# HPV Primary Screening Update

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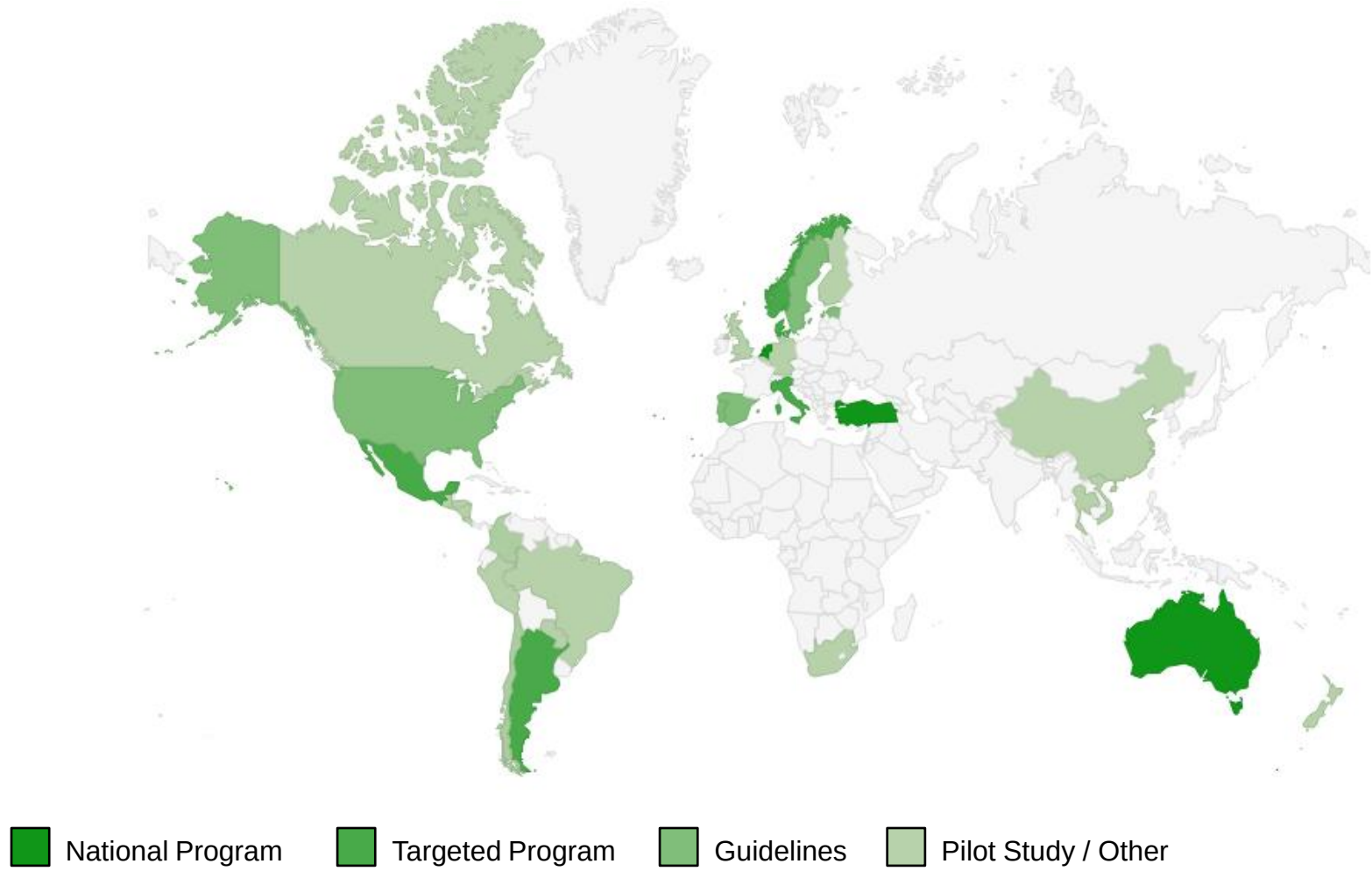
# Who can we not worry about?

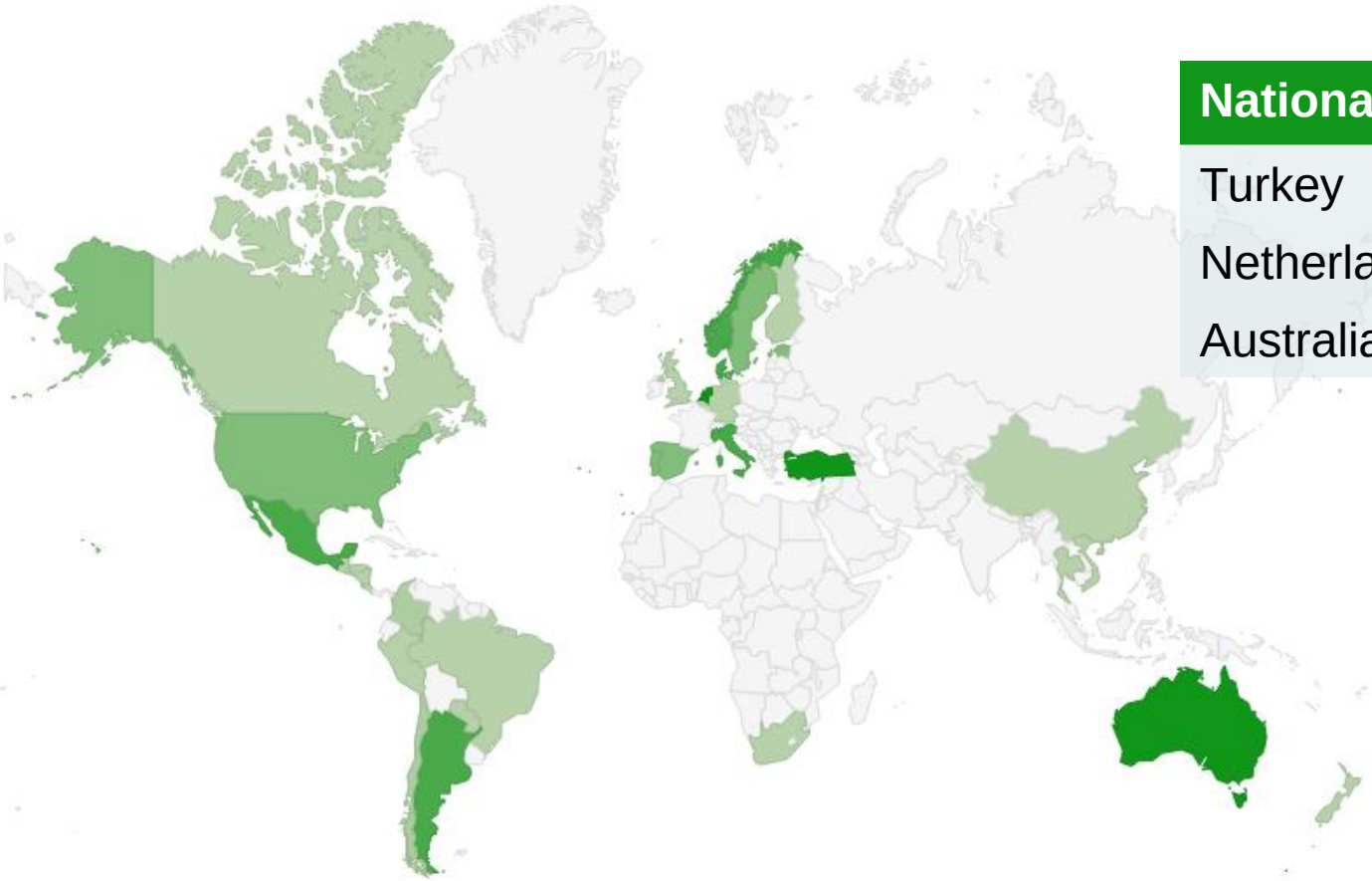
# Key questions

- Who should be screened?
  - Starting age?  Ending age?  How often?
- How to manage results?
  - Positive results?
    - Cytology?
    - Genotyping?
    - Other options?
  - Negative results?
- What are the budget and health economic implications?

# HPV DNA primary screening
## Progress around the world



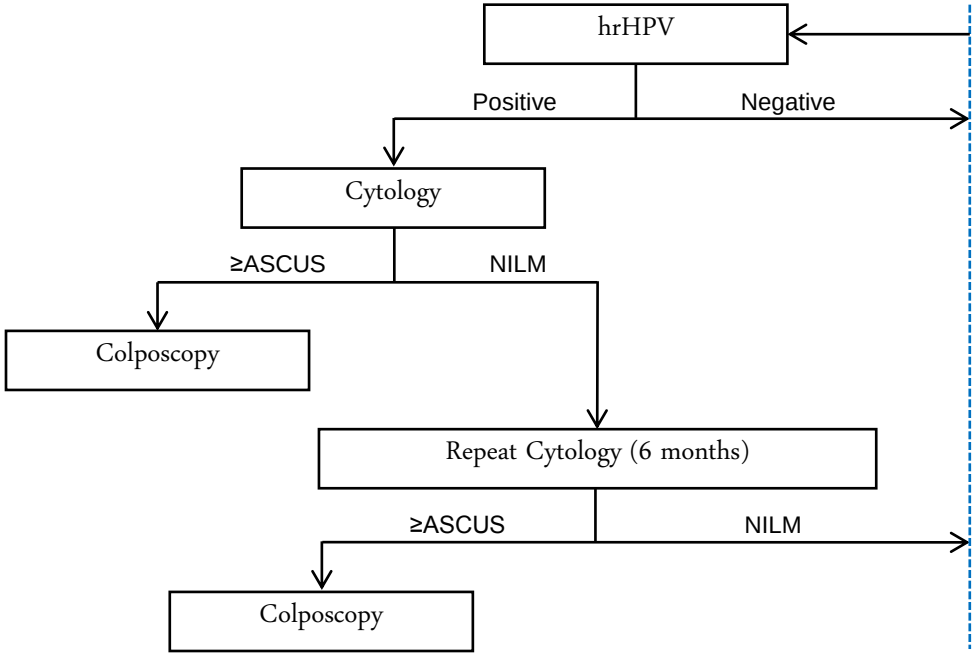
# HPV DNA primary screening
## Progress around the world



| National Program | |
|---|---|
| Turkey | 2015 |
| Netherlands | 2016 |
| Australia | 2017 |

