Updates on cervical cancer prevention and control

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Declaration of Conflict of Interest and acknowledgement

- Advisor to GSK and MSD cervical cancer control and prevention
- PI of HPV vaccines clinical trials GSK and MSD
- Received sponsorships or honoraria from GSK; MSD and Roche as speaker, expert consultant and/or member of Advisory Board
- Some slides were courtesy of Dr. J Tan and MSD medical support team

Incidence of cervical cancer 2004-2011 Hong Kong

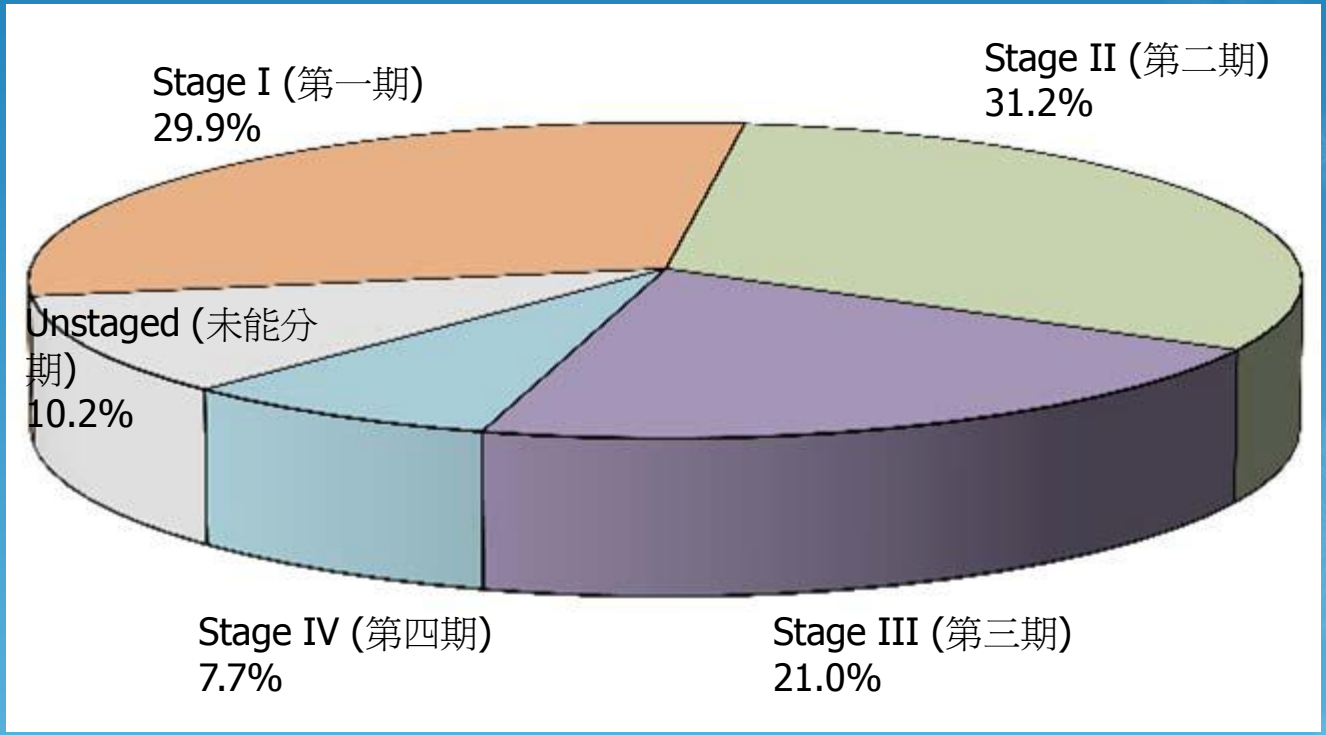
Year	Number	Crude rate	ASR
2004	439	12.5	9.5
2005	376	10.6	7.8
2006	459	12.8	9.4
2007	399	11	7.7
2008	358	12.3	6.9
2009	453	10.7	8.4
2010	400	10.4	7.3
2011	391	11.2	7.2

Prevalence of cervical cancer in Hong Kong

- Hong Kong:
- 391 new cases (2011), 151 death (2011)
- Rank 9th in incidence and 8th in mortality
- Crude incidence of 10.4 and age standardized incidence of 7.2/100,000
- Crude death rate of 4 and age standardized death rate of 2.5/100,000
- Median age 53

Hong Kong Cancer Registry 2013

Stage Distribution of Cervical Cancer in 2011 Hong Kong



How to further prevent or control cervical cancer

- Vaccination
  - 2 effective and safe HPV vaccination against HPV 16 and 18 infection
- Cervical cancer screening
  - Effective with repeated cytology screening

We got the tool, but why we cannot achieve what we want

Possible obstacles in vaccination

- Cost
- Not sure of efficacy out of clinical trial
- Length of protection
- Screening is still recommended, adding to cost of whole prg
- Political will
- Acceptance by public

Cost

- Population screening increase the bulk can decrease cost
- Support from GAVI and other agency to low income country
- Can we reduce the number of doses to be injected, immediate 1/3 cost off

Gardasil: 2 doses (9-13F) is non-inferior to 3 doses (16-26F)

Table 3. Summary of Month 7,18, 24, and 36 Anti–Human Papillomavirus Competitive Immunoassay Geometric Mean Titers in the Per-Protocol Population

	Girls, 9-13 y				Women, 16-26 y		GMT Ratio (95% CI), mMU/mL		
	2 Doses		3 Doses		3 Doses				
Antibodies	No. of Patients[a]	GMT (95% CI), mMU/mL	No. of Patients[a]	GMT (95% CI), mMU/mL	No. of Patients[a]	GMT (95% CI), mMU/mL	Girls (2-Dose)/Women (3-Dose)	Girls (2-Dose)/Girls (3-Dose)	Girls (3-Dose)/Women (3-Dose)
Month 7									
HPV-16	243	7457 (6388-8704)	251	7640 (6561-8896)	246	3574 (3065-4169)	2.09 (1.61-2.71)[b]	0.98 (0.75-1.27)	2.14 (1.65-2.77)
HPV-18	243	1207 (1054-1384)	252	1703 (1489-1946)	264	661 (580-754)	1.83 (1.46-2.29)[b]	0.71 (0.56-0.89)	2.57 (2.06-3.22)
HPV-6	241	2186 (1846-2588)	248	1856 (1571-2192)	256	938 (796-1105)	2.33 (1.76-3.09)	1.18 (0.89-1.56)	1.98 (1.50-2.62)
HPV-11	243	2348 (2090-2638)	251	2096 (1869-2350)	269	1277 (1144-1427)	1.84 (1.52-2.23)	1.12 (0.92-1.36)	1.64 (1.36-1.98)
Month 18									
HPV-16	96	1598 (1333-1916)	98	1804 (1508-2160)	92	837 (695-1008)	1.91 (1.40-2.60)	0.89 (0.65-1.20)	2.16 (1.58-2.94)
HPV-18	96	137 (106-177)	99	236 (184-304)	95	74 (57-95)	1.86 (1.21-2.87)	0.58 (0.38-0.89)	3.21 (2.09-4.93)
HPV-6	96	347 (291-414)	97	351 (294-418)	93	200 (168-240)	1.73 (1.28-2.34)	0.99 (0.74-1.33)	1.75 (1.30-2.36)
HPV-11	96	451 (380-535)	99	424 (359-502)	98	281 (238-333)	1.60 (1.20-2.14)	1.06 (0.80-1.42)	1.51 (1.13-2.01)
Month 24									
HPV-16	195	1414 (1235-1618)	186	1739 (1514-1998)	189	813 (709-933)	1.74 (1.38-2.19)	0.81 (0.64-1.02)	2.14 (1.69-2.70)
HPV-18	195	132 (109-160)	187	267 (220-324)	202	91 (76-110)	1.44 (1.05-1.99)	0.49 (0.36-0.68)	2.92 (2.11-4.03)
HPV-6	193	276 (243-313)	186	359 (315-409)	195	197 (173-224)	1.40 (1.13-1.74)	0.77 (0.62-0.96)	1.82 (1.47-2.27)
HPV-11	195	368 (324-420)	186	422 (369-482)	206	267 (235-303)	1.38 (1.11-1.72)	0.87 (0.70-1.09)	1.58 (1.27-1.97)
Month 36									
HPV-16	86	1151 (918-1444)	83	1413 (1122-1780)	86	678 (540-850)	1.70 (1.16-2.49)	0.81 (0.55-1.20)	2.09 (1.42-3.07)
HPV-18	86	104 (77-141)	83	239 (175-327)	96	71 (53-95)	1.46 (0.88-2.41)	0.43 (0.26-0.73)	3.35 (2.02-5.58)
HPV-6	84	239 (195-292)	83	372 (304-456)	92	176 (145-213)	1.36 (0.97-1.90)	0.64 (0.46-0.90)	2.12 (1.51-2.96)
HPV-11	86	298 (244-364)	82	410 (335-503)	97	208 (172-251)	1.43 (1.03-1.99)	0.73 (0.52-1.02)	1.97 (1.42-2.75)

