Laboratory update for Cervical Skills Training

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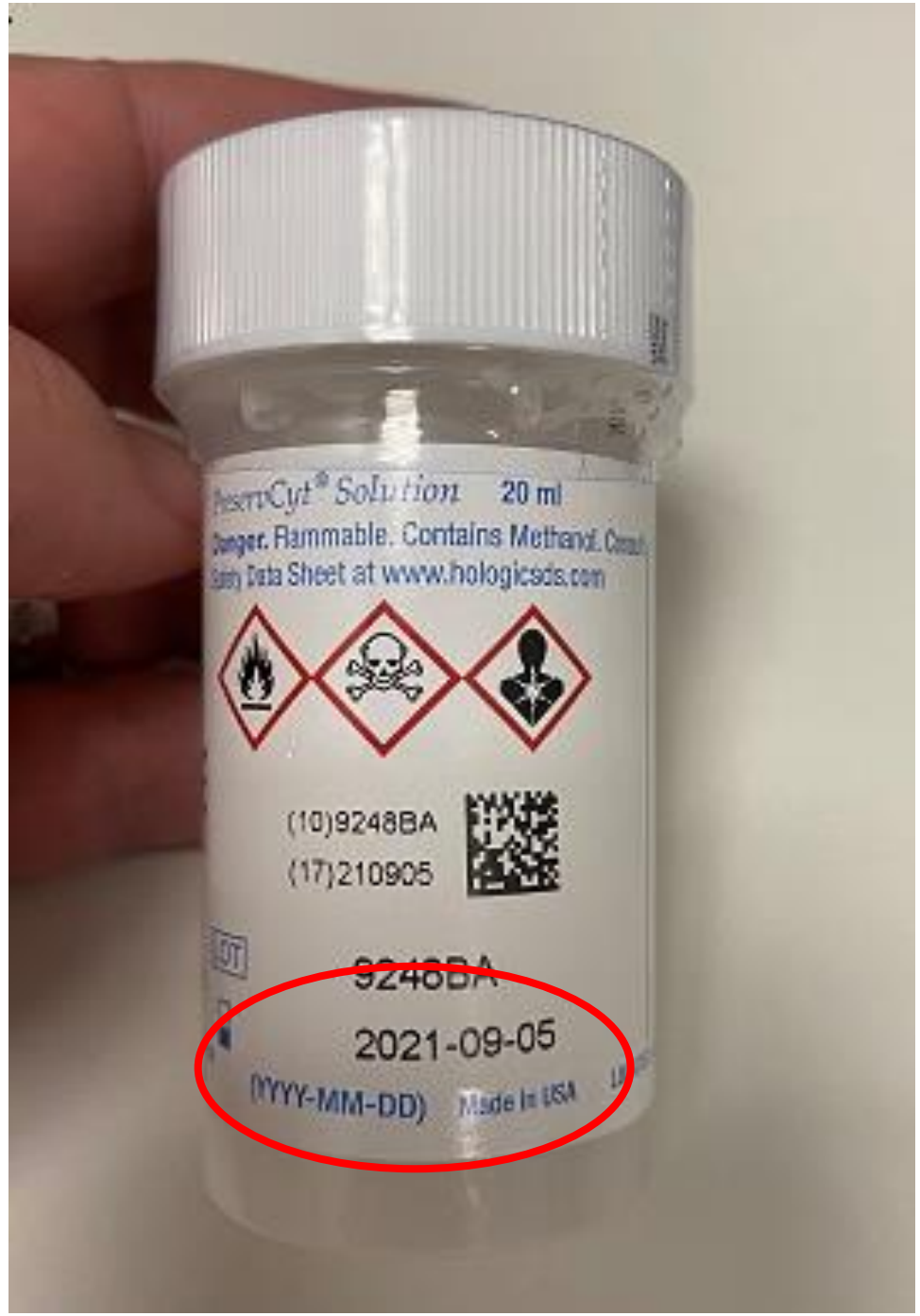
QEUH

Overview

- Changes to the screening programme from March 2020
- Overview of HPV
  - What is HPV and what is its role in cervical cancer
  - What do women know about it?
  - HPV vaccination
- The new pathways
- Symptomatic patients
- Duty of candour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Changes to the screening programme from March 2020

- The laboratory component of the screening programme has been centralised
- QEUH (NHS GGC, Grampian, Tayside, Ayrshire and Arran, Orkney, Shetland)
- Monklands (NHS Lanarkshire, Lothian, Forth Valley, Borders, Dumfries &Galloway, Fife, Highland, Western Isles)
- Samples are collected in the same way as before
- All patients have been allocated a “pathway” (visible on SCCRS)
- All samples are initially tested for HrHPV – HPV triage
- Samples which are positive for HrHPV get cervical cytology

