Cervical Skills: Core Training
An Overview of Cervical Screening

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QEUH

Overview

- What is screening?
- Pathophysiology of cervical cancer
- Taking a smear
  - When to take and not to take a smear
  - What happens at the lab – HPV testing, cytology
  - What happens after the lab – management of different results
- HPV vaccination
- Duty of Candour

What is screening?

- A test offered to an apparently well person with the possibility of detecting a serious disease before any symptoms are evident
- The cervical screening programme uses **early disease detection** – discovering and curing conditions which have already produced pathological change but which have not so far reached a stage at which medical aid is sought spontaneously

What is screening

- Screening is NOT a diagnostic test
  - Patients who have an abnormal screening test need further investigation for diagnosis and to guide management

Criteria for a screening programme

- Important problem
- Treatment available
- Facilities to treat
- Recognisable early/latent stage, natural history of disease understood
- Suitable test available (from a medical and patient perspective)
- Policy on who to treat
- Economically viable
- Ongoing case finding process
- Quality assurance
- Informed choice
- Promotion of equity
- Benefits should outweigh harm

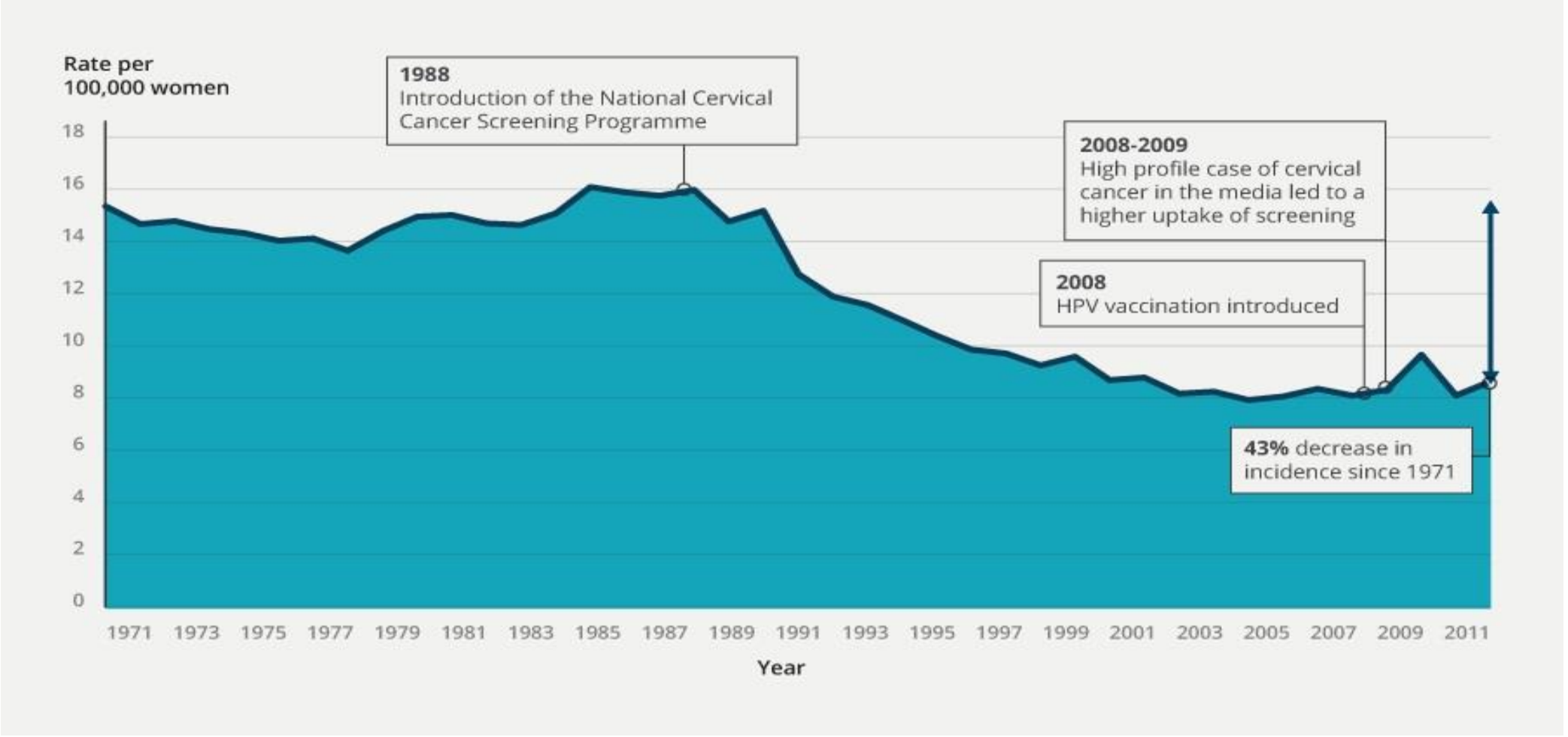
The aim of cervical screening

- To reduce the number of people who develop invasive cervical cancer (incidence)
- To reduce the number of people who die from cervical cancer (mortality)
- This is achieved by detecting and removing precancerous conditions (CIN and CGIN)

Statistics from CRUK

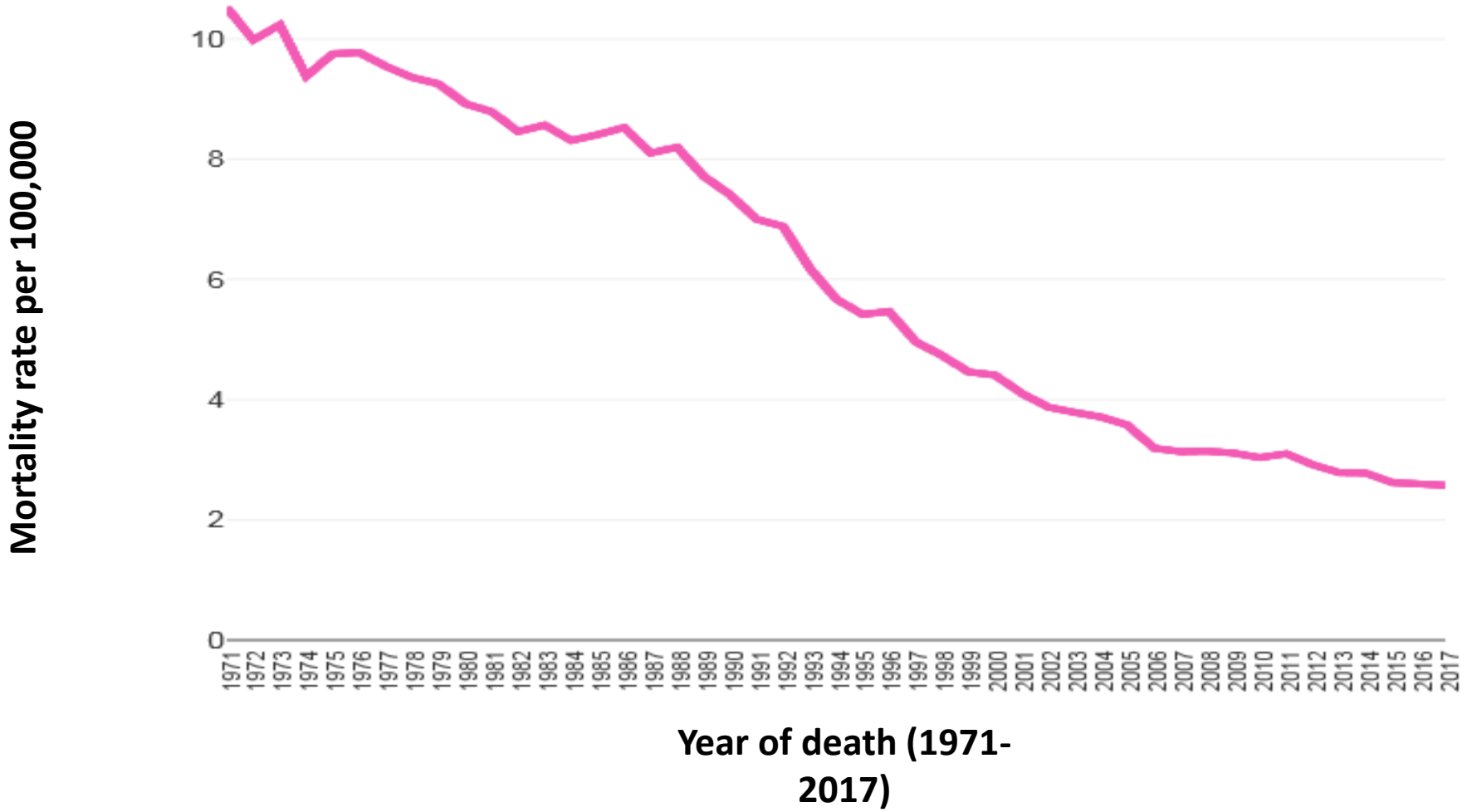
- In2017 there were 277 cases of cervical cancer in Scotland and 3101 in the UK as a whole
- Incidence was 10.1 per 100,000 in Scotland and 9.3 for UK
- In 2017 there were 105 deaths from cervical cancer in Scotland and 852 in the UK as a whole

Cervical cancer incidence per 100,000 females, England, 1971-2011



Office for National Statistics,
http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--42--2011/sty-cervical-cancer.html,
Accessed October 2016.

