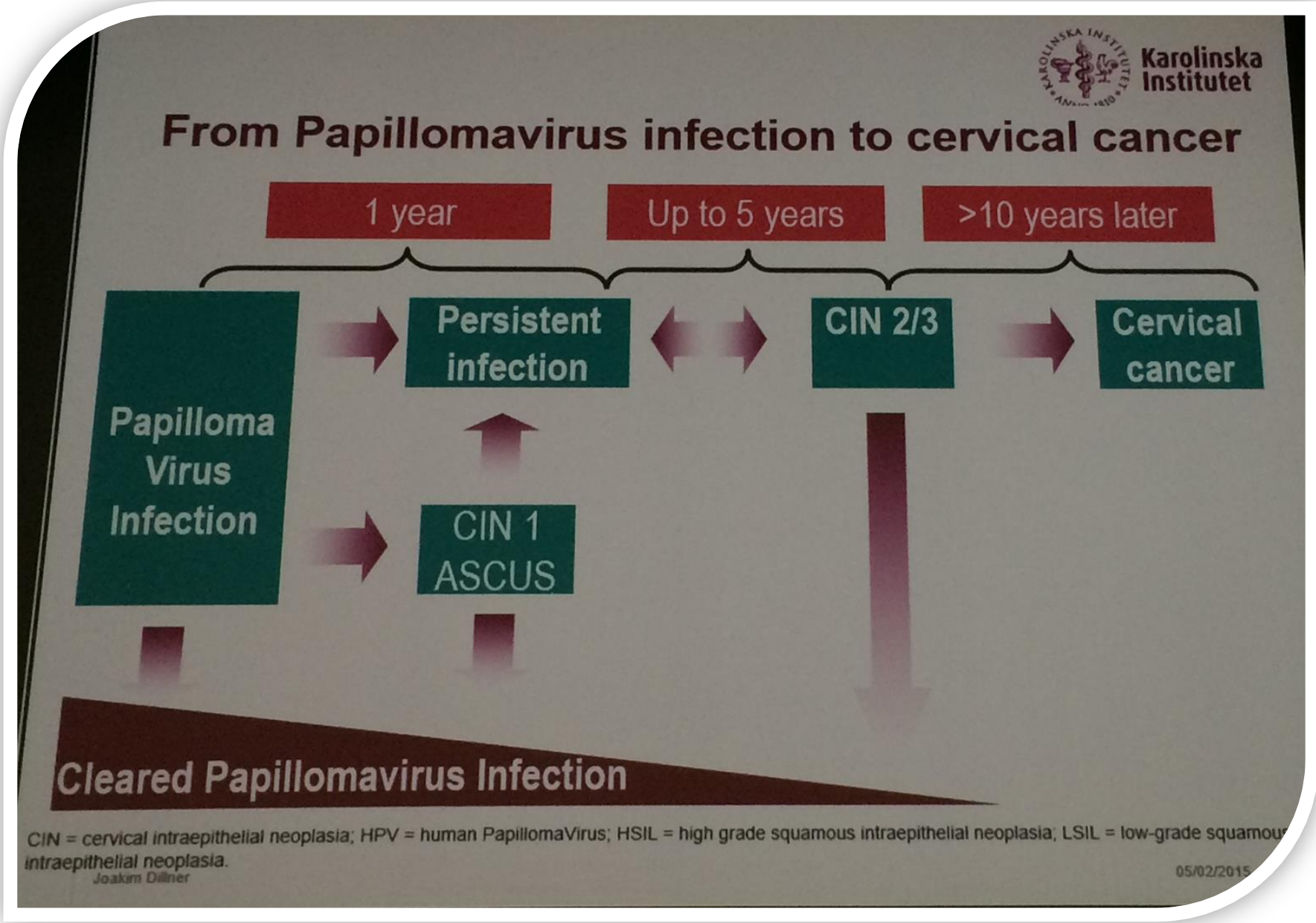
Cervical Cancer Screening

S.A. NADJI, PHD

ASSOCIATE PROFESSOR OF VIROLOGY

HEAD, VIROLOGY RESEARCH CENTER, NRITLD, SBMU



Virology Research Center
مرکز تحقیقات ویروس شناسی

Ranking of the 7 most common HPV types

Rank	Cervix	Vulva	Vagina	Penis	Anus
1	HPV 16	HPV 16	HPV 16	HPV 16	HPV 16
2	HPV 18	HPV 33	HPV 31	*HPV 6*	HPV 18
3	HPV 45	HPV 18	HPV 18	HPV 33	HPV 33
4	HPV 33	HPV 45	HPV 33	HPV 45,35	HPV 31
5	HPV 31	HPV 52	HPV 45,58	HPV 59	HPV 58,*6*
6	HPV 52	HPV 56	HPV 52	HPV 18,52,*11*	HPV 35
7	HPV 58	HPV 31,58,74	HPV 51	HPV 58	*HPV 11*

