, C.J. (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet, 383(9916), 524-532,

FDA: Using HPV Testing to Improve Screening

Which test is right for you? - Clinical validation

- Because of the potential for harm, HPV tests require extensive clinical validation before they should be used for routine clinical care.
- Guidelines for clinical validation are well established but require trials that are beyond the scope of most individual laboratories.
- In the United States, only use FDA-approved HPV tests that have undergone extensive clinical validation.

FDA-approved HPV tests

Comparison of tests and indications

HPV Assay	Method	Typing	ASC-US Triage	Cotest	Primary
Hybrid Capture 2	DNA - genomic DNA:RNA Hybridization	No	✓	✓	
Cervista	DNA Invader Technology	16/18 reflex	✓	✓	
cobas HPV	L1 DNA PCR Taqman	16/18	✓	✓	✓
APTIMA	E6/E7 mRNA TMA	16/18, 45 reflex	✓	✓	
BD Onclarity	E6/E7 DNA	16/18/45	✓	✓	✓

Evidence Based Medicine - Randomized Clinical Trials

- Ronco G, et al. Lancer, 2014, 383 pp 524-532
- Dillner J, et al. BMJ. 2008, 13;337:1754
- Katki HA et al. Lancer Oncol, 2011, 12(7):663
- POBASCAM Study: The Netherlands (Meijer et al., In J Cancer 2004; Bulkmans et al, Lancet 2007)
- Osmanabad Trial: India (Sankaranarayanan et al., NEJM 2009)
- ARTISTIC Trial: UK (Kitchener et al., Lancet Oncol 2009)
- NTCC Italian Study (Ronco et al., Lancet Oncol 2006; JNCI 2009)
- SWEDESCREEN: Swedish Trial (Elfgren et al., AJOG 2005; Naucler et al., NEJM 2007; JNCI 2009)
- Finnish Trial (Kotaniemi et al., BJC 2005; Eur J Cancer 2008; IJC 2008; Leinonen et al., JNCI 2009)
- CCCaST Study: Canada (Mayrand et al., IJC 2006; NEJM 2007)
- HPV Focal: British Columbia (Ogilvie et al., BJC 2012)
- Athena Trial: US (Castle et al., Lancet Oncol 2011)

FDA-approved HPV tests

The first FDA approved test was: **Hybrid Capture 2** (hc2), using a solution hybridization method. Two panels were approved, including a HR panel with 13 types.

Low-risk

6, 11, 42, 43, 44

For clinical management related to cancer screening

High-risk

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 56, 59, 68

FDA-approved HPV tests

The second FDA approved test was: **Cervista®** HPV HR, using an isothermal enzymatic DNA amplification process. The test detects 14 HR types

High-risk
16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 56, 59, 66, 68

3 - Cervista® HPV 16/18 type specific testing (FDA approved 2009)

FDA-approved HPV tests

Cobas® 4800 HPV test (FDA approved 2011) — Roche

- PCR-based
- 14 HR HPV types
  - Genotyping for HPV 16 and 18 integrated into the assay
  - Concurrently detects remaining 12 types as a group

FDA-approved HPV testing

Aptima® (FDA-approved for testing on Hologic system 2013)

- Detects E6/E7 mRNA expression of 14 HR HPV types
- Genotyping for HPV 16, 18 and 45
- HPV E6/E7 over expression: necessary condition for the start and progression of cervical neoplasia
- Rationale: E6 and E7 inactivates p53 and pRb suppressor proteins
  - Is HPV mRNA a true biomarker for CIN 3?
  - 94% and 100% of women with CIN 3 and cancer were + for E6/E7 mRNA activity

Castle et al. Clin CA 2007;13

FDA-approved HPV testing

BD Onclarity™ (FDA-approved 2018)

