PRoF Award abstract – Call 2015

Personalised Management

in Cervical Cancer Prevention

(PERSONAL)

1. Research Outline

Acronym	PERSONAL
Project name in English	Personalised Management in Cervical Cancer Prevention
Pitch (1 sentence)	Personalised user-friendly care for women with cervical precancer
Executive summary (max. 10 lines)	
Establishing that HPV is causally associated with cervical cancer has led to major advances in cervical cancer primary and secondary prevention but also has set new challenges for cost effective screening for the future. In the recent years, there has been an explosion of new tests and HPV-related biomarkers targeting the viral genome and assessing different stages of the disease expression. The outcomes from PERSONAL apply to individual, health organisation and policy makers' level. The prognostic models, the IT software/platform and mobile application incorporating risk factors and selected biomarkers allow user-friendly, sustainable and reproducible use of systems for quantification of the individual's risk.	

2. Cause and context of the research

Establishing that HPV is causally associated with cervical cancer has led to major advances in cervical cancer primary and secondary prevention but also sets new challenges for cost effective screening for the future (1). Previously established recommendations and algorithms for management are likely to be less applicable in future screening settings, while new tests based on the viral genome may allow improved cost-effective personalised management of women with abnormalities detected at screening. HPV vaccination for the 2 commonest oncogenic HPV subtypes (2) and the expected transition from cytology- to HPV-based population screening (3) will need new management strategies at micro- (individual), meso- (health systems/organisations) and macro- (policy/decision makers) level.

The previous relatively simple algorithms for management of women with either low- or high-grade abnormalities at cytology have been effective at reducing the incidence of cervical cancer, albeit based on clinical tests that have limited sensitivity and specificity. Management of HPV-positive women, taking into account the variability in risk profile of future vaccinated cohorts, can be modified by cytological and molecular biomarkers that could stratify which lesions are at high risk of invasion and, conversely, which are likely to regress. Investing in the assessment of the clinical utility and performance of individual or panel of biomarkers is particularly important. A robust evidence base was required so that risk assessment based on molecular biomarkers can be utilised within management protocols in non-vaccinated but also future vaccinated cohorts that will be soon eligible for screening.

The management of women with screen-detected disease by molecular biomarkers requires robust evaluation of these technologies and the establishment of *de nuovo* algorithms and guidelines for personalised cost-effective management pathways within current budgets

across Europe (4). Their use could improve diagnosis, optimise clinical management, reduce treatment-associated morbidity (5-7) and could identify factors affecting HPV persistence leading to dysplasia and, ultimately, invasion.

The impact of these individual biomarkers, or panel of biomarkers, on cervical screening programmes has not been previously adequately assessed within Health Technology Assessments. In this project that encompasses collaborations with an international recognised group of scientists, epidemiologists, statisticians, clinicians and health economists, we assessed a novel and innovative new healthcare project and product that will substantially improve clinical practice and services across Europe.

Advances in technology and scientific techniques created new horizons for improved understanding of the diseases' processes at a molecular level. In the field of cervical pre-invasive and invasive disease, this affords the opportunity to further explore the neoplastic mechanisms at a molecular level with the aim to promote prevention, personalise management and improve targeted therapy.

3. Innovation results achieved

Almost one in ten women screened in the UK have abnormal cytology (8). The introduction of HPV-based screening will further increase the number of women that test positive, while evidence on how to optimally triage them has yet to be produced. The national call and recall system costs £175 million annually in England alone (8) and the financial impact of novel biomarker triage in pre and post vaccination populations needs to be assessed. The adaptation of clinical practice to the quickly evolving technologies and discoveries requires urgent assessment in order to improve cost-effective personalised outcomes and enhance our understanding of the disease process. Although national HPV vaccination programs have been established, it will take decades to achieve the full impact, coverage is unlikely to

be complete, and population exchange from less affluent countries will continue for decades, dictating that the NHS maintains a screening programme for both vaccinated and non vaccinated women.

This multidisciplinary proposal included research to identify new biomarkers but also to evaluate the clinical utility of existing molecular tests utilising specimens from biobanks, and also included systematic reviews of the current literature.

Through this project we aimed to develop algorithms and guidelines based on molecular markers that are more tailored to the individual patient's risk of developing invasive disease.

We managed:

1. To evaluate the use of new diagnostic tools in women with screening abnormalities and develop diagnostic models for personalised care.

2. To assess factors that promote HPV persistence and carcinogenesis with an aim to improve both oncologic and reproductive outcomes of women with pre-invasive disease

3. To make recommendations and contribute to guidelines for decision makers based on benefit and risk of alternative options for diagnosis, prognosis and treatment.

4. To empower the health care service consumer by providing accessible and understandable summaries of the available evidence and by developing a user-friendly software tool.

