Dr Hazel Lewis

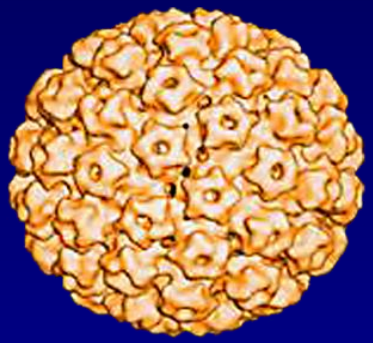
Clinical Leader

National Cervical Screening Programme

HPV Testing- It's Role in Cervical Screening - Concurrent Workshop Repeated

Friday, 16 August 2013	Start 2:00pm	Duration: 55mins	Van Gogh
	Start 3:05pm	Duration: 55mins	Van Gogh

HPV testing: its role in cervical screening



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Overview

- hrHPV risk and pathogenesis
- hrHPV testing in the NCSP
- Case scenarios
- Future direction of the NCSP

Workshop Learning's

Who is at risk of acquiring HPV

Describe progression from hrHPV infection to cervical cancer

Name the transmission routes of hrHPV infection

Identify the most common hrHPV types that are associated with cervical cancer

Know about when to refer to colposcopy

Understand when to test for hrHPV test (Guidelines for Cervical Screening in New Zealand, 2008)

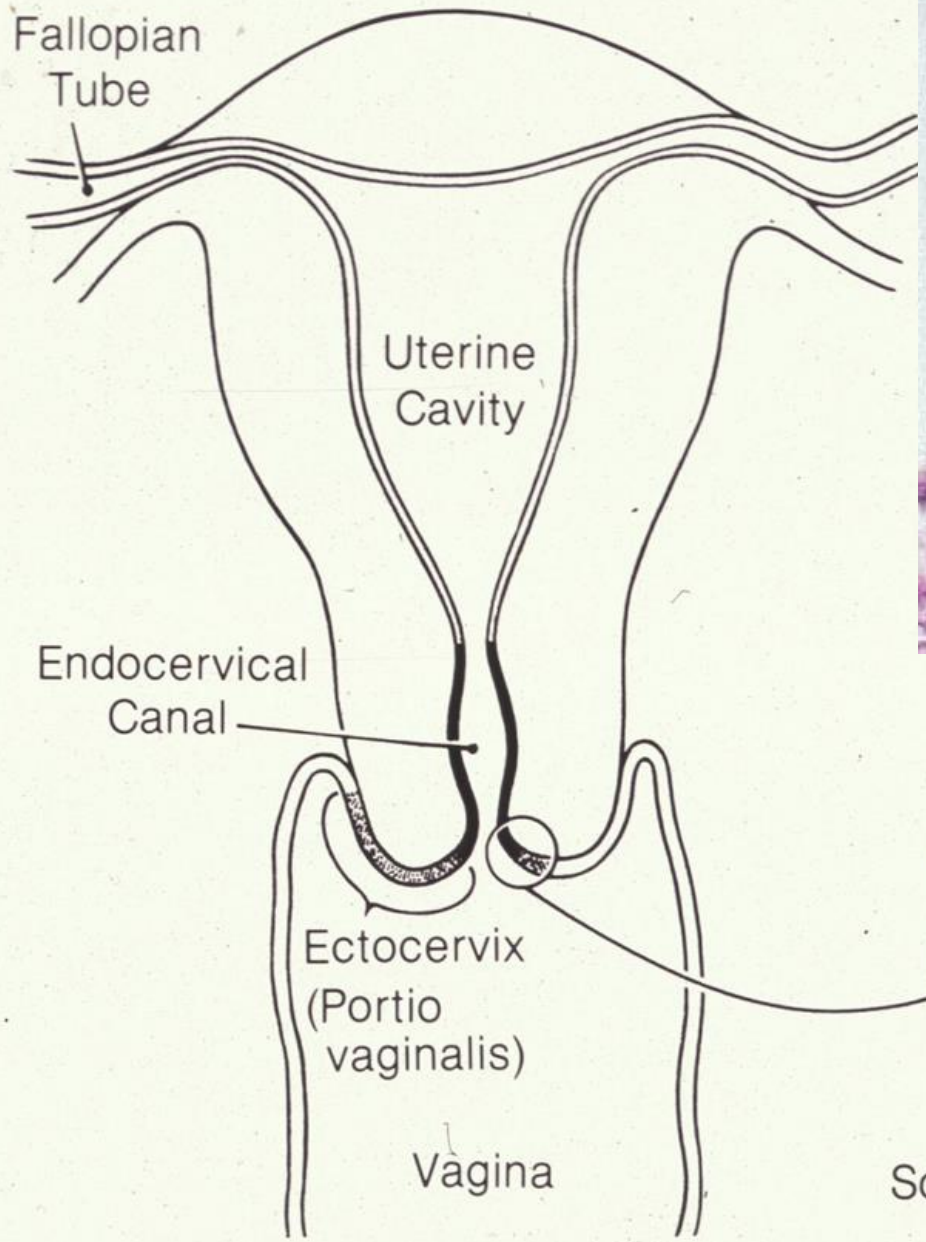
Understand how to interpret hrHPV test results