European Age-Standardised Mortality Rates per 100,000 Population, Females, UK, 1971-2017



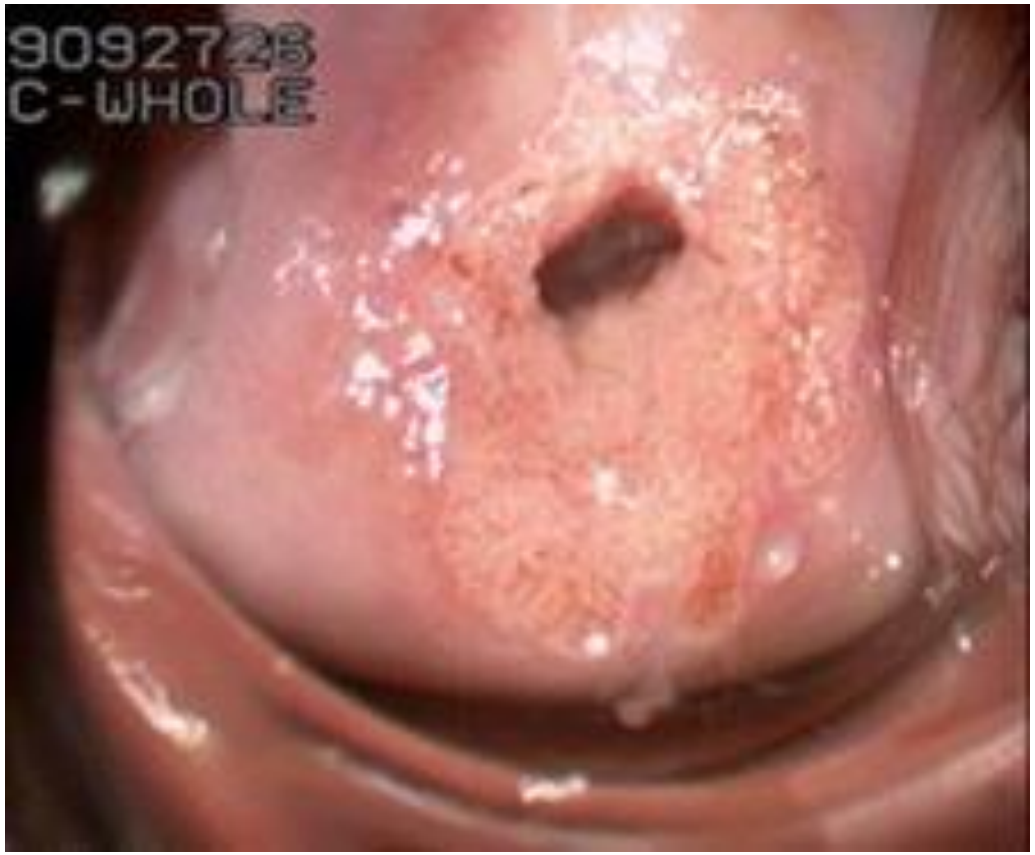
Pathophysiology of cervical cancer

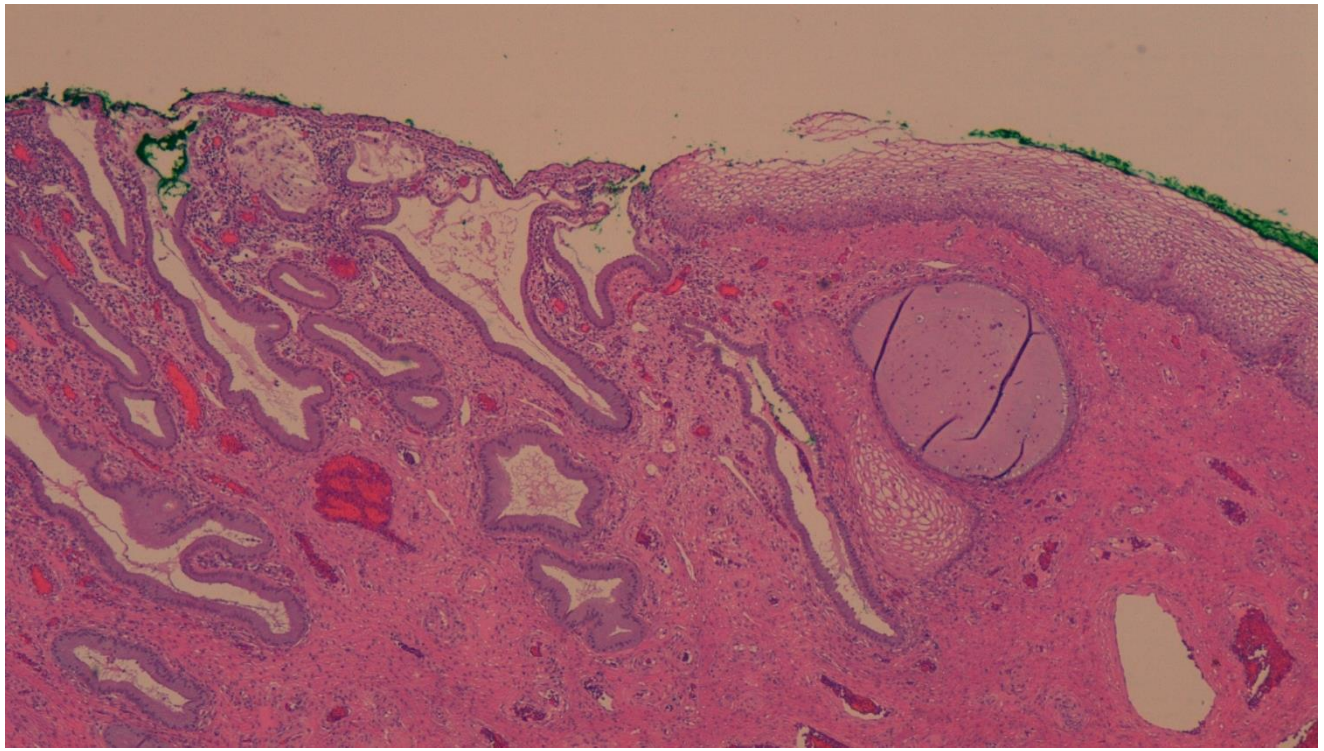
- The majority of cervical cancers have a high risk subtype of HPV (HrHPV) as an underlying cause
- Persistent infection with HrHPV *can* cause changes in cells which in *some people* progress to cancer
- Other risk factors:
  - Smoking
  - Poor immune function e.g. immunosuppression
  - Multiple sexual partners

Pathophysiology of cervical cancer 2

- Human papilloma viruses are a group of DNA viruses, which are grouped into high risk and low risk
- There are over 200 types, around 40 of which can be transmitted sexually
- 80% of sexually active people will become infected at some point during their lifetime
- Most people will clear the infection within 8 months to 2 years with no intervention
- Patients who have persisting infection with a high risk oncogenic subtype of HPV are at risk of developing pre-cancerous changes and cervical cancer

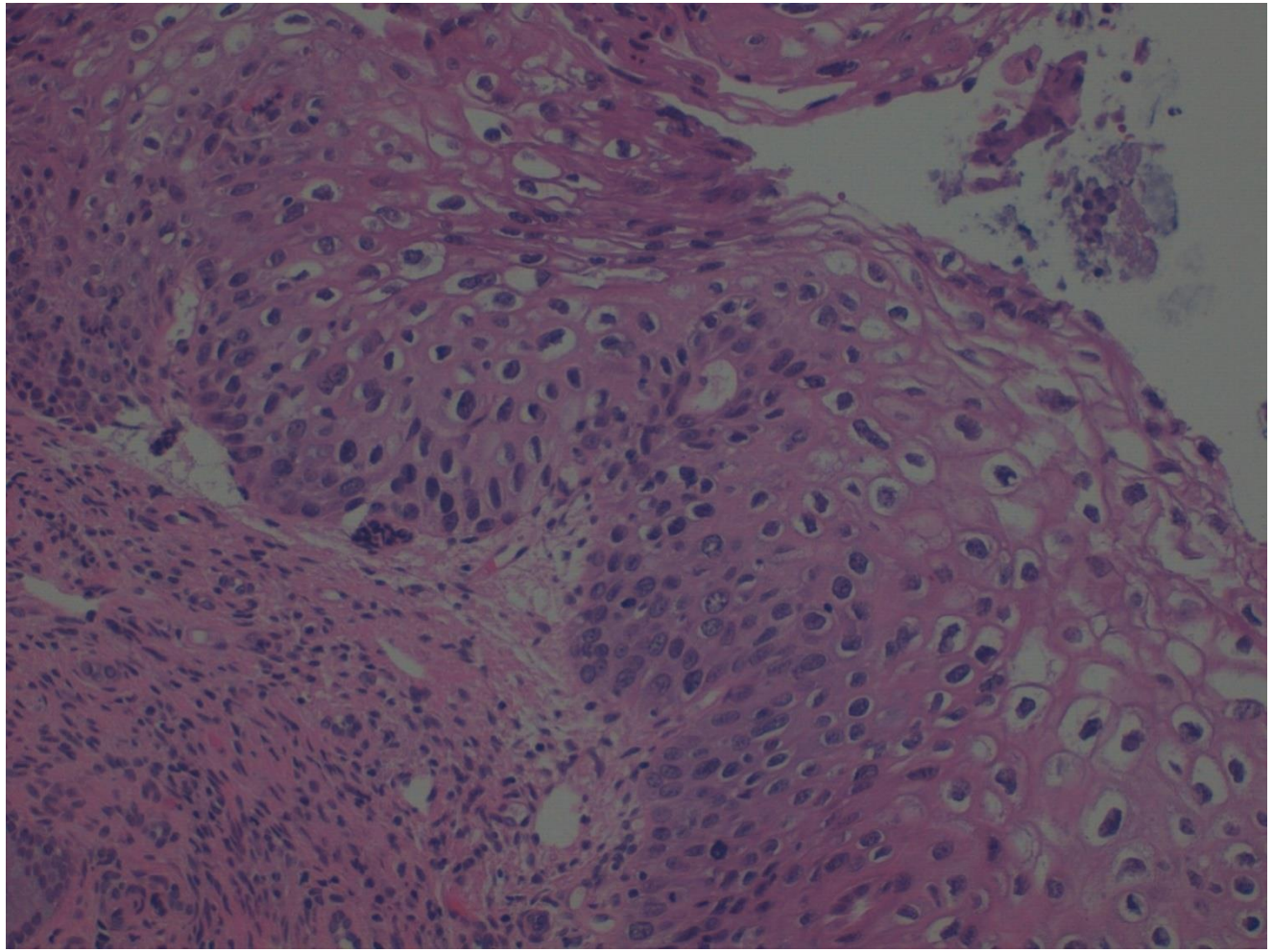
Human Papilloma Virus and cervical cancer