More specifically:

1. We used previously collected biobanks of cytology/tissue in Greece and in the UK with clinical/epidemiological data to perform full HPV profiling and biomarker testing. We lined up

data from this established biobank initiative in in-vitro models of identified clinical groups and the outputs were fed into the project. This included:

a. Triage of HPV positive women (3)

b. Triage of low-grade cytology (9, 10)

c. Post-treatment follow-up (4, 11)

d. Untreated grade 2 cervical intra-epithelial neoplasia (CIN)

We assessed commercially available or experimental diagnostic tests/biomarkers, such as HPV DNA test, genotyping, viral load; HPV E6/E7 mRNA test; p16/Ki67 immunostaining. Further marker analyses (vaginal microbiome/virome, metabonomics with MS/NMR/FTR spectroscopy, proteomics) on archived biospecimen also revealed new diagnostic and prognostic markers (see details WP2)(4, 12).

2. We investigated the effect of the host's genome, defense mechanisms and vaginal microenvironment on the chances of persistent HPV infection, regressive/progressive CIN and adverse reproductive outcomes.

We now understand better:

a. How the immune defences and the vaginal microbiome/virome and metabonome differs in the presence of HPV or cervical precancer as compared to normal controls and how this correlates to the severity/grade of cervical precancer and chances of progression/regression

b. How the treatment for cervical precancer impacts on these and

In a previously collected local biobank of serial samples, we assessed the *vaginal microbiome* by amplification of the bacterial 16S rRNA genes with MiSeq pyrosequencing(13, 14) and *metabonomics* by UPLC-MS, NMR and FTR-spectroscopy to assess the biochemical interface of the microbiota and host(15, 16). Future experiments will assess *antimicrobial peptides* (hCAP18/LL-37, SLPI, elafin) by ELISA(17), *leucocyte subpopulations* by flow cytometry(18).

Our data demonstrate that the biochemical interface of the microbiota and the host affects HPV persistence and the process of tumorigenesis (14).

3 & 4.

We conducted a series of meta-analyses to assess the diagnostic accuracy of tests and to compare oncological and pregnancy outcomes for different treatment techniques.

We have built a diagnostic mathematical model of risk (Scoring System) using epidemiological data and combinations of biomarkers. This was transformed into an IT software through Artificial Intelligence Systems. This is now transformed into a mobile application based on the diagnostic models that will quantify the individual's risk for end-users.

4. Link to the PRoF values

The outcomes of PERSONAL apply to individual, health organisation and policy makers' level. The prognostic models and IT software/platform incorporating risk factors and selected biomarkers allow sustainable and reproducible use of systems for quantification of the individual's risk and will inform decision-making **at patient interaction level** leading to major

advances in the patients' safety, care and patient choice. This evidence-based user-friendly framework for **clinicians and health managers** will lead to major cost savings as health resources will be targeted to individuals at high risk of cancer, in both vaccinated and non vaccinated cohorts. An ongoing comprehensive cost-effectiveness evaluation will further inform **policy makers and recommendations**. The research team has existing links with healthcare policy makers in the UK (BSCCP), Europe (EFC) and internationally (IFCPC - IARC) and will engage with them for the incorporation of the produced outputs.

This is in line with the 8 PRoF values as the output/end-product of this project will ensure improved care, personalized management of women with abnormalities at screening making the best use of the available health resources ***(respect, flexibility, minimal confort).*** This will minimize unnecessary referrals ***(minimal comfort, non stigmatizing solutions, privacy),*** will improve prevention of cervical cancer ***(security, anti-loneliness).***

This innovative approach was based on an interdisciplinary and inter-university collaboration and produced outputs that will allow sustainable improvement of the healthcare systems and the society.

5. Applicable IPR rules

The proposed prognostic model, IT software and mobile appplication is an innovative idea and the research group retains the intellectual property for this project. The group is in the process of registering this and obatining patent for this product.

6. Information on the partners

This patented innovative approach was the product of an interdisciplinary and inter-university collaboration amongst several European countries.

UK

Imperial College London: Dr M Kyrgiou (PI) – Dept of Surgery and Cancer

University of Lancaster: Prof Martin-Hirsch / Prof F Martin – Dept of Physics

Greece

Hellenic Cervical Pathology Academic Group (HeCPA): multicetric collaboration of the 7 academic departments in Obstetrics and Gynaecology in Greece

University of Ioannina: Prof E Paraskevaidis (PI) – Dept of Obstetrics & Gynaecology

University of Athens: Prof P Karakitsos (PI) – Dept of Cytopathology

University of Athens: Prof Koutsouris(PI) – School of Engineering-Information Technology

Belgium

Instutute of Public Health: Dr M Arbyn – Epidemiology & Statistics

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