- **Type distribution for nearly 30'000 HPV related cancers from 38 countries participants in ICO surveys 2005 - 2014**

Burden of HPV related Cancers

	CERVIX	VULVA	VAGINA	PENIS	ANUS
Incidence [1,2]	14.0%	0- 4.6%	0.5- 1.7%	14.0%	1.0%
Annual number of cancers [3]	530,000	27,000	13,000	22,000	27,000
Cancers attributable to HPV [3]	530,000	12,000	9,000	11,000	24,000
HPV prevalence [3]	100%	43%	70%	50%	88%

Worldwide population attributable fraction **4.8%** [3]

1) Age-standardized incidence rate per 100,000 women per year
2) de Martel C et al. Lancet Oncol 2012;13(6):607-15
3) Forman et al. *Vaccine*. 2012;30S:F12–F23

Estimation of HPV attributable fractions (AF) from cancer case series

HPV-related cancer site		Region	AF (%)
Cervix uteri	PCR	World	100
Anus	PCR	World	88
Penis	PCR	World	51
Vagina	PCR	World	78
Vulva	PCR	Age 15–54 years	48
		Age 55–64 years	28
		Age 65+	15
Oropharynx (including tonsils and base of Tongue)	PCR + E6/E7 mRNA	North America	51
		North-West Europe	42
		East Europe	50
		South Europe	24
		China	23
		Japan	46
		India	22
		Rep. Korea	60
		Australia	41
		Elsewhere	13
Oral cavity/Larynx	E6/E7 mRNA	World	4

HPV PREVALENCE IN IRANIAN FEMALES

HPV screening, 2011

- 5353 ThinPreps, 11 provinces
- 320 HPV+ (6%)
  - 99 HR-HPV (31%) [type16/18]
  - 36 LR-HPV (11.3%) [type 6/11]

HPV screening in addicted females,2009

- 118 vaginal swabs, TEHRAN
- 59 HPV+ (50%)
- 11 HR-HPV (19%) [type16/18]

Int J Gynecol Obstet, 2009

STI screening in Vulnerable women,2015

- With collaboration of 15 Medical Science Universities
- 1337 vaginal swabs, 13 provinces
- 559 Human Papillomavirus: 41.8% (95%CI: 39.2, 44.5)
- 144 HR-HPV (25.8%) [type16/18]
- other STI prevalence

  Syphilis 0.4% (95%CI: 0.2, 1.0); Gonorrhea: 1.3% (95%CI: 0.8, 2.1); Chlamydia: 6.0% (95% CI: 4.8, 7.4); Trichomoniasis: 11.9% (95% CI: 8.5, 16.5);

AIDS 2016
DURBAN, SOUTH AFRICA
#AIDS2016 | @AIDS_CONFERENCE

Number of Isolated Genotypes

Virology Research Center
مرکز تحقیقات ویروس شناسی

1	G 89	7
2	G 87	1
3	G 84	5
4	G 83	1
5	G 81	1
6	G 73	2
7	G 70	1
8	G 69	1
9	G 68	12
10	G 67	3
11	G 66	37
12	G 62	6
13	G 61	1
14	G 59	7
15	G 58	5
16	G 56	10
17	G 54	4
18	G 53	7
19	G 52	4
20	G 51	18
21	G 45	8
22	G 44	46
23	G 43	5
24	G 42	14
25	G 40	1
26	G 39	6
27	G 35	10
28	G 33	3
29	G 31	9
30	G 26	1
31	G 18	18
32	G 16	83
	G16 or G18	99
33-34	G 6/11	36

Objective of Screening

- **Prevent morbidity and mortality from cervical cancer**
- **Prevent overzealous management of precursor lesions that most likely will regress or disappear and for which the risks of management outweigh the benefits**

How good is Cytology in Cervical cancer Screening?