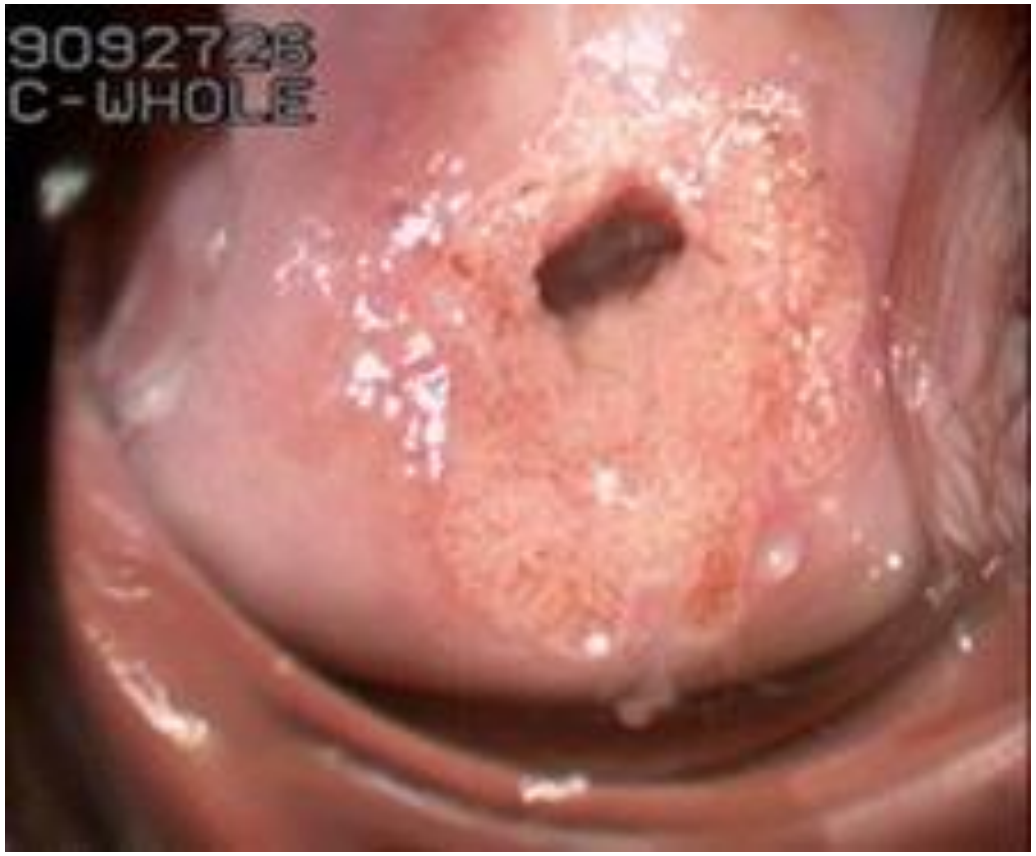
Human Papilloma Virus and cervical cancer

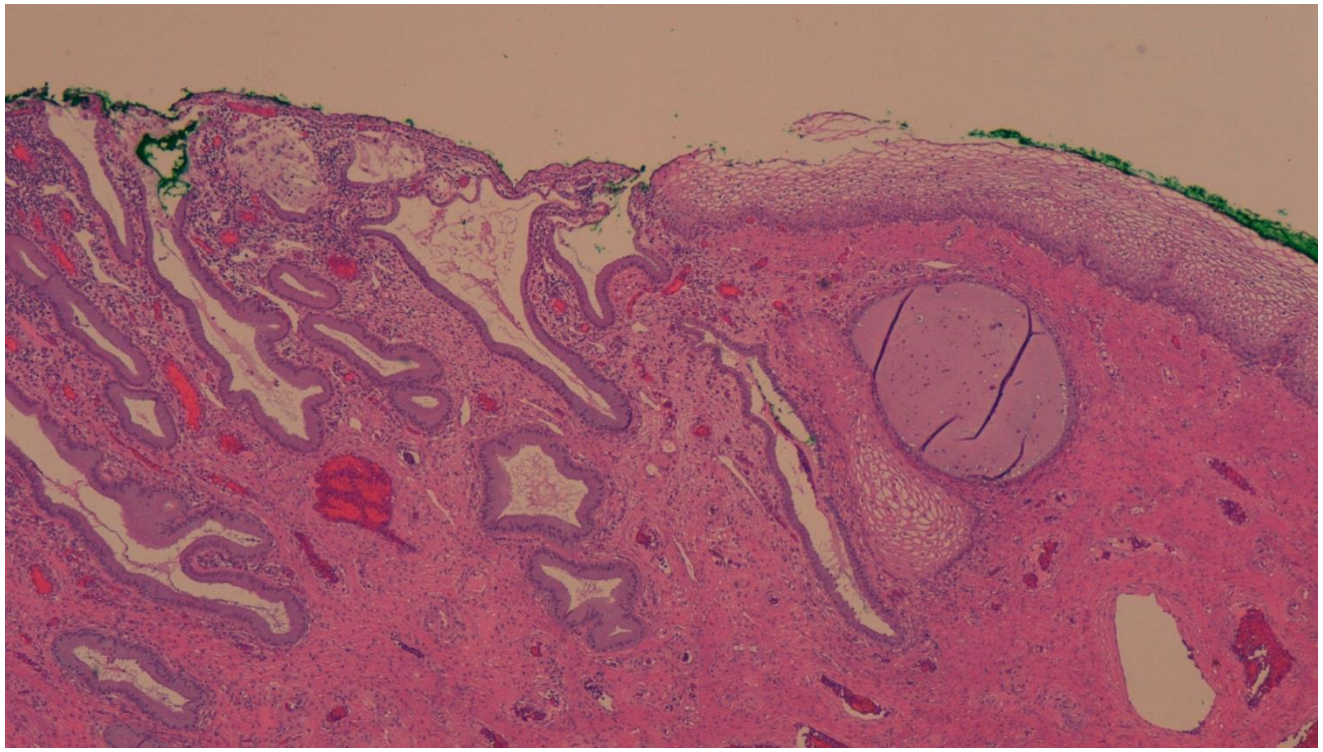
- The majority of cervical cancers have a high risk subtype of HPV (HrHPV) as an underlying cause
- Persistent infection with HrHPV *can* cause changes in cells which in *some people* progress to cancer
- Other risk factors:
  - Smoking
  - Poor immune function e.g. immunosuppression
  - Multiple sexual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

Human Papilloma Virus and cervical cancer

- 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
- HPV is ubiquitous and 80% of sexually active people will become infected at some point during their lifetime – it should not be a stigma to be HPV positive
- 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