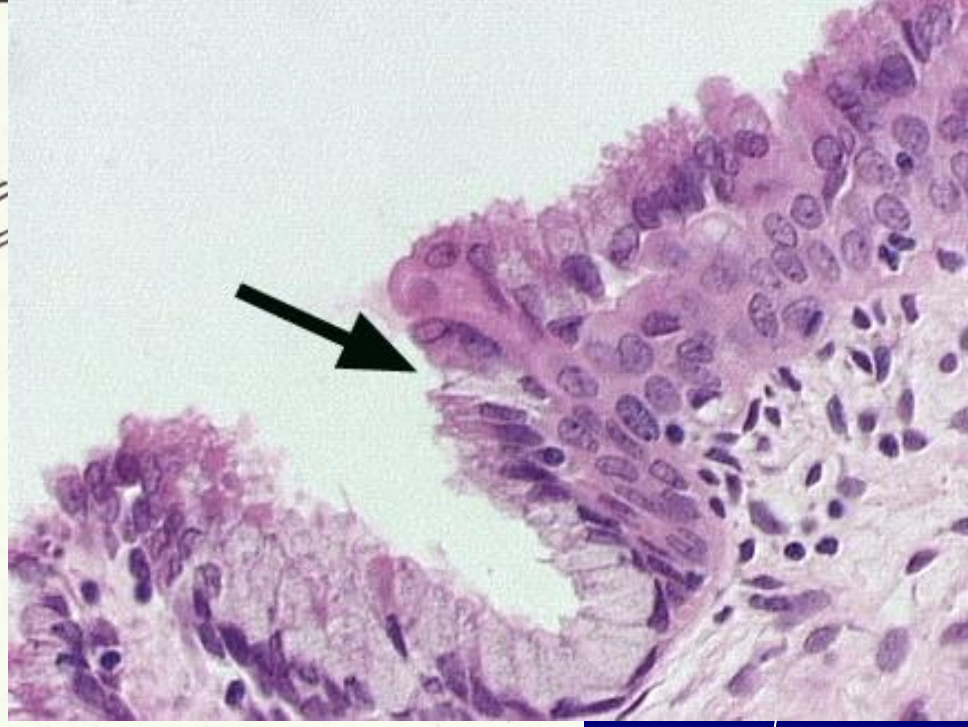
Understand how to manage women hrHPV positive

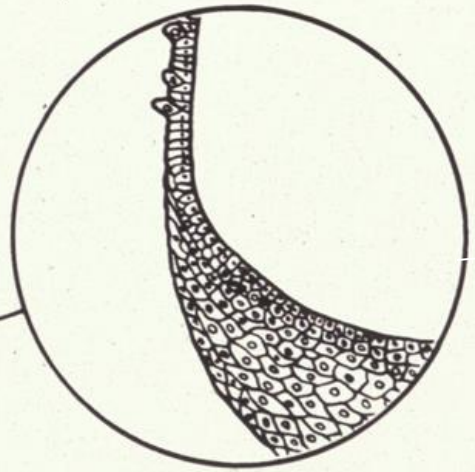
Explain the importance of cervical screening following HPV immunisation

