Conclusion* Dynamic dose fractionation HDR-brachytherapy, as 1st step of preoperative chemo-irradiation, allows to reach the total tumor regression, which enable further ablastic surgery and relapse-free follow-up.

199 RANDOMISED PHASE II BGOG/ENGOT-CX1 STUDY OF PACLITAXEL-CARBOPLATIN WITH OR WITHOUT NINTEDANIB IN FIRST-LINE RECURRENT OR ADVANCED CERVICAL CANCER

[1]IB Vergote*, [2]E Van Nieuwenhuysen, [3]A Casado, [4]A Laenen, [5]D Lorusso, [6]I Braicu, [7]E Guerra-Alia, [8]P Zola, [9]P Wimberger, [10]P Debruyne, [11]E Falcó, [12]A Ferrero, [13]MZ Muallem, [14]J Kerger, [15]E Garcia Martinez, [16]S Pignata, [17]J Sehouli, [2]T Van Gorp, [18]C Gennigens, [19]MJ Rubio Pérez. *[1]University Hospitals Leuven, Belgium and BGOG, Belgium; [2]University Hospitals Leuven, Belgium and BGOG; [3]Hospital Clínico San Carlos, Madrid Spain and GEICO; [4]Catholic University Leuven, Belgium; [5]Policlinico Universitario Agostino Gemelli, Italy and ENGOT; [6]Charité Universitätsmedizin Berlin and ENGOT; [7]Hospital Ramón y Cajal, Madrid Spain and GEICO; [8]Univeristy of Turin, Italy and ENGOT; [9]Universitätsklinikum Carl Gustav Carus, Dresden, Germany and ENGOT; [10]AZ Groeninge, Kortrijk, Belgium; [11]Hospital Son Llatzer, Palma de Mallorca, Spain and GEICO; [12]Mauriziano Hospital, Torino, Italy and ENGOT; [13]Charité Universitätsmedizin Berlin, Berlin, Germany; [14]Institut Jules Bordet, Brussels, Belgium and BGOG; [15]Hospital Universitario Morales Meseguer, Murcia Spain and GEICO; [16]Instituto Nazionale Tumor, Napoli, Italy and ENGOT; [17]Charité Universitätsmedizin Berlin, Berlin, Germany and ENGOT; [18]University Hospital (CHU) of Liege, Belgium and BGOG; [19]Hospital Universitario Reina Sofía, Córdoba, Spain and GEICO*

10.1136/ijgc-2021-ESGO.16

Introduction/Background* Platinum in combination with paclitaxel (P) and bevacizumab is the standard of care in first-line recurrent/advanced cervical cancer (Tewari, NEJM 2020). Nintedanib is an oral tyrosine kinase inhibitor targeting, among others, vascular endothelial growth factor receptor.

Methodology Double-blind phase II randomised study in patients with first-line recurrent or primary advanced (FIGO stage IVB) cervical cancer. Patients received carboplatin AUC 5-6 and paclitaxel 175mg/m^2 q 3 weeks with oral nintedanib 200 mg BID/placebo. Stratification factor was primary advanced versus recurrent disease. The primary endpoint was progression-free survival (PFS) at 1,5 years with at least 87 events and α=0.15, β=80%, one sided, in favor of the nintedanib (N) versus control (C) arm. The study (NCT02009579) was performed according to the ENGOT model A.

Result(s)* 120 patients (62 N, 58 C) were randomised between March 2014 and October 2018. Median follow-up was 35 months. Baseline characteristics were similar in both groups (total population: squamous cell carcinoma 62%, prior radiotherapy 64%, primary advanced 25%, recurrent 75%). The primary endpoint was met with a PFS at 1.5 years of 15.1% versus 12.8% in favour of the nintedanib arm (p = 0.057). Median overall survival (OS) was 21.7 and 16.4 months for N and C, respectively. Subgroup analysis did not demonstrate a difference in PFS in the primary advanced setting, but in the recurrent setting the 1 year PFS was 22.8% and 14.9% for N and C, respectively. Confirmed RECIST response rate was 48% for N and 39% for C. No new adverse events were noted for N. However N was associated with numerically more serious adverse events for anemia and febrile neutropenia. Discontinuation of chemotherapy was similar in both groups. N was discontinued in 3% versus placebo in 1.6% of the patients. Dose reduction of N was necessary in 53% of the patients.

