

Current HPV tests



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UZ/U Gent – UHasselt

Symposium “HPV – future challenges”
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Cervical cancer: **role of human papillomavirus (HPV)**



Harald zur Hausen

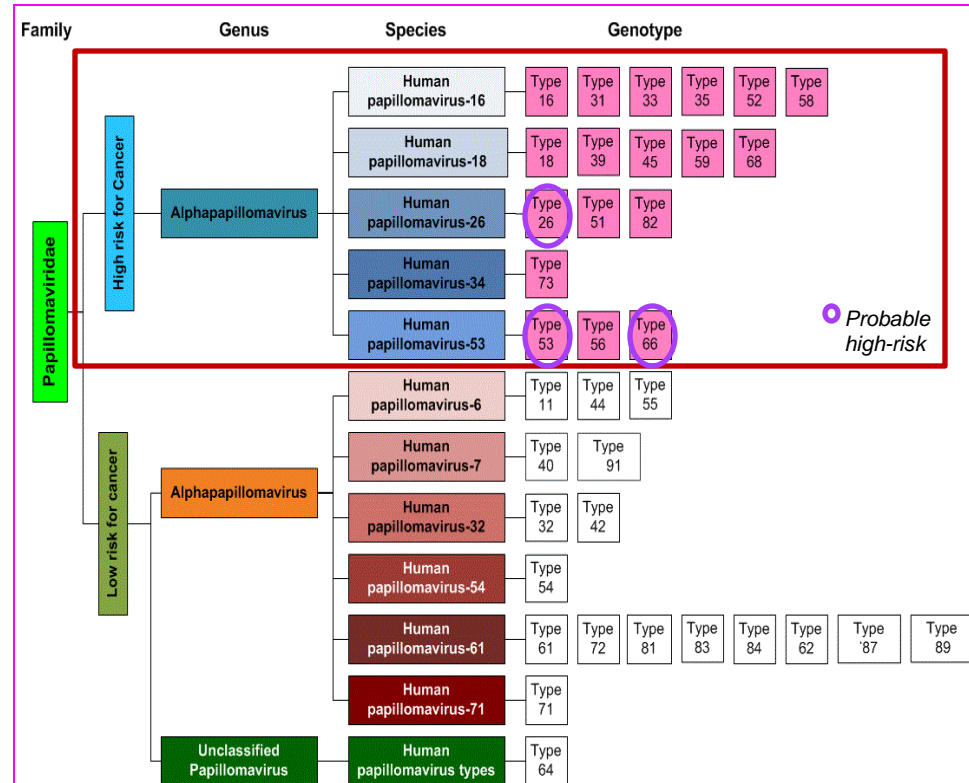
Infection with certain types of HPV is the primary risk factor for the development of cervical cancer and its precursor lesions

Cervical cancer: role of human papillomavirus (HPV)



Harald zur Hausen

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Clifford et al., *Br J Cancer* 2003;88:63-73

Munoz et al., *N Engl J Med.* 2003 Feb 6;348(6):518-27

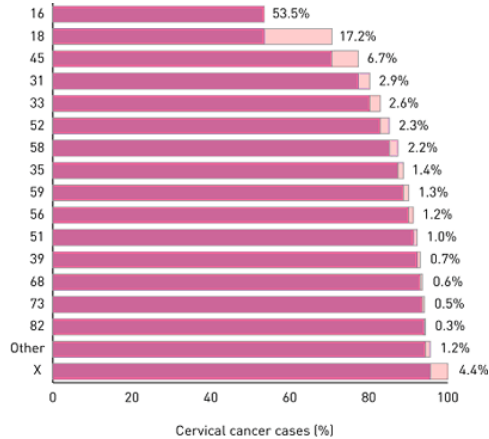
Smith et al., *Int J Cancer* 2007;121:621-32

Cervical cancer: role of human papillomavirus (HPV)

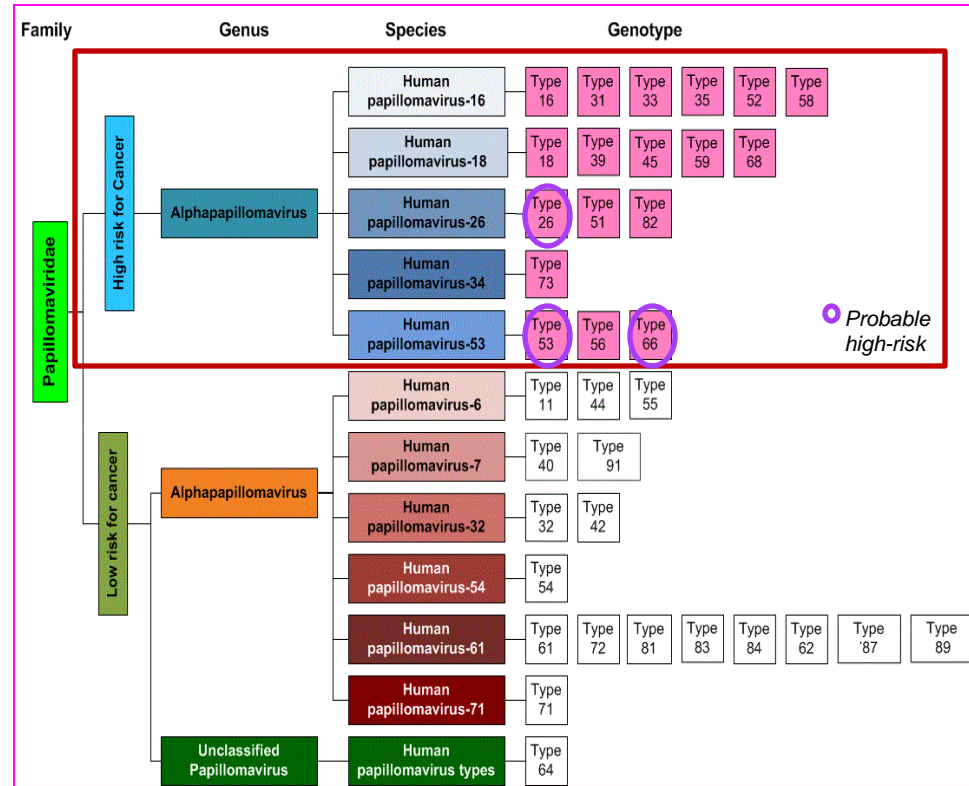


Harald zur Hausen

Infection with **certain types of HPV** is the primary risk factor for the development of cervical cancer and its precursor lesions



Cervical cancer cases attributed to the most frequent HPV types



- ✓ HPV 16, 18, 45, 31, 33, 52, 58 and 35 (= **8 most common genotypes**) are responsible for **~90%** of all cervical cancers
- ✓ Cervical adenocarcinoma:
 - ✓ 10-20% of all cervical cancers
 - ✓ Almost solely related to HPV 16, 18 and 45

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Current HPV tests: **variety**



Current HPV tests: **variety**

Hybrid Capture 2 (HC2) HPV DNA Test (QIAGEN Inc., Gaithersburg, MD, USA (previously Digene Corp.))
EIA kit HPV GP HR (Diassay, Rijswijk, The Netherlands)
Cervista® HPV HR Test (Hologic, Madison, WI)
CareHPV™ Test (QIAGEN Inc., Gaithersburg, MD, USA)
Amplicor HPV Test (Roche Molecular Systems Inc., Alameda, CA, USA)
HPV4A ACE Screening CE (Seegene, Seoul, Korea)
HPV/STD4 ACE Screening CE (Seegene, Seoul, Korea)
13 High-risk HPV Real Time PCR (HybriBio, Beijing, China)
Biorad Dx HR-HPV Test (Bio-Rad)
Urine-Based HPV (High and Low Risk) PCR Detection Kit (Norgen, Thorold, Canada)
Absolute HPV HR Test (BioSewoom, Seoul, Korea)
HPV High Risk Screen (Sacace, Como, Italy)
HPV High Risk Screen FEP (Sacace, Como, Italy)
HPV High Risk Screen Real-TM Quant (Sacace, Como, Italy)
HPV High Risk Screen Real-TM Quant 2 x (Sacace, Como, Italy)
STD kit (Autoimmun Diagnostika GmbH, Strassberg, Germany)
Human (hPV) 12 Multiplex Real-time PCR Kit (USBio, Swampscott, MS)
Biovue's Sharpvue HPV detection kit (Biovue Technology Ltd, Shanghai, China)
AmpliSens® HPV HCR screen-Eph PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)
AmpliSens® HPV HCR screen-titre-FRT PCR kit (2x;4x) (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)
AmpliSens® HPV HCR screen-FEP PCR kit (3x) (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)
HPV-DNA Assay Kit (Tofema, Seoul, Korea)
HPV Total & High Risk (Clonit, Milano, Italy)
cobas® 4800 HPV Test (Roche Molecular Systems Inc., Alameda, CA, USA)
RealTime High Risk HPV test (Abbott Molecular, Des Plaines, IL)
BD Viper HPV Test/BD HPV-GT Assay (BD Diagnostics, Sparks, MD)
14 High-risk HPV with 16/18 Genotyping Real-time PCR Kit (HybriBio, Beijing, China)
Realquality RQ-HPV HR (AB Analitica, Padova, Italy)
GenoFlow HPV-HR Screening Test (DiagCor Bioscience, Hong Kong)
AID HPV screening kit (Autoimmun Diagnostika GmbH, Strassberg, Germany)
AdvanSure HPV Screening real-time PCR (LGLS Diagnostics, Seoul, Korea)
GenoID Real-time HPV test (GenoID, Budapest, Hungary)
AmpliSens® HPV HCR screen-FEP PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)
RealLine HPV High Risk, Genotype (Str-format); (Fla-format) (Bioron Diagnostics GmbH, Ludwigshafen, Germany)
RealLine HPV High Risk, Genotype quantitative (Str-format) (Bioron Diagnostics GmbH, Ludwigshafen, Germany)
Cervista® HPV 16/18 Test (Hologic, Madison, WI)
digene® HPV Genotyping PS Test, RUO (Qiagen Gaithersburg, Inc., MD, USA (previously Digene Corp.))
HPV 16/18 Real-TM Quant (Sacace, Como, Italy)
Human papillomavirus 16/18 (Sacace, Como, Italy)
HPV 16/18 FEP (Sacace, Como, Italy)
HPV-TS-16 and HPV-TS-18 PCR-DEIA (Labo Bio-medical Products, Ev Rijswijk, The Netherlands)
HPV-TS-31 and HPV TS-45 PCR-DEIA (Labo Bio-medical Products, Ev Rijswijk, The Netherlands)