- **Duke report (Nada et al.,2000): sensitivity= 51% & specificity= 98%**
- **Pooled analysis of European and Canadian Studies (Cuzick et al.,2006): sensitivity= 53% & specificity= 96%**
- **Cytology Screening programs have to compensate for the low sensitivity by acquiring 2-3 annual cytology tests**

Other Issue to consider with Cytology

- **Highly subjective test: substantial inter- and intra- laboratory variability and limited reproducibility, particularly for equivocal and low grade test results**
- **Unable to identify women at future risk of developing cervical cancer precursors**
- **Unclear how cytology will perform as HPV vaccine uptake rates increase**

New ACS/ASCCP/ASCP Guidelines
when to begin screening

Cervical cancer screening should begin at age 21

Women <21 should not be screened regardless of age of sexual onset

SASLOW D, SOLOMON D, LAWSON H, …. CA: A CANCER J FOR CLINICIANS, 2012, 62(3):147-72

2012 ACS/ASCCP/ASCP screening guidelines

Screening for age 21-29

- Cytology alone every 3 years
- HPV testing "should not be used to screen"
  - Not as a component of contesting
  - Not as a primary stand –alone screen

Screening for age 30-64

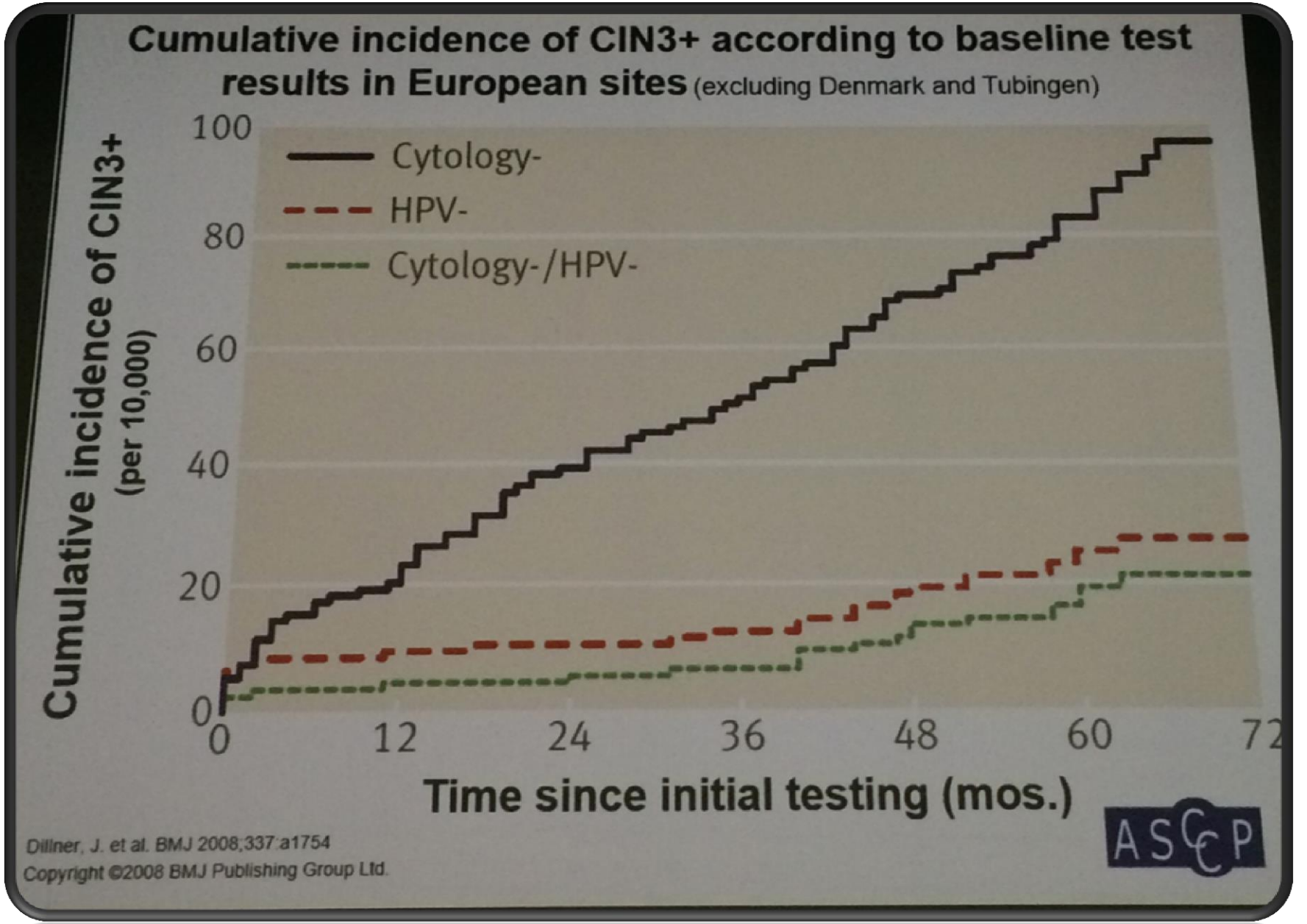
- Cytology + HPV testing (contesting) every 5 years is **PREFERRED**
- Cytology alone every 3 years is **ACCEPTABLE**