Conclusion* The study met its primary endpoint with a prolonged PFS in the N arm. No new safety signals were observed.

200 CAN METHYLATION SIGNALS OF CERVICAL CANCER ENHANCE CERVICAL SCREENING?: AN EPIGENOME-WIDE ASSOCIATION STUDY ON THE ILLUMINA 850K ARRAY

[1;2]S Bowden*, [3]B Bodinier, [4]M Paraskevaidi, [1]I Kalliala, [5]N Chaitrakulthong, [1]A Mitra, [1]M Tzafetas, [4]K Lathouras, [6]M Nasioutziki, [5]J Flanagan, [3]M Chadeau-Hyam, [2;4]M Kyrgiou. *[1]Instiute of Reproductive and Developmental Biology, Department of Surgery and Cancer – Metabolism, Digestion and Reproduction, UK; [2]West London Gynaecological Cancer Centre, Hammersmith Hospital, London, UK; [3]Imperial College London, School of Public Health , Biostastistics and Epidemiology, London; [4]Imperial College London, Institute of Reproductive and Developmental Biology, Department of Surgery and Cancer – Metabolism, Digestion and Reproduction, UK; [5]Imperial College London, Institute of Developmental and Reproductive Biology, Surgery and Cancer, London, UK; [6]Aristotle University, Cytopathology, Thessaloniki, Greece*

10.1136/ijgc-2021-ESGO.17

Introduction/Background* Cervical cancer is one of the most prevalent and leading cause of cancer mortality for women worldwide. Persistent infection with HPV is associated with the development of cervical cancer. Although most infections are cleared by the immune response, the factors related to persistent infection and carcinogenesis are less well understood. Epigenetic alterations are essential in the development of many cancers; while aberrant hypermethylation in cervical carcinogenesis has been identified in several targeted studies, epigenome-wide exploration has been limited. In this epigenome-wide association study (EWAS) we explore differential DNA methylation signatures associated to CIN3 and Cervical Cancer, to better understand potential drivers and biomarkers of cervical carcinogenesis.

Methodology 247 women (119 normal, 74 CIN3/CGIN and 54 cervical cancer) attending gynaecological appointments, cervical screening and oncological treatment between 2014-2020 at English and Greek referral hospitals were recruited. Methylation signatures were obtained following bisulphite conversion of DNA extracted from exfoliated cervical cells and sequenced using the Illumina 850k array data. After normalisaton and data QC, mixed linear models and a penalised regression were used to test for independent associations between methylation CpG sites and case-control status. P-values were Bonferroni corrected and adjusted for batch, chip, age and HPV status.

Result(s)* 177 CpG sites were strongly assosicated with CIN3 or cervical cancer, as measured by a *P*-value $<5x10^{-8}$ and a gain/loss in methylation of >15% between cases and controls. Epigenetic signals were located in over 141 unique genes genome-wide, with a gain in methylation in CIN3 or cancer cases being more common (n=77/80).

Conclusion* This is potentially the first adequately powered study to highlight genome-wide epigenetic signatures associated to carcinoma *in situ* and cervical cancer. This builds on previous genetic signals associated with cervical cancer identified by our group (Bowden *et al*, Lancet Oncol, 2021). While around 59 genes were previously reported associations to CIN or cervical cancer, the remaining 82 signals appear to be novel. Functional annotation highlighted several genes related to tumour suppresor function, transcription factors and apoptosis – important for cervical cancer tumorigenesis.

