



# Serviks Patolojilerinin Toplum Bazlı Değerlendirilmesi Ve Önlenmesi

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**Jinekolojik Onkoloji Kliniği**

# Serviks Kanseri

- Yarım milyon yeni olgu
- %50 Mortalite
- > %90-99.7 HPV ilişkili
- Önlenebilir Kanser

HPV Aşısı, Sigara ile Mücadele

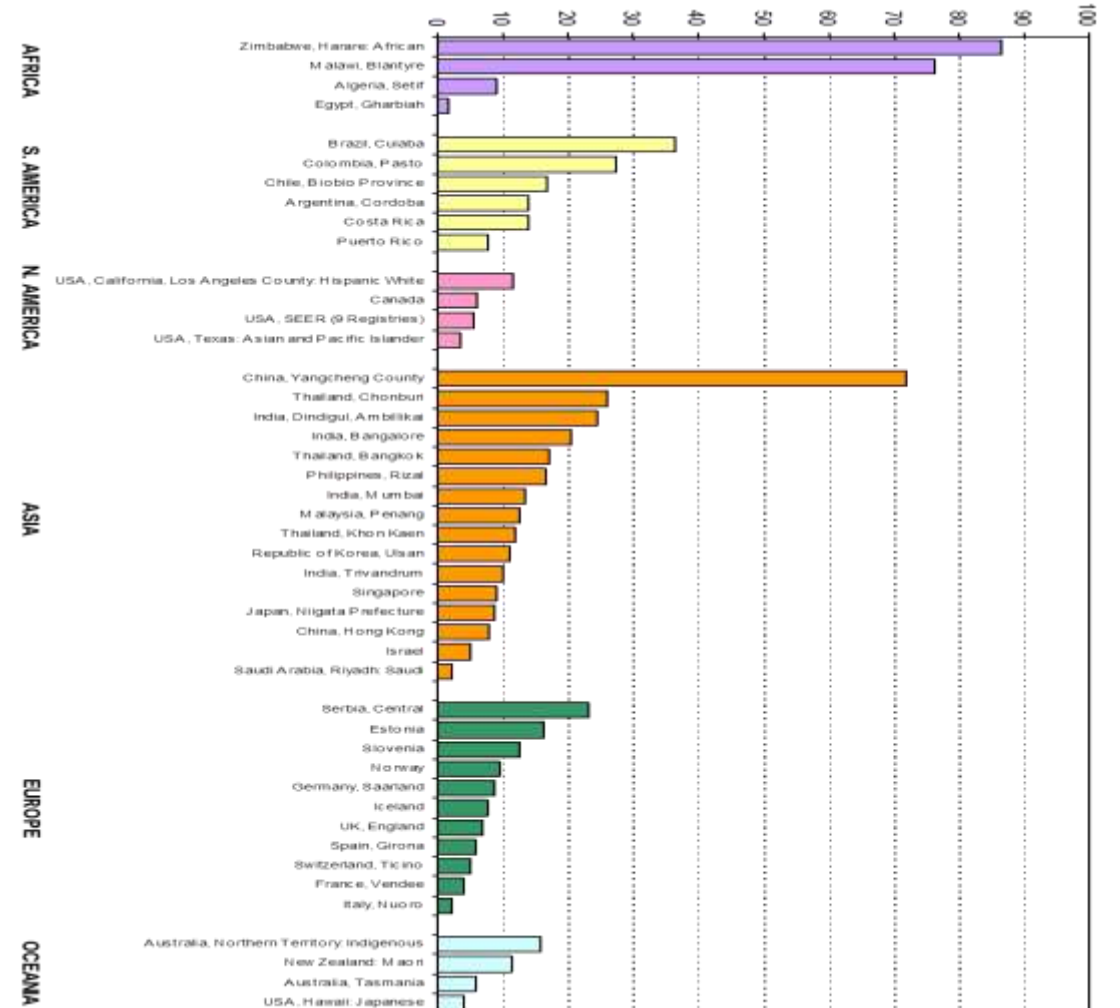
- Erken tanı mümkün
  - VIA-VILI / Smear / HPV / Kombinasyon / Diğer
  - **Eradike edilebilir tek kanser**
-

# Dünyada Servikal Kanser

- Kadınlarda 4. sırada
- 2012 yılında 528,000 yeni vaka
- 266,000 ölüm
- Yaklaşık % 85'i az gelişmiş bölgelerdeki ülkelerde görülüyor.

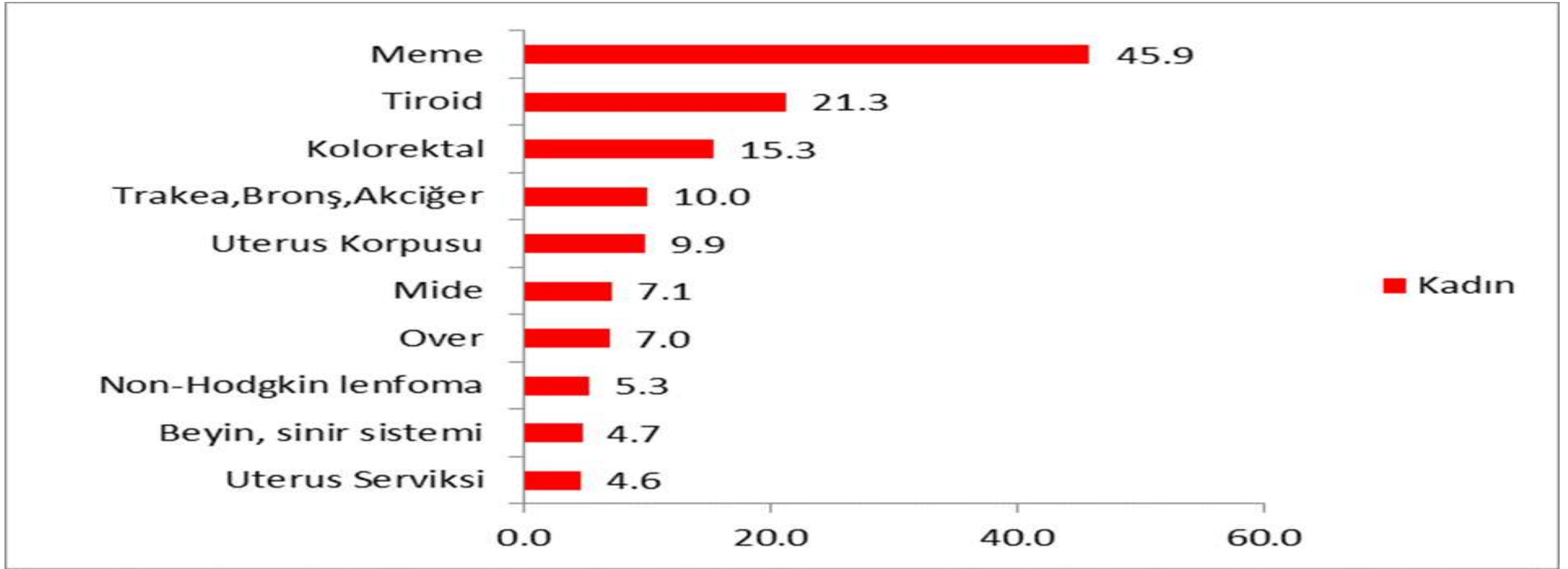
Source: Ferlay et al., GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013.

Available from: <http://globocan.iarc.fr>, accessed on 17/02/2014.



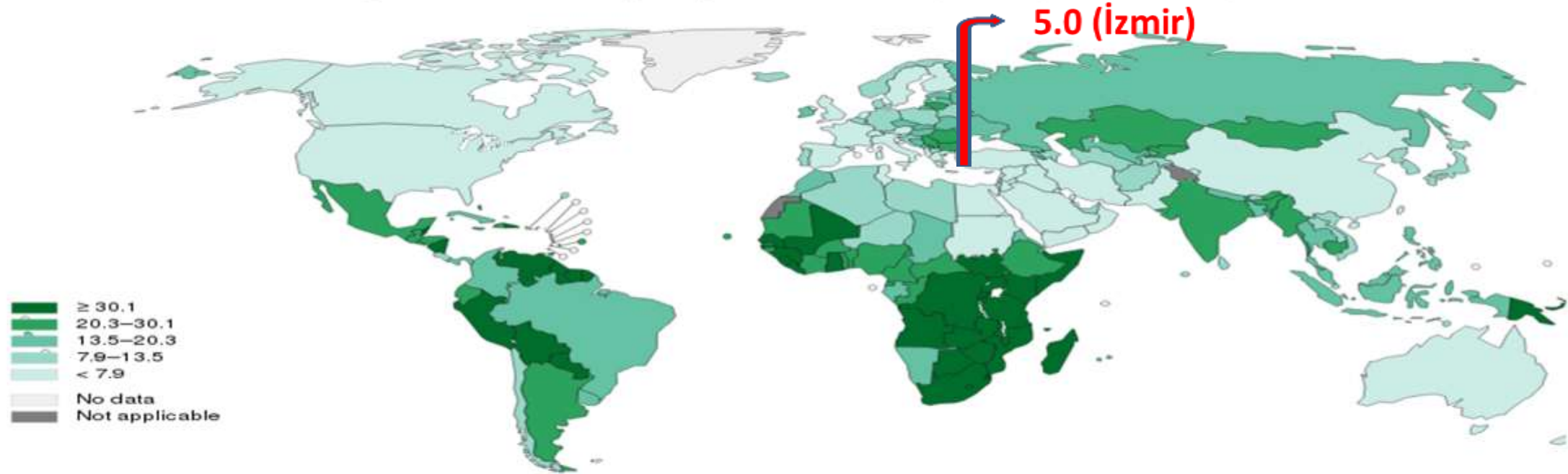
SOURCE: Forman et al., (2013) Cancer Incidence in Five Continents, Vol. X (electronic version) Lyon, IARC. <http://ci5.iarc.fr> last accessed on 18/02/2014.