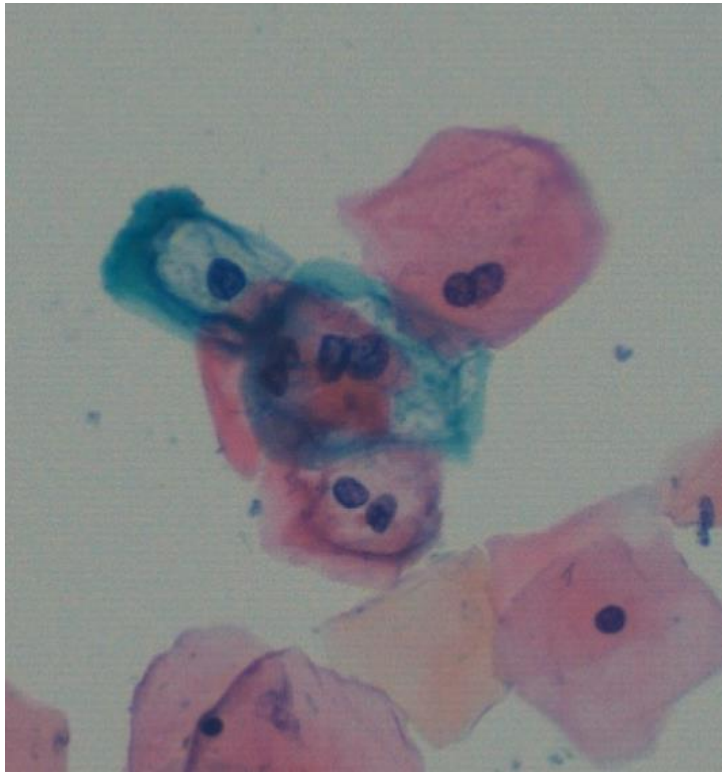




- Virus enters cervical epithelia at the transformation zone

Human Papilloma Virus and cervical cancer





- HPV replicates in maturing squamous cells producing koilocytes

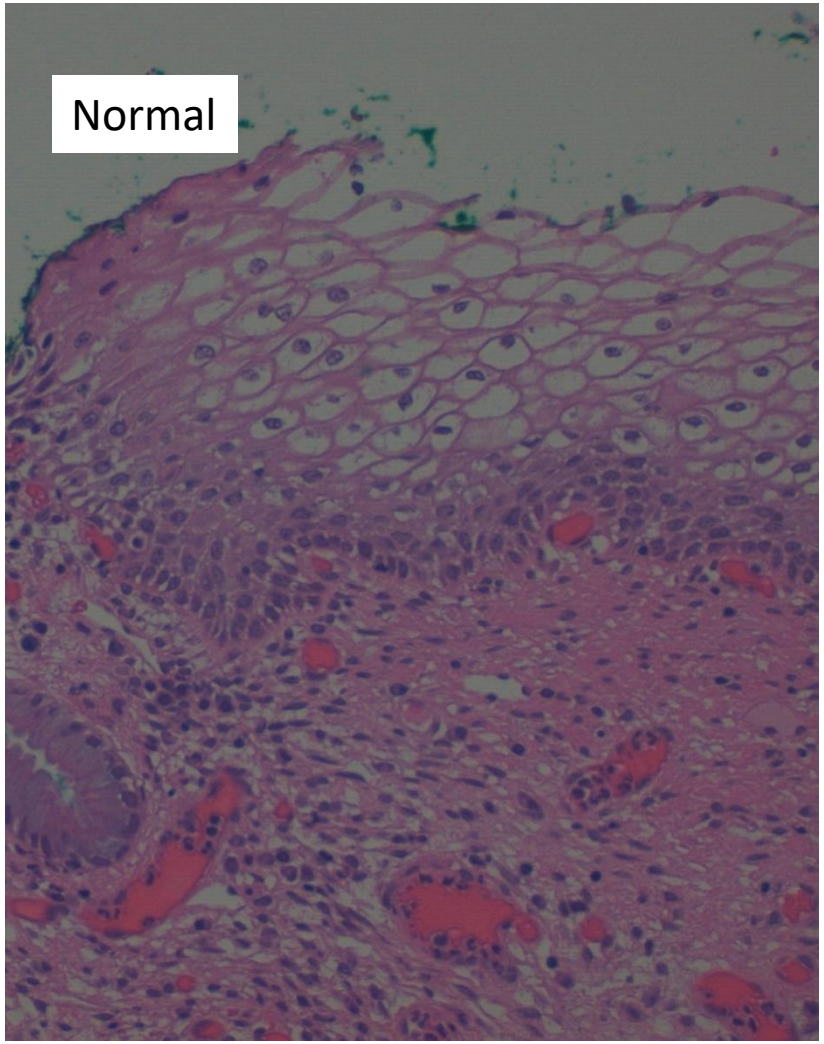
Human Papilloma Virus and cervical cancer

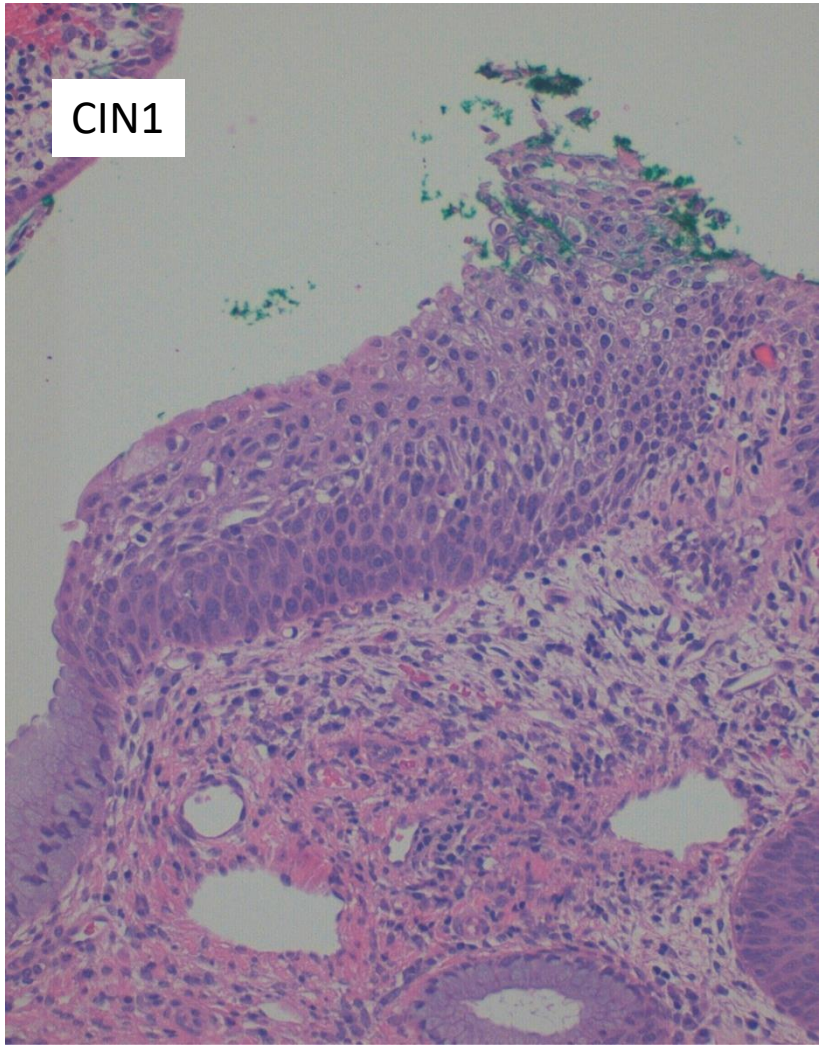
- Low risk HPV subtypes tend to result in free viral DNA within the cell
- They are responsible for viral warts (e.g. 6, 11, 42, 44)
- High risk HPV subtypes incorporate their DNA into that of the host cell
- It is persistent infection with these which is a risk for developing cervical cancer
- High risk subtypes include 16, 18, 31 and 45 but there are numerous others

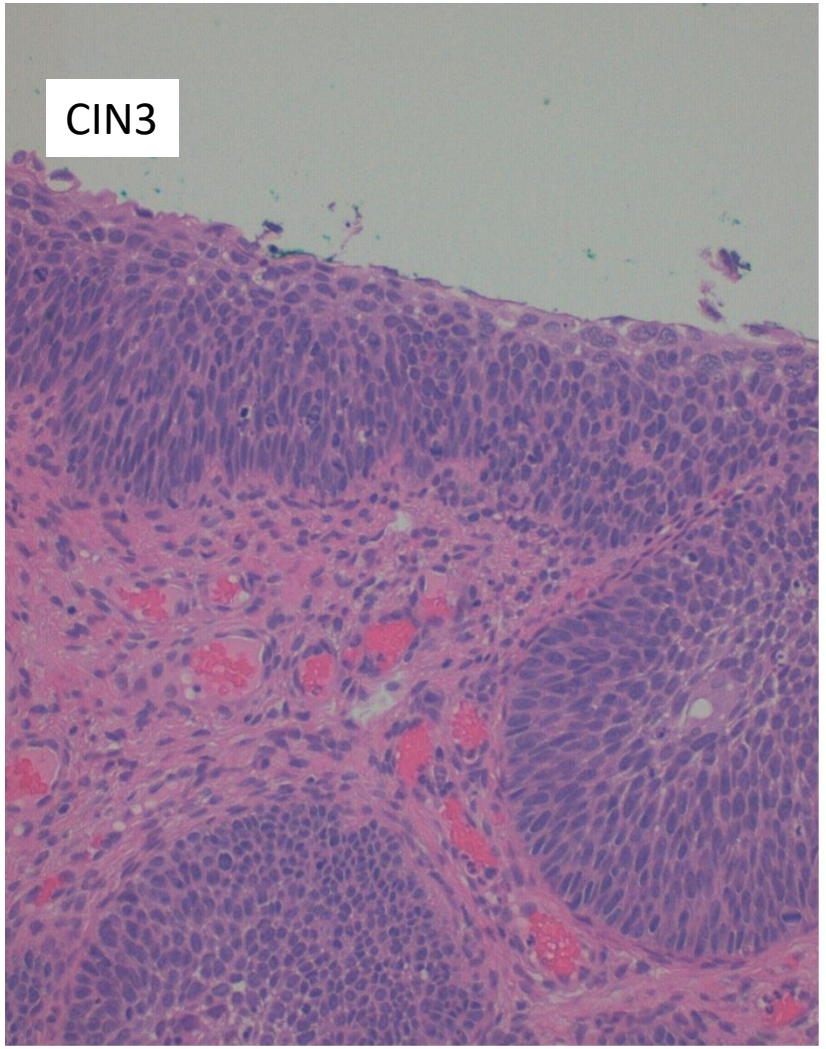
Human Papilloma Virus and cervical cancer

- Viral E6 and E7 proteins are responsible for reactivating the cell cycle in cells which are not normally proliferating
  - Bind to RB, which results in promoting the cell cycle
  - Bind to p53 disrupting cell death and prolonging the life of the cell
  - Induce centrosome duplication and genomic instability
  - Upregulate telomerase preventing replicative senescence
- Persistent infection and disruption of the cell cycle results in proliferation of the epithelial cells without an external stimulus – precursor lesions for cervical cancer
- CIN and CGIN are the precursor lesions

Human Papilloma Virus and cervical cancer







When to take a smear

- Patients within the screening age range
  - Age 25 to 65
  - Some patients called up to age 70 if abnormal results towards end of normal screening age range
- Patients who have been called by SCCRS
- Opportunistic testing in those who are in the age range but are not up to date with screening

When **not** to take a smear

- Patients who are outwith the screening age range (usually these patients are not on SCCRS)
- When the smear is not due
- After a total hysterectomy (unless there was CIN in the hysterectomy, and these patients should be seen back in colposcopy)
- After chemo/radiotherapy
- Less than 12 weeks post partum – currently under review
- Patients with symptoms – screening is not a diagnostic test