Abbreviations: GMT, geometric mean titer; HPV, human papillomavirus; mMU/mL, milli-Merck units per milliliter.
[a] Number of negative samples available for a specific HPV genotype at baseline. Per-protocol population criteria also required a negative HPV DNA vaginal swab result at baseline for the specific HPV genotype.
[b] Results corresponding to the primary objective.

Dobson SR Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 dos

Bivalent HPV vaccine: 2 doses (9-14F) is non-inferior to 3 doses (15-25F)

Table 2. HPV-16 and HPV-18 GMT ratios for 3D schedule in women aged 15–25 y over 2D schedule in girls aged 9–14 y at months 36 and 48 (according-to-protocol month 36 and 48 immunogenicity cohorts, subjects seronegative at baseline)

Antigen	Group	Age (y)	N	GMT (95% CI), EU/mL	GMT ratio (3D/2D) (95% CI)
Month 36					
HPV-16	3D 20/20 M0,1,6	15–25	85	1592.0 (1282.6, 1975.9)	1.00 (0.73, 1.37)
	2D 20/20 M0,6	9–14	53	1595.1 (1298.2, 1960.0)	-
HPV-18	3D 20/20 M0,1,6	15–25	81	712.3 (560.3, 905.6)	1.03 (0.72, 1.49)
	2D 20/20 M0,6	9–14	52	689.3 (530.4, 895.9)	-
Month 48					
HPV-16	3D 20/20 M0,1,6	15–25	80	1419.6 (1133.9, 1777.2)	1.08 (0.78, 1.48)
	2D 20/20 M0,6	9–14	53	1319.8 (1084.1, 1606.7)	-
HPV-18	3D 20/20 M0,1,6	15–25	79	604.5 (475.9, 768.0)	1.11 (0.78, 1.58)
	2D 20/20 M0,6	9–14	52	542.9 (426.5, 691.0)	-

2D, 2-dose schedule; 3D, 3-dose schedule; 20/20, 20 µg each of HPV-16 and -18 L1 virus-like particles; 95% CI, exact 95% confidence interval; EU/mL, ELISA unit per milliliter; GMT, geometric mean antibody titer; M, month; N, number of evaluable seronegative subjects in the according-to-protocol immunogenicity cohort.

Romanowski B Hum Vaccin Immunother. 2014 Feb 27;10(5)

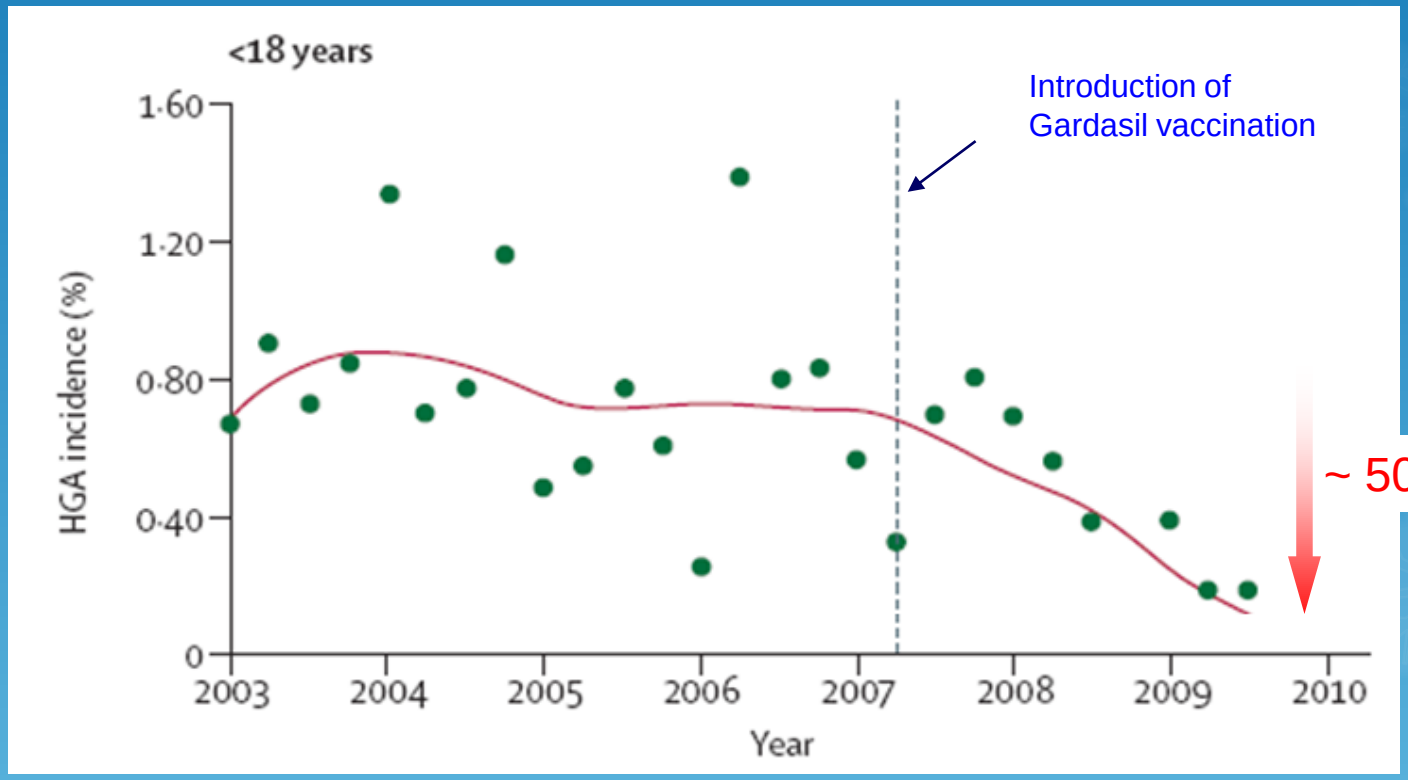
Is 2-dose enough for young girls <15?

