HPV: Cervical Cancer Testing and Beyond

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1. Brief history of HPV and cervical cancer screening

2. Approved HPV tests

3. Practice guidelines

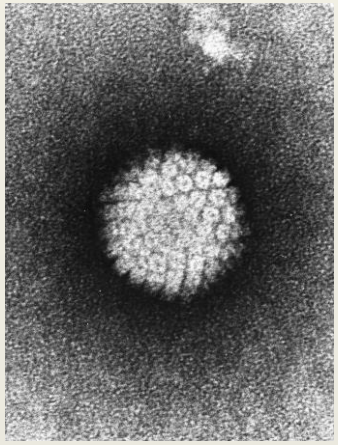
4. HPV vaccines

5. Future of HPV testing

Virology

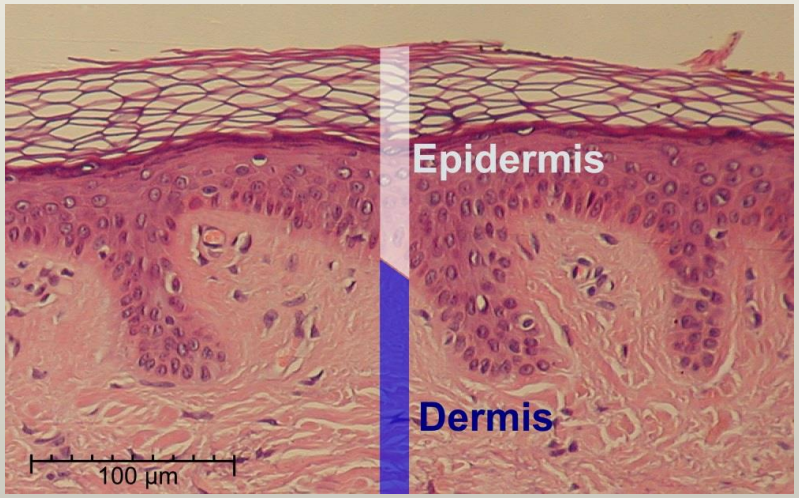
Human papillomavirus (HPV) is a small double-stranded circular DNA virus with a genome of approximately 8000 base pairs.

There are more than 150 sub-types, categorized as either high-risk or low-risk based on their association with oncogenesis.

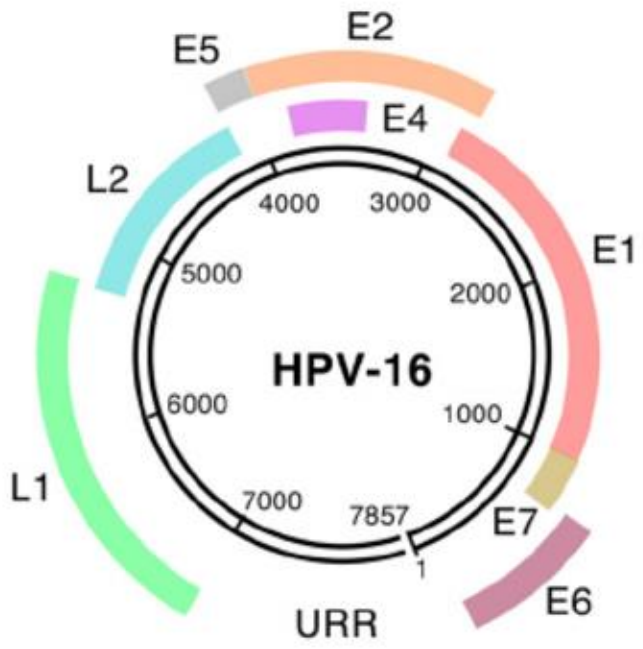


HPV infection is limited to the basal cells of the epithelium; the outermost layer of skin (epidermis) is composed of dead squamous epithelial cells, as are the mucous membranes lining the inside of mouths and body cavities.

Route of infection is from micro-abrasion of the squamous epithelium which allows viral access to basal cells.



Virology



Gene	Function
L1	Major capsid protein.
L2	Minor capsid protein.
E1	Transcription factor, helicase activity. Mediates episomal DNA replication.
E2	Transcription factor. Regulates viral copy number.
E4	Facilitates virion release.
E5	Stimulates cell proliferation and prevents differentiation. Downregulates surface MHC class I expression.
E6	Deregulates cell cycle control through p53 inactivation/degradation. Induces malignant transformation together with E7.
E7	Keeps cells active in the cell cycle through Rb inactivation. Induces malignant transformation alone and together with E6.

Epidemiology

- HPV is a significant source of morbidity and mortality worldwide.
- High-risk, oncogenic HPV types (including HPV 16 and HPV 18) are associated with 99.7% of all cervical cancers, as well as low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), and abnormal Papanicolaou (Pap) test results, which carry significant health care costs and psychosocial morbidity.
- Low-risk HPV types (HPV 6 and HPV 11) are responsible for additional abnormal Pap test results, as well as almost all cases of genital warts.
- HPV is so common that more than half of all sexually active adults will be infected in their lifetime, although young, sexually active women bear the brunt of both infection and clinical complications.