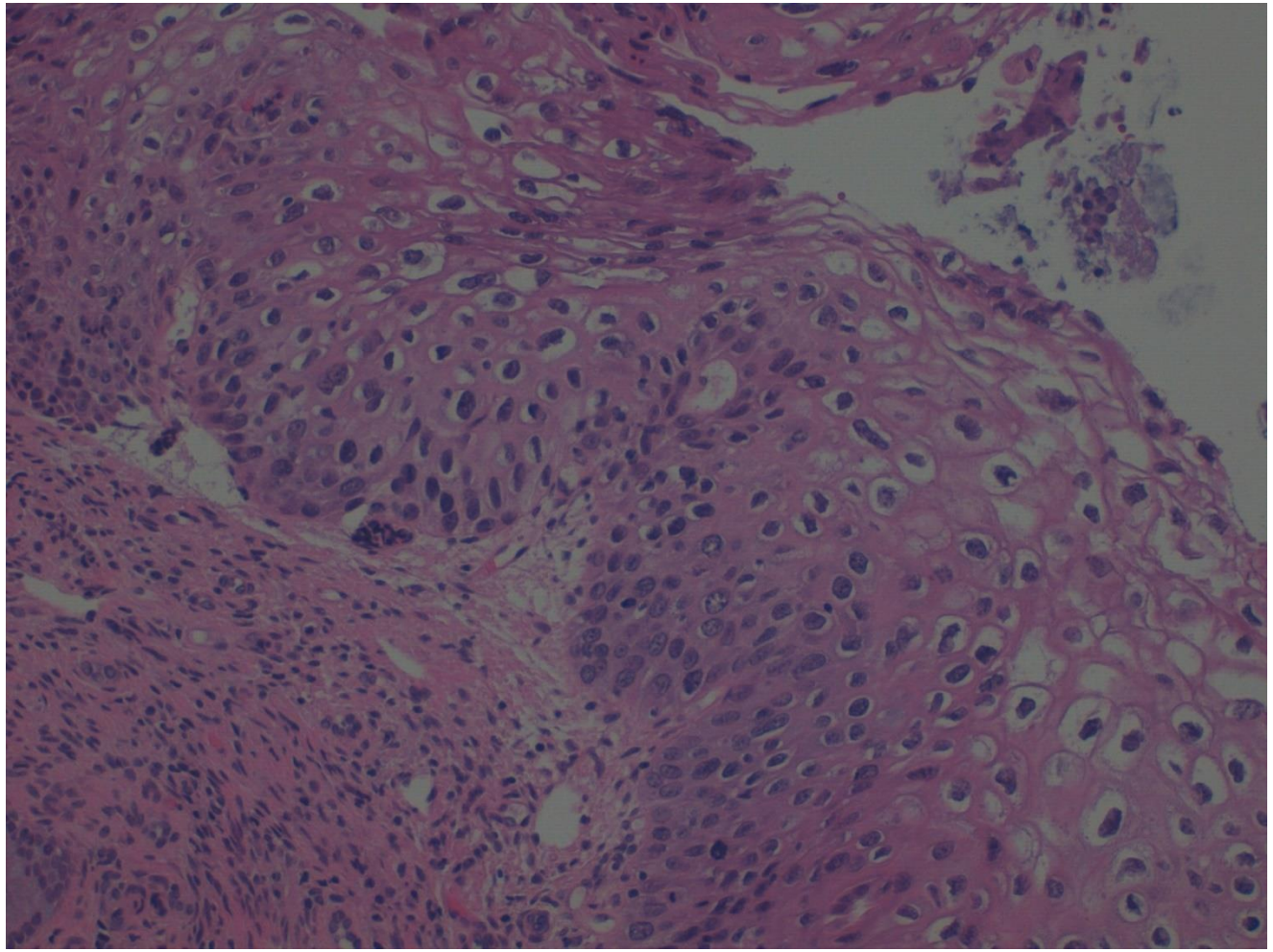
Human Papilloma Virus and cervical cancer