Work through case scenarios

HPV Risk and Pathogenesis

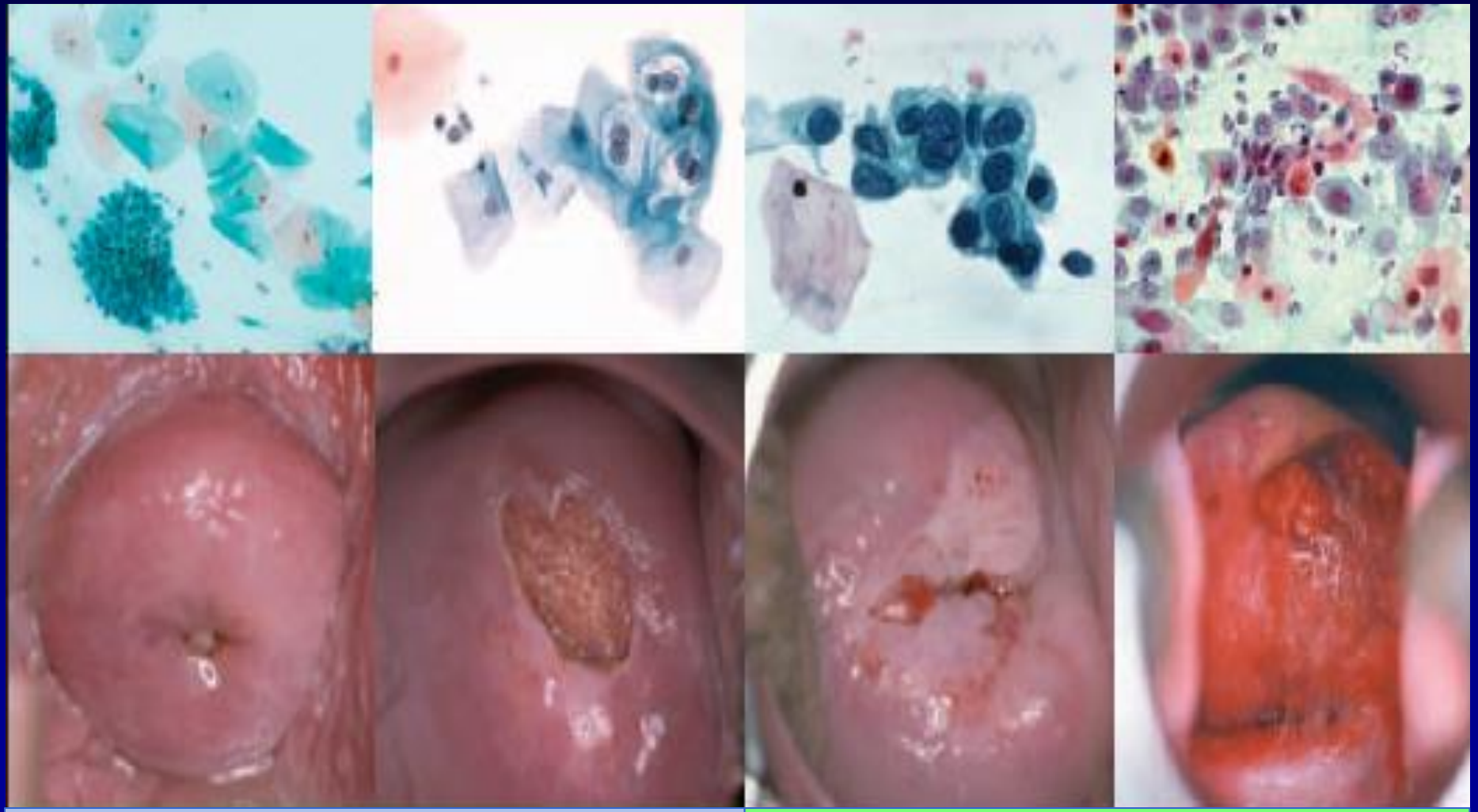






Squamocolumnar Junction
(Transformation Zone)

