HPV testing in the context of post-treatment follow up

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Overview

- Background – cervical disease prevention and management in Scotland
- How test of cure was set up in Scotland
- Multi HPV platform study in a test of cure context: STOCS-H
- Scottish National Data - including roll-out
- Associated research interests.

Scotland's Cervical Screening Programme

- Scotland - 5.3 million popn. ~400,000 cervical smears/year
- National, organised call/recall programme - cytology based
- Liquid based cytology (PreservCyt)
- Age range 20 -60 years. **To change** to 25-65 year olds June 2016. 3 yearly screening up to age 50 then 5-yearly
- ~70% uptake
- Centralised screening IT system. This captures - cytology, call recall, histology, colposcopy, HPV and immunisation status
- HPV Immunisation as a national programme since Sept 2008

- HPV testing performed as a **test of cure of treatment** (not as triage)
- Business case for primary HPV testing to be submitted in 2016

negative/ borderline	LG dyskaryosis	HG dyskaryosis
95.4%	3.4%	1.2%

Reporting rates of adequate smears- 2014/15

Treatment of High Grade Lesions CIN2/CIN3

- Untreated CIN3: 31% risk to progress in 30 y (McCreddie, Lancet Oncol 2008)
- Increased risk of invasive CC up to 20 y after treatment (Strander 2007)
- Women diagnosed and treated for CIN3 between 1958-2000 in Sweden – substantially increased mortality from vaginal or cervical cancer compared to general population - standardised mortality ration of 2.35 (Strander 2014)
- Treatment of CIN2+ by removal of affected area indicated/justified
- Important to establish/monitor success of treatment
- High sensitivity and negative predictive value of HPV testing can provide insight into treatment success or “Test of Cure”

Test of Cure: International picture

Country	Post treatment recommendation	Reference
US (ASCCP)	Co-testing at 12 and 24 m	Massad et al 2013[16]
UK	Co-testing - between 1 to 2 time-points depending on country	http://www.cancerscreening.nhs.uk/cervical/hpv-triage-test-flowchart-201407.pdf
The Netherlands	3 Paps at 6,12, 24 months Proposal cotesting at 6 and 24 months	Uijterwaal et al 2013[18]
Denmark	Co-testing and margin assessment at (6 m) and	(http://sundhedsstyrelsen.dk) Cervical cancer screening recommendation, version 2012 (Appendix 10, pp. 139).
Sweden	cytology tests	
Norway	Co-testing at 3-6 and 12 months	http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/veileder-i-gynekologisk-onkologi-2009/Premaligne-lidelser-i-cervix-uteri/
Belgium	Co-testing at two time points	Marc Arbyn - personal communication
Australia	Co-testing at 12 and 24 m	National Health and Medical Research Council. Screening to Prevent Cervical Cancer: Guidelines for the Management of Women with Screen Detected Abnormalities. Canberra: NHRMC, 2005.
EU guidelines	3 Paps at 6,12, 24 months cotesting with HPV recommended	Jordan 2008 Cytopathology[2]; Arbyn AnnOncol 2010[54]