Source: https://www.cancer.gov/types/cervical/pap-hpv-testing-fact-sheet

Epidemiology

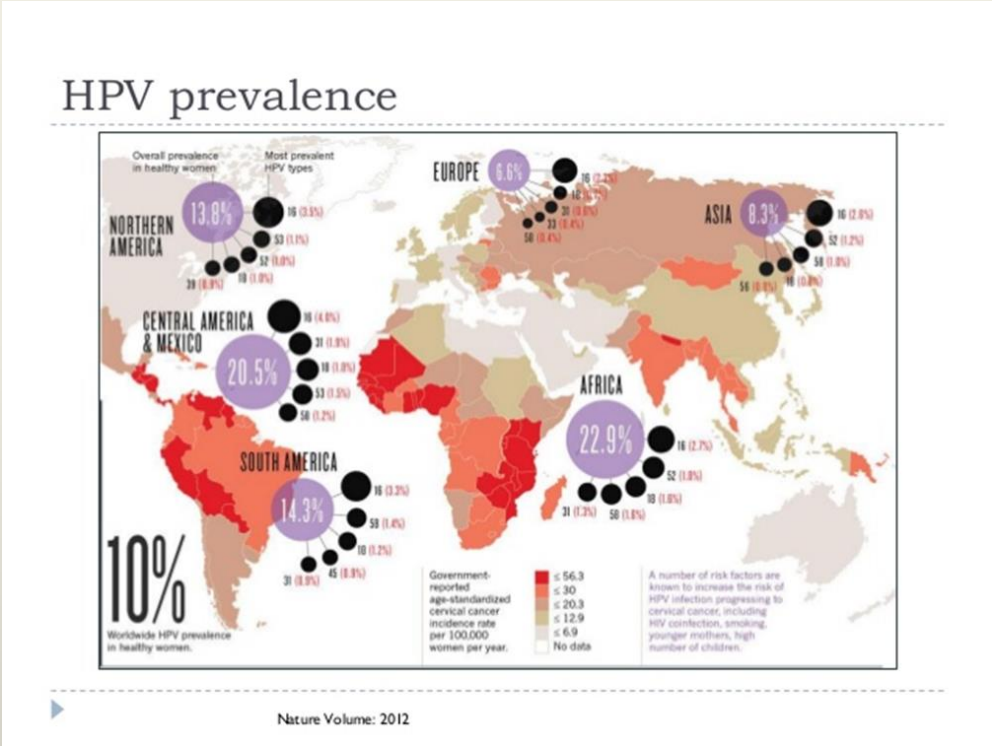
- Worldwide, cervical cancer is the fourth most frequent cancer in women with an estimated 530 000 new cases in 2012 representing 7.5% of all female cancer deaths.
- Of the estimated more than 270,000 deaths from cervical cancer every year, more than 85% of these occur in less developed regions.
- In developed countries, programs are in place which enable women to get screened, making most pre-cancerous lesions identifiable at stages when they can easily be treated. Early treatment prevents up to 80% of cervical cancers in these countries.

Source: http://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer

Epidemiology

- In developing countries, limited access to effective screening means that the disease is often not identified until it is further advanced and symptoms develop.

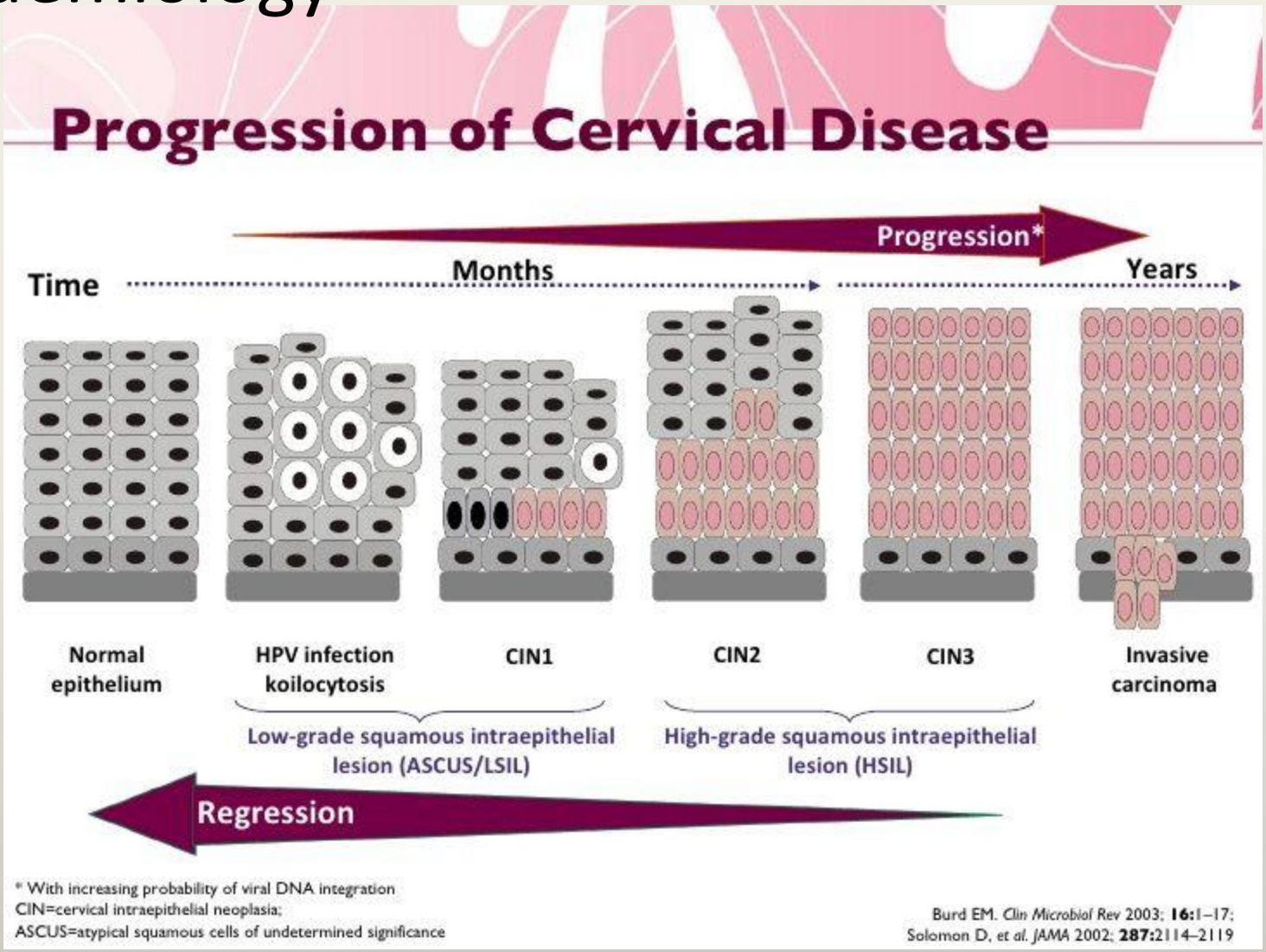
- Prospects for treatment of such late-stage disease may be poor, resulting in a higher rate of death from cervical cancer in these countries.