New model of cervical carcinogenesis



Transient infection

Persistent HPV

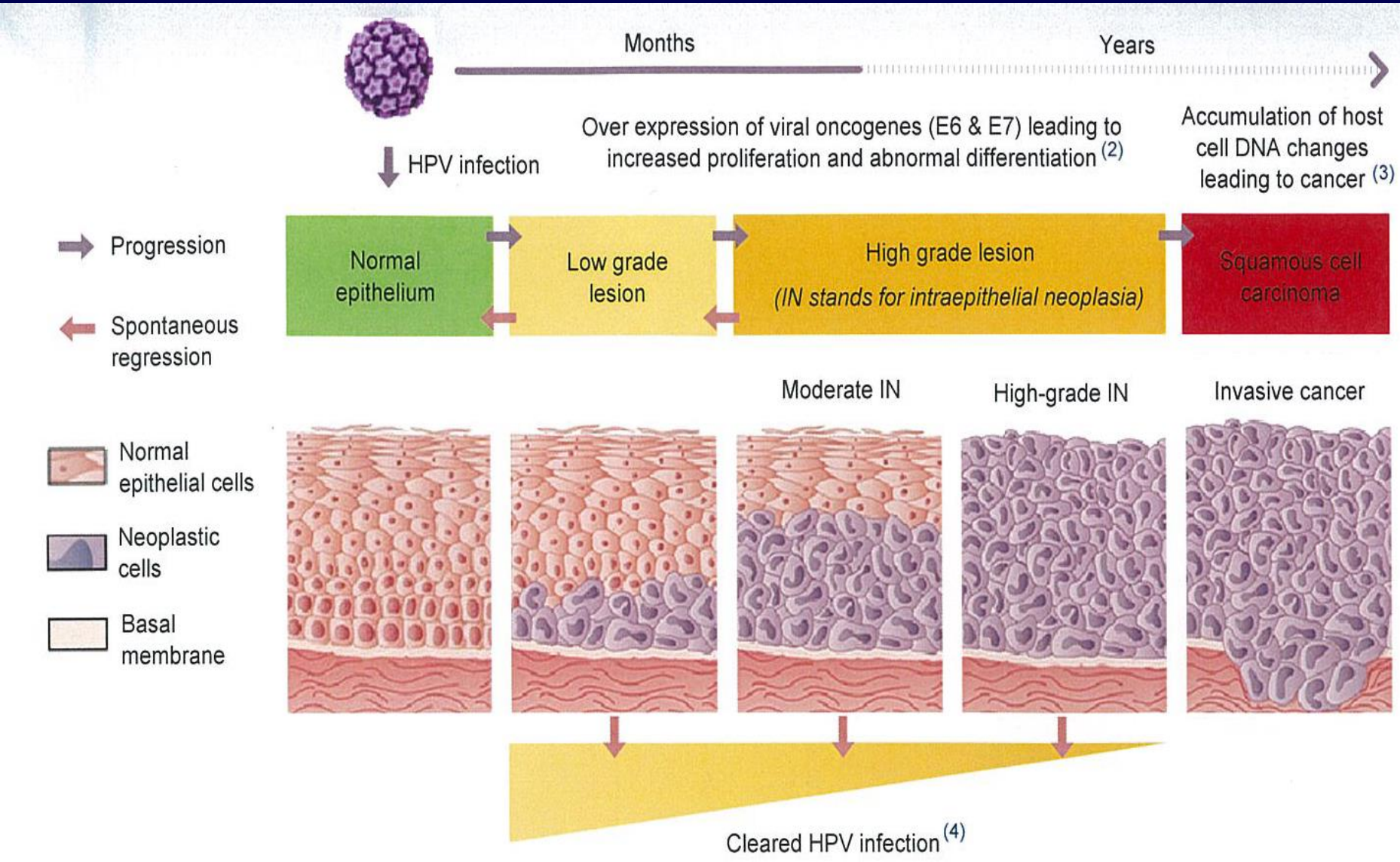
Normal cervix → INFECTION → **HPV-infected cervix** → PROGRESSION → **Precancer** → INVASION → **Cancer**

HPV-infected cervix → CLEARANCE → **Normal cervix**

HPV-infected cervix → REGRESSION? → **Normal cervix**

Pathogenesis of HPV infection of the cervical epithelium

Reference: EUROGIN 2012



HPV risk and pathogenesis

- HPV causes ~5% (10% in women) of all cancers worldwide
- HPV - the number 2 human carcinogen (after tobacco)

- Worldwide estimates on HPV burden: (EUROGIN 2010)
  - 1 out of 600 infections may lead to cancer
  - 1 out of 20 high grade lesions may lead to cervical cancer
  - 1 out of 60 low grade lesions may lead to cervical cancer

- HPV infections most commonly spread by genital to genital contact but also:
  - genital - anal
  - oral - genital
  - oral - oral
  - manual - genital

  And non sexual:
  - mother to newborn (vertical transmission)
  - mother to foetus (transplacental transmission)
  - fomites (eg underwear, gloves)

HPV risk and pathogenesis

- Most women and men get an HPV infection at some stage, most are unaware of infection and spread
- Risk of exposure related to sexual activity
- Individuals commonly carry multiple infections
- Most women and men control an HPV infection
- Few people develop HPV associated cancers:
  - linked to high risk HPV infection
  - linked to poor clearance of an HPV infection

  ie persistence
- Proper condom use may help to reduce risk but not fully protective against infections