Variety in post treatment follow up algorithms including use of co-testing

Co-testing = HPV and cytology

Relative performance of tests in a Test of Cure context – Meta Analysis

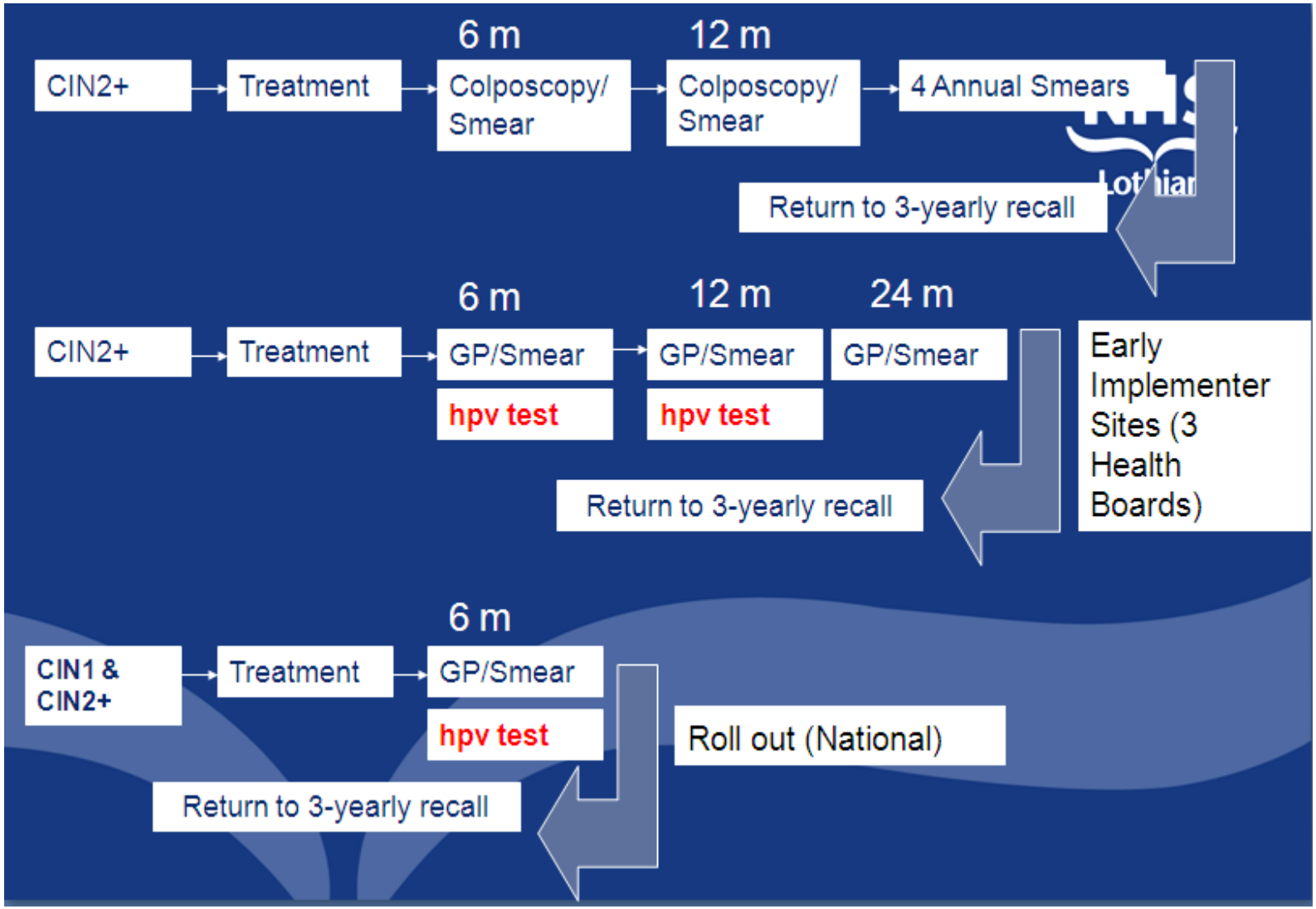
A: Test	Absolute sensitivity (95% CI)	Absolute specificity (95% CI)
HPV testing (HC2 or PCR)	94% (88-97)	80 (74-85)
Cytology (ASC-US+)	72% (66-78)	85% (81-88)
Co-testing	95% (88-98)	69 (62-77)

B: Test comparison	Relative sensitivity (95% CI)	Relative specificity (95% CI)
HPV vs Cytology (ASC-US+)	1.29 (1.18-1.40)	0.94 (0.90-0.99)
Co-testing vs HPV	1.07 (0.97-1.17)	0.93 (0.88-0.97)

Updated from Arbyn et al 2012

Introducing test of cure in Scotland - Key stages

- Set up of working group to review evidence and establish algorithms
- Modification to IT system “Scottish Cervical Call Recall System (SCCRs)” to accommodate HPV results
- Development & dissemination of information materials
- Development of Operational SOPs
  - Interface between virology/cytology
- Evaluation of Early Implementation phase
- Ongoing quality monitoring



Post treatment algorithms in Scotland – Pre HPV test of cure, early implementation and roll-out.