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Epigenetic determinants of cervical disease

Dr Sarah Bowden

Wellcome Trust 4i Clinical PhD Fellow in Obstetrics and Gynaecology
Section of Gynaecological Oncology, Department MDR.
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Funding

- Wellcome Trust NIHR BRC 4i Clinical PhD Fellowship (2018-21)

- Genesis Research Trust PhD consumables grant (2018)

- Imperial Healthcare Charity predoctoral fellowship (2018)

- NIHR Academic Clinical Fellowship (2015-18)

Supervisors

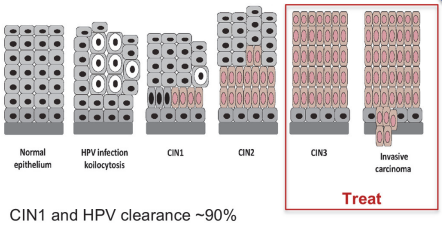
Dr M Kyrgiou

Dr James Flanagan

Prof Marc Chadeau-Hyam

Imperial College London

Natural history of CIN and cervical cancer



CIN1 and HPV clearance ~90%

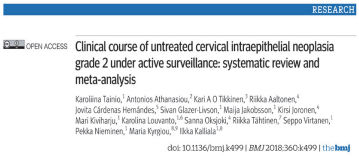
Moscicki 2006

40-50%

CIN2 regression 50-60% in 24 months

Tainio 2018

What is happening in the interactive host-viral system to dictate progression or regression??



RESEARCH

OPEN ACCESS Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis

Karoliina Tainio,[1] Antonios Athanasiou,[2] Kari A O Tikkinen,[3] Riikka Aaltonen,[4] Jovita Cárdenas Hernández,[5] Sivan Glazer-Livson,[1] Maija Jakobsson,[6] Kirsi Joronen,[4] Mari Kivihaju,[1] Karolina Louvanto,[7,8] Sanna Oksjoki,[9] Riikka Tähtinen,[1] Seppo Virtanen,[1] Pekka Nieminen,[1] Maria Kyrgiou,[8,9] Ikka Kalliala[1,8]

doi: 10.1136/bmj.k499 | BMJ 2018;360:k499 | the bmj

Meta-analysis of 1470 women
50% regression of CIN2 in 2 years
60% in <30yrs (**BMJ 2018**)

- HPV infection is common however the majority of infections are cleared

- Not all CIN2 lesions are the same

But

why.....?

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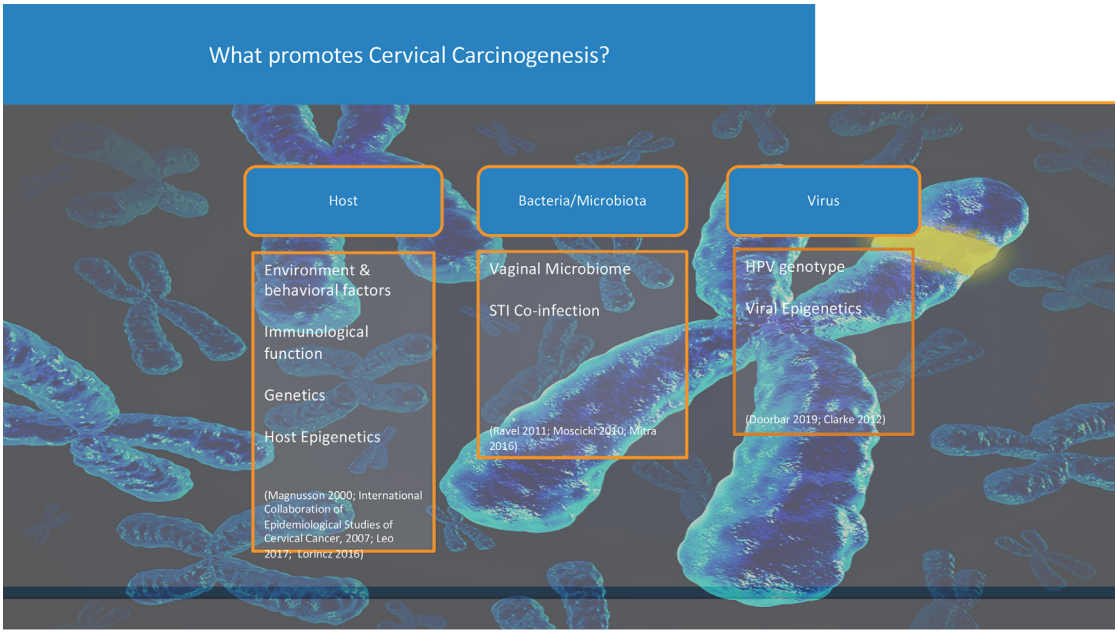