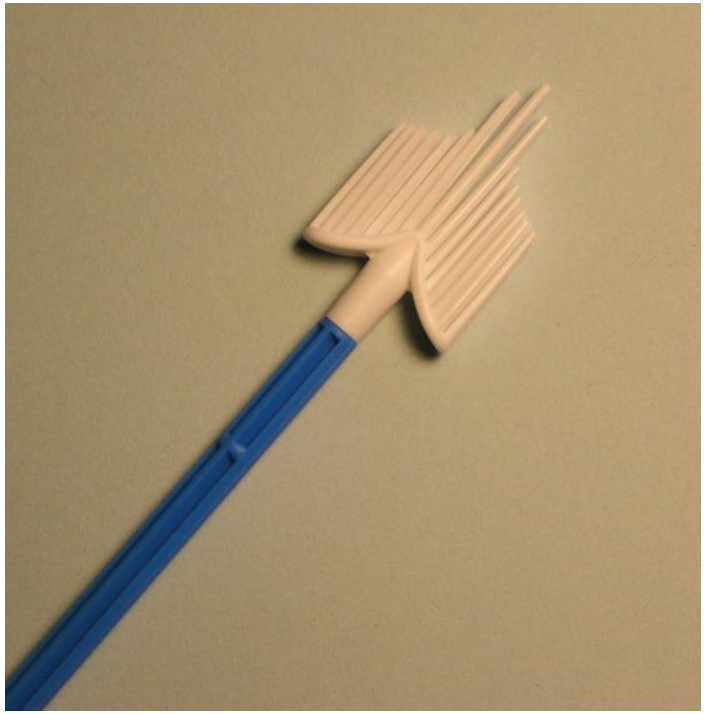
Patients with symptoms

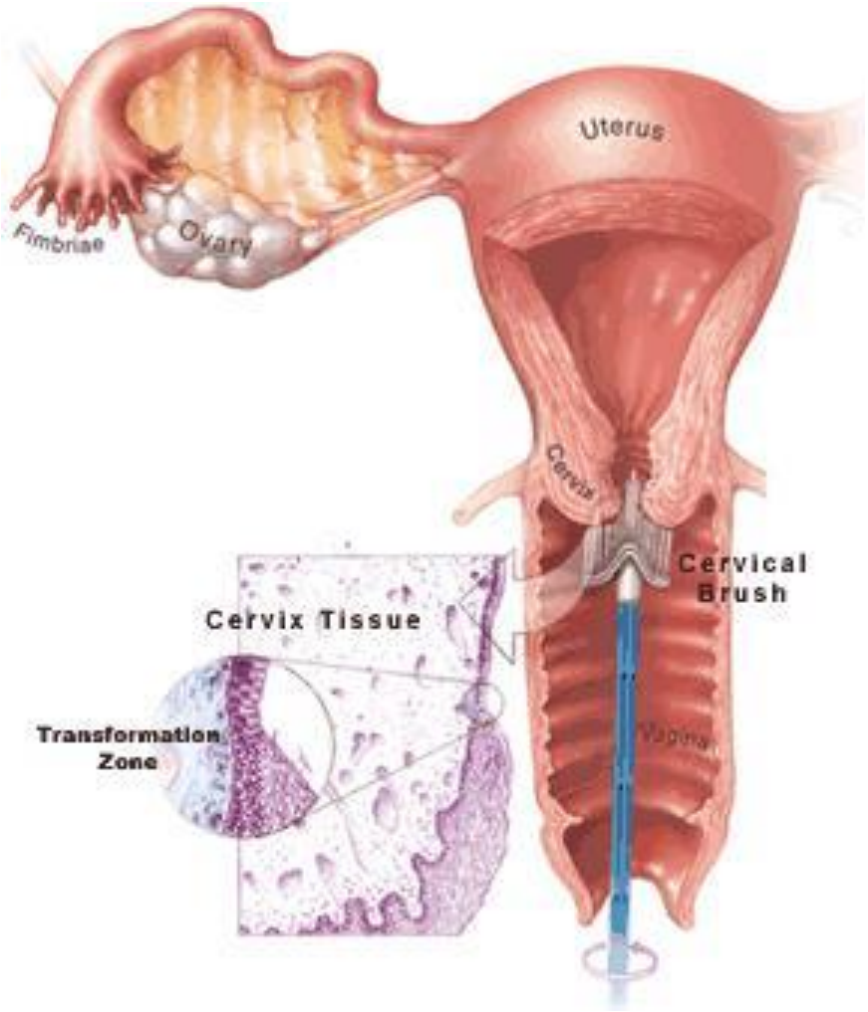
- Postcoital or intermenstrual bleeding
- Irregular bleeding
- Pelvic pain
- These patients require investigation of their symptoms
  - Visual inspection of cervix
  - STI screen
  - Referral if symptoms unexplained
- Smears are a **screening test**. If negative, this does not help identify the cause of the symptoms (falsely reassuring).

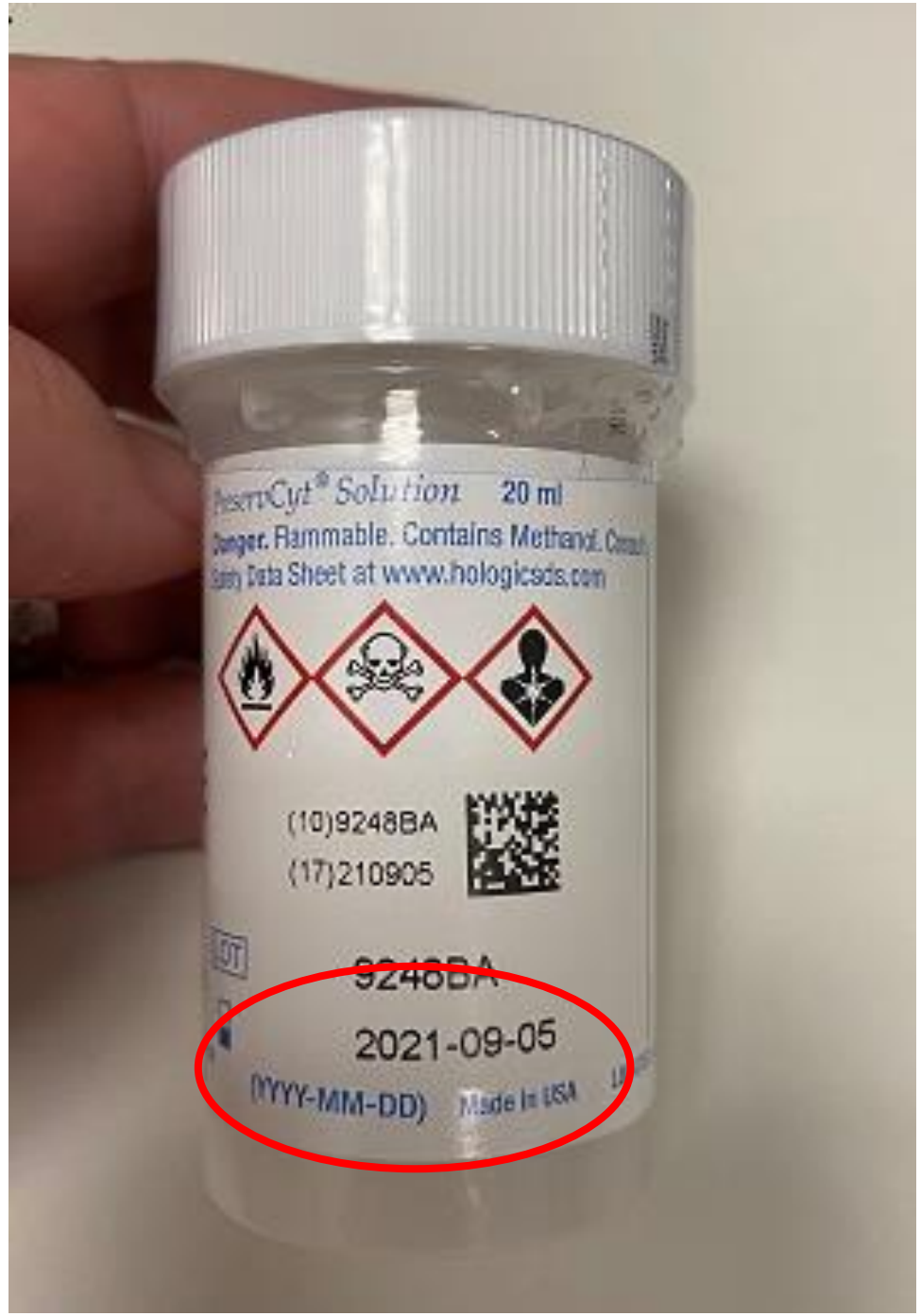
The lab – what we want you to do

- Visualise the cervix
- Check the date on the pot – samples in out of date vials will be rejected
- Don’t use lubricant (warm water is OK, if absolutely necessary a small amount of a water based lubricant can be applied away from the tip of the speculum)

The cervical screening test



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The lab – what happens to the sample?

- HrHPV testing (all samples)
- Cytology testing (around 15% of samples)
  - Samples with a positive HPV test (primary screening pathway)
  - Samples from patients on follow up pathways (test of cure, conservative management, cytology surveillance)

HrHPV testing

HrHPV testing

- The Hologic Panther tests for viral E6/E7 mRNA from 14 high risk HPV subtypes
- Results are positive, negative or fail
- Cannot report which subtype was present in a sample
- Management:
  - Patients on the primary screening pathway who have a negative HPV test have an automated result and recall in 5 years
  - There is no human checkpoint in the lab

Cytology


ThinPrep® Process
1. DISPERSION
2. CELL COLLECTION
3. CELL TRANSFER
THE ThinPrep PAP TEST

