CERVICAL SCREENING PRESENTATIONS

FOR PROVIDERS OF MEDICAL PRACTITIONER EDUCATION IN QUEENSLAND
Section 4: Clinical Skills

- (4.1 Communication Skills – see SET CD)
- 4.2 The Pap Smear
- 4.3 Interpretation of Cytology Reports
- 4.4 Management of Screen Detected Abnormalities
- 4.5 Follow-up and Referral
- 4.6 New Technologies
- 4.7 HPV Vaccine and HPV Testing
4.2 The Pap Smear
A Pap smear is a cytological test designed to detect abnormal cervical cells.
Screening test characteristics:

- **Sensitivity**: the ability of a test to pick up disease in those who have the disease. High sensitivity minimizes the false negative rate.
- **Specificity**: the ability of a test to tell someone who does not have a disease that they do not have it. High specificity minimizes the false positive rate.
Suitable cut-off point for a screening test

- Well subjects
- Diseased subjects

- 100% sensitivity
  - High FPR

- 100% specificity
  - High FNR

Suitable cut-off
The Pap smear is regarded to be very specific but only moderately sensitive. Regular screening prevents adverse outcome from uncommon false negative results. At least 90% of squamous cell cervical cancer can be prevented by regular 2-yearly screening.
Anatomy of the cervix:

- Cervical stroma – fibromuscular tissue
- Non-keratinising stratified squamous epithelium: protection glycogen for sperm
- Simple columnar epithelium (glandular): secreting ciliated
  - extends into endocervical glands
The transformation zone (TZ) is the area on the cervix where the squamo-columnar junction (SCJ) is, or has ever been.

The SCJ is the point at which the columnar cells of the endo-cervical canal meet the squamous cells of the ecto-cervix.
The position of the SCJ changes during a woman’s life under the influence of hormones.

The process by which the columnar cells are transformed into squamous cells, thus moving the position of the SCJ, is called squamous metaplasia.

Squamous metaplasia is a normal process.
THE TRANSFORMATION ZONE

columnar cells

area of metaplasia (transformation zone)
original squamo-columnar junction

squamous cells

cells lining endocervical canal

transformation zone

cells on ectocervix
Transformation Zone

Cervix and cervical canal

Squamo-columnar junction

Transformation zone

Squamo-columnar junction
Squamocolumnar Junction:
Equipment for Pap Smear Collection
Which Implement?

- Can you see SCJ?
- Where is it?
- Sample the Transformation zone
- In most premenopausal women - sampler alone or spatula plus cytobrush are equivalent for sample quality
Nulliparous:
Multiparous:
Wide Ectropion:
Atrophic:
Difficultysampling
transformation zone

- Post-menopausal
  (TZ moves up canal- vaginal oestrogen prior to test improves adequacy)
- Past cervical surgery eg diathermy, LLETZ, cone biopsy

*Always use cytobrush in addition to (after!) sampler or spatula*
There is consensus that a satisfactory Pap smear should:

- Contain sufficient cellular material from transformation zone (≥ 10,000 squamous epithelial cells)
- Be appropriately fixed
- Have clearly visible cellular material which is not obscured by blood or inflammatory cells
Endocervical cells:

- Good indicator that TZ has been sampled
- Provide opportunity to detect glandular abnormalities
- No evidence that a lack of endocervical cells is associated with a decreased detection rate of abnormalities
Endocervical cells cont’d:

- It is recommended that an endocervical component is present in at least 85% of smears collected.
- It is more important that the practitioner has visualised and sampled TZ.
4.3 Interpretation of Results
Include all relevant information on the Pap smear request form to assist interpretation and recommendations:

- Identifying details
- LNMP
- Hormonal therapy
- Symptoms e.g. PCB, IMB
- Abnormal appearance of cervix
- Pregnancy
- Past history of abnormal smears
- ATSI status
Pap smear results are now reported using the Australian Modified Bethesda System (AMBS) 2004 terminology.