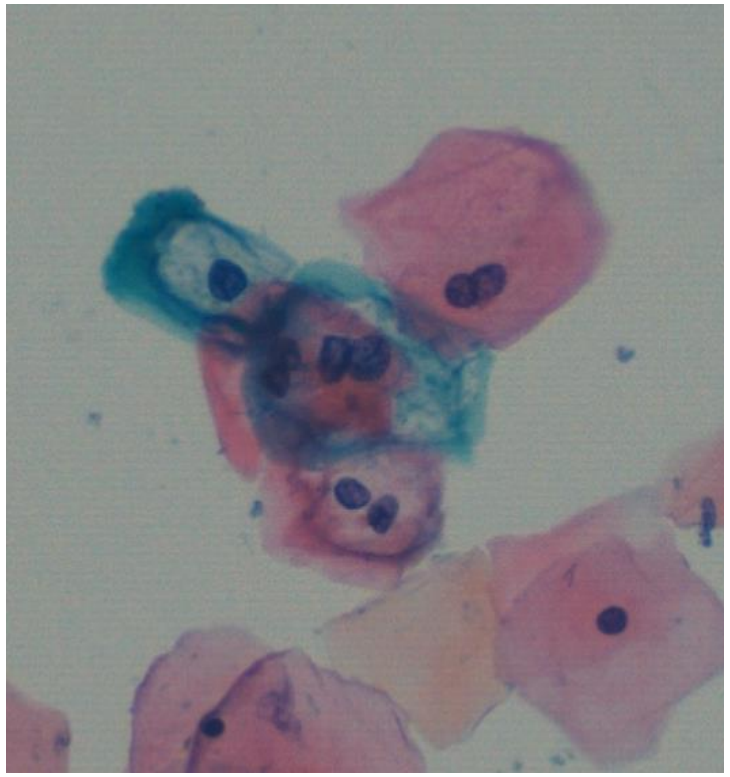




- Virus enters cervical epithelia at the transformation zone

Human Papilloma Virus and cervical cancer





- HPV replicates in maturing squamous cells producing koilocytes

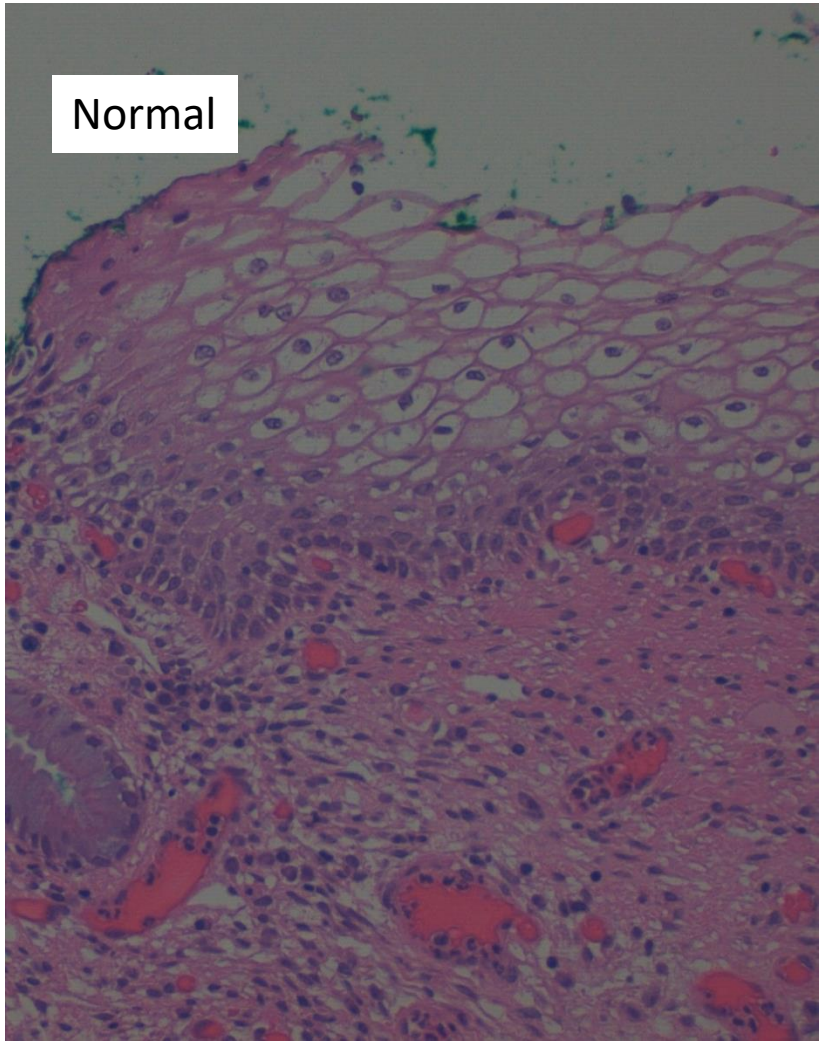
Human Papilloma Virus and cervical cancer

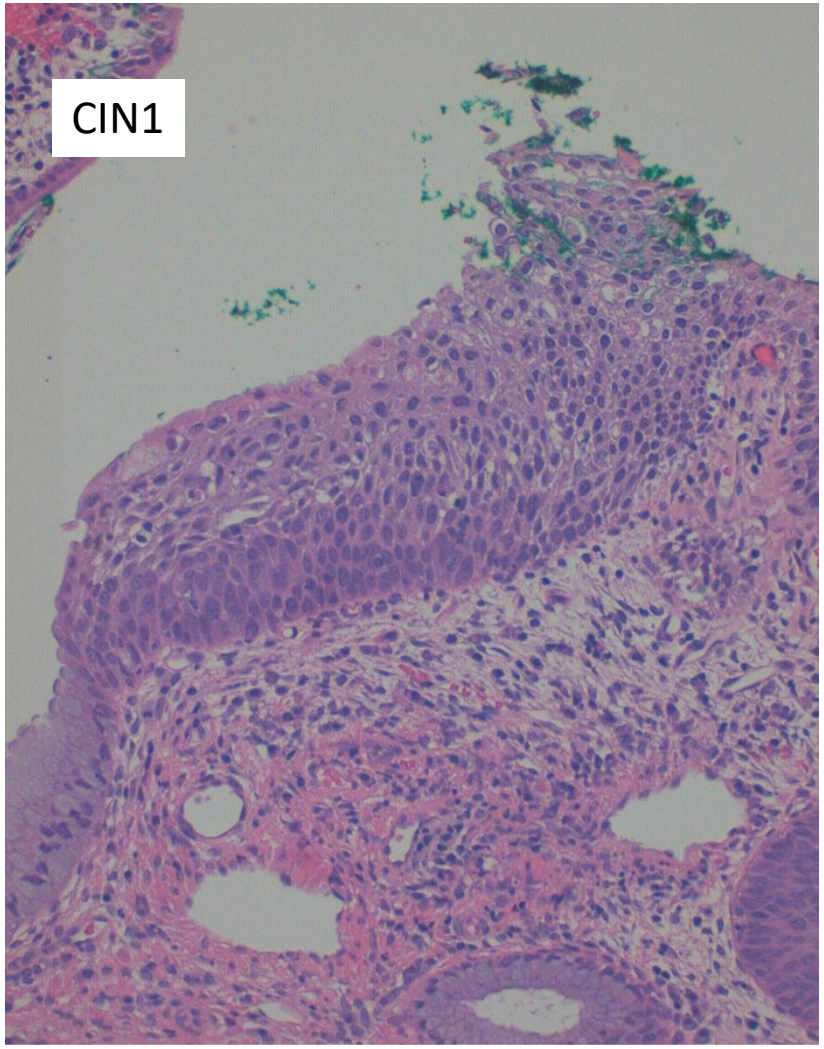
- Low risk HPV subtypes tend to result in free viral DNA within the cell
- They are responsible for viral warts (e.g. 6, 11, 42, 44)
- High risk HPV subtypes incorporate their DNA into that of the host cell
- It is persistent infection with these which is a risk for developing cervical cancer
- High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

