HPV

Test of Risk or Test of Disease?

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Acknowledgements

- CSW Modernisation Programme HPV implementation project
- PHE Primary HPV Pilot Project
- CERVIVA and the Irish Research Council
- “**Cervical Screening: *Time for Biology to Inform the Future”.*** *Prof. John J O’Leary. Cervical Screening Wales HPV Stakeholder Conference. September 2016.*

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Background

- While UK studies initially demonstrated equivalence between HPV and cytology primary screening, indicated benefits by HPV primary screening in the longer term.
- International studies demonstrated clear benefits to HPV primary screening – primarily regarding NPP.....

Background

- Negative HPV test is as reliable at 6 years as negative cytology is at 3, so potential to increase screening interval with cost savings even if HPV primary screening is slightly more expensive

- All of this is great news.....but what about the woman who has a HrHPV positive result??

Down to Sensitivity and Specificity after all!

- Hr HPV testing is 20-30% more sensitive than cytology for the detection of ≥ CIN3
- Hr HPV testing is almost as specific as cytology for ≥ CIN3

	Sensitivity % (95% CI)	Specificity % (95% CI)
Cytology[1]	53.0% (48.6–57.4)	96.3% (96.1–96.5)
HPV DNA[1]	96.1% (94.2–97.4)	90.7% (90.4–91.1)
HPV mRNA[2]	92.0 (86.4-97.6)	91.8 (91.0-92.6)

Potential for Extended Recall

- Potential to increase screening interval (negative HPV test is as reliable at 6 years as negative cytology is at 3) resulting in cost benefits even if HPV primary screening is slightly more expensive
- The down side to this approach is that it will increase the level of workload fluctuation compared to current levels.
- This would increase burden on the CSP
- ScHARR are currently working to finalise operational Call/Recall strategies to minimise this effect

Background – Proving Concepts

- HPV Primary Screening project implemented in England
- Cervical Modernisation Project (HPV Implementation Workstream) in Wales.

The Pilots in England

- 6 Sentinel sites – 3 SurePath, 3 ThinPrep.
- Variety of different NHSCSP approved HR-HPV testing platforms in use across the sites.
- Each pilot site was directed to include only part of their geographical area in the pilot. Concern was that the pilot should be able to be rolled back to cytology primary screening if found necessary.
- First site live April 2013, however September 2013 before all sites within the pilot were live.

HPV Implementation in Wales

- Bit slow off the molecular mark.....!
  - Sept 2014.....HPV Test of Cure
  - November 2015.....ToC catch-up cohort
  - May 2016..... HPV Triage of LG cytology
- Planning for:
  - HPV Primary Test Implementation Pilot – April 2017
  - Full HPV Primary Testing – 2018-19

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Approval Timelines

January 2016 – UK NSC recommendation to Minister for Health

June 2016 – Minister appoves HPV test for primary screening in England

October 2016 – Minister for Health in WG approves move to HPV primary testing.

Participant Pathways

- Initially:
  - HPV-ve = routine recall (3 or 5 years)
  - HPV+ve/ Cyto+ve = refer
  - HPV+ve/Cyto-ve = 12 months repeat
  - If 3 consecutive HPV+ve/Cyto-ve = Colp referral

Participant Pathways

Subsequently in the pilot:

- Decision taken to consider referring on 2nd HPV+ve/Cyto–ve if both tests showed HPV 16 or 18.
- 3 pilot sites moved to this protoco/, other 3 remained on original one.
- Untreated CIN 1 and CGIN ToC pathways came into being – HPV primary screening versions of these also introduced

This is good news if the woman has a HrHPV –ve result

✔

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What if its HrHPV +ve??

- That's OK....
  - We have Cytology, don't we! 😍
  - And.....Colposcopy! 😂

So all is well?

Not quite.....

Variable Positivity rates

- HPV positivity rate of all sites varies between 10-15% which translates to 15% of the cytology preparations in a cytology primary test model
- The variation in HPV+ rate appears to be HPV/LBC platform related (although screening populations may factor also)
- This may impact on increased colposcopy rates.