- The high mortality rate from cervical cancer globally (52%) could be reduced by effective screening and treatment programs.

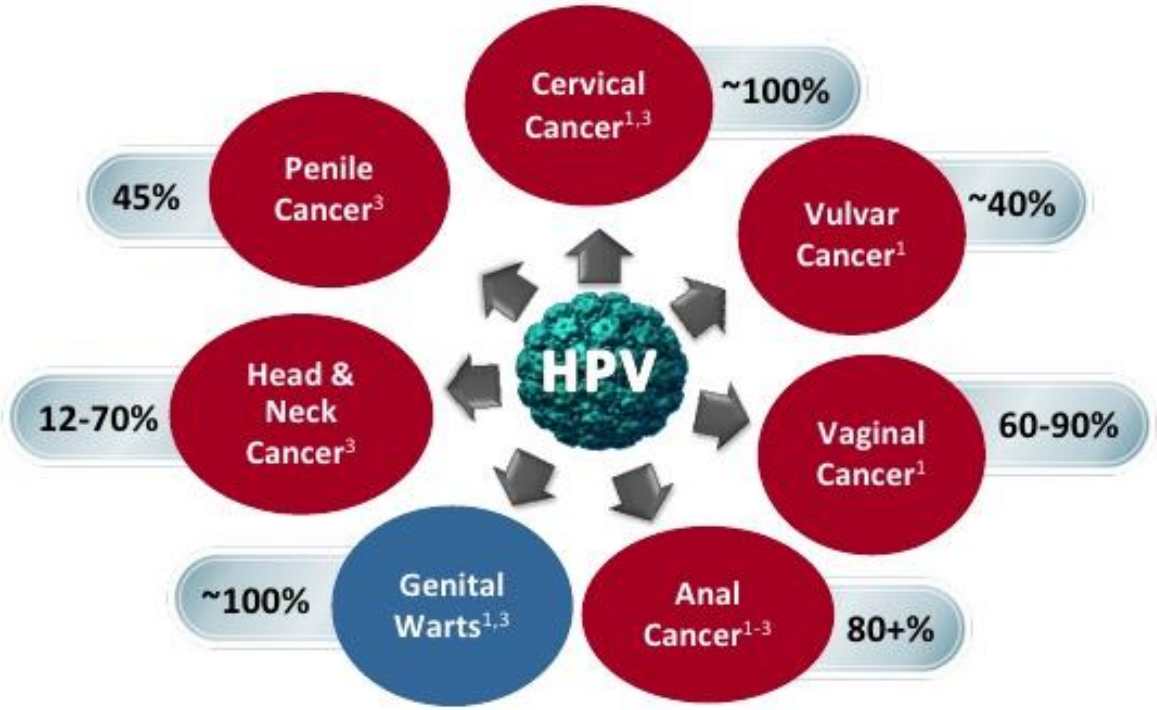
Source: http://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer

Epidemiology



Epidemiology

HPV causes more than cervical cancer



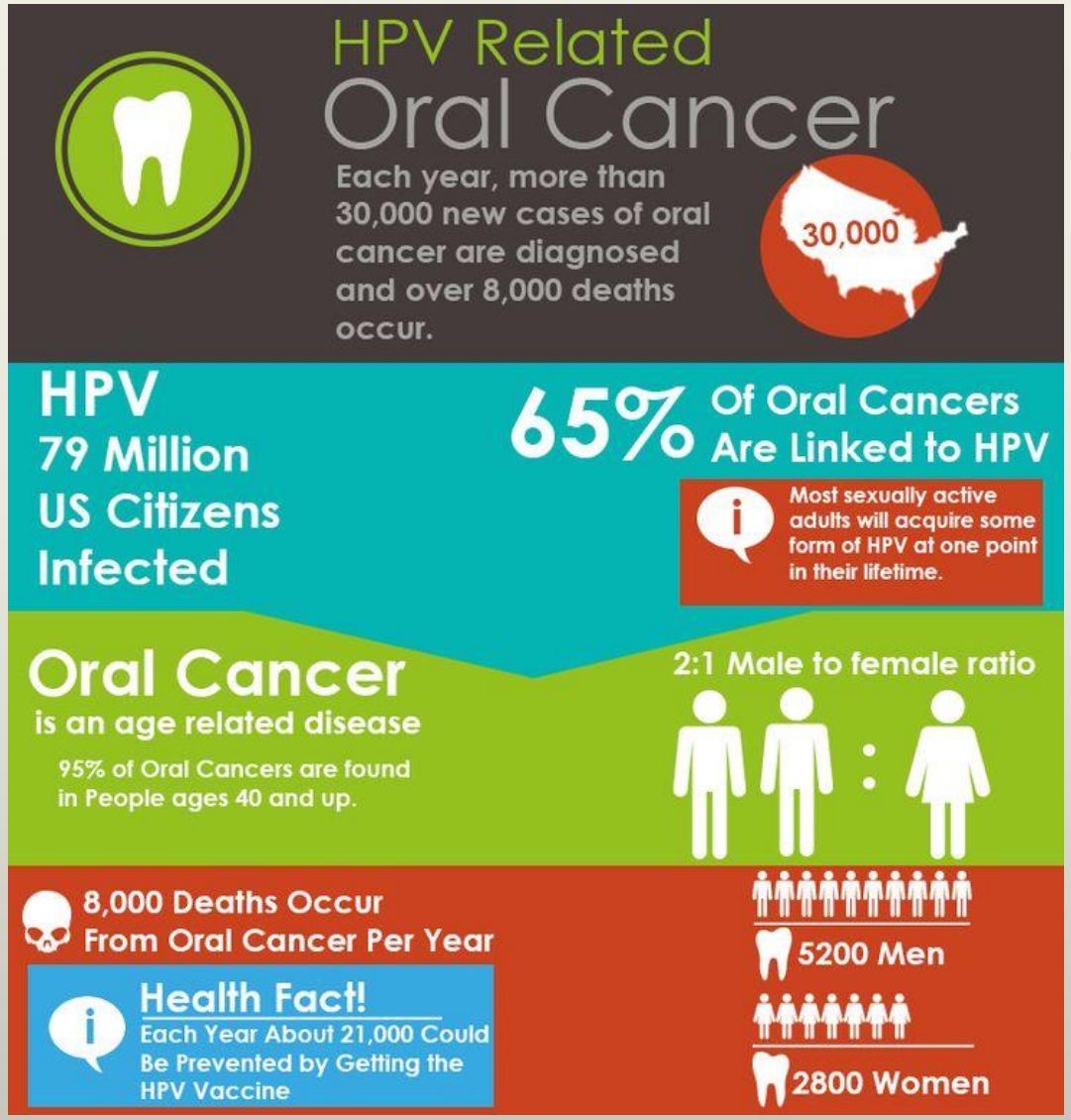
Percentages represent cases atrributable to HPV infection