HPV Testing into Primary Screening

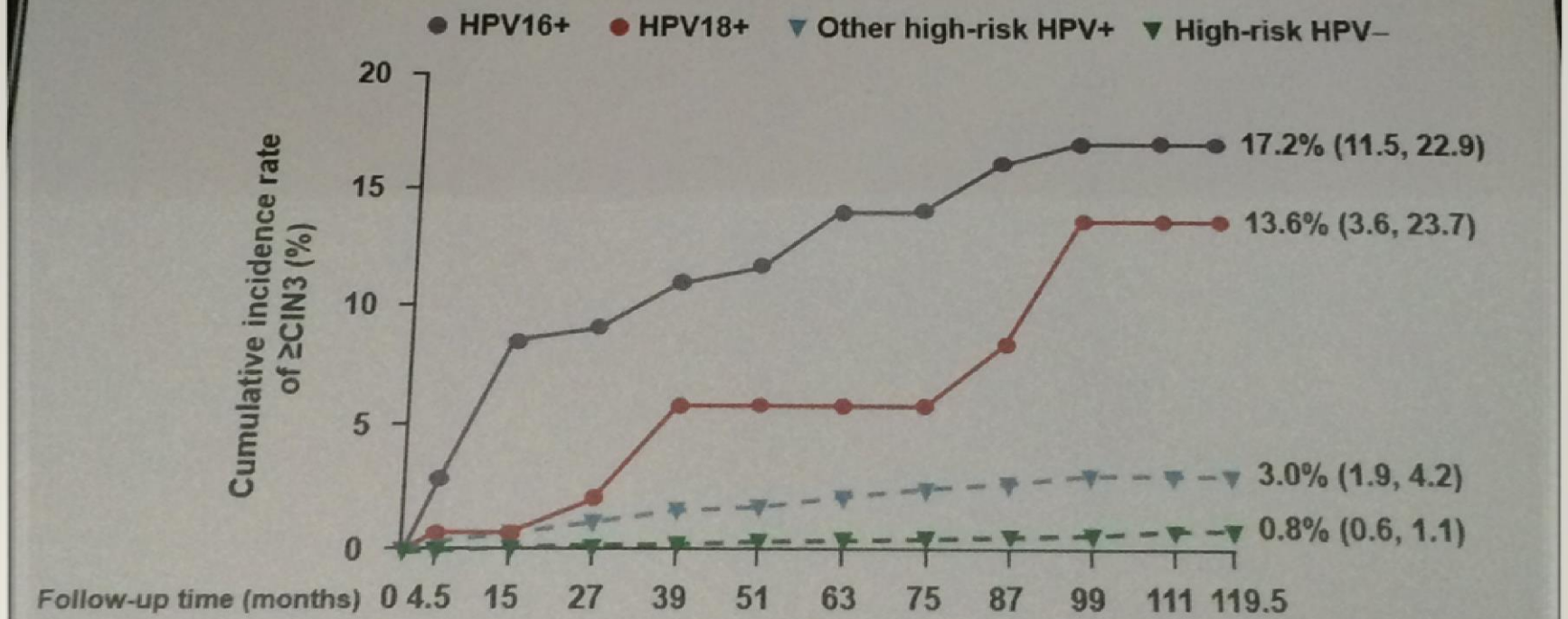
Cotesting vs. Primary stand -alone HPV testing

RCTs of HPV Testing in Screening

- POBASCAN study: the Netherlands (Mej\ijer et al., Int J Cancer 2004; Bulkmans et al., Lancet 2007)
- Indian Trial (Osmanabad) (Sankaranarayanan et al. NEJM 2009)
- ARTISTIC trial: UK (Kitchener et al. Lancet Oncol 2009)
- NTCC Italian Study (Ronco et al., Lancet Oncol, 2006; JNCI 2006)
- SWEDESCREEN: Swedish trial(Elfgren et al., AJOG 2005; Naucler et al., NEJM 2007; JNCI 2009)
- Finnish RCT (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)
- BC RCT (HPV FOCAL): Canada (Ogilvie et al., Br J Cancer 2012)
- Athena Trial: United States (Wright, et al., GynOnc 2015)