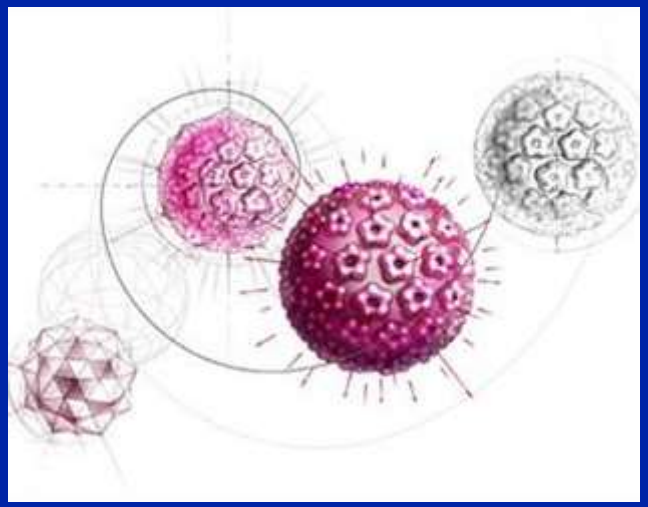
- Utilizes amplification of target DNA by PCR and nucleic acid hybridization
- **Detects 14 HR HPV types**
  - **E6/E7 DNA**. Specifically identifies types **16, 18 and 45**
  - Concurrently detects 11 other HR HPV types that include 31, 33, 35, 39, 51, 52, 56, 58, 59, 66 and 68

FDA-approved HPV tests

Comparison of tests and indications

HPV Assay	Method	Typing	ASC-US Triage	Cotest	Primary
Hybrid Capture 2	DNA - genomic DNA:RNA Hybridization	No	✓	✓	
Cervista	DNA Invader Technology	16/18 reflex	✓	✓	
cobas HPV	L1 DNA PCR Taqman	16/18	✓	✓	✓
APTIMA	E6/E7 mRNA TMA	16/18, 45 reflex	✓	✓	
BD Onclarity	E6/E7 DNA	16/18/45	✓	✓	✓

What is the Rationale for Combined Screening with HPV test plus Pap?



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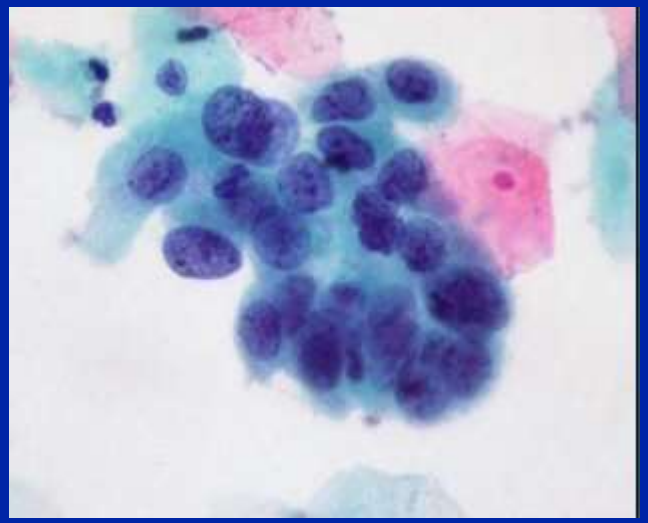


Using HPV Testing to Improve Screening

- The higher sensitivity of HPV testing compared with cytology means we should be able to use HPV testing to improve screening.

Prevalence of HPV+/Cytology- Findings

Various studies in women ≥30 y[1, 2, 3, 4, 5]

Study	Test	N	High-risk HPV+
Kaiser[4]	hc2	853,465	4.2%
ATHENA[1]	cobas	32,260	6.7%
CLEAR2[2]	APTIMA	10,871	5.0%
NTCC[3]	hc2	1,933	6.0%
Mayrand[5]	hc2	10,151	4.9%

hc2 = Hybrid Capture 2

[1]Wright TC Jr, Stoler MH, Sharma A, et al. Am J Clin Pathol. 2011;136(4):578-586. [2]APTIMA [package insert]. San Diego, CA: Hologic; 2015 [3]Ronco G, Segnan N, Giorgi-Rossi P, et al. Journal of the National Cancer Institute. 2006;98:765-74. [4]Castle PE, Fetterman B, Thomas Cox J, et al. Obstet Gynecol. 2010;116(1):76-84. [5]Mayrand MH, Duerte-Franco E, Rodrigues |, et al. N Engl J Med. 2007;357(16):1579-1588.