Reflex Cytology

- Residual cytology will be around 15% of previous level, but:
- Number of screeners required will be greater than 15% due to need to perform other duties.
- Given NHSCSP maximum of 5.5 hours daily screening, around 40% of existing screeners required.
- Commitment to CBMS and pathologists is 85% of that of cytology primary screening – reflecting the fact that the disease levels will not change dramatically

Reflex Cytology

- Cytology will still be required as a reflex test in managing HPV +ve women
- Suggested that primary cytology screeners will no longer be required as the primary screening function will be replaced by the HPV test
- Unpublished study from Sheffield indicates that primary screeners are the most efficient staff in detecting dyskaryosis.
- CSP would be advised to operate the screening/reporting pathway which has served the UK so well to date.- **IF IT AINT BROKE.....!!**

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MANAGING STAFFING AGAINST A BACKGROUND OF ZERO RECRUITMENT / VIRTUALLY ZERO TRAINING WILL BE A HUGE CHALLENGE FOR THE CSP

WHAT ARE THE ALTERNATIVES?

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Laboratory Service Design - Key Issues

- Must be large enough to maintain services and quality
- Recruit, maintain and develop staff
- Support colposcopy services
- Have appropriate IT systems and connectivity
- Be able to provide value for money
- Be flexible enough to absorb and manage service change

Computer Assisted Screening

- FocalPoint/NFR is NOT approved for NHSCSP use for HPV primary screening.
- It may be possible to perform a re-validation of the technology for a HPV primary test/reflex cytology screening modality
- ThinPrep™ Imager is only used in Scotland. Its applicability in a HPV Primary test modality is not known.

Colposcopy in the HPV primary screening world

- From HPV primary site data:
  - Referral rates not appreciably changed in first year
  - Slight increase in yr 2 if referring on second 16/18 positive following cytology negative along with cytology positive cases at 12/12 repeat.
  - Bigger increase in yr 2 with all HPV+ve/cyto–ve as well as 2 month repeats that are cyto+ve
- Interesting to note that the Referral Value for persistent cyto –ve/HPV +ve is low (Sheffield data)

Possible Molecular Approaches Post Primary HPV Screening

(Assuming Primary HPV DNA)

- HPV 16/18 Genotyping
- HPV mRNA testing
- p16/p16-ki67
- Methylation Markers
- Other Biomarkers

HPV16/18 Genotyping to Stratify High-risk Patients

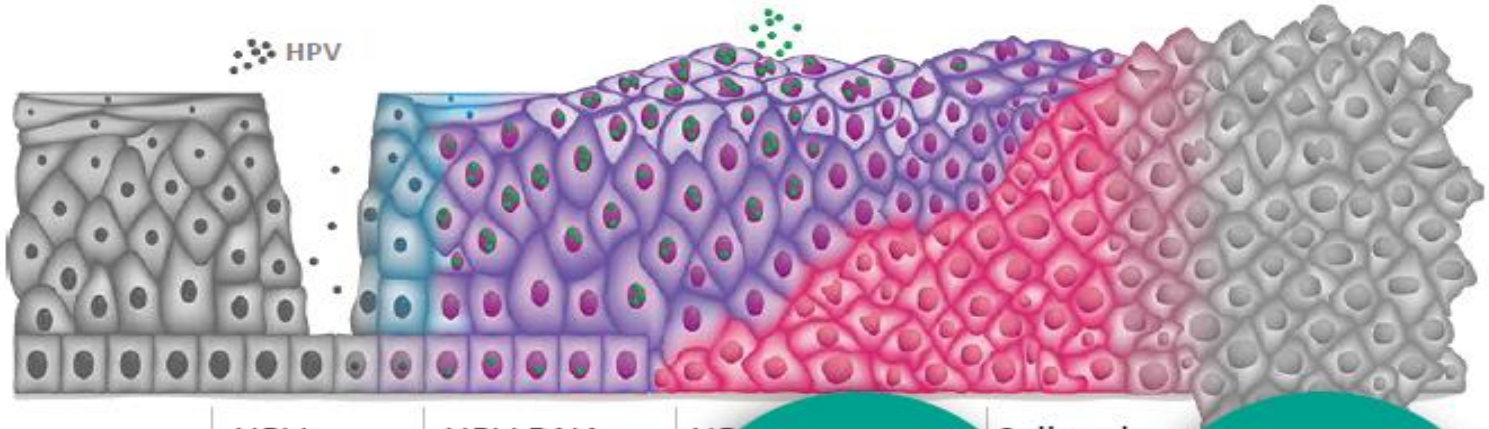
- 10-year cumulative incidence rate of ≥CIN3 by hrHPV status (Portland-Kaiser Cohort). HPV screening that identifies HPV16 and HPV18 from other oncogenic HPV types may identify women at greatest risk of developing high-grade cervical lesions
- Athena Study - combination of HPV 16/18 genotyping and cytology provides a good balance between maximizing sensitivity and specificity by limiting the number of colposcopies
- This strategy is currently under evaluation in the English primary HPV pilot