- Both HPV vaccines showed non-inferiority in young girls <15 (2-dose) when compared with adult women (3-dose).
- Both HPV vaccines have received the EU Approvals for 2-dose schedule in young girls. Monitoring of clinical efficacy and duration of protection is needed.
- Countries implementing a two-dose vaccine schedule should devise risk management strategies to minimize the potential impact on cancer prevention
- For girls $\geq$ 15 or adults, 2-dose schedule is not recommended.

Efficacy

- HPV vaccination has been shown to decrease abnormal cytology, high grade lesion, need for colposcopy and treatment by many countries

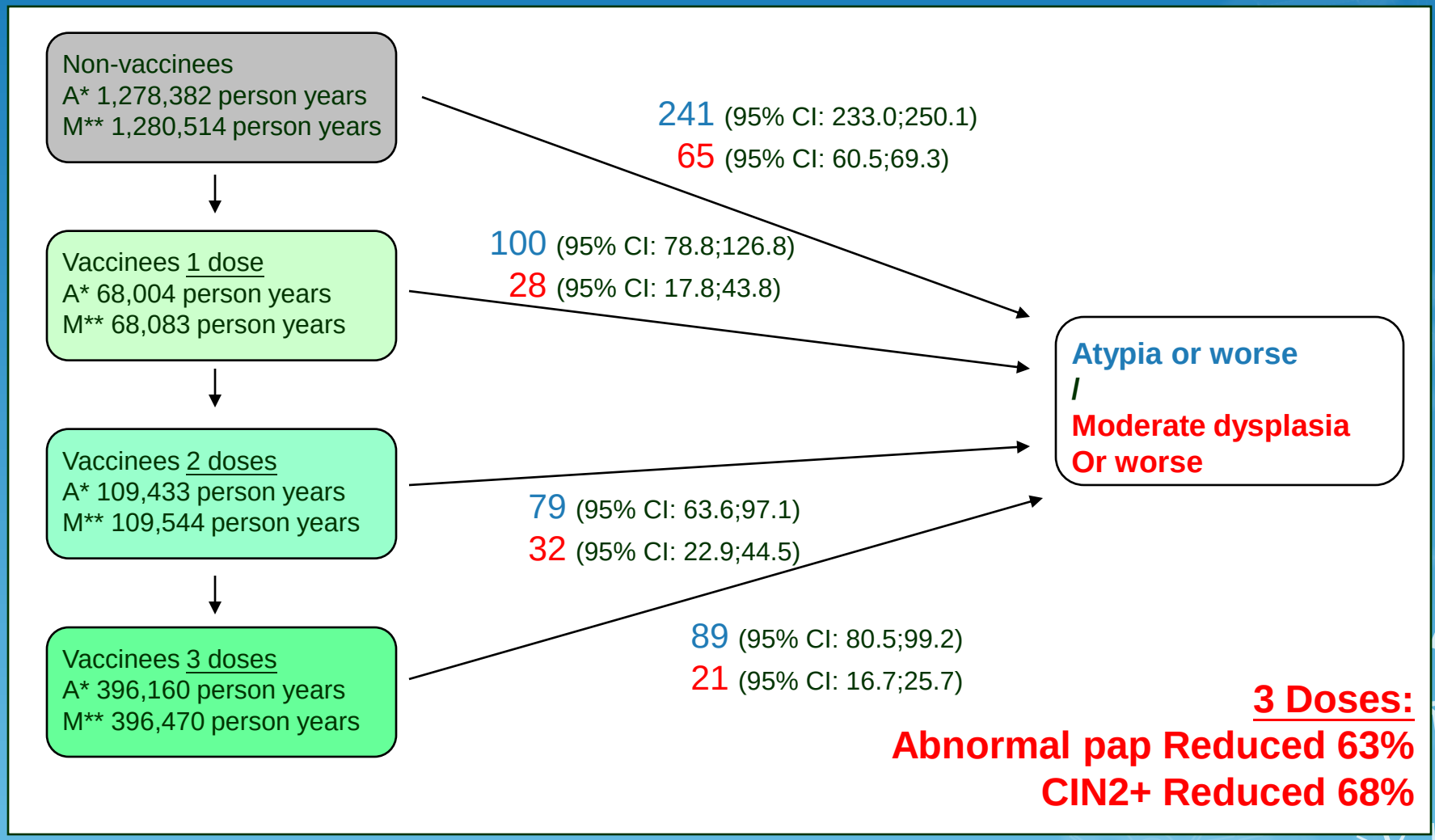
First report of a decrease of CIN 2/3 or AIS after Gardasil vaccination program in Australia



HGA = **high-grade cervical abnormalities** (cervical intraepithelial neoplasia of grade 2 or worse or adenocarcinoma in situ)