# 2012-TCSB Kadınlarda En Sık Görülen 10 Kanserin Yaşa Göre Standardize Edilmiş Hızları (Türkiye Birleşik Veri Tabanı, 2013) (Dünya Standart Nüfusu, 100.000 Kişide)



# YSH insidans, Kadın, Servikal kanser, Dünya, 2012

Estimated age-standardized rates (World) of incidence cases, females, cervical cancer, worldwide in 2012



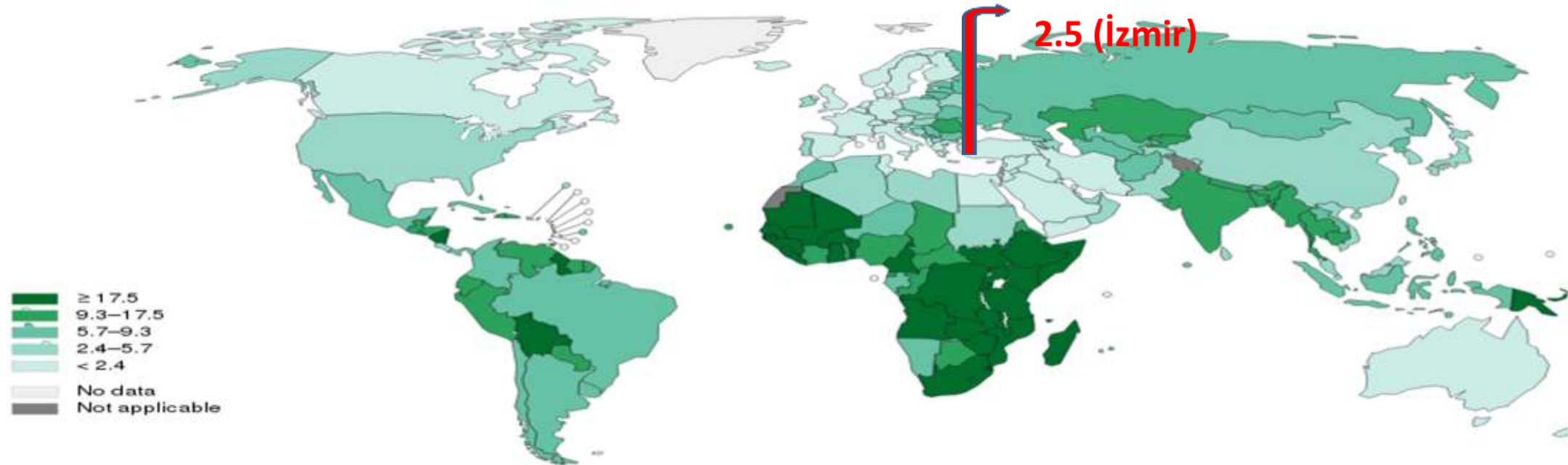
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Data source: GLOBOCAN 2012  
Map production: IARC  
(<http://gco.iarc.fr/today>)  
World Health Organization

 World Health Organization  
© International Agency for Research on Cancer 2016

# YSH Mortalite,Kadın,Servikal kanser, Dünya, 2012

Estimated age-standardized rates (World) of deaths, females, cervical cancer, worldwide in 2012



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Data source: GLOBOCAN 2012  
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(<http://gco.iarc.fr/today>)  
World Health Organization

 World Health Organization  
© International Agency for Research on Cancer 2016

# Servikal Kanseri Niin Tarıyoruz?

- Mortaliteyi düşürmek,
  - İnsidansı düşürmek
  - CIN'lerin en uygun tespiti
  - Kolposkopiye refere edilen hasta sayısını düşürmek
  - Gereksiz girişimleri azaltmak,
  - Tedaviyi cost-effektif hale getirmek.
-

# Serviks Kanseri

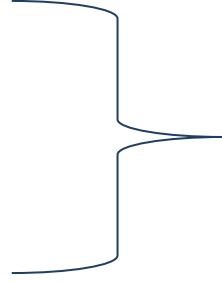
- MÖ 500-Hipocrates(tedavisiz hastalık)
  - 1900-Yetim bırakan hastalık.
  - İlk Epidemiyolojik Çalışmalar:
    - Rahibelerde hastalığın hiç görülmemesi
    - İlk eşleri serviks kanserinden ölen erkeklerin ikinci eşlerinin de aynı hastalıktan ölmesi
  - 1940-Sitolojinin keşfi (G. Papanikolaou)
  - 1960 -Tarama programları
  - 1990-HPV ve bugün (önlenebilir ölüm nedeni)
-



# DSÖ Önerisi

Mutlaka Tarayın:

- Meme kanseri
- Servikal kanser
- Kolorektal kanser



Tüm yurttta

- **Serviks Kanseri için**
    - 25 yaş altını taramayın
    - 65 yaş üstünü taramayın
    - Asla yıllık tarama yapmayın
  - **Kendi ulusal stratejinizi geliştirin**
-

# Servikal Kanser Tarama Yöntemleri

- Konvansiyonel veya Sıvı Bazlı Sitoloji

## *Sitolojinin Alternatifleri*

- HPV testi
- VIA(Visual Inspection with 3-5% Acetic acid)
- VIAM(VIA with low level (2-4X) magnification)
- VILI(Visual inspection with Lugol' s iodine)
- 

*Testin yüksek sensitivitesi az gelişmiş ülkelerde erken tanı için çok önemlidir.*

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# Toplum Bazlı Tarama Programı Amaç

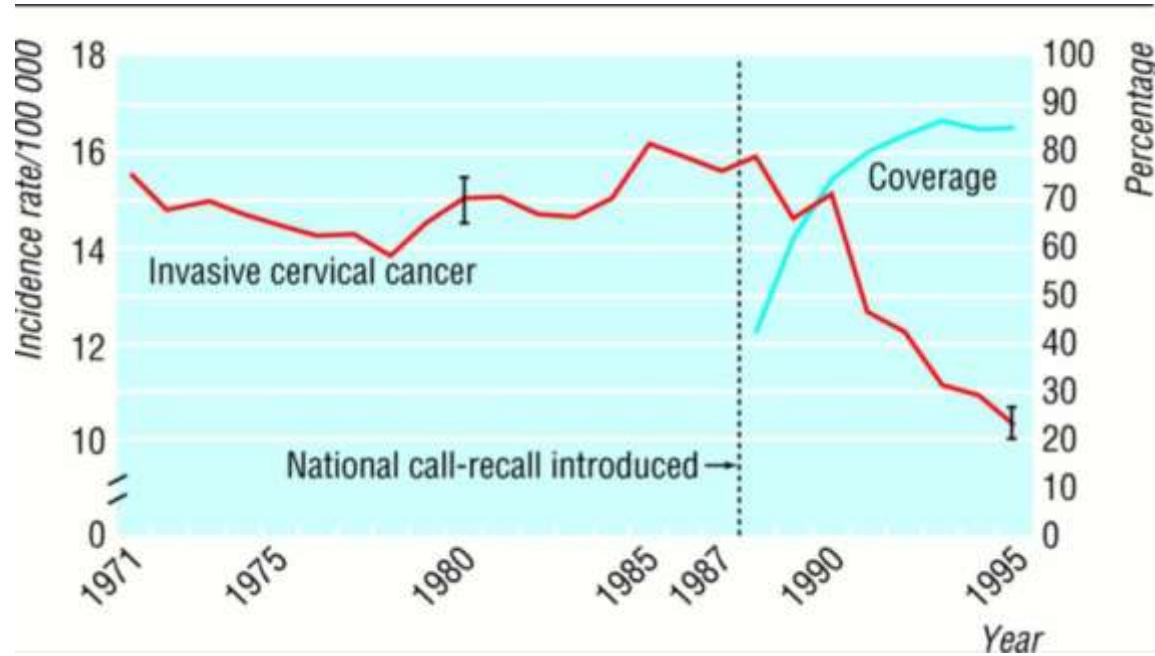
Serviks kanserinin taranmasındaki temel amaç; **ülke çapında** oluşturulacak **ulusal** bir tarama programını **hedef popülasyona** uygulayarak, servikal patolojileri **henüz premalign veya erken evrede** iken tespit etmek, etkin ve **basit yöntemlerle tedavi etmek** suretiyle de invazif kanser sıklığını, buna bağlı **morbidite ve mortaliteyi** düşürerek olası karmaşık ve pahalı tedavileri önlemektir.

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# AB Ülkelerinde Tarama Politikaları

Ülkeler	Hedef Grup		Tarama Aralığı	Kadın başına smear sayısı	Kapsanan popülasyon
	Başlangıç	Bitiş			
Belçika	25	64	3	14	58
Danimarka	23	59	3	13	100
Finlandiya	30	60	5	7	100
Fransa	25	65	3	14	5
Almanya	20	70+	1	>50	90
Yunanistan	25	64	3	14	-
İrlanda	25	60	5	8	-
İtalya	25	64	3	14	13
Hollanda	30	60	5	7	100
Portekiz	20	65	3	16	-
İspanya	25	65	3	14	-
İsveç	20	59	3	14	100

- Sitoloji tabanlı tarama programları servikal kanserin insidans ve mortalitesini %70'ten fazla bir oranda azalttı.



# Ulusal Tarama Programı Sorunları

- Kalabalık hedef nüfus (15 milyon)
  - İnsan kaynakları yetersizliği (teknisyen, uzman)
  - İnsan kaynaklarındaki sık yer deęişiklikleri
  - Farkındalığın az olması (tıbbi personel ve halk)
  - Coęrafi kısıtlılıklar (geniş yüz ölçümü, mevsimsel zorluklar, nakliye zorlukları)
  - Kalite kontrolü
-

# HPV Testi? PAP Smear?

- CIN2+ lezyonlar için tek bir pap-testin sensitivitesi çok düşüktür.
  - Pap-testin yanlış negatiflik oranı çok yüksektir.
  - Pap-testin tekrarlanabilirliği düşüktür.
  - Pap-test servikal adenokarsinom tanısı koymada yetersizdir.
-

# Sitolojik Taramanın Sorunları

- CIN2+ lezyonlar için tek bir pap-testin sensitivitesi çok düşüktür.
- Tek bir pap-testin sensitivitesi %50-60'tır.
- Sık tekrar edilmesi gerekir.

Nanda K, et al, systematic review, Ann Intern Med. 2000;132(10):810-819

Kitchener HC, Castle PE, Cox JT. Chapter 7: Achievements and limitations of cervical cytology screening. Vaccine 2006;24:S63-70

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# Sitolojik Taramanın Sorunları

- Pap-testin yanlış negatiflik oranı çok yüksektir.