HPV as Primary Screening Test

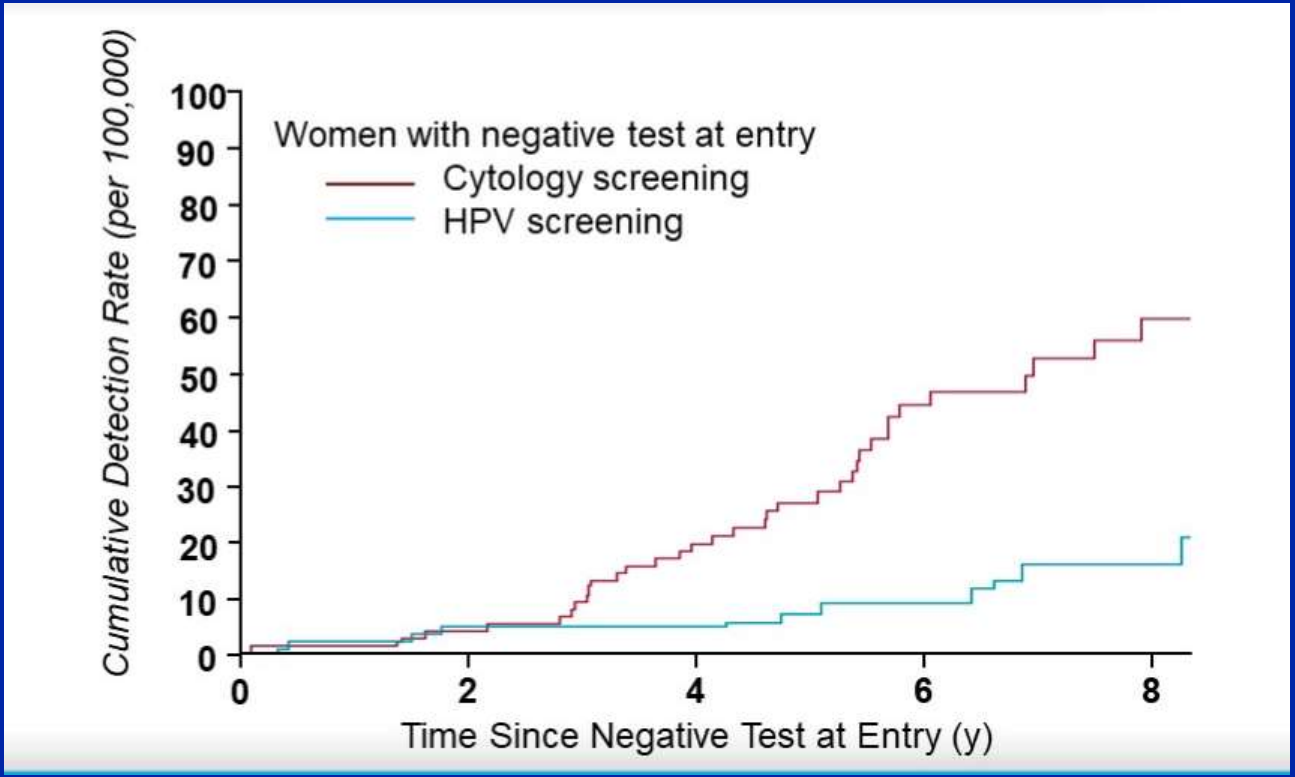
What does cytology really add?

- Data obtained from the European co-testing trials made it clear that **cytology adds little to HPV** as the initial screen.

  - European randomized screening trials: NTCC, POBOSCAM, VUSA, ARTISTIC, SWEDESCREEN
  - One US observational trial: ATHENA
  - One large US registry study: National Cancer Institute-Kaiser Northern California.