Current HPV tests: **variety**

AmpliSens® HPV 16/18-FRT PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli s.r.o, Bratislava, Slovak Republic)
AmpliSens® HPV 16/18-EPh PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli s.r.o, Bratislava, Slovak Republic)
AmpliSens® HPV 16/18-FEP PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli s.r.o, Bratislava, Slovak Republic)
Linear Array® HPV Genotyping Test (Roche Molecular Systems Inc., Alameda, CA, USA)
HPV SPF10 LiPA25_{version 1} (Labo Bio-Medical Products, Ev Rijswijk, The Netherlands)
HPV PCR-DEIA (SPF10) (Labo Bio-Medical Products, Ev Rijswijk, The Netherlands) + HPV SPF10 LiPA25_{version 1}
INNO-LiPA HPV Genotyping Extra (Innogenetics NV, Gent, Belgium)
digene® HPV Genotyping RH Test (Qiagen Gaithersburg, Inc., MD, USA (previously Digene Corp.))
EasyChip® HPV Blot Kit (King Car, Taiwan)
REBA HPV-ID (Catch by Gene, Gangwon-do, Korea)
PGMY-CHUV low cost Test (World Health Organisation)
AmpliQuality HPV-type (AB Analitica, Padova, Italy)
AmpliQuality HPV-type HR (AB Analitica, Padova, Italy)
AmpliQuality HPV-type express (AB Analitica, Padova, Italy)
AmpliQuality HPV-type HS (AB Analitica, Padova, Italy)
GenoFlow HPV Array Test (DiagCor Bioscience, Hong Kong, China)
HPV Direct-Flow Chip (Master Diagnostica, Granada, Spain; Hospitex Diagnostics, Firenze, Italy)
AID HPV typing kit (Autoimmun Diagnostika GmbH, Strassberg, Germany)
Full Spectrum Genital Human Papillomavirus PCR Amplification and Genotyping Kit (GenoID, Budapest, Hungary)
PapillomaStrip High Risk (Operon, Zaragoza, Spain)
PapillomaStrip Low Risk (Operon, Zaragoza, Spain) PapilloCheck® HPV-Screening Test (Greiner Bio-One, Frickenhausen, Germany)
PapilloCheck® High-risk Test (Greiner Bio-One, Frickenhausen, Germany)
Clart® HPV 2 - Papillomavirus Clinical Arrays (Genomica, Coslada, Spain)
21 HPV GenoArray Test Kit (HybriBio Limited, Hong Kong)
GeneTrack HPV DNA Chip (Genomic Tree, Daejeon, South Korea)
GeneSQUARE HPV Microarray (Kurabo Industries, Osaka, Japan)
Infiniti® HPV Genotyping Test (AutoGenomics, Carlsbad, CA)
Infiniti® HPV-HR Quad Test (AutoGenomics, Carlsbad, CA)
Infiniti® HPV-Quad Test (AutoGenomics, Carlsbad, CA)
PANArray™ HPV Genotyping Chip (PANAGENE, Daejeon, Korea)
HPVDNAChip (Biomedlab, Seoul, South Korea)
GG HPVCHIP (GoodGene, Seoul, Korea)
BMT HPV 9G DNA Kit™ (Biometrix Technology, Chuncheon, Korea)
BMT HPV Genotyping 9G Membrane Kit (Biometrix Technology, Chuncheon, Korea)
ProDect® Chip HPV Typing kit (Bcs Biotech, Cagliari, Italy)
HPV type 3.5 LCD-Array Kit (Chipron, Berlin, Germany)
Decipher HPV23^{genotyping DNA chip} (Yaneng Bioscience, Shenzhen, China)
Multiplex HPV Genotyping Kit (Progen/Multimetrix, Heidelberg, Germany)
digene® HPV Genotyping LQ Test (Qiagen Gaithersburg, Inc., MD, USA (previously Digene Corp.))
PapType HR HPV detection and genotyping (Genera Biosystems, Melbourne, Australia)
GENOSEARCH-HPV31 (Medical & Biological Laboratories, Nagoya, Japan)
Tellgenplex™ High-risk HPV Genotyping Panel (Tellgen, Shanghai, China)

Current HPV tests: **variety**

Tellgenplex™ 26 HPV Genotyping Panel (Tellgen, Shanghai, China)
HPV genotyping kit (PlexBio, Taipei, Taiwan)
HPV Liquid Beads Microarray Genotype PCR Kit (Innomeditech, Seoul, Korea)
HPV Liquid Beads Microarray Genotype Kit (Innomeditech, Seoul, Korea)
BIOTYPAP Kit (Biotools, Madrid, Spain)
PCR Human Papillomavirus Typing Set (Takara Bio Inc, Shiga, Japan)
Human papilloma virus genotyping (Genekam Biotechnology, Duisburg, Germany)
f-HPV typing™ (Genomed Diagnostics, Wollerau, Switzerland; Molgentix, Barcelona, Spain)
HPV High Risk Typing (Sacace, Como, Italy)
HPV High Risk Screen Real-TM (Sacace, Como, Italy)
AmpliSens® HPV HCR genotype-FRT PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)
Uterine Cervix Cancer of High-risk HPV Genotype Related Real Time PCR Kit (Liferiver, Shanghai, China)
High-risk HPV 13 Genotypes Related Real-time PCR Kit (Liferiver, Shanghai, China)
SuperFast HPV 12 Multiplex Real-time PCR Kit (Kogenebiotech, Seoul, Korea)
HPV MassArray (Sequenom, San Diego, CA)
AdvanSure HPV 16/18 real-time PCR (LGLS Diagnostics, Seoul, Korea)
Human papilloma virus HPV (16, 18) (DNA-Technology LLC, Moscow, Russia)
HPV 16 & 18 Real Time PCR Kit (Liferiver, Shanghai, China)
HPV 6 & 11 Real Time PCR Kit (Liferiver, Shanghai, China)
Quantification of Human Papillomavirus 6; 11; 16; 18; 33; 52; 58 (*PrimerDesign*, Southampton, UK)
AmpliSens® HPV 6/11-FRT PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)
AmpliSens® HPV 6/11-FEP PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)
AccuPower® HPV16 & 18 Real-Time PCR Kit (Bioneer, Daejeon, Korea)
Human Papilloma Virus (HPV-16) (high risk profile) (Genekam Biotechnology, Duisburg, Germany)
Human Papilloma Virus (HPV-18) (high risk profile) (Genekam Biotechnology, Duisburg, Germany)
SuperFast HPV 16, 18, 6, 11 Multiplex Real-time PCR Kit (Kogenebiotech, Seoul, Korea)
SuperFast HPV 16, 18 Multiplex Real-time PCR Kit (Kogenebiotech, Seoul, Korea)
SuperFast HPV 5 Low risk Multiplex Real-time PCR Kit (Kogenebiotech, Seoul, Korea)
Human Papilloma Virus (HPV) (Types 16 and 18) PCR Kit (Daan Diagnostics, Burnaby, Canada)
Human Papilloma Virus (HPV) (Types 6 and 11) PCR Kit (Daan Diagnostics, Burnaby, Canada)
High-risk Human Papilloma Virus (HR-HPV) PCR Kit (Daan Diagnostics, Burnaby, Canada)
RealLine HPV 16/18; 52/56; 51/58; 35/45; 31/33; 6/11 (Str-format) (Bioron Diagnostics GmbH, Ludwigshafen, Germany)
RealLine HPV 16/18; 52/56; 51/58; 35/45; 31/33; 6/11 (Fla-format) (Bioron Diagnostics GmbH, Ludwigshafen, Germany)
Human papilloma virus, HPV (6, 11) (DNA-Technology LLC, Moscow, Russia)
HPV, Mixed Type, L1 Genes Primer Set (Maxim Biotech, Rockville, MD)
HPV-1; HPV-6; HPV-11; HPV-16; HPV-18; HPV-31; HPV-33; E6 Gene Primer Set (Maxim Biotech, Rockville, MD)
MPCR Kit for Human Papillomavirus (Maxim Biotech, Rockville, MD)
AmpliSens® HPV 31/33-EPh PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)
AmpliSens® HPV 35/45-EPh PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)
AmpliSens® HPV 6/11-EPh PCR kit (Federal State Institution of Science, Moscow, Russia; Ecoli, Bratislava, Slovak Republic)

Current HPV tests: **variety**

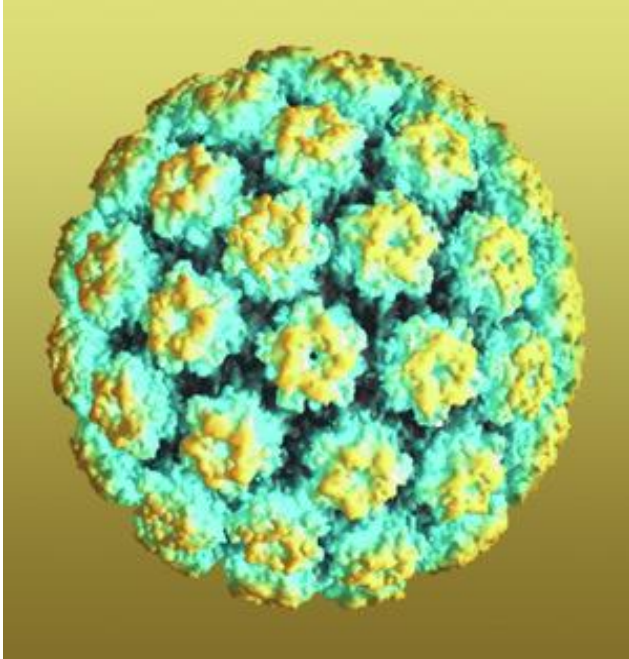
HPV-2; HPV-4; HPV-7 (Genekam Biotechnology, Duisburg, Germany) HPV-16; HPV-16/18; HPV-18; HPV-31; HPV-33; HPV-35; HPV-39 (Genekam Biotechnology, Duisburg, Germany)
HPV-51; HPV-56; HPV-58; HPV-59; HPV-66; HPV-68 (Genekam Biotechnology, Duisburg, Germany) HPV-6; HPV-6/11; HPV-11 (Genekam Biotechnology, Duisburg, Germany)
HPV-42; HPV-43; HPV-44; HPV-45 (Genekam Biotechnology, Duisburg, Germany)
APTIMA® HPV Test (Gen-Probe Inc., San Diego, CA)
PreTect HPV-Proofer (NorChip, Klokkestua, Norway)
NucliSENS EasyQ® HPV (Biomerieux, Marcy l'Etoile, France)
Quantivirus™ HPV E6/E7 RNA 3.0 Assay (bDNA) (DiaCarta LLC, Hayward, CA)
INFORM HPV II Family 6 Probe (B) (Ventana, Tucson, AZ)
INFORM HPV III Family 16 Probe (B) (Ventana, Tucson, AZ)
GenPoint™ HPV Biotinylated DNA probe (Types 16/18/31/33/35/39/45/51/52/56/58/59/68) (Dako, Glostrup, Denmark)
Wide Spectrum HPV Biotinylated DNA Probe (Types 6/11/16/18/31/33/35/39/45/51/52) (Dako, Glostrup, Denmark)
HPV Types 6/11; 16/18; 31/33 Biotinylated DNA Probes (Dako, Glostrup, Denmark)
ZytoFast HPV type 6/11; 16/18; 31/33 Probes (ZytoVision, Bremerhaven, Germany)
ZytoFast HPV type 16/18/31/33/35 Probe (ZytoVision, Bremerhaven, Germany)
ZytoFast HPV type 16/18/31/33/35/45/51/82 Probe (ZytoVision, Bremerhaven, Germany)
ZytoFast HPV type 6/11/16/18/31/33/35 Screening Probe (ZytoVision, Bremerhaven, Germany)
ZytoFast HPV type 6/11/16/18/31/33/35/45/51/82 Screening Probe (ZytoVision, Bremerhaven, Germany)
HPV Screening (HPV6/11/16/18/31/33) (PanPath, Amsterdam, The Netherlands)
HPV typing: HPV 6; 11; 16; 18; 31; 33; 6/11; 16/18; 31/33 DNA probe (PanPath, Amsterdam, The Netherlands)
HPV In Situ Hybridization/Detection Kit (Types 6/11/16/18/31/33) (Maxim Biotech, Rockville, MD)
HPV In Situ Hybridization/Detection Kit (Types 6/11) (Maxim Biotech, Rockville, MD)
HPV In Situ Hybridization/Detection Kit (Types 16/18) (Maxim Biotech, Rockville, MD)
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- ✓ **Unusually excessive variety of commercially available tests**
- ✓ **HPV is the most interesting microbial target for molecular diagnostic companies**
- ✓ **HPV tests are one of the least regulated on the market:**
 - only 10-15% of available tests have **documented clinical performance**
 - >75% of tests **do not have a single publication** in peer-reviewed literature