2275 servikal kanser vakasının tarama öyküsü:

Tarama Öyküsü (%)	İtalyan Verisi <sub>1</sub>	Kaiser Verisi <sub>2</sub>	İsviçre Verisi <sub>3</sub>
Taranmadı	%62	%56	%64
Normal Sitoloji	%14	%32	%24
Anormal sitoloji & Yetersiz takip	%24	%13	%7
	n=262	n=833	n=1180

1 Amadori A, et al. Int J Gyn Can 1998, 8; 251-256

2 Leyden WA, et al. J Nat Can Ins 2005, 97; 675-683

3 Andrae B, et al. JNCI 2008, 100; 622-629

# Sitolojik Taramanın Sorunları

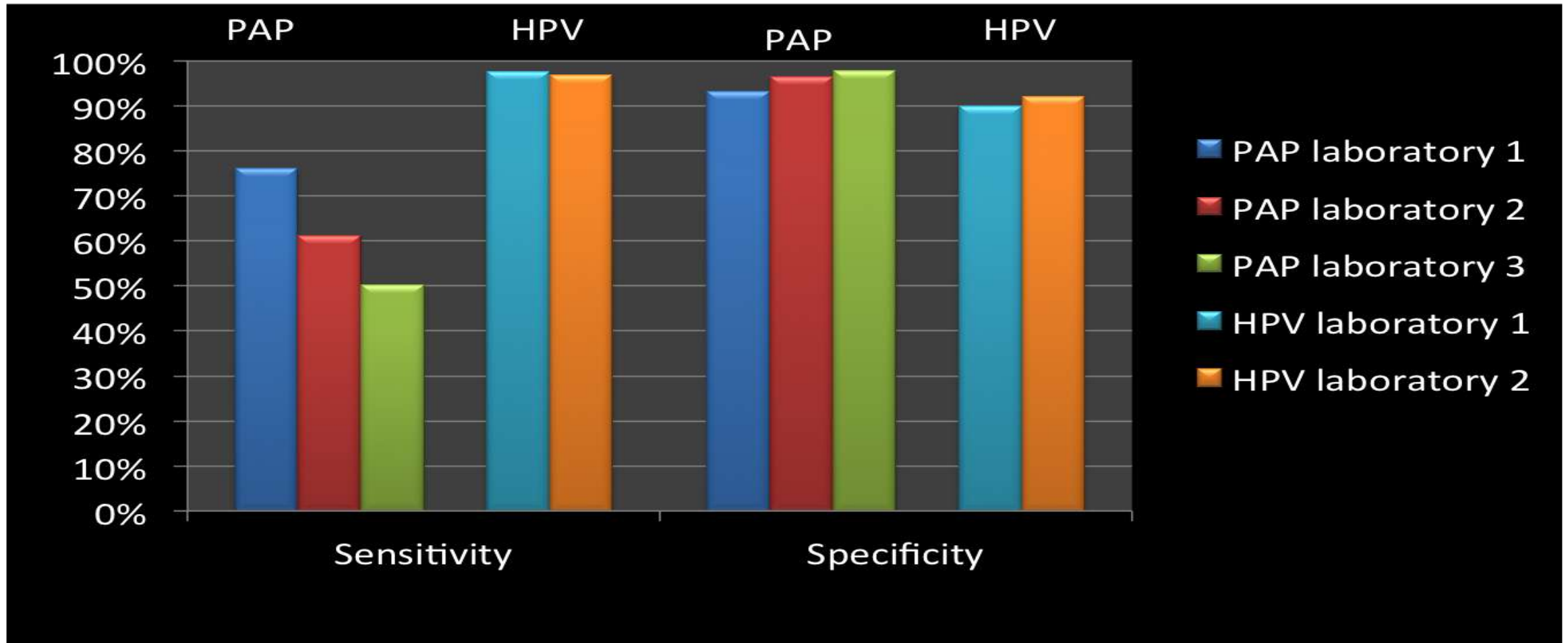
## •Pap-testin tekrarlanabilirliđi dūşüktür.

- İnter-observer ve inter-laboratuar variabilitesi yüksektir.
- Bu variabilite klinik tutarlılıđı azaltır.
- Eđitim farkı arttıkça variabilite daha da belirginleşir.
- Bu durum özellikle taramanın yeni başlatılacağı yerler için önemli.

Castle PE et al. ATHENA study. 2011 Lancet Oncol 12:880-90

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# Sitoloji ve HPV Testinin Laboratuvar Performansının Etkisi (CCCaST Study)



Mayrand MH, Unpublished Data

# Sitoloji Tabanlı Taramanın Sorunları

## •Pap-test servikal adenokarsinom tanısı koymada yetersizdir.

- Sitoloji tabanlı etkin taramalara rağmen servikal adenokarsinom insidansı artmaktadır.

Ault KA et al. 2011 Int J Can. 128, 1344-1353

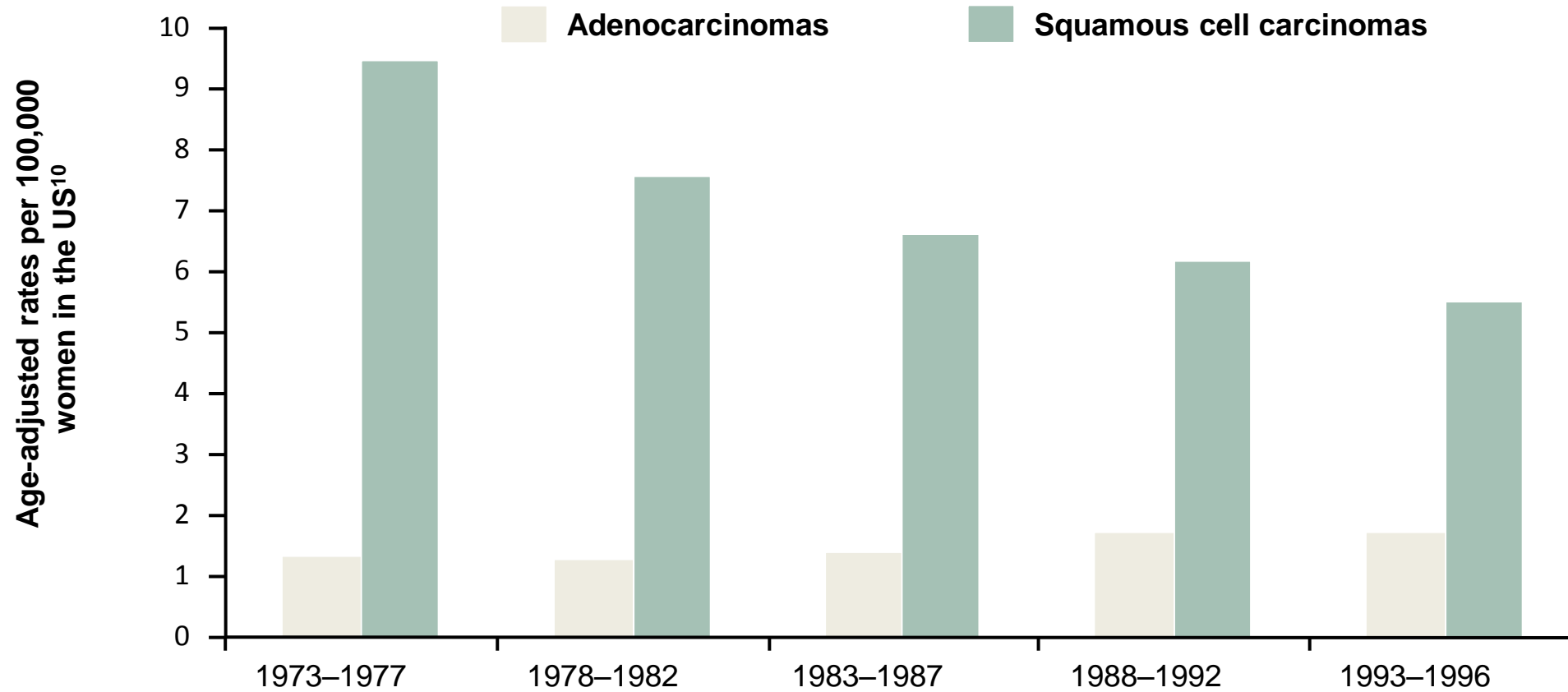
- AIS özellikle <40 yaş grubunda artmaktadır.

Saslow D et al. 2012 CA Can J Clin. 62(3):147-172

- SCC'lerin %70'i HPV16/18'e bağılıken adenokarsinomların %85-90'ı bu tiplerle ilişkilidir.

Katki HA et al. Lancet Oncol 2011;12:663-672

# Adenokarsinoma insidansı yükseliyor



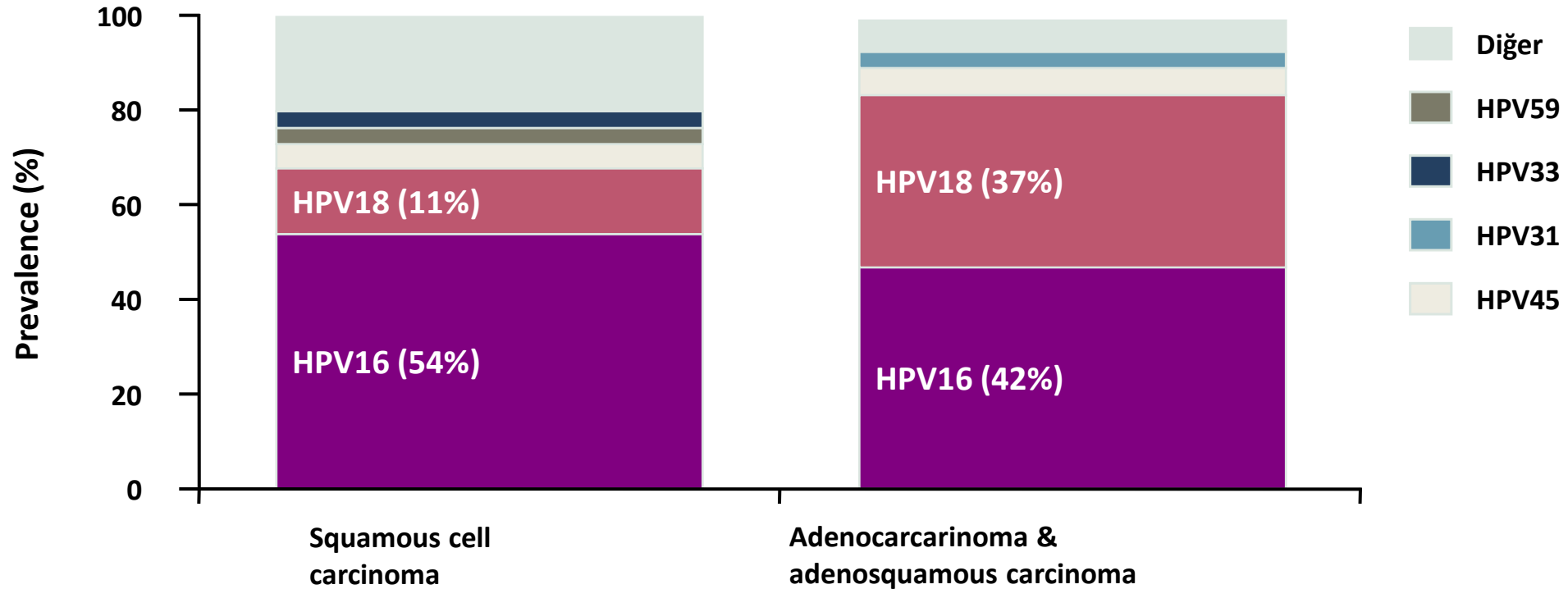
- Adenocarcinoma incidence rates have increased in Europe<sup>11</sup>
- ~0.5% per annum in Denmark, Sweden, and Switzerland
- ≥3% per annum in Finland, Slovakia, and Slovenia