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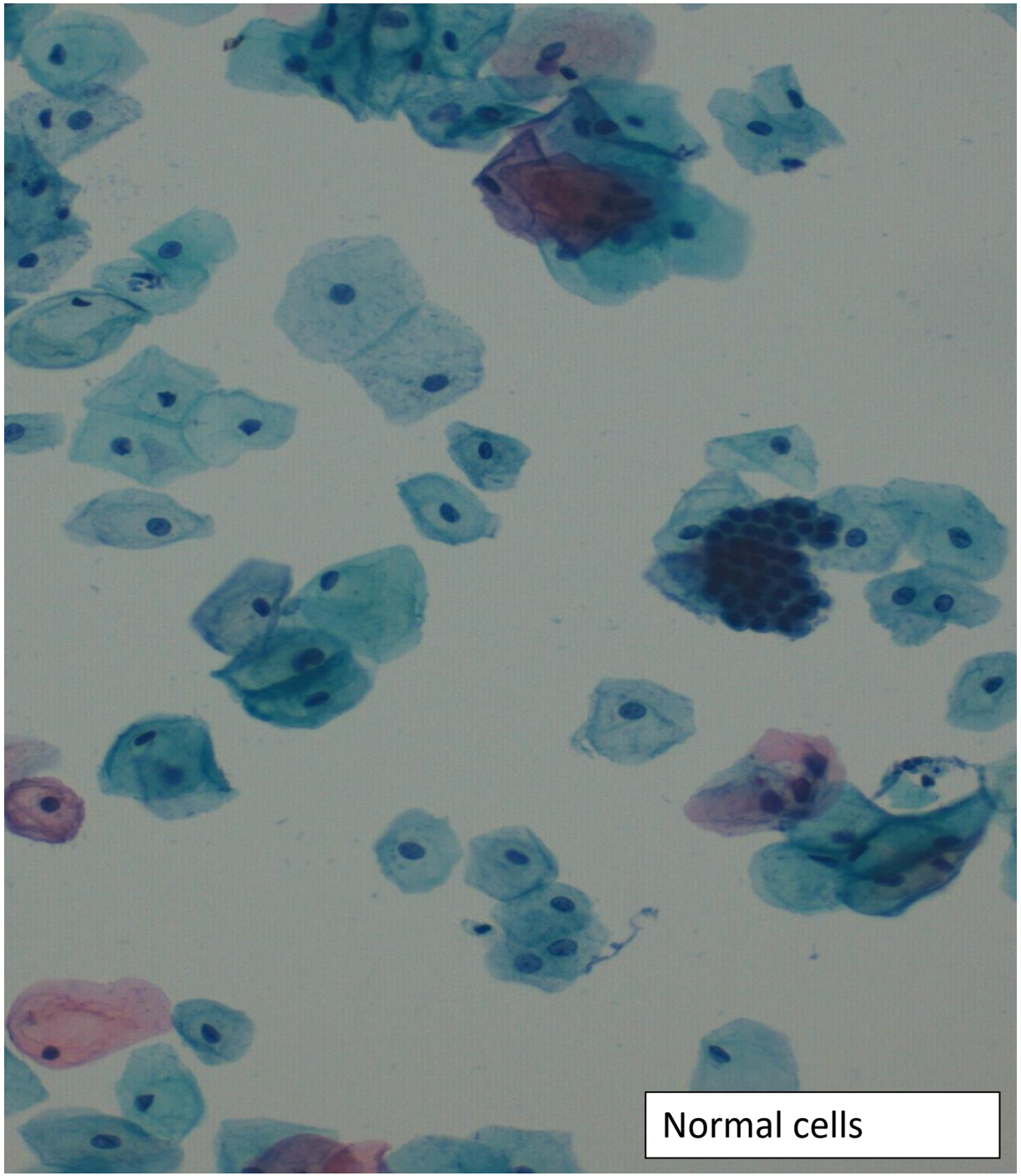
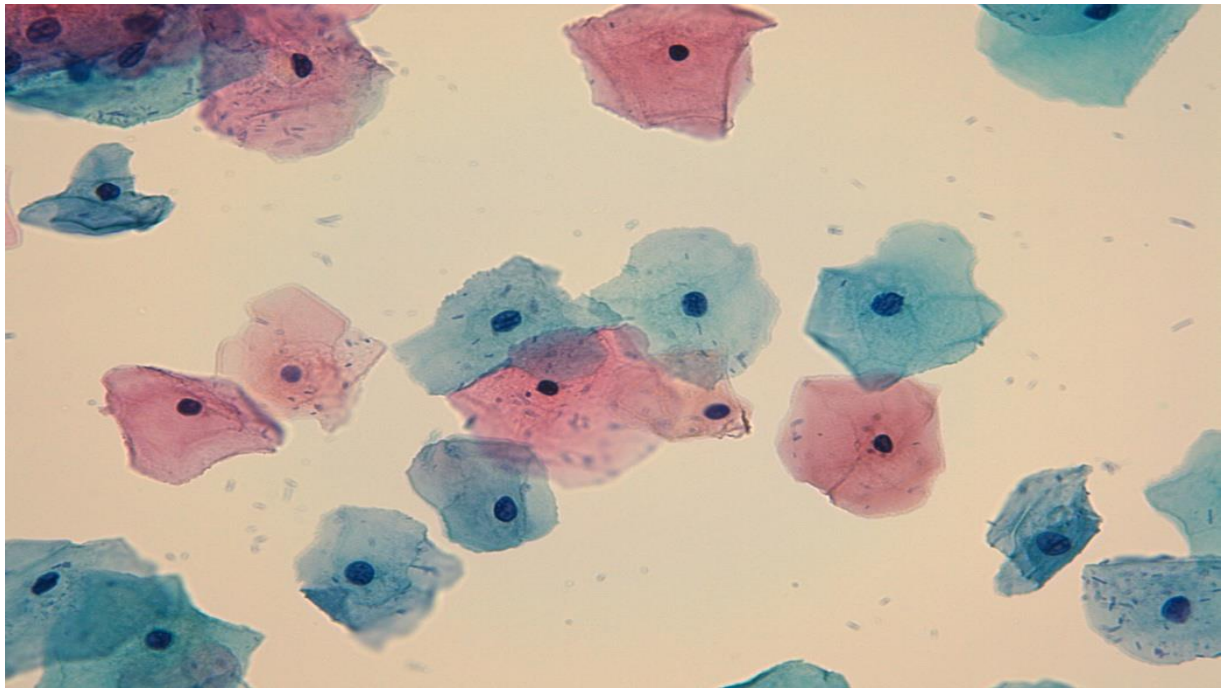
Cytology reporting categories

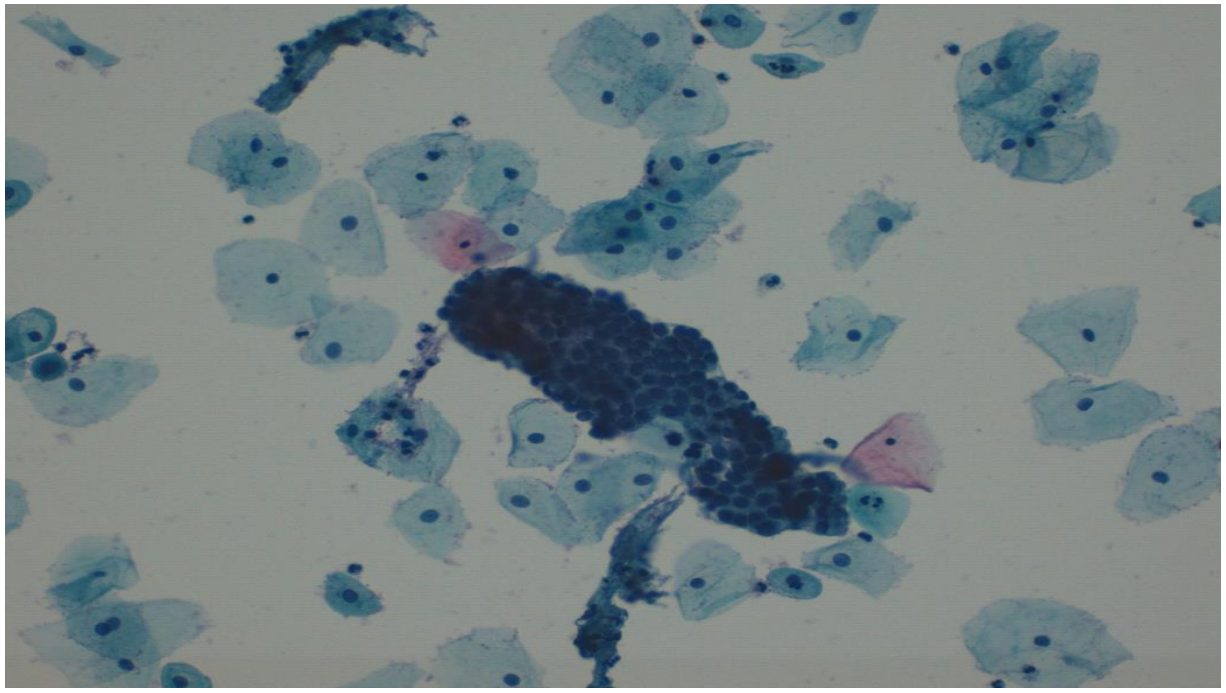
- Unsatisfactory
- Negative
- Borderline changes in squamous cells
- Borderline changes in endocervical cells
- Low grade dyskaryosis
- High grade dyskaryosis (moderate)
- High grade dyskaryosis (severe)
- High grade dyskaryosis (severe ?invasive)
- Glandular abnormality
- Endocervical adenocarcinoma
- Endometrial or other malignancy

Negative

- Satisfactory sample with adequate numbers of well preserved and well visualised squamous cells
- Adequate endocervical component
- Management:
  - Patients on primary screening – positive HPV test but negative cytology are recalled in 12 months
  - Organisms can also be reported – Fungal, ALOs, TV, Herpes. TV and Herpes require microbiological confirmation.