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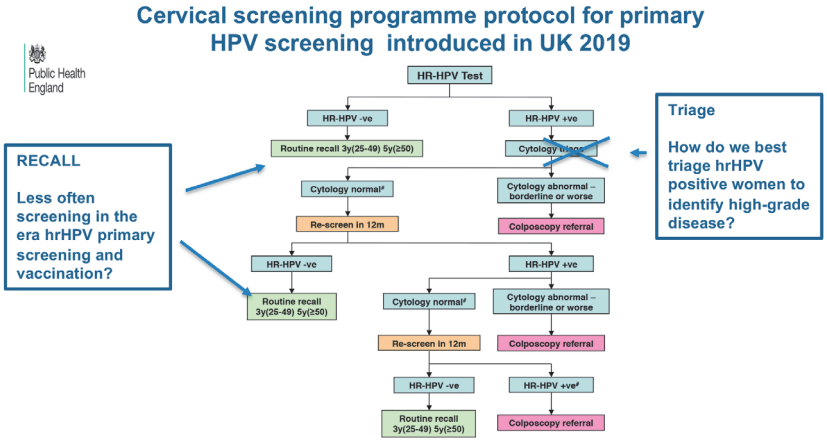
Genetic and epigenetic determinants of cervical disease
S Bowden 31st October 2020



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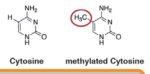
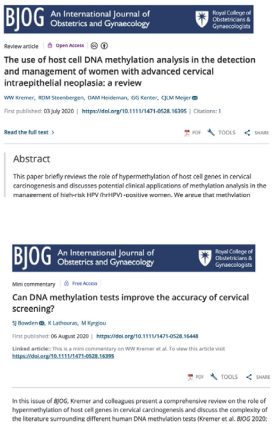


Human Epigenome in Cervical Cancer

- Host methylation sites, including CADM1, EPB41L3, FAM19A4, PAX1, MAL, MIR124-2 and SOX1 have been identified as candidate markers for cervical cancer in targeted epigenetic studies.
- The full spectrum of epigenetic marks is currently unknown, but is potentially enormous, the diploid human epigenome contains >10^8 Cytosines of which >10^7 are CpGs, and >10^8 histone tails, that can all potentially vary [Rakyan 2012]
- Epigenome-wide association studies have identified epigenetic signatures associated with other cancers (e.g breast, colon, ovarian) including up to 5 years before cancer diagnosis [Roos 2016; Van Veldhoven 2015; Johansson 2017]


BJOG An International Journal of Obstetrics and Gynaecology

The use of host cell DNA methylation analysis in the detection and management of women with advanced cervical intraepithelial neoplasia: a review

Abstract

This paper briefly reviews the role of hypermethylation of host cell genes in cervical carcinogenesis and discusses potential clinical applications of methylation analysis in the management of high-risk HPV (hrHPV)-positive women. We argue that methylation

BJOG An International Journal of Obstetrics and Gynaecology

Can DNA methylation tests improve the accuracy of cervical screening?