Molecular HPV testing: **particular feature**



✓ **Analytic sensitivity** for the detection of HPV is not the prime driver of test performance

✓ The majority of currently available tests have **high analytic sensitivity without established clinical cut-offs** leading to a substantial yield of clinically insignificantly positives

→ **false referrals** for colposcopy and biopsy

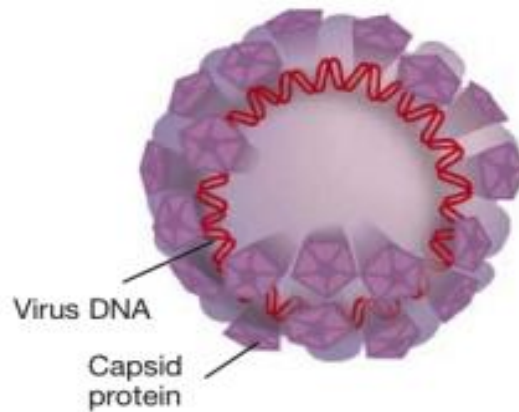
→ decreased correlation with histology

→ **unnecessary treatment of healthy women**

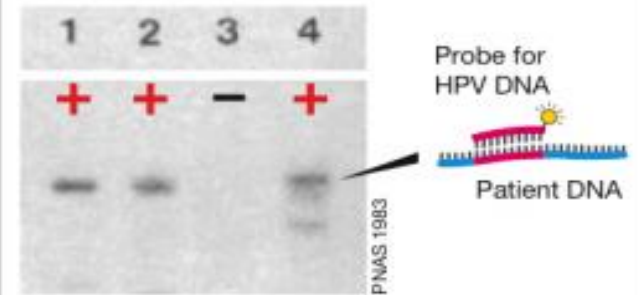
HPV – human papilloma virus

HPV has a circular, double stranded DNA, protected by capsid proteins.

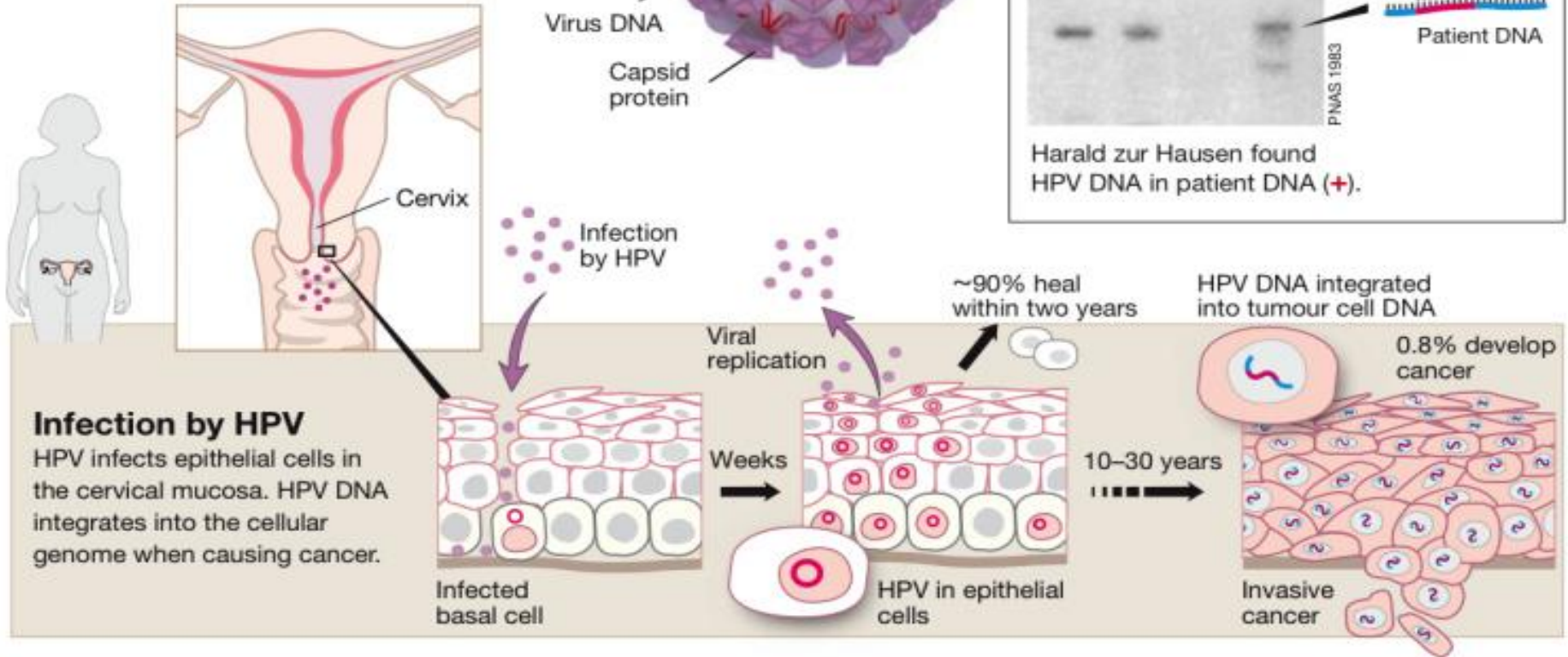
More than 100 HPV-types are known. HPV16 and 18 cause 70% of all cervix cancers.



Discovery of HPV DNA in cancer cells



Harald zur Hausen found HPV DNA in patient DNA (+).



Infection by HPV

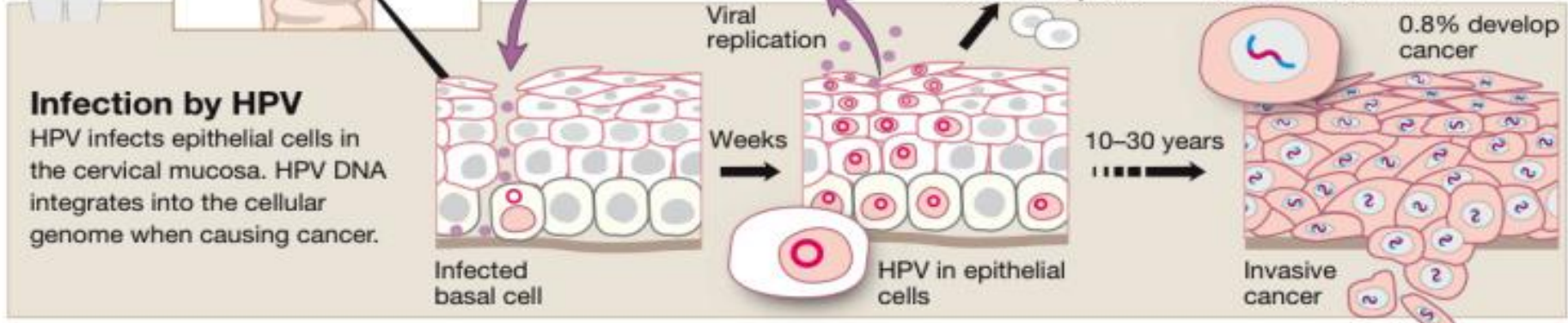
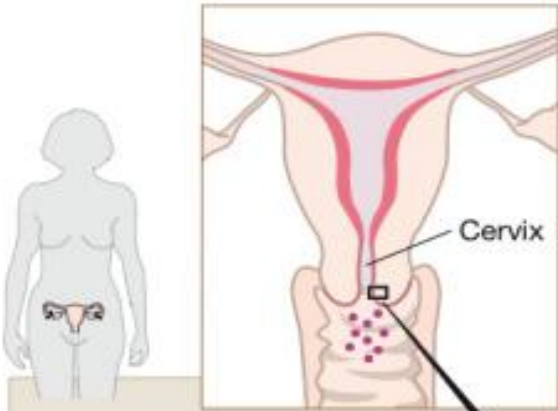
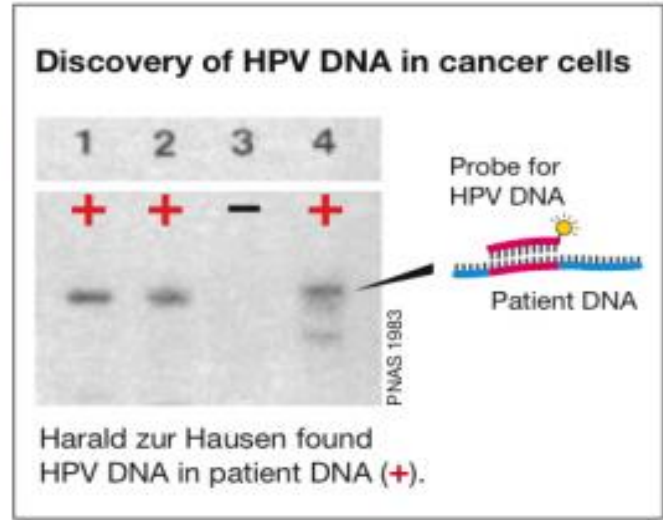
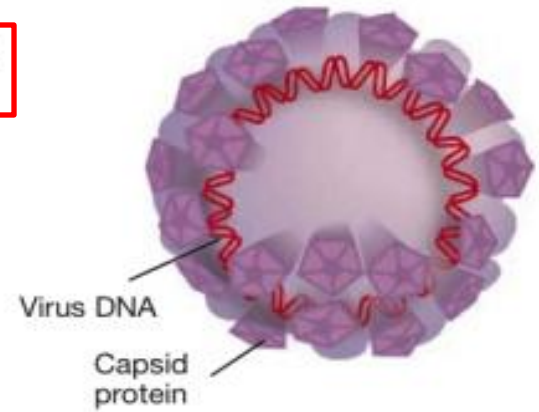
HPV infects epithelial cells in the cervical mucosa. HPV DNA integrates into the cellular genome when causing cancer.