National Program

# Netherlands Screening Program



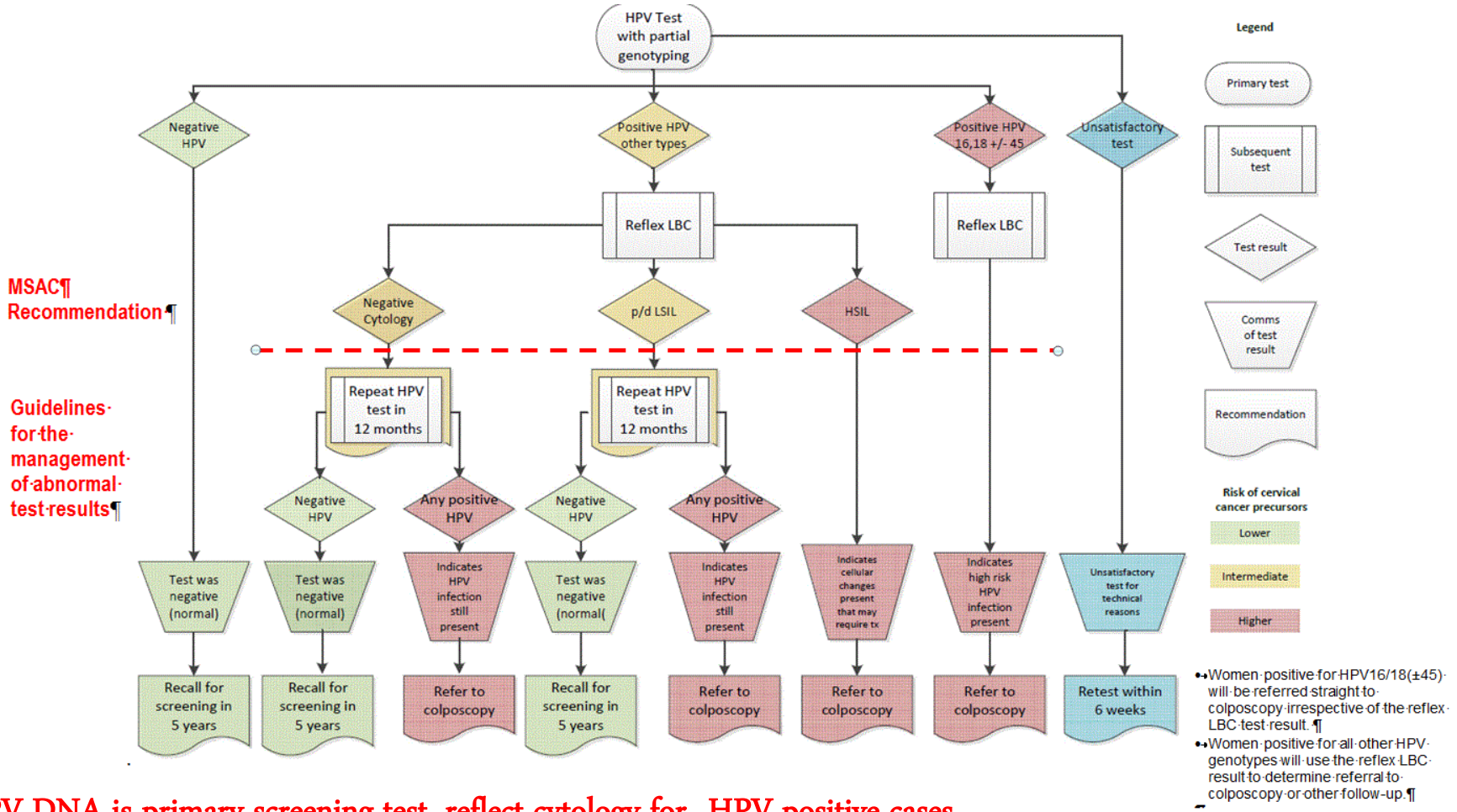

**Screening Program**

- HPV test performed at 30, 35, 40, 50 and 60 years (reduces number of tests from 7 to 5 in a lifetime)
- Genotyping could be considered but is not part of the formal recommendation

HPV DNA is primary screening test, reflect cytology for HPV positive cases

# Australian Screening Program

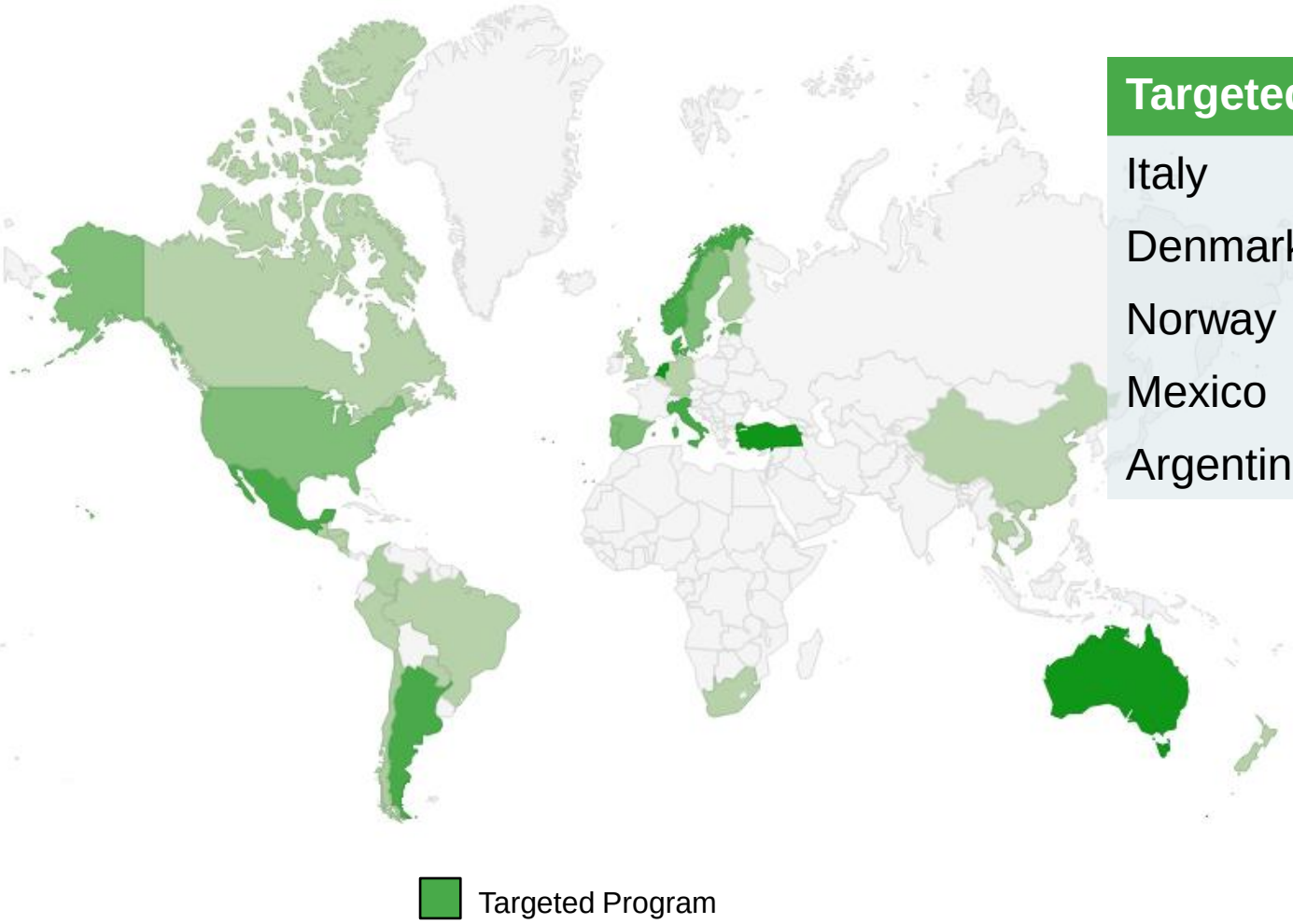
## Medical Services Advisory Committee recommendations