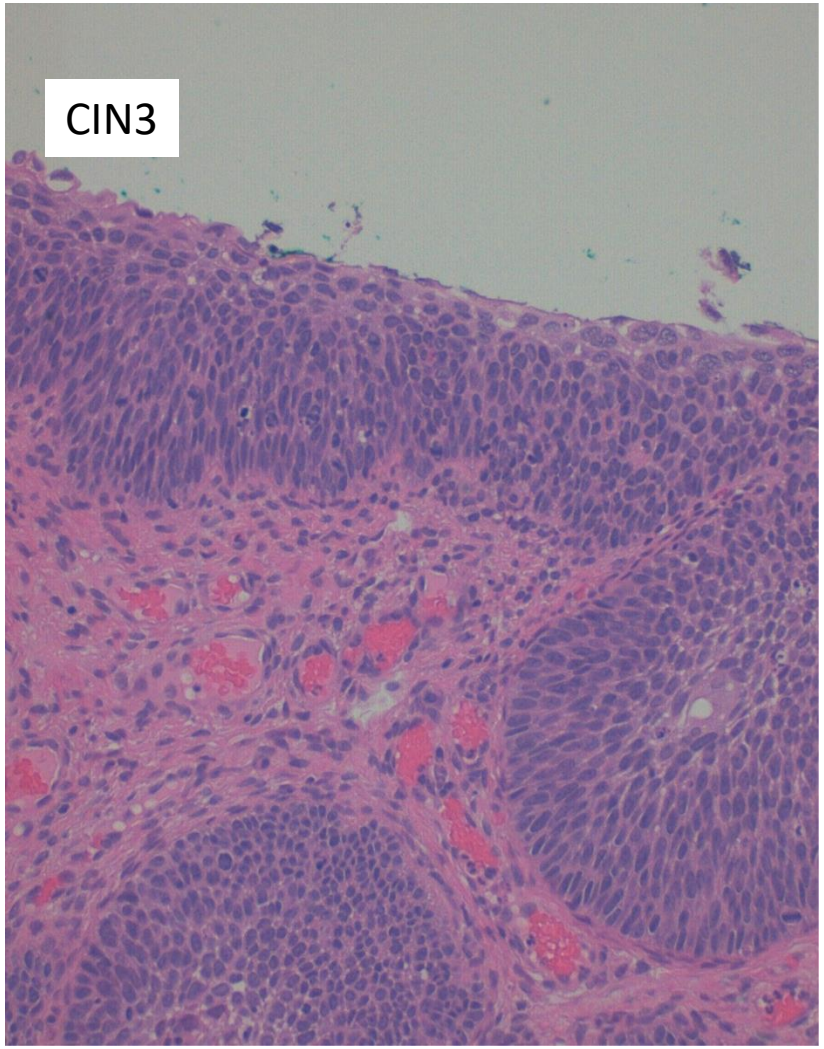
Human Papilloma Virus and cervical cancer

- 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







Why are we testing for HrHPV?

- There are pitfalls in cytology – cervical atrophy or inflamed metaplastic cells can be difficult to distinguish from high grade dyskaryosis
- HrHPV testing has increased sensitivity compared to cytology alone
- It has a high negative predictive value, so the screening interval can be increased for those who have a negative test result
  - A negative HrHPV test carries a very low risk of a patient developing cervical cancer and they will be recalled in 5 years
- As the number of immunised women in the screening cohort increases there is less disease to find, and HrHPV testing is more sensitive in this patient cohort

BUT:

- It is less specific for CIN (would generate too many false positives to be acceptable) so a second test is needed. Those who have a positive HrHPV test go on to have cytology and if there are abnormalities on cytology the patient is referred to colposcopy.
- In the first round of screening a larger number of colposcopy referrals are expected

What do women know about HPV?

- Discussions were undertaken with 100 women across Scotland in research undertaken by Research Scotland
- They were not given information about HPV beforehand
- Half of the women had not heard of HPV and there was a lot of worry and confusion
- Even women who had heard of HPV did not always know it was linked with cervical cancer
- Those who had heard of it often said it was because of the vaccination that girls get at school

What do women know about HPV?

- How would you feel if the results of a cervical screening (smear) test told you you had HPV?
  - Unsure or confused
  - Worried, anxious or scared – some because they did not know what HPV was
  - Some thought it sounded like HIV
- Session with a researcher explaining key messages about HPV. After this:
  - Most participants said they would feel slightly less worried, nervous and anxious than they did before the discussion, because they felt more informed, confident and aware of what HPV was
  - Most were still worried and confused over what happens next

Key messages from the session with the researcher

- HPV causes 99% of cases of cervical cancer
- There is research showing that the HPV test is a better way of identifying those at risk
- Nearly everyone gets HPV at one point in time (4 out of 5)
- Most of us can get rid of HPV, like we do with a common cold
- You cannot prevent HPV
- HPV is spread through skin to skin, intimate contact
- HPV can stay in the body un-noticed for a long period of time – up to 20 years
- Because the test is better, women who don't have HPV will be invited for tests every 5 years

What do women know about HPV?

- Positive messages:
  - Research shows that the HPV test is a better way of identifying those at risk
  - Australia is on track to eradicate cervical cancer because of a similar approach
  - If high risk HPV is treated it is unlikely to lead to cervical cancer
  - HPV causes 99% of cervical cancer
  - HPV is spread through skin to skin intimate contact (for a few lesbian women, this message was important and confirmed the importance of screening for them)
- Mixed reviews:
  - Nearly everyone gets HPV at one point in time – although change in stance “HPV is common” thought to be useful as discussions went on
  - Most of us can get rid of HPV like a common cold (reassuring vs not reflecting the seriousness of screening)
- Potential negative impact:
  - HPV can stay in the body un-noticed for a long time (up to 20 years)
  - Because the test is better, women who don’t have HPV will be invited for a test every 5 years

Recommendations from the research

- Women need to understand that:
  - HPV is common
  - It usually clears from the body on its own
  - It rarely leads to cervical cancer
  - Cervical cancer usually develops slowly, over 10 to 20 years
  - Women with HPV will be called back for regular re-testing
  - If HPV developed it would cause cell changes – which would be picked up in the cervical screening test
  - Cell changes can normally be treated
  - Anyone who has ever had skin to skin intimate contact is at risk of developing HPV, regardless of who this is with (man or woman), how long ago this was, how many different people it is with or how often it is.