# Sitoloji Tabanlı Taramanın Sorunları

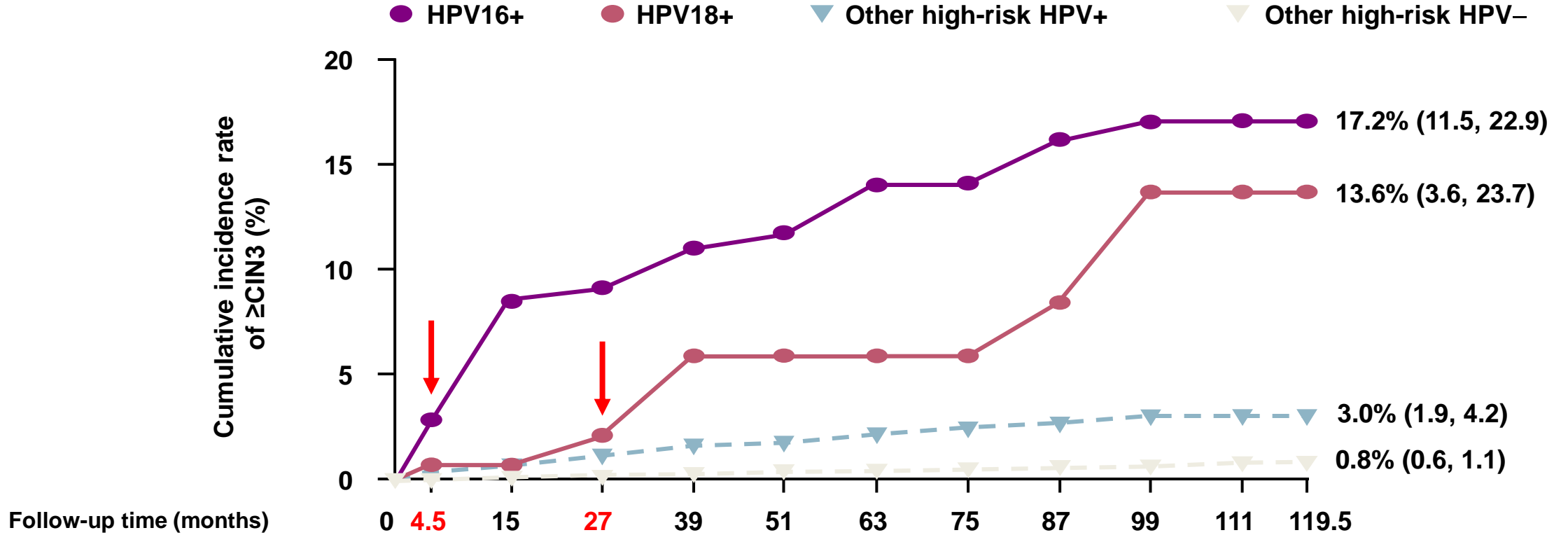
- Pap-test servikal adenokarsinom tanısı koymada yetersizdir.**

Histoloji (n)	Sensitivite		
	Sitoloji	HPV	
CIN3 (254)	%52	%92	
AIS (16)	%63*	%88	*%25 fark %25
Adenoca ve Adenosq ca (1)	%100	%100	
SCC (3)	%100	%100	

# HPV 18 primer olarak glandüler hastalıklarla ilişkilidir



# HPV16 ve HPV18 pozitif olan kadınlar daha önce HG servikal hastalık geliştirir



HPV16/18 genotipleme servikal hastalığı daha önce tanımlayarak tedavi başarısını artırır



# Türkiye için Neden HPV?

- Daha yüksek negatif prediktif değer
  - Daha yüksek sensitivite
  - İş gücü avantajı
  - Merkezi kalite kontrolü
  - Düşük HPV pozitifliği (düşük prevalans)
  - Kesin tanı için geçen zamanın kısalması
  - Gelecekte kendi kendine örnek alma (Self-test) imkanı
  - Farkındalığın yeniden sağlanması için yeni bir test
-

# HPV vs Sitoloji Sensitivitesi

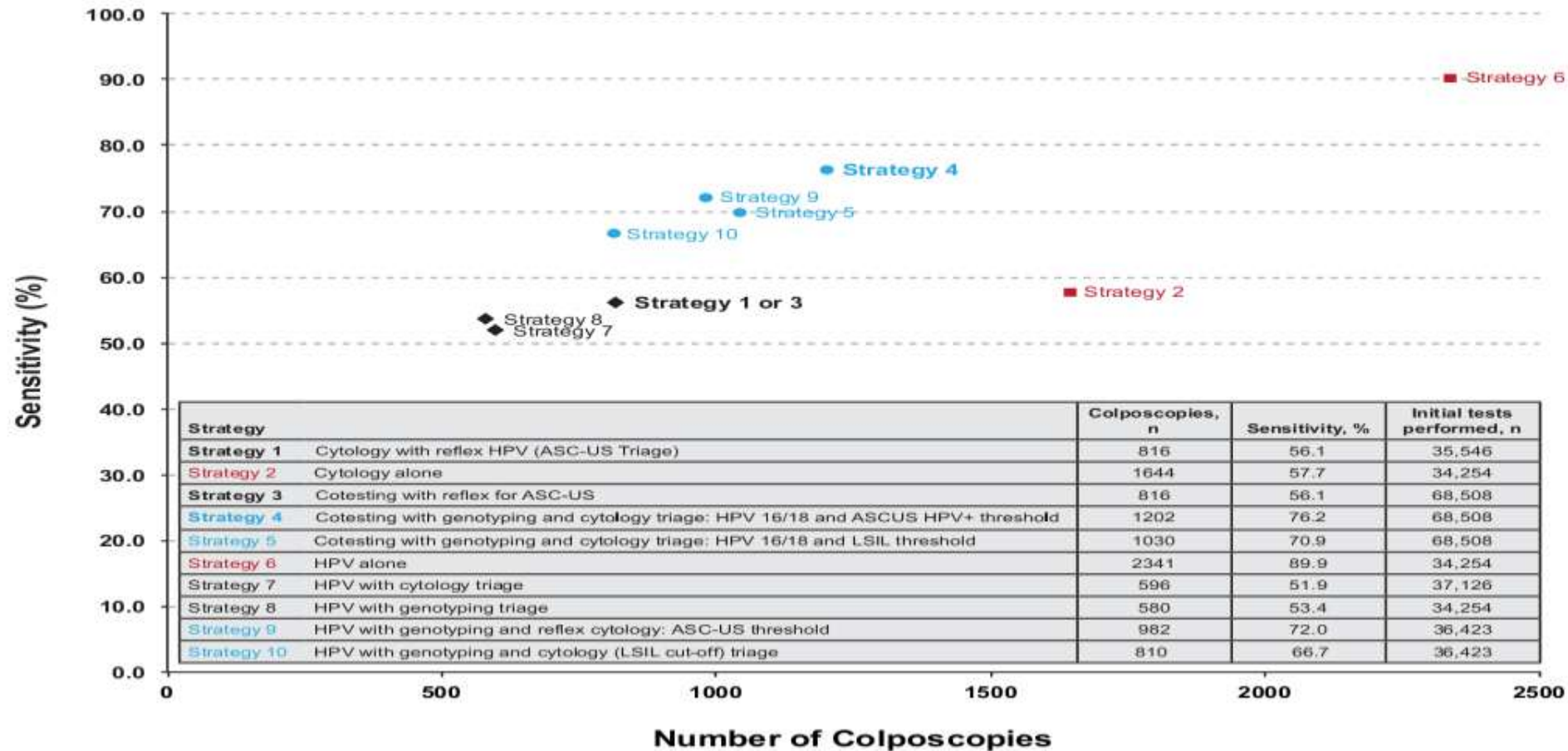
	Sensitivite	Spesifisite
Sitoloji	%53	%97
HPV testi	%96	%92

## GENERAL GYNECOLOGY

# Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study

J. Thomas Cox, MD; Phillip E. Castle, PhD, MPH; Catherine M. Behrens, MD, PhD; Abha Sharma, PhD; Thomas C. Wright Jr, MD; Jack Cuzick, PhD; and the Athena HPV Study Group

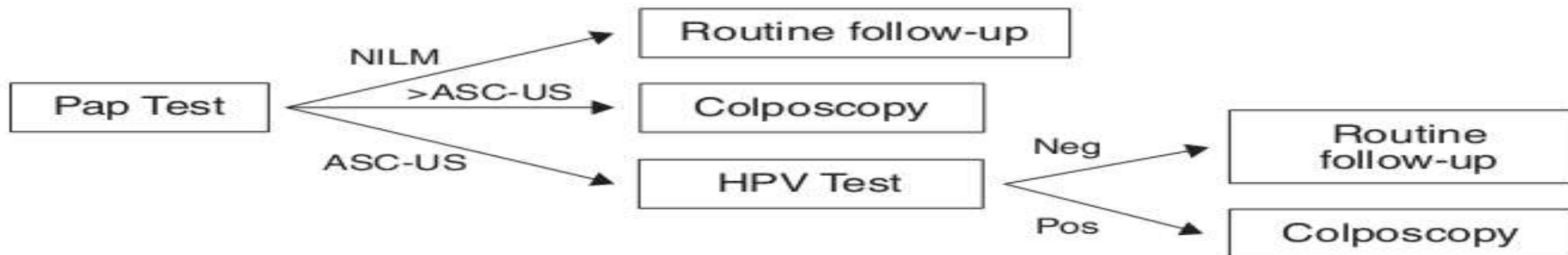
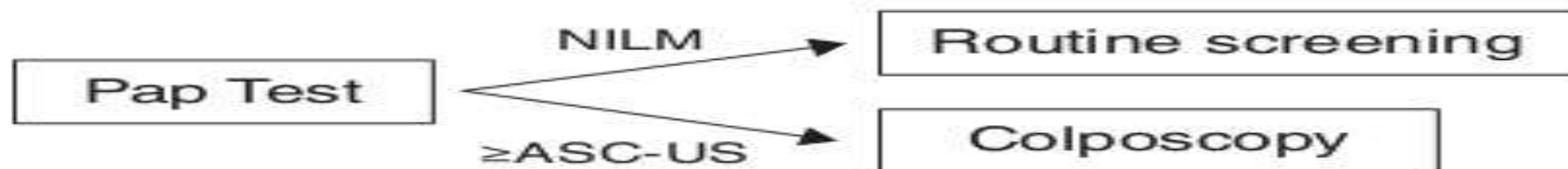
Primary Screening Strategies For CIN3+ Endpoint