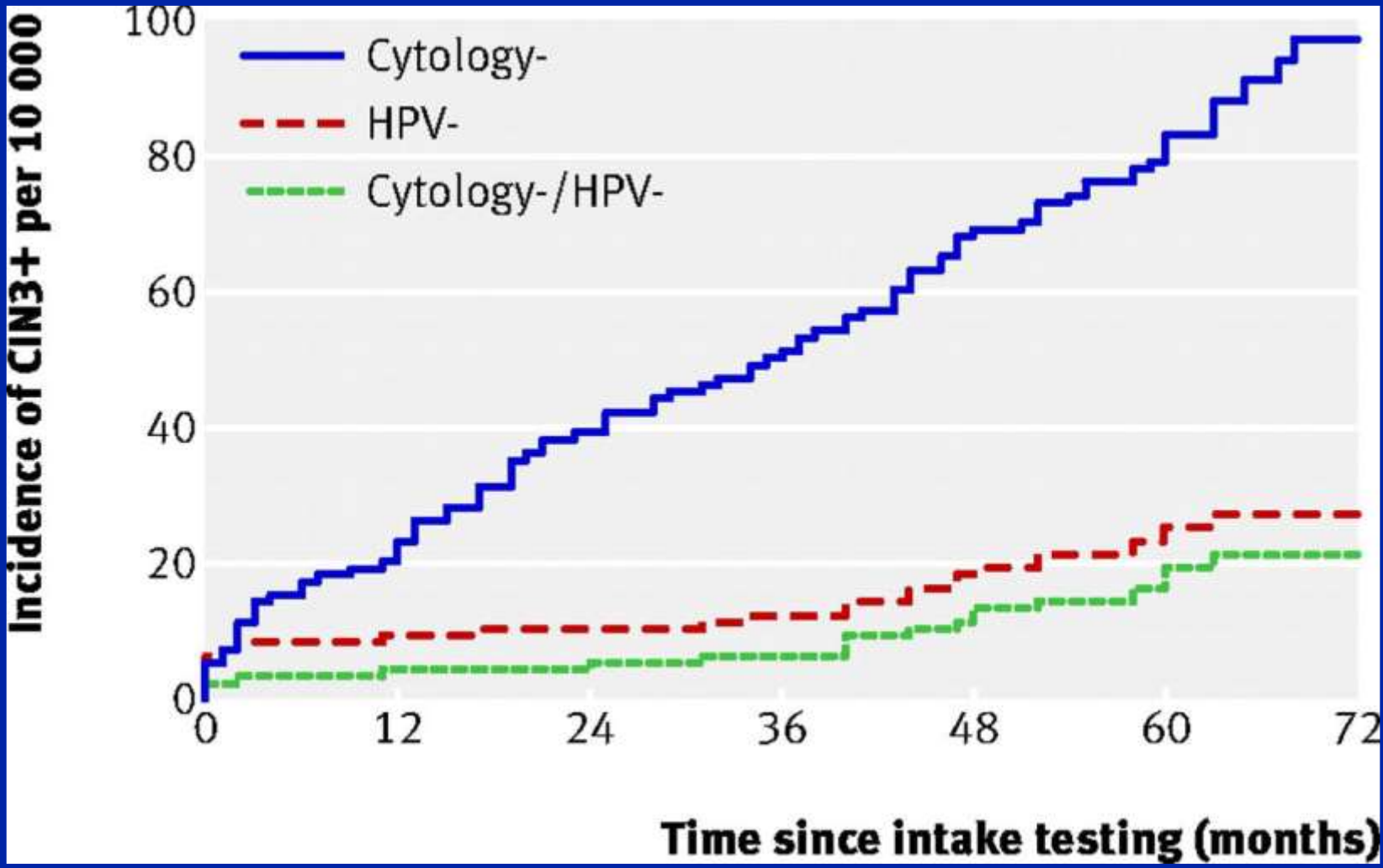
Incidence of Cervical Cancer in women with a negative test