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)
- 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)

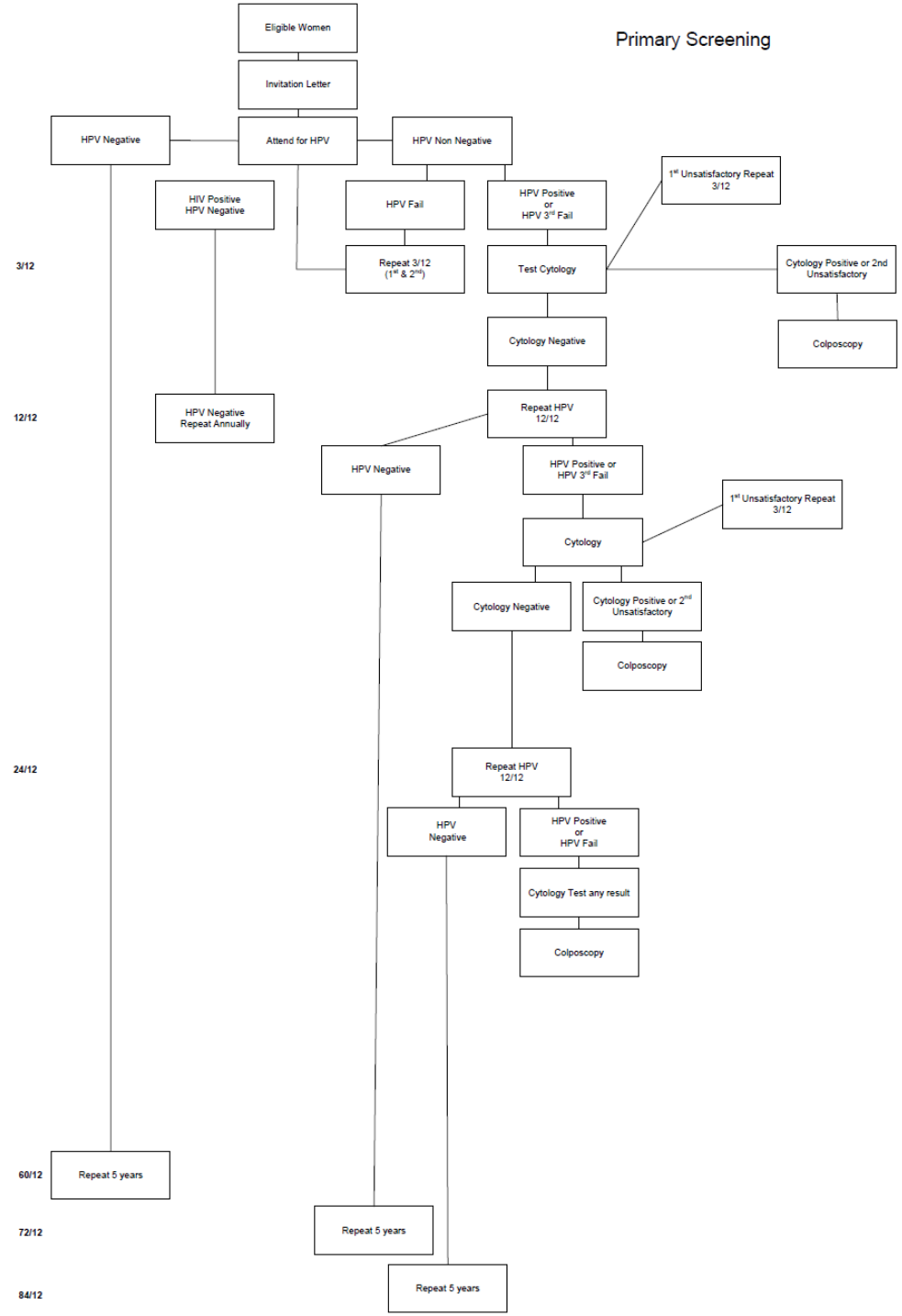
The new pathways

- 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 before March 2020
- Also applies to patients who had a borderline/low grade smear and were being recalled in 6 months for follow up
- 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

Primary Screening



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
  - This is the same as prior to March 2020