## GENERAL GYNECOLOGY

**Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study**

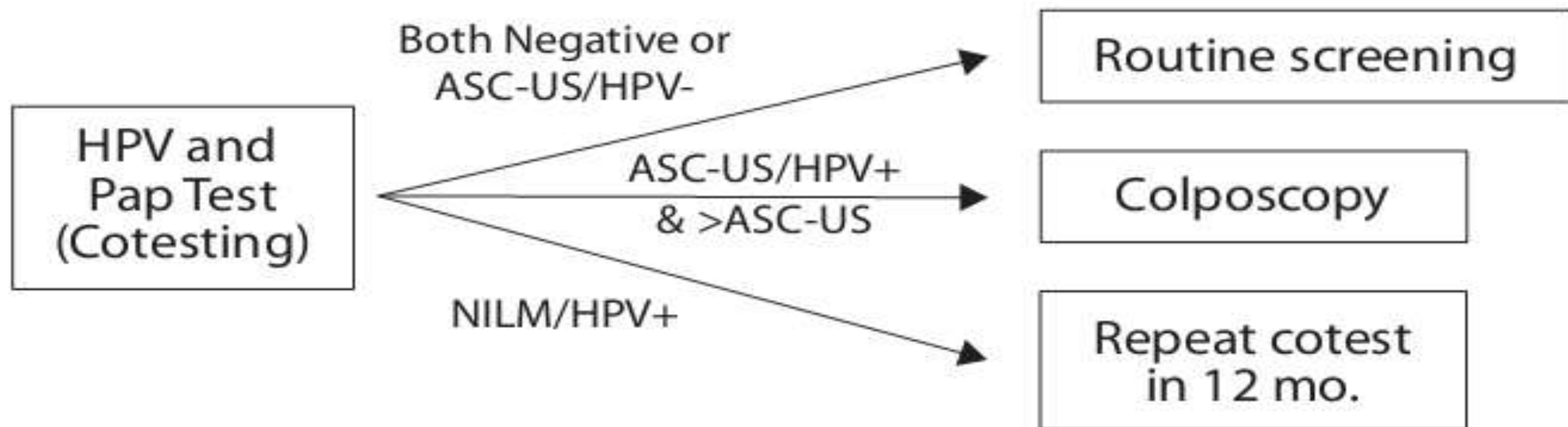
J. Thomas Cox, MD; Phillip E. Castle, PhD, MPH; Catherine M. Behrens, MD, PhD; Abha Sharma, PhD; Thomas C. Wright Jr, MD; Jack Cuzick, PhD; and the Athena HPV Study Group

**Strategy 1: Cytology with reflex HPV (ASC-US triage)****Strategy 2: Cytology Alone**

## GENERAL GYNECOLOGY

**Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study**

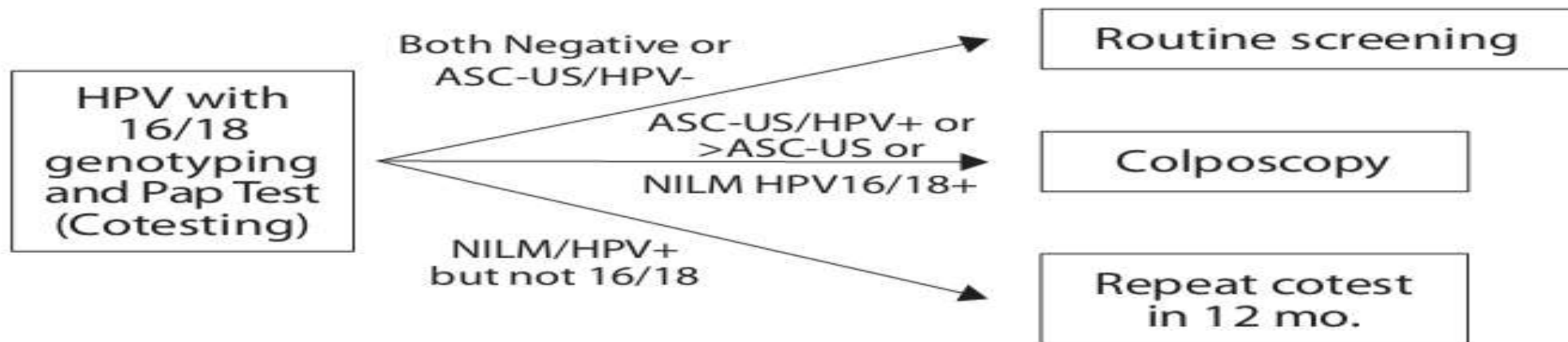
J. Thomas Cox, MD; Phillip E. Castle, PhD, MPH; Catherine M. Behrens, MD, PhD; Abha Sharma, PhD; Thomas C. Wright Jr, MD; Jack Cuzick, PhD; and the Athena HPV Study Group

**Strategy 3: Cotesting with reflex for ASC-US**

## GENERAL GYNECOLOGY

**Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study**

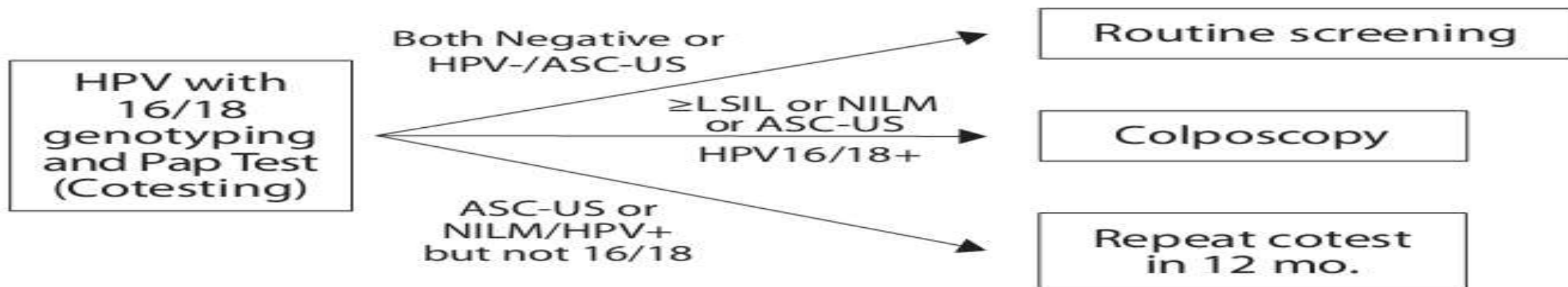
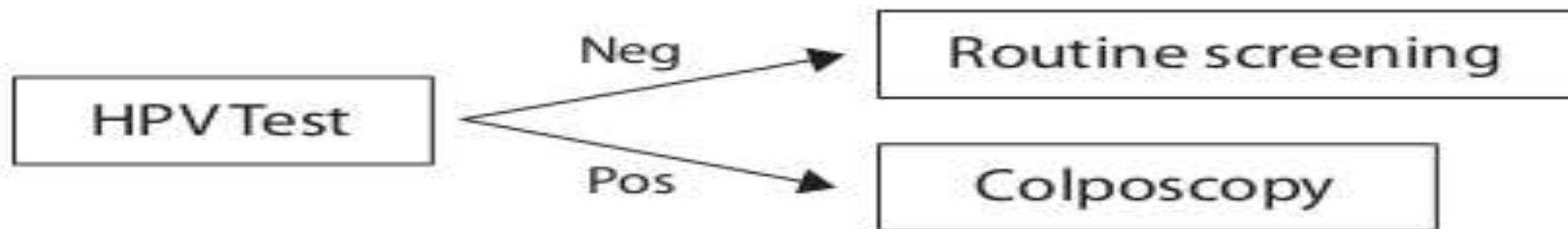
J. Thomas Cox, MD; Phillip E. Castle, PhD, MPH; Catherine M. Behrens, MD, PhD; Abha Sharma, PhD; Thomas C. Wright Jr, MD; Jack Cuzick, PhD; and the Athena HPV Study Group

**Strategy 4: Cotesting with genotyping and cytology triage: HPV 16/18 & ASC-US HPV+ threshold**

## GENERAL GYNECOLOGY

**Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study**

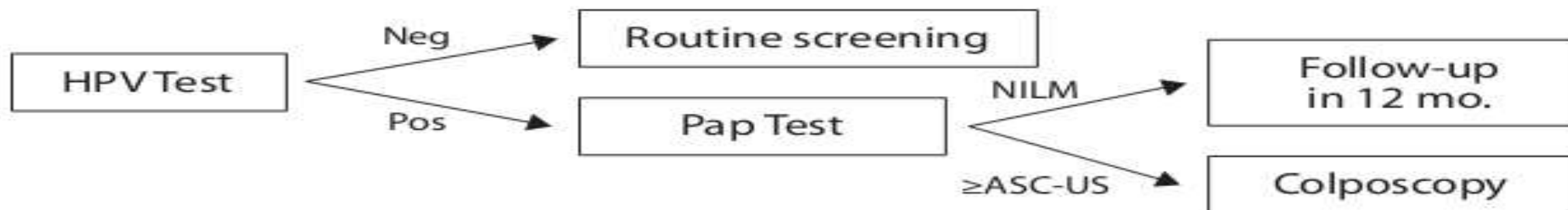
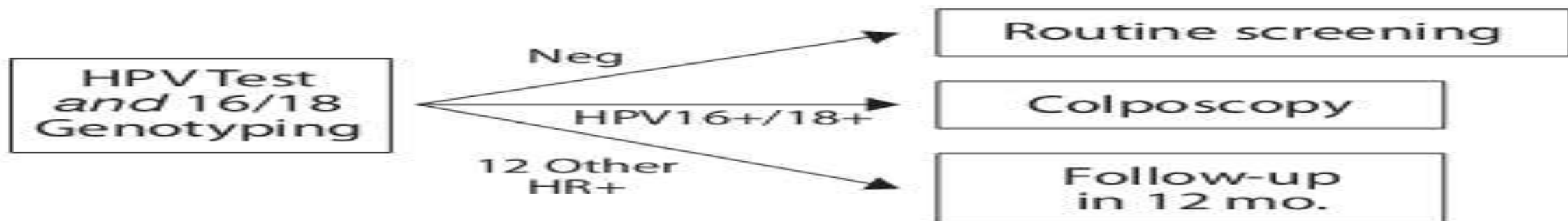
J. Thomas Cox, MD; Phillip E. Castle, PhD, MPH; Catherine M. Behrens, MD, PhD; Abha Sharma, PhD; Thomas C. Wright Jr, MD; Jack Cuzick, PhD; and the Athena HPV Study Group

**Strategy 5: Cotesting with genotyping and cytology triage: HPV 16/18 & LSIL threshold****Strategy 6: HPV alone**

## GENERAL GYNECOLOGY

**Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study**

J. Thomas Cox, MD; Phillip E. Castle, PhD, MPH; Catherine M. Behrens, MD, PhD; Abha Sharma, PhD; Thomas C. Wright Jr, MD; Jack Cuzick, PhD; and the Athena HPV Study Group