Braaten KP et al. Rev Obstet Gynecol. 2008;1:2–10.

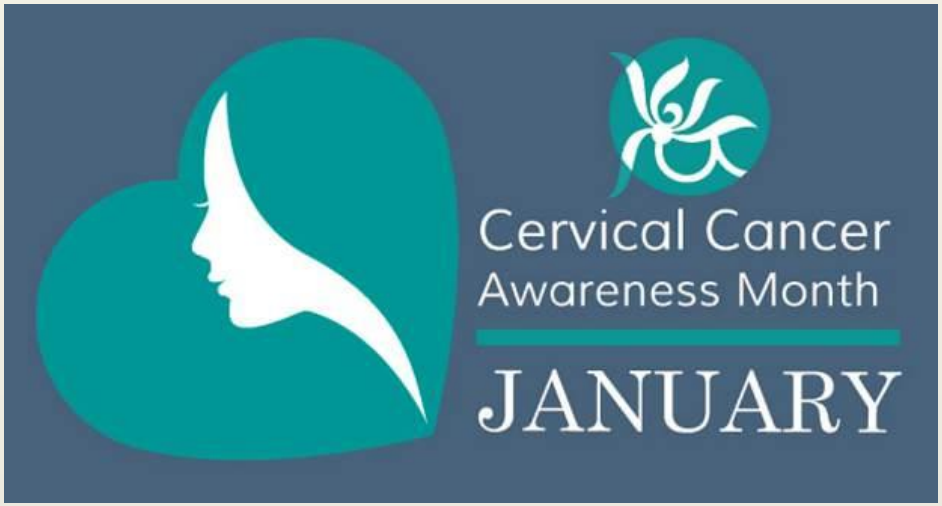
Hoots BE et al. Int J Cancer. 2009;124:2375–2383.

IARC. IARC monographs on the evaluation of carcinogenic risks to humans. Human papillomaviruses. Vol 90. Lyon, France: IARC, 2007.

Epidemiology



Screening



- Cervical cancer screening is an essential part of a woman's routine health care.
- It is a way to detect abnormal cervical cells, including precancerous cervical lesions, as well as early cervical cancers.
- Routine cervical screening has been shown to greatly reduce both the number of new cervical cancers diagnosed each year and deaths from the disease.

Source: https://www.cancer.gov/types/cervical/pap-hpv-testing-fact-sheet

Screening

- Cervical cancer screening includes two types of screening tests: cytology-based screening, known as the Pap test or Pap smear, and HPV testing.
- The main purpose of screening with the Pap test is to detect abnormal cells that may develop into cancer if left untreated. The Pap test can also find noncancerous conditions, such as infections and inflammation
- The Pap test identifies most abnormal cells before they become cancer.

Source: https://www.cancer.gov/types/cervical/pap-hpv-testing-fact-sheet

Screening

- HPV testing is used to look for the presence of high-risk HPV types in cervical cells. These tests can detect HPV infections that cause cell abnormalities, sometimes even before cell abnormalities are evident.

- Several different HPV tests have been approved for screening. Most tests detect the DNA of high-risk HPV, although one test detects the RNA of high-risk HPV.

