

A novel biomarker panel for the risk stratification of Human Papillomavirus (HPV) infection to detect clinically relevant cervical disease

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Introduction

Cervical cancer is caused by high risk HPV (HR-HPV) and HR-HPV based primary cervical screening has been implemented in several countries.

Robust strategies for the risk stratification of HR-HPV positive women are now needed to prioritise which women need clinical examination compared to those who can be managed more conservatively.

Objective

To produce a simple laboratory biomarker test to identify HR-HPV women at greater risk of developing cervical disease and thus improve cervical screening. If successful, this test could have global impacts in reducing cervical healthcare costs and improving women's health.

Methods

Cervical samples originally taken due to routine screening and subsequently stored in the **Scottish HPV Archive** were requested (Fig 1).

To date, six different applications have been approved. Samples have been used for:

- ✓ Proof of concept (Fig.2, using a disease enriched population)
- ✓ Initial development of protein biomarkers
- ✓ Clinical validation of protein biomarkers
- ✓ Validation of mRNA biomarkers (on-going)

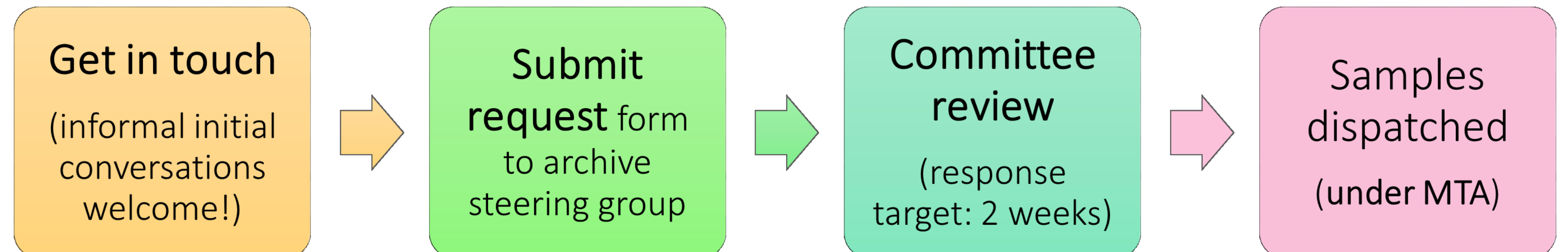
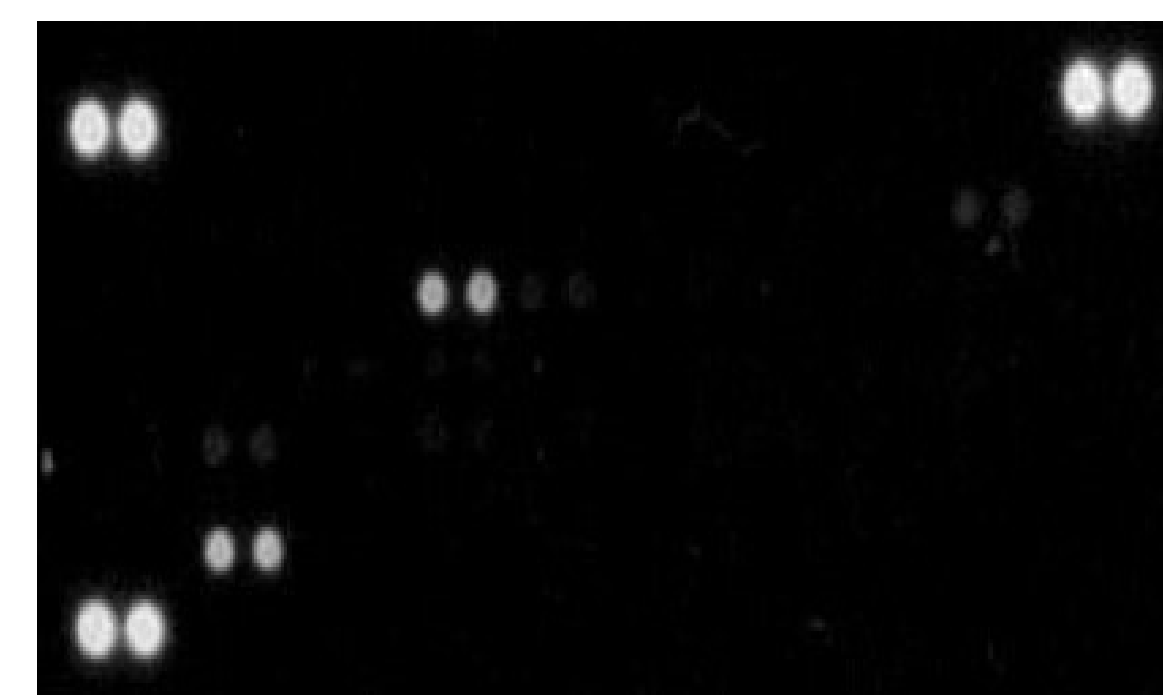


Fig.1. Schematics for requesting samples to the Scottish HPV Archive.

Results

A panel of immunological markers (chemokines) was found which separates women with and without disease.



Chemokine production (white circles) in normal tissue.



Chemokine production (white circles) in high grade cervical lesions.

Fig.2. Different chemokine proteins are associated disease vs no disease. Each chemokine is printed in duplicate in the arrays. Patients with cervical lesions showed a very different pattern of chemokine expression compared to healthy individuals.

Outputs	Impact
Publications	Two peer-reviewed papers: <i>Canham et al. 2014</i> ¹ and <i>Bhatia et al. 2018</i> ²
Grants	Chief Scientist Office of the Scottish Government (x2), SBRI-Innovative UK (x2), University of Edinburgh confidence in concept award (MRC CiC) (x1) ~700k in grant funding
Engagement	Talks at scientific conferences at national and international level (including International Papillomavirus meeting). Presentations at the multidisciplinary Scottish HPV Investigators Network (SHiNE) meetings, which include representation from third sector and lay audience.
Patent	Patent filed for "HPV biomarkers" covering protein and mRNA work (Number GB1509300.8)
New company	Set up of a spinout company via University of Edinburgh Technology Transfer team – Precidar Diagnostics
Collaborations	Academic: Trinity College Dublin (Ireland) and London School of Hygiene and Tropical Medicine (UK) leading to coapplications for equitable grant funding and production of health economic reports relating to the impact of the biomarkers. Commercial: Euroimmun Dx (Germany) and Ulisse Biomed (Italy) has already led to funding and future collaborations to support further development and application of the biomarkers.

Conclusion and Impact

A biomarker test has been developed which could serve as an objective test for significant cervical disease. This has high potential to improve cervical screening and disease management. Engagement with commercial collaborators to further refine the test to industry standards is ongoing.

References:

- ¹ Canham M, Charsoo C, Stewart J, Moncur S, Hoodless L, Bhatia R, Cong D, Cubie H, Busby-Earle C, Williams A, McLoughlin V, Campbell JD, Cuschieri K, Howie S. Increased cycling cell numbers and stem cell associated proteins as potential biomarkers for high grade human papillomavirus+ve pre-neoplastic cervical disease. *PLoS One*. 2014 Dec 22;9(12):e115379.
² Bhatia, R, Kavanagh, K, Stewart, J, Moncur, S, Serrano, I, Cong, D, Cubie, H, Haas, J, Busby-Earle, C, Williams, A, Howie, S & Cuschieri, K. Host chemokine signature as a biomarker for the detection of pre-cancerous cervical lesions. *Oncotarget*, 2018, vol 9, pp. 18548-18558.