IT system – incorporation of a “new” virology module

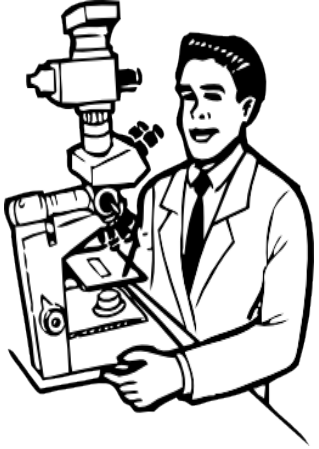
- National IT system
- Functionality for:
  - Book-in (paperless)
  - Worksheet generation, label printing (to support lab operational processes)
    - HPV result entry/authorisation

Then:

- Composite result (cytology & HPV) indicates subsequent management

Primary Care

Sent to cytology lab– booked in to IT system* - “pop up” appears if eligible for test of cure



Cytological Assessment

Prequat for HPV testing sent to SHVPRL

HPV Testing

Composite Result

* IT system contains women's screening/treatment history algorithm reviews history (ie treatment for “X” within the last “Y” months to determine whether eligible for test of cure

Scottish Cervical Screening Programme

HPV testing for women following treatment for CIN

Information for women

Why am I being tested for HPV following treatment for CIN (cervical intraepithelial neoplasia)?

The follow up of women who have been treated for CIN currently involves having a cervical smear performed annually for five years following treatment before they can be returned to routine three yearly screening. The HPV test is important because we now know that women who are HPV negative at six months and twelve months following treatment, and who also have no abnormal cells found in their cervical smear at 6, 12 and 24 months can return to routine three yearly screening. This means women can return to routine screening 3 years earlier than at present.

What happens if I've got HPV?

If HPV is found in your sample and/or your cervical smear shows abnormal cells you will be invited to attend for colposcopy again for assessment and followed up in the usual way.

What happens if I don't have HPV?

If HPV is not found in your sample and your cervical smears show no abnormal cells (after 6, 12 and 24 months following treatment) you will return to a routine three yearly screening.

What is HPV?

HPV stands for Human Papilloma Virus.

HPV is a very common infection of the cervix.

Most women get the virus at some time in their life. In most cases it does not need treatment and the body will clear the virus on its own.

There are lots of types of HPV and most are harmless. Some virus types can cause cervical abnormalities. Often, cervical abnormalities clear up when the virus clears. However, in some women the virus can persist and these women are at greater risk of developing CIN which may require treatment.

How do people get HPV?

HPV is a very common infection amongst people who have ever been sexually active. As the virus shows no symptoms it is therefore possible that the person may have had the infection for many years without knowing about it. A partner may have been infected many years ago and again not know.

Where can I find out more about HPV?

If you would like more information about HPV testing or anything else mentioned in this factsheet you can talk to your practice nurse or staff at the colposcopy clinic. Additional information about cervical cancer and HPV is also available on the British Society for Colposcopy and Cervical Pathology website at: www.BSCCP.org.uk. Other sources of information include NHS24 and www.fightcervicalcancer.org.uk

Which HPV test?

- Sensitivity of HPV testing in this context is important given
  - additional risk of this population
  - negative test indicates 3 yearly recall
- However, HPV positive cytology negative women are challenging to manage – getting the balance right!
- Few HPV assay comparisons in post treatment setting
- …STOCS-H study: Scottish Test of Cure Study HPV

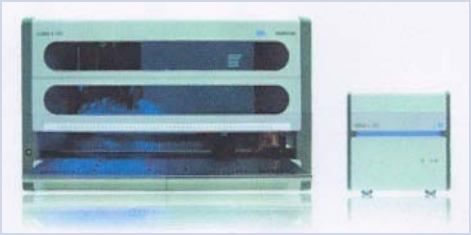
STOCS -H

Assessment of ~1020 samples obtained from TOC during early implementation phase

Sample taken at 6 months after treatment tested by 5 platforms below. HC2 was standard of care.