HPV infections

- Most HPV infections in young women are transient, harmless and asymptomatic
- Infection does not protect against a subsequent infection with the same time or another type
- Over 50% new infections are cleared in 6-18 months, 80 – 90% in 2-5 years
- Rarely, infection becomes persistent

HPV infections

- Two major risk factors for cancer
  - HPV genotype
  - Persistent HPV infection
- ~ 40 oncogenic genotypes affect the genital tract
- ~ 15 are high risk types, types 16 and 18 most high risk
- Other risk factors: viral load, immunosuppression, smoking, other STIs, oral contraceptives, other

Cancer development

- If balance between the host and the virus disturbed - the virus escapes the immune system

- Persistent infection (not cleared in 2 years) increases the risk of pre-cancer

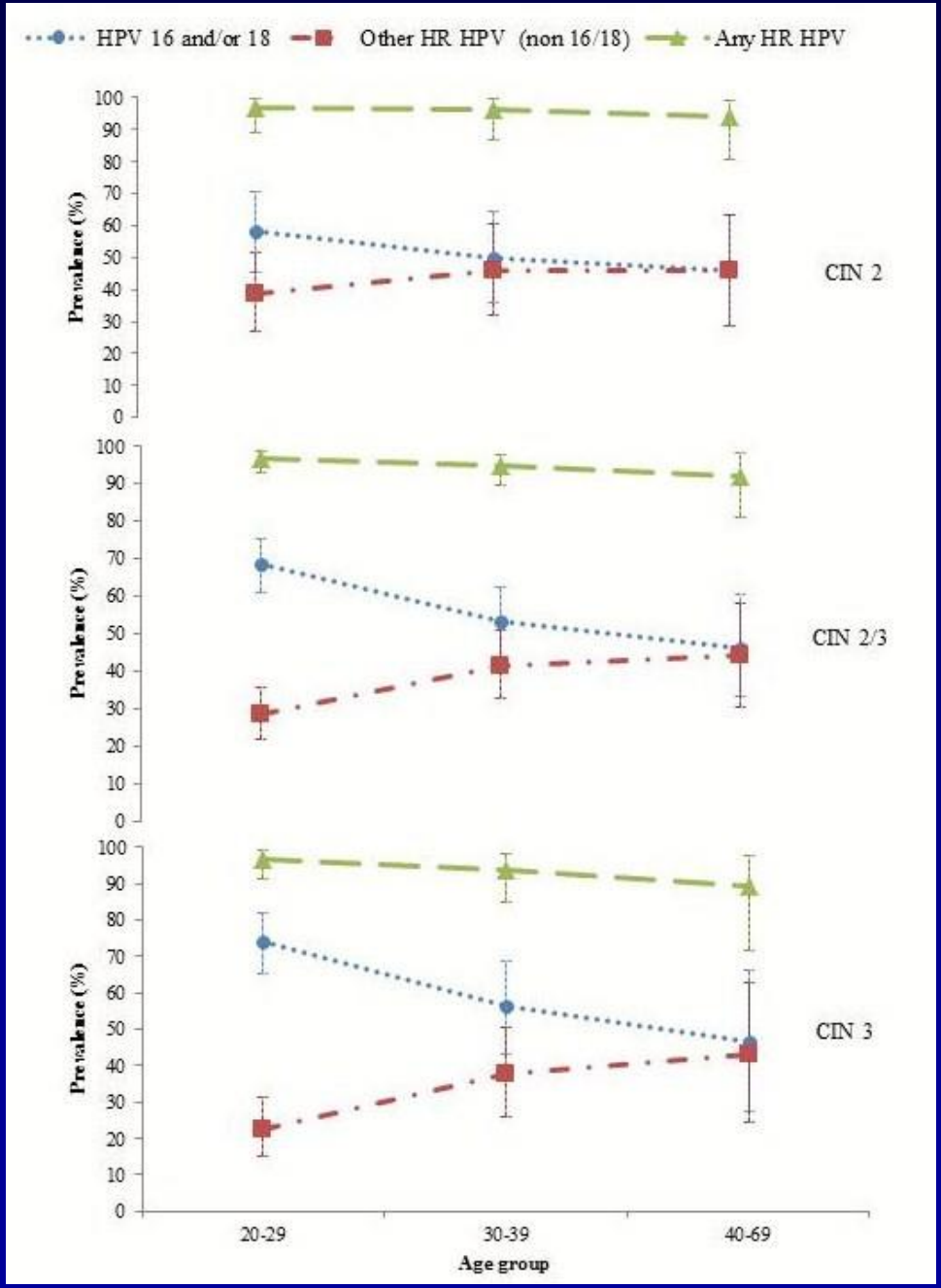
- Other factors (HPV genotype, infection with multiple HPV genotypes etc, and co-factors (immune status, nutritional factors, tobacco etc) may be important