Cumulative incidence of CIN3+ according to baseline test results in European sites (excluding Denmark and Tubingen)
Cumulative incidence of CIN3+ (per 10,000)
100
80
60
40
20
0
Cytology-
HPV-
Cytology-/HPV-
0
12
24
36
48
60
72
Time since initial testing (mos.)
Dillner, J. et al. BMJ 2008;337:a1754
Copyright ©2008 BMJ Publishing Group Ltd.
ASCCP

Women with HPV16 and HPV18 Infections More Likely to Develop High-grade Disease



Chan MJ, *et al. J Natl Cancer Inst* 2005; 97:1072–1079

ASCCP

Test Result	5-year Risk	Excess Risk
HPV+	7.6%	7.4%
HPV-	0.2%	
Cytol+	4.7%	4.3%
Cytol-	0.4%	

HPV Test	Cytol. Test	5-year Risk	Excess Risk
HPV+	Cytol+	12%	6%
HPV+	Cytol-	6%	
HPV-	Cytol+	0.9%	0.7%
HPV-	Cytol-	0.2%	

HPV Testing Finds More Women at High 5- year Risk of Cancer or Precancer

Katki et al, Lancet Oncology, 2011

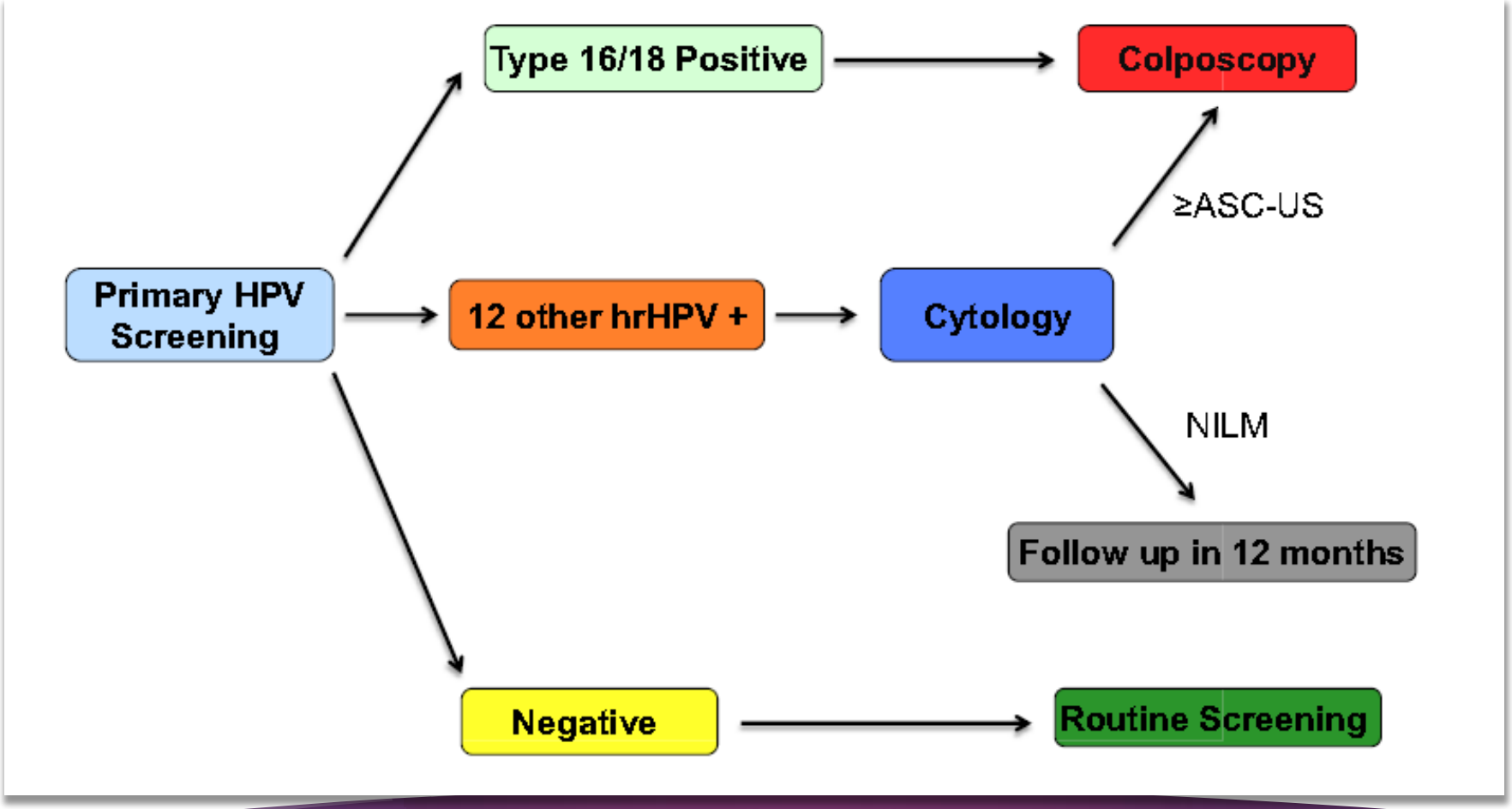
Why is HPV DNA Testing an Attractive Option for Cervical Cancer Screening?