Brotherton JML The Lancet Vol. 377 No. 9783 pp 2085-2092

Denmark: CIN2+ 2005-2012

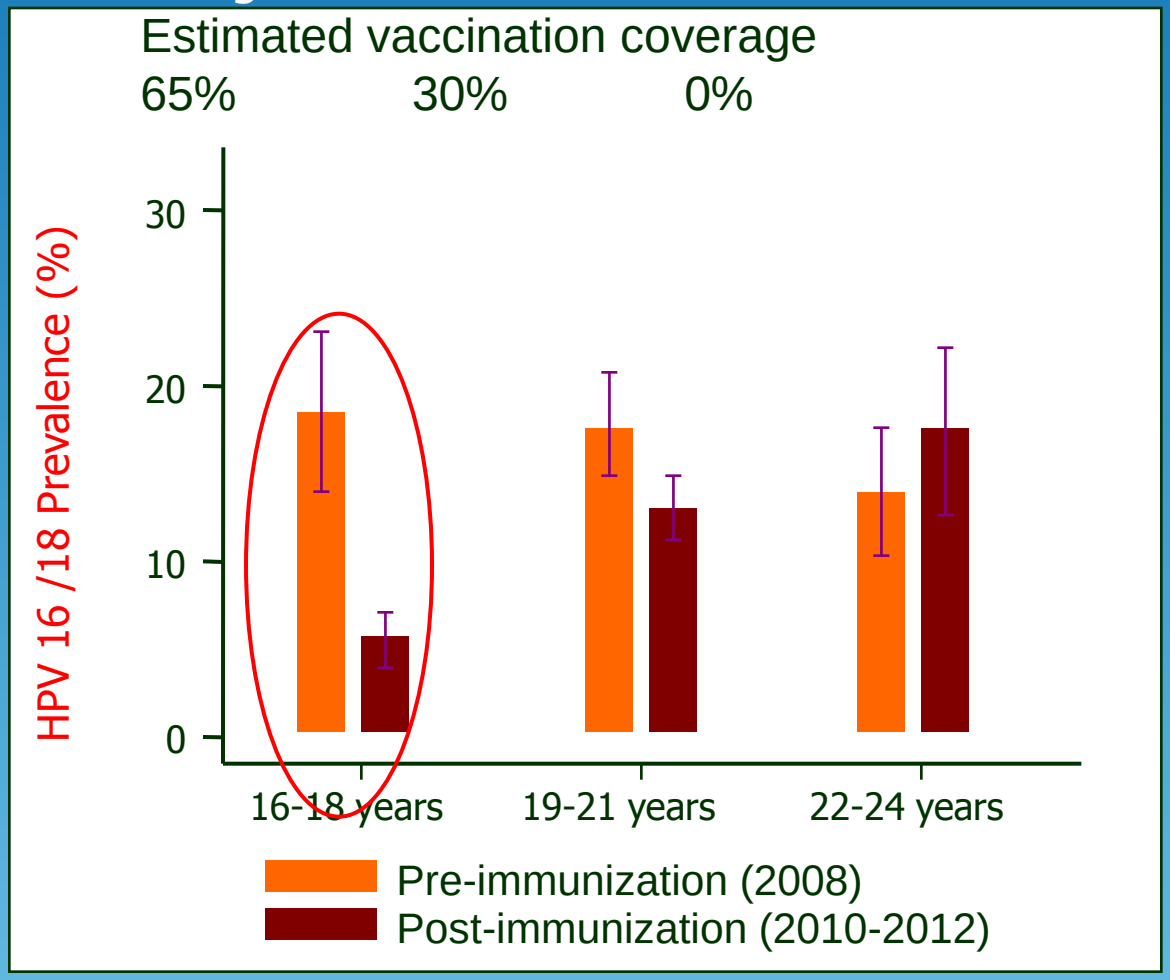


Kjaer SK et al IPC 2012 Nov 30 – Dec 6, Puerto Rico, EO7-669

UK: HPV infection surveillan

HPV 16, 18 infection significantly decreased

16-24 girls (n= 4,195) Vulva-vaginal swap undergo Chlamydia screening



Significant decrease of HPV 16/18 infections was observed in 16-18 years girls

DNA test changed from HC2 with linear array to Luminex based genotyping system

Mesher D Vaccine. 2013 Dec 17;32(1) 26-32

Length of protection

- Only time can tell but ..
- Mathematical model suggested protection over 20 years
- Even if booster is needed, both vaccines had demonstrated increase antibodies after booster. With the cost coming down, it could remain cost effective

Cost of screening

- Currently after the bi-valent or quadrivalent HPV vaccination, screening is still recommended because of 70%, and maybe 80% protection.
- Screening method need to be revisit as conventional cytology screening may become less sensitive
- Must screening be continued after vaccination even if prevention more than 90%

9-valent HPV vaccine

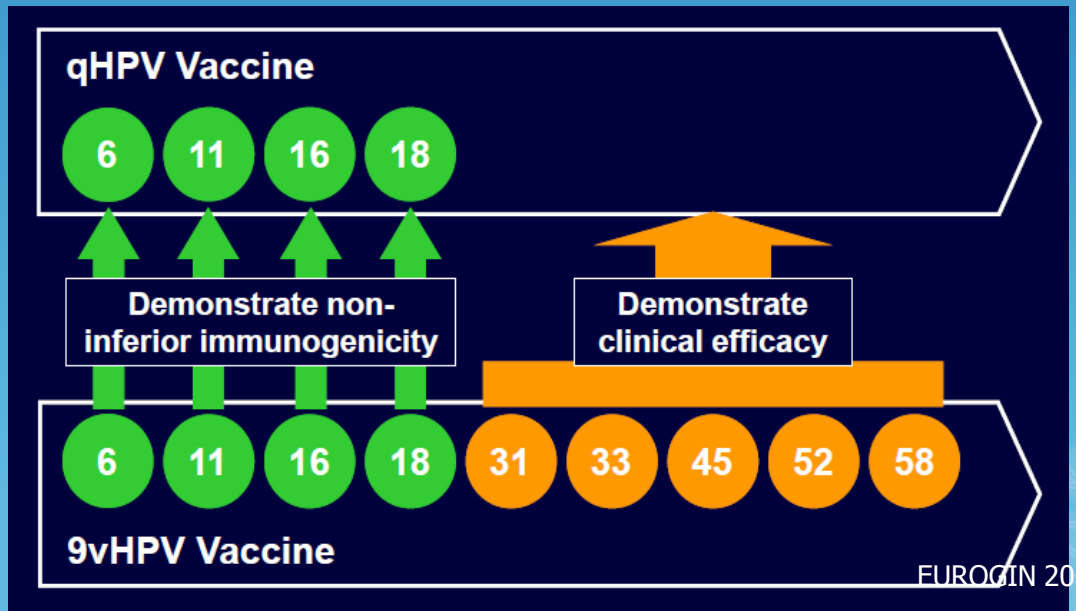
- Quadrivalent HPV vaccine (qHPV)

  HPV 6, 11 ~90% anogenital warts

  HPV 16, 18 ~70% CaCx

- Additional 5 oncogenic types:

  HPV 31, 33, 45, 52 and 58 account for ~20% of CaCx



Pivotal efficacy study (P001)

Efficacy

HPV types 6, 11, 16, 18: Non-inferior immune response

HPV types 31, 33, 45, 52, 58: ~97% reduction in diseases (≥CIN2, VIN2/3, VaIN2/3)

Safety

Generally well tolerated in >7,000 young women

Adverse experiences profile generally comparable between 9vHPV vaccine and qHPV vaccine

Higher frequency of injection-site AEs with 9vHPV vaccine

Most were of mild or moderate intensity

Adult-Adolescent immunobridging (P002)

Immunogenicity

Non-inferior immunogenicity in adolescent girls and boys vs. young women for all 9 vaccine HPV types

Supports bridging of efficacy findings in young women, 16 to 26 years of age, to girls and boys, 9 to 15 years of age

Immunogenicity comparable in boys vs. girls

Safety

Generally well tolerated in all 3 demographic groups

qHPV-9vHPV immunobridging (P009)

Immunogenicity

Comparable anti-HPV 6/11/16/18 GMTs in adolescent girls who received 9vHPV vaccine vs. adolescent girls who received qHPVvaccine

Supports bridging of efficacy findings with qHPV vaccine to 9vHPV vaccine

Safety

Safety profile comparable between 9vHPV vaccine and qHPV vaccine

Most injection-site reactions were of mild or moderate intensity

Conclusion of 9-valent HPV vaccine

Phase III clinical development program

- ~97% protection against HPV 31, 33, 45, 52, 58-related disease
- Non-inferior anti-HPV 6, 11, 16, 18 responses vs. qHPV vaccine
- Non-inferior immunogenicity in adolescents vs. adults
- Generally well tolerated

Current status

Investigational product currently under FDA review

Biggest hurdle

- Political will
- Public acceptance and implementation

Screening

- Cervical cytology has been used for cervical cancer screening
- It is effective with repeated screening
- Need infrastructure and quality assurance
- Follow-up colposcopy and treatment
- Good specificity but fair sensitivity despite use of computer aided screening and liquid based cytology
- High coverage of target population is needed

- Can we increase our screening performance?

What is the role of HPV testing in screening

- HPV testing alone yielded 97% sensitivity but only 94% specificity, 7% PPV and 6% colposcopy referral
- Alternative strategy: HPV testing – Pap triage – repeat HPV testing 12 months later for those with a positive HPV test but a negative Pap smear. 54% sensitive and 99% specific with 21 % PPV and 1.1% colposcopy referral
- Co-testing is 100% sensitive but 92% specific with 5.5% PPV and 7.9% colposcopy referral

Primary HPV Screening

USA - Co-testing (Cytology and HPV testing)
- Primary HPV screening with genotyping for women 25yo and older

Intention to commence in 2016

Netherlands - HPV testing with reflex LBC (Liquid based cytology)

Australia - HPV testing with partial genotyping and reflex LBC

USA

Screening For Women Ages 30-64

- Cytology + HPV testing (Cotesting) every 5 years is preferred
- Cytology alone every 3 years is acceptable

Rationale for Cotesting, Ages 30-64

- Increased detection of prevalent CIN3
- Decreased CIN3 in subsequent screening rounds
- Achieves risk of CIN3 equal to cytology alone @ 1-3year intervals
- Enhances detection of adenocarcinoma/AIS
- Minimizes the increased number of colposcopies, thus it reduces harms.