- Cancer development is a rare occurrence of HPV infection

NZ age-specific prevalence of grouped oncogenic HPV types by histology grade

Simonella, Lewis, Smith, Neal,Bromhead, Canfell
Type-specific oncogenic human papillomavirus infection in high grade cervical disease in NZ.
BMC Infectious Diseases. 2013

Most common HPV types in women with CIN 2/3 were:
HPV 16 (51%)
HPV18 (12%)
HPV52 (19%)
HPV31 (17%)
HPV33 (13%)



QUESTION 1

Who is at risk of being infected with HPV?

- Only women
- Only sexually active men and women
- Only young men and women
- All men and women are susceptible to HPV

✓

Question 2

Which of the following are true or false?

- HPV infection is a necessary factor for cervical cancer development.

  True

- Most HPV infections clear within a few months

  True

- Cervical cancer is a rare outcome of HPV infection

  True

- The majority of HPV infections are without symptoms

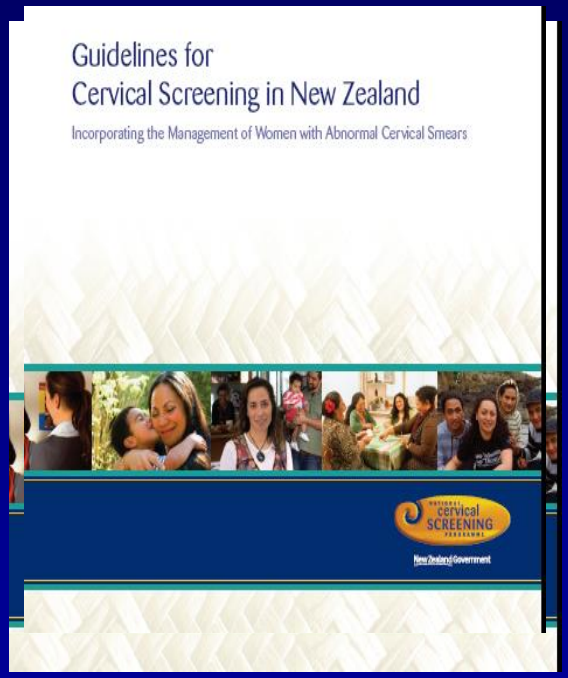
  True

Question 3

Name 3 factors which increase the risk of persistence of HPV infection

- Age
- Viral load
- HPV genotype
- Immunosuppression
- Smoking
- Oral contraception
- Other STIs

hrHPV testing
Guidelines for Cervical Screening in NZ



http://www.nsu.govt.nz/health-professionals/2747.aspx

NCSP Guidelines

- Cytology still the primary screening test
- 100% to LBC (liquid based cytology) for all cervical smears (ThinPrep + SurePath)
- Introduced HPV testing as adjunctive test in 3 situations:
  - triage women over 30 years, with ASCUS/LSIL smears
  - ‘test of cure’ after colposcopy and for ‘historical testing’ to manage women to 3 yearly screening following a high grade
  - manage women with discordant results at colposcopy

hrHPV triage for ASCUS/LSIL smear

- Women 30 years and over with ASC-US or LSIL result
- No abnormal smear report in last 5 years
- If positive for hrHPV, refer to colposcopy
- If negative hrHPV, recall in 12 months

NOTE: Laboratories will automatically carry out hrHPV testing on all women > 30 years who are assessed as ASCUS/LSIL. Women must be informed of this and any objection must be recorded on the laboratory request form

hrHPV testing post treatment or historical high grade abnormality on the NCSP Register

- Following treatment for CIN 2/3 lesions
- Previous HSIL / ASC-H cytology results
- 2 negative hrHPV and cytology results over 2 years – return to normal 3 yearly screening

NOTE: Informed consent for 1st hrHPV test request must be obtained for women who have had a high grade squamous abnormality recorded on the register

hrHPV testing clinical safety issues

- Guidelines for cervical screening recommend retesting at 12 monthly intervals
- However this may not be always realistic ie women may not return at the recommended time for follow up
- If two hrHPV test results are negative within approximately 24 months, recommend return to three yearly screening
- Where there are no high grade cytology / histology results recorded, it cannot be assumed that these are ‘squamous’ in origin, therefore hrHPV testing should not be requested