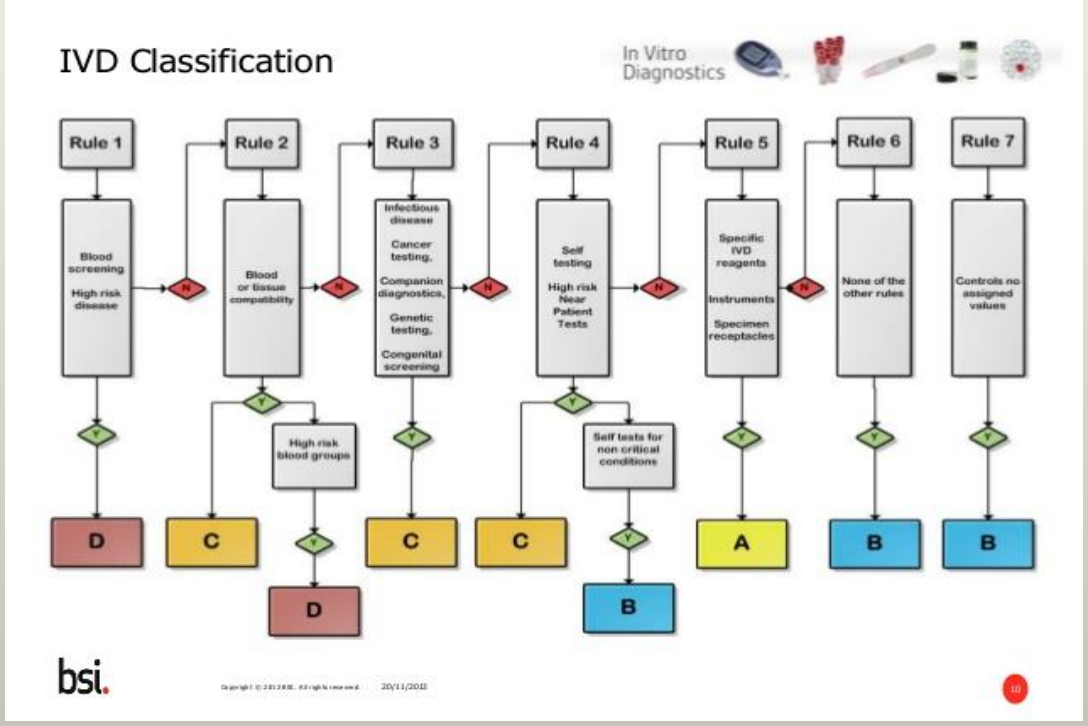
- HPV vaccination does not replace cervical cancer screening. In countries where HPV vaccine is introduced, screening programs may still need to be developed or strengthened.

Source: https://www.cancer.gov/types/cervical/pap-hpv-testing-fact-sheet

Regulatory Landscape

US
Class 3 devices

EU
IVDD – Self-certification
IVDR - Typically Class C (screening; staging of cancer)



US Diagnostic Landscape

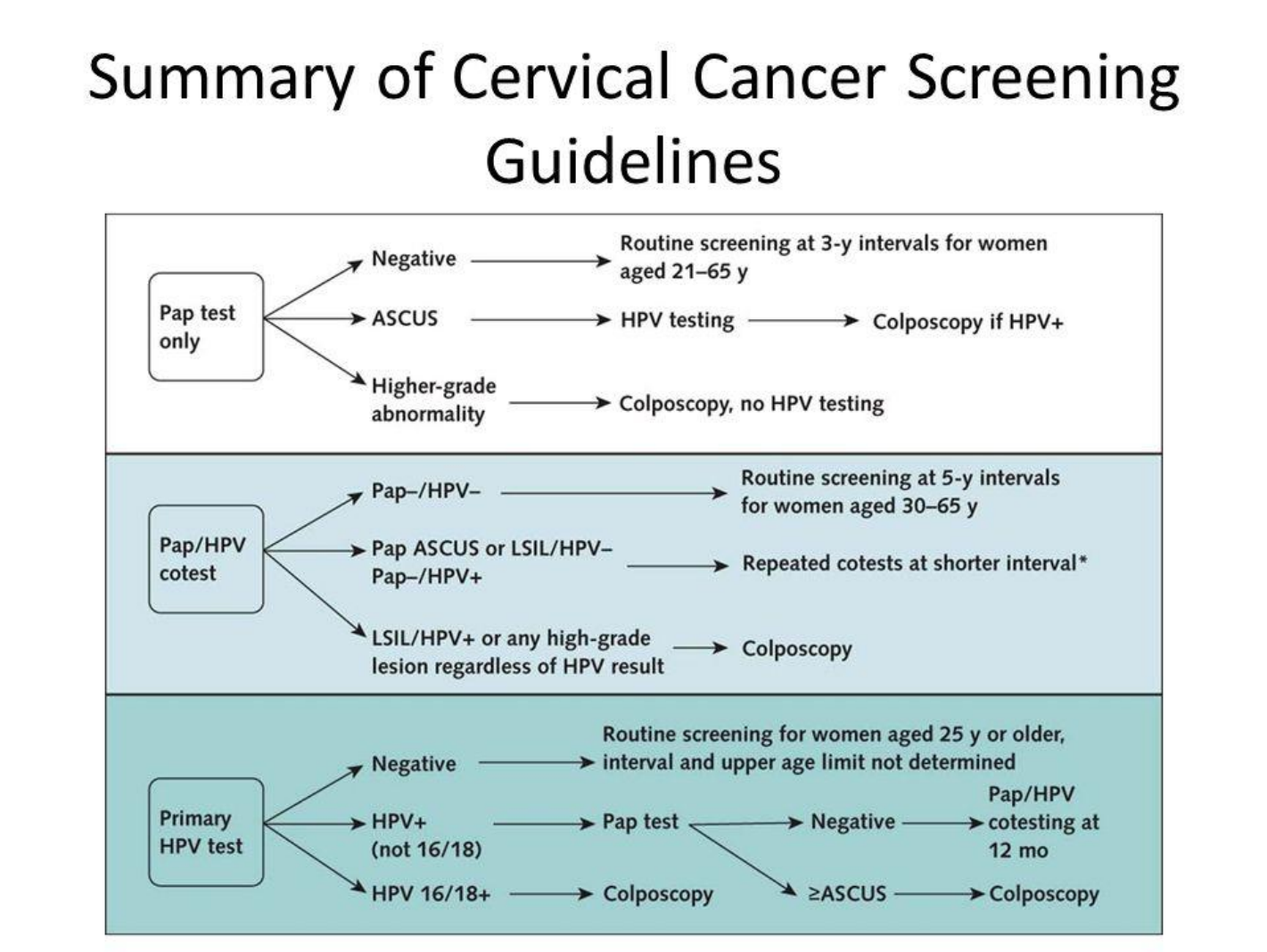
- BD FOX PCR Extraction Tubes; BD Onclarity HPV Assay LBC Diluent; BD Onclarity™ HPV Assay; BD Viper PCR Extraction Reagent Trough with Piercing Tool; Control set for the BD Onclarity HPV Assay
  BECTON, DICKINSON & CO.
- Cervista HPV HR High-Throughput Automation (HTA); Cervista HPV HR Test Kit(s)
  HOLOGIC, INC.
- digene® HC2 High-Risk HPV DNA Test; digene® HC2 High-Risk HPV DNA Test (4 plate); digene® HC2 HPV DNA Test; DML 3000
  digene® HPV Genotyping PS Test
  QIAGEN
- cobas HPV Test; cobas x480 system; cobas z480 Analyzer; cobas z480 system
  ROCHE MOLECULAR SYSTEMS, INC
- INFORM HPV II Family 6 Probe; INFORM HPV III Family 16 Probe (B); KIT cobas 4800 HPV AMP/DET 960T CE-IVD; KIT COBAS 6800/8800 HPV 480T IVD; KIT COBAS 6800/8800 HPV RMC IVD
  VENTANA MEDICAL SYSTEMS, INC.