HPV – human papilloma virus

hrHPV DNA

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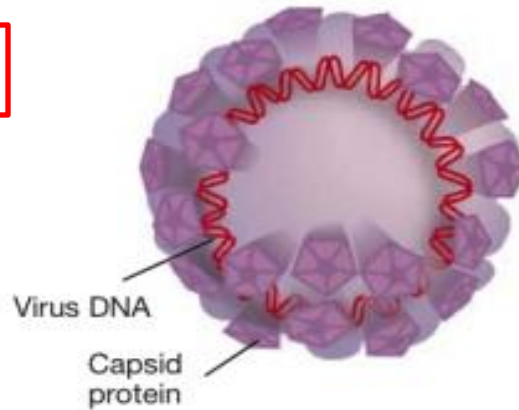
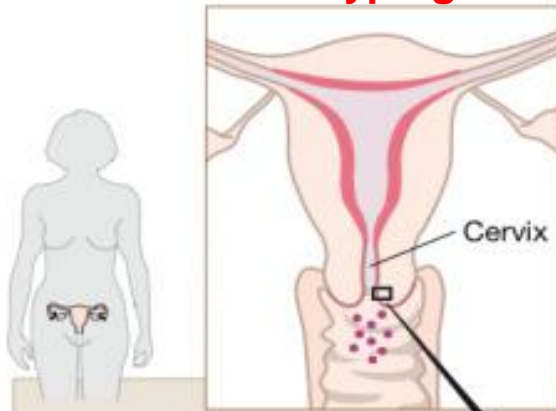
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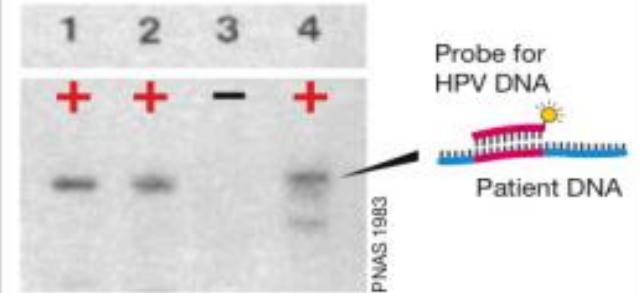
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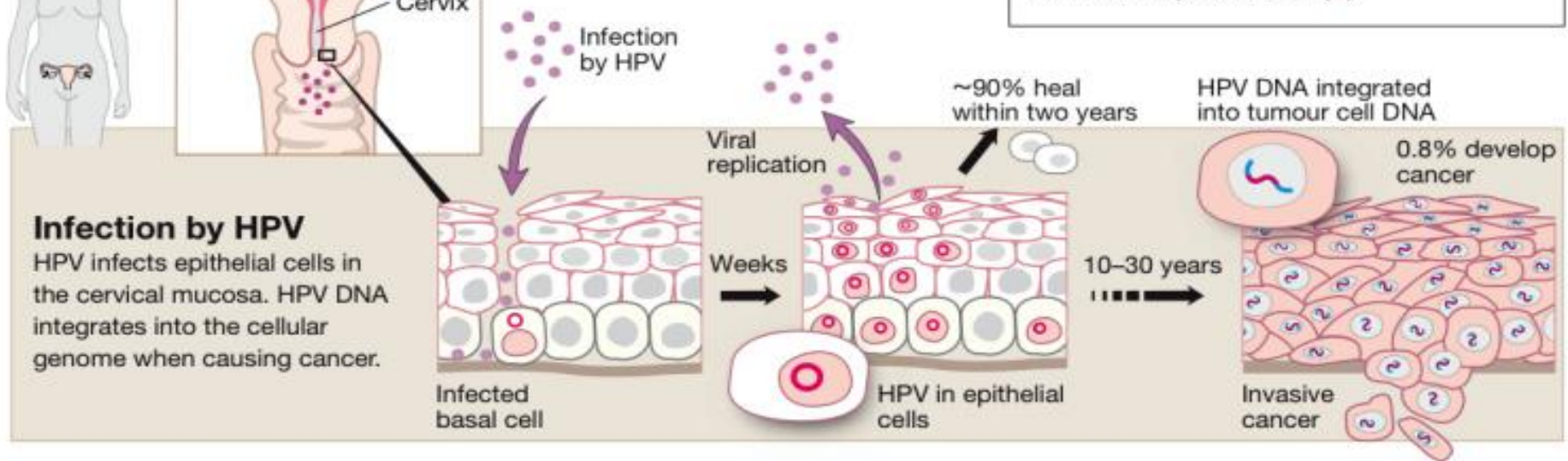
HPV typing



Discovery of HPV DNA in cancer cells



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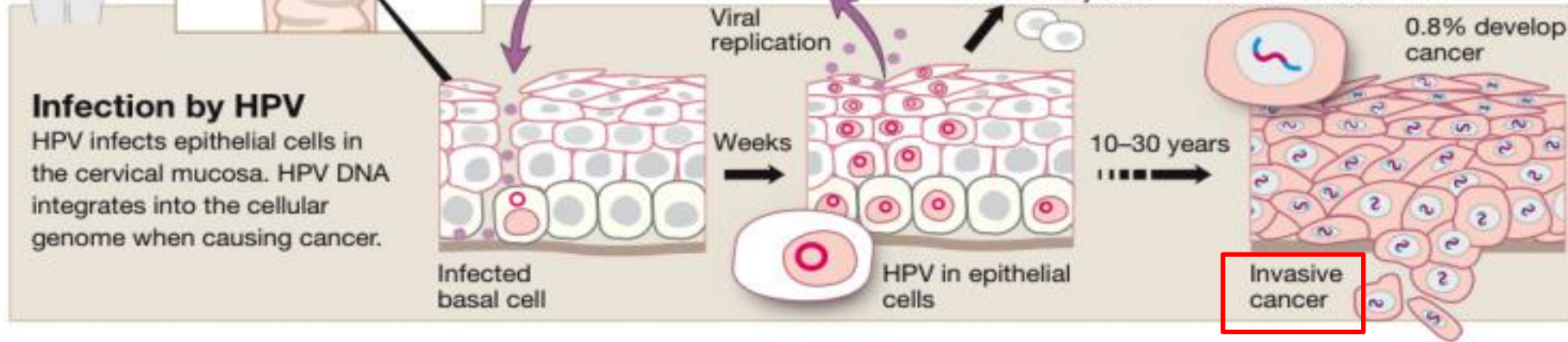
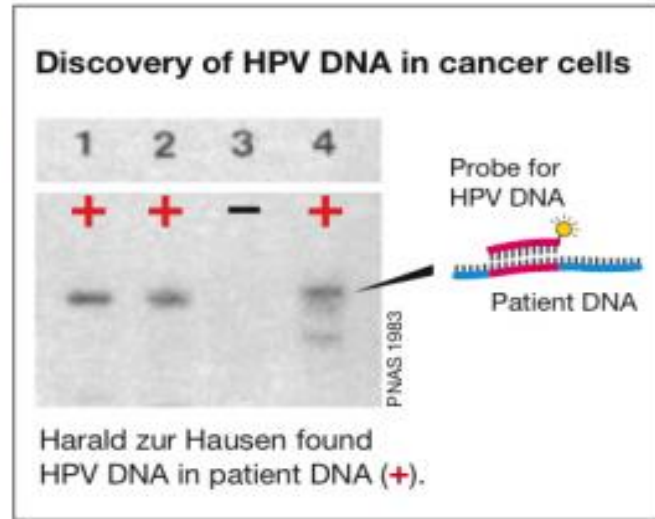
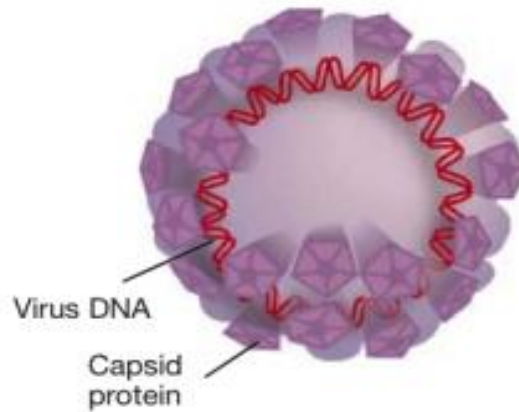
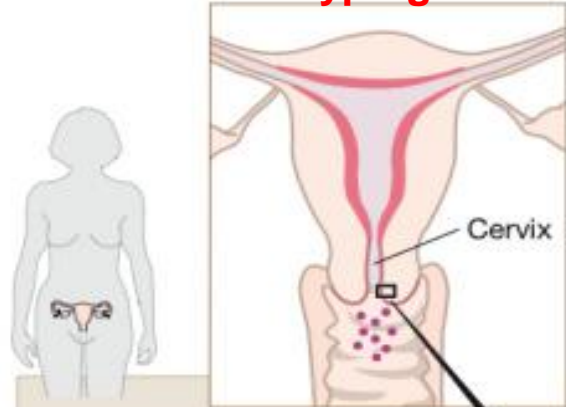
HPV- human papilloma virus

hrHPV DNA

HPV has a circular, double stranded DNA, protected by capsid proteins.

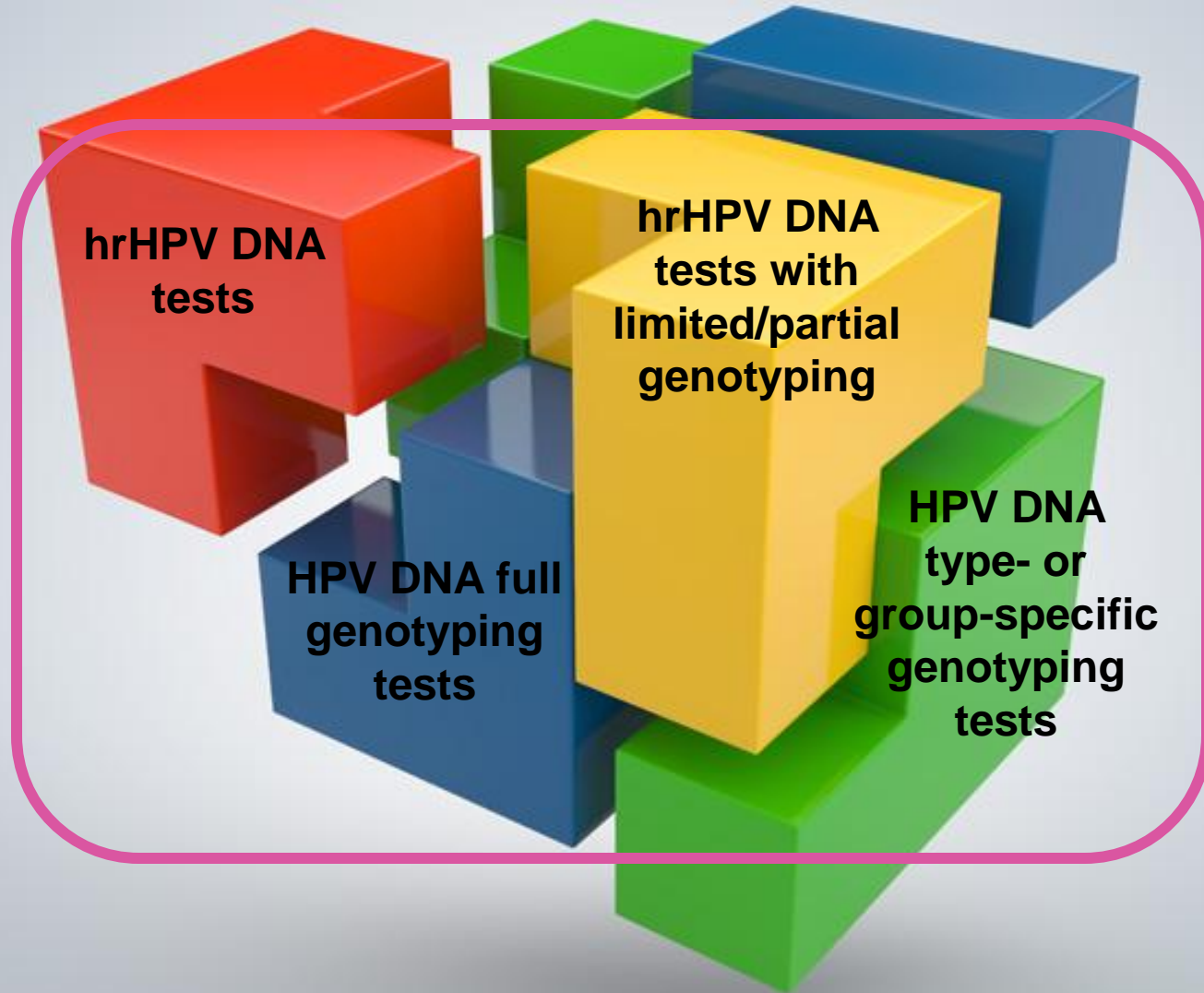
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HPV typing