**HPV DNA is primary screening test, reflect cytology for HPV positive cases**

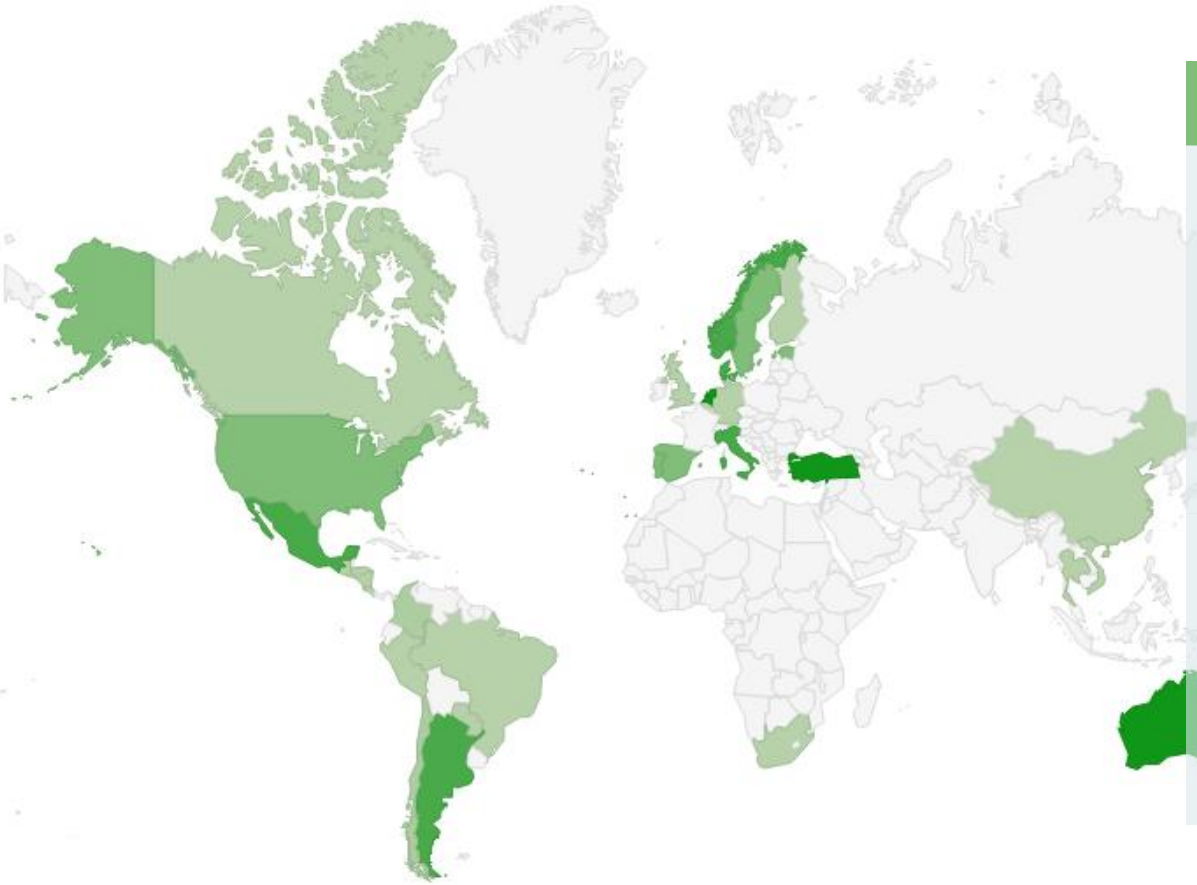
Initial screen at age 25, 5 year intervals, exit screen between 70 and 74

# HPV DNA primary screening
## Progress around the world




| Targeted Program | |
|---|---|
| Italy | Regional |
| Denmark | Women 60+ |
| Norway | Regional |
| Mexico | Government |
| Argentina | Regional |

# HPV DNA primary screening
## National guideline




| Guidelines | |
|---|---|
| WHO | International Recommendations |
| Sweden | Guidelines |
| Spain | Guidelines |
| Portugal | Guidelines |
| Estonia | Guidelines |
| USA | FDA Approval & Guidance |
| Thailand | Guideline |

# Snapshot of Primary Screening in the US

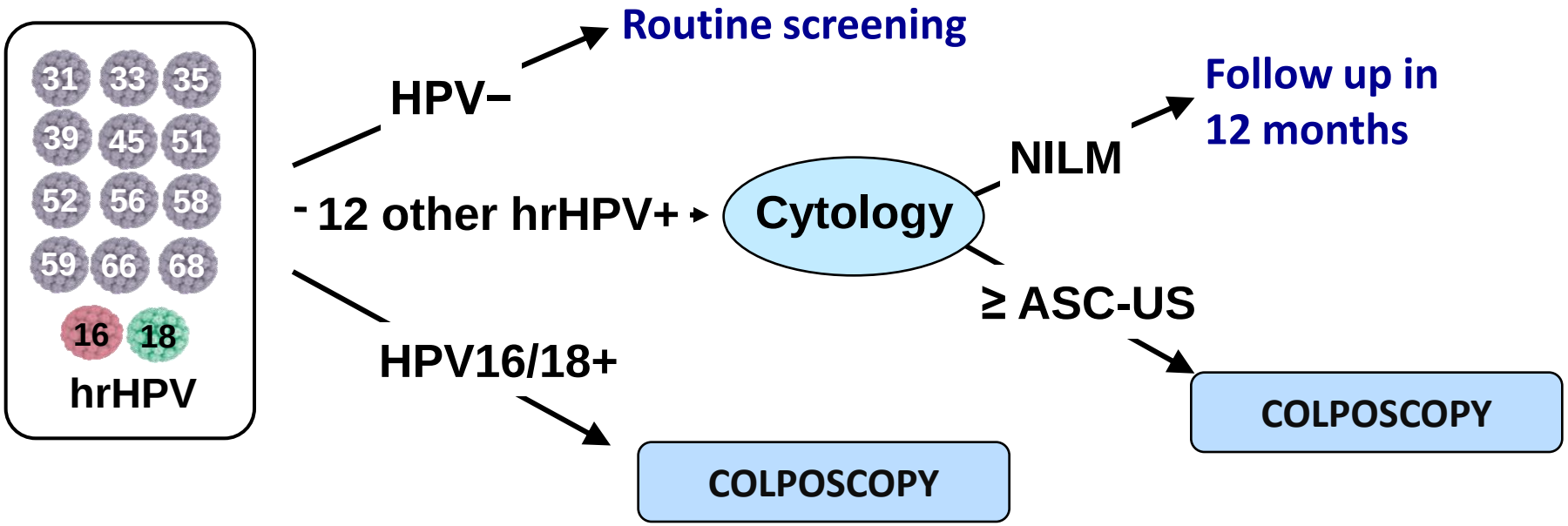
- **March 2014** Microbiology Panel recommended FDA approval of **cobas**® HPV test for Primary screening intended use
- **April 2014** FDA approved Primary Screening assay
- **January 2015** SGO/ ASCCP issue Interim Clinical Guidelines citing hrHPV primary screening as superior to cytology based strategies and at least as effective as co testing strategy.

# US Guidance on Primary HPV Screening

- Primary HPV testing can be considered as an alternative to current US cytology-based cervical cancer screening methods for women starting at age 25.
- Women with a negative primary HPV test result should not be retested again for at least three years.
- An HPV test positive for HPV 16 or 18 should be followed with colposcopy.
- A test that is positive for the 12 other high risk types should be followed with cytology testing.
- Clinicians should not use an FDA-approved test without a specific primary hrHPV screening indication.

Huh, W. et al. *Gynecol Oncol.* 2015 doi:10.1016/j.ygyno.2014.12.022
Huh, W. et al. *Obstet Gynecol* 2015; 125: 330-337