FDA NEWS RELEASE

For Immediate Release: April 24, 2014
Media Inquiries: Susan Laine, 301-796-5349 , susan.laine@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

Español

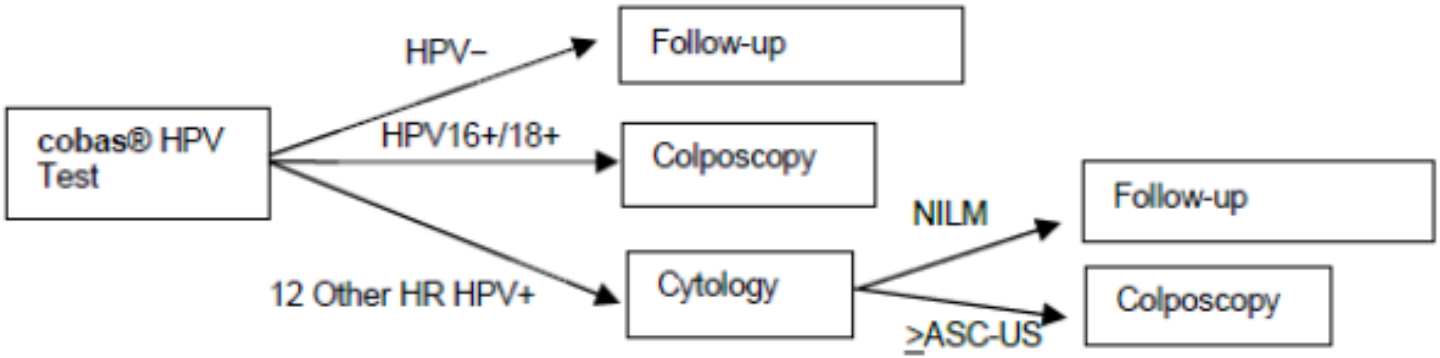
FDA approves first human papillomavirus test for primary cervical cancer screening

The U.S. Food and Drug Administration today approved the first FDA-approved HPV DNA test for women 25 and older that can be used alone to help a health care professional assess the need for a woman to undergo additional diagnostic testing for cervical cancer. The test also can provide information about the patient's risk for developing cervical cancer in the future.

Using a sample of cervical cells, the cobas HPV Test detects DNA from 14 high-risk HPV types. The test specifically identifies HPV 16 and HPV 18, while concurrently detecting 12 other types of high-risk HPVs.

Based on results of the cobas HPV Test, women who test positive for HPV 16 or HPV 18 should have a colposcopy, an exam using a device that illuminates and magnifies the cervix so a physician can directly observe the cervical cells. Women testing positive for one or more of the 12 other high-risk HPV types should have a Pap test to determine the need for a colposcopy. Health care professionals should use the cobas HPV Test results together with other information, such as the patient screening history and risk factors, and current professional guidelines.

Proposed New Indication - Candidate



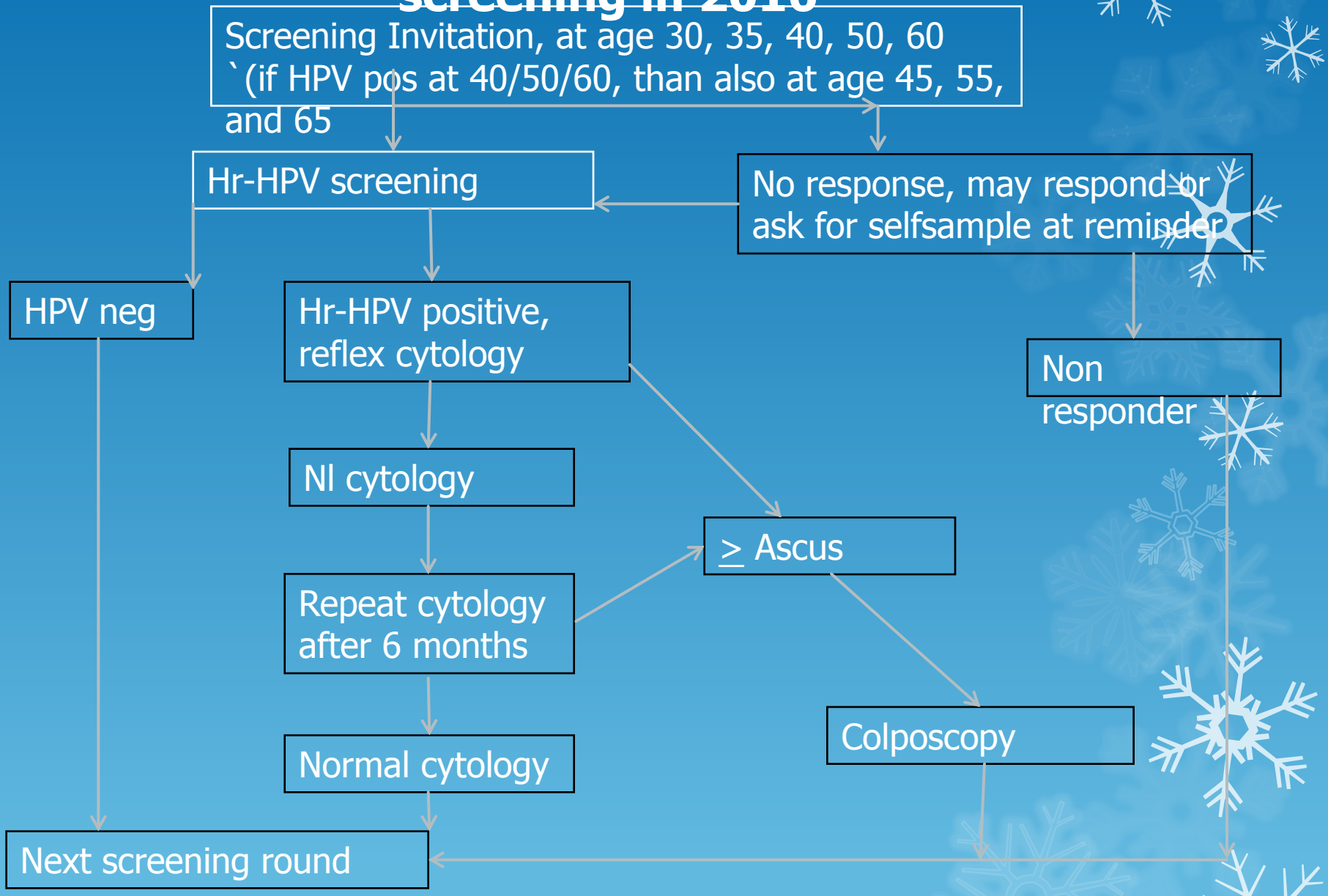
Cumulative incidence of invasive cervical carcinoma in women with negative entry test

	3.5 years	5.5 years
Experimental arm (HPV-based)	4.6 per 10^5 (1.1 – 12.1)	8.7 per 10^5 (3.3 – 18.6)
Control arm (cytology based)	15.4 per 10^5 (7.9 – 27.0)	36.0 per 10^5 (23.2 – 53.5)
Rate ratio was 0.30 (0.15 – 0.60)		

HPV-based screening provides 60 – 70% greater protection against invasive cervical carcinomas compared with cytology.