Performance measured according to cumulative incidence of CIN2 or minimum ~13 months after initial treatment

- Hybrid Capture 2 (Qiagen)
- *rT* High Risk HPV Test (Abbot)
- COBAS 4800 HPV system (Roche)
- APTIMA HPV Assay (GenProbe/Hologic)
- Cervista HPV Test (Hologic)

Test	Target	Image
Qiagen HC-2	DNA, 13 High Risk Types in aggregate, signal amplification	
Abbott *rt*HPV	DNA, 14 High Risk Types in aggregate, limited typing of 16/18 concurrently, target amplification	
Hologic Aptima	RNA, 14 High Risk Types in aggregate, target amplification	
Hologic CerVista	DNA, 14 High Risk Types in aggregate, signal amplification	 
Roche cobas 4800	DNA, 14 High Risk Types in aggregate, limited typing of 16/18 concurrently, target amplification	

STOCS –H - Characteristics

- 1020 samples tested by all five platforms
- HC2 assessed at 2 cut offs: 1 and 2.
- 23 women had residual CIN2 or worse during follow up period (2.2%)
  - 14 CIN3 or worse (1 cancer)

Analysis

- Overall HPV positivity
- Between assay agreement
- Clinical Performance for residual disease

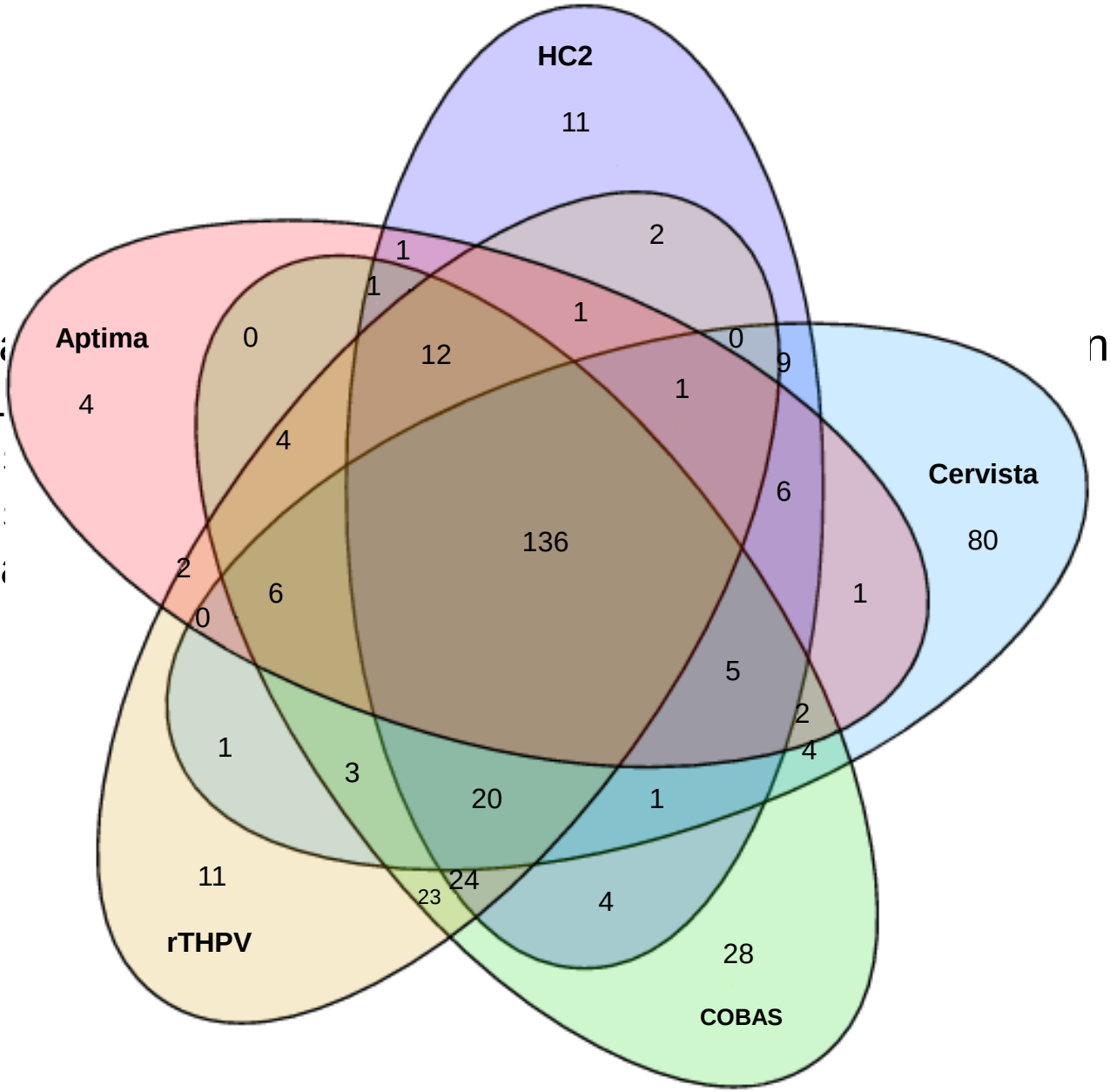
1020 cases – first follow up smear, HPV positivity according to assay