# US HPV Primary Screening Algorithm




hrHPV, high risk HPV

# The ATHENA trial overview

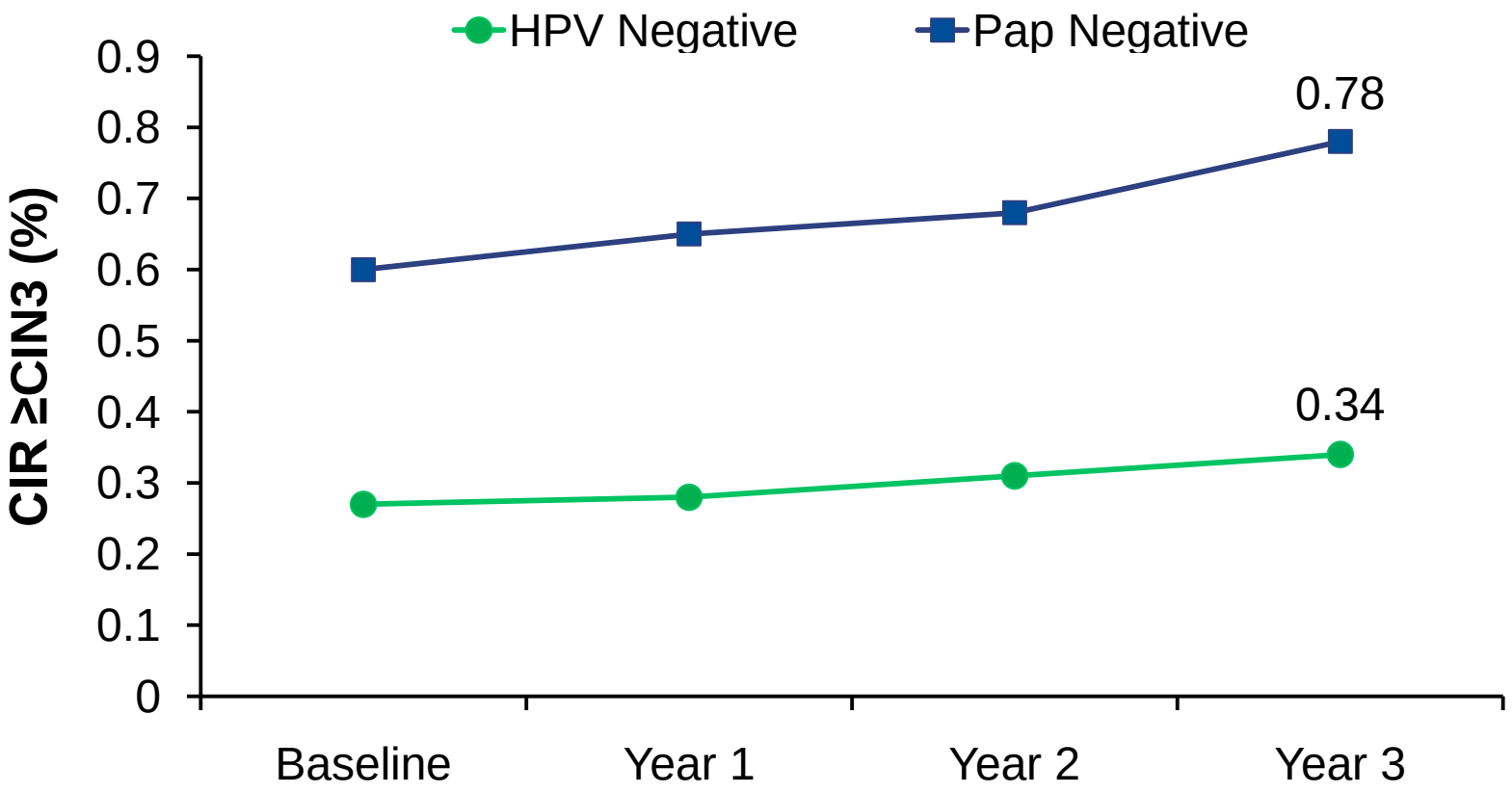

- LBC Pap and hrHPV testing at enrollment
- Colposcopy for:
  - Women with abnormal Pap or baseline positive hrHPV test results
  - A random subset of women negative on both tests
  - Year 3, any screening result

Wright TC Jr, et al. *AJOG* 2012; 206:46.e1.

# The ATHENA trial overview

- Longitude study in USA
  - 47,208 women ≥21 at 61 sites, 23 cities)
  - 4 labs
  - Follow up in 3 years
- FDA approved for cobas HPV test in:
  - ASC-US Triage
  - Co-testing
  - Primary screening

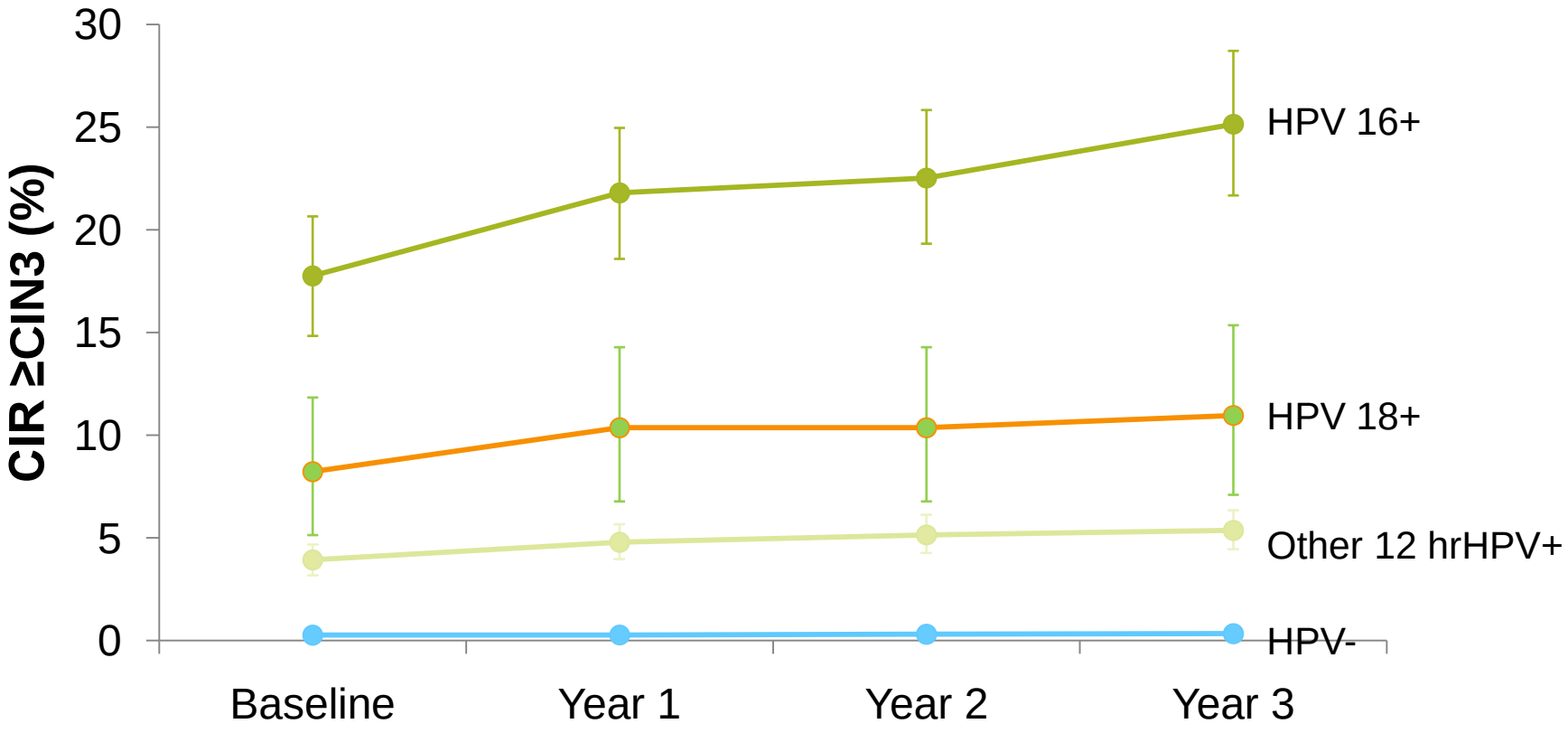
# Evaluating Women Who Screen HPV(-)




**The lower risk of disease of a negative hrHPV at Baseline confirms the safety of a negative hrHPV result over 3 years**

Presented to FDA panel, 12 March 2014

# ATHENA: 3 Year CIR of ≥CIN3
## Stratified by Screening Test Result at Baseline

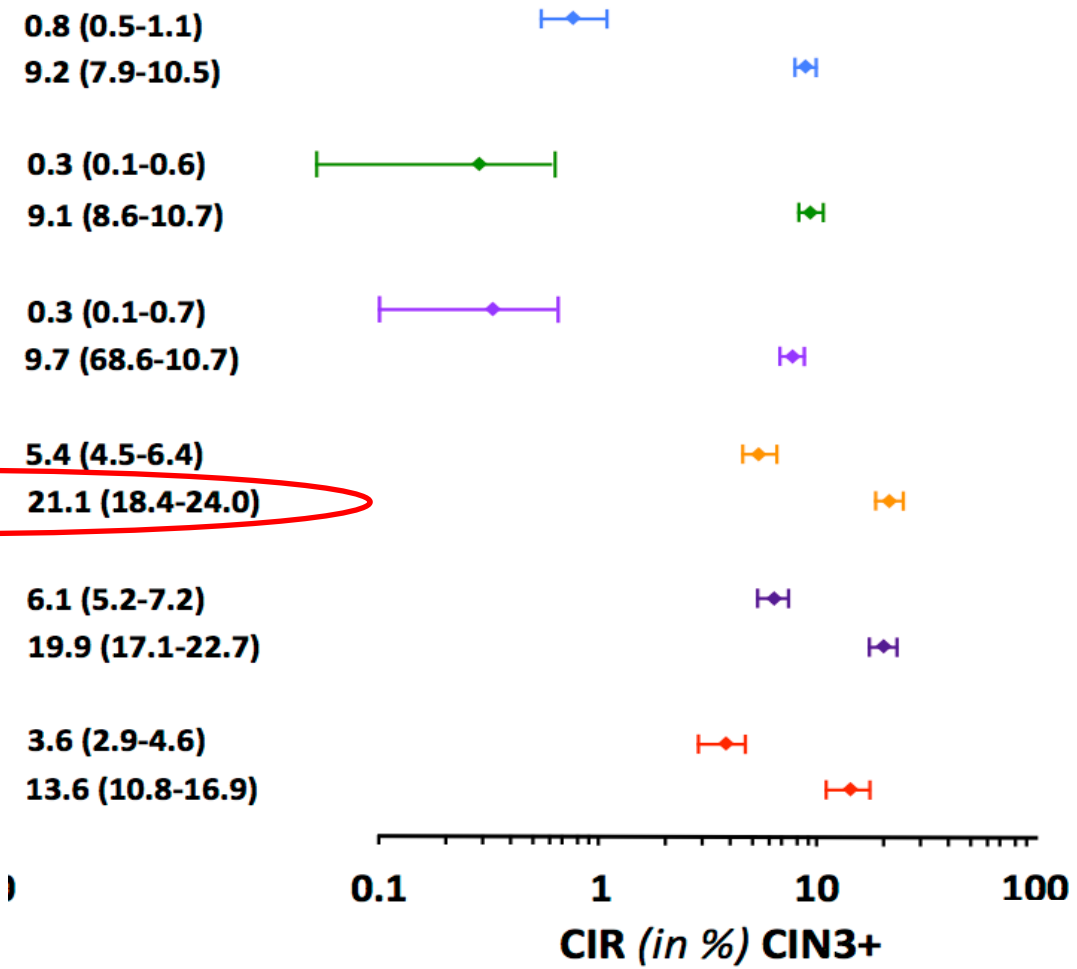



**Those who were HPV 16 positive had a cumulative risk of approximately 25% at 3 years.**

Athena trial

# 3 Year Cumulative Incidence of CIN 3+
## ATHENA trial

| N (% of 40,901) | Screening Test | CIR (95% CI) |
|---|---|---|
| 38,284 (93.6) | Normal cytology | 0.8 (0.5-1.1) |
| 2,617 (6.4) | Abnormal cytology | 9.2 (7.9-10.5) |
| 35,118 (85.9) | Normal cytology & HPV - | 0.3 (0.1-0.6) |
| 5,783 (14.1) | Abnormal cytology &/or HPV + | 9.1 (8.6-10.7) |
| 36,626 (89.5) | HPV - | 0.3 (0.1-0.7) |
| 4.275 (10.5) | HPV + | 9.7 (68.6-10.7) |
| 3,108 (7.6) | HPV 12 other | 5.4 (4.5-6.4) |
| 1,167 (2.9) | HPV 16/18 | 21.1 (18.4-24.0) |
| 3,166 (7.7) | Normal cytology & HPV + | 6.1 (5.2-7.2) |
| 1,109 (2.7) | Abnormal cytology & HPV + | 19.9 (17.1-22.7) |
| 2,388 (5.8) | Normal cytology & HPV 12 other | 3.6 (2.9-4.6) |
| 778 (1.9) | Normal cytology & HPV 16/18 | 13.6 (10.8-16.9) |