Guglielmo Ronco et al Lancet 2014;383:524-532

Netherlands proposed primary HPV screening in 2016



Renewal of the National Cervical Screening Program in Australia

Current Australian Screening Program

- Commence at Age 18
- 2-yearly pap smears
- Ceased at Age 70.

Renewal of the National Cervical Screening Program in Australia

Recommendations announced in April 2014

To commence 2016

Medical Services Advisory Committee (MSAC) Recommendations

- **five-yearly cervical screening** using a **primary human papillomavirus (HPV) test with partial HPV genotyping and reflex liquid-based cytology (LBC) triage**, for HPV vaccinated and unvaccinated **women 25 to 69 years of age**, with **exit testing of women 70 to 74 years of age**;

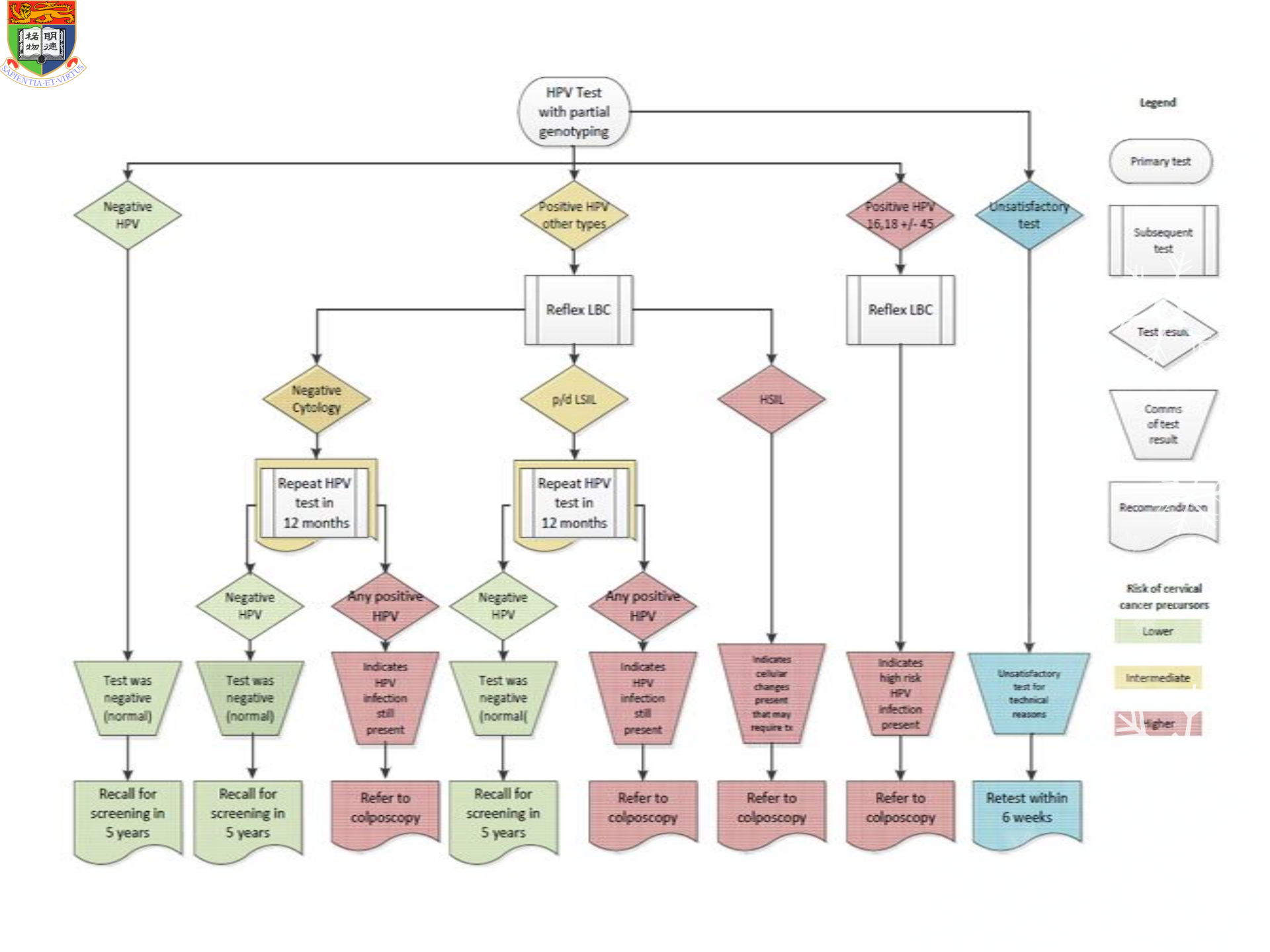
- self-collection of an HPV sample, for an under-screened or never-screened woman, which has been facilitated by a medical or nurse practitioner (or on behalf of a medical practitioner) who also offers mainstream cervical screening;

- invitations and reminders to be sent to women 25 to 69 years of age, and exit letters to be sent to women 70 to 74 years of age, to ensure the effectiveness of the program; and

- the de-listing of the Medicare Benefits Schedule (MBS) items for the existing cervical cancer screening test MBS items over a 6 to 12 month transition period.