- More sensitive and reproducible than cytology
- More "upstream" in carcinogenic process, thus enabling a longer safety margin for screening intervals
- Assesses future risk (and not just the presence of current disease)
- Can be automated, centralized, and quality- checked for large specimen throughput
- May be more cost- effective than cytology if deployed for high volume testing, such as primary screening
- A more logic choice for screening women vaccinated against HPV infection.

Risk of ≥CIN3 After a Negative Screening Test
3 Years of Follow-up

	Cytology	HPV	Cotest
Dillner et al.	0.50%	0.11%	0.06%
Katki et al.	0.17%	0.06%	0.05%
Rijkaart et al.	0.26%	0.06%	0.05%
ATHENA	0.78%	0.34%	0.30%

HPV testing used an HPV assay other than the cobas® HPV test (except ATHENA data)
Dillner et al. *BMJ* 2009;377; 21,351 women ≥20 years; Katki et al. *Lancet Oncol.* 2011;12:663; >300,000 women ≥30 years; Rijkaart et al. *Br. J. Cancer* 2012;106:975; >25,658 women 29-61 years; ATHENA; 41,955 women ≥25 years



HPV As an Initial Screening Test

Proposed Primary Screening Algorithm

HPV with 16/18 genotyping and reflex cytology

From 3/12/2014 FDA panel Materials

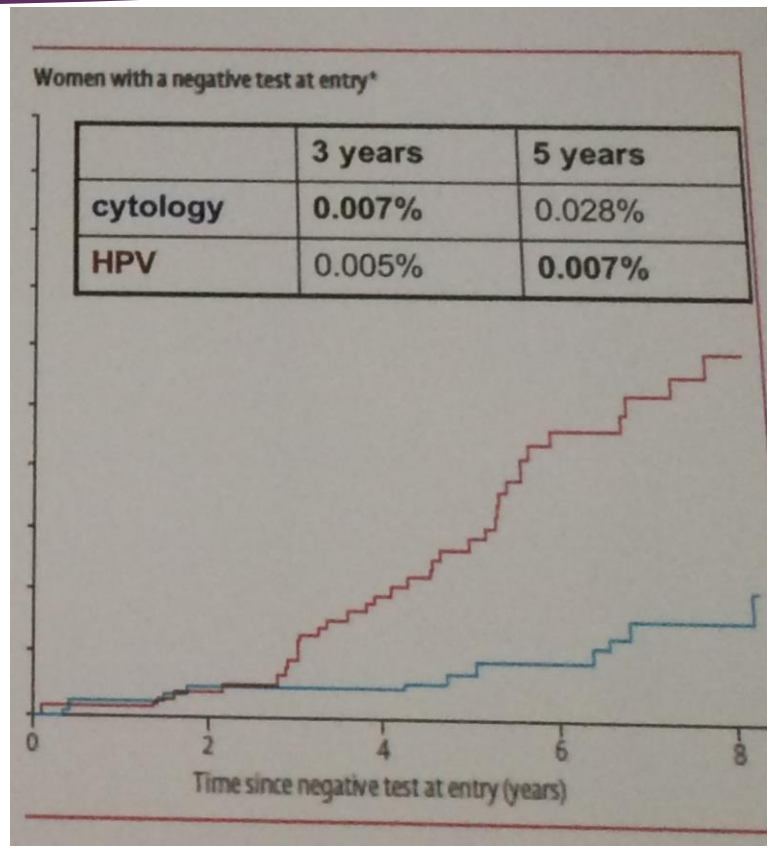
HPV Primary Screening for Cervical Cancer