p16INK4a Triage of HPV Positive Women

- Sensitivity of p16 at 3 years follow-up for detection of CIN3+ was higher than conventional cytology across all age groups (77.8%)
- HPV positive/p16 negative women could be safely returned to routine recall

- Carozzi et al. *Lancet. 2013;14:168-176.*

HPV DNA and p16/ki-67 identify both risk & progression



	HPV infection	HPV DNA replication	HP	Cell cycle eregulat
HPV DNA Test	-	+		
HPV E6/E7 mRNA Test	-	-		
p16/Ki-67 Test	-	-	-	+

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Cintec PLUS™

- Evaluated by the HPV Sentinel sites
- Results disappointing.
- Republic of Ireland report better findings, related to limitations around the automation performing the staining
- Using “on-slide” controls allowing better control and evaluation

HPV mRNA Triage of HPV Positive Women

- Predictors studies (2008, 2013): LSIL/ASCUS triage
- Danish study, 2013, Waldstrom et al.
- High sensitivity for CIN3, but
- Low specificity (39%) and
- High referral rate (69%)

Methylation Markers for the Triage of HPV Positive Women

- Hypermethylation of tumour suppressor genes involved in cervical cancer
- –CADM1 and MAL
- –mIR-124-2
- –In hrHPV positive women, these methylation markers were at least equally discriminatory for high-grade CIN as cytology, or as cytology with the detection of HPV16/18
- Hesselink et al. *Clin Cancer Res. 2011;17(8):2459-2465*

Biomarkers in Cervical Cancer /Precancer

- Geminin ; mcm 2,3,4,5,7,10 ;P16 ;PCNA/ki-67; HOX C6; HOX C10; Topoisomerase IIa
- Survivin; Prostaglandin E synthase; Serine/threonine kinase 6; Cyclins A2, B2, E1, E2, F,
- E2F; cdc 6, 14, 28; hTERT; cdcA11(nuf2); SMAD 3, 4
- **No single study has yet evaluated in parallel all biomarkers in the context of HPV primary screening**

Cytology in the Triage of HPV Positive Women

- VUSA-screen study, compared NPV and PPV of 14 different triage methods
- Triage of HPV positive women by cytology, followed by repeat cytology at 12 months yielded a high NPV of 99.3% and modest Colposcopy referral rate of 33.4%

- Rijkaart et al. *Int J Cancer. 2012;130: 602–610.*

Cytology Best to Triage HPV Positive cases?

- Has a high specificity for high grade disease
- Coupled with reasonable referral rates to Colposcopy

- Probably the HPV+ve Triage tool of choice at the present time
- **A good Test of Disease!**

The Future.....