- Adopted in Australia in July 2006

Rationale for terminology change

- Poor reproducibility for distinguishing between the 3 subtypes of low-grade cytology (Atypia/CIN 1/HPV)
- New knowledge that low grade cytology mostly represents the changes of HPV infection in the squamous cells
- Brings Australian terminology closer to the international Bethesda terminology

Slide courtesy of Dr James Nicklin
<table>
<thead>
<tr>
<th>2006 Terminology</th>
<th>1994 Terminology</th>
</tr>
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<tbody>
<tr>
<td>Unsatisfactory</td>
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</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Squamous abnormalities (squamous intraepithelial lesions- SILs)</td>
<td>Low-grade abnormalities</td>
</tr>
<tr>
<td>● Possible LSIL</td>
<td>● Non-specific minor change</td>
</tr>
<tr>
<td>● LSIL</td>
<td>● HPV effect</td>
</tr>
<tr>
<td>● Possible HSIL</td>
<td>● CIN1</td>
</tr>
<tr>
<td>● HSIL</td>
<td>● Glandular changes</td>
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<td>Glandular abnormalities</td>
<td>Inconclusive</td>
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<td></td>
<td>High-grade abnormalities</td>
</tr>
<tr>
<td></td>
<td>● CIN2, CIN3, AIS</td>
</tr>
<tr>
<td></td>
<td>● Cancer</td>
</tr>
</tbody>
</table>
1. Squamous abnormalities

- Possible low-grade squamous intraepithelial lesion (LSIL)
- LSIL
  - previous HPV effect or CIN 1
- Possible high-grade squamous intraepithelial lesion (HSIL)
  - previous inconclusive
- HSIL
  - previous CIN 2 or 3
- Squamous cell carcinoma
2. Glandular abnormalities

- Atypical endocervical cells of uncertain significance
- Atypical glandular cells of uncertain significance
- Possible high-grade glandular lesion
- Endocervical adenocarcinoma-in-situ
- Adenocarcinoma
Technically Unsatisfactory

- Material inadequate for assessment due to:
  - paucity of squamous cells on slide
  - covering of blood or inflammatory exudate*
  - poor fixation
  - Atrophic*

Repeat in 6-12 weeks
*after correction of problem
Pap smear report forms:

Differ in their format but include the following categories

- Specimen
- Category/diagnosis
- Adequacy
- Descriptive diagnosis
- Recommendations
Pap smear report forms:

Lab No: 27960-6523 RB06CG27937
Specimen: Cervix, Conventional Smear

RESULT
NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY

SPECIFIC DIAGNOSIS
No cellular evidence of neoplasia.
An endocervical component is present.

RECOMMENDATION
Please repeat in 2 years, unless there is a clinical indication or specialist directive to the contrary.

Reported for:
Dr Daniel James
Director of Cytopathology.
Histology Results:

- Terminology for cervical histology remains unchanged, and will be reported as CIN 1,2 or 3
4.4 Management of Screen Detected Abnormalities
NHMRC Guidelines apply for the management of asymptomatic women. Women who are symptomatic need to be managed accordingly irrespective of their results from the cervical screening process.
Why Change?

- 1994 guidelines rescinded by NH&MRC
- Terminology not internationally consistent
- **New knowledge about HPV**
  - Unnecessary investigation and treatment (especially young women)
  - Unnecessary anxiety about cancer
  - Costs of treatment – physical, fertility, emotional, psychosexual, financial
New Information

High quality Australian evidence available following the introduction of Pap Smear Registers (large cohort studies)

- Increased number of ‘unnecessary’ repeat Pap smears for a small group of women
- Increased number of referral for colposcopy after any single change
- Invasive cancer still more likely in the unscreened population
Key Changes in New Guidelines

- Terminology
- More conservative management of women with LSIL
- Specific recommendations related to colposcopy and treatment
- Treatment of low grade lesions not recommended
- Clear pathway for women back to routine screening
- Follow up for all glandular lesions and possible HSIL results (Inconclusive) more specific
- Specific guidelines relating to high grade squamous and high grade glandular lesions
- Special circumstances also includes immunosuppressed women, women exposed to DES (previous - pregnancy and post hysterectomy only)
- Normal endometrial cells won’t be reported
Management of abnormal smears is now simplified into two main streams.
### Summary of the Previous Guidelines (1994)