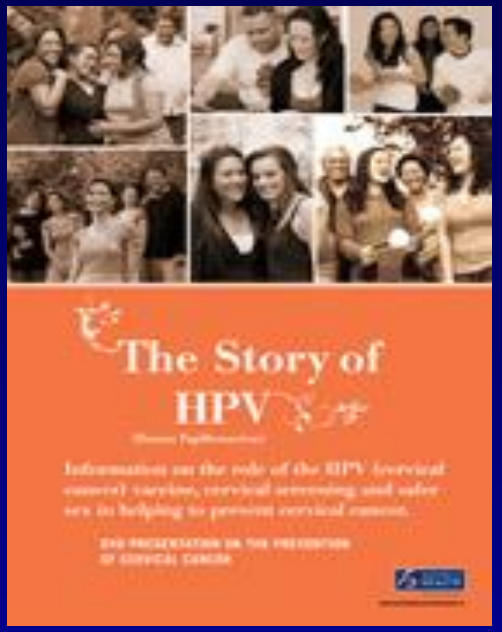
Interpreting HPV results …Principles

- Detects any of 14 hrHPV types
- ‘hrHPV detected’ means an infection with HPV, not necessarily persistent, nor disease of the cervix
- hrHPV test and cytology test both normal – very little risk of serious changes in cervix over 3-5 years
- hrHPV test is positive and cytology negative - most infections clear on their own. Cell changes may occur if HPV persists
- Specific interpretation and management of a positive or repeat positive hrHPV test depends on indication for and context of the test

Dual approach to cervical cancer prevention

- Cervical Screening
  www.cervicalscreening.govt.nz

- HPV vaccination
  www.cervicalcancervaccine.govt.nz



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Case Scenarios

CASE 1

Regular normal smears until 2008 when she had “atypical endometrial cells”. This was then labelled as “High Grade”. Despite a reason for the abnormal endometrial cells being found (not cervical) she has continued to be labelled as previous high grade. Because of this a smear taker requested hrHPV which was positive but cytology negative. Lab report recommended specialist referral. She never had a squamous lesion. She had a polyp. She had no clinical symptoms of concern. How would you manage?

- No cyto or histo HG hx, no reason to do hrHPV test
- However, request made and hrHPV positive, cyto neg, does not require referral
- Repeat hrHPV test in 12 months if negative, 3 yly screening, if positive, repeat yearly until negative

CASE 2

Had an ASC-H smear a year ago, was found to be low grade only at colposcopy. The cytology result remained as high grade on the register as there was no histo/cyto correlation amendment sent to the register following biopsy. Smear taker requested a hrHPV test a year after discharge from colposcopy, which was positive but her cyto result was negative. The lab report said refer to colposcopy. What would you do?

Refer to colposcopy? Yes. (persistent infection?) Cyto may be false neg? Colp may d/c if nothing found

Repeat hrHPV test in 1 year if pos, but cyto neg refer to colp? No, retest

Continue to test hrHPV and cyto annually until both negative? Yes unless concerned clinically or anxious woman – then refer

CASE 3

A 21 year old women attends your practice for contraceptive advice. On questioning she tells you she has had the HPV vaccine. What is your advice

Answer

Ask if she has she had 3 doses of the vaccine

Advise her that she still needs to participate in cervical screening and ensure she is entered on your screening recall register

Note that she has received HPV vaccine, on the laboratory request form for a cervical smear

CASE 4

Previous history of CIN3, treated by hysterectomy. Histology at hysterectomy showed the cervix to have some areas of squamous metaplasia, inflammation and repair. There was no evidence of CIN. There was no screening history on the NCSP register.

How would you manage this woman? Continue screening

Does she need yearly vault smears? Yes as hx of CIN3

Does she need HPV testing? Yes, if definitive CIN3, hrHPV testing x2 years, 12 months apart, then 3 yrly screening

Case 5

- 1999 cervical biopsy showed CIN 1 (LSIL)
- Normal cyto in subsequent years
- Total hysterectomy 2005 in the year
- Histology of cervix negative at hysterectomy

How would you manage this woman?

Stop screening as reverted to normal prior to hysterectomy.