**Strategy 7: HPV with reflex to cytology****Strategy 8: HPV with genotyping**

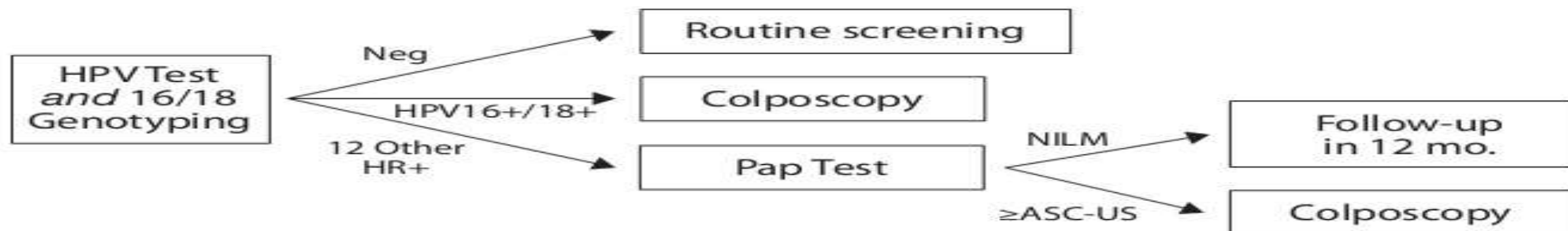


## GENERAL GYNECOLOGY

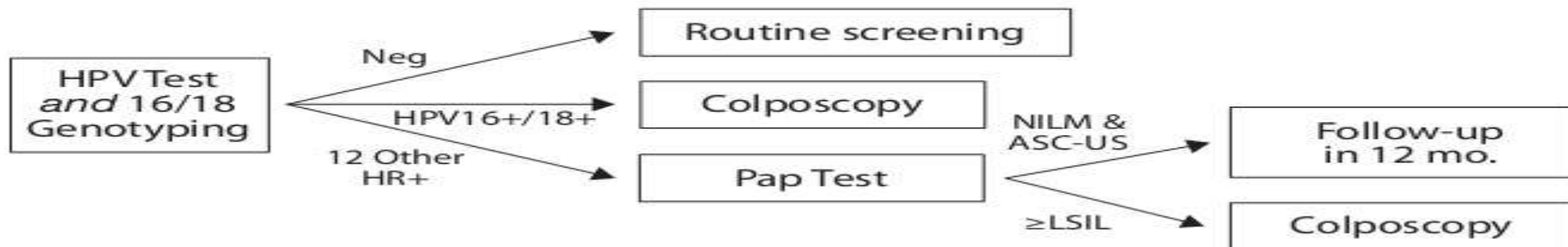
## Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study

J. Thomas Cox, MD; Phillip E. Castle, PhD, MPH; Catherine M. Behrens, MD, PhD; Abha Sharma, PhD; Thomas C. Wright Jr, MD; Jack Cuzick, PhD; and the Athena HPV Study Group

### Strategy 9: HPV with genotyping and reflex cytology: ASC-US threshold



### Strategy 10: HPV with genotyping and reflex cytology: LSIL threshold





**Yüksek Riskli HPV Testi**

**(13 Yüksek riskli HPV Tipi**

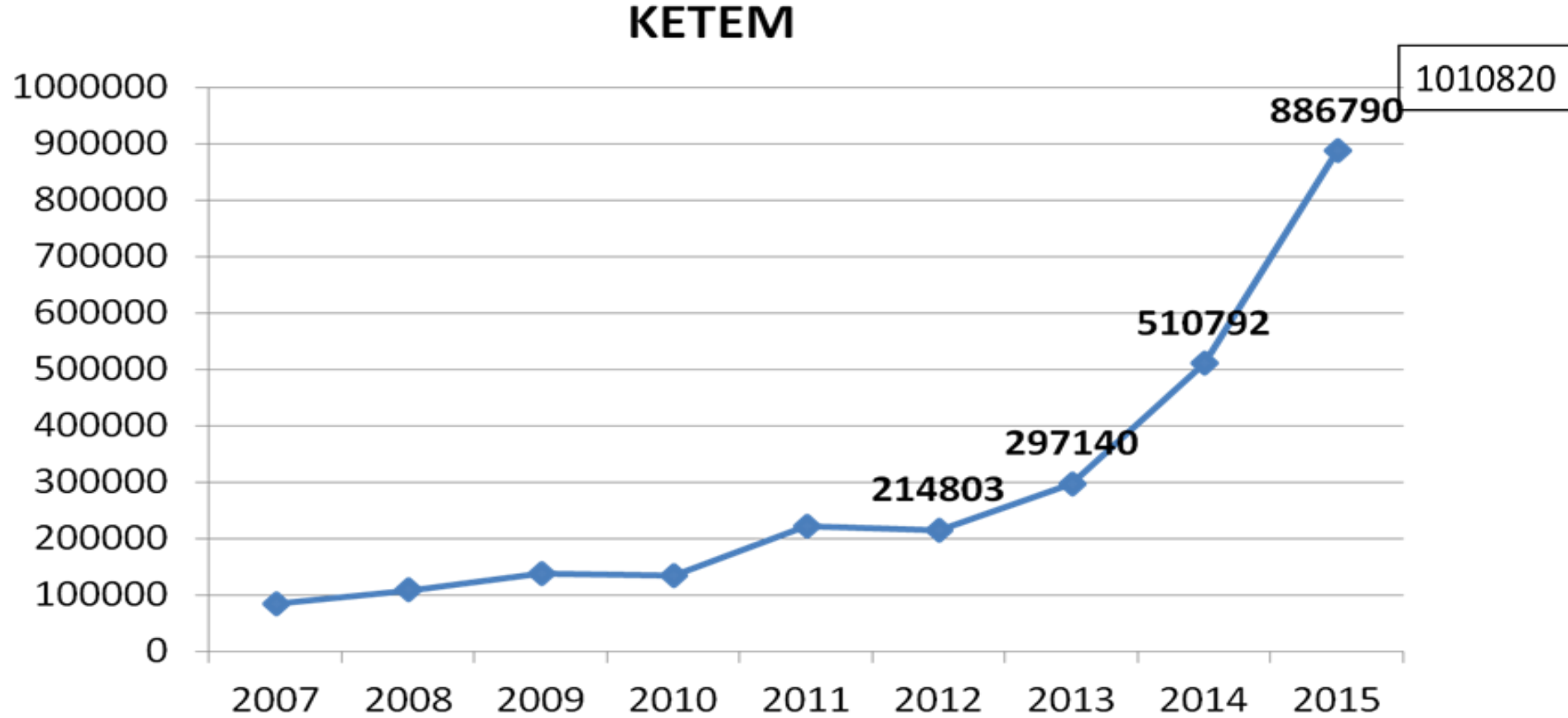
**16/18/31/33/35/39/45/51/52/56/58/59/68)**

**Pozitif (+) olgularda , refleks sitoloji ve  
Genotiplendirme**

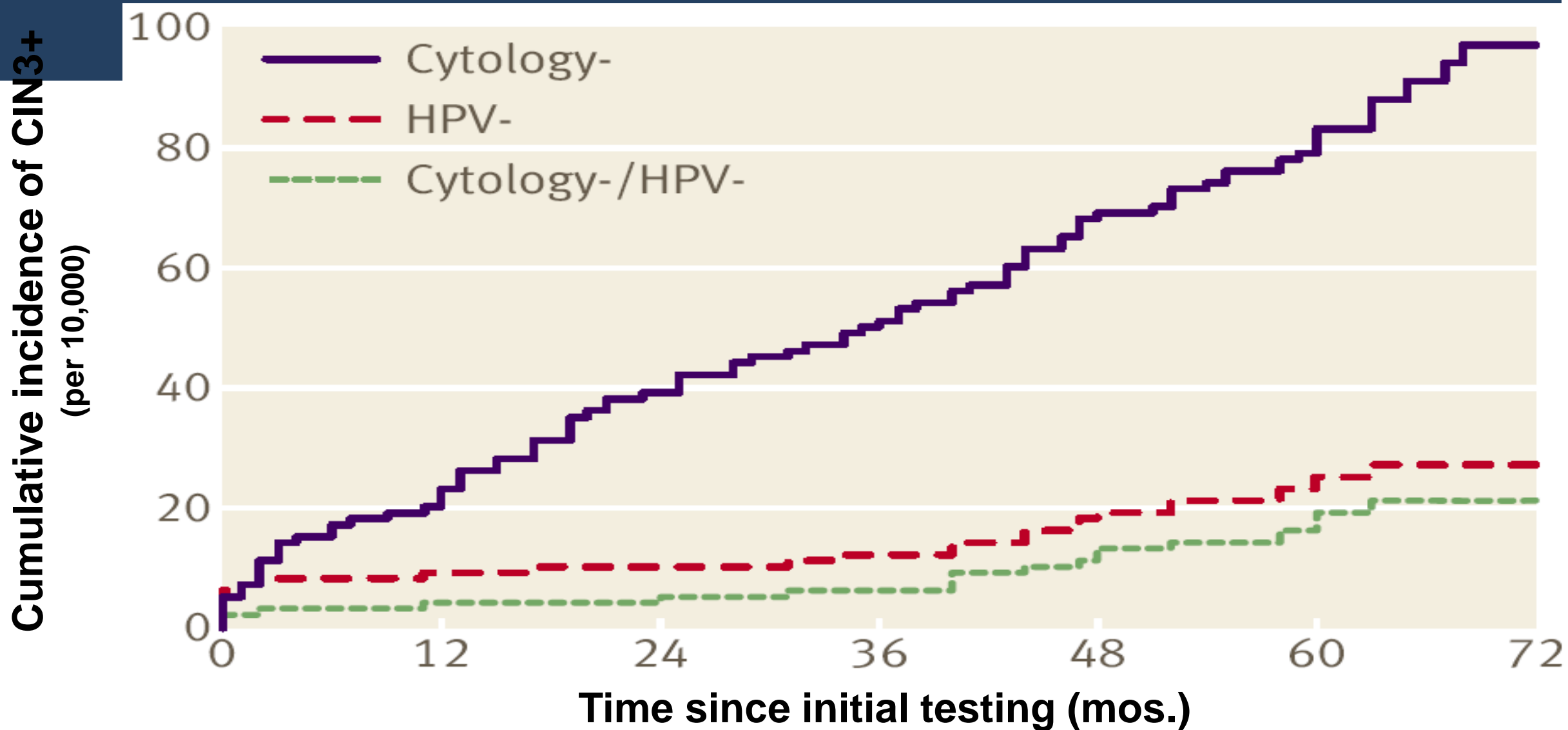
**Numunelerin laboratuvara ulaşımından  
sonra 7 gün içerisinde sonuç verilmesi**