	N positive	% positive	95% CI for percentage
HC2 [cut-off=1]	234	22.94	(20.39, 25.65)
HC2 [cut-off=2]	201	19.71	(17.31, 22.28)
Cervista	275	26.96	(24.26, 29.80)
COBAS	273	26.76	(24.07, 29.60)
rTHPV	246	24.12	(21.52, 26.86)
Aptima	182	17.84	(15.54, 20.33)
Cytology*	62	6.08	(4.69, 7.72)

* at low grade or worse

Range of 17.84% to 26.96%

- Perfect a n
  753 of 1
  - 136
  - 617
  - 80 s



HPV positivity in 1020 samples, compared with cytology grade & assay

Cytology	HC2: c/o 1.0 n pos/total % (95% CI)	HC2: c/o 2.0 n pos/total % (95% CI)	rtHPV n pos/total % (95% CI)	AHPV n pos/total % (95% CI)	Cervista n pos/total % (95% CI)	COBAS n pos/total % (95% CI)	No of CIN2+
Negative or borderline	181/955 18.9 (16.6, 21.6)	150/955 15.7 (13.5, 18.1)	194/955 20.3 (17.8, 23.0)	130/955 13.6 (11.5, 15.9)	223/955 23.3 (20.8, 26.1)	220/955 23.0 (20.5, 25.8)	4
Mild	25/32 78.1 (61.2, 89.0)	25/32 78.1 (61.2, 89.0)	24/32 75.0 (57.9, 86.7)	24/32 75.0 (57.9, 86.7)	26/32 81.2 (64.7, 91.1)	25/32 78.1 (61.2, 89.0)	3
Moderate or severe*	28/33 84.8 (69.1, 93.3)	26/33 78.8 (62.2,89.3)	28/33 84.8 (69.1, 93.3)	28/33 84.8 (69.1, 93.3)	26/33 78.8 (62.2,89.3)	28/33 84.8 (69.1, 93.3)	16
Total	234/1020 22.9 (20.5, 25.6)	201/1020 19.7 (17.4, 22.2)	246/1020 24.1 (21.6, 26.8)	182/1020 17.8 (15.6, 20.3)	275/1020 26.9 (24.3, 29.8)	273/1020 26.8 (24.1, 29.6)	23

Clinical Performance – for detection of CIN2+

	Sensitivity (95% CI)	Specificity (95% CI)
HC2 @1	100% Lower bound of 95% CI (85)	79% (76, 81)
HC2 @2	96% (78, 100)	82% (80, 84)
Cervista	96% (78, 100)	75% (72, 77)
COBAS	100% Lower bound of 95% CI (85)	75% (72, 78)
rTHPV	100% Lower bound of 95% CI (85)	78% (75, 80)
Aptima	91% (72, 99)	84% (81, 86)
Cytology	83% (61, 95)	95% (94, 97)