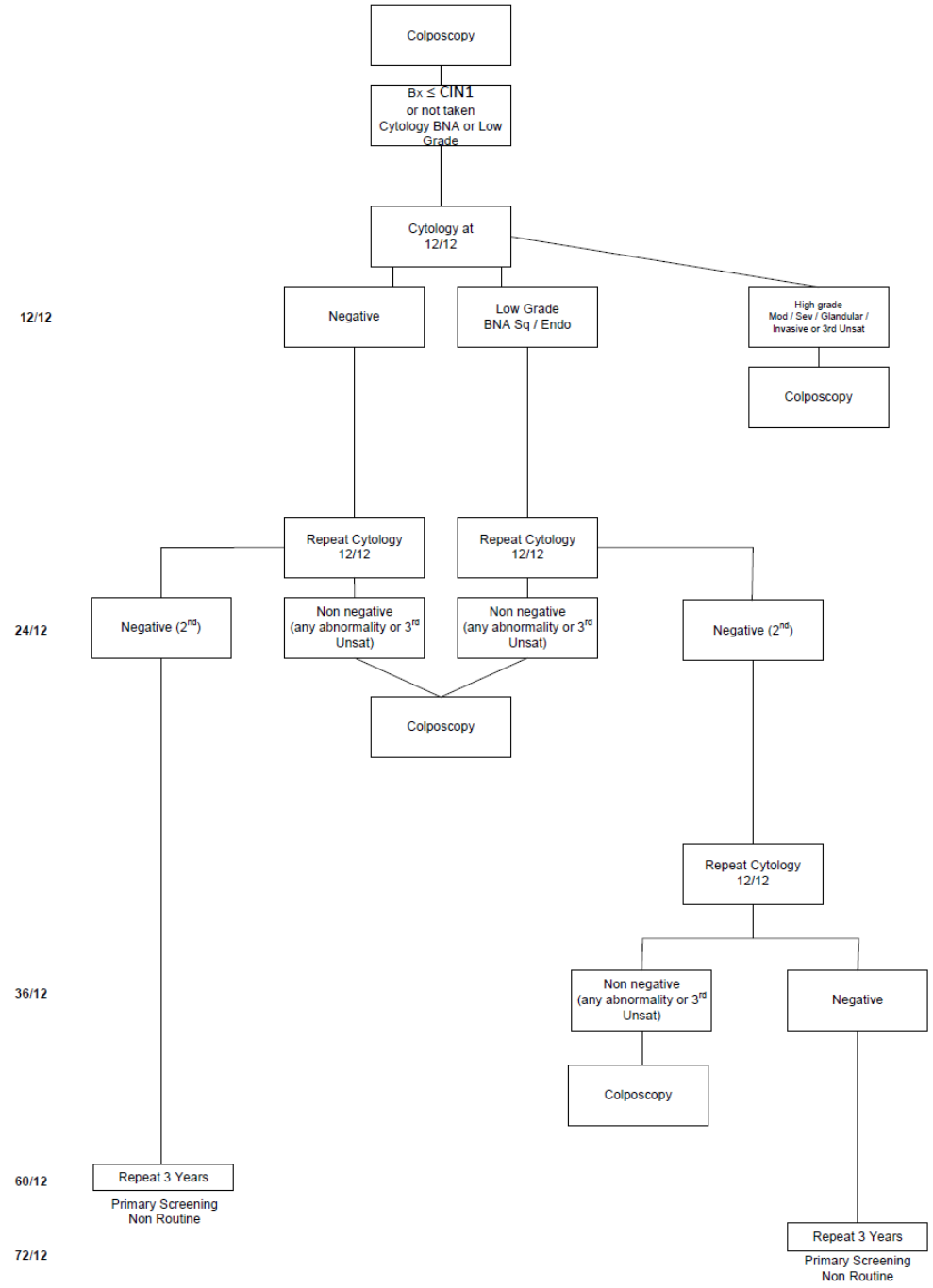
Test of cure

HPV result	**Cytology result**	**Recommended recall advice**	**New Participant Pathway**
Negative	Negative BNA Sq	Non routine recall 3 years	PS
Positive	Unsatisfactory Negative Any abnormality except endometrial or other malignancy	Refer to colposcopy	No change
Negative or fail	Low grade High grade mod/sev/?invasive Glandular abnormality Endocervical adenocarcinoma	Refer to colposcopy	No change
Negative or fail	BNA endo	6 months	No change
	Second BNA endo	Refer to colposcopy	
Positive, negative or fail	Endometrial or other malignancy	Refer to gynaecology	PS
Negative or fail	Unsatisfactory (first or second)	3 months	No change
Negative or fail	Unsatisfactory (third)	Refer to colposcopy	No change
Fail	Negative BNA Sq	6 months	No change

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

Conservative Management



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.

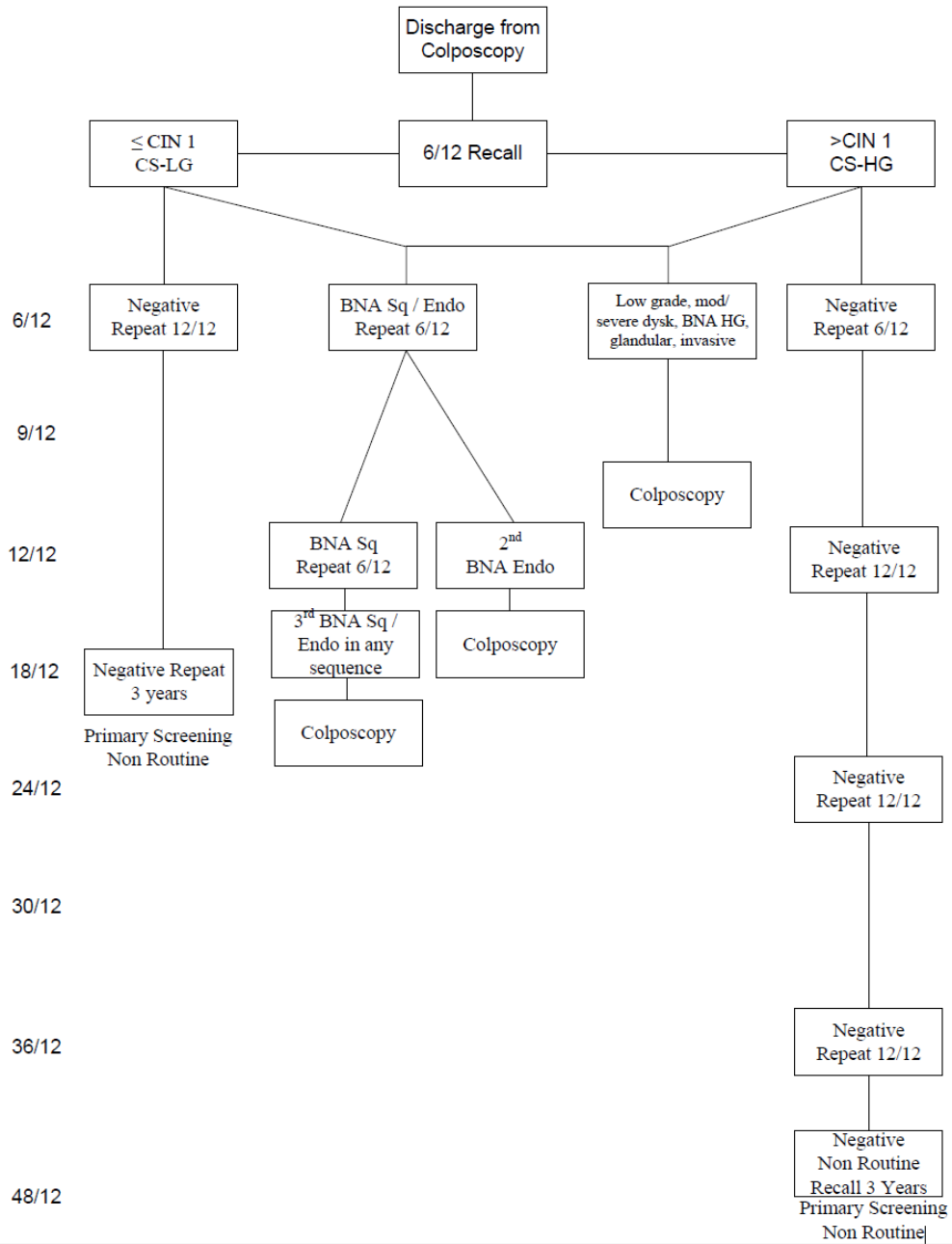
Cytology surveillance – low grade (CS-LG)