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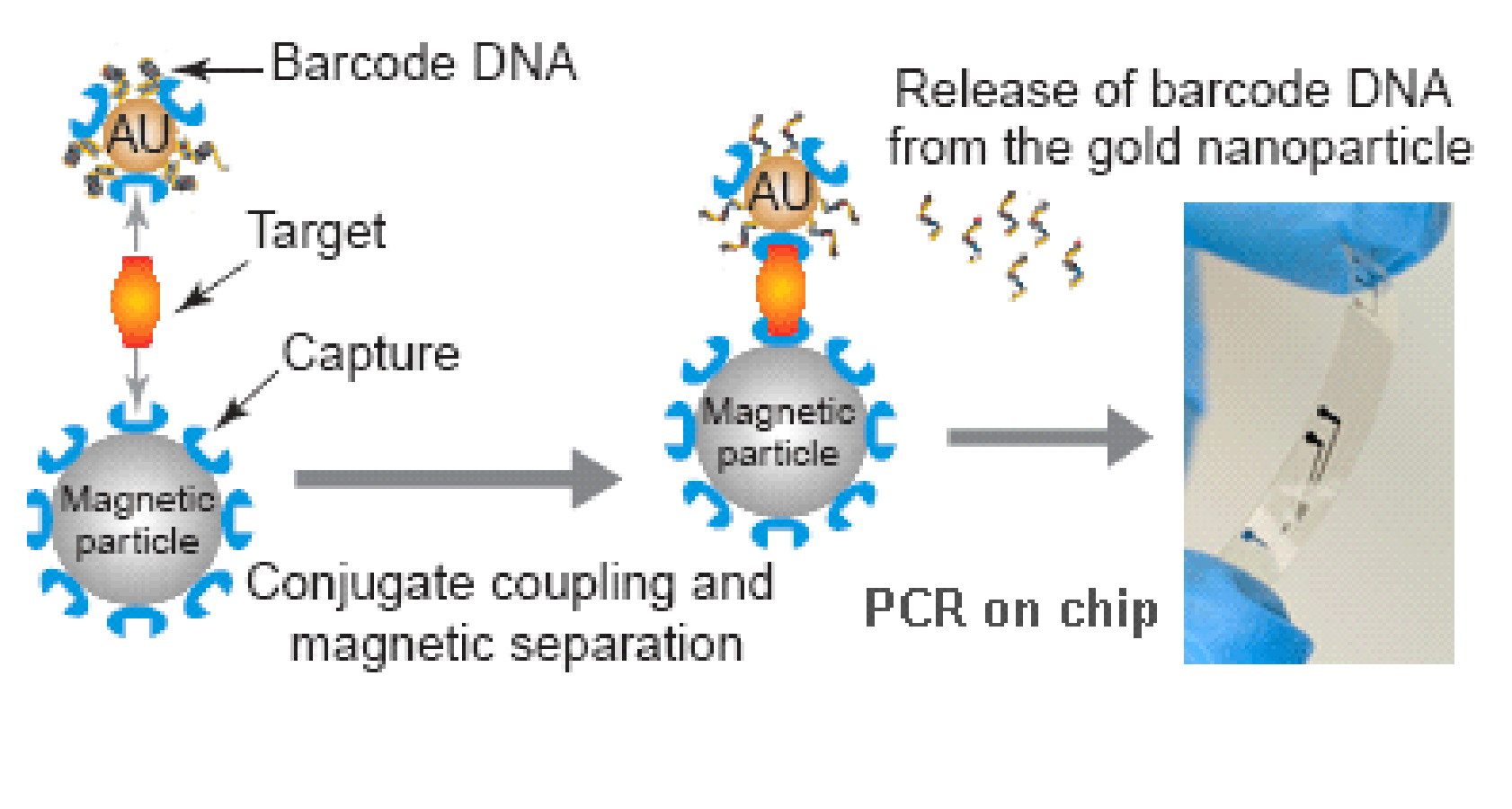
The Ultimate HPV Test

DNA, mRNA and protein - in one test!