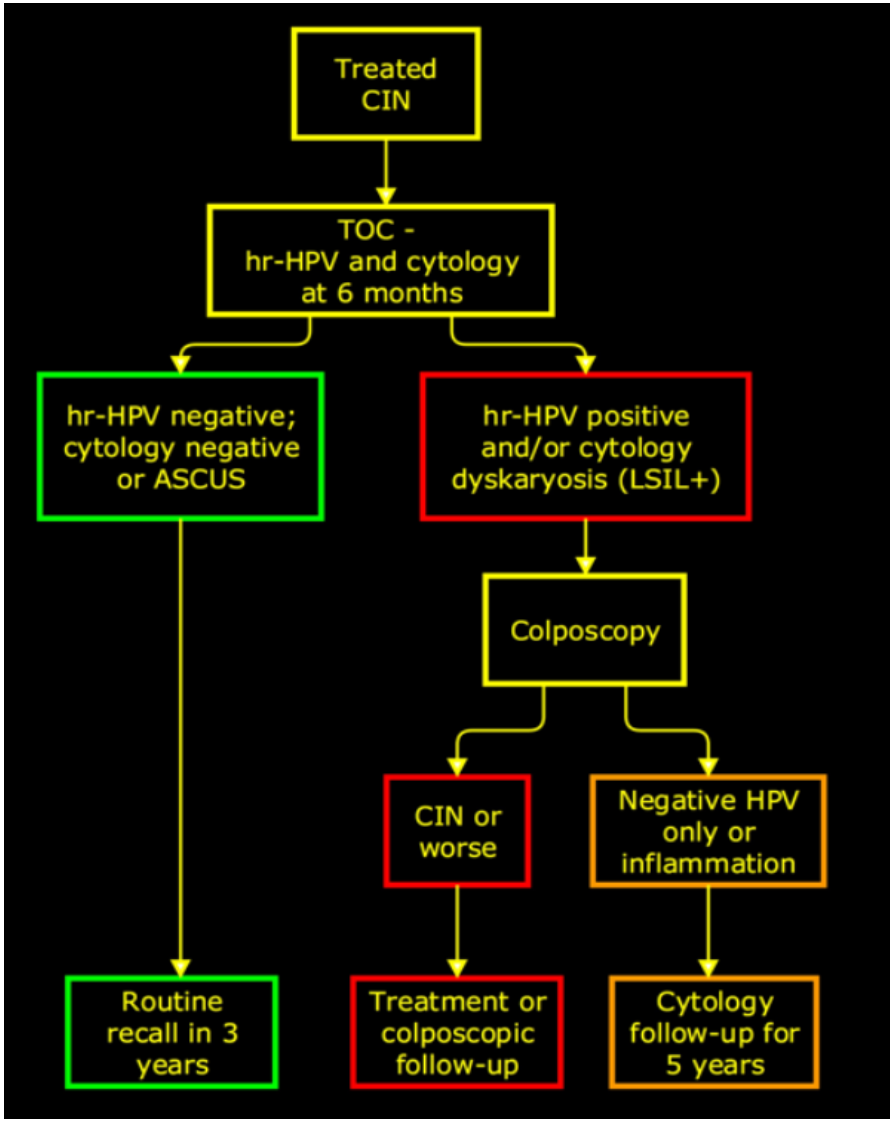
3/5 HPV assays detected all cases of residual CIN2, 1/5 missed one case of CIN2 and 1/5 missed two cases of CIN2. At a cut off of low grade dyskaryosis, cytology missed 4 cases of CIN2, at a cut off of borderline/ASCUS, it missed 3 cases

All 14 cases of CIN3+ were detected by all HPV assays and cytology

STOCS-H - Summary

- HPV tests reassuringly sensitive for the detection of CIN3+
- Some between-assay differences in detection of CIN2+
- HPV Positivity at 6 months post-treatment ranged from 18% to 27% depending on assay
- Observations of between assay differences are consistent with other multi-platform studies in different contexts (primary screening, LG triage)
- Assessment of longer term follow-up ongoing

Scottish “routine” data - preliminary



Current TOC management algorithm in Scotland

Scottish “routine” data (2)

Number of TOC tests April 2012 – Nov 2015

= 14, 156 (@ 6 months post treatment)