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Epigenome-wide association study

480 women recruited to the PRECAC study (2014-2020)
(PI: M Kyrgiou)

Aristotle University of Thessaloniki Biobank
(PI: M Nasioutziki)

LBC sample

-113 ICC/CIN3
-113 Normal/borderline cytology (HPV+ or -)

-12 ICC/CIN3
-12 Normal cytology (HPV-)

250 women included
Age 20-75

	Levels	n of overall	% of overall
Total number of samples		250	
Case control status	Control	121	48.40%
	Case	129	51.60%
	NA	0	0.00%
Worst histopathology outcome	Cancer	52	20.80%
	CGIN	5	2.00%
	CIN3	71	28.40%
	Metaplasia	3	1.20%
	Normal	89	35.60%
	NA	30	12.00%
Ethnicity	African or Afrocaribbean (Black)	1	0.40%
	Asian	15	6.00%
	Asian, Indian	1	0.40%
	Black	7	2.80%
	Black African	2	0.80%
	Black africanbbean	1	0.40%
	British	1	0.40%
	Caucasian	162	64.80%
	Chinese	1	0.40%
	East Asian	1	0.40%
	Greek	26	10.40%
	Indian	3	1.20%
	Middle Eastern	4	1.60%
	Mixed; White; African	1	0.40%
	Mixed: Black, white	1	0.40%
	Mixed: Burmese, afrocarribean	1	0.40%
	mixed: white, Asian	1	0.40%
	Pakistani	1	0.40%
	Phillipines	1	0.40%
	Serbian	1	0.40%
	South Asian	2	0.80%
	South East Asian	1	0.40%
	Syrian	1	0.40%
	Turkish	1	0.40%
	White	2	0.80%
	NA	11	4.40%
Mean age / Standard Deviation (years)		46.79 (13.17)	
Comorbidity status	No comorbidities	88	35.20%
	One or more comorbidities	60	24.00%
	NA	102	40.80%
HPV status	HPV negative	57	22.80%
	HPV positive	111	44.40%
	NA	82	32.80%
Body Mass Index	Low	3	1.20%
	Normal	66	26.40%
	Obese	7	2.80%
	Overweight	9	3.60%
	Severely obese	1	0.40%
	NA	164	65.60%
Smoking Status	Non-smoker	103	41.20%
	Smoker	19	7.60%
	NA	128	51.20%

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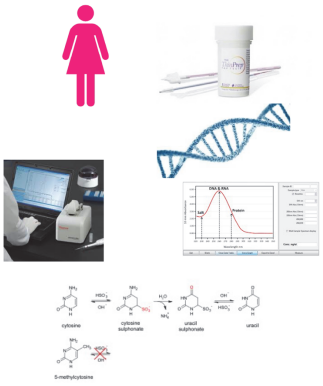
EWAS pipeline



2-4mls LBC sample

DNA extraction

QC: Nanodrop and Picogreen spectra

Bisulphite conversion

850K Illumina Array (n=250)

Bioinformatic Analysis: normalisation, QC, conversion to mvals and mixed multilinear regression model in R
(n=246)
CpG ~ CIN3/ICC batch, chip position, DNA quality, cell types, HPV status.

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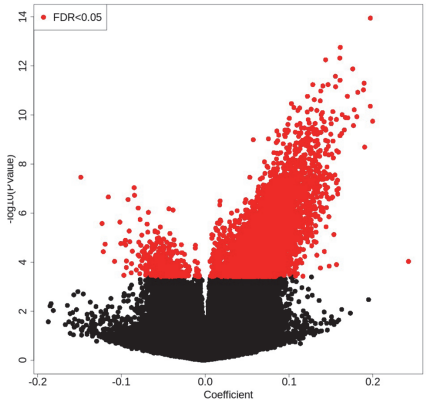
Genetic and epigenetic determinants of cervical disease

Coeff vs. Pval spread



Volcano plot of –log10(p-value) versus coefficient (methylation % change) in cases vs controls.
Red dots represent those with a false discovery rate <0.05

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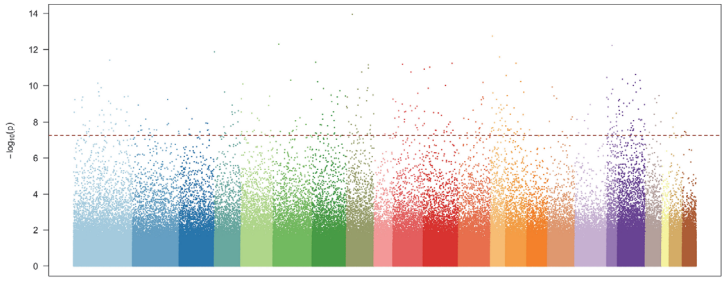
Annotation of top methylation sites