#### Low Grade Epithelial Abnormalities

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<td>Non-specific minor squamous cell changes/atypia</td>
<td>Repeat smear in 6 months using cytobrush and spatula. If low grade abnormality persists, refer for colposcopy and biopsy if indicated.</td>
<td>Repeat smear at 12 monthly intervals until it reverts to normal.</td>
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<td>Repeat smear at 6 monthly intervals. If HPV-associated cell changes persist after 12 months, refer for colposcopy.</td>
<td>If endocervical cell abnormality confirmed, refer to gynaecologist for appropriate treatment.</td>
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**Anything high grade = refer**

Repeat smear 6 months x 2, colp if persists

Repeat smear 12 months

CIN 1 = Refer for colposcopy

Slide courtesy of Dr James Nicklin
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Refer any glandular abnormality

Repeat smear in 12 months

Anything high grade = refer
Management of abnormal smears

- **Squamous abnormality**
  - Possible low-grade
  - Low-grade
  - Possible high grade
  - High grade

- **Glandular abnormality**
  - Atypical cells
  - Possible high grade
  - High grade

- Rpt pap at 12 months

- Colposcopy

Slide courtesy of Dr James Nicklin
Management of abnormal smears

- **Squamous abnormality**
  - Possible low-grade
  - Low-grade
  - Possible high grade
  - High grade
  - Rpt pap at 12 months

- **Glandular abnormality**
  - Atypical cells
  - Possible high grade
  - High grade
  - Colposcopy
Follow-up:

- LSIL smears
  - repeat cytology at 12 months
  - if LSIL persists:
    → Colposcopy and biopsy

If confirmed low grade change-NO TREATMENT
INDEX SMEAR

LSIL
Definite or possible

ALL AGES

Repeat Pap test at 12 months

NEGATIVE

Repeat Pap test at 12 months

NEGATIVE

ROUTINE SCREENING

LSIL
Definite or possible

HSIL
Definite or possible

COLPOSCOPY

If the woman is aged more than 30 years, and has no history of negative cytology in the previous 2–3 years, she should be offered immediate colposcopy or a repeat smear in 6 months.

LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion.

See Section 6.7 for discussion and a guideline on fluctuating abnormalities.

Figure 6.1 Management of a cytological prediction of possible or definite LSIL.
- Low grade abnormalities are the result of a productive HPV infection
- Most HPV will clear
- “The common cold of sexual activity”

.............Professor Ian Hammond

Slide courtesy of Dr James Nicklin
HSIL smears → colposcopy ± biopsy

NO CHANGE in management

NB. following treatment, HPV typing is recommended as “test of cure” before resuming 2 yrly smears
Proposed management pathway

CIN 2/3 treated

Colposcopy & cytology at 4-6 month

HPV test & cytology at 12 months

HPV test & cytology at 24 months

HPV positive & Negative Pap test

Yearly smear & HPV test continues

HPV negative & smear negative x 2

HPV negative & Pap test negative x 2

Usual screening interval

* Women only managed on this pathway if normal cytology
* Safely evaluated at 5 & 10 years

High Grade: Follow up after treatment of HGEA

Slide courtesy of Dr James Nicklin
Currently prevent 1200 cancers/year
Still 400 invasive cancers per year in women aged 20-69 yrs, almost all of whom lack a regular screening history.
Most of the benefit comes from identifying and treating high grade cytology
Most of the harm comes from investigating and treating women with low grade cytology
Glandular Smear Abnormalities

- Rare ~ 1 in 1500 ♀ have glandular smear abnormality (cf 1 in 75 – 100 squamous)

- Important because ~ 20% of all cervical cancers are adenocarcinoma.
Glandular abnormalities - all require colposcopy
Abnormal Smear in Pregnancy

- Management of low grade smear same as for the non-pregnant patient
- High grade smear - colposcopy
Immunosuppressed Women

- Colposcopy even for women with low grade cytology
- Follow-up after treatment should include cytology and colposcopy
- Follow-up should be annual and indefinite
Diethylstilboestrol (DES) Exposed (in utero) Women