- **Because of equivalent or superior effectiveness, primary hrHPV screening can be considered as best alternative to current cervical cancer screening methods.**

- **Based on limited data, triage of HPV+ women using a combination of genotyping for HPV16&18 and reflex cytology for women + for the 12 other HPV genotypes appears to be a reasonable approach to managing HPV + women.**

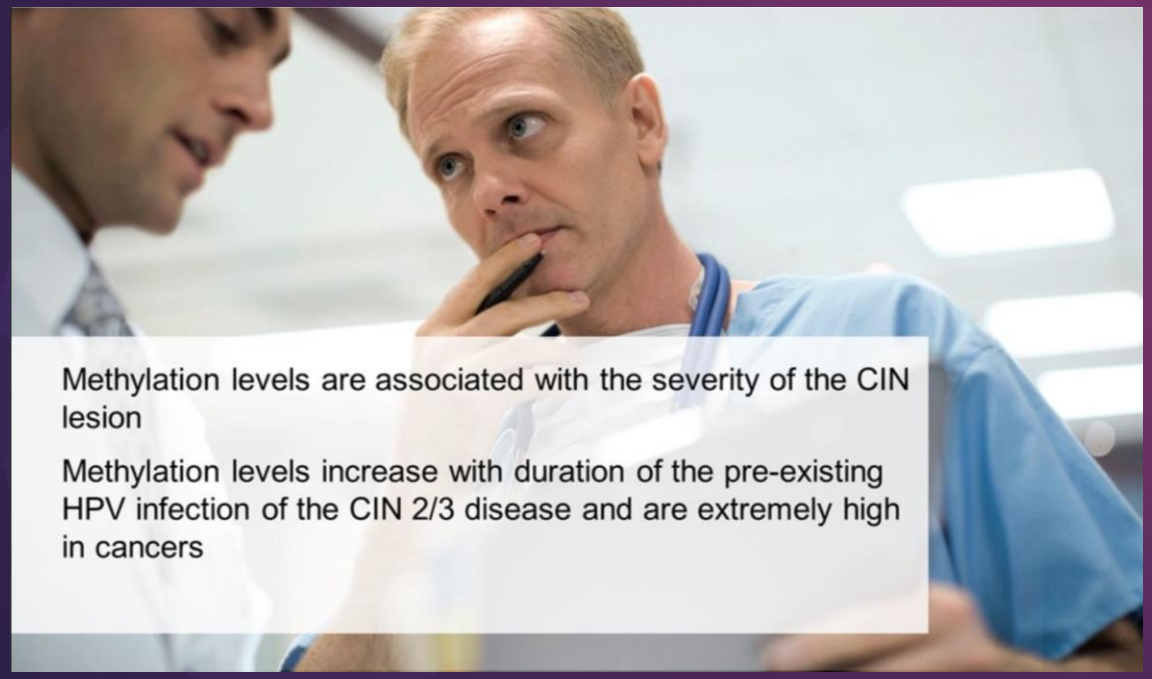
What to do if HPV-? Interval of screening

- **3 yearly wth Cytology**
- **5 yearly wth HPV**
- **Screening interval for HPV – women is more political than scientific question.**
  - **Balancing health gain, resource, side effect, and convenience**
  - **From 3 to 10 years interval in different EU countries**