Manhattan plots showing the associations between CPG and CIN3/ICC (N=245). CPGs (N=850,000) are ordered by their position on the genome (X-axis). The p-values, measuring the strength of association, are derived from multilinear mixed models and are represented on the -log10 scale (Y-axis). The epigenome-wide significance level is set to 5x10-8 (horizontal red line).

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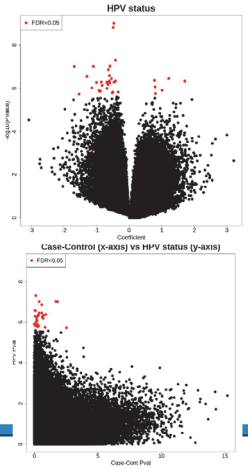
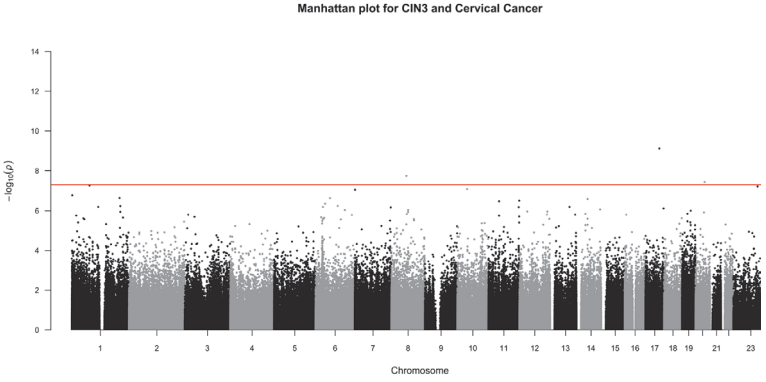
Genetic and epigenetic determinants of cervical disease

HPV adjustment





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Future work

- Finalise EWAS model, explore HPV effect on methylation
- Validate EWAS findings in our lab in a separate cohort of women with CIN and cancer