- “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

Cytology Surveillance

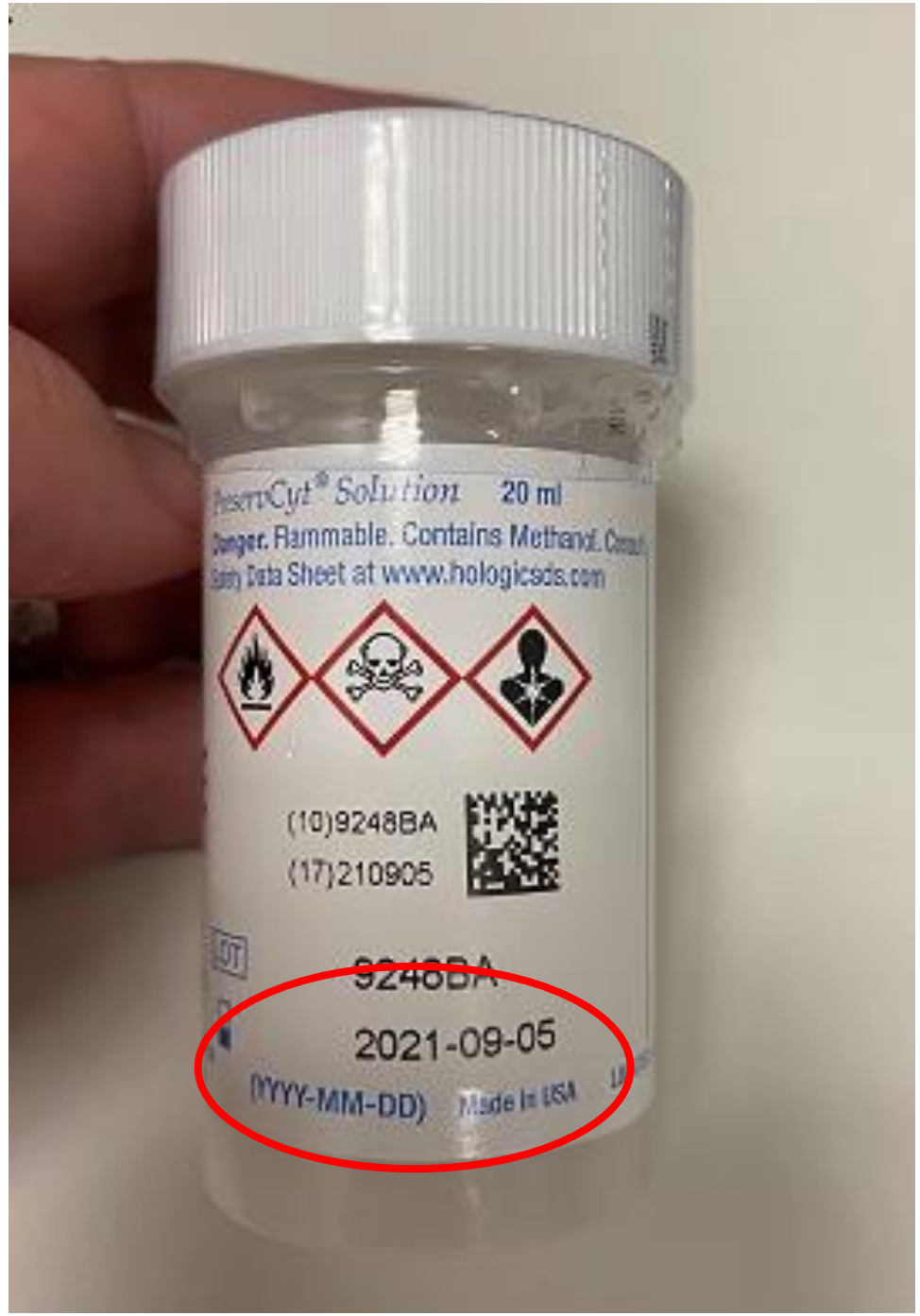


Symptoms

- Patients with abnormal bleeding
  - Post coital
  - Intermenstrual
  - Post menopausal
- Visualise the cervix
- Do not take a smear (unless it is due)
- Refer to gynaecology if symptoms cannot be explained

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.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Additional resources

- http://www.healthscotland.scot/health-topics/screening/cervical-screening
  - Link to Women's understanding of the introduction of HPV testing to the cervical screening programme in Scotland 09/05/2019
- http://www.healthscotland.scot/publications/scottish-cervical-screening-programme-primary-care-resources
  - Final CPD slides
  - Primary care briefing
  - FAQs