Elfsfrom, 2014, bmj

Methylation Markers in Cervical Carcinogenesis

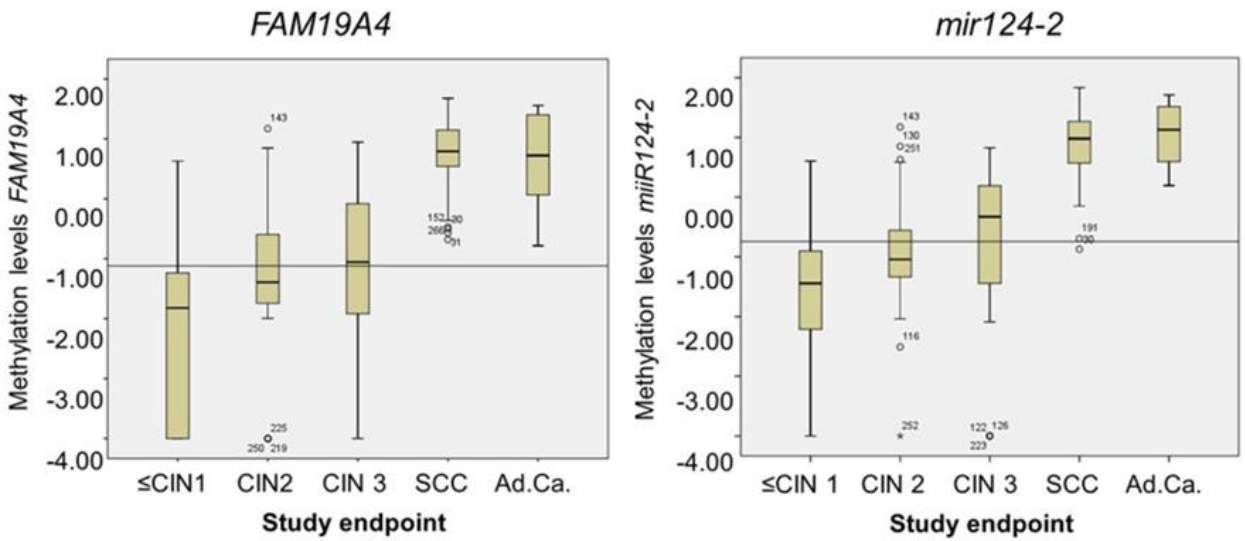


- ***FAM19A4* family** with sequence similarity 19 (chemokine (C-C motif)-like) memberA4
  - Identified by methylation-specific digital karyotyping of HPV16 E6/E7 immortalized human keratinocytes
- **mir124-2** encodes microRNA
  - Identified by candidate gene approach

Steenbergen, R.D., et al. (2014). Nature Rev. Cancer **14**, 395–405; Wilting, S.M., et al. (2010). Mol. Cancer **9**, 167.

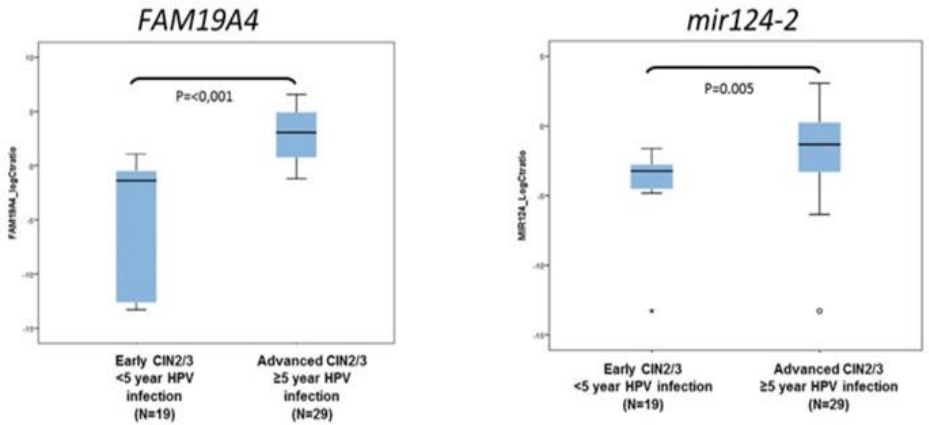
Virology Research Center
مرکز تحقیقات ویروس شناسی

Increased methylation levels in cervical scrapes proportional to severity of cervical disease



Similiar data for self samples

Increased methylation levels in cervical scrapes of women with CIN 2/3 with longer duration of pre-existing HPV infection



- Hypermethylation particularly associated with advanced disease; all advanced CIN 2/3 lesions (100%; 29/29; 95%CI: 88–100) scored methylation–positive for *FAM19A4* and/or *mir124-2*, compared with 47% (9/19; 95%CI: 27–69) of early CIN 2/3 lesions

- *FAM19A4/mir124-2* methylation analysis specifically detects “advanced” CIN lesions, which harbor a cancer-like methylation profile and have an expected high short-term risk of progression to cancer

Current Screening Dilemma in Iran

- Cotesting or HPV primary testing?
  - Is there additional benefit to contesting vs. 1° HPV testing alone?
- Which platform can be used in primary HPV Screening?
  - Can we integrate all the screening
  - Laboratory facilities & structures
  - Importing lab, technology or domestic production?
    - Test Validation; test specification
- How do we perform screening and management guidance?

The last but not the least …

- **“ the biggest gain in reducing cervical cancer incidence and mortality would be achieved by increasing screening rate among WOMEN RARELY OR NEVER SCREENED …**
- **Clinician, hospitals, health plans, and public health officials should seek to identify and screen these women.”**