Comparing cytology alone to HPV testing



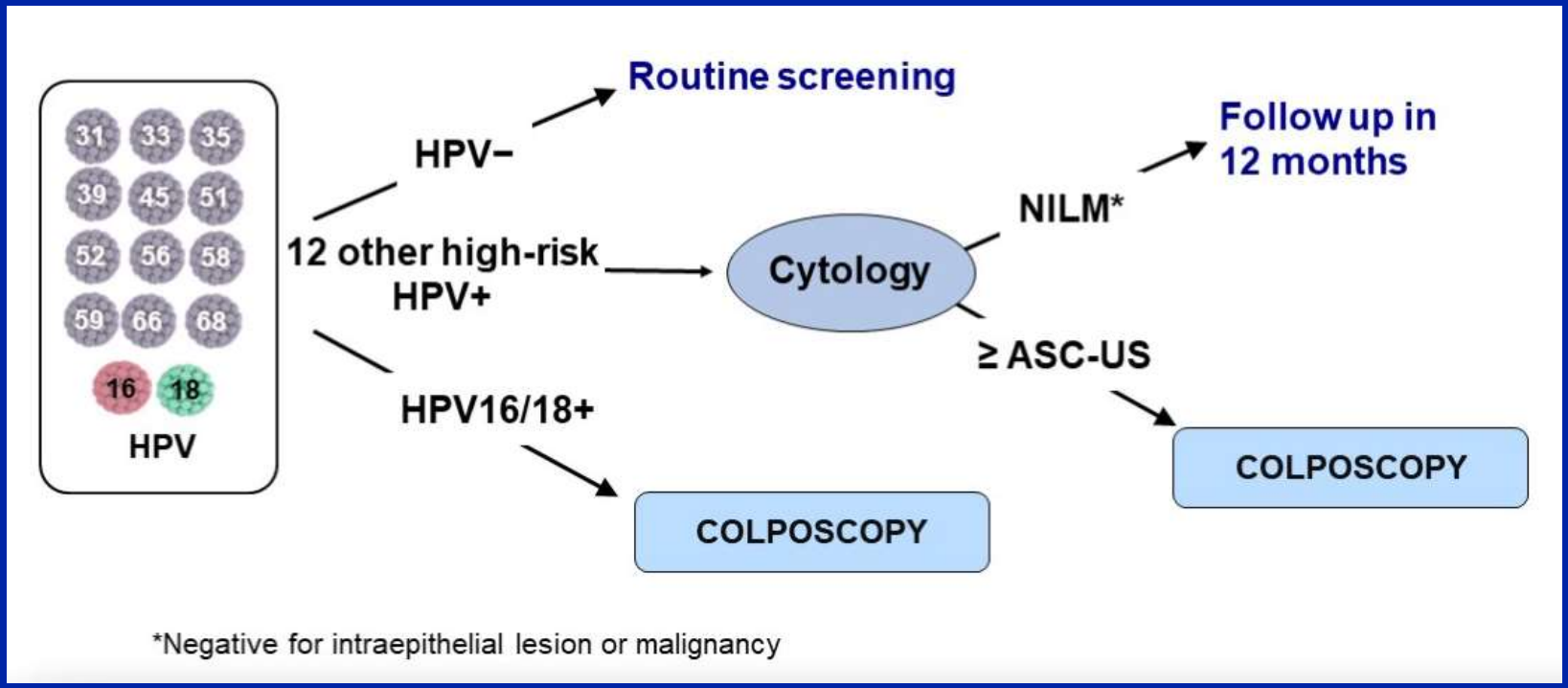
Ronco G, Dillner J, Elfstrom M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow up of four European randomized controlled trials. Lancet 2014;383:524-532

Dillner J et al. BMJ 2008;337:a1754



HPV Primary Screening Algorithm

Triage with HPV 16/18 genotyping and reflex cytology[30]



[30]Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. Gynecol Oncol. 2015;136(2):189—197.

HPV Primary Screening

SGO/ASCCP interim guidance[45]

- In January 2015, the Society of Gynecologic Oncologists (SGO) and ASCCP published interim guidance on HPV primary screening.
- HPV primary screening beginning not before 25 yrs. with a 3 year interval was considered a reasonable screening approach.
- Considered the FDA-algorithm as a reasonable approach to managing HPV (+) women.

[45]Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Gynecol Oncol. 2015;136(2):178—182.

Countries Implementing HPV Primary Screening

- Netherlands: Minister of Health approved HPV primary screening beginning in 2016.
- Australia: National Health Service adopted screening with HPV 16/18 genotyping starting at age 25 y at 5-y intervals up to age 70-74 y.
- United Kingdom: Evaluating in large national pilot study at 6 National Health Service screening sites including London, Liverpool, Bristol, and Manchester.
- Italy: A number of regions have adopted primary screening.

Preparing providers and the public for the future

- Pap tests are an inferior test compared to HPV-based screening.
- Pap tests are minimally effective in women who have been vaccinated.
- Pap tests will be phased out.
- Co-testing offers minimal benefit compared to primary HPV screening, and will be phased out.
- Self-collected sampling for HPV testing is effective and acceptable by women who are not getting screened.
- Vaccination will permit less frequent screening.
- Vaccination will permit later starting age for screening.

Debbie Saslow, PhD
Managing Director, HPV & GYN Cancers, American Cancer Society

Σας ευχαριστώ!