(If CIN1 at hysterectomy, ie repeat smears annually x2, then stop screening if both negative)

Future Direction of NCSP: the next 5 years

Challenges

- Improve coverage
- Achieve equity in coverage and incidence
- Adapt to the HPV vaccination era

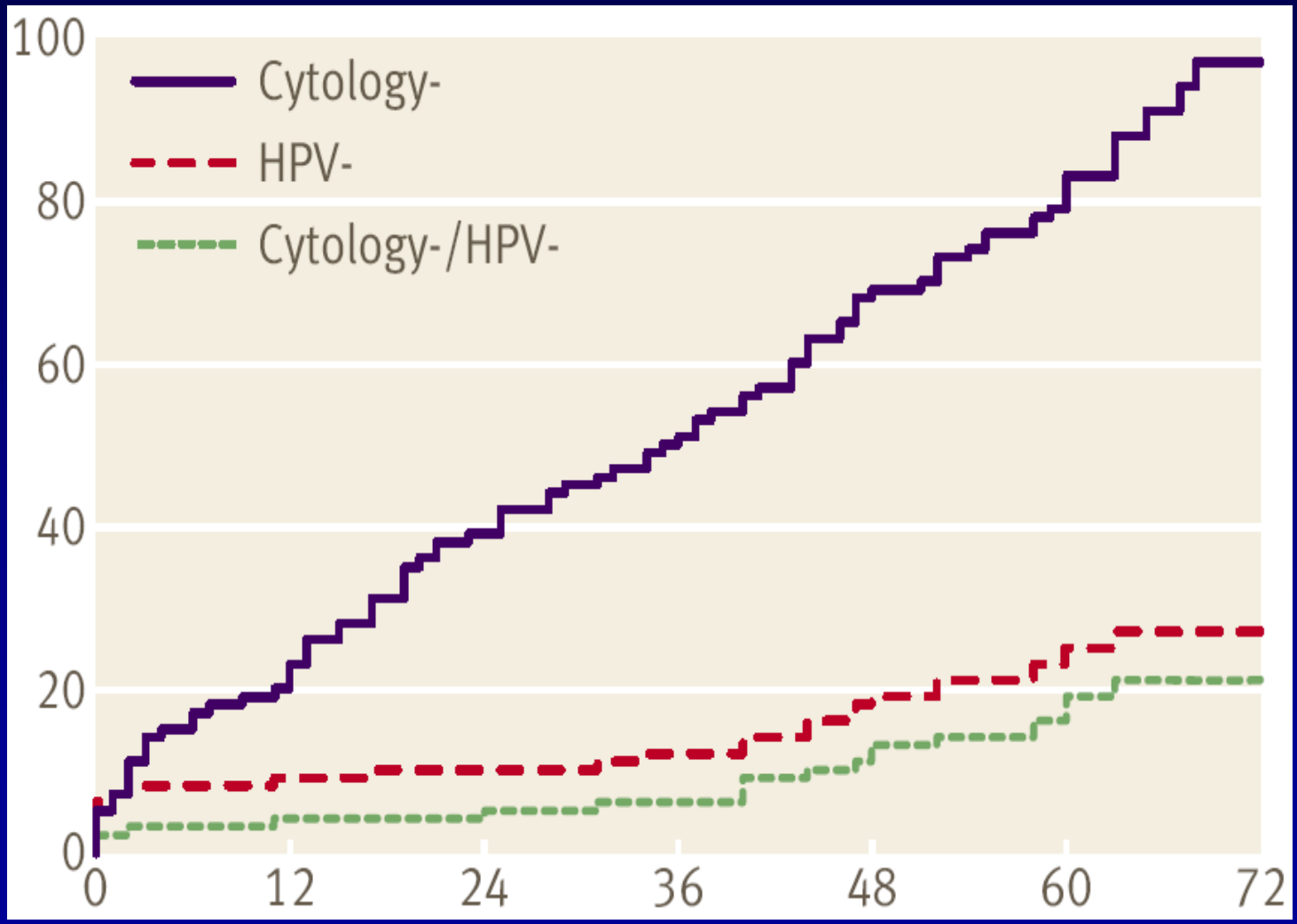
Planning for the future

- New strategies for screening could:
  - Improve effectiveness and cost-effectiveness
  - Maintain cost-effectiveness over the long term in context of vaccination

- **Consideration of transition to primary HPV screening at longer intervals**

HPV as primary screening test

Risk of CIN3 following a negative screening test



Dillner *et al*., BMJ, 2008

Thank you for your attention!

MINISTRY OF HEALTH
MANATŪ HAUORA

National cervical SCREENING PROGRAMME