Medical Services Advisory Committee (MSAC) **Recommendations**

- **five-yearly cervical screening**
- **(HPV) test with partial HPV genotyping**
- **reflex liquid-based cytology (LBC) triage,**
- **women 25 to 69 years of age**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Positive HPV other types
Positive HPV 16,18 +/- 45
Unsatisfactory test
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Negative Cytology
p/d LSIL
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Retest within 6 weeks
Legend
Primary test
Subsequent test
Test result
Comms of test result
Recommendation
Risk of cervical cancer precursors
Lower
Intermediate
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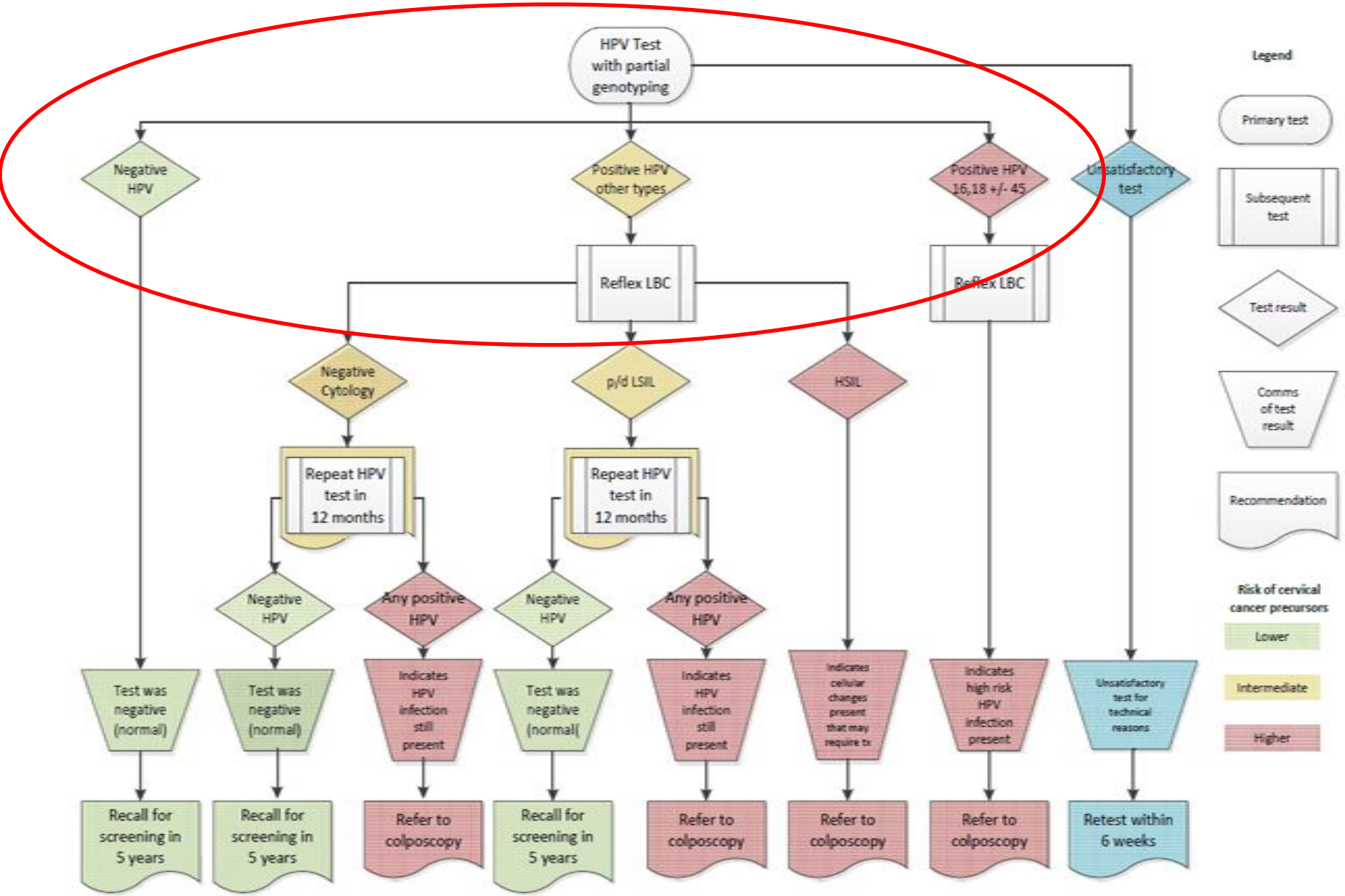
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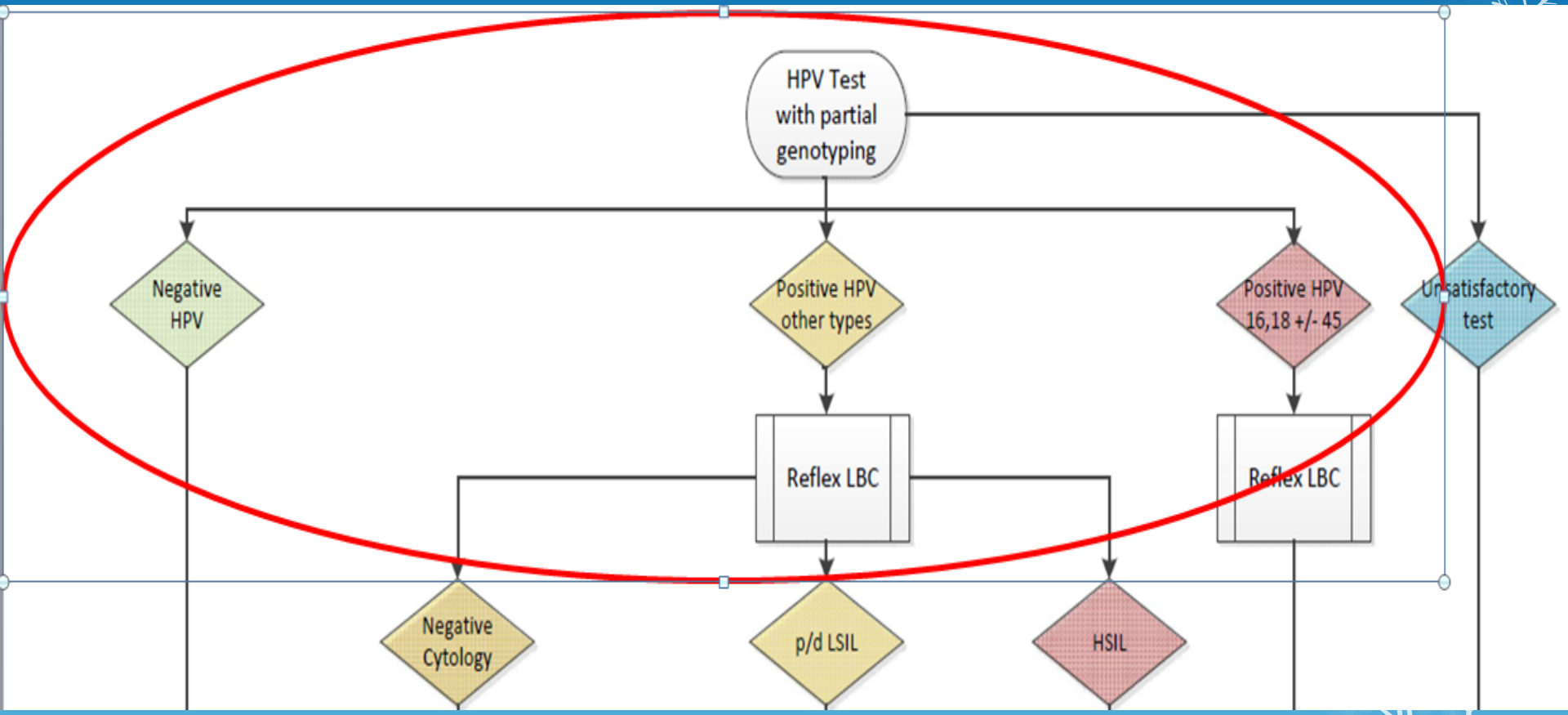
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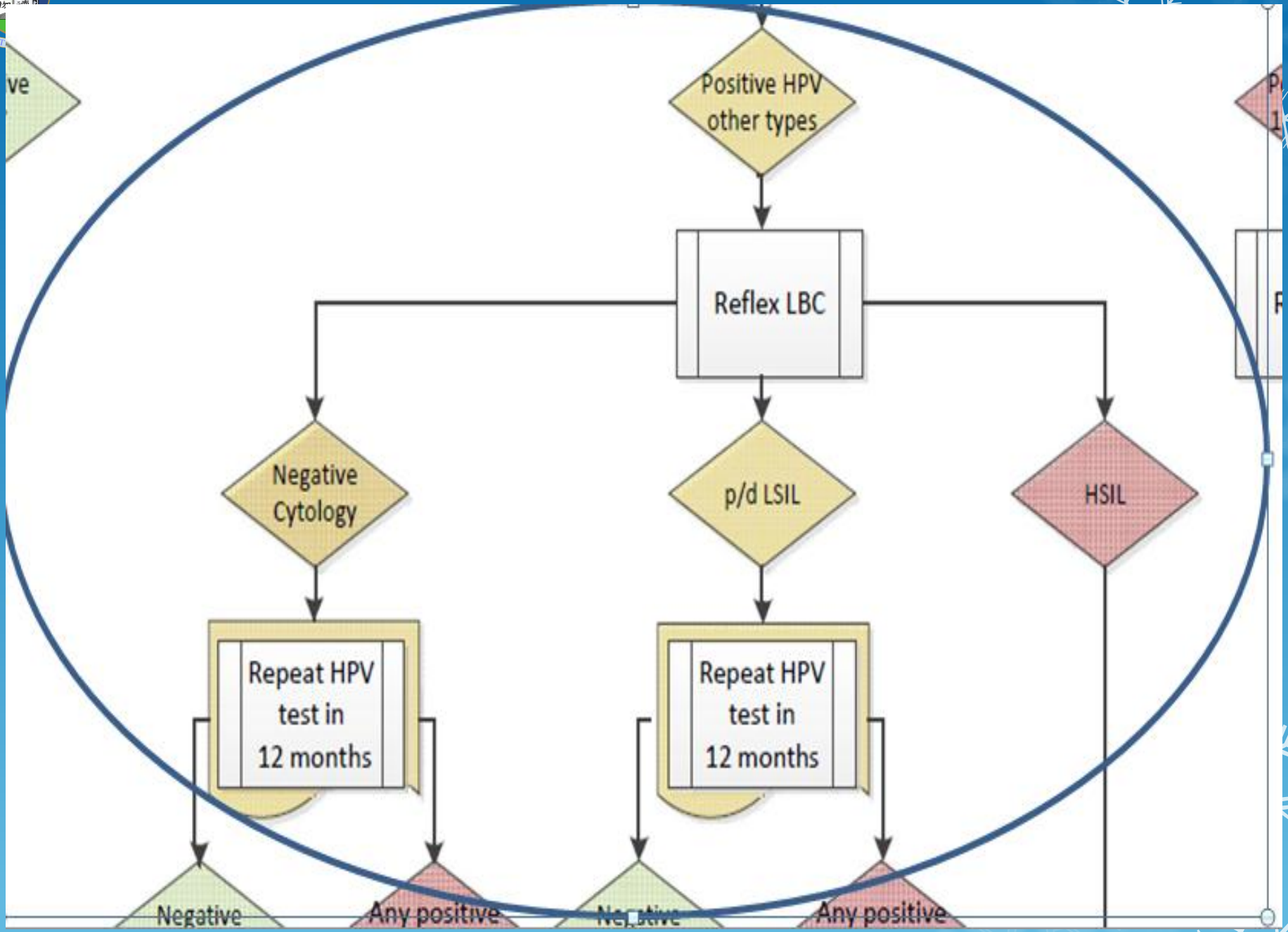
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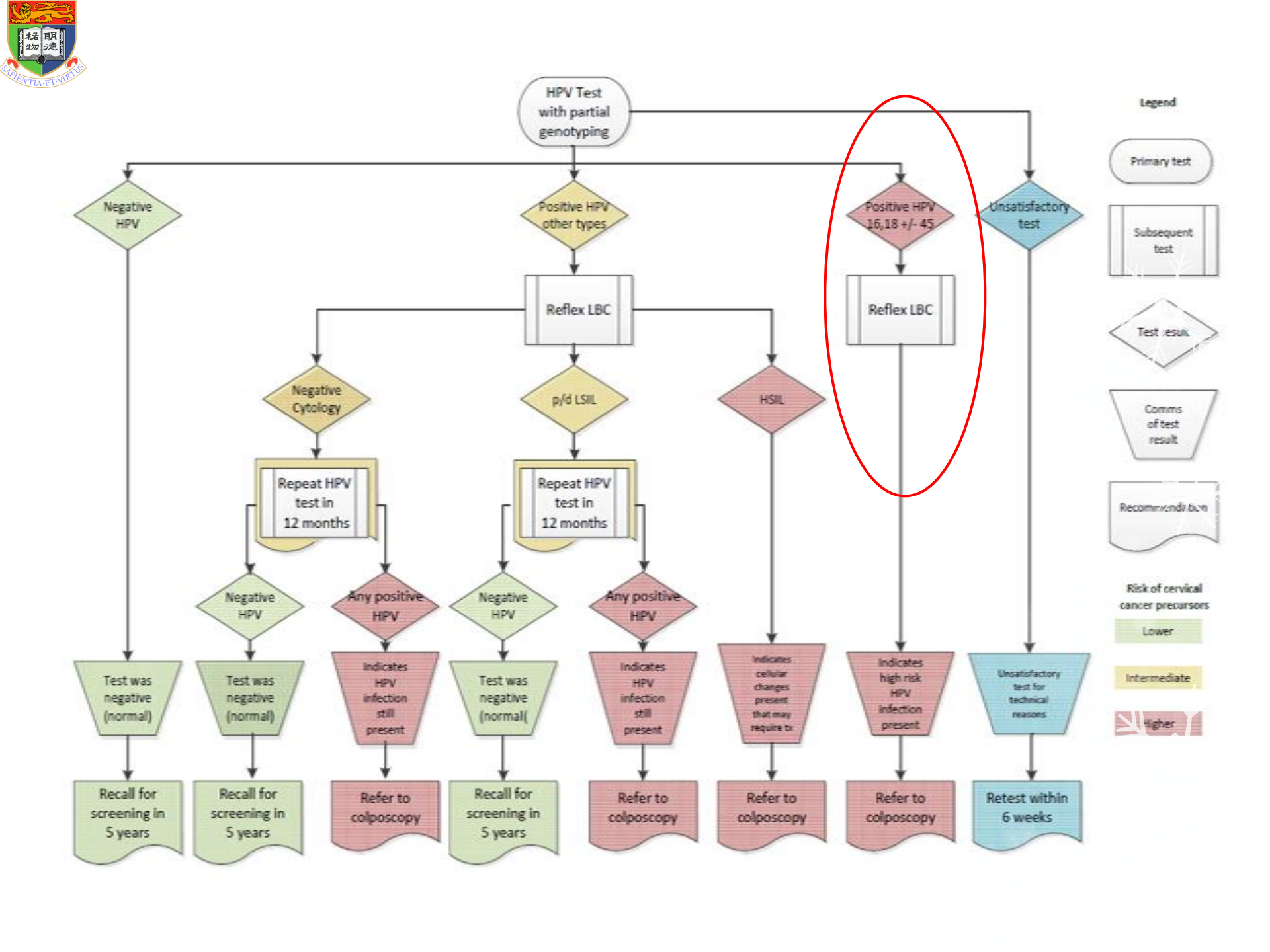
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Primary screening with HPV testing

- All agreed that the high negative predictive value is reassuring and can increase space between screening
- The challenge is on the best way to manage positive HPV testing

A randomized controlled trial comparing concomitant HPV–cytology testing with cytology testing for the detection of high grade cervical intraepithelial neoplasia in primary cervical cancer screening in Hong Kong

Department of Obs. & Gyn

The University of Hong Kong

- Positive HPV test in 8.7% of screened population
- Among them, 76% had normal cytology
- Referring all for colposcopy is not recommended
- We need good triaging to reduce unnecessary colposcopy and treatment

What other options for triage apart from cytology and genotyping?

Other options for triage after a positive HPV test

1. Dual staining: p16 and Ki67
2. RNA based test
3. Methylation Markers

Conclusions

- Cervical cancer prevention and control need further improvement
- Vaccination should be implemented now
- New screening strategy with HPV testing is forthcoming and new and better triaging test to be developed
- Need support from government and community