Normal cells

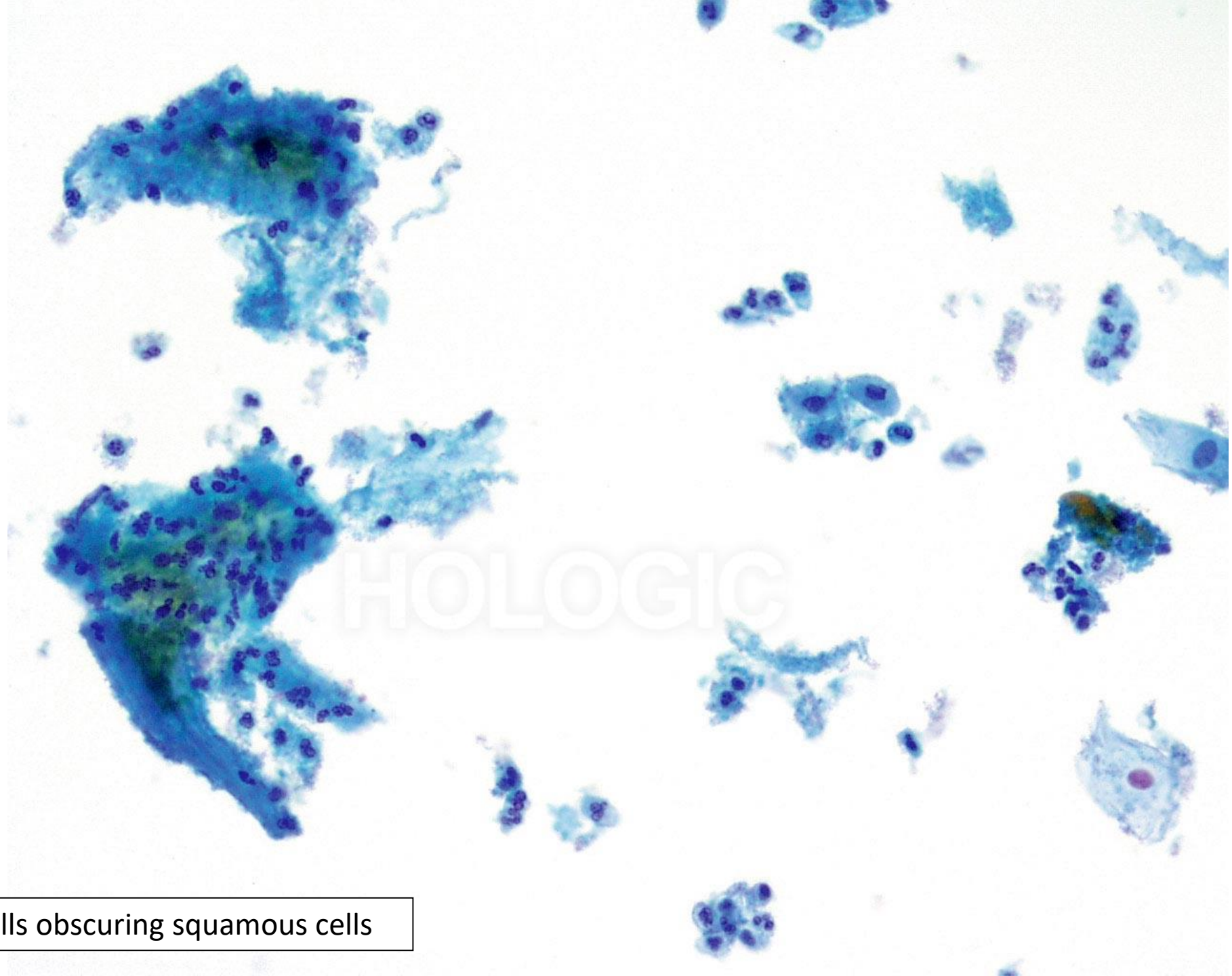




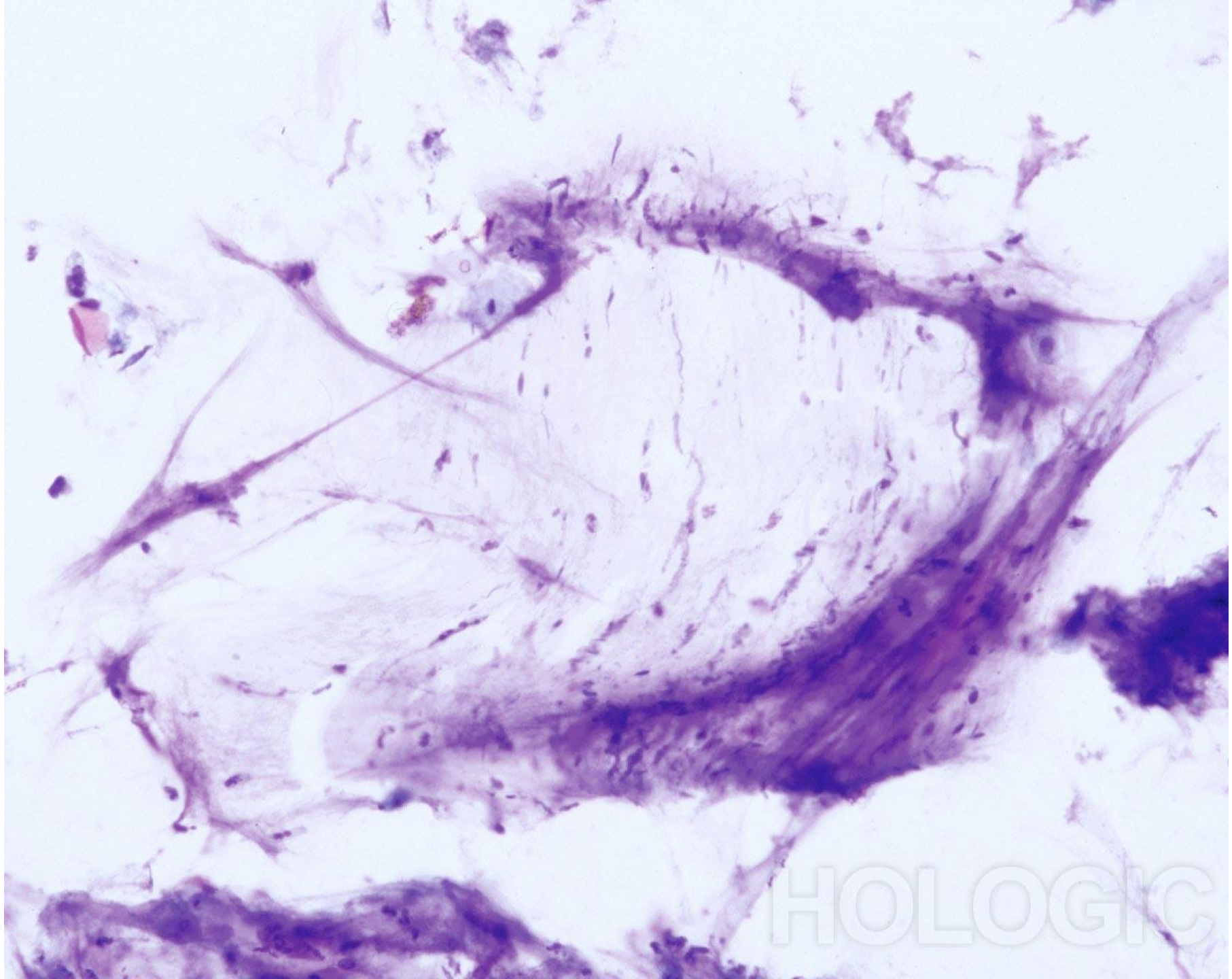
Unsatisfactory

- Scanty cellular material
- Heavy blood staining
- Cellular material obscured by debris or inflammatory cells
- Lubricant obscuring cells

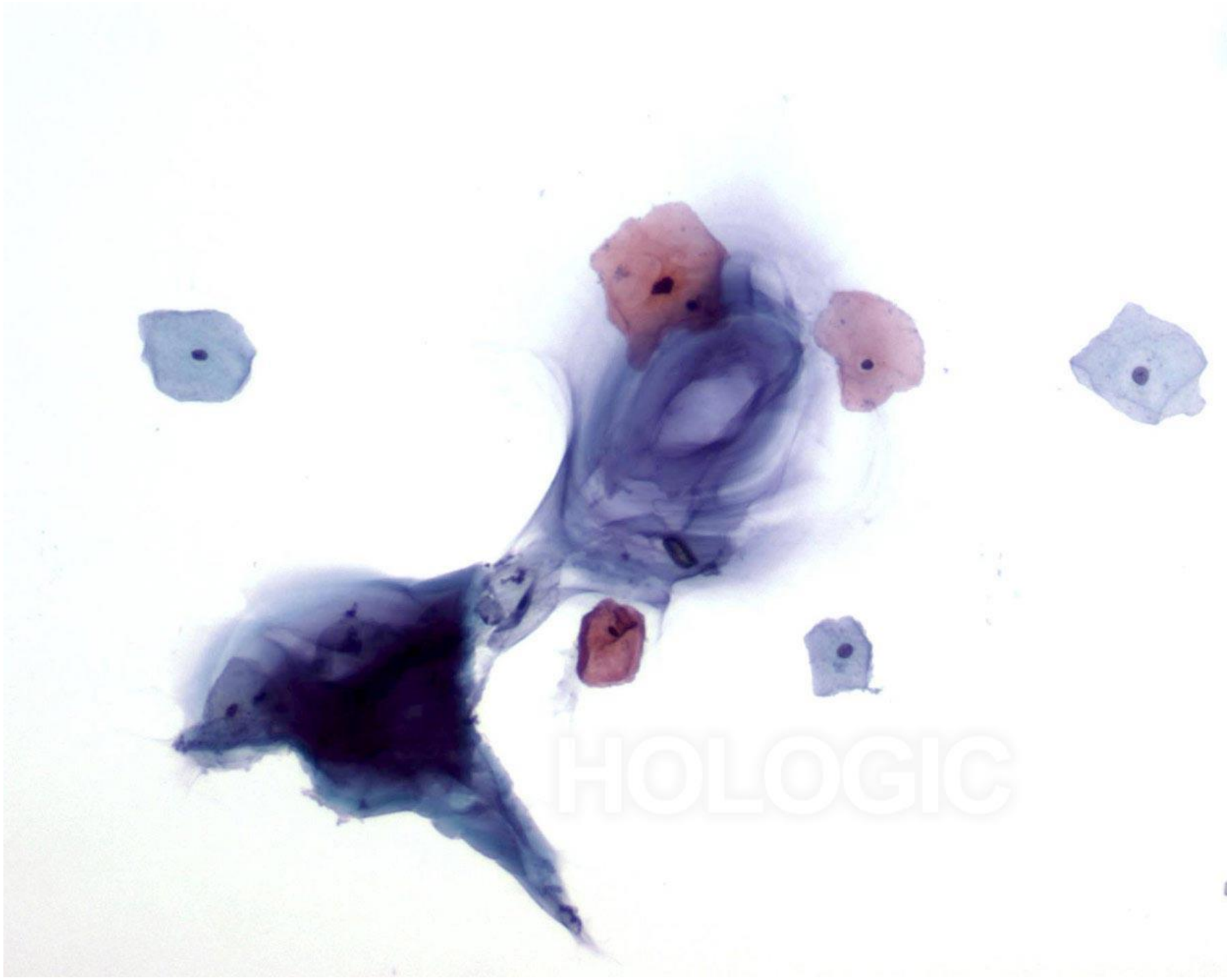
- Samples with patient ID issues or received in an out of date vial are not accepted by the laboratory and no report will be issued