EU Diagnostic Landscape…

- Hybrid Capture 2, QIAGEN
- Digene HPV genotypingRH, QIAGEN
- Digene HPV genotypingLX , QIAGEN
- AmplicorHPV, Roche
- Cobas4800 HPV, Roche
- Linear array, Roche
- SPF10/LiPa, DDL
- NucliSensEasyQHPV, Biomerieux
- Aptima, Gen-Probe
- CervistaHPV HR, Hologic
- BIOPAP QTS HPV, Loxo
- Reveal HPV Real-Time HPV, GenoID
- AID STD, GenID
- AID HPV screening, GenID
- AID HPV typing, GenID
- Linear ArrayExtraHPV Genotyping, Innogenetics
- PCR Human Papillomavirus Detection, Takara MirusBio
- HPV DNA Chip, Biomedlab
- Array Papillomavirus, Genomica
- ProDectChip HPV typing, BcsBiotech S.P.A
- PapType, Genera Biosystems
- LCD Array HPV 3.5, Chipron
- Abbott RT HR HPV, Abbott
- AnyplexII HPV28, Seegene®
- HPV riskTestSelf-Screen, ViroactivVirofem
- HPV OncoTest, InvirionDiagnostics
- GenpointTm HPV, Dako-Oxoid
- LuminexHPV Genotyping, Multimetrix/Progen
- PapillocheckGreiner, BioOne
- PreTectHPV Proofer, Norchip
- GP5+/6+-PCR, Diassay
- BD Onclarity HPV, Becton Dickinson

…for the time being

Practice Guidelines



Source: https://www.lvhn.org/conditions_treatments/cancer/cervical_cancer/why_choose_us/cervical_cancer_screening_updates

Practice Guidelines

ACOG guidelines reflect these age-based recommendations for cervical cancer screening[3]

Age	Pap†	High-risk HPV	HPV genotyping
Under 21	Not recommended	Not recommended	Not recommended
21 - 29	Recommended every 3 years	Recommended to be used as a *"reflex test"* only when Pap result is ASC-US	Not recommended
30 - 65	Recommended co-testing (using Pap and HPV concurrently) every 5 years (preferred), or cytology alone every 3 years		Option to use as *"reflex test"* in co-tested patients whose Pap is negative and HPV result is positive
Over 65	Screening should be discontinued if patient has had adequate negative prior screening results‡ and no history of CIN2+ Recommend continuing age-based screening for ≥20 years in those patients with a history of CIN2, CIN3, or adenocarcinoma *in situ*		

Source: https://www.lvhn.org/conditions_treatments/cancer/cervical_cancer/why_choose_us/cervical_cancer_screening_updates

Practice Guidelines

August 21, 2018 – The U.S. Preventive Services Task Force released today a final recommendation statement on screening for cervical cancer. The Task Force found that women aged 21 to 65 years benefit from screening.

USPSTF Recommendations:

1) Pap test for women aged 21 to 29 years

2) Three strategies to screen women aged 30 to 65 years: Pap test, HPV test, or both in combination (cotesting).

3) No screening in women younger than 21 years and in women older than 65 years who have had adequate prior screening.

4) No screening at any age in women who do not have a cervix.

The final recommendation statement can also be found in the August 21 online issue of JAMA.USPSTF

Practice Guidelines

Roche's cobas HPV Test receives FDA approval for first-line cervical cancer screening using SurePath preservative fluid
Tucson, July 30, 2018

Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that it has received U.S. Food and Drug Administration (FDA) approval for the cobas® HPV Test to be used as the first-line screening test for cervical cancer in women 25 and older using cervical specimens collected in SurePath preservative fluid, a collection medium commonly used for Pap tests. The Roche test is now the only Human Papillomavirus (HPV) test approved for use as a primary (first-line) screening test with both SurePath and ThinPrep PreservCyt Solution, the two types of liquid media used to collect samples for the vast majority of Pap or HPV tests in the U.S.

With this FDA decision, the cobas HPV Test is now approved for all of the cervical cancer screening indications that are supported by professional society guidelines—primary screening in women 25 and older, reflex (follow-up) testing of unclear Pap test results in women 21 and older and co-testing with a Pap test in women 30 and older—with both of the primary collection media types.