**Yılda 1 Milyon Tarama**

# Toplum Tabanlı Tarama Sonuçları

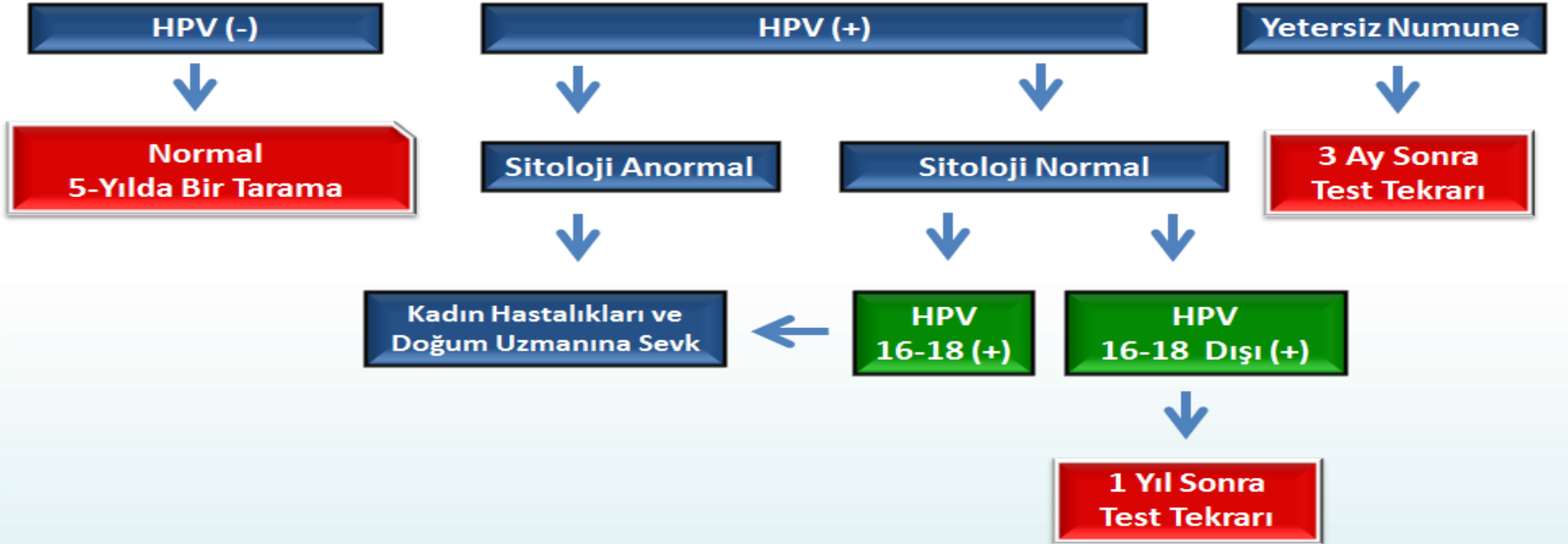


# Cumulative incidence of CIN3+ according to baseline test results in European sites (excluding Denmark and Tübingen)



# HPV Bazlı Tarama Programı

“Yeni Tarama Algoritmi – 30-64 Yaş Kadınlar”



# Türkiye HPV Prevelans Haritası

## HPV POZİTİFLİK ORANLARI TÜRKİYE HARİTASI (GENEL POZİTİF YÜZDESİ : 3,81)

Türkiye Geneli Pozitif Sayıları Dağılımı



< 1 1 - 2 2 - 3 3 - 5 5 - 100

agersoft.com © Natural Earth

Erişim Tarihi 14/10/16

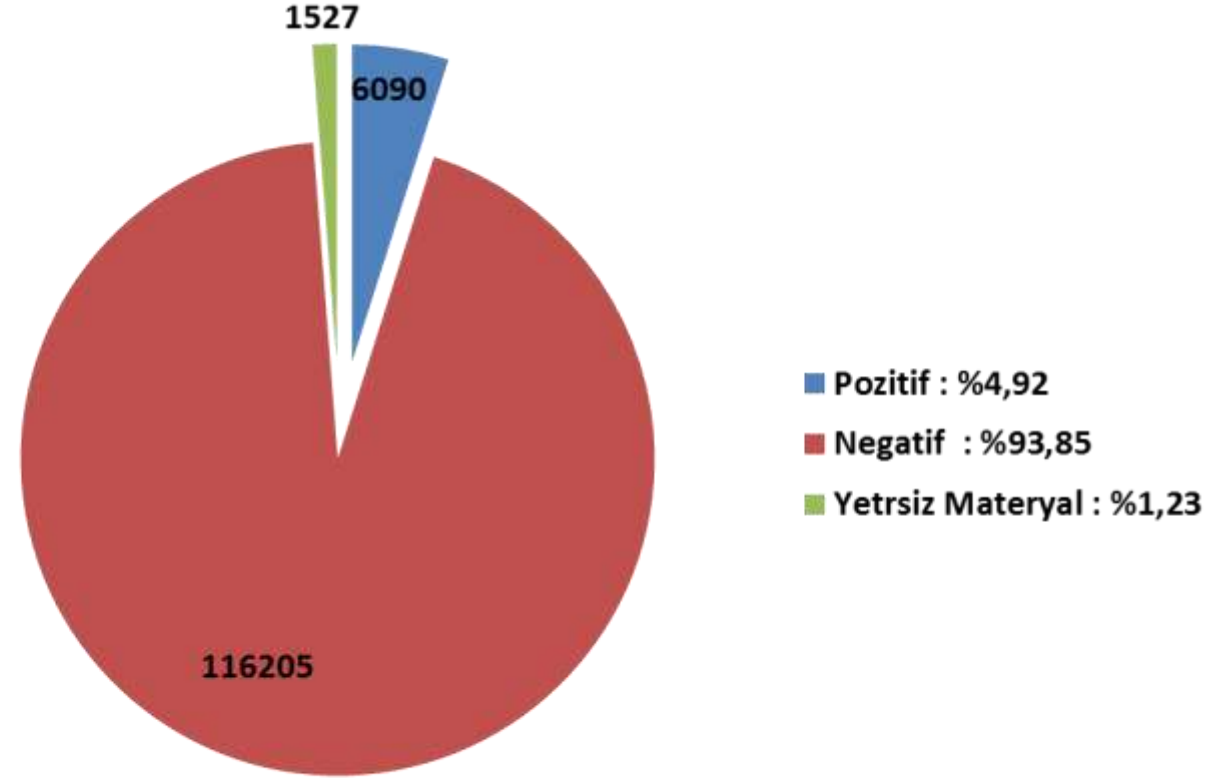
- ✓ HPV testi ile 2.000.000 kadın tarandı
- ✓ Yaklaşık 7,000 preinvaziv dönemde lezyon yakalandı
- ✓ (ASC-US dışında ) HPV Haritası

# 2015 yılı ve 2016 yılı 11 aylık HPV-DNA sonuçları,İzmir

<b>2015</b>	Sonuç Sayısı	Pozitif	Pozitif %	Tip 16	Tip 18	Genotip Diğer
<b>2015 İzmir</b>	<b>53.763</b>	<b>2565</b>	<b>4,77</b>	<b>744</b>	<b>194</b>	<b>2145</b>

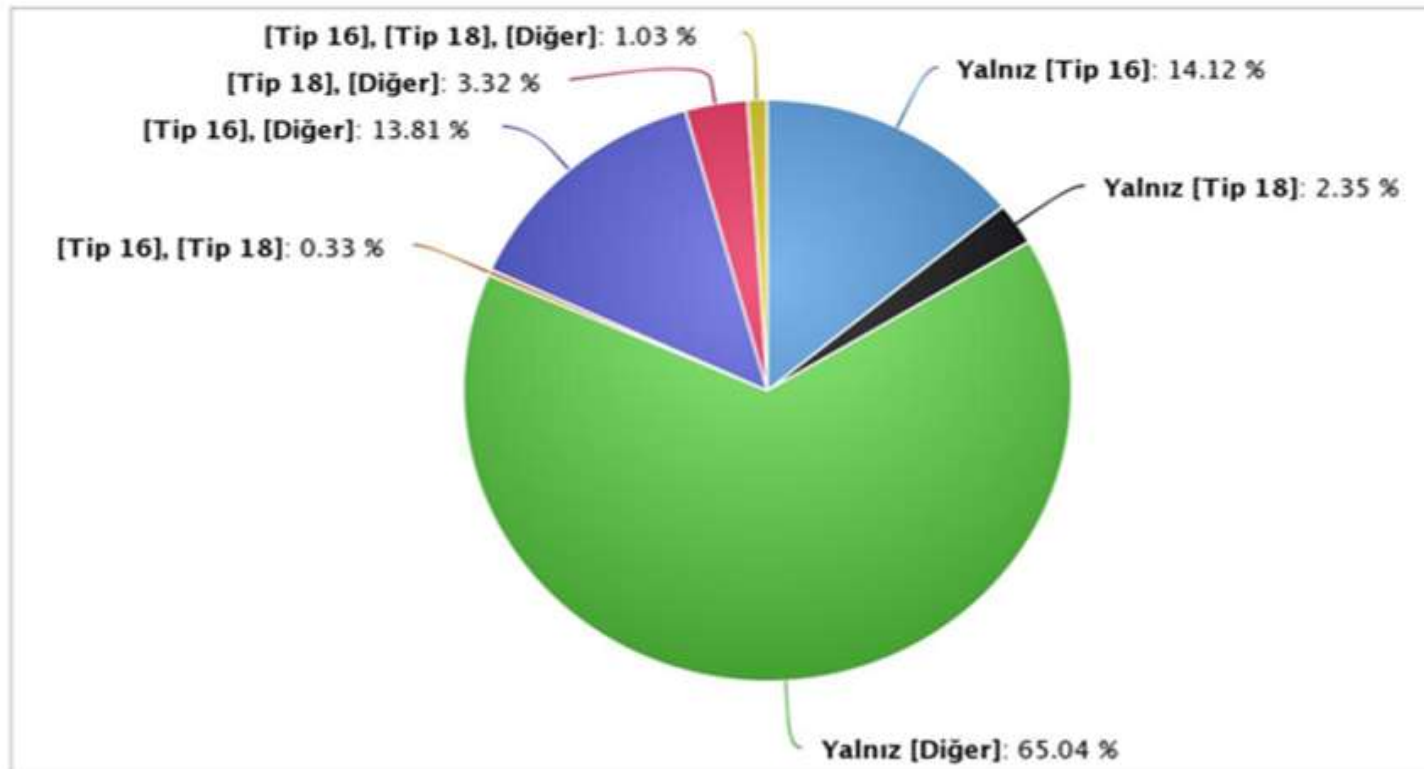
<b>2016 (11 ay)</b>	Sonuç Sayısı	Pozitif	Pozitif %	Tip 16	Tip 18	Genotip Diğer
<b>2016 İzmir</b>	<b>55.026</b>	<b>2947</b>	<b>5,36</b>	<b>882</b>	<b>202</b>	<b>2454</b>