- Annual cytology and colposcopy of the cervix and vagina
- Continued indefinitely (balanced perspective maintained)
Endometrial cells

- Current evidence does not support an association between normal endometrial cells on a smear in post-menopausal women and abnormality esp. endometrial carcinoma
- New guidelines → normal endometrial cells should not be reported in asymptomatic post-menopausal women
Inflammatory Smear

- If there are no abnormal cells and the smear is satisfactory, repeat as usual.
- If smear is unsatisfactory repeat in 6-8 weeks, after treatment for any specific organism present on smear or swabs (use LBC with repeat).
- If smear is persistently inflammatory and unsatisfactory refer for colposcopy.
Evidence based guidelines

Guidelines are not prescriptive (except to laboratories)

Clinicians and women can still customise the management of individual women.

A safety monitoring program has been developed and will be overseen by a “transparent”, multidisciplinary team including consumers Australian Screening Advisory Committee.
4.5 Follow-up and Referral
• It is the responsibility of the Pap smear provider to establish with a woman a mutually acceptable method of obtaining the results of her Pap smear.
• The practitioner has a duty of care to ensure that abnormal results are communicated.
• If referral is necessary, attendance for assessment must be monitored.
A protocol for notifying women of abnormal results and a documented recall system is an important risk management strategy.

The most frequent legal claims against Pap smear providers concern failure to communicate test findings.
4.6 New Technologies
The limitations of the Pap smear have generated development of devices to improve sensitivity and specificity and address workforce shortages of cytologists.
At present, the relative improvement in sensitivity conferred by the new technologies is not sufficient to mandate their universal introduction. Until there are data demonstrating cost effectiveness of the new technologies on a population basis, their increased uptake cannot be justified from a public health perspective.

Australian Health Technology Advisory Committee (1998). MSAC is presently reviewing automated Liquid Based Cytology in Australia.
False Negative Results

- Sampling - no abnormal cells in sample because of failure to collect or transfer
- Laboratory - abnormal cells not detected or misinterpreted by the laboratory
- False negatives in women whose disease is thought to be rapidly progressive (considered to be uncommon)
False Negatives

- 5-10% for low-grade and high-grade abnormalities
- Improvements in sensitivity using new technologies would mean that the rate of abnormalities reported as high-grade would alter from about 1% of all smears to 1.05%
Two groups of technologies:
1. Liquid-based Cytology (LBC)-ThinPrep®
   - allows removal of excess blood, inflammatory exudate and mucus
   - produces a monolayer of cells on the slide
   (this slide preparation method may reduce unsatisfactory results and increase sensitivity)
2. Computer-assisted Screening (AutoPap®, AutoCyte SCREEN®, PAPNET®)

- device reviews slide and determines “most diagnostic” cell groups for presentation to the cytologist.
Role of LBC

- No Guidelines on the place of LBC and semi-automated cervical screening devices
- MSAC reviewed 2002 – no change in recommendations for HIC funding of LBC
- In some other countries being used as primary screening method (UK - 3 yrly screening with LBC only)
Qld Health policy for the use of LBC:

The use of LBC as an adjunctive (split sample) test is recommended if:

- The woman’s last Pap smear was unsatisfactory because of inflammatory cells or blood
- The woman has a history of unsatisfactory smears
- There are clinical indications that the current Pap smear will result in an unsatisfactory report
LBC – meta analysis

- Australian Meta analysis of 56 studies
  (Lancet 2006; 367:122-31)
- no evidence that LBC detected more high grade lesions OR reduced proportion of unsatisfactory
- Equivalent performance may justify use if it has other advantages eg HPV DNA testing, reduces reading times or is more economical
New Tests for Cervical Cancer Screening:

<table>
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<tr>
<th>Test</th>
<th>Goals</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<td>Liquid-based preparations e.g. ThinPrep, AutoCyte Prep</td>
<td>Improve the quality of the Pap smear. Decrease unsatisfactory Pap smears. Increase detection of cancer precursors</td>
<td>High-quality smear for review. Improved transfer of cells from collection device. Residual material may be used for HPV testing.</td>
<td>Cost. Increased detection of low-grade lesions*. Retraining of cytologists</td>
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<td>Computer-assisted screening e.g. AutoCyte Screen, AutoPap, PAPNET</td>
<td>Improve Pap smear interpretation. Increase lab. productivity. Increase detection of cancer precursors</td>
<td>Increase cytologist productivity. May decrease false-negative reports.</td>
<td>Cost. From studies on PAPNET, increased detection of low-grade lesions*</td>
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*controversy about whether this benefits patients

Nuovo et al. Amer Fam Physician 2001
Tru Screen® Optoelectronic Screening

- No evidence supporting a benefit in screening individual women or population
- High rate of false positives
- Doesn’t distinguish between low and high grade abnormalities
- Unnecessary cost for women as well as potential for anxiety provoked by false positive
Focal Point ™ Slide Profiler

- Prioritises the slides based on the likelihood of abnormality
- Reduces incidents of false negatives
- Cost $30.00 (no medical rebate)
Australia has one of the most highly regulated and effective Cervical Screening Services in the world with high quality conventional cytology.
4.7 HPV Vaccine and HPV Testing
>99.7% of squamous cell cervical cancers test positive for high-risk HPV
Recent Advances:

HPV DNA testing
- HPV Digene Hybrid Capture test:
  detects presence or absence of high-risk HPV types
  (16, 18, 31, 33, 35, 39, 45, 51, 56, 58, 59, 68)
HPV testing- what could it add?

- Testing women for high risk HPV:
  1. *With low grade abnormalities* - colp / follow-up if positive, routine screening if negative (US have adopted)

MSAC (2002) concluded that in the Australian setting HPV DNA testing was not a cost effective tool for triaging women with minor screen detected abnormalities.
2. *After treatment of HGEA to determine follow up/test of cure*

Has been approved in Australia and now covered by Medicare Australia. HPV DNA testing and Pap smear are recommended at 12 and 24 months post-treatment. After 2 consecutive negative results for both tests, the woman may return to routine screening.

3. *As adjunct to routine screening in over 30s - longer screening interval if negative*
HPV Vaccines

miracle man

Professor Ian Frazer risked everything to find a vaccine for cervical cancer, even remortgaging his home to fund the research. Now his gamble has paid off, big time.
HPV type 16 and 18 are:

- linked to 70-80% of cervical cancers
- linked to 50% of high grade cervical precancerous lesions
- account for 25% of low grade cervical abnormalities
Preventative vaccines

- Gardasil® quadrivalent vaccine against HPV types 6, 11, 16 and 18
- licensed for use in females aged 9 to 26 and males 9 to 15 years
- comprised of 3 doses
- Gardasil® is included in the Australian National HPV Vaccination Program
Preventive Vaccines cont.

- **Cervarix®** (GlaxoSmithKline)
- licensed for use in Australian women aged 10 to 45 years
- 3 doses - bivalent vaccine (HPV 16, 18)
- different adjuvant → ?greater immune response
- ‘cancer prevention’ not ‘STI’
- Both vaccines are most effective when administered before commencement of sexual activity
Duration of immunity

- Not known, research has shown that Gardasil® confers protective immunity and efficacy for at least 5 years
- No indication for boosters at this stage
- There is evidence of immune memory response
National HPV Vaccination Program

- School based program commenced April 2007
- Community Vaccination Program - July 2007 to June 2009 (first dose)
There are three aspects to the National HPV Vaccination Program:

- Ongoing vaccination program for all 12 year old girls (school based program)
- A two year catch-up program for school girls aged 13-18 (school based program which ends 2009)
- GP based program for women 19-26 years (ends 2009)
A National HPV Vaccination Register established in 2008

For more information see website www.hpvregister.org.au
B: Therapeutic

-for those already infected

-~5 million women will develop cervical cancer in next 25 yrs

-still being investigated
HPV vaccine with MMR

- Cervical cancer may eventually become a thing of the past!!
- However at present women whether vaccinated or not will require regular cervical screening