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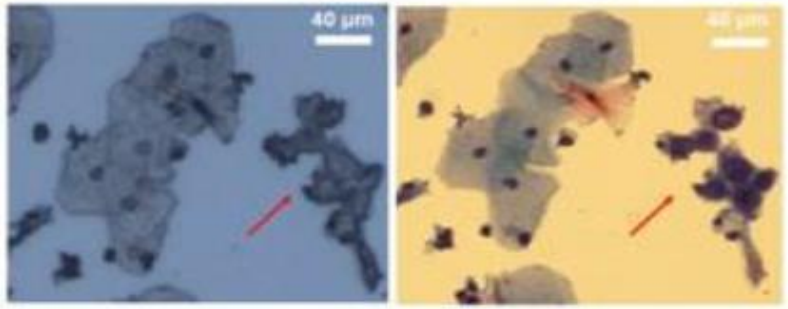
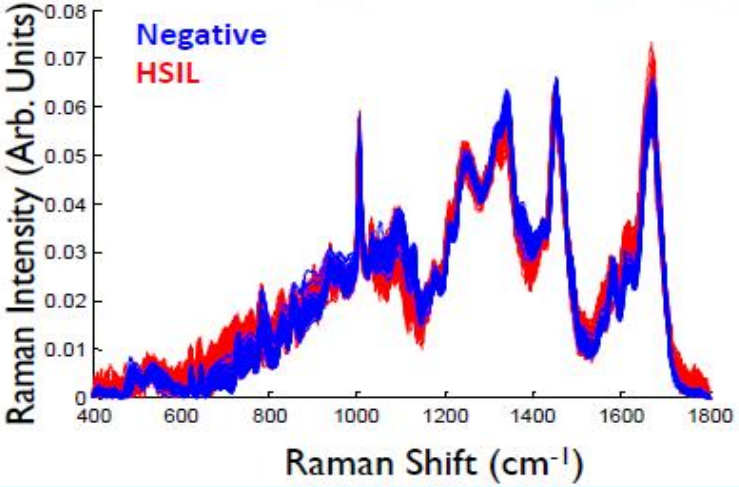
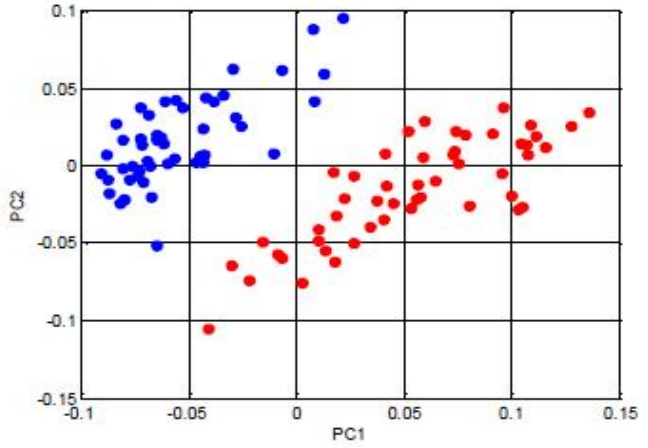
Raman Spectroscopy for Cervical Cytology

[Biochemical fingerprinting of cells]

Negative vs High Grade Cytology

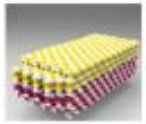


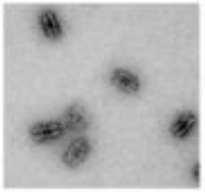


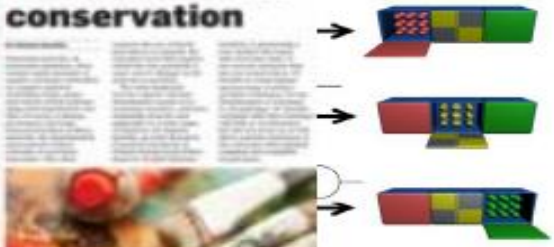


Nanobots and biobots to detect cancer

[the next generation of cancer diagnostics]







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Thanks for listening!

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