*Wright et al. Gynecol Oncol 2015*

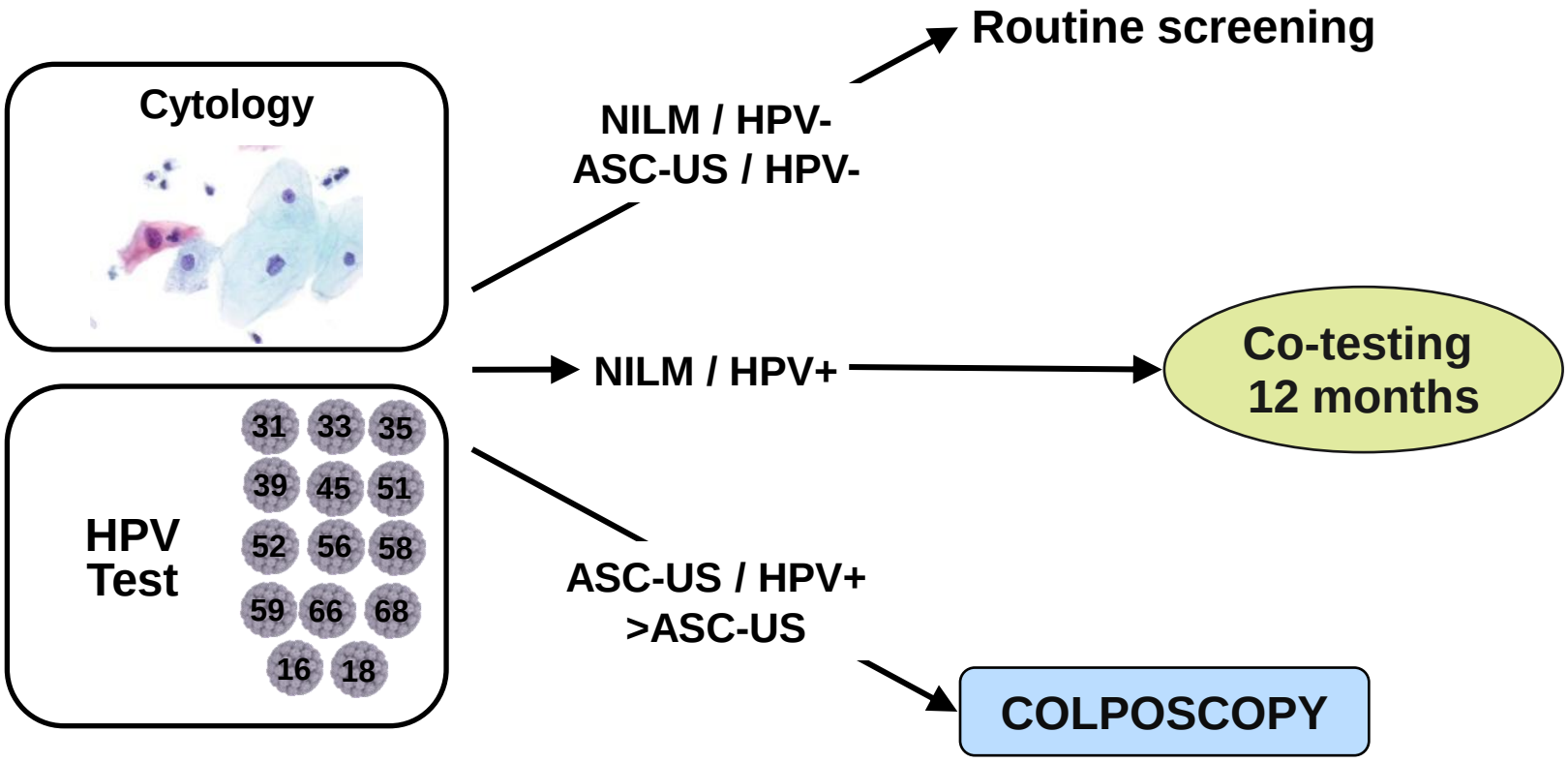
# Evaluating Screening Algorithms

- The performance of different screening algorithms was evaluated in women ≥25 years
- Strategies that were evaluated included:
  - Cytology
  - Primary HPV testing with 16/18 genotyping and reflex cytology if 12 “other” hrHPV (+)
  - Co-testing*

*Co-testing for women ≥30 years, cytology for women 25-29
US Guidelines do not recommend co-testing for women <30 years

Wright, et al. *Gynecol Oncol.* 2015 doi:10.1016/j.ygyno.2014.11.076

# Co-testing
## HPV and Cytology for All



# ATHENA 3-year end-of-study results:
## Measures of Clinical Management for Disease (≥CIN3)

| Algorithm | Screening Tests | ≥CIN3 Cases | Colpos | Colpos per ≥CIN3 |
|---|---|---|---|---|
| **Cytology** | **45,166** | **179** | **1,934** | **10.8** |
| **Primary HPV** | **52,651** | **294** | **3,769** | **12.8** |
| **Co-testing*** | **82,994** | **240** | **3,097** | **12.9** |

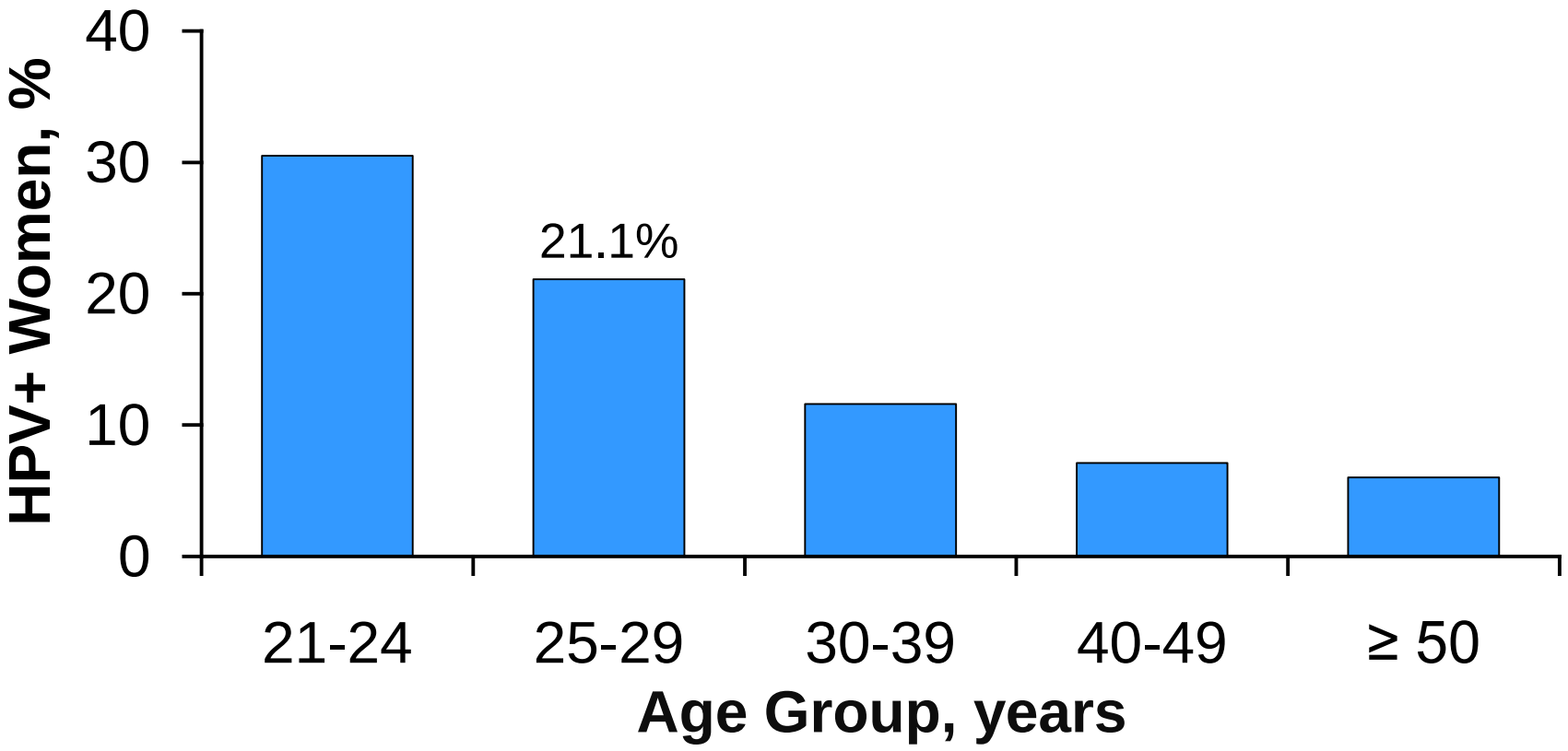
*Co-testing for women ≥30 years, cytology for women 25-29
US Guidelines do not recommend co-testing for women <30 years