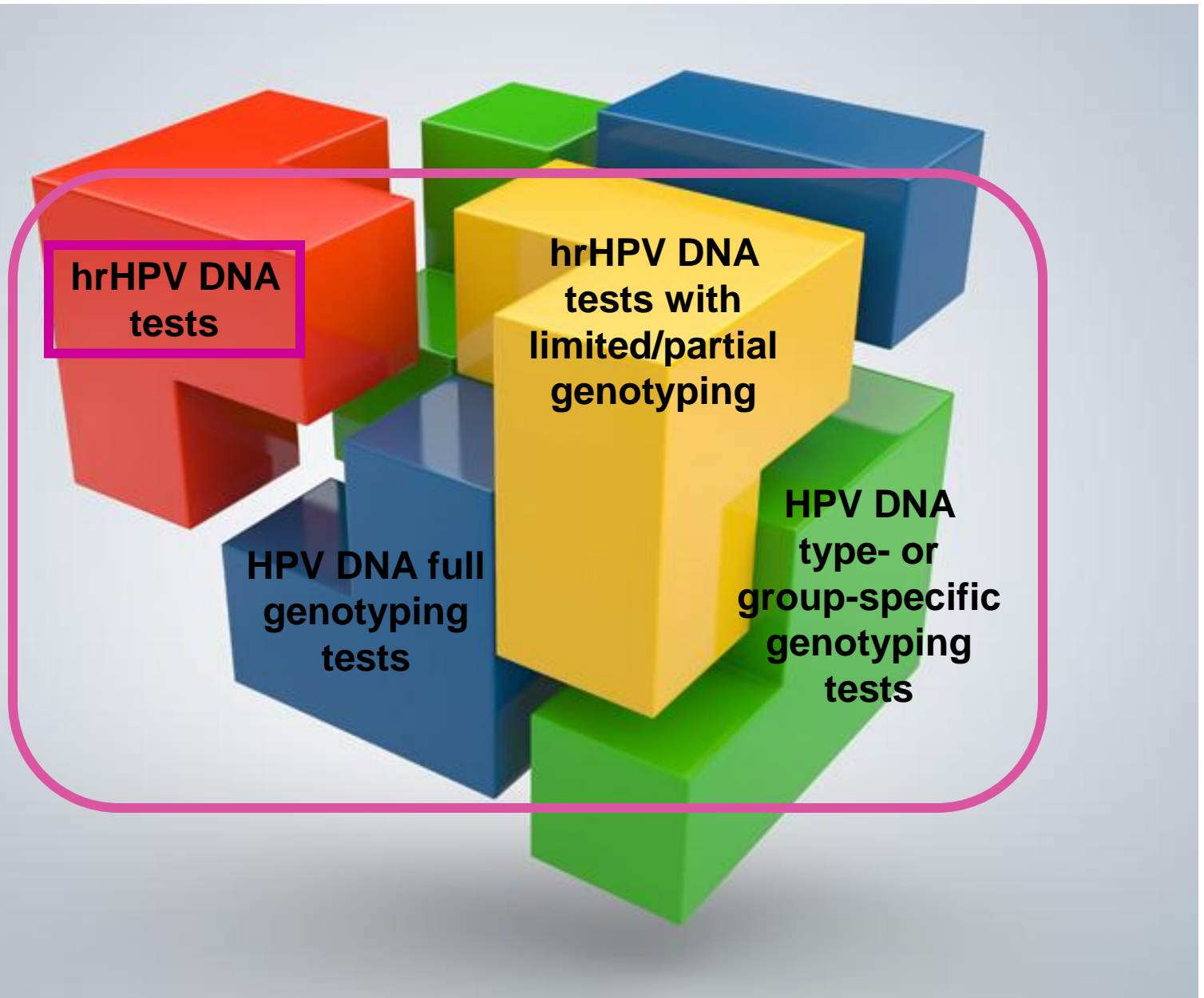


HPV mRNA of viral oncoproteins E6 and E7

Current HPV tests: hrHPV DNA-based



Current HPV tests: hrHPV DNA-based



Current HPV tests: hrHPV DNA tests

= group of qualitative or semi-quantitative tests detecting hrHPV types without distinction of individual HPV type(s)

✓ Hybrid Capture[®] 2 (HC2) HPV DNA test (Digene Corporation, USA → Qiagen, USA)

✓ The most frequently used HPV test worldwide

✓ B-probe targeting IARC-2009 12 hrHPV + HPV68

✓ Evaluated in numerous randomized, controlled and cohort studies demonstrating the **clinical value of HPV testing in general**

→ New HPV tests do not require extensive longitudinal clinical trials but should show equivalent (non-inferior) clinical characteristics as compared to HC2

✓ PCR-based consensus GP5+/6+ primers test (commercialized as EIA kit HPV GP HR by Diassay, The Netherlands)

✓ Second most evaluated test in clinical trials

✓ Cervista[®] HPV HR Test (Third Wave Technologies, USA → Hologic, USA)

✓ Signal amplification Invader chemistry

✓ Targets IARC-2009 12 hrHPV + HPV68

✓ careHPV[™] Test (Qiagen, USA)

✓ Simplified HC2 technology

✓ In setting lacking specific laboratory infrastructure

Arbyn M. et al., Vaccine 2012;30(S5):F88-99

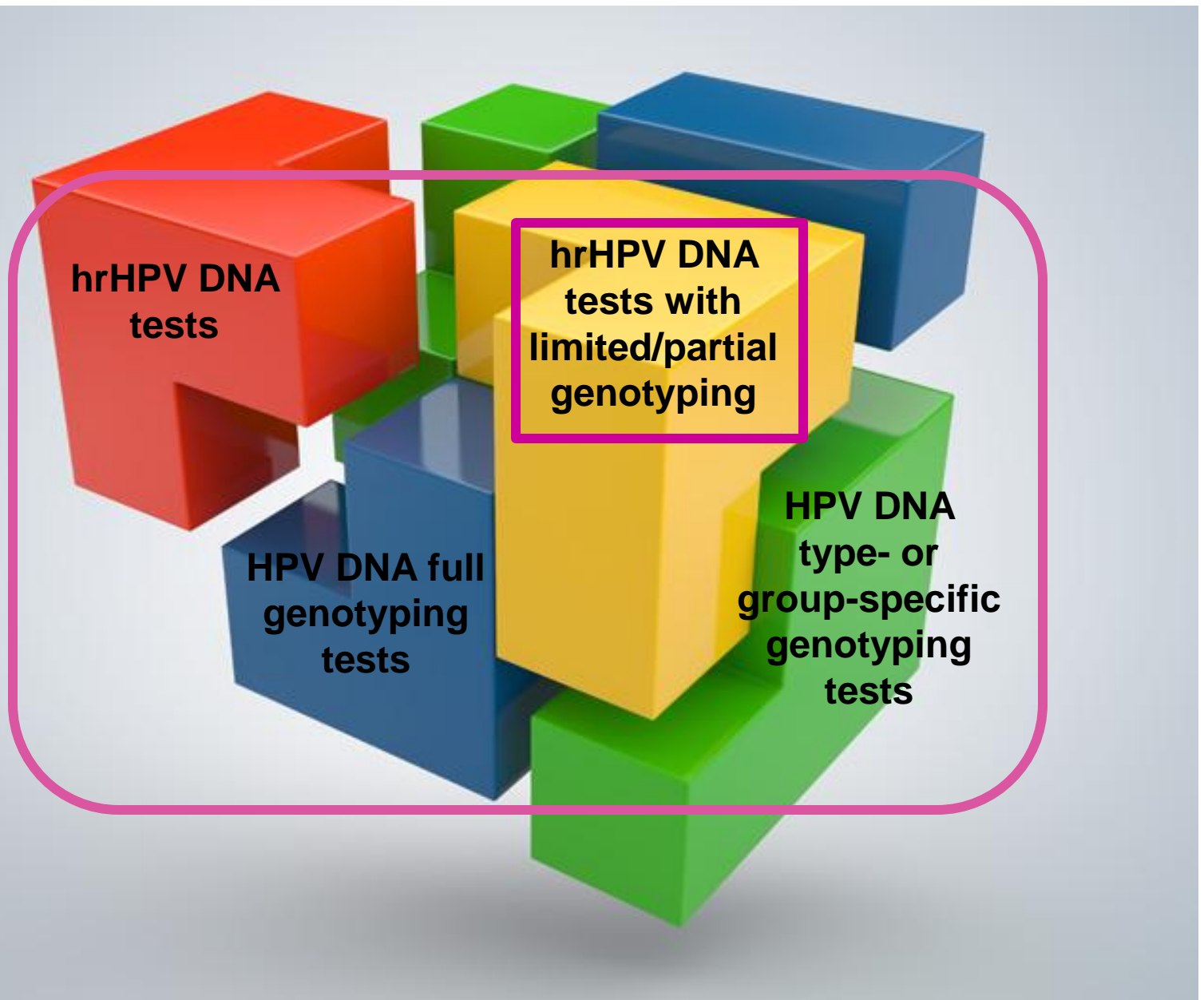
Belinson JL. et al., Am J Clin Pathol 2011;135:790-5

Poljak M., Kocjan BJ. Exp Rev Anti Infect Ther 2010;8:1139-62

Qiao YL. et al., Lancet Oncol 2008;9:929-36

Cuzick J. et al., Int J Cancer 2006;119:1095-1101

Current HPV tests: hrHPV DNA-based



Current HPV tests: hrHPV DNA tests with limited/partial genotyping

= group of novel HPV tests with detection of 13 or 14 HPV types with concurrent or reflex HPV16 and HPV18 or other main HPV types genotyping

→ design of these assays is based on exceptionally high oncogenic potential of HPV16 and HPV18 as compared to other hrHPV

→ **tests with HPV16 and HPV18 genotyping may identify women at greatest risk of CIN3 and permit less aggressive management for other -hrHPV-positive women**

✓ cobas[®] 4800 HPV test (Roche Diagnostics, Switzerland)

✓ Multiplex real-time PCR

✓ Detection for hrHPV and partial individual typing for HPV16 + HPV18

✓ Targeting IARC-2009 12 hrHPV + HPV66 + HPV68

✓ Abbott RealTime High Risk HPV test (Abbott, USA)

✓ Multiplex real-time PCR

✓ Detection for hrHPV and partial individual typing for HPV16 + HPV18

✓ Targeting IARC-2009 12 hrHPV + HPV66 + HPV68

✓ Cervista[®] HPV 16/18 Test (Hologic, USA)