Diagnostic Landscape

Ireland's Cervical Check Controversy – September 2018

- Cervical Check is a free smear test (cytology) offered to women 25 to 60 years of age.
- One woman screened as all clear in 2013 developed cervical cancer 3 years later. She died from the disease on Oct. 7, 2018.
- Review of Cervical Check program identified more than 400 cases that should have undergone further review

Cervical cancer developed in 206 of those cases

HPV Vaccines

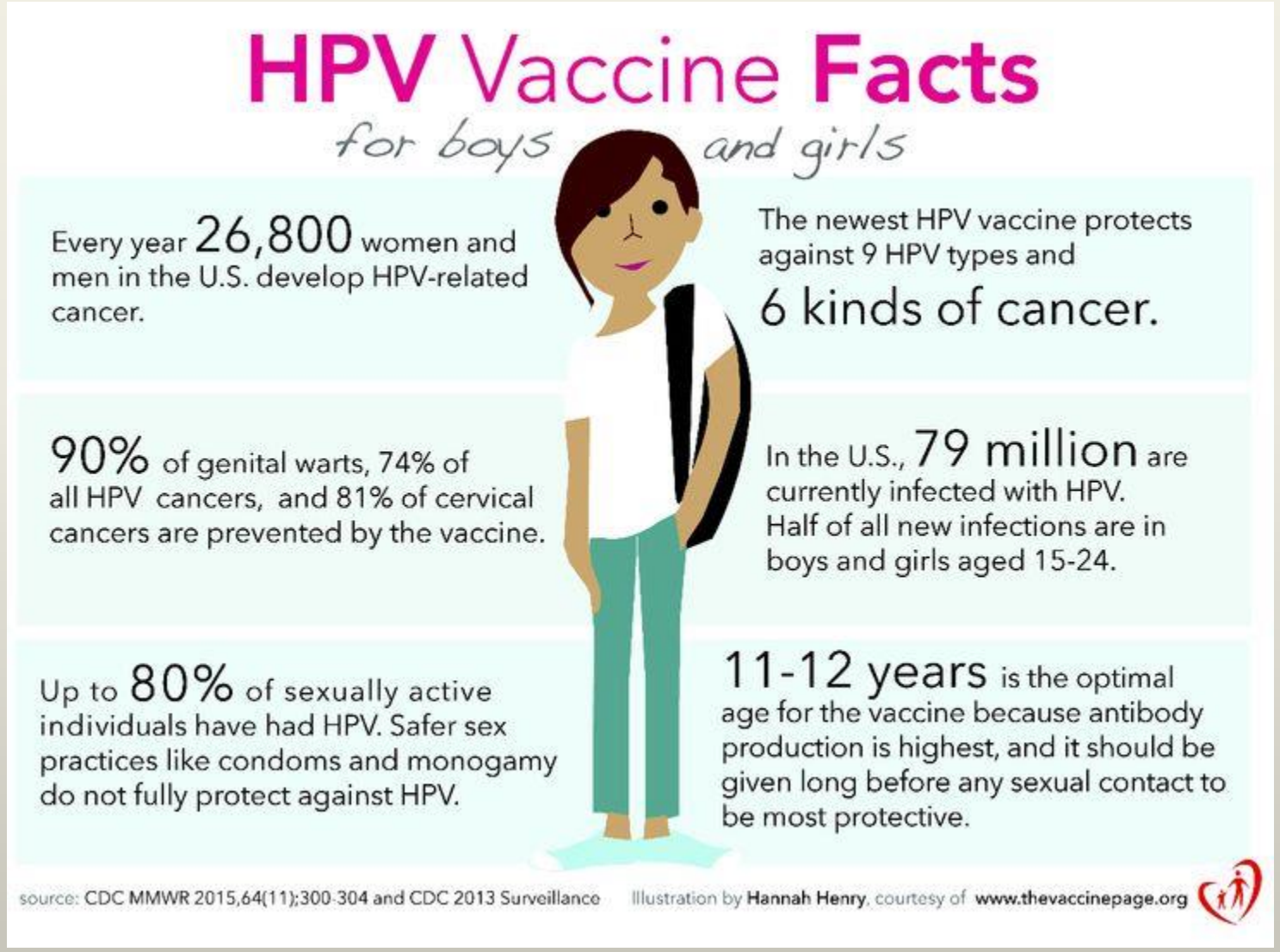
FDA (CBER) and EMA

Gardasil
Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant
- 90% of genital warts and 70% of HPV-related cancers

Cervarix
Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant
- Different adjuvant conferring higher immune response

Gardasil 9
Human Papillomavirus 9-valent Vaccine (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant
- 90% of genital warts and 90% of HPV-related cancers

HPV Vaccines



HPV Vaccines

FDA News Release

FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old

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For Immediate Release October 5, 2018

Release

The U.S. Food and Drug Administration today approved a supplemental application for Gardasil 9 (Human Papillomavirus (HPV) 9-valent Vaccine, Recombinant) expanding the approved use of the vaccine to include women and men aged 27 through 45 years. Gardasil 9 prevents certain cancers and diseases caused by the nine HPV types covered by the vaccine.

"Today's approval represents an important opportunity to help prevent HPV-related diseases and cancers in a broader age range," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research. "The Centers for Disease Control and Prevention has stated that HPV vaccination prior to becoming infected with the HPV types covered by the vaccine has the potential to prevent more than 90 percent of these cancers, or 31,200 cases every year, from ever developing."

According to the CDC, every year about 14 million Americans become infected with HPV; about 12,000 women are diagnosed with and about 4,000 women die from cervical cancer caused by certain HPV viruses. Additionally, HPV viruses are associated with several other forms of cancer affecting men and women.

Gardasil, a vaccine approved by the FDA in 2006 to prevent certain cancers and diseases caused by four HPV types, is no longer distributed in the U.S. In 2014, the FDA approved Gardasil 9, which covers the same four HPV types as Gardasil, as well as an additional five HPV types. Gardasil 9 was approved for use in males and females aged 9 through 26 years.