Wright, et al. *Gynecol Oncol.* 2015 doi:10.1016/j.ygyno.2014.11.076

Total ≥CIN3 cases = 347

# Why should start at age 25?

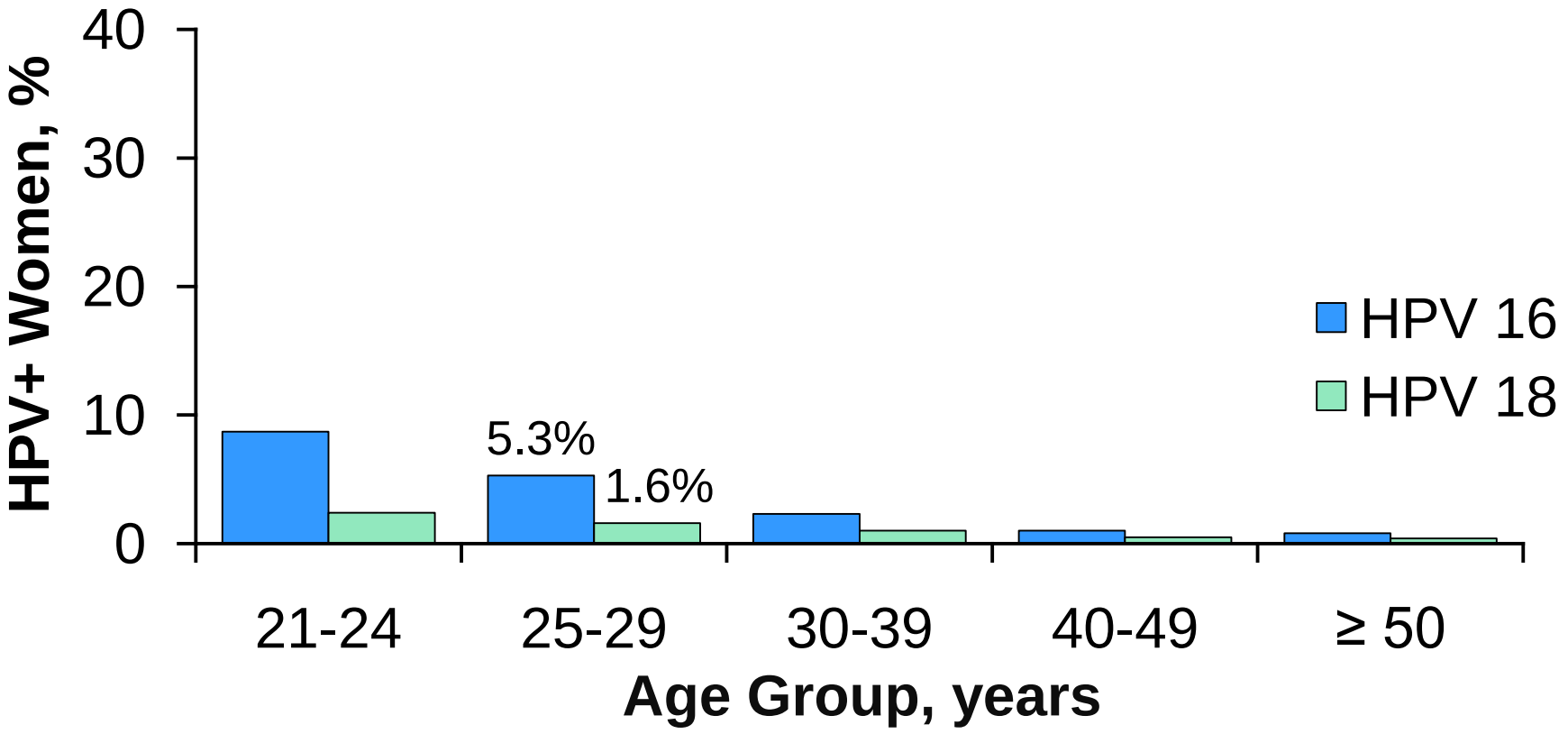
# Incidence of HPV by Age
## Results from ATHENA




Wright TC Jr, et al. *Am J Obstet Gynecol*. 2012;206:46.e1-46.e11

N = 46,601

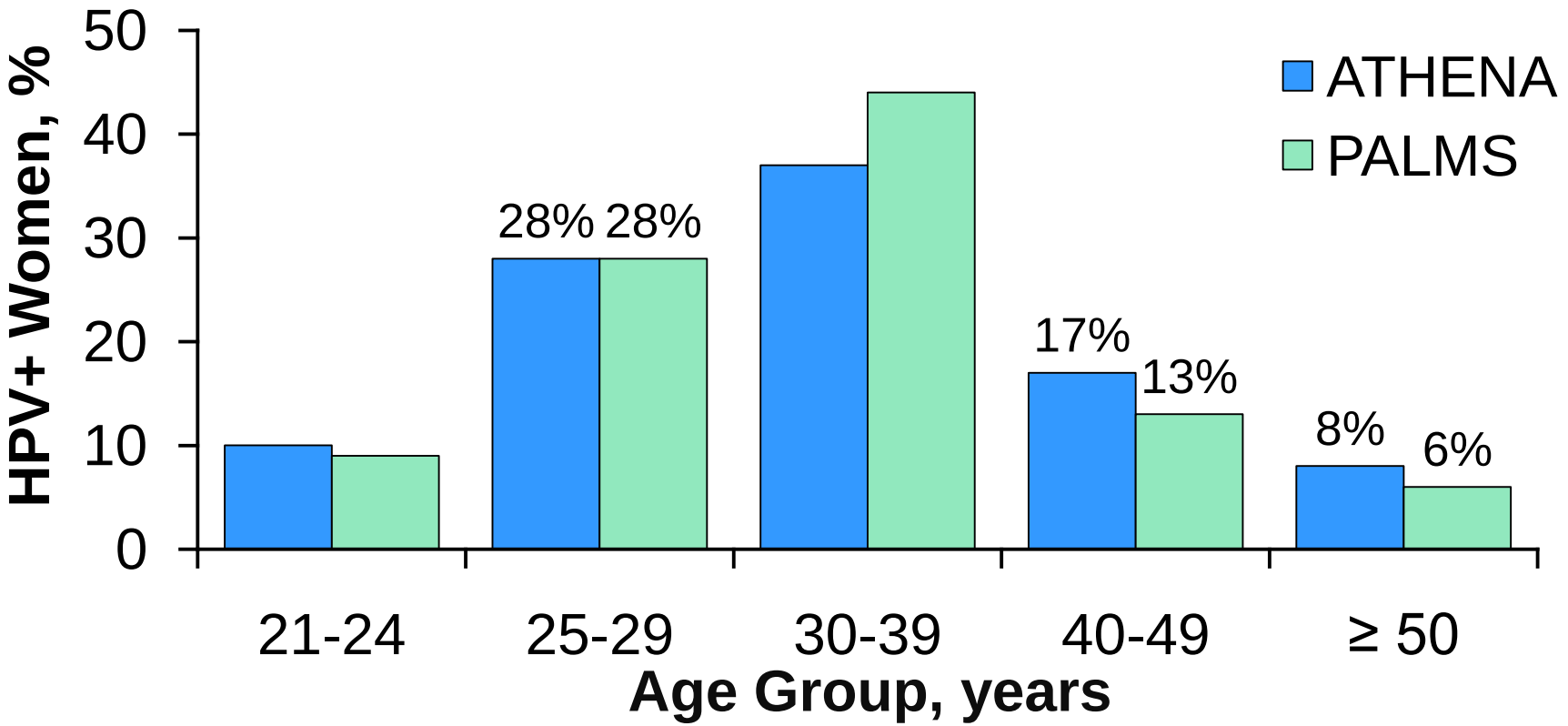
# Incidence of HPV 16/18 by Age
## Results from ATHENA