✓ Reflex test for Cervista HPV HR + samples

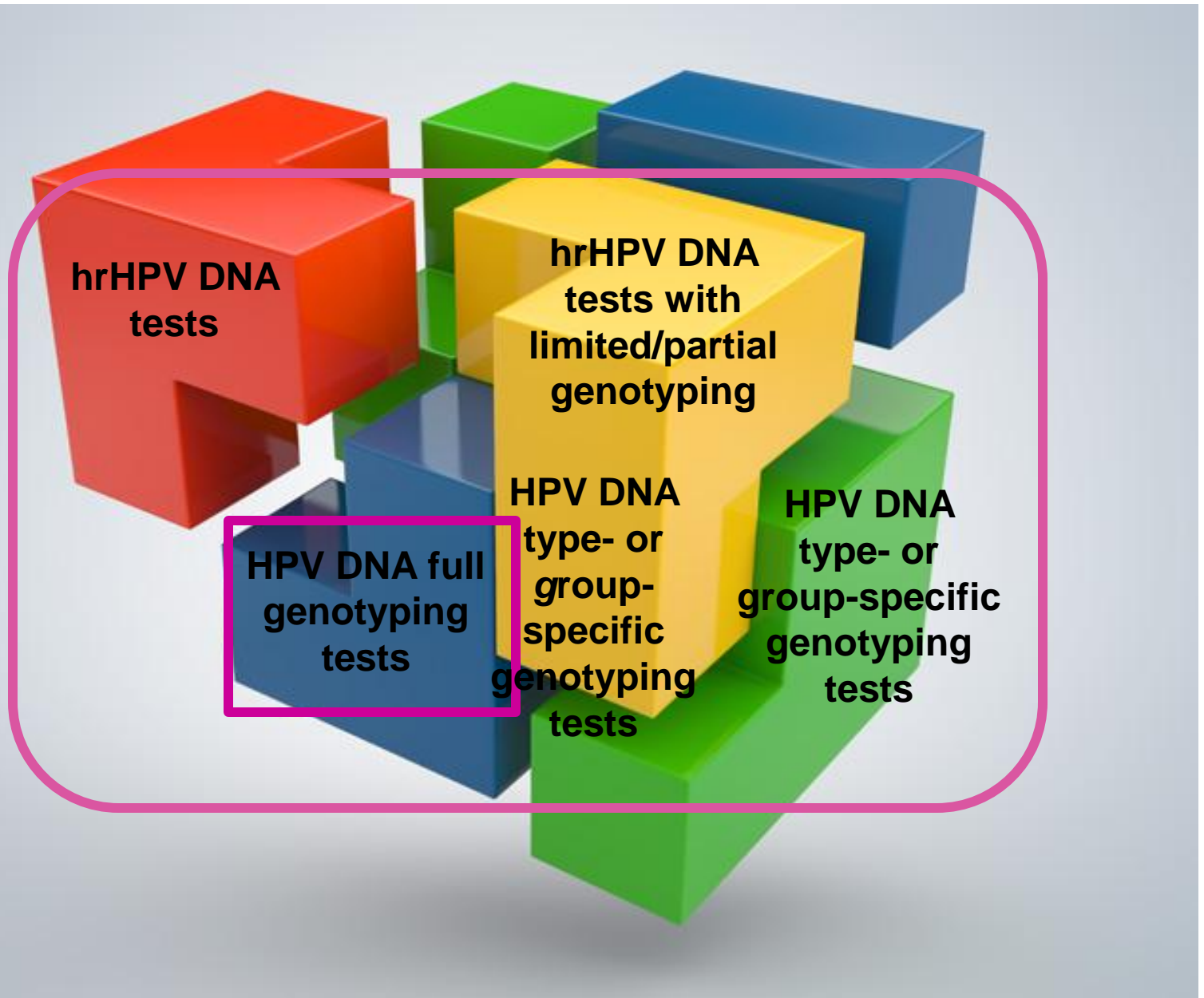
Khan MJ. et al., J Natl Cancer Inst 2005;97:1072-9

Wright Jr TC. et al., Am J Clin Pathol 2011;136:578-86

Einstein MH. et al., Gynecol Oncol 2010;118:116-22

Cuzick J. et al., J Med Virol 2010;82:1186-91

Current HPV tests: hrHPV DNA-based



Current HPV tests: HPV DNA full genotyping tests

= group of HPV tests with detection and individual determination of multiple HPV types

→ in contrast to previous groups of tests **the clinical value of HPV full genotyping has not been definitely established**

→ mostly use in research settings (natural history, transmission, pathogenesis, prevention)

→ analytical performance different (= **higher analytical sensitivity**) from the tests with clinically validated cut-offs

→ role in the surveillance of vaccine effectiveness on population level

→ substantial technological variety:

✓ Reverse hybridization

✓ Most frequently used HPV DNA full genotyping tests

✓ Linear Array[®] HPV Genotyping Test (Roche Diagnostics, Switzerland)/HPV SPF10 LiPA25_{version1} (Labo Bio-Medical Products, The Netherlands)/INNO-LiPA HPV Genotyping test (several versions) (Innogenetics, Belgium) → Fujirebio, Japan)

✓ Most extensive data in peer-reviewed literature

✓ Microarray-based tests

✓ PapilloCheck[®] HPV-Screening Test/PapilloCheck High-risk Test (Greiner Bio-One, Germany)/Clart[®] HPV2-Papillomavirus Clinical Arrays (Genomica, Spain)

✓ Microsphere beads-based tests

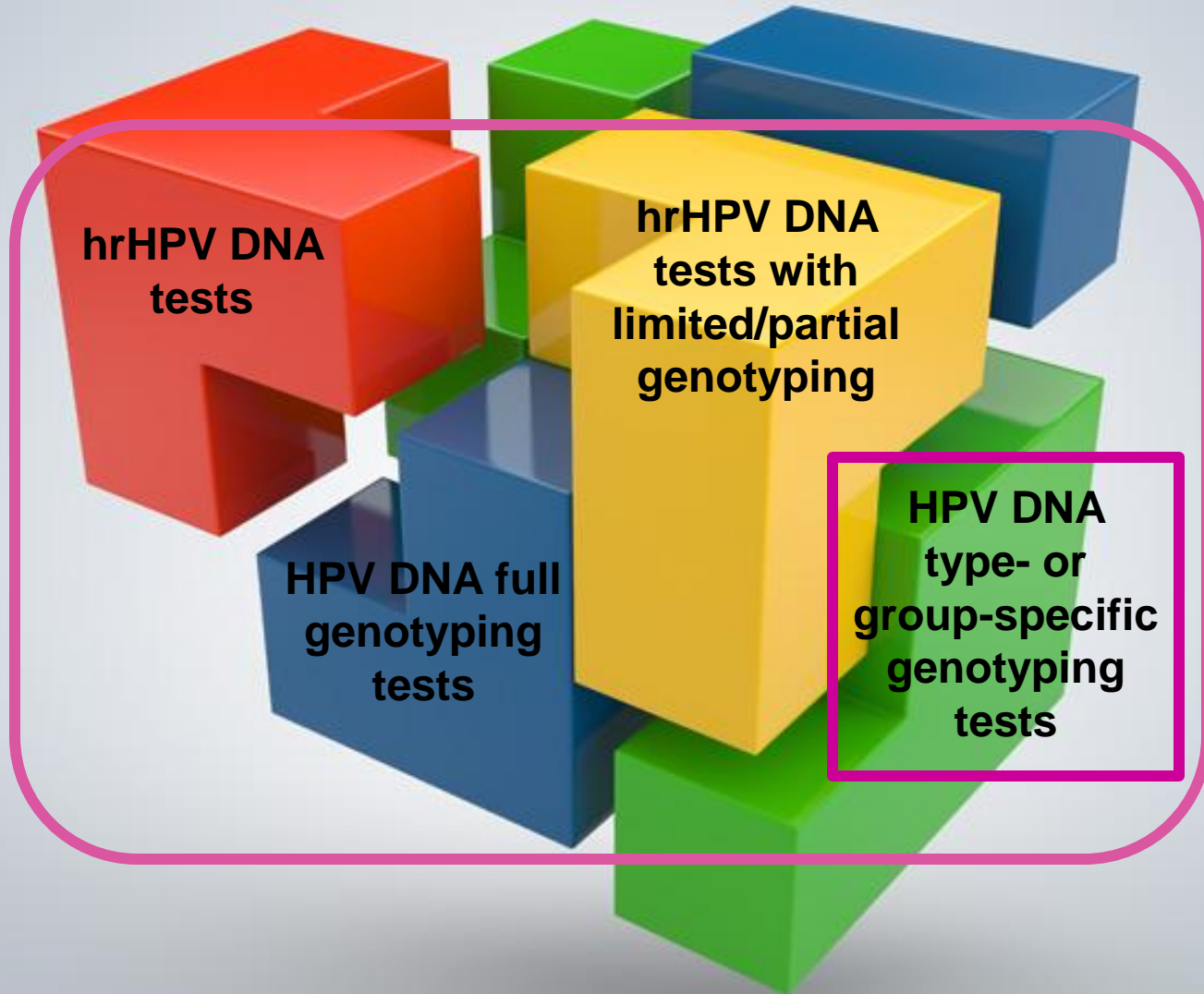
✓ Ultrasensitive methods

Gravitt PE. et al., Vaccine 2008;26(S10):K42-52

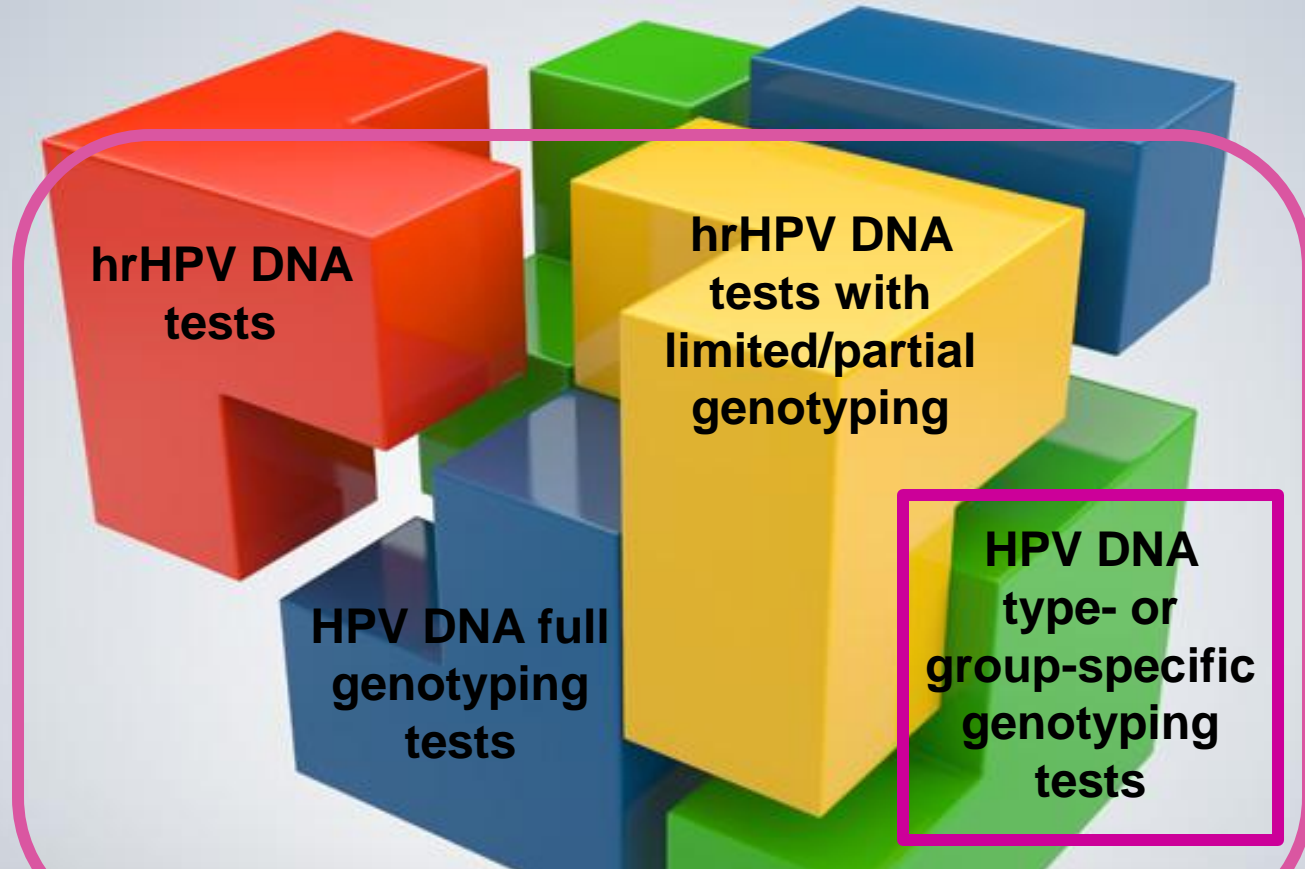
Hesselink AT. et al., J Clin Microbiol 2010;48:797-801