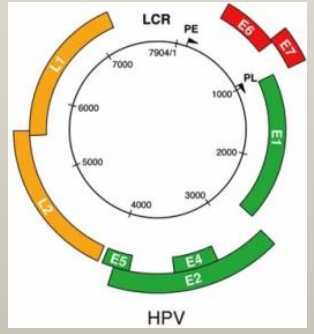
Future of HPV Testing

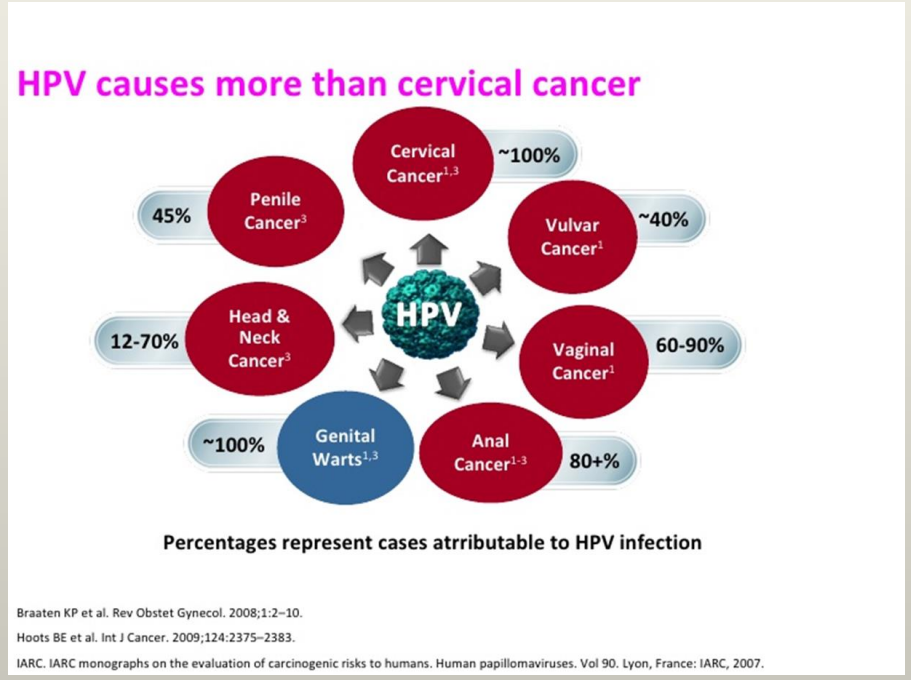
Primary: Cervical Cancer Screening

- Will HPV tests replace cytology?
- Do molecular tests become more sophisticated, i.e. , as a prognostic?

Secondary:
Other HPV-related cancers

- Does HPV diagnosis impact patient treatment decisions?

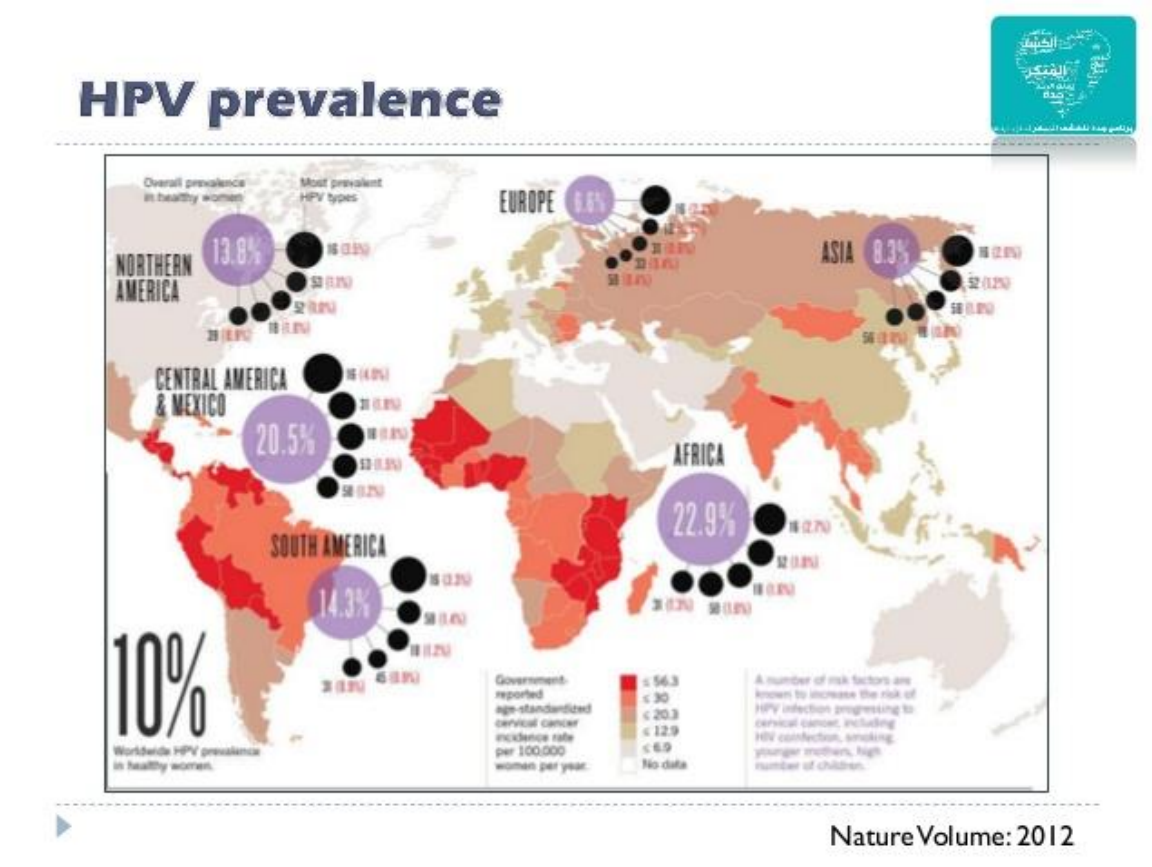




Future of HPV Testing

What is the long term impact of vaccinations on HPV prevalence?

And on what time horizon?



Questions?