Number of TOC tests	TOC negative	TOC positive
14,156	10324	3552

25% positive at 6 months (using HC2 assay, then changed to rT HPV test)

Results
Women with follow-up following TOC

		TOC negative	TOC positive	
			-ve colp	+ve colp
Eligible for follow-up		10324	3132	403
Total with follow-up*		1503	1966	403
Cytology	negative	1445	1494	
	Borderline	31	196	
	Low grade	23 (1.5%)	212 (10.8%)	
	High grade	4 (0.3%)	64 (3.3%)	
Histology	Negative	8	189	
	CIN 1	1 (0.06%)	18 (0.9%)	180 (44.7%)
	CIN 2+	3 (0.2%)	56 (2.8%)	223 (55.3%)

*: smears reported as inadequate for diagnosis not included
Duration of follow-up: <= 42 months

negative/ borderline	LG dyskaryosis	HG dyskaryosis
95.4%	3.4%	1.2%

Reporting/abnormal rates in general screening population in Scotland

Negative/ borderline	LG dyskaryosis	HG dyskaryosis
96.1%	1.5%	0.3%

Reporting abnormal rates in women with a negative test of cure (f.up of 6-42 months)

Test of Cure – implementation and assessment

- **Operationally – national test of cure in Scotland was rolled out successfully after an early implementation phase.**
- **Having an national IT system for cervical screening that could be adapted was helpful in this endeavour - as were nationally agreed guidelines and protocols**
- **Some issues with compliance to TOC algorithm – women turning up “early” after testing negative (ie aligning with “old” protocol)**
- **In process of collating more and longer term follow up – stay tuned!**

Micro-invasive and glandular lesions and SMILe evaluation (MAGS)

- Currently women with glandular lesions or micro-invasive disease are not included in test of cure in Scotland
- Comparative little information on performance of test of cure in the above- with some notable exceptions (Costa et al 2007, 2012, 2015)
- Meta analysis/reviews rarely separate out squamous from glandular lesions or provide detail on the inclusion of microinvasive disease;

Assessing the performance of HPV test of cure in women treated for micro-invasive and glandular lesions and SMILe (MAGS)

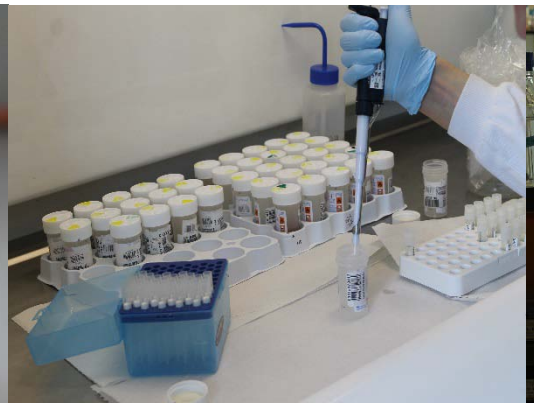
- Scotland-wide evaluation
- Women treated for glandular lesions, micro-invasive cancer and SMILe* have "traditional" recall – but also receive HPV testing at 6 & 12 months. HPV test not acted on but collation of follow up data will provide insight into the utility of this approach
- Recruited 400

Path	Number per category
High grade CGIN (4 with SMILe)	277
Low grade CGIN	9
SMILe	9
Microinvasive SCC (1 with HG CGIN)	89
Microinvasive Adenocarcioma	16
	Total =400

HPV neg	HPV pos	Total
332	**68 (17%)**	**400**

Building capacity for relevant research – The Scottish HPV Archive

- Started in 2009
- Archive of largely cervical samples from women in Scotland
- Data linkage to immunisation/screening records possible
- Can be used for HPV related research
- Over 30,000 and counting…. Multiple aliquots e


INTERESTED IN USING THE ARCHIVE? Get in touch –
HPVarchive@ed.ac.uk
0131 242 6625 – Dr Ramya Bhatia - archive manager

Thanks to

- Scottish Cervical Screening Programme – Dr Timothy Palmer (Lead for clinical Cytology)
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- All Scottish Pathology Laboratories
- Scottish HPV Investigators Network (SHINe)
- GISCi