Schmitt M. et al., J Clin Microbiol 2010;48:143-9

Current HPV tests: hrHPV DNA-based



Current HPV tests: hrHPV DNA-based

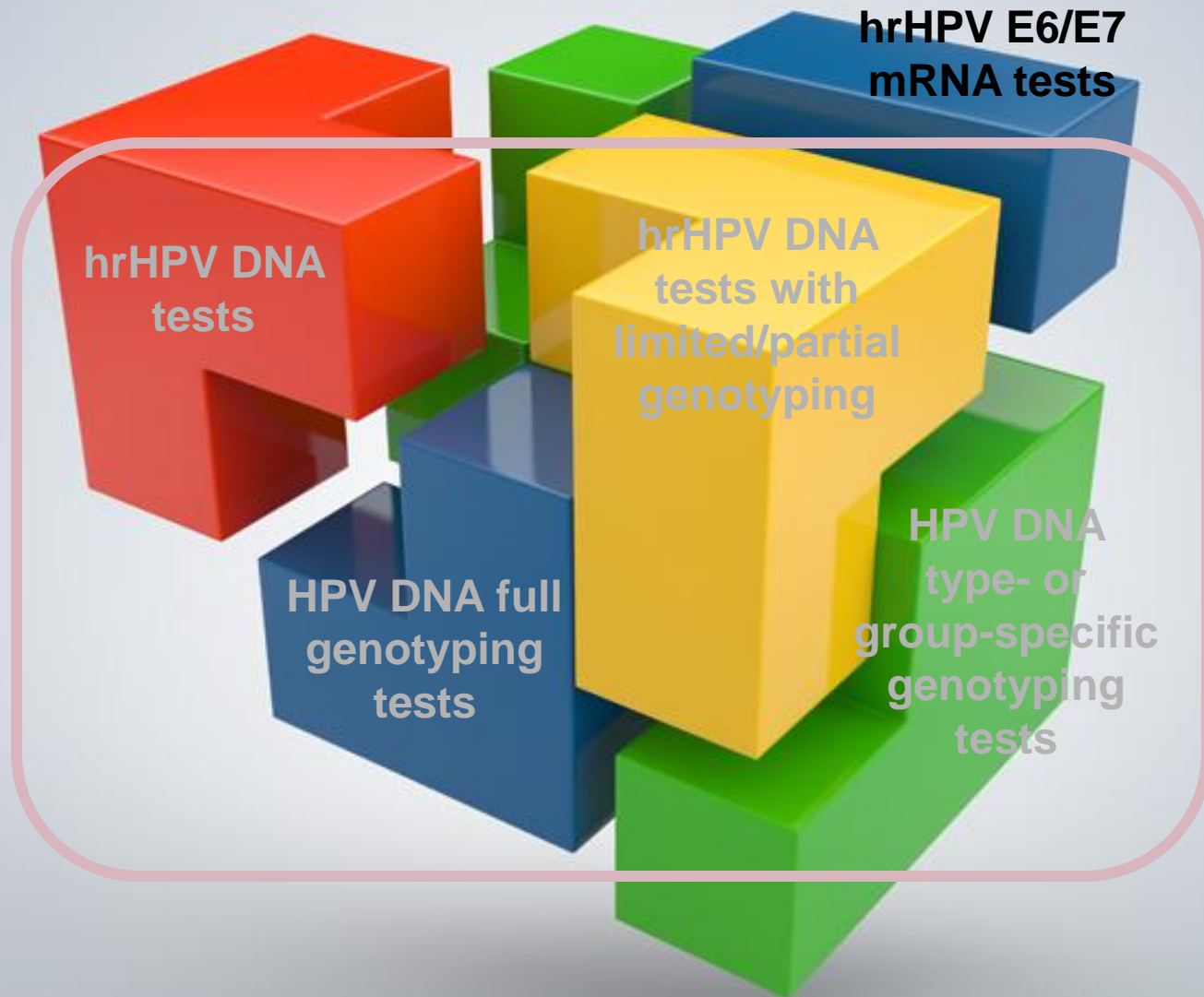


= individual determination of only a limited number of clinically important HPV types

✓ large group of tests

✓ **clinical value is has not been definitely established**

Current HPV tests: hrHPV mRNA-based



Current HPV tests: hrHPV mRNA tests

→ Most relevant transcripts for diagnostic purposes are those encoding viral oncoproteins E6 and E7

→ Reverse-transcriptase PCR of nucleic acid sequence-based amplification (NASBA)

✓ APTIMA[®] HPV Assay (Gene-Probe, USA → Hologic, USA)

✓ Targets E6/E7 mRNA of 12 hrHPV + HPV66 + HPV68

✓ No discrimination among 14 targeted HPV types

✓ No cellularity control

✓ Not only HPV mRNA but also HPV dsDNA detection

✓ In triage settings: = **sensitivity** but **↑ specificity** than HC2 for detecting cervical precancer lesions

✓ PreTect HPV-Proofer (NorChip, Norway)/NucliSens EasyQ[®] HPV V1 test (Biomerieux, France)

✓ Detection of E6/E7 mRNA of the 5 most frequent hrHPV types = HPV16, HPV18, HPV31, HPV33, HPV45

✓ Not only HPV mRNA but also HPV dsDNA detection

✓ **↓ sensitivity** but **↑↑ specificity** than DNA-based tests for CIN2+

Arbyn M. et al., Vaccine 2012;30(S5):F88-99

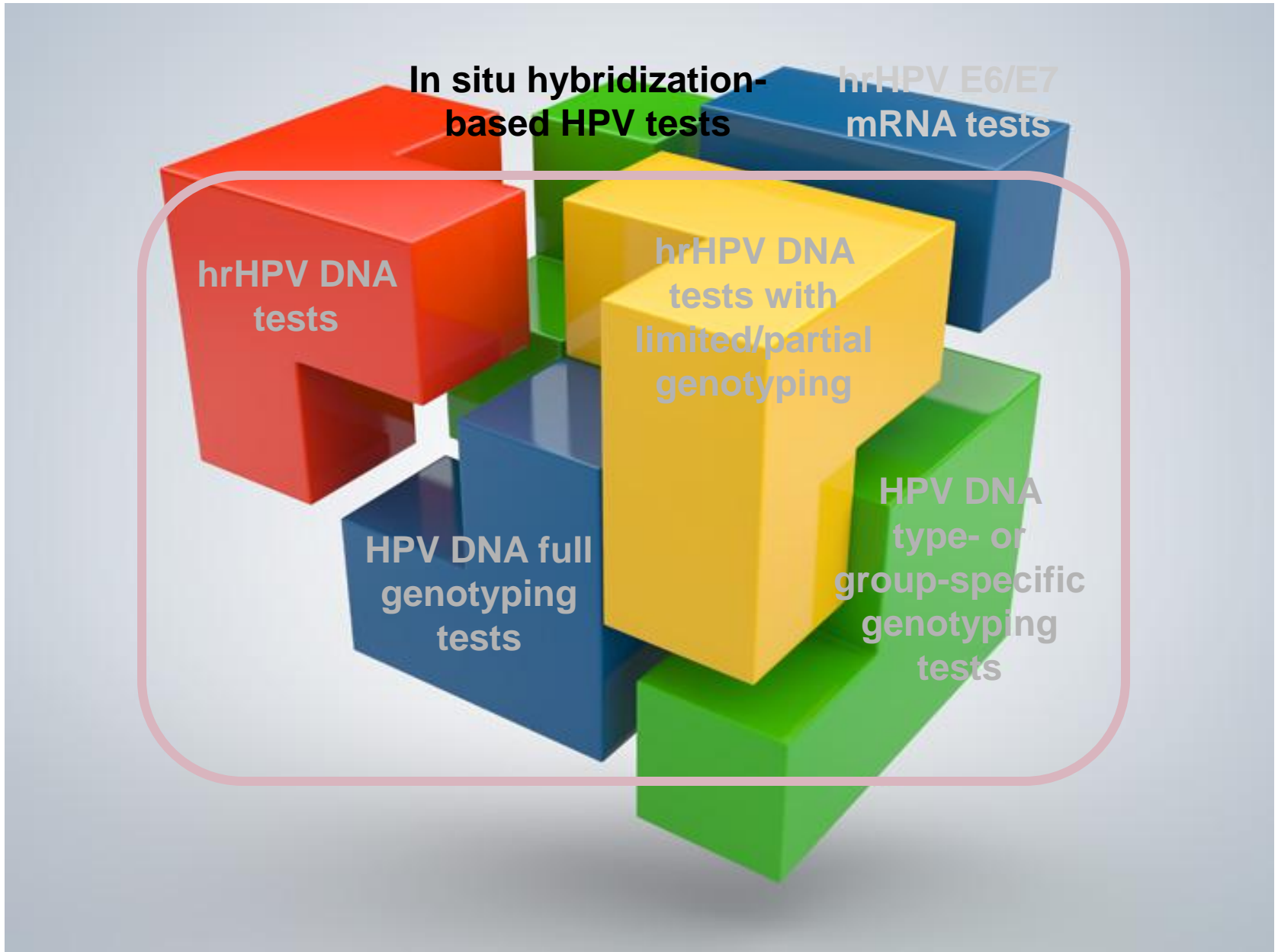
Getman D. et al., J Clin Virol 2009;45(S1):S49-54