Inflammatory cells obscuring squamous cells



Lubricant

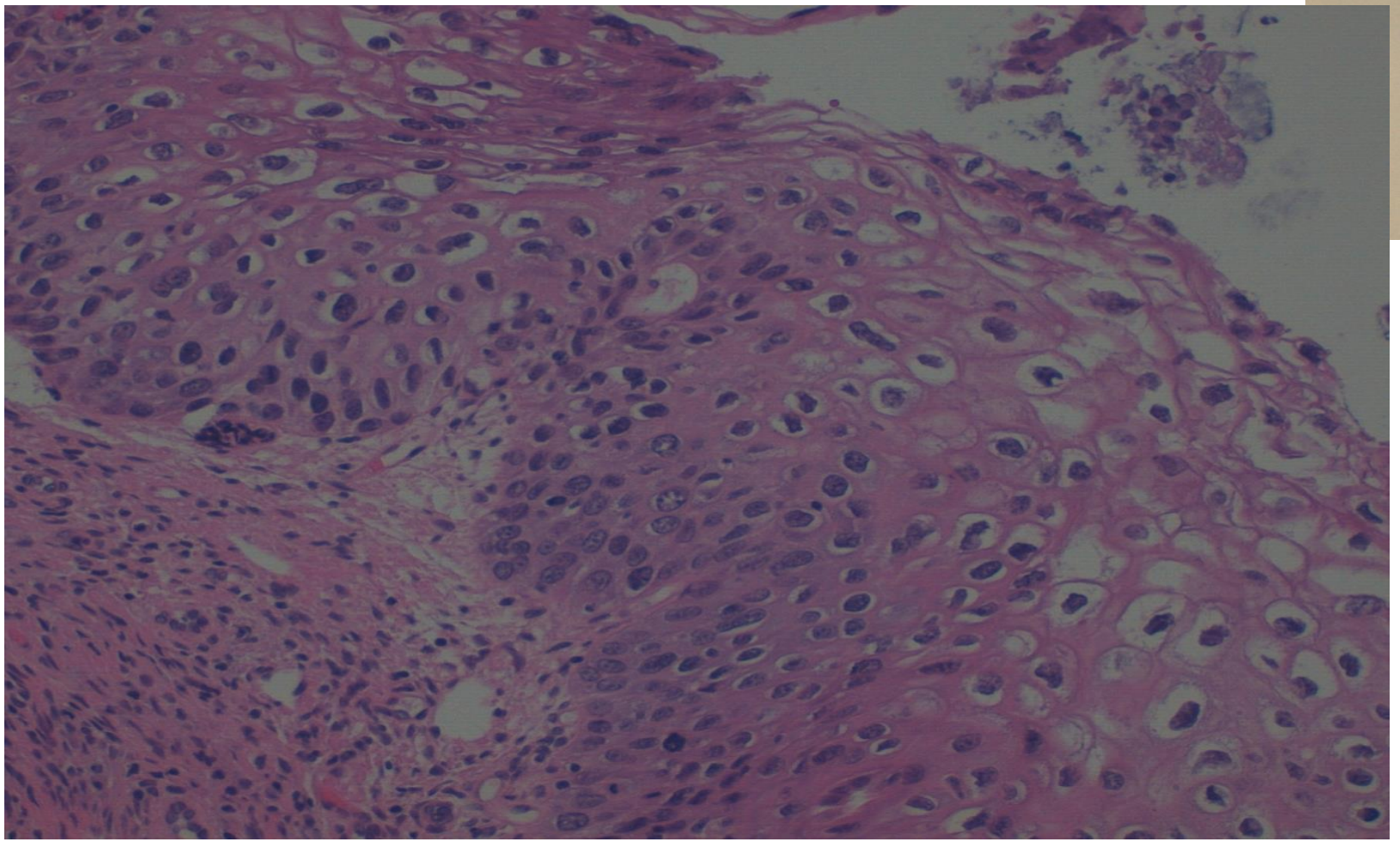


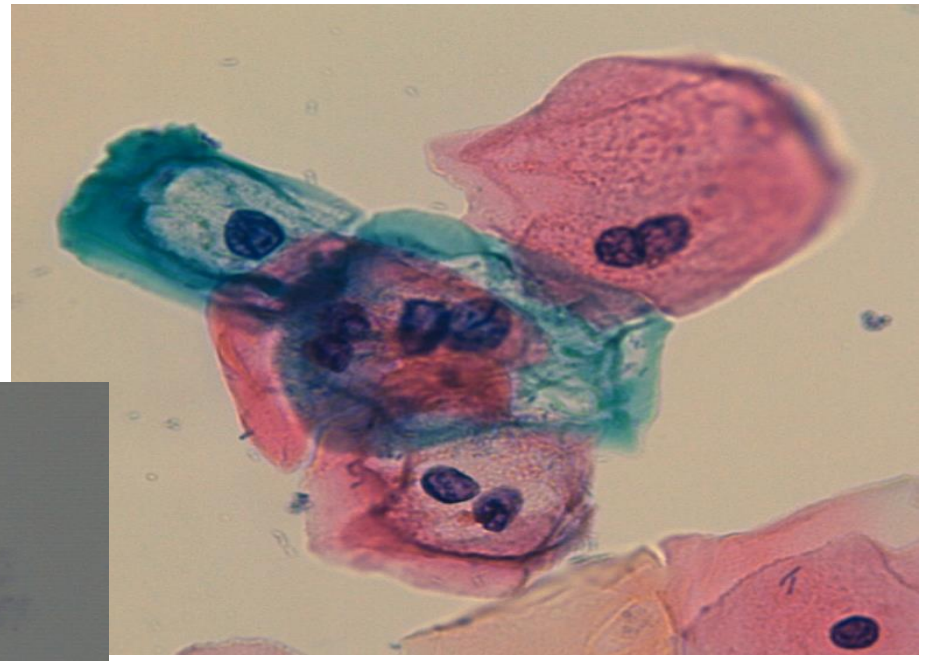
Lubricant

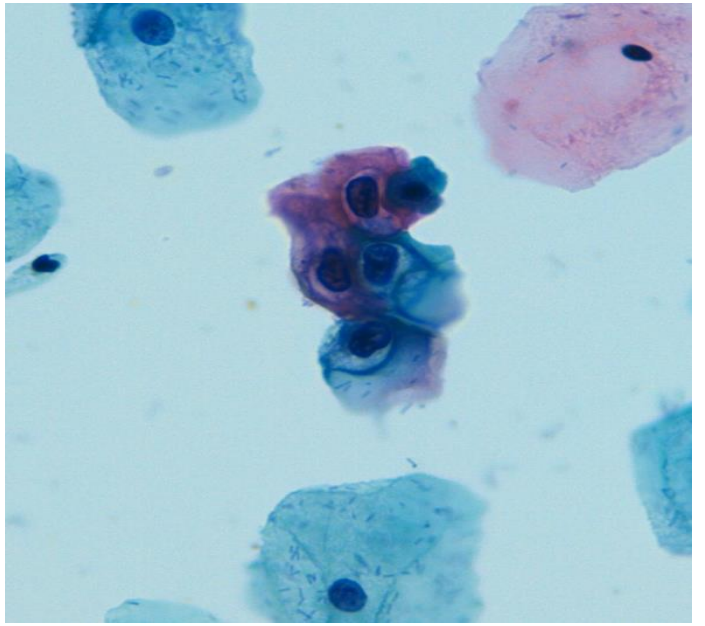
Low grade dyskaryosis

- Abnormality of squamous cells:
  - Increased nuclear size
  - Irregularities of nuclear membrane
  - Coarsening of chromatin
  - Hyperchromasia of nucleus
- This category includes koilocytes – the term used to describe the appearances when cells are infected with HPV

HPV - koilocytes





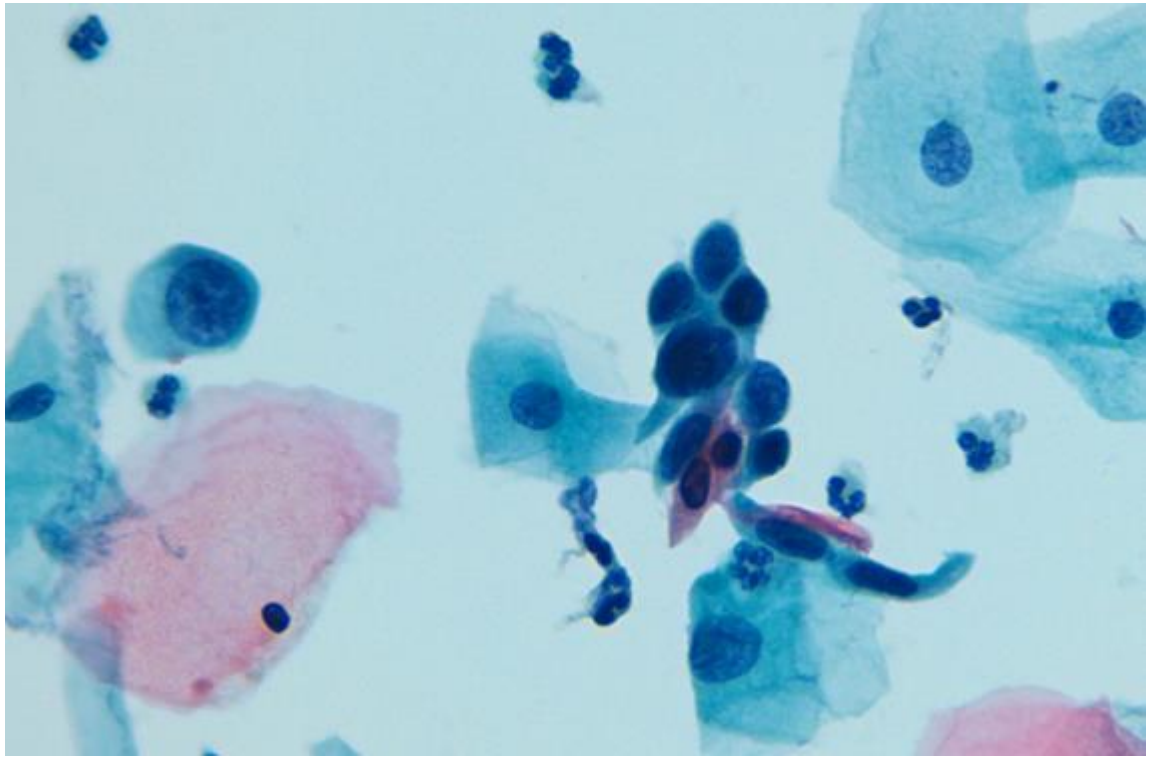


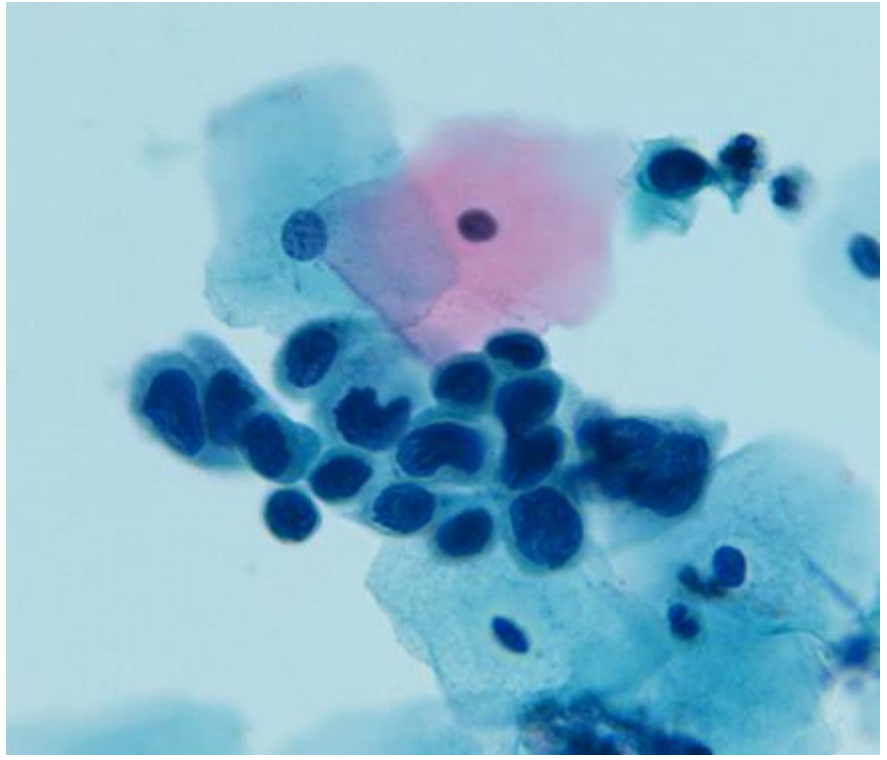
Low grade dyskaryosis – management

- On primary screening pathway these changes are referred to colposcopy
- The majority will have either appearances suggestive of HPV infection, CIN1 or nothing to see
- Colposcopists can choose to biopsy or not
- Most biopsies will show koilocytes or CIN1
- This is unlikely to progress to cancer and could resolve without treatment
- Patients are usually followed up – the **conservative management** pathway