Wright TC Jr, et al. *Am J Obstet Gynecol*. 2012;206:46.e1-46.e11

N = 46,601

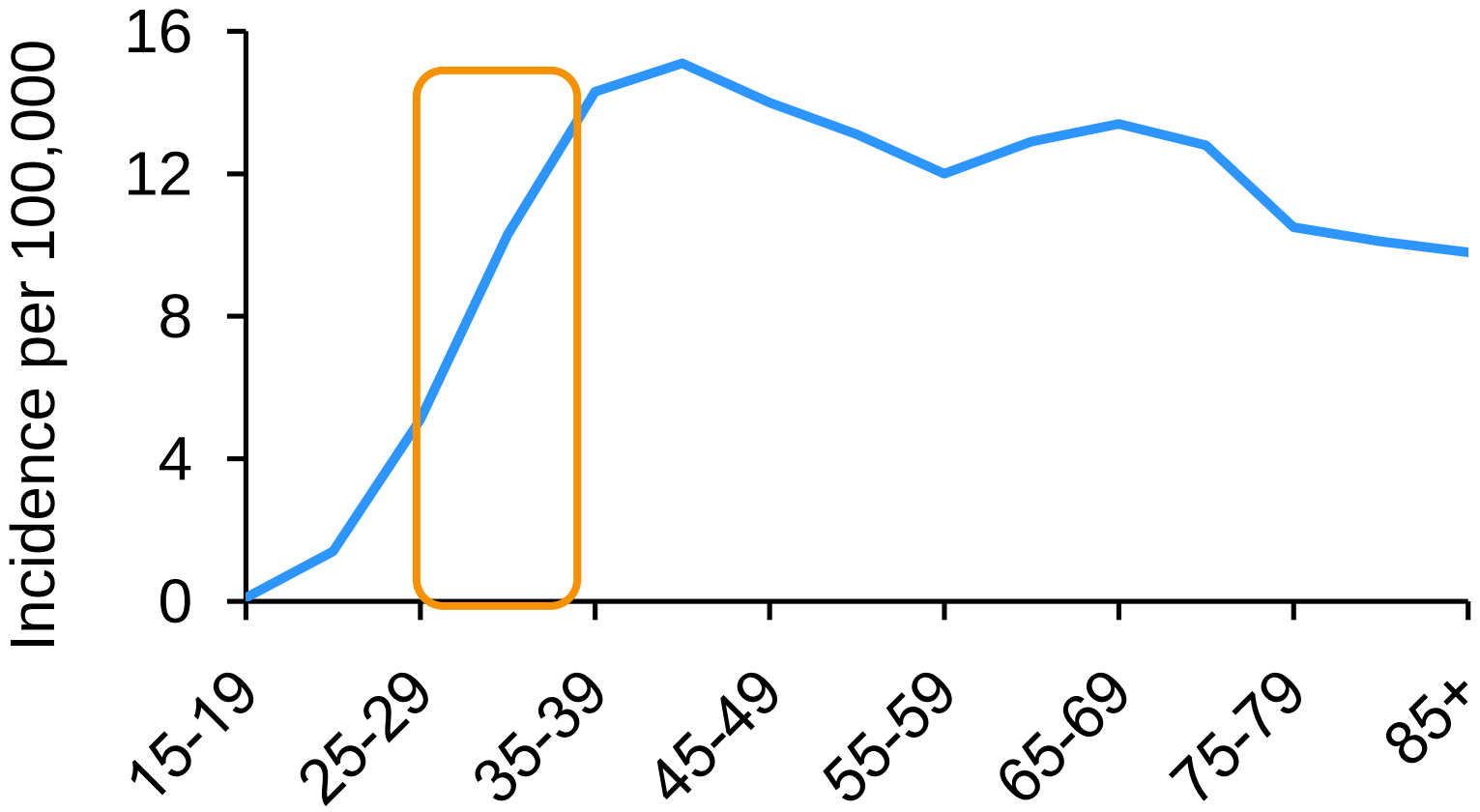
# Incidence of HPV by Age
## Results from ATHENA and PALMS




Population of women aged ≥ 40 years is 3x that of the age 25 to 29 group.
Aged 25 to 29: n = 6767 (ATHENA) and 3373 (PALMS).

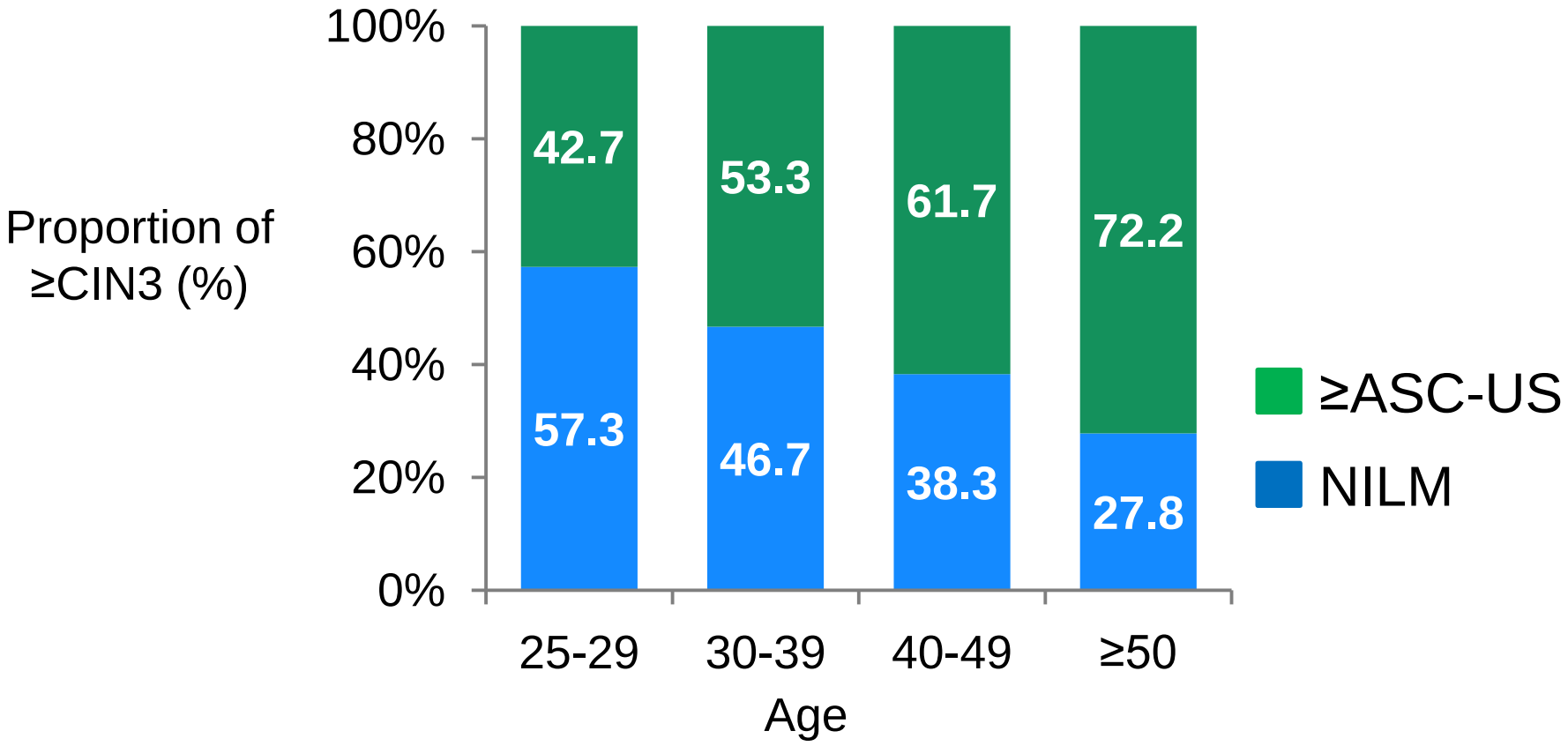
Wright TC Jr, et al. *Am J Obstet Gynecol*. 2012;206:46.e1-46.e11; Ventana data on file

# Invasive Cervical Cancer in the U.S.
## SEER Tumor Registry (1975-2010)




http://seer.cancer.gov/csr/1975_2010/

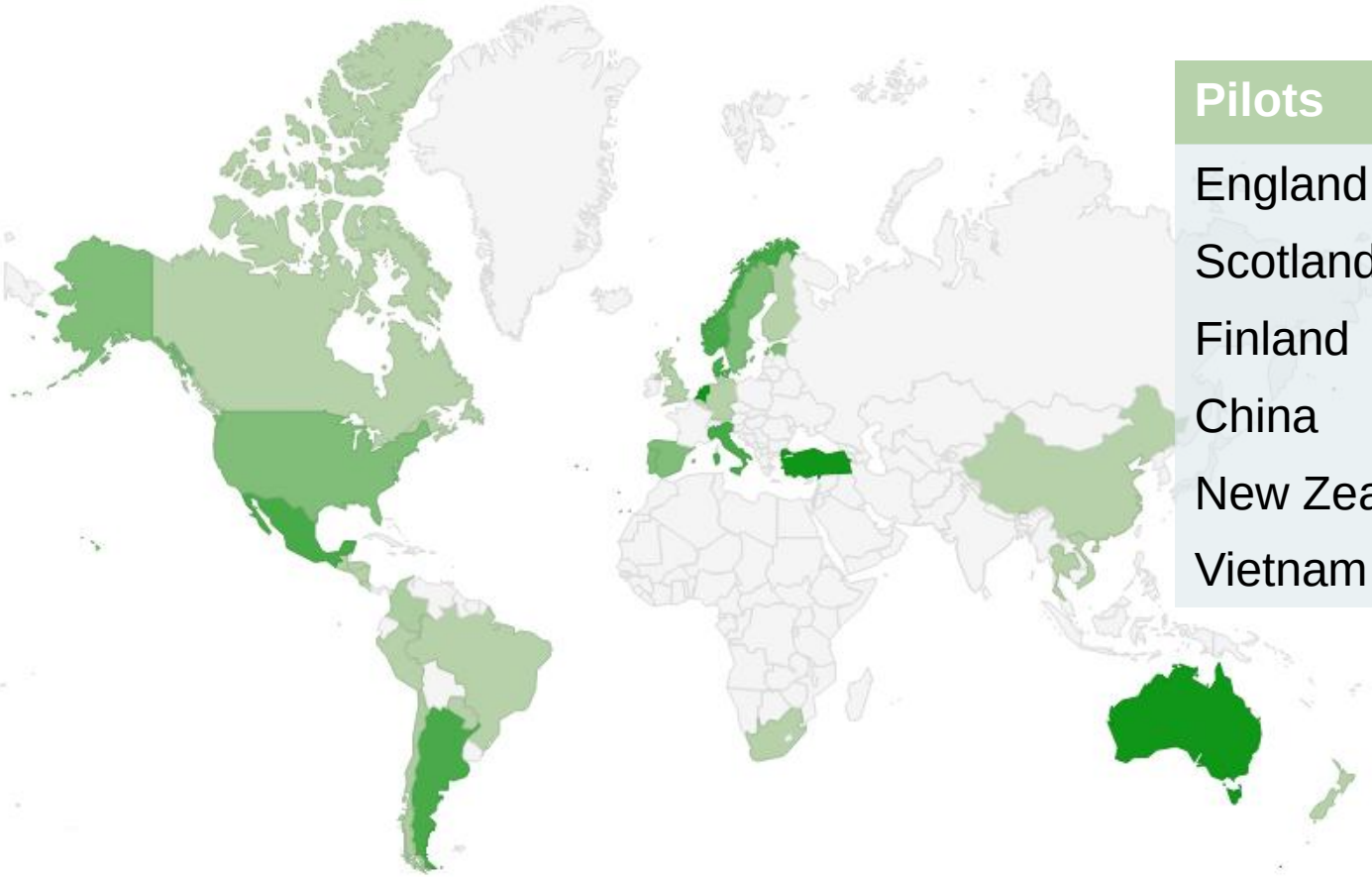
# Why Not Cytology for Women 25 -29 Years?
## Results From ATHENA