Cuschiere K. et al., Cancer Epidemiol Biomarkers Prev 2008;17:2536-45

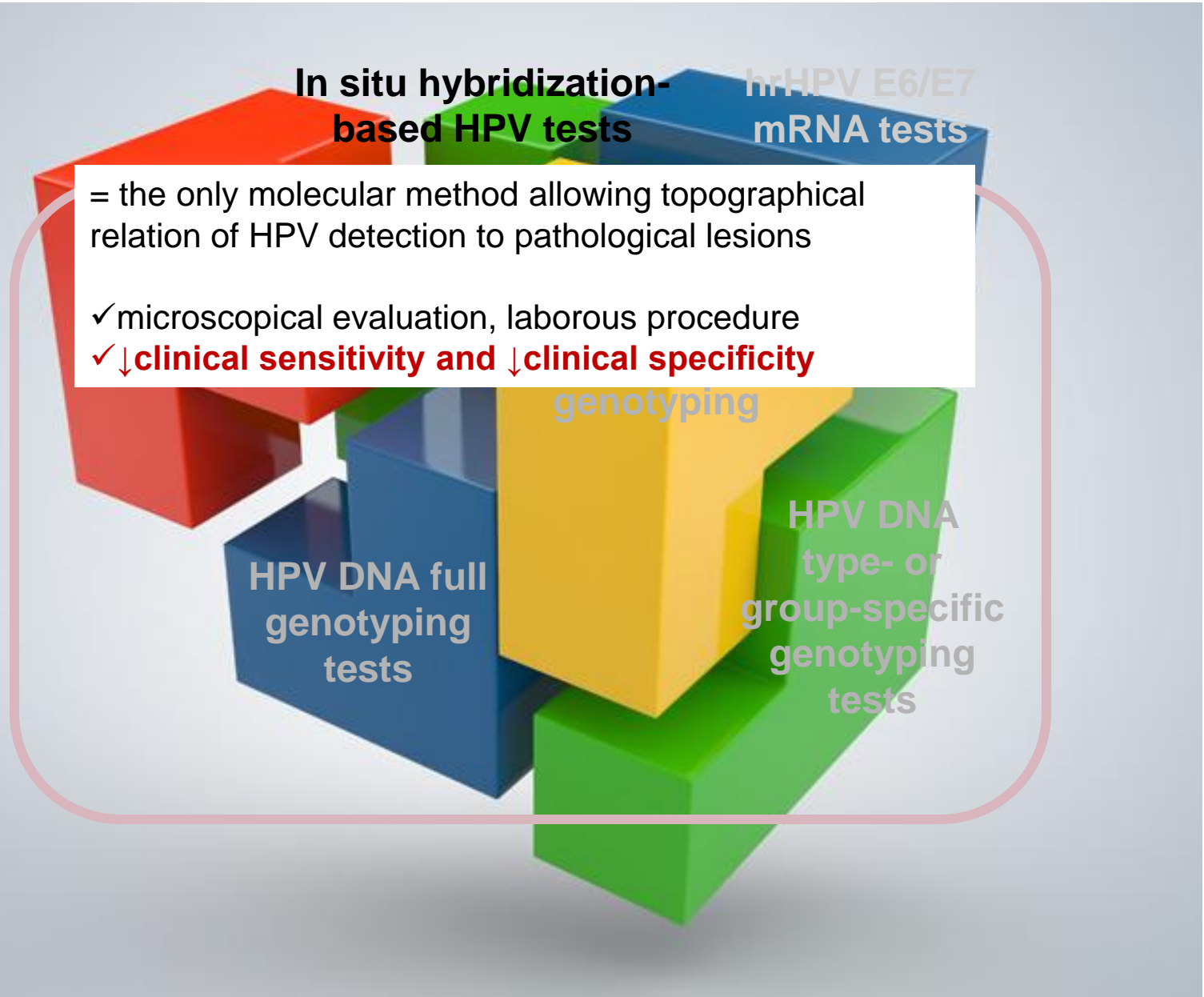
Boulet GA. et al., J Clin Microbiol 2010;48:2524-9

Padalko E. et al., J Med Virol 2013;85:1242-9

Current HPV tests: in situ hybridization-based HPV tests



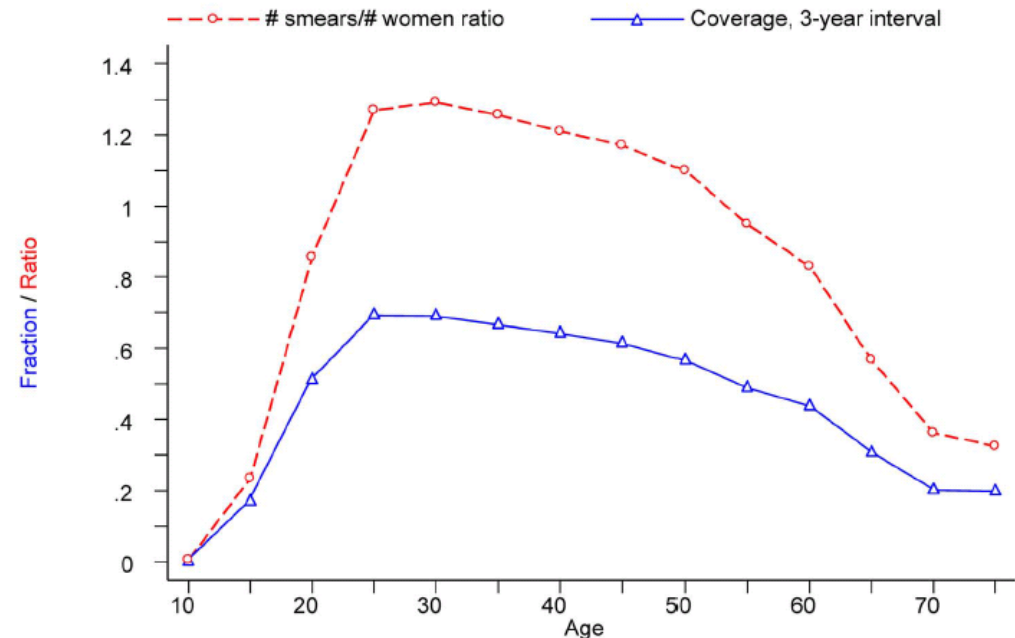
Current HPV tests: in situ hybridization-based HPV tests



Cytology-based screening: Belgian situation (2002-2006)

Area	Mean female population (25-64 years)	Number of smears taken	Number of women screened <3years ago	3-yr coverage	# smears / #women ratio
Belgium	2,785,516	3,199,984	1,706,043	61.2%	1.15
Flemish Region	1,614,285	1,778,783	968,385	60.0%	1.10
Walloon Region	897,182	1,091,051	568,004	63.3%	1.22
Brussels	274,052	330,150	169,654	61.9%	1.20

- ✓ Sufficient smears taken to cover 100% of target population (= **substantial overscreening**) but coverage only 61% (= **substantial underscreening**)
- ✓ The median screening interval was 13 months
- ✓ Differences between the 3 regions are small



Cervical cancer screening programs: possible solutions for increase in participation rate

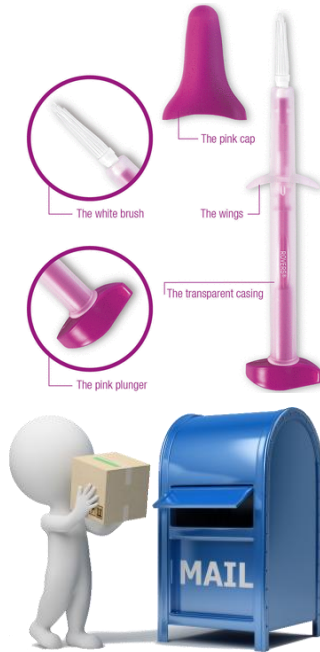
Self-sampling of cervico-vaginal material for hrHPV

HPV testing

↑ sensitivity

↑ participation

HPV testing



Test	Number of studies (number of test-device combinations)	Relative sensitivity	Relative specificity
HC2	18	0.85 (0.81-0.90)*	0.96 (0.93-0.98)*
PCR GPs+/6+	5	0.95 (0.89-1.01)	1.11 (0.95-1.29)
CareHPV (at RLU≤ 0.5)	1	0.90 (0.79-1.04)	0.98 (0.95-1.00)
CareHPV (at RLU≤ 1)	1	0.86 (0.73-1.03)	1.00 (0.98-1.02)
PCR-SPF10	2	0.96 (0.89-1.02)	1.10 (0.85-1.41)
Abbott Real Time hrHPV Test	1	1.00 (0.75-1.34)	1.07 (0.65-1.78)
Cervista	1	0.76 (0.70-0.83)*	0.95 (0.94-0.96)*
APTIMA	1	0.64 (0.46-0.90)*	0.99 (0.98-1.01)
DNA chip	1	1.03 (0.89-1.19)	0.88 (0.55-1.42)
Modified GPs+/6+ PCR with Luminex reading	1	0.96 (0.75-1.24)	0.94 (0.67-1.33)
Linear Array	1	0.79 (0.54-1.16)	1.00 (0.89-1.12)
MALDI-TOF	1	1.00 (0.95-1.05)	0.98 (0.97-0.99)*
Other nonGPs+/6+ PCR	7	0.82 (0.66-1.01)	1.02 (0.97-1.07)
Collection device for self-sampling			
Brush	18 (24)	0.89 (0.83-0.94)*	0.98 (0.97-0.99)*
Lavage	5 (6)	0.94 (0.85-1.03)	0.95 (0.68-1.34)
Swab	10	0.86 (0.80-0.92)*	0.95 (0.90-1.01)
Tampon	1	0.71 (0.62-0.83)*	1.01 (1.00-1.02)*
Income status of country			
Low-income and middle-income countries	19 (23)	0.85 (0.79-0.91)*	0.97 (0.95-0.99)*
High-income countries	14 (17)	0.94 (0.90-0.97)*	0.99 (0.93-1.06)

RLU=relative light units. *Statistically significantly different from unity (1 excluded from 95% CI).

Table 4: Subgroup meta-analysis of the relative sensitivity and specificity of human papillomavirus (self-sampled vs clinician sampled) testing for cervical intraepithelial neoplasia of grade 2 or worse, by covariate

✓ Clinical performance:

- ✓ hrHPV testing on self-taken samples is **at least as, if not more, sensitive for \geq CIN2+ as cytology on clinician-obtained cervical samples**, though often less specific
- ✓ Variations in clinical performance likely to reflect **the use of different combinations of collection devices and HPV tests**

Arbyn M., et al. *Lancet Oncol* 2014;15:172-83

Snijders P. et al., *Int J Cancer* 2013;132:2223-36

Gok M. et al., *BMJ* 2010;340:c1040

Cervical cancer screening programs: possible solutions for increase in participation rate

Self-sampling of cervico-vaginal material for hrHPV



HPV testing

↑ sensitivity

↑ participation

HPV testing

✓ Compliance:

- ✓ Self-sampling is **less costly and less invasive** collection method
 - ✓ It has been shown to **increase participation rate**: ~1/3 of non-attendees submit self-sampled material for HPV testing when HPV self-sampling is offered
 - ✓ Self-sampling is **superior in activation of non-attendees to a recall invitation for cytology**
- ✓ Self-sampling facilitates **access to cervical screening for women in low resource areas**

hrHPV self-sampling can be a valid and even better alternative to current cytology-based call-recall programs

Current HPV tests: **conclusions**

- ✓ **Unusually high variety** of commercially available technologically diverse tests
- ✓ Establishment of **clinically relevant cut-offs in a limited number of tests**
- ✓ Growing data on **potential use of self-sampling** for increase of coverage and in resource-poor setting

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