High grade dyskaryosis

- The features are similar to low grade dyskaryosis but the nuclear to cytoplasmic ratio is higher (50-70% of cell for moderate dyskaryosis and over 70% of the cells for severe)





High grade dyskaryosis – management

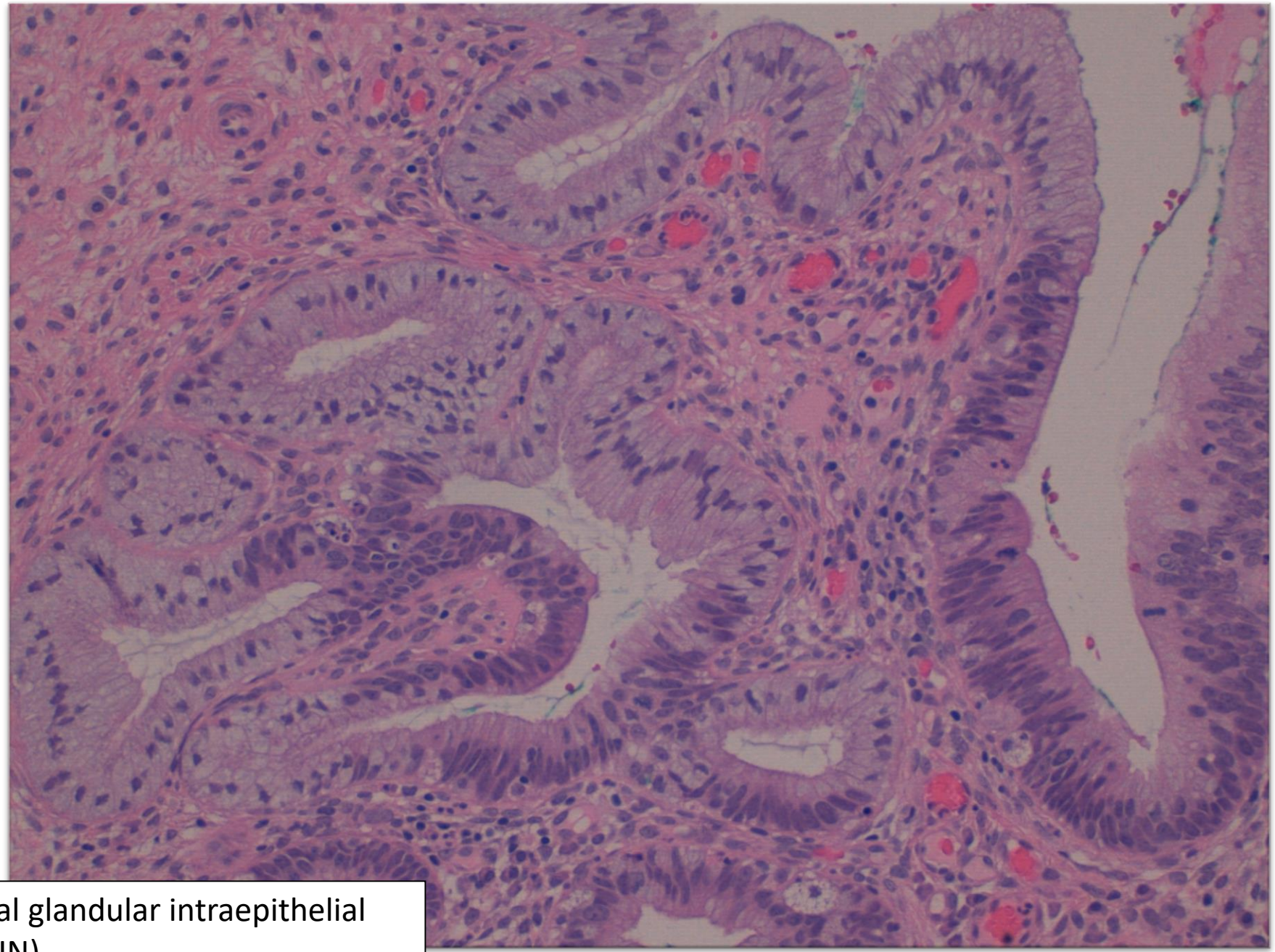
- On all pathways high grade dyskaryosis (moderate, severe and ?invasive) are referred to colposcopy
- These are intended to equate to the precursor lesions CIN2, CIN3 and invasive squamous cell carcinoma respectively
- At colposcopy a biopsy is usually taken to confirm and categorise the disease
- CIN2 and CIN3 can be treated in colposcopy
- Early cancers can also be treated in colposcopy, but should be discussed at the gynaecology oncology MDT meeting

High grade dyskaryosis – management 2

- Treatment options
  - Destructive treatment – cold coagulation
  - Removal of lesion – LLETZ
- Following treatment patients can be discharged to primary care for a smear in 6 months on the **test of cure** pathway
- When they return for a smear, this is automatically tested for both HPV and cytology in the lab
- If both are negative they are recalled in 3 years and patient is transferred back to primary screening pathway
- If either is positive (cytology low grade dyskaryosis or worse) then are referred back to colposcopy

Glandular abnormality

- An abnormality of the endocervical cells
- Management
  - These patients are always referred to colposcopy
  - They often have high grade CGIN – the precursor for endocervical adenocarcinoma
  - This requires confirmation and excision
  - Following this they can be discharged onto the **cytology surveillance (high grade)** pathway for 5 years of cytological follow up



High grade cervical glandular intraepithelial neoplasia (HG CGIN)

Overview of patient pathways

- All patients were allocated a pathway when the data was transitioned from the older version of SCCRS to the new one at the end of March 2020
- The pathway depends on the screening history and any investigations/treatments at colposcopy
- When a patient has been discharged from colposcopy, the colposcopist selects a new pathway
- Primary screening
- Test of cure
- Conservative management
- Cytology surveillance (high grade or low grade)

Primary screening

- Patients who are on routine recall
  - No screening history
  - Entirely negative screening history
  - Previous abnormalities but follow up is complete and they have been returned to routine recall
  - Also applies to patients who had a borderline/low grade smear and were being recalled in 6 months for follow up prior to March 2020 (and had not been previously tested for HPV)
- Samples are tested for HPV first
  - Negative for HPV – recall in 5 years
  - Positive for HPV – a cytology sample is made – any abnormalities and the patient is referred to colposcopy.
  - Patients with positive HPV test but negative cytology are recalled in 12 months

Test of cure

- Patients who have had a **treatment for CIN** of any grade e.g. LLETZ, cold coagulation
- They have been discharged from colposcopy and a recall of 6 months applied
- Not for CGIN or small cancers which have been treated conservatively
- Samples are tested for HPV and cytology
  - If both are negative the patient is recalled in 3 years. This appears as “Primary screening (non routine)” in the patient pathway
  - If either the HPV test is positive or the cytology is low grade (or worse) the patient is referred to colposcopy

Conservative management

- Patients who were referred to colposcopy with low grade dyskaryosis or borderline changes in squamous cells, and at colposcopy there was no abnormality (and no biopsy was taken) or a biopsy was taken and showed no abnormality, HPV or CIN1
- Samples are tested for HPV and cytology, but only the cytology result is used to determine the patient management.
  - Patients are followed up at 12 month intervals
  - If they have 2 negative tests, they are recalled in 3 years – Primary screening (non routine)
  - If they have borderline or low grade changes on more than one occasion they are referred to colposcopy
  - High grade changes are referred to colposcopy

Cytology surveillance – high grade (CS-HG)

- This pathway is suitable for a variety of patients who have either high grade cytology or high grade biopsies but are unsuitable for test of cure. It includes:
  - Patients who have had treatment for HGCGIN, SMILE or microinvasive carcinoma
  - Patients who have a high grade cytology result but biopsy shows CIN1 or less
  - “Failed test of cure for CIN2 or worse” – patients who had treatment for CIN2 or CIN3 followed by test of cure, but were referred back to colposcopy due to positive HrHPV test and/or cytology of low grade dyskaryosis or worse. No further treatment was undertaken.

Cytology surveillance – low grade (CS-LG)

- “Failed test of cure for CIN1” – patients who had treatment for CIN1 followed by test of cure, but were referred back to colposcopy due to positive HrHPV test and/or cytology of low grade dyskaryosis or worse. No further treatment was undertaken.

Cytology surveillance

- Samples are tested for HPV and cytology, but only the cytology result is used to determine the patient management.
- If the cytology is negative the patient is recalled at 12 month intervals (except the first test on the high grade pathway which is 6 months)
- For CS-HG 5 negative samples are required before the patient is put to 3 year recall
- For CS-LG 2 negative samples are required before the patient is put to 3 year recall
- Borderline changes are repeated in 6 months (and 3 borderlines results in a colposcopy referral)
- Low grade cytology or worse is referred to colposcopy on the first occasion

HPV vaccination

- The HPV vaccination programme started in 2008, with vaccination of girls aged 11-13
- In September 2012 the vaccine was changed from Cervarix (HPV 16 and 18) to Gardasil (HPV 16, 18, 6 and 11)
- From September 2019 the vaccine has also been offered to boys (S1)
- Change in 2022 to Gardasil 9 (HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58).
- Prevalence of HPV 16/18 before vaccination was 14%
- Prevalence of HPV 16/18 after vaccination was 1.6%
- Some cross protection against 31/33/45
- (Mesher et al, Inf Dis Journal 2018)

Duty of Candour

- In April 2018 the Scottish Government introduced new legislation requiring everyone to be open and honest with people who use our services and to apologise when things go wrong.
- This also applies to the cervical screening programme.
- The Invasive Cancer Audit has been undertaken for many years as a teaching/learning exercise. DOC now applies and any mistakes need to be discussed with the patient once investigation is complete.
- Screening tests cannot offer 100% sensitivity or specificity.