# 2014-2016 (28 aylık) HPV-DNA Test Sonuçları

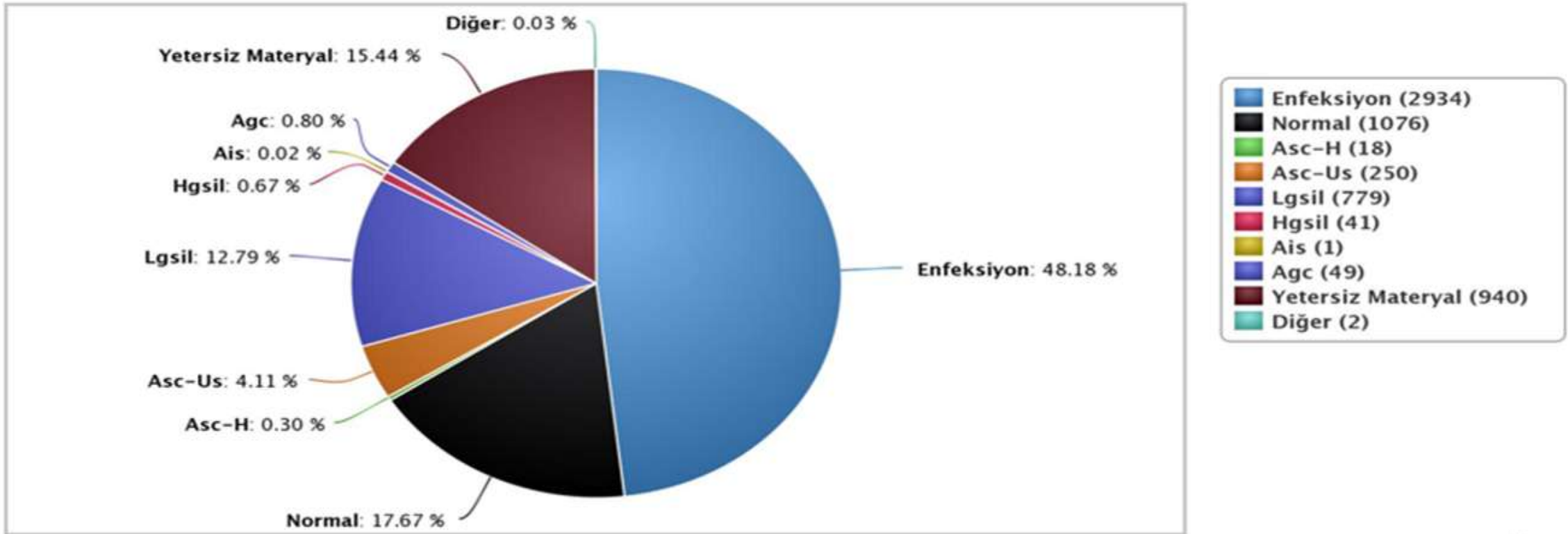




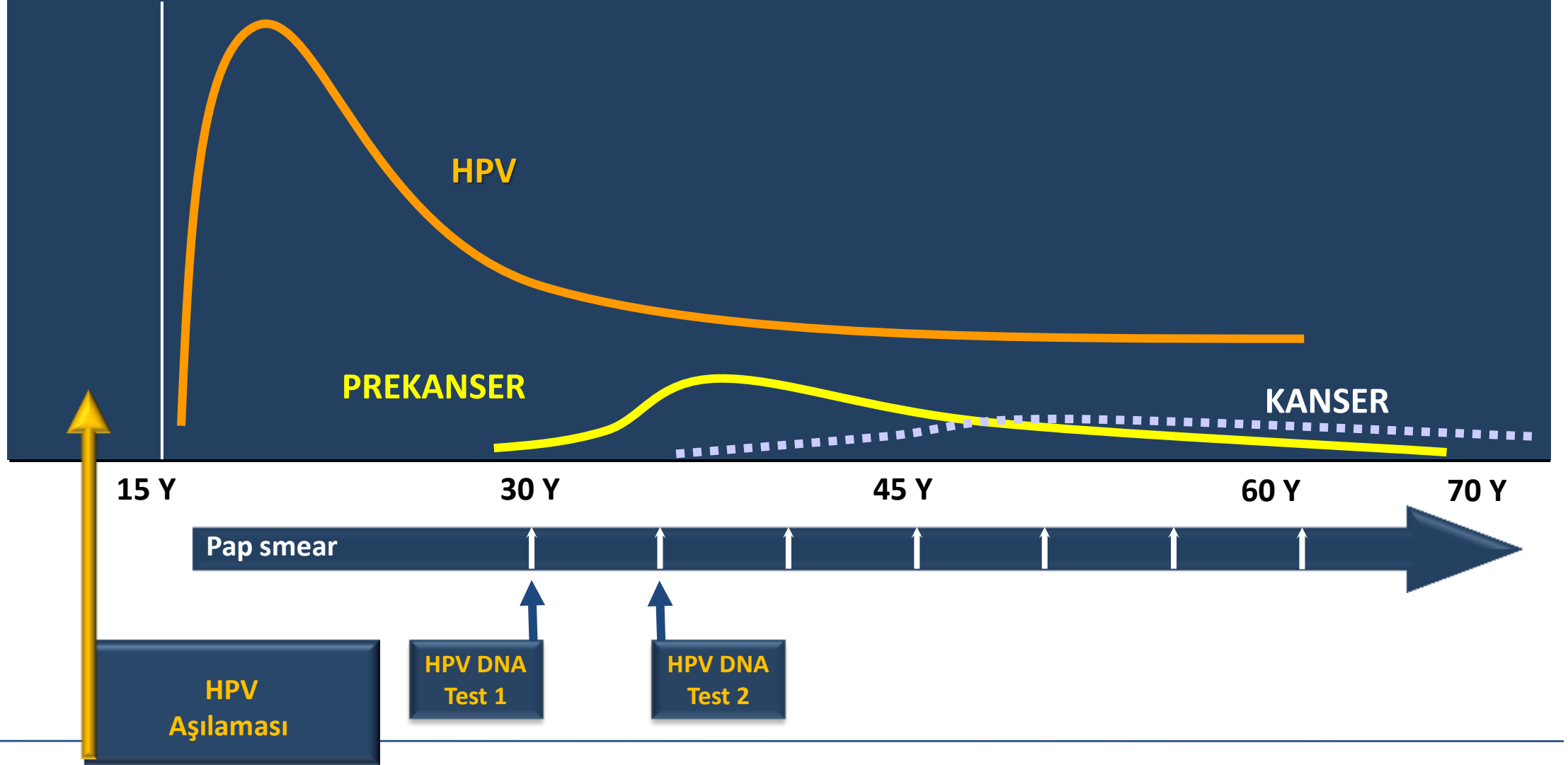
# 2014-2016 (28 aylık) HPV-DNA Testi Genotiplendirme



# 2014-2016 (28 aylık) HPV-DNA Testi Servikal Sitoloji Sonuçları,izmir



# Servikal Kanser Taramalarında Uygulanan ve Gelecekteki Stratejiler



# Primer HPV Testi ile Tarama

## Avrupa

- Eğilim pap yerine HPV tarafına kaymış durumda
  - Pap ile triaj
- Çoğu çalışma tamamlandı
- Pek çok ülkede pilot çalışma var
- Ulusal taramaya adapte edildi (Hollanda, İtalya)

Cuzick, J. Clinical workshop IPV 2012, Puerto Rico

## Kuzey Amerika

- 2012 ACS/ASCCP ve 2013 ACOG servikal tarama rehberlerine göre pap+HPV testi (co-testing) önerilen strateji
  - HPV+/Cyto- vakaların HPV16/18 tiplemesi ya da 12 ayda bir izlemi triaj önerisi

Saslow, D. Et. al. CA Cancer J Clin. 2012 May-Jun 62(3):147-72

# ACS/ASCCP/ASCP Guidelines-Mart 2012

Populasyon	Tarama Yöntemi
<21 yaş	Tarama Yok
21 - 29 yaş	3 yılda bir Pap Test ile Tarama
30-65 yaş	Her 5 yılda bir HPV ve Sitoloji "co-testing" (tercih edilir)*
>65 yaş	Eğer daha önceki tarama sonuçları normal ise tarama kesilir

\*Yalnız Sitoloji ile taranır ise 3 yılda bir (kabul edilebilir)

**Servical Kanser Taramaları**

**Uluslararası GUIDELINE  
Karşılaştırmaları:**

# CTFPHC vs. International Guidelines (1)

Organization	<20 years	20-24 years	25-29 years	30-69 years	70+ years	HPV testing*
<b>Task Force 2012</b> <b>Canada*</b>	Recommend against routine screening	Recommend against routine screening	Recommend routine screening every three years with cervical cytology	Recommend routine screening every three years with cervical cytology	Recommend routine screening every three years with cervical cytology if inadequately screened. Otherwise screening may cease.	No recommendation made. Will revisit the issue of HPV testing as new data becomes available.
<b>Previous Task Force (1994)</b> <b>Canada</b>	Annual screening with cervical cytology following initiation of sexual activity or at age 18	After 2 normal Pap tests, screening then recommended every three years to age 69. Frequency of screening may be increased in the presence of risk factors			Screening not recommended	Not applicable
<b>USPSTF 2012</b> <b>United States</b>	Recommend against routine screening under the age of 21	Recommend against routine screening under the age of 21  Recommend screening for cervical cancer in women ages 21 to 65 years with Pap test every 3 years  Recommend against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer			Recommend against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer	For women ages 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years (co-testing)

\* Recommendations for primary (HPV testing alone), co-testing (with Pap test), or triage/reflex testing (after abnormal Pap test) were considered

# CTFPHC vs. International Guidelines (2)

Organization	<20 years	20-24 years	25-29 years	30-69 years	70+ years	HPV testing*
<b>Australian Government</b> <b>Australia</b> <b>(May 2011)</b>	First Pap test around age 18 to 20, or a year or two after first having sex, whichever is the later	Regular Pap tests recommended every two years			Practitioner may advise that it is safe to stop having Pap tests if previous tests have been normal	No recommendation made
<b>NHS Cervical Screening Program</b> <b>England</b> <b>(August 2011)</b>	Not invited to screen	Not invited to screen	<p>Women aged 25-49 invited to screen every three years with cervical cytology</p> <p>Women aged 50-64 invited to screen every 5 years with cervical cytology</p> <p>Women aged 65+ screened only if not screened since age 50 or have had recent abnormal tests</p>	Women aged 65+ screened only if not screened since age 50 or have had recent abnormal tests	Women aged 65+ screened only if not screened since age 50 or have had recent abnormal tests	Additional (triage) HPV testing is recommended for women 25 years and older with abnormal Pap test results in some circumstances
<b>Health Council of the Netherlands</b> <b>Netherlands</b> <b>(May 2011)</b>	Not invited to screen	Not invited to screen	Not invited to screen	<p>Women aged 30-40 invited to screen every 5 years.</p> <p>Women aged 50-60 invited to screen every 10 years.</p> <p>(Women would be tested at the ages of 30, 35, 40, 50 and 60)</p>	Not invited to screen	Recommendation that HPV testing should replace cytology as the primary screening method. If cytology testing, additional (triage) HPV testing is recommended for women 30 years and older with abnormal Pap test results in some circumstances

\* Recommendations for primary (HPV testing alone), co-testing (with Pap test), or triage/reflex testing (after abnormal Pap test) were considered



# CTFPHC vs. International Guidelines (3)

Organization	<20 years	20-24 years	25-29 years	30-69 years	70+ years	HPV testing*
<b>National Cancer Screening Service Ireland (2011)</b>	Not invited to screen	Not invited to screen	Women aged 25 to 44 invited to screen every 3 years.  Women aged 45 to 60 invited every 5 years.  Regardless of the age of a woman when she has her first screen, she needs to have two normal results - 3 years apart, before moving to a 5 year screening interval.		Not invited to screen	No recommendation made
<b>NHS Scotland Scotland (2010)</b>	Not invited to screen	Women aged 20 – 60 invited to screen every 3 years.			Not invited to screen	No recommendation made

\*Recommendations for primary (HPV testing alone), co-testing (with Pap test), or triage/reflex testing (after abnormal Pap test) were considered

# HPV-DNA GENOTİPLENDİRME 2014-2016