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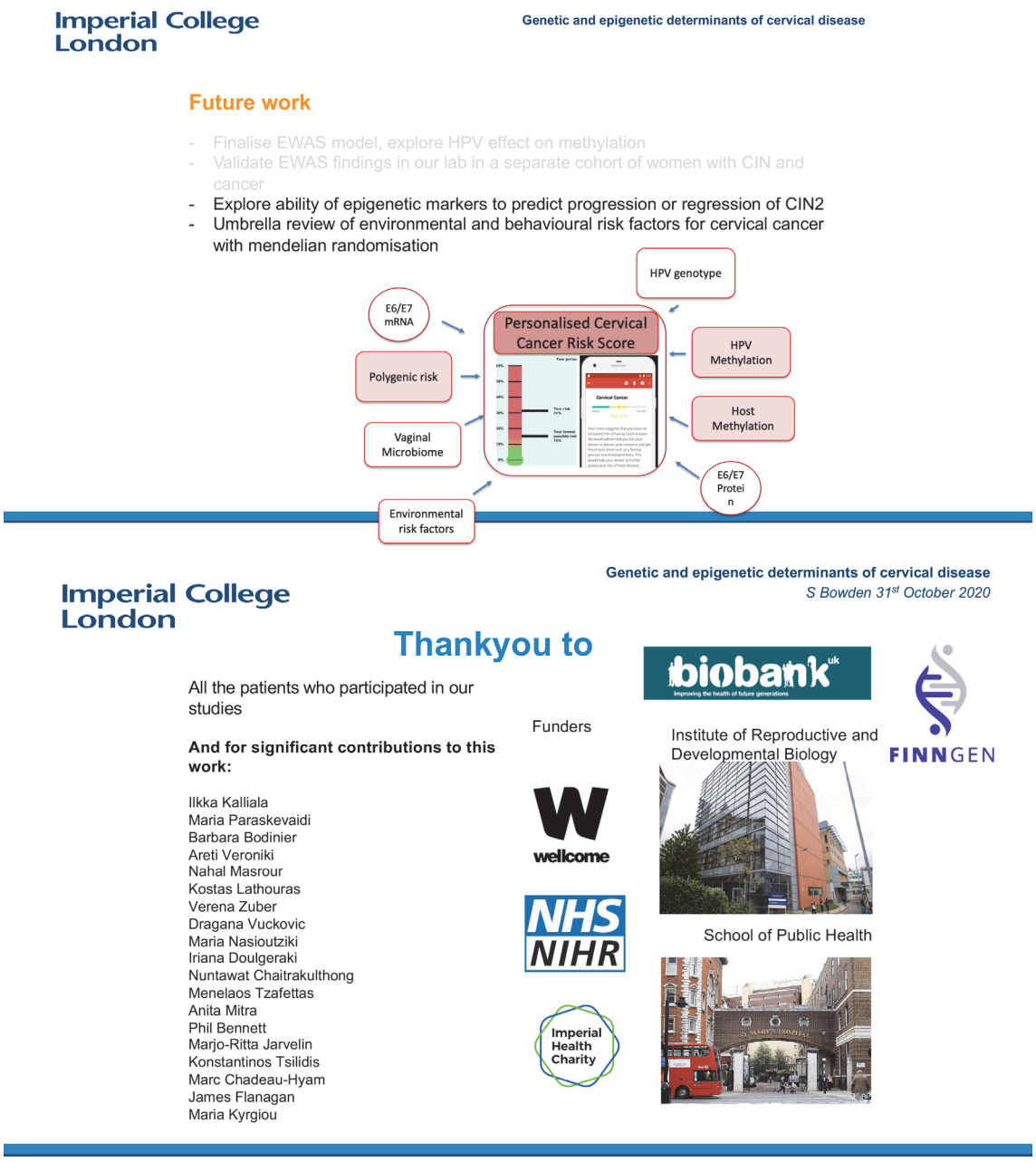

Abstract 200 Figure 1

Methylation signatures of cervical cancer genes are promising for future diagnostic and prognostic tools.

218 WORSE PROGNOSIS OF HUMAN PAPILLOMAVIRUS NEGATIVE COMPARED TO HUMAN PAPILLOMAVIRUS POSITIVE CERVICAL CANCER

[1]N Kugelman*, [1]E Siegler, [1]L Mackuli, [1]O Lavie, [1]M Schmidt, [2]P Shaked Mishan, [1]Y Segev. *[1]Carmel Medical Center, Obstetrics and Gynecology, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [2]Carmel Medical Center, Clinical Serology and Virology Laboratory, Haifa, Israel*

10.1136/ijgc-2021-ESGO.18

Introduction/Background* To evaluate the prevalence and prognosis of human papillomavirus (HPV)-negative cervical cancer (CC), and compare these to data for HPV-positive CC.

Methodology This retrospective cohort study compared between HPV-negative CC and HPV-positive CC patients. Primary endpoints were recurrence-free survival, disease-free survival, and overall survival. Secondary endpoints were demographic and clinical variables including histological diagnosis, stage, and treatment.

Result(s)* Of 233 women with CC, 18 (8%) were HPV negative. During a median follow up of 45 months, 33 (14%) recurrences and 41 (18%) deaths were observed. Eleven (61%) of the 18 women who were HPV negative and 41 (19%) of the 215 who were HPV positive had only adenocarcinoma ($P<0.001$). In a multivariate logistic regression analysis, adenocarcinoma histology at diagnosis ($P=0.010$) and primary treatment with chemotherapy or radiotherapy ($P=0.011$) remained statistically significant for recurrence. The factors associated with lower survival were advanced age ($P=0.008$), higher stage at diagnosis ($P<0.001$) and HPV

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