Percentages shown are for hrHPV+ women with ≥CIN3, N=252

Huw W, et al. 27th IPV Conference, Berlin, Germany, September 17–22, 2011, OP-229.

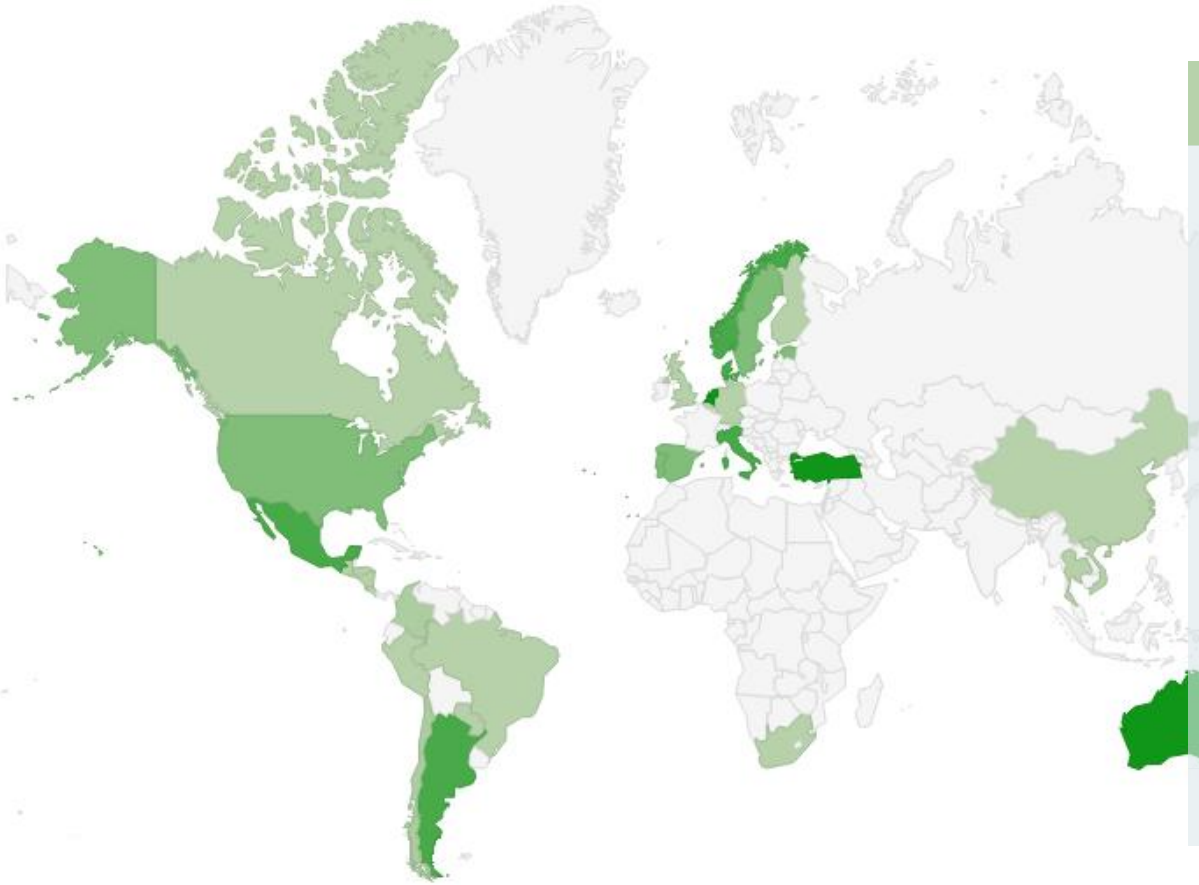
# HPV DNA primary screening
## Pilot program



| Pilots | |
|---|---|
| England | National |
| Scotland | National |
| Finland | National |
| China | National |
| New Zealand | National |
| Vietnam | National? |

Pilot Study / Other

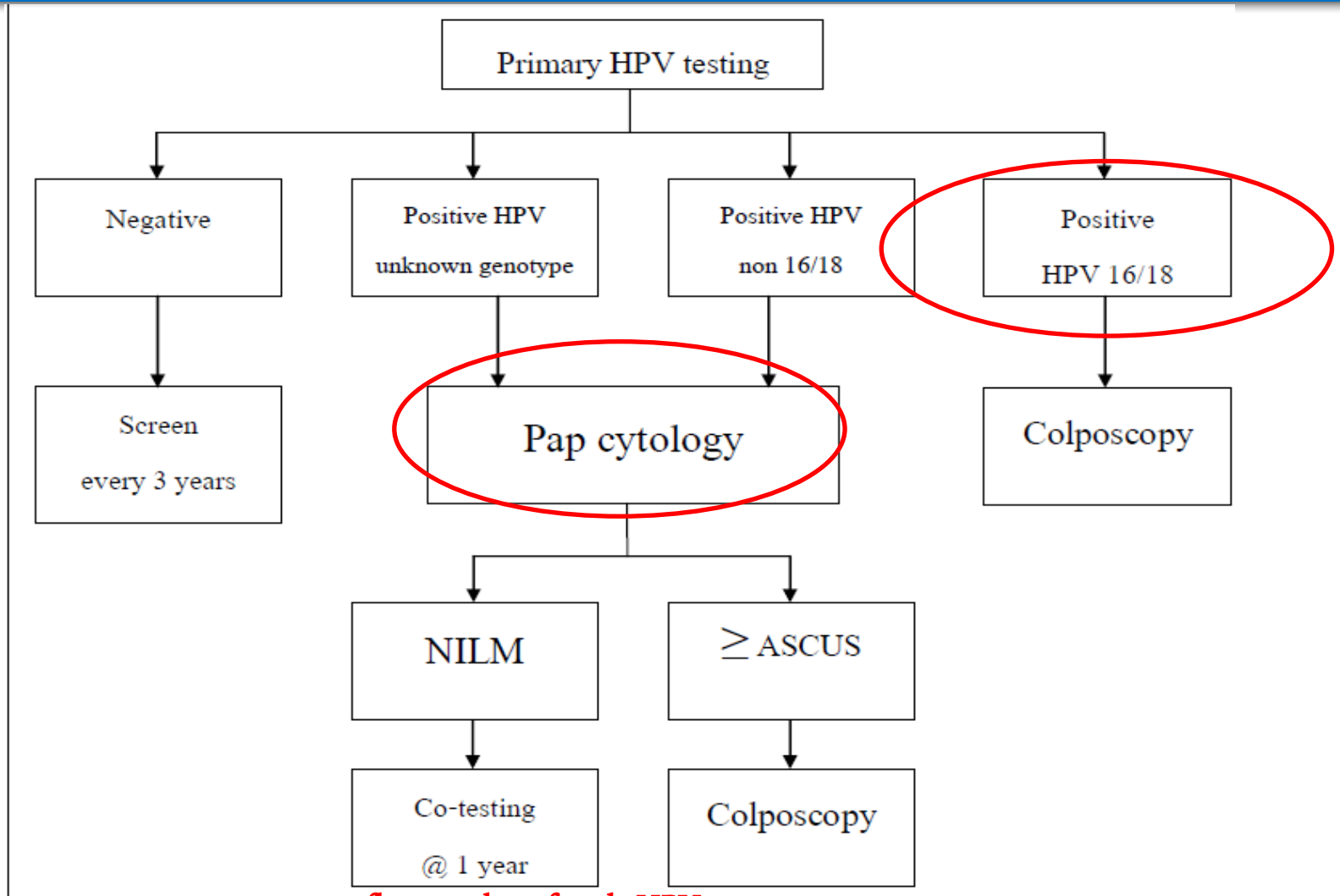
# HPV DNA primary screening
## Progress around the world



| Other | |
|---|---|
| Canada | Local guidelines |
| European | Guideline review |
| Germany | Guideline review |
| Belgium | Guideline review |
| Chile | Guideline review |
| Colombia | Guideline review |
| Barbados | Guideline review |
| S. Africa | Guideline review |
| LATAM | ESTAMPA |

Pilot Study / Other

# ThaiLand screening guideline




HPV DNA is primary screening test, reflect cytology for hrHPV positive cases

Colposcopy is recommended for HPV 16/18 positive

# Conclusions

- Countries around the world are moving toward HPV based cervical cancer screening
  - Many similarities among various programs